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Synthesis of Desfluorinated Nebivolol Isomers

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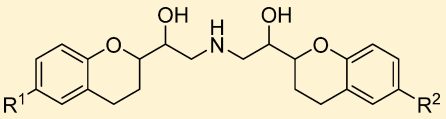
Supporting Information

ABSTRACT: The syntheses of all possible stereoisomers of desfluorinated side products of the potent antihypertensive β-blocker nebivolol are reported. A straightforward approach using a common racemic precursor was employed to obtain the desired optically active building blocks. For one series of compounds, a Sharpless asymmetric epoxidation (SAE) route yielded in a direct fashion the required compounds whereas a Mitsunobu reaction was selected to obtain the other series of compounds. This offers a flexible approach to all desfluoronebivolol side-products in order to fully characterize them.



$R^1 = R^2$ = F: Nebivolol

R^1 and/or R^2 = H: Desfluoro By-products

INTRODUCTION

α,α'-[Iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] (**1**), known as nebivolol, is a potent and selective β_1-adrenergic blocker with potent antihypertensive activity (Figure 1).[1] A general nonstereoselective access to this

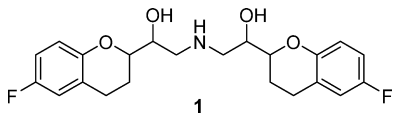


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Figure 1. Nebivolol (NBV).

pharmacologically active molecule has been disclosed for the first time by scientists at Janssen[1a,2] who also published the first scalable and stereoselective synthesis.[3] Nebivolol is marketed as hydrochloride salt and is manufactured as a racemate which consists of the enantiomers (+)- and (−)-nebivolol **1a** and **1b** (Figure 2).[4]

The compound has four chiral centers and can therefore exist in a theoretical number of 16 stereoisomers. As there is a symmetry plane through the nitrogen atom, the number of possible stereoisomers is actually reduced to 10[5] as illustrated in Table 1. NBV 1/2, NBV 3/4, NBV 5/6, and NBV 7/8 generate enantiomeric pairs whereas NBV 9 and NBV 10 are meso compounds.

A huge number of syntheses of nebivolol have been described in the patent[2,3,6] and scientific[7] literature. Usually, the last step in the manufacturing sequence is the catalytic hydrogenation of *N*-Bn-nebivolol **2**. A potential side reaction in this step is desfluorination, leading to various desfluorinated NBV isomers as depicted in Scheme 1.

Desfluorination has been mentioned for the first time by the Zach group[6i] and was observed at greater than 2% level under standard hydrogenation conditions, which is unacceptable from a pharmaceutical point of view. Principally, this side reaction can be significantly suppressed using chemical transfer hydrogenation. Unfortunately, the general structure of monodesfluoronebivolol has been deducted only from MS investigations, and the various potential isomers have not been separated.[8] From an analytical point of view, it would be advantageous to have the various desfluoro compounds available for reaction optimization, quality control, and final batch release. Since in the manufacture of nebivolol the isomers NBV 3−10 can be suppressed to less than 0.1%, we decided to synthesize all potential desfluoro compounds that can be generated from compounds **1a**,**b**. Totally, two pairs of enantiomeric monofluoro compounds can be obtained because of the dissymmetry of nebivolol and two bisdesfluoro compounds as illustrated in Scheme 1 (generally, desfluorinated nebivolol compounds can also result from chiral 3,4-dihydro-1*H*-1-benzopyran-2-carboxylic acid, the desfluoro starting material of our synthesis, which is carried over during the synthesis, but as this desfluoro starting material is present at less than 0.1% in the starting material, with all likelihood the desfluoro derivatives are obtained only at the hydrogenation step).[9]

Strategy. Basically, the simplest way to access the desfluorinated nebivolol compounds is to perform the hydrogenation step under forced conditions, but we were not able to separate the desfluoro compounds from the product by chromatography. Recently, we have shown a highly economical entry to nebivolol by enzymatic reduction as the key step,[10] which avoids unnecessary chromatographic purification steps and allows for full control of all stereogenic centers. Although this route could be used for an effective synthesis of all nebivolol

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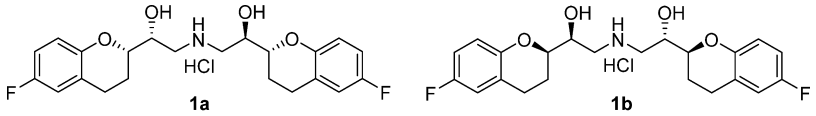
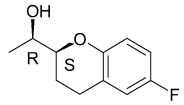
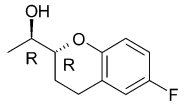
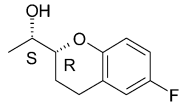
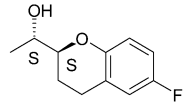
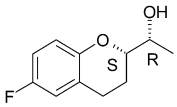
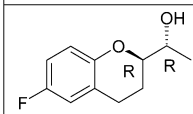
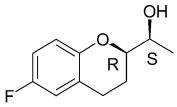
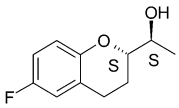


Figure 2. Manufactured racemate of nebivolol.

Table 1. Possible Stereoisomers of Nebivolol (NBV)

R1 \ R2				
	SRRS NBV-6	***(+)*- nebivolol** SRRR = RRRS NBV-1	(meso 1) SRSR = RSRS NBV-9	SRSS = SSRS NBV-8
	***(+)*- nebivolol** SRRR = RRRS NBV-1	RRRR NBV-4	RRSR = RSRR NBV-7	(meso 2) RRSS = SSRR NBV-10
	SRSR = RSRS NBV-9	RRSR = RSRR NBV-7	RSSR NBV-5	***(-)*-nebivolol** RSSS = SSSR NBV-2
	SRSS = SSRS NBV-8	SRSS = SSRS NBV-8	***(-)*-nebivolol** RSSS = SSSR NBV-2	SSSS NBV-3

stereoisomers, we failed to synthesize the desfluoro compounds by this strategy (formation of chloroaryl derivatives in the preparation of desfluorochloroketone). Therefore, we planned to apply an independent route to all desfluorinated nebivolol building blocks using a common racemic precursor. We selected a Sharpless asymmetric epoxidation (SAE) route[7a,11] for this purpose. Scheme 2 describes our overall strategy. 1,2-Dihydrobenzopyranone **A** is a suitable starting material which can be easily reduced to the lactol derivative **B** using DIBAL-H. Wittig-type chemistry or alternative reduction methodology of propargylic alcohols should give a stereoselective access to the allylic alcohols **C** and **D** which then can undergo enantioselective epoxidation to give the chiral epoxides **E**, **F**, **G**, and **H**, respectively.

During the course of experiments, we figured out that in the *Z*-series (**D**) only moderate enantioselectivity could be obtained in the SAE route furnishing **G** and **H**. This is consistent with earlier findings by K. Barry Sharpless et al., who could demonstrate that *Z*-disubstituted allylic alcohols require longer reaction times.[12] The authors also found that such slowly reacting substances require more catalyst and slightly higher reaction temperatures than in the comparable *E*-series. All together, *Z*-disubstituted allylic alcohols are least reactive and in general lower stereoselectivity will be obtained.[13] We therefore decided to change our strategy and switched to a Corey–Fuchs[14] protocol, generating the propargyl alcohol **9**, which was readily reduced in the presence of Red-Al with high stereoselectivity.[15] Compound **9** was easily available in an one-pot reaction of *n*-BuLi and paraformaldehyde on the geminal dibromide **8**. Furthermore, then we only used the *E*-series **10** for the SAE protocol and inverted the absolute configuration of the secondary alcohol in compounds **11** and **14** by a Mitsunobu[10,16] reaction to obtain the desired opposite configurations (compounds **18** and **22**). By this strategy we could overcome the low selectivity in the SAE route using the *Z*-series (**D**). Altogether, compound **10** offered a simple and robust manifold to approach all stereoisomers required for our study.

RESULTS AND DISCUSSION

2-Chromanone **6** is reduced in the presence of DIBAL-H to obtain the desired lactol **7** in high chemical yield (Scheme 3).[17] Reaction of **7** with carbon tetrabromide and triphenylphosphine provides geminal dibromide **8**, and subsequent addition of *n*-butyllithium in the presence of paraformaldehyde affords propargyl alcohol **9** in high chemical yield. Efficient reduction of **9** with Red-Al resulted in the formation of the required *E*-

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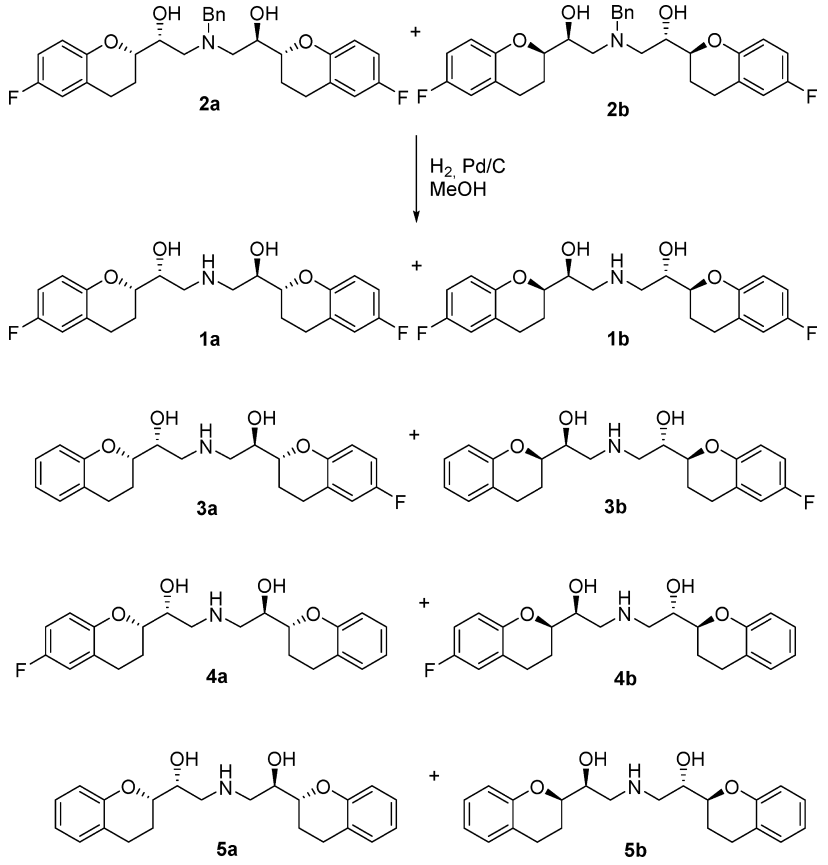
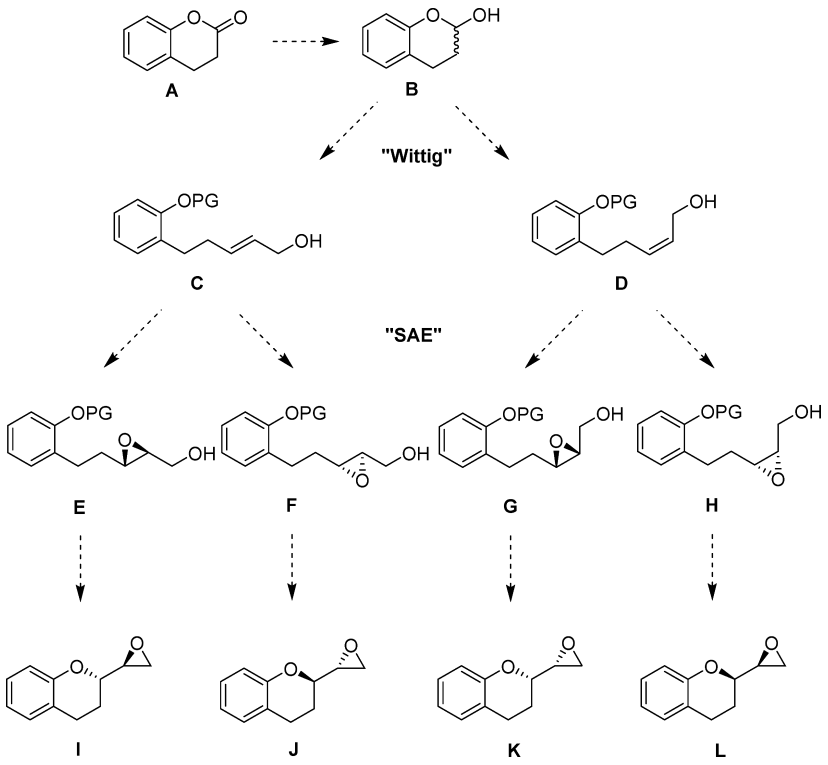
Scheme 1. Products and Impurities from the Debenzylation Reaction of *N*-Bn-Nebivolol



Scheme 2. General Strategy



allylic alcohol **10** in 83% yield. Compound **10** can be directly transformed into the desired diols **11** and **14** via SAE and in situ epoxide opening in the presence of sodium hydroxide. Both enantiomeric series are available based on the absolute configuration of tartaric acid used in the SAE protocol. Compound **11** [SAE with (−)-DET)] can be chemoselectively

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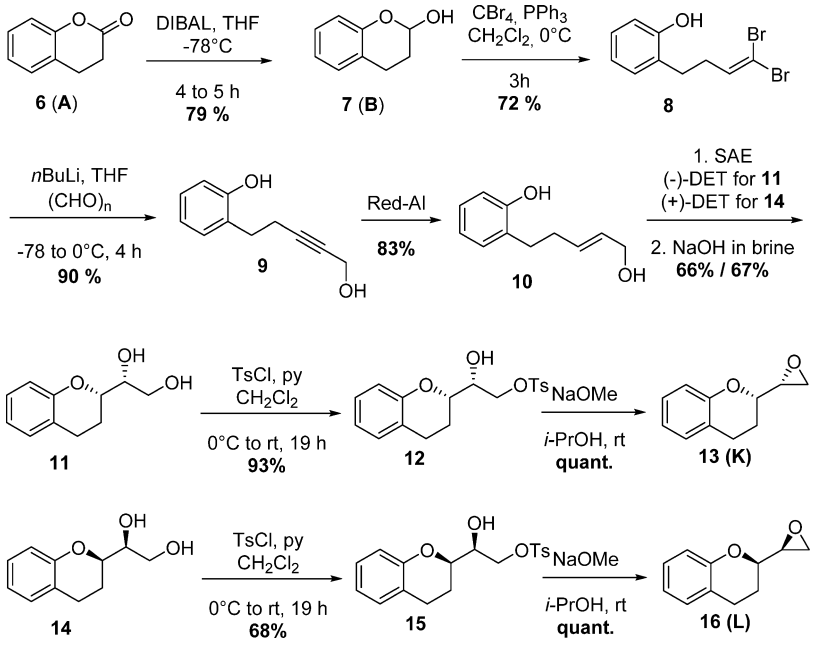
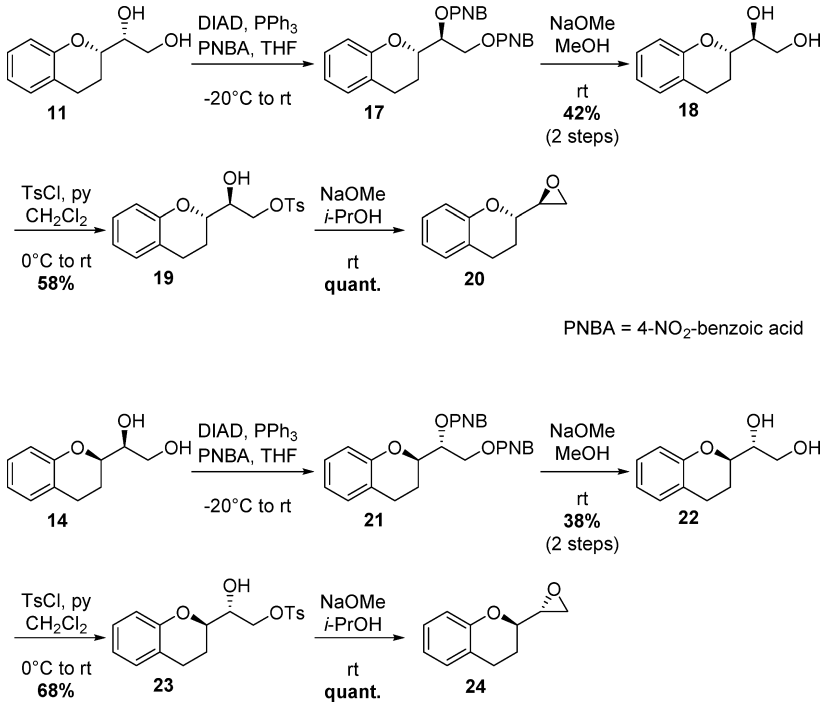
Scheme 3. SAE Route to Chiral Epoxides



Scheme 4. Mitsunobu Route to Chiral Epoxides



transformed into tosylate **12** followed by base-induced epoxide formation in the presence of sodium methoxide to give **13**. The same protocol yields epoxide **16** using (+)-DET as the chiral auxiliary for SAE.

The reverse absolute configuration concerning the secondary alcohol group can be achieved by a Mitsunobu reaction of compounds **11** and **14** with diisopropyl azodicarboxylate (DIAD), triphenylphosphine (TPP), and *p*-nitrobenzoic acid (PNBA). The desired inverted secondary alcohols **18** and **22** are then generated by saponification of the obtained PNBA esters **17** and **21** without loss of enantiomeric purity. Compounds **18** and **22** can be converted into the required epoxides **20** and **24** using the same protocol as described before (Scheme 4).

With all epoxide compounds in hand, the coupling with benzylamine could be envisioned. As shown in Scheme 5, a smooth transformation took place for each of the intended compounds. Finally, a transfer hydrogenation provided all vitally needed desfluoro nebivolol isomers in very high stereochemical purity and high chemical yield (Figure 3).

■ CONCLUSION

For the first time, a general strategy to obtain all possible desfluoronebivolol isomers has been described and offers the

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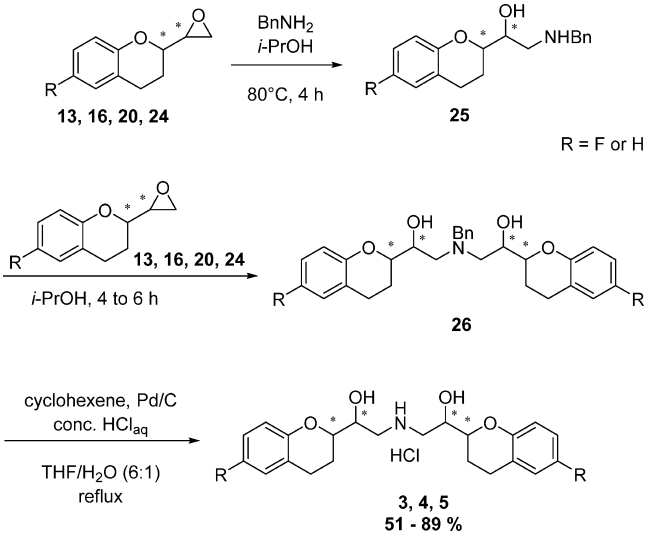
Scheme 5. Coupling with Chromane Epoxides and Debenzylation



possibility to fully analyze and characterize the side-products in a very important pharmaceutical manufacturing process. In addition, the chemistry presented provides useful insights for a variety of fundamental reactions leading to quite complex intermediates that could be coupled in a straightforward way to obtain large quantities of pure isomers that have been observed only by mass spectroscopy in the past. Altogether, this sheds some light on the scale-up synthesis of a potent and selective β-blocker with high antihypertensive activity.

EXPERIMENTAL SECTION

General. Solvents were dried by standard procedures and redistilled under N_2 atmosphere prior to use. All organometallic reactions were run under nitrogen. The products were purified by flash chromatography on Merck silica gel 60 (40−63 mm). High-resolution mass spectra (EI 70 eV, double focusing sector mass spectrometer) were obtained by the peak matching method (reference PFK, accuracy ±2 ppm). NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C).

*Chroman-2-ol (**7**).* In a 1 L two-necked round-bottom flask equipped with magnetic bead and a water condenser connected to a nitrogen inlet, dihydrocoumarin (10 g, 67.49 mmol, 1.00 equiv) **6** was dissolved in THF (472 mL, 7 mL/mmol). The mixture was cooled to −78 °C under a N_2 atmosphere. DIBAl-H (1 M in hexane, 81 mL; 81 mmol, 1.20 equiv) was added dropwise over 20 min, and stirring of the reaction was continued at −78 °C. After 4 h, the reaction was complete (TLC monitoring in pentane/EtOAc 4:1). The reaction was quenched by the addition of H_2O (20 mL) and then warmed to room temperature (2 h). Anhydrous $MgSO_{4(s)}$ (50 g) was added, and the reaction was stirred vigorously and then filtered through a sintered funnel. The solids were thoroughly washed with pentane (100 mL). Combined organic fractions were concentrated under vacuum and purified by flash chromatography on silica gel using pentane/EtOAc (9:1 to 4:1) to provide the product **7** (7.89 g, 52.54 mmol) with an isolated yield of 79% as a colorless oil. R_f = 0.39 in 4:1 pentane/EtOAc (vanillin stain); ^{1}H NMR ($CDCl_3$): δ 7.14−7.15 (m, 2H); 6.90−6.81 (m, 2H); 5.61(dd, 1H, J = 2.71 Hz, 1,05 Hz); 3.32−3.05 (br, OH); 3.07 (ddd, 1H, J = 5.33 Hz, 10.45 Hz, 16.43 Hz), 2.08−1.98 (m, 2H).[17]

*2-(4,4-Dibromo-but-3-enyl)phenol (**8**).* A CH_2Cl_2 solution (750 mL, 3.2 mL/mmol) of CBr_4 (169 g, 468.15 mmol, 2 equiv) in a 2 L three-necked RB flask equipped with a double-surface water condenser, N_2 inlet, 250 mL pressure equalizing dropping funnel, and a magnetic bead was cooled to 0 °C under a N_2 atmosphere. A CH_2Cl_2 solution (500 mL) of PPh_3 (245.58 g, 936.30 mmol, 4 equiv) was added dropwise to the reaction over a period of 90 min and stirred for further 30 min at 0 °C. Subsequently a CH_2Cl_2 solution (175 mL) of chromanol **2** (35.19 g, 234.07 mmol, 1.00 equiv) was added through a 500 mL pressure equalizing dropping funnel over a period of 20 min. The reaction slowly turned from wine-red to a pale brown and was continued for a further 1 h period at 0 °C. Progress of the reaction was monitored by TLC (Et_2O). The reaction was quenched by the addition of water (400 mL) and then warmed to room temperature. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). Combined organic portions were washed with brine solution (600 mL), dried over Na_2SO_4, filtered, and concentrated. To the resulting brown syrupy liquid was added Et_2O (1 L) to precipitate PPh_3O. This was removed via filtration through a sintered funnel, and the solid residue was rinsed with Et_2O (1 L). The combined Et_2O fractions were concentrated, and the resulting suspension was purified by flash chromatography on silica gel using 7:1 pentane/Et_2O as the eluent system to furnish 2-(4,4-dibromobut-3-enyl)phenol **8** (52.01 g, 169.57 mmol) in 72% isolated yield. R_f = 0.8 in Et_2O (vanillin stain); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14−7.14 (m, 2H); 6.89 (t, J = 7.45 Hz, 1H); 6.74 (d, J = 8.49 Hz); 6.45 (t, J = 7.10 Hz, 1H); 4.81 (s, 1H); 2.74 (t, J = 7.41 Hz, 2H); 2.43 (q, J = 7.84 Hz, 2H); HRMS (EI) (m/z) $[C_{10}H_{10}OBr_2]^+$: Calcd 303.9093, Found 303.9090.[15]

*2-(5-Hydroxypent-3-yn-1-yl)phenol (**9**).* A THF (424 mL) (3.4 mL/mmol) solution of the dibromide **3** (38.31 g, 124.91 mmol, 1.00 equiv) was taken into a 2 L three-necked RB flask equipped with a magnetic bead, low temperature thermometer, 250 mL pressure equalizing dropping funnel, and water condenser equipped with a nitrogen inlet. The reaction was cooled to −78 °C under a stream of N_2. *n*-Buli (2.5 M

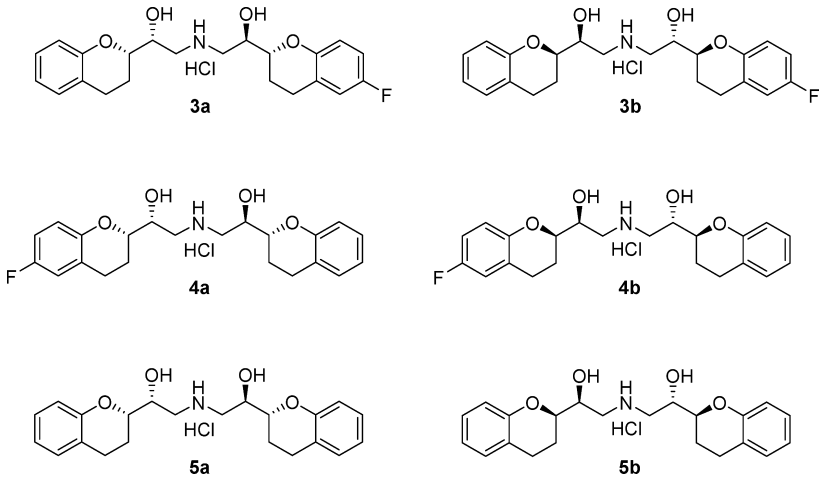


Figure 3. Synthesized desfluoronebivolol isomers.

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in hexane, 180.89 mL, 452.19 mmol, 3.62 equiv) was dropwise added over a period of 1 h while maintaining the internal temperature around −72 to −75 °C. The reaction was continued at −78 °C for 1 h. Paraformaldehyde (11.20 g, 374.74 mmol, 3 equiv) was added in one portion at −78 °C to the reaction. After this, the dry ice bath was removed and the reaction was allowed to warm to room temperature and continued for an additional 1 h. After the reaction was completed (TLC monitoring in Et_2O), it was quenched at room temperature by the addition of saturated aqueous NH_4Cl solution (600 mL) to the vigorously stirred reaction. After dilution with EtOAc (150 mL), the layers were separated and the aqueous portion was extracted with EtOAc (3 × 150 mL). Combined organic portions were dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel was performed using pentane/EtOAc (7:3 to 1:1) furnishing 2-(5-hydroxypent-3-ynyl)phenol **9** (19.81 g, 112, 56 mmol) in 90% isolated yield as a colorless syrupy liquid. R_f = 0.38 in Et_2O ($KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$): δ 7.16−7.06 (m, 2H); 6.87 (t, J = 7.44 Hz, 1H); 6.77 (d, J = 7.87 Hz, 1H); 5.89−5.55 (br, 1H, OH); 4.23 (t, J = 2.13 Hz, 2H); 2.84 (2.84, J = 7.45, 2H); 2.53 (m, 2H); 2.35−1.86 (br, 1H, OH); HRMS (EI) (m/z) $[C_{11}H_{12}O_2]^+$: Calcd 176.0832, Found 176.0832.[15]

*(E)-2-(5-Hydroxypent-3-en-1-yl)phenol (**10**).* A solution of Red-Al (65% in toluene, 47.71 mL, 153.39 mmol, 2.47 equiv) in Et_2O (64 mL) was cooled under a N_2 atmosphere to 0 °C. A solution of the alkyne **9** (10.93 g, 62.10 mmol, 1.00 equiv) in Et_2O (44 mL) was dropwise added over 10 min, and then the reaction was warmed to room temperature and stirred overnight. After 18 h, the reaction mixture was cooled to 0 °C and a saturated aqueous Rochelle's salt (366 mL) solution was very carefully added dropwise. The reaction was stirred vigorously at 0 °C for a period of 1 h and then warmed to room temperature. The mixture was extracted with EtOAc (3 × 100 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel using pentane/Et_2O (1:1 to 3:7) furnished (*E*)-2-(5-hydroxypent-3-enyl)phenol **10** (9.21 g, 51.74 mmol) in 83% isolated yield. R_f = 0.36 in 100% Et_2O ($KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$): δ 7.12−7.03 (m, 2H); 6.85 (t, J = 7.58 Hz, 1H); 6.74 (d, J = 7.86 Hz, 1H); 5.81−5.61 (m, 2H); 4.08 (d, J = 5.61 Hz, 2H); 2.70 (t, J = 7.30 Hz); 2.37 (q, J = 7.30 and 14.60 Hz, 2H); HRMS (EI) (m/z) $[C_{11}H_{14}O_2]^+$: Calcd 178.0988, Found 178.0987.[15]

General Experimental Procedure for the Synthesis of the Chromane Diols 11 and 14 via One-Pot Sharpless Asymmetric Epoxidation. *Step 1. Sharpless Asymmetric Epoxidation (SAE).* Under a N_2 atmosphere, a suspension of the activated 4 Å molecular sieves (0.5 g/mmol) in CH_2Cl_2 (5 mL/mmol) was cooled to −20 °C (ethylene glycol/H_2O (1:1) with dry ice). A solution of the appropriate optically pure diethyl tartrate (1.09 equiv) in CH_2Cl_2 (2.5 mL/mmol) was added. Then $Ti(OiPr)_4$ (1.20 equiv) followed by TBHP (5.5 M in nonane) (3.92 equiv) were successively introduced into the reaction. The mixture was stirred at −20 °C for 20 min, and then a solution of the *E*-allyl alcohol (1.00 equiv) **10** in CH_2Cl_2 (2 mL/mmol) was dropwise added in over a period of 30 min. The reaction was continued for further 4 h at −20 °C. After completion of the reaction (TLC monitoring in Et_2O), it was warmed to 0 °C and then poured into a freshly prepared solution of $FeSO_4{\cdot}7H_2O$ (0.330 g/mmol) and tartaric acid (0.100 g/mmol) in water (1 mL/mmol) which was cooled to 0 °C. The two-phase mixture was stirred for 45 min, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. Combined organic portions were concentrated to 1/3 volume and used directly in the next step of the sequence leading to the chromane diol.

Step 2. Base-Catalyzed Intramolecular Cyclization. The pale yellow viscous epoxide solution obtained from step 1 was cooled to 0 °C under N_2 atmosphere. A 30% aqueous NaOH solution in brine (2.9 mL/mmol) was added [Note 1: 100 mL of a 30% NaOH in brine solution is prepared by the addition of NaCl (5 g) to a solution of NaOH (30 g) in water (90 mL)]. The reaction mixture turned from pale yellow to pale violet and after about 10 min it turned colorless. The reaction was stirred at 0 °C for 1 h and subsequently warmed to room temperature. The layers were separated, and the aqueous phase was extracted thrice with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel was performed using Et_2O/MeOH (96:4 to 92:8) to furnish the chromane diol as a white crystalline solid product.

*(R)-1-((S)-Chroman-2yl-ethane-1,2-diol (**11**).* Yield: 3.29 g (66%) as colorless solid (mp 78 °C); $[\alpha]_D^{20}$ = +86.7 (c = 0.475 in MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 7.10−7.01 (m, 2H); 6.90−6.81 (t, J = 8.33 Hz, 1H); 6.81−6.74 (d, J = 8.33 Hz, 1H); 4.07−3.95 (m, 1H); 3.92−3.76 (m, 3H); 3.36−3.08 (br, OH); 2.88−2.72 (m, 2H); 2.16−2.08 (m, 1H); 1.91−1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 129.7, 127.4, 122.2, 120.6, 116.7, 76.4, 73.4, 63.5, 24.4, 23.3; HRMS (EI) (m/z) $[C_{11}H_{14}O_3]^+$: Calcd 194.0937, Found 194.0938.

*(S)-1-((R)-Chroman-2-yl)ethane-1,2-diol (**14**).* Yield: 3.30 g (66%) as colorless solid (mp 76 °C); $[\alpha]_D^{20}$ = −74.9 (c = 0.865 in MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 7.12−7.01 (m, 2H); 6.89−6.81 (t, J = 7.46 Hz, 1H); 6.81−6.73 (d, J = 8.46 Hz, 1H); 4.10−3.96 (m, 1H); 3.92−3.77 (m, 3H); 3.04−2.64 (br, 4H); 2.17−2.07 (m, 1H); 2.16−2.08 (m, 1H); 1.92−1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 129.7, 127.4, 122.2, 120.7, 116.8, 76.6, 73.4, 63.5, 24.4, 23.4; HRMS (EI) (m/z) $[C_{11}H_{14}O_3]^+$: Calcd 194.0937, Found 194.0939.

General Experimental Procedure for the Two-Step Mitsunobu Inversion of the Chromane Diols 11 and 14 to the Chromane Diols 18 and 22. *Step 1: Chromane Diol to Bis(4-nitrobenzoate) Esters.* Diisopropyl azodicarboxylate (DIAD) (6.00 equiv) was dissolved in THF (7.14 mL/mmol) and cooled to −20 °C under N_2 atmosphere. To this was dropwise added a THF solution (7.14 mL/mmol) of PPh_3 (6.00 equiv) while maintaining the internal temperature at −20 °C. A solution of chromane diol (1.00 equiv) in THF (2.9 mL/mmol) was dropwise added. Finally a *p*-nitrobenzoic acid (6.00 equiv) solution in THF (6 mL/mmol) was dropwise added. The reaction mixture was stirred at −20 °C for 5 h. The progress of the reaction was monitored by TLC (100% Et_2O, $KMnO_4$ stain). The cooling bath was removed, and the reaction was warmed to room temperature. The solvent was evaporated under vacuum. To the resulting pale yellow syrup was added Et_2O to precipitate PPh_3O. The combined organic portions were concentrated and then purified by flash chromatography on silica gel using Et_2O/MeOH (20:1 to 9:1). Although, the obtained material still contained PPh_3O and diisopropylurea, it was used for the next step.

Step 2: Saponification of the Bis(4-nitrobenzoate) Ester. The diester (1.00 equiv) from step 1 was dissolved in MeOH, and NaOMe (95% pure, 3.00 equiv) was added at room temperature. Slowly the reaction turned into a homogeneous pale yellow solution. The reaction was continued at room temperature overnight under nitrogen atmosphere. After 16 h, the solvent was removed under vacuum. CH_2Cl_2 was added to the resulting pale pink solid product to provide a clear pale yellow solution. After addition of saturated aqueous NH_4Cl, the layers were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic portions were successively washed with H_2O and brine solution, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel was performed using 100% Et_2O to Et_2O/MeOH (9:1), furnishing the chromane diol.

*(S)-1-((S)-Chroman-2-yl)ethane-1,2-diyl Bis(4-nitrobenzoate) (**17**).* Light yellow solid; mp 119 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.37−8.30 (m, 4H); 7.92−7.80 (m, 4H); 7.13 (dd, J = 9.28 Hz, 1.94 Hz, 1 H); 7.06 (d, J = 7.34 Hz, 1H); 6.93−6.83 (m, 2H); 5.80 (ddd, J = 8.63 Hz, 5.61 Hz, 3.45 Hz, 1H); 4.91−4.84 (d, J = 5.72 Hz, 2H); 4.46−4.39 (m, 1H); 3.02−2.77 (m, 2H); 2.16−1.90 (m, 2H); HRMS (EI) (m/z) $[C_{25}H_{20}O_9N_2]^+$: Calcd 492.1169, Found 492.1163.

*(R)-1-((R)-Chroman-2-yl)ethane-1,2-diyl Bis(4-nitrobenzoate) (**21**).* Light yellow solid; mp 115 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36−8.31 (m, 4H); 7.90−7.88 (m, 4H); 7.13 (ddd, J = 8.34 Hz, 7.56 Hz, 1.46 Hz, 1 H); 7.06 (d, J = 7.44 Hz, 1H); 6.92−6.85 (m, 2H); 5.81 (ddd, J = 8.84 Hz, 5.61 Hz, 3.38 Hz, 1H); 5.02−4.92 (m, 2H); 4.89 (d, J = 5.68 Hz, 2H); 4.44 (ddd, J = 10.87 Hz, 3.28 Hz, 2.37 Hz, 1H); 2.96 (ddd, J = 17.02 Hz, 12.09 Hz, 6.11 Hz, 1H); 2.82 (ddd, J = 16.49 Hz, 5.32 Hz, 2.30 Hz, 1H); 2.16−2.07 (m, 1H); 2.04−1.91 (m, 1H); HRMS (EI) (m/z) $[C_{25}H_{20}O_9N_2]^+$: Calcd 492.1169, Found 492.1163.

*(S)-1-((S)-Chroman-2-yl)ethane-1,2-diol (**18**).* Yield: 1.27 g (42% over two steps starting from **11**) as a colorless solid (mp 116 °C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.18−7.00 (m, 2H); 6.92−6.75 (m, 2H); 4.13−4.03 (m, 1H); 3.85−3.67 (m, 3H); 2.95−2.82 (m, 2H); 2.82−2.73

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(m, 1H); 2.56−2.39 (br, OH); 2.05−1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 129.7, 127.4, 121.8, 120.0, 116.8, 76.8, 73.9, 63.8, 24.6, 23.9; HRMS (EI) (m/z) $[C_{11}H_{14}O_3]^+$: Calcd 194.0937, Found 194.0938.

*(R)-1-((R)-Chroman-2-yl)ethane-1,2-diol (**22**).* Yield: 0.94 g (28% over two steps starting from **14**) as colorless solid (mp 116 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12−7.02 (m, 2H); 6.89−6.79 (m, 2H); 4.12−4.06 (m, 1H); 3.89−3.75 (m, 3H); 2.95−2.83 (m, 2H); 2.78 (ddd, J = 16.33 Hz, 5.49 Hz, 2.69 Hz, 1H); 2.52−2.45 (br, OH); 2.06−1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 129.6, 127.3, 121.9, 120.7, 116.7, 76.7, 73.8, 63.6, 24.5, 23.8. HRMS (EI) (m/z) $[C_{11}H_{14}O_3]^+$: Calcd 194.0937, Found 194.0938.

General Experimental Procedure for the Primary Tosylation of the Chromane Diols. Pyridine (2.42 equiv) was added to a CH_2Cl_2 (3 mL/mmol) solution of the corresponding chromane diol (1.00 equiv) at room temperature under a nitrogen atmosphere. The mixture was cooled to 0 °C, and a solution of the tosyl chloride (1.11 equiv) in CH_2Cl_2 (1 mL/mmol) was added dropwise. After being stirred at the same temperature for a further 30 min, the reaction was warmed to room temperature and stirred overnight. After completion of the reaction (19 to 24 h, TLC monitoring in Et_2O), the reaction was quenched by the addition of saturated aqueous $CuSO_4$ solution (3.7 mL/mmol) and stirred vigorously at room temperature. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (three times). The combined organic portions were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. Flash chromatography of the crude product on silica gel was performed using pentane/Et_2O (6:1 to 4:1), furnishing the corresponding primary tosylate in 56% to 93% isolated yield. Only one of the four compounds (**19**) was characterizable by ^{13}C NMR. We could not obtain ^{13}C NMR spectra of compounds **12**, **15**, and **23** because of instability.

*(R)-2-((S)-Chroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate (**12**).* Yield: 0.70 g (93%) as off-white wax; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.99 Hz, 2H); 7.34 (d, J = 7.99 Hz, 2H); 7.08−6.86 (m, 2H); 6.87−6.75 (m, 1H); 6.83 (dt, J = 7.73 Hz, 1.26 Hz, 1H); 6.66 (d, J = 8.15 Hz, 1H); 4.38 (dd, J = 10.54 Hz, 2.95 Hz, 1H); 4.25−4.18 (dd, J = 10.74 Hz, 5.62 Hz, 1H); 3.98−3.89 (m, 2H); 2.84−2.70 (m, 2H); 2.44 (s, 3H); 2.21−2.14 (m, 1H); 1.84−1.72 (m, 1H); HRMS (EI) (m/z) $[C_{18}H_{20}O_5S]^+$: Calcd 348.1026, Found 348.1030.

*(S)-2-((R)-Chroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate (**15**).* Yield: 1.56 g (68%) as off-white wax; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.71 Hz, 2H); 7.34 (d, J = 8.48 Hz, 2H); 7.15−6.97 (m, 2H); 7.15−6.97 (m, 2H); 6.89−6.79 (m, 1H); 6.72−6.61 (d, J = 7.71 Hz, 1H); 4.42−4.36 (dd, 4.38 (dd, J = 10.79 Hz, 3.08 Hz, 1H); 4.25−4.19 (dd, J = 10.02 Hz, 6.16 Hz, 1H); 3.97−3.87 (m, 2H); 2.85−2.70 (m, 2H); 2.44 (s, 3H); 2.22−2.14 (m, 1H); 1.84−1.72 (m, 1H); HRMS (EI) (m/z) $[C_{18}H_{20}O_5S]^+$: Calcd 348.1026, Found 348.1030.

*(S)-2-((S)-Chroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate (**19**).* Yield: 1.22 g (58%) as off-white wax; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.69 Hz, 2H); 7.33 (d, J = 8.07 Hz, 2H); 7.10−7.01 (m, 2H); 6.90−6.81 (m, 1H), 6.71 (d, J = 8.69 Hz, 1H); 4.25−4.20 (dd, J = 5.89 Hz, 1.57 Hz, 1H); 4.06−3.99 (m, 1H); 3.98−3.89 (m, 1H); 2.43 (s, 3H): 2.92−2.71 (m, 2H); 2.00−1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 145.2, 12.7, 130.1, 129.8, 128.1, 127.4, 121.9, 121.0, 116.8, 76.8, 74.9, 71.3, 70.1, 24.7, 23.6, 21.8); HRMS (EI) (m/z) $[C_{18}H_{20}O_5S]^+$: Calcd 348.1026, Found 348.1027.

*(R)-2-((R)-Chroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate (**23**).* Yield: 1.48 g (68%) as off-white wax; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.23 Hz, 2H); 7.34 (dd, J = 8.62 Hz, 0.57 Hz, 2H); 7.10−7.02 (m, 2H); 6.86 (J = ddd, 8.60 Hz, 7.28 Hz, 1.34 Hz, 1H), 6.72 (dd, J = 8.09 Hz, 1.00 Hz, 1H); 4.23 (dd, J = 5.75 Hz, 1.39 Hz, 1H); 4.06−4.01 (m, 1H); 3.98−3.91 (m, 1H); 2.44 (s, 3H): 2.92−2.73 (m, 2H); 1.99−1.92 (m, 2H); HRMS (EI) (m/z) $[C_{18}H_{20}O_5S]^+$: Calcd 348.1026, Found 348.1024.

General Experimental Method for the Peparation of Chromane Epoxides from Tosylates. NaOMe (95% pure, 1.10 equiv) was added in small portions to a solution of the primary tosylate (1.00 equiv) in 2-propanol (1.15 mL/mmol) at room temperature under dry nitrogen atmosphere. The mixture was stirred for 1 h. The reaction was quenched by the addition of AcOH (0.13 equiv) in 2-propanol (0.2 mL/mmol). The crude mixture was filtered through a short pad of Dicalite over sand and thoroughly washed with 2-propanol (three times). The combined organic portions were concentrated to furnish the corresponding chromane epoxide, which were immediately used for further transformations.

General Experimental Method for the Preparation of *N*-Benzylamino Chromanes Alcohol from from Chromane Epoxides. Benzylamine (5 equiv) was dissolved in 2-propanol (0.6 mL/mmol) and heated to 80 °C under N_2 atmosphere. A solution of the chromane epoxide (1.00 equiv) in 2-propanol (2 mL/mmol) was added dropwise over a period of 2 h, and the mixture was further heated to 80 °C for an additional 2 h. After completion of the reaction (TLC monitoring in CH_2Cl_2/MeOH (5:1) solvent system), the reaction mixture was cooled to 0 °C (1 h) and additional 2-propanol was added to facilitate the crystallization. The solid material was isolated by filtration and dried under high vacuum.

General Experimental Method for the Preparation of the *N*-Benzyldesfluoronebivolol Framework. The chromane epoxide (1.10 equiv) and *N*-benzylamino alcohol (1.00 equiv) were dissolved in 2-propanol (3.6 mL/mmol) and were heated to reflux under a dry nitrogen atmosphere. After completion of the reaction (4 to 6 h and TLC monitoring in CH_2Cl_2/MeOH (9:1)), the solvent was removed under vacuum. Flash chromatography on silica gel using a CH_2Cl_2/MeOH (15:1) eluent system furnished the product as a white solid in 89% to quantitative yield.

General Experimental Method for the N-Debenzylation via Transfer Hydrogenation Using Pd/C and Cyclohexene. To a THF/H_2O (6:1) (5.6 mL/mmol) solution of the *N*-benzyldesfluoronebivolol compound (1.00 equiv) were added concentrated aqueous HCl (1.12 equiv), Pd/C (dry, 10%), and finally cyclohexene (10 equiv), and the reaction was heated to reflux. After completion of the reaction (2 to 6 h, TLC monitoring in CH_2Cl_2/MeOH (9:1)), it was brought to room temperature and filtered through a short pad of Dicalite over sand. The solids were thoroughly washed with THF (three times). The combined organic portions were concentrated under vacuum to a small volume, resulting in a solid−liquid suspension. Isopropyl acetate or EtOAc (2 mL/mmol) was added to facilitate the crystallization of the desfluoronebivolol hydrochloride salt, which were obtained in 72% to 95% isolated yields as white solid products.

*(R)-1-((S)-Chroman-2-yl)-2-(((R)-2-((R)-6-fluorochroman-2-yl)-2-hydroxyethyl)amino)ethan-1-ol Hydrochloride (**3a**).* Yield: 412 mg (82%) as white crystals; mp 185 °C; $[\alpha]_D^{20}$ = +16.5 (c = 0.34 in MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.99−8.59 (br, NH_2); 7.11−7.03 (m, 2H); 6.98−6.87 (m, 2H); 6.82 (t, J = 7.72 Hz, 1.29 Hz, 1H); 6.79−6.71 (m, 2H); 5.97 (d, J = 5.57 Hz, OH); 5.78 (d, J = 5.57 Hz, OH); 4.15−4.06 (m, 1H); 4.06−3.95 (m, 2H); 3.94−3.85 (m, 1H); 3.43−3.34 (br, 1H masked with water signal); 3.28−3.13 (m, 2H); 3.12−2.99 (m, 1H); 2.89−2.63 (m, 4H); 2.19−2.06 (m, 1H); 1.99−1.86 (m, 1H); 1.84−1.62 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.9 (d, J = 235.78 Hz, C−F), 153.9, 150.5, 129.6, 127.1, 123.7 (d, J = 8.49 Hz), 122.2, 120.3, 117.4 (d, J = 8.49 Hz), 116.3, 115.3 (d, J = 22.44 Hz), 113.7 (d, J = 23.04 Hz), 76.0, 76.8, 67.6, 67.3, 50.0, 49.5, 24.2, 23.4, 22.8, 22.2; IR ν = 3057, 2858, 1491, 1233, 1217, 1080, 749 cm^{-1}; HRMS (EI) (m/z) $[C_{22}H_{26}O_4NF]^+$: Calcd 387.1840, Found 387.1841.

*(S)-1-((R)-Chroman-2-yl)-2-(((S)-2-((S)-6-fluorochroman-2-yl)-2-hydroxyethyl)amino)ethan-1-ol Hydrochloride (**3b**).* Yield: 393 mg (81%) as white crystals; mp 182 °C; $[\alpha]_D^{20}$ = −28.9 (c = 0.65 in MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.84 (br s, NH_2); 7.09−7.03 (m, 2H); 6.95−6.87 (m, 2H); 6.85−6.79 (m, 1H); 6.78−6.73 (m, 2H); 5.99 (d, J = 5.6 Hz, OH); 5.81 (d, J = 5.6 Hz, OH); 4.16−4.08 (m, 1H); 4.07−3.96 (m, 2H); 3.95−3.88 (m, 1H); 3.42−3.34 (br, 1H partly overlapped by water signal); 3.28−3.13 (m, 2H); 3.12−3.02 (m, 1H); 2.88−2.65 (m, 4H); 2.18−2.09 (m, 1H); 1.98−1.89 (m, 1H); 1.84−1.64 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.9 (d, $^1J_{C-F}$ = 236 Hz), 153.8, 150.5 (d, J = 1.2 Hz), 129.6, 127.0, 123.7 (d, J = 7.5 Hz), 122.2, 120.2, 117.4 (d, J = 8.2 Hz), 116.3, 115.3 (d, J = 22.5 Hz), 113.6 (d, J = 23.0 Hz), 77.0, 76.8, 67.6, 67.3, 50.0, 49.5, 24.1, 23.4, 22.8, 22.2 ppm; IR ν = 3056, 2858, 1491, 1232, 1216, 1080, 749 cm^{-1}; HRMS (EI) (m/z) $[C_{22}H_{26}O_4NF]^+$: Calcd 387.1840, Found 387.1841.

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*(R)-1-((R)-Chroman-2-yl)-2-(((R)-2-((S)-6-fluorochroman-2-yl)-2-hydroxyethyl)amino)ethan-1-ol Hydrochloride (**4a**).* Yield: 406 mg (88%) as white crystals; mp 203 °C; $[\alpha]_D^{20}$ = +21.4 (*c* = 1 in MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.84 (br s, NH_2); 7.09−7.03 (m, 2H); 6.96−6.87 (m, 2H); 6.81 (dt, *J* = 7.4 Hz; 1.1 Hz, 1H); 6.79−6.73 (m, 2H); 6.00 (d, *J* = 5.6 Hz, OH); 5.97 (d, *J* = 5.6 Hz, OH); 4.16−4.09 (m, 1H); 4.07−3.98 (m, 2H); 3.93−3.86 (m, 1H); 3.38 (br s, 1H partly overlapped by water signal); 3.29−3.13 (m, 2H); 3.12−3.00 (m, 1H); 2.89−2.65 (m, 4H); 2.16−2.07 (m, 1H); 1.99−1.90 (m, 1H); 1.85−1.63 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0 (d, *J* = 236 Hz, C−F), 154.2, 150.1 (d, *J* = 1.6 Hz), 129.5, 127.0, 123.8 (d, *J* = 7.5 Hz), 122.1, 120.0, 117.4 (d, *J* = 8.2 Hz), 116.3, 115.3 (d, *J* = 22.6 Hz), 113.7 (d, *J* = 23.2 Hz), 77.1, 76.7, 67.5, 67.3, 49.9, 49.5, 24.1, 23.6, 22.5, 22.4; IR ν = 3374, 3072, 2859, 1488, 1236, 1216, 1075, 745 cm^{-1}; HRMS (EI) (*m*/*z*) $[C_{22}H_{26}O_4NF]^+$: Calcd 387.1840, Found 387.1841.

*(S)-1-((S)-Chroman-2-yl)-2-(((S)-2-((R)-6-fluorochroman-2-yl)-2-hydroxyethyl)amino)ethan-1-ol Hydrochloride (**4b**).* Yield: 321 mg (89%) as white crystals; mp 195 °C; $[\alpha]_D^{20}$ = −24.4 (*c* = 1 in MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.98−8.44 (br, NH.HCl); 7.12−7.02 (m, 2H); 7.00−6.86 (m, 2H); 6.86−6.66 (m, 3H); 6.08−5.88 (br, OH); 5.86−5.84 (br, OH); 4.17−4.06 (m, 1H); 4.06−3.95 (m, 2H); 3.94−3.84 (m, 1H); 3.34 (br, 1H masked with water signal); 3.28−3.12 (m, 3H); 3.05 (dd, *J* = 12.32 Hz, 9.93 Hz, 1H); 2.90−2.62 (m, 4H); 2.18−2.05 (m, 1H); 2.00−1.88 (m, 1H); 1.86−1.59 (m, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 155.6 (d, *J* = 234.67 Hz, C−F), 154.9, 154.3, 150.1 (d, *J* = 1.69 Hz), 129.5, 127.1, 123.8 (d, *J* = 6.94 Hz), 122.2, 120.2, 117.4 (d, *J* = 8.44 Hz), 117.4, 116.3, 115.4 (d, *J* = 22.34 Hz), 113.8 (d, *J* = 22.84 Hz), 77.1, 76.7, 67.6, 67.5, 49.9, 49.5, 24.1, 23.6, 22.6, 22.4; IR ν = 3372, 3072, 2858, 1488, 1236, 1216, 1075, 745 cm^{-1}; HRMS (EI) (*m*/*z*) $[C_{22}H_{26}O_4NF]^+$: Calcd 387.1840, Found 387.1842.

*(R)-1-((R)-Chroman-2-yl)-2-(((R)-2-((S)-chroman-2-yl)-2-hydroxyethyl)amino)ethan-1-ol Hydrochloride (**5a**).* Yield: 553 mg (86%) as white crystals; mp 194 °C; $[\alpha]_D^{20}$ = +15.7 (*c* = 1 in MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.81 (br s, NH_2); 7.09−7.04 (m, 4H); 6.85−6.79 (m, 2H); 6.78−6.74 (m, 2H); 5.99 (d, *J* = 5.6 Hz, OH); 5.79 (d, *J* = 5.6 Hz, OH); 4.16−4.08 (m, 1H); 4.07−3.97 (m, 2H); 3.95−3.88 (m, 1H); 3.43−3.35 (m, 1H partly overlapped by water signal); 3.29−3.14 (m, 2H); 3.12−3.02 (m, 1H); 2.88−2.65 (m, 4H); 2.18−2.09 (m, 1H); 1.98−1.90 (m, 1H); 1.85−1.65 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.3, 153.9, 129.6, 129.5, 127.1, 127.0, 122.2, 122.1, 120.2, 120.1, 116.3 (×2), 77.0, 76.7, 67.6, 67.4, 50.0, 49.5, 24.1, 23.5, 22.8, 22.6; IR ν = 3057, 2861, 1585, 1489, 1232, 1080, 747 cm^{-1}; HRMS (EI) (*m*/*z*) $[C_{22}H_{27}O_4N]^+$: Calcd 369.1935, Found 369.1934.

*(S)-1-((R)-Chroman-2-yl)-2-(((S)-2-((S)-chroman-2-yl)-2-hydroxyethyl)amino)ethan-1-ol Hydrochloride (**5b**).* Yield: 154 mg (51%) as white crystals; mp 184 °C; $[\alpha]_D^{20}$ = −27.3 (*c* = 0.355 in MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.01−8.52 (br, NH_2); 7.18−7.01 (m, 4H); 6.94−6.67 (m, 4H); 5.97 (d, *J* = 5.62 Hz, OH); 5.78 (d, *J* = 5.87 Hz, OH); 4.20−4.07 (m, 1H); 4.07−3.96 (m, 2H); 3.96−3.82 (m, 1H); 3.29−3.14 (m, 2H); 3.34 (br, 1H masked with water signal at 3.34); 3.14−2.94 (m, 1H); 2.89−2.65 (m, 4H); 2.20−2.04 (m, 1H); 1.99−1.89 (m, 1H); 1.86−1.64 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.3, 153.9, 129.6, 129.5, 127.1, 127.9, 122.2, 122.2, 120.3, 120.1, 116.3, 116.3, 77.0, 76.7, 67.6, 67.4, 50.0, 49.5, 24.1, 23.4, 22.8, 22.6; ; IR ν = 3067, 2858, 1584, 1489, 1232, 1080, 748 cm^{-1}; HRMS (EI) (*m*/*z*) $[C_{22}H_{27}O_4N]^+$: Calcd 369.1935, Found 369.1936.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Van Lommen, G. R. E.; De Bruyn, M. F. L.; Schroven, M. F. J. Derivatives of 2,2′-iminobisethanol. European Patent 0145067, Jan 25, 1989. (b) Pauwels, P. J.; Gommeren, W.; van Lommen, G.; Janssen, P. A. J.; Leysen, J. E. *Mol. Pharmacol.* **1988**, *34*, 843. (c) van de Water, A.; Jansssens, W.; van Neuten, J.; Xhonneux, R.; DeCree, J. *J. Cardiovasc. Pharmacol.* **1988**, *11*, 552.

(2) Van Lommen, G. R. E.; De Bruyn, M. F. L.; Schroven, M. F. J. Derivatives of 2,2′-iminobisethanol. U.S. Patent 4,654,362, Mar 31, 1987.

(3) Xhonneux, R. M.; Van Lommen, G. R. E. Agents for lowering the blood pressure. European Patent 0334429, Nov 19, 1992.

(4) Nebivolol is marketed as racemate although both enantiomers are reported to have slightly different pharmacological properties (see ref 3).

(5) Janssen, P. A. J. *Clin. Drug Invest.* **1991**, *3* (Supplement), 1−2.

(6) (a) Bader, T.; Stutz, A.; Hofmeier, H.; Bichsel, H.-U. A process for preparation of racemic Nebivolol. European Patent Application 1803715, Jul 24, 2007. (b) Stutz, A. A process for preparation of racemic Nebivolol. European Patent 1803716, Jul 25, 2012. (c) Noe, C. R.; Jasic, M.; Kollmann, H.; Lachmann, B. Method for producing nebivolol. PCT Patent Application WO2007/009143, Jan 25, 2007. (d) Volpicelli, R.; Maragni, P., Cotarca, L.; Foletto, J. Process for preparing nebivolol. PCT Patent Application WO2008/040528, Apr 10, 2008. (e) Ullucci, E.; Maragni, P.; Cotarca, L.; Foletto, J. Process for preparing nebivolol. PCT Patent Application WO2008/064826, Jun 5, 2008. (f) Volpicelli, R.; Maragni, P.; Cotarca, L.; Foletto, J.; Massacesi, F. Process for preparing nebivolol. PCT application WO2008/064827, Jun 5, 2008. (g) Volpicelli, R.; Maragni, P.; Massaccesi, F.; Munari, D.; Cotarca, L.; Foletto, J. Process for preparing nebivolol. PCT Patent Application WO2009/121710, Oct 8, 2009. (h) Derrien, Y.; Chenard, E.; Burgos, A. Method for preparing nebivolol. PCT Patent Application WO2010/034927, Apr 1, 2010. (i) Maragni, P.; Michieletto, I.; Volpicelli, R.; Soriato, G.; Foletto, J.; Cotarca, L.; Verzini, M. Process for preparing nebivolol. WO2010/049455, May 6, 2010. (j) Cotarca, L.; Foletto, J.; Maragni, P.; Soriato, G.; Urbani, D.; Verzini, M. Process for preparing nebivolol. PCT Patent Application WO2011/009628, Jan 27, 2011. (k) Volpicelli, R.; Maragni, P.; Cotarca, L.; Foletto, J.; Massaccesi, F. Nebivolol formate. European patent 2228374, Jun 5, 2013. (l) Bartoli, S.; Cipollone, A.; Fattori, D. Process for the preparation of nebivolol. PCT Patent Application WO2011/098474, Aug 18, 2011. (m) Mauro, S.; Fattori, D.; D'Andrea, P.; Cipollone, A. Process for the preparation of nebivolol. PCT Patent Application WO2012/095707, Jul 19, 2012. (n) Satyanarayana Reddy, M.; Eswaraiah, S.; Sahadeva Reddy, M. Improved process for the preparation of nebivolol hydrochloride. PCT Patent Application WO2010/089764, Aug 12, 2010. (o) Sheth, R.; Attanti, S. V.; Patel, H. M.; Gupta, V.; Nadkarni, S. S. Nebivolol and its pharmaceutically acceptable salts, process for preparation and pharmaceutical composition of nebivolol. PCT Patent Application WO2006/025070, Mar 9, 2006. (p) Parthasaradhi Reddy, B.; Rathnakar Reddy, K.; Raji Reddy, R.; Muralidhara Reddy, D.; Srinivas Reddy, I. A novel process for preparation of nebivolol intermediates. PCT Patent Application WO2006/016376, Feb 16, 2006. (q) Parthasaradhi Reddy, B.; Rathnakar Reddy, K.; Raji Reddy, R.; Muralidhara Reddy, D.; Srinivas Reddy, I. Process for isolation of desired isomers of nebivolol intermediates. PCT Patent Application WO2007/083318, Jul 26, 2007. (r) Trinka, P.; Reiter, J.; Berecz, G.; Simig, G. New process for the preparation of racemic ([2S[2R*[R[R*]]]] and ([2R[2S*[S[S*]]]]-(±)-α,α′-[imino-bis[methylene)]-bis[6-fluoro-chroman-2-methanol] and its pure ([2S[2R*[R[R*]]]] and ([2R[2S*[S[S*]]]] enantiomers. PCT Patent Application WO2004/041805, May 21, 2004. (s) Khamar, Thakor, I.; Patel, M.; Jadav, K.; Parikh, A.; Joshi, A. C. An improved

DOI: 10.1021/acs.joc.5b00263
J. Org. Chem. 2015, 80, 3965−3973

process for the preparation of nebivolol hydrochloride. European Patent 2163551, Nov 16, 2011. (t) Wang, G.; Chen, X.; Hou, J. Process for isolation of a mixture of RRRS and SSSR configurations of nebivolol intermediates. European Patent 2236510, Apr 30, 2014. (u) Cipollone, A.; D'Andrea, P.; Fattori, D. Process for the preparation of epoxides as intermediates for the synthesis of nebivolol. PCT Patent Application WO2013/018053, Feb 7, 2013. (v) Chen, P.; Lv, C. A method for the preparation of D,L-nebivolol and its hydrochloride salt. PCT Patent Application WO2006/092086, Sep 08, 2006.

(7) (a) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron* **2000**, *56*, 6339−6344. (b) Johannes, C. W.; Visser, M. S.; Weatherhead, G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340−8347. (c) Carreno, M. C.; Hernadez-Torres, G.; Urbano, A.; Colobert, F. *Eur. J. Org. Chem.* **2008**, 2035−2038. (d) Wang, N.-X.; Yu, A.-G.; Wang, G.-X.; Zhang, X.-H.; Li, Q.-S.; Li, Z. *Synthesis* **2007**, 1154−1158. (e) Yihui, B.; Xinzhi, C. *J. Chem. Res.* **2006**, 807−808. (f) Yang, Y. X.; Wang, N. X.; Xing, Y. L.; Wang, W. W.; Zhao, J.; Wang, G. X.; Tang, S. *Chin. Chem. Lett.* **2005**, *16*, 1577−1580.

(8) Formally, all desfluorinated NBV compounds are part of the claims in refs 2 and 3, and at least one monodesfluoro isomer has been described in the experimental part of ref 3, but no analytical details are given.

(9) Jas, G.; Freifeld, I.; Kesseler, K. Verfahren zur Herstellung von Epoxiden die in der Herstellung von Nebivolol und dessen Derivaten einsetzbar sind. German Patent Application DE 10 2014 107 132, submitted May 5, 2014.

(10) (a) Jas, G.; Freifeld, I.; Kesseler, K. Method for producing nebivolol. PCT Patent Application WO2011/091968, Aug 4, 2011. (b) Jas, G.; Freifeld, I.; Kesseler, K. A new method for producing nebivolol hydrochloride of high purity. European Patent Application 14155300, unpublished.

(11) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976.

(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(13) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 103−158.

(14) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769−3772.

(15) Cannon, J.; Olson, A.; Overman, L.; Solomon, N. *J. Org. Chem.* **2012**, *77*, 1961−1973.

(16) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(17) Peters, M.; Trobe, M.; Tan, H.; Kleineschwede, R.; Breinbauer, R. *Chem.—Eur. J.* **2013**, *19*, 2442−2449.

DOI: 10.1021/acs.joc.5b00263
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