Chapter 4

Studies on the Synthesis of (+)-Nebivolol Intermediates via Ar–O and ArO–C Bond-Forming Reactions of Vicinal Diols

Work of this Chapter has resulted in the following publication:

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4.1. Introduction

α,α′-[Iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] (**1**, Figure 4.1), better known as nebivolol, is a third-generation β-adrenergic receptor antagonist (β-blocker) [1-4]. Currently, it is marketed as the racemic mixture of hydrochloride salts of enantiomers (*S*,*R*,*R*,*R*)- or *d*-nebivolol (**1a**) and (*R*,*S*,*S*,*S*)- or *l*-nebivolol (**1b**, Figure 4.1). Owing to the presence of four chiral centers and one σ plane, **1** can have 10 stereoisomers. A general nonstereoselective synthesis and biological evaluation of **1** were first reported by researchers at Janssen [1,2]. Subsequently, they employed chiral HPLC separation technique to acquire various stereoisomers of **1** in enantiomerically pure form [5].

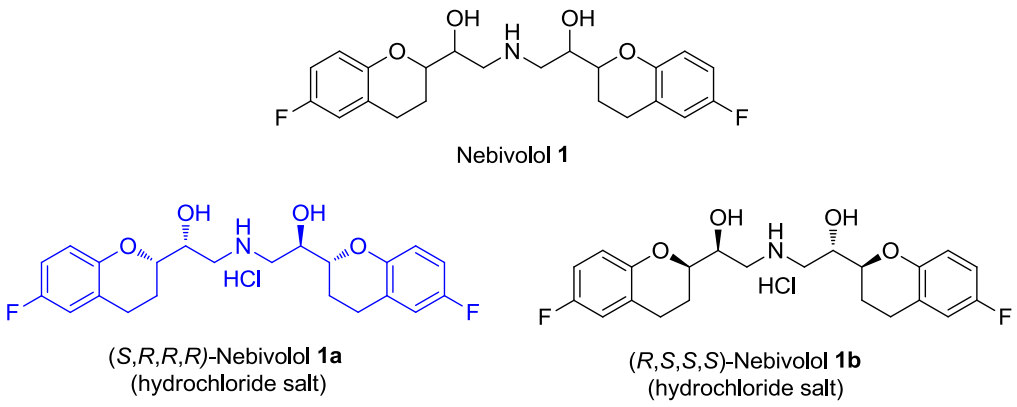


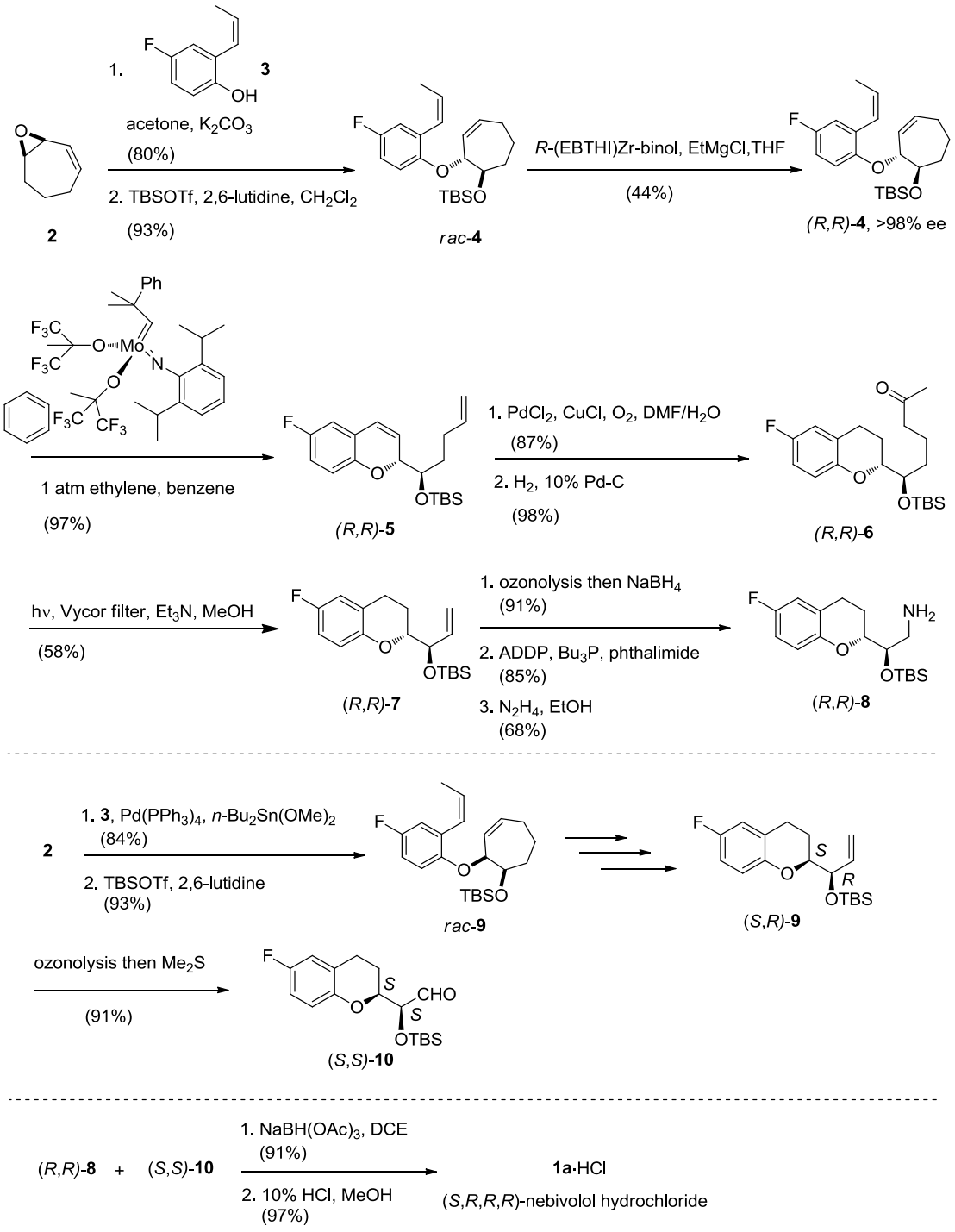
Figure 4.1. Antihypertensive drug nebivolol and its biologically active stereoisomers

Out of the ten possible stereoisomers of **1**, **1a** was found to be a potent β_1-adrenergic receptor blocker [6-8]. On the other hand, the corresponding enantiomeric form, **1b**, was found to be devoid of β_1-antagonist activity ─ but it showed a significant synergistic effect on the antihypertensive proficiency of the **1a** [9-12]. Furthermore, **1b** exhibited positive influence on the antihypertensive properties of related β_1-blockers propanolol, atenolol, and metoprolol [9-12].

4.2. Literature Known Methods to Access (*S*,*R*,*R*,*R*)-Nebivolol

Since the *d*-isomer {(*S*,*R*,*R*,*R*)- or *d*-nebivolol (**1a**)} is mainly responsible for the β_1 adrenoreceptor blocking activity, it has become an target of many synthetic chemistry groups. The first enantioselective total synthesis of **1a** was achieved by the group of Hoveyda in 1998 using a Zr-catalyzed kinetic resolution of cyclic allylic styrenyl ethers and their Mo-catalyzed ring-opening and ring-closing metathesis as key steps (Scheme

4.1) [13]. Their synthesis began with the regio- and stereoselective nucleophilic opening of racemic allylic epoxide **2** with styrenyl phenol **3** followed by TBS protection of the resulting secondary alcohol furnished compound *rac*-**4**.



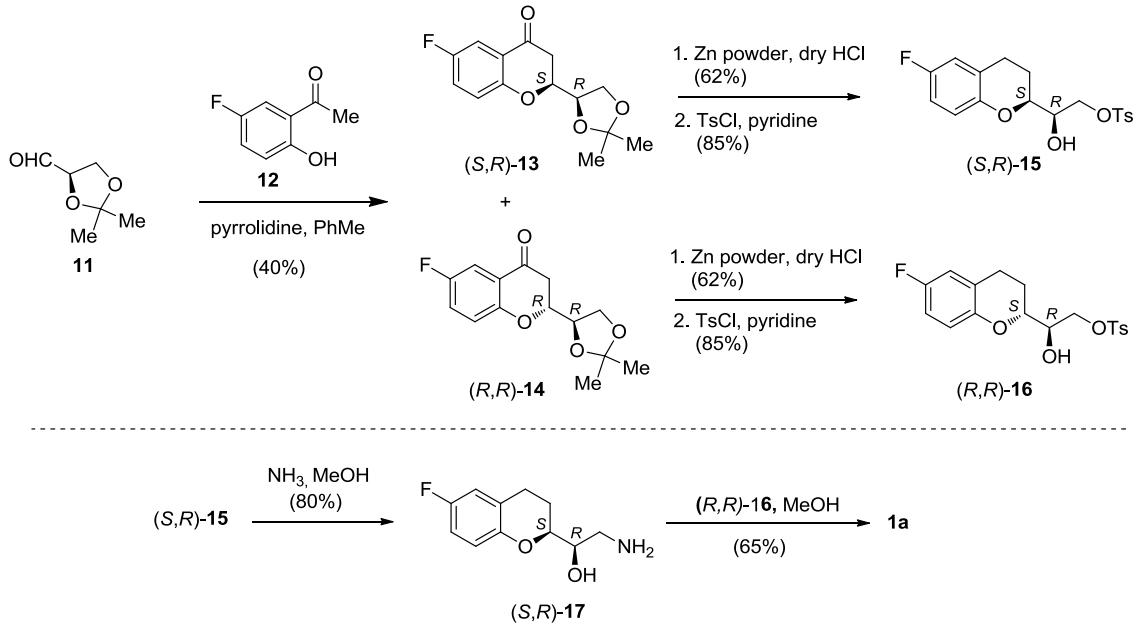
Scheme 4.1. **First asymmetric total synthesis of (*S*,*R*,*R*,*R*)-nebivolol 1a**

Next, Zr-catalyzed kinetic resolution of *rac*-**4** provided the recovered starting material (*R*,*R*)-**4** in >98% ee and 44% yield. Mo-catalyzed ring-closing metathesis furnished of

(*R*,*R*)-**4** furnished chromene derivative (*R*,*R*)-**5**. Regioselective Wacker oxidation of the terminal olefin of (*R*,*R*)-**5** followed by catalytic hydrogenation of the resulting methyl ketone furnished chroman derivative (*R*,*R*)-**6**. Photochemical Norrish type II cleavage of **6** furnished chroman derivative (*R*,*R*)-**7.** An ozonolytic cleavage ─ reduction sequence on olefin (*R*,*R*)-**7** followed by conversion of the resulting primary alcohol into a primary amine resulted in chiral chroman derivative (*R*,*R*)-**8**. On the other hand, *syn*-selective ring-opening of allylic epoxide *rac*-**2** with styrenyl phenol **3** furnished *rac*-**9** in very good yield and excellent regio- and stereoselectivity. Then, conversion of *rac*-**9** to (*S*,*R*)-**9** was carried out efficiently following a similar reaction sequence to that of the synthesis of (*R*,*R*)-**7**. Ozonolysis of (*S*,*R*)-**9** produced chroman-based aldehyde (*S*,*S*)-**10**. Finally, (*R*,*R*)-**8** was united with (*S*,*S*)-**10** by a reductive amination to complete the first asymmetric total synthesis of (*S*,*R*,*R*,*R*)-nebivolol **1a**.

Next approach to the synthesis of **1a** was reported from the research group of Chandrasekhar. This work has already been described in the **Chapter 1** (**Scheme 1.9)** of this thesis**.**

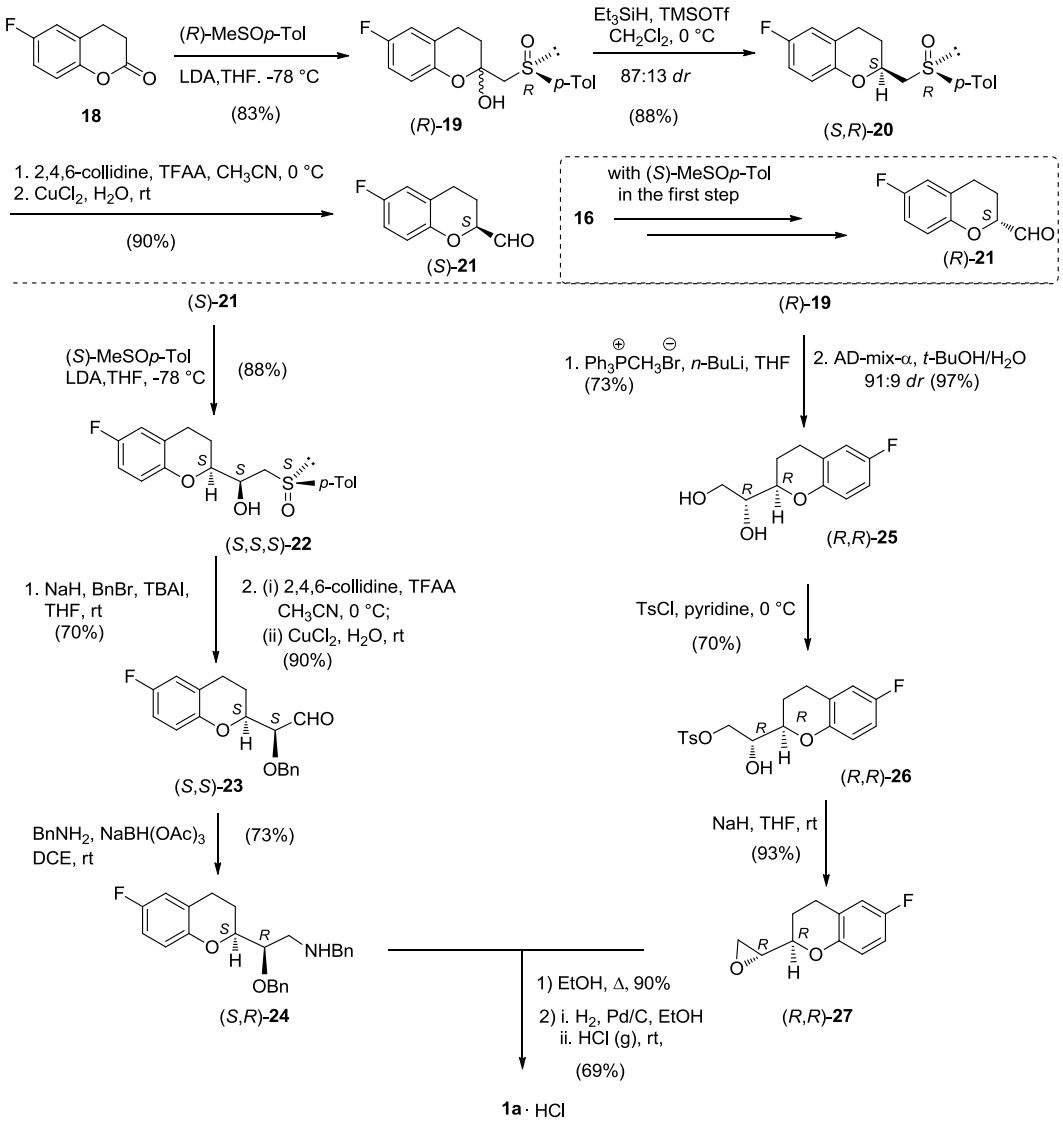
Another asymmetric synthesis of **1a** used (*R*)-2,3-isopropylideneglyceraldehyde **11** (synthesized readily from D-mannitol) as the source of chirality [14]. Thus, Kabbe reaction between **11** and 2-acetyl-4-fluorophenol **12** furnished a 60:40 diastereomeric mixture of chromanones (*S*,*R*)-**13** and (*R*,*R*)-**14** in 40% yield (Scheme 4.2). (*S*,*R*)-**13** and (*R*,*R*)-**14** were smoothly separated by column chromatography.



Scheme 4.2. **Chiral pool approach for the asymmetric synthesis of (*S*,*R*,*R*,*R*)-nebivolol 1a**

Next, simultaneous Clemmensen reduction and acetonide deprotection of (*S*,*R*)-**13** and (*R*,*R*)-**14** with zinc powder in HCl produced the corresponding diols which were then tosylated to give (*S*,*R*)-**15** and (*R*,*R*)-**16**, respectively. Treatment of (*S*,*R*)-**15** with ammonia produced amino alcohol (*S*,*R*)-**17**. Finally, *N*-alkylation of (*S*,*R*)-**17** with tosylate (*R*,*R*)-**16** furnished the desired compound **1a**.

A more recently strategy for the synthesis of **1a** engaged chiral sulfoxides to control the stereochemical outcome [15]. The synthesis began with the treatment of 6-fluorochroman- 2-one **18** with (*R*)-methyl-*p*-tolylsulfoxide in the presence of LDA to obtain the corresponding lactol (*R*)-**19** as a mixture of C-2 epimers which on treatment with Et_3SiH and TMSOTf afforded chroman derivative (*S*,*R*)-**20** *via* a stereoselective reductive deoxygenation process (Scheme 4.3).



Scheme 4.3. Chiral sulfoxides-induced asymmetric synthesis of (*S*,*R*,*R*,*R*)-nebivolol 1a

Next, aldehyde (*S*)-**21** was obtained from (*S*,*R*)-**20** through a Pummerer reaction. Starting with **16**, following the same sequence but changing the absolute configuration at the sulfur atom, the enantiomeric aldehyde (*R*)-**21** was synthesized. Addition of the lithium anion derived from (*S*)-methyl-*p*-tolyl sulfoxide to aldehyde (*S*)-**21** provided (*S*,*S*,*S*)-**22**. Benzyl protection of the hydroxyl group of (*S*,*S*,*S*)-**22** followed by Pummerer reaction offered aldehyde (*S*,*S*)-**23** which on reductive amination with benzylamine afforded protected amino alcohol (*S*,*R*)-**24**. On the other hand, Wittig olefination of aldehyde (*R*)-**21** followed Sharpless asymmetric dihydroxylation of the resulting 2-vinylchroman derivative with AD-mix-α furnished a 91:9 mixture of the corresponding diastereoisomeric diols (in 97% yield), from which (*R*,*R*)-**25** was isolated in 88% yield. Regioselective tosylation of the primary hydroxy group of (*R*,*R*)-**25** yielded the corresponding hydroxy tosylate (*R*,*R*)-**26** which on base-mediated epoxidation supplied epoxide (*R*,*R*)-**27**. *N*-alkylation of (*S*,*R*)-**24** with epoxide (*R*,*R*)-**27** was achieved in refluxing ethanol. *N*-Debenzylation of the resulting product followed by acidic treatment allowed the synthesis of hydrochloride salt of **1a**.

A number of other syntheses of nebivolol and their intermediates have been reported (which are not described here) in the patent literature [16-18].

4.3. Background and Objectives

Most of these reports have demonstrated that the synthesis of **1a** could be achieved using 2-substituted chroman derivatives (*R*)-1-((*R*)-6-fluorochroman-2-yl)ethane-1,2-diol (*R*,*R*)-**25** and (*R*)-1-((*S*)-6-fluorochroman-2-yl)ethane-1,2-diol (*S*,*R*)-**28** or the corresponding chroman epoxides (*R*,*R*)-**27** and (*S*,*R*)-**29** as late-stage intermediates (Figure 4.2).

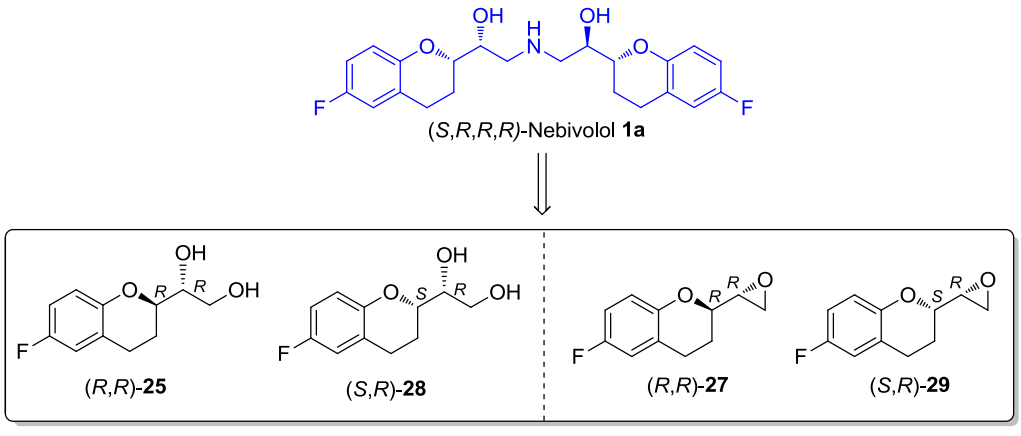
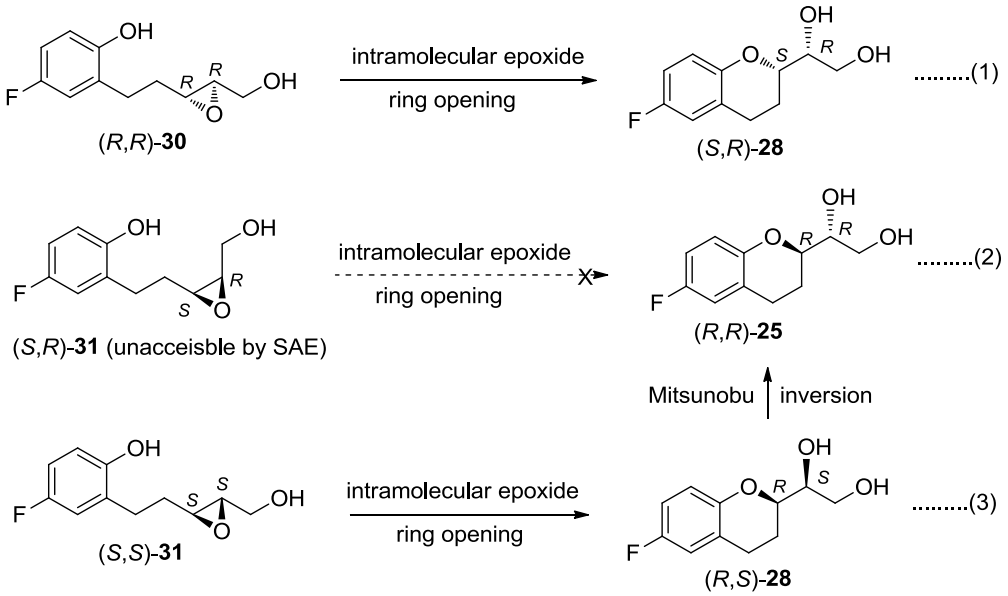


Figure 4.2. **Late-stage intermediates for the asymmetric synthesis of (*S*,*R*,*R*,*R*)-nebivolol 1a**

Although the consensus synthetic strategy for **1a** involved the convergent assembly of these chroman-based key subunits, but the questions of how best to access these still remain open. Intramolecular ring-opening of enantiomerically pure epoxides by phenolic –OH group has been one of the most popular methods to construct (*S*,*R*)-**28** (Scheme 4.4, method 1). For this purpose, the necessary epoxide substrate (*R*,*R*)-**30** could be obtained from the parent *E*-allylic alcohol by the Sharpless asymmetric epoxidation (SAE). However, the corresponding parent *Z* allylic alcohol appears to be unsuitable to provide (*S*,*R*)-**31** under SAE condition [19]. This has eliminated the possibility of obtaining (*R*,*R*)-**25** via intramolecular epoxide ring-opening of **31** (method 2). Consequently, an alternative pathway involving Mitsunobu inversion of (*R*,*S*)-**28** (obtained by intramolecular epoxide ring-opening of (*S*,*S*)-**31**) has been followed to obtain (*R*,*R*)-**25** (method 3) whereupon the overall yield of the reaction sequence diminished [20].



Scheme 4.4. **Synthetic strategies toward late-stage intermediates of (*S*,*R*,*R*,*R*)-nebivolol 1a**

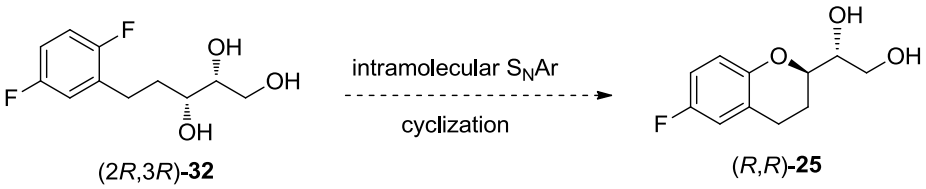
On the other hand, the Sharpless asymmetric dihydroxylation (SAD) has been a powerful synthetic tool for gaining enantiomerically pure/enriched vicinal-diols [21]. The extensive work in this field has resulted in the discovery of a number of cinchona alkaloid-derived ligands which allow dihydroxylation of alkenes of almost all substitution patterns with high enantioselectivity. Noteworthy is that SAD is not limited to only *E*-allylic alcohols in its choice of substrates as is the SAE process. Furthermore, SAD is much more superior in terms of operational simplicity as unlike SAE, it can be run at 0 °C in water as a co-solvent and under an open atmosphere of air. As already

mentioned in the Chapter 1 of this thesis, application of SAD-derived vicinal diols in the synthesis of acyclic molecules and saturated heterocycles has been amazing ─ however, their utilities in the synthesis of chiral benzo-annulated heterocycles have been relatively limited. To the best of our knowledge, nebivolol or its intermediates have never been synthesized using Sharpless asymmetric dihydroxylation as the *sole source of chirality*. The aim of the research work described in this chapter was to synthesize (*R*,*R*)-**25**, (*S*,*R*)-**28,** (*R*,*R*)-**27** and (*S*,*R*)-**29** ─ the late-stage intermediates of **1a** ─ using SAD-derived chiral diols via different cyclization strategies, thereby completing a formal total synthesis of (*S*,*R*,*R*,*R*)-nebivolol (**1a**).

4.4. Results and Discussion

4.4.1. Attempted Synthesis of Chroman Derivative via S_NAr Reaction

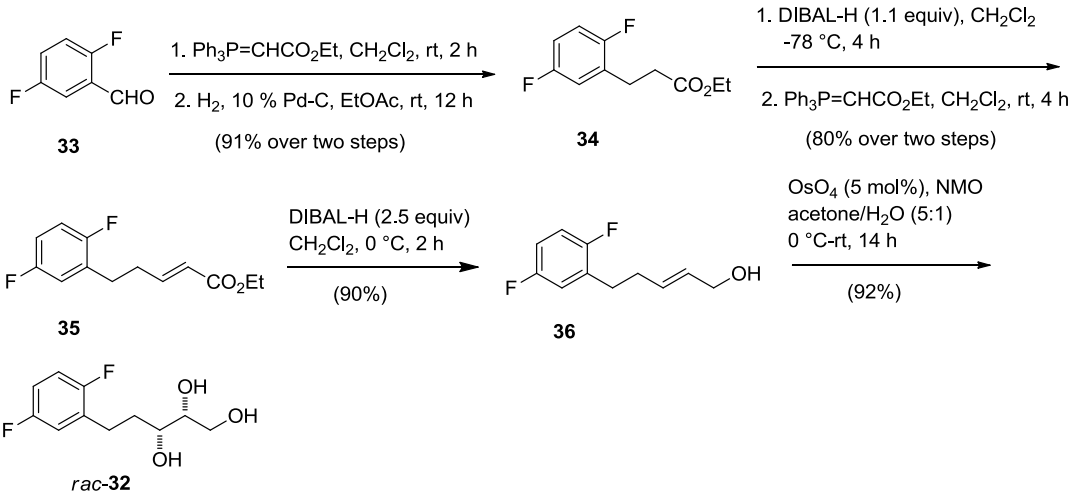
As shown in the Scheme 4.5, for the synthesis of chroman derivative (*R*,*R*)-**25**, first a base-mediated intramolecular S_NAr reaction [22,23] of triol (*R*,*R*)-**25** was envisioned for the aryl C–O bond formation under transition-metal-free conditions. The additional beauty of this strategy, if successful, would be the non-requirement of any protecting group to construct the chroman ring.



(2*R*,3*R*)-**32** (*R*,*R*)-**25**

Scheme 4.5. Envisioned construction of (*R*,*R*)-25 from a chiral triol precursor

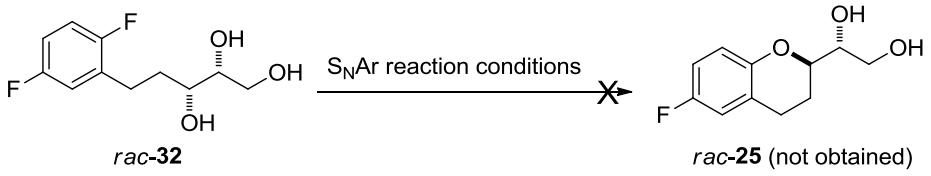
To test this seemingly straightforward approach, we initially undertook the synthesis of *rac*-**32** (Scheme 4.6). Thus, Wittig olefination of commercially available 2,5-difluorobenzaldehyde **33** with $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 followed by hydrogenation of the resulting α,β-unsaturated ester with Pd-C and H_2 at rt in EtOAc produced ester **34** in 91% yield over two steps. Next, DIBAL-H (1.1 equiv, –78 °C) reduction of the ester group of **34** followed by Wittig olefination of the resulting crude aldehyde with $Ph_3P{=}CHCO_2Et$ provided (*E*)- α,β-unsaturated ester **35**. Further DIBAL-H (2.5 equiv, 0 °C) reduction of **35** delivered (*E*)-allylic alcohol **36** in 90% yield. Dihydroxylation of **36** under the Upjohn conditions (cat. OsO_4/NMO) provided triol *rac*-**32** in high yield (92%).



Scheme 4.6. Synthesis of the triol precursor

With access to *rac*-**32** we were in a position to investigate the key cyclization involving an intramolecular S_NAr to deliver *rac*-**25**. Unfortunately, however, all attempts of cyclizing *rac*-**32** to obtain chroman derivative *rac*-**25** under various S_NAr reaction conditions were met with failure (Table 4.1). Treatment of *rac*-**32** with KO*t*Bu/THF (65 °C), NaH/DMF (80 °C), NaH/DMSO (100 °C) and KO*t*Bu/toluene (110 °C) did not lead to any conversion (Table 4.1, entries 1-4). However, more forcing condition such as NaH/NMP (130 °C) led to partial decomposition of the starting material (entry 5).

Table 4.1. Attempted S_NAr-based cyclization of *rac*-32



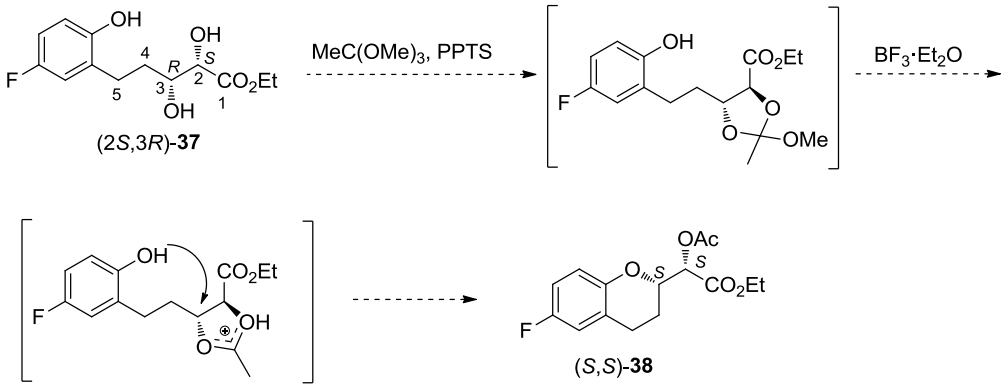
entry	reaction conditions[a]	result
1	KO*t*Bu, THF, 65 °C, 48 h	recovery of *rac*-**32**
2	NaH, DMF, 80 °C, 48 h	recovery of *rac*-**32**
3	NaH, DMSO, 100 °C, 48 h	recovery of *rac*-**32**
4	KO*t*Bu, toluene, 110 °C, 48 h	recovery of *rac*-**32**
5	NaH, NMP, 130 °C, 48 h	partial recovery of *rac*-**32**

[a] ***rac*-32** (0.1 mmol) and base (0.4 mmol)

These results indicated that intramolecular S_NAr reaction of triol *rac*-**32** to form *rac*-**25** is not feasible ─ presence of an activating substituent (*e.g.* $–NO_2$ group) at C-5 position at the benzene ring would be helpful in synthesizing molecules similar to **2** [24,25].

4.4.2. Attempted Synthesis of Chroman Derivative via Intramolecular Ring-Opening of Cyclic Orthoester

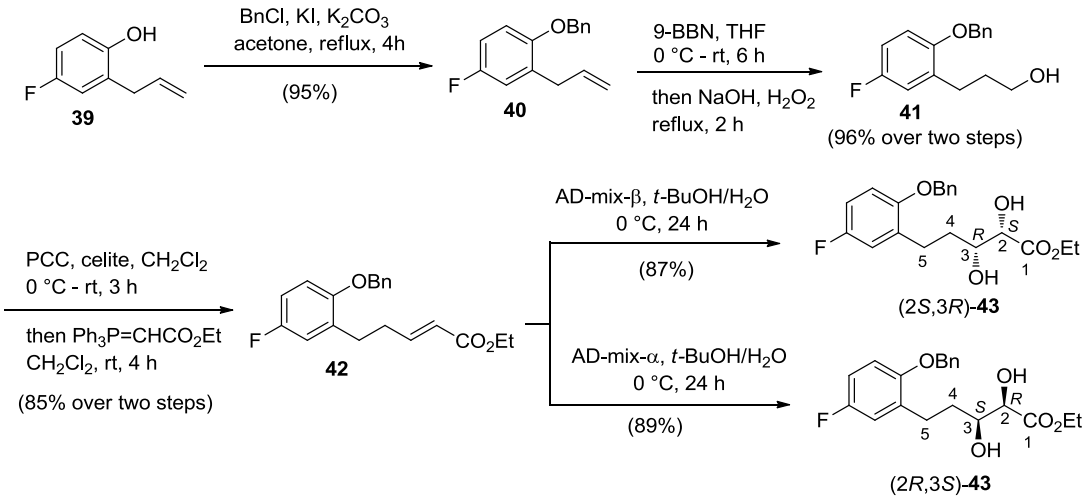
Failure to accomplish intramolecular cyclization of diol via an S_NAr reaction instigated us to inspect other cyclization approaches to synthesize 2-substituted chroman derivatives from which the late stage nebivolol intermediates could be synthesized. In 2005, Borhan et al. described construction of tetrahydrofuran and tetrahydropyran structures from 1,2,n-triols via an elegant cyclization involving Lewis acid-mediated cyclization of *in situ* generated cyclic orthoesters [26]. We speculated that a similar reaction sequence, involving transorthoesterification of trimethyl orthoacetate with (2*S*,3*R*)-**37** followed by in situ treatment of the resulting orthoester with catalytic amount of $BF_3{\cdot}Et_2O$, should produce 2-substituted chroman derivative (*S*,*S*)-**38** via 6-*exo*-*tet* cyclization (Scheme 4.7).



Scheme 4.7. Envisioned construction of (*S*,*S*)-38 from a chiral diol precursor based on Borhan's approach

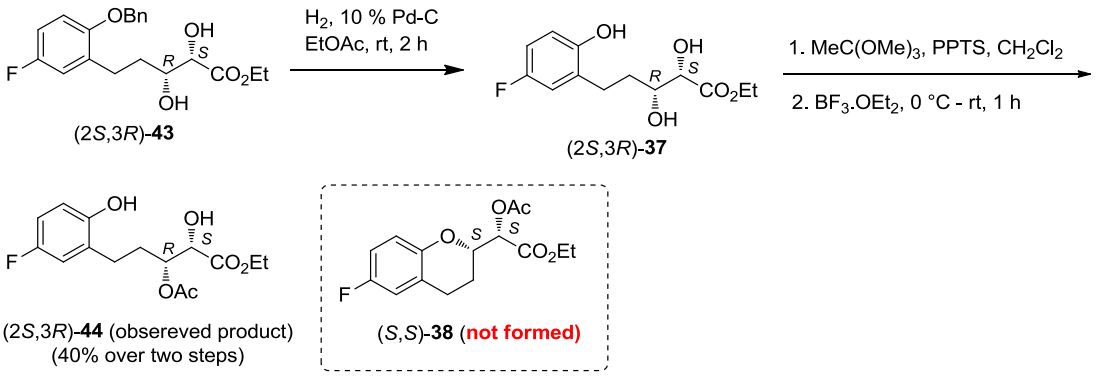
To authenticate this hitherto unexplored approach, we first needed to synthesize (2*S*,3*R*)-**37**. Toward that objective, 2-allyl-4-fluorophenol **39** was benzylated with BnCl and anhydrous K_2CO_3 in the presence of KI in acetone under reflux condition to obtain benzyl ether **40** (Scheme 4.8). Subsequent hydroboration of the allyl group of **40** with 9-BBN and *in situ* oxidation of the resulting organoborane with NaOH and H_2O_2 furnished alcohol **41** in 96% yield. A one-pot PCC oxidation-Wittig olefination (with $Ph_3P{=}CHCO_2Et$) of **41** provided (*E*)-α,β-unsaturated ester **42** in 85% yield over the two

steps. Compound **42** was then subjected to Sharpless asymmetric dihydroxylation with AD-mix-β in *t*-BuOH/H_2O (1:1) at 0 °C for 24 h furnishing *syn*-2,3-dihydroxy ester (2*S*,3*R*)-**43** in high yield of 87%. For the synthesis of *syn*-2,3-dihydroxy ester (2*R*,3*S*)-**43**, AD-mix-α was employed.



Scheme 4.8. Synthesis of chiral *syn*-2,3-dihydroxy esters

Compound (2*S*,3*R*)-**43** was subjected to the debenzylation reaction in the presence of Pd-C and H_2 to obtain compound (2*S*,3*R*)-**37** which was then exposed to Borhan's cyclization reaction conditions that involved its treatment with 1.2 equiv of trimethyl orthoacetate and a catalytic amount of PPTS (0.1 equiv) in dichloromethane, followed by addition of 0.1 equiv of $BF_3{\cdot}Et_2O$ (Scheme 4.9).



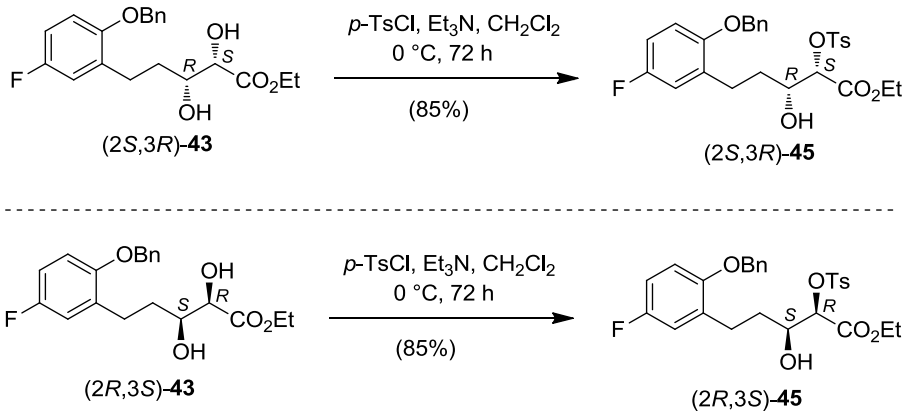
Scheme 4.9. Attempted cyclization by Borhan's method

To our dismay, however, the desired formation of (*S*,*S*)-**38**, through the nucleophilic attack of the tethered phenolic-OH onto the reactive acetoxonium species, did not take

place ─ analysis of the major product suggested that hydrolysis of the intermediate orthoester had occurred to furnish (2*S*,3*R*)-**44**. This different outcome of this reaction compared to Borhan's results might be attributed to the lower nucleophilicity of phenols compared to alcohols.

4.4.3. Synthesis of Chroman Derivative via One-Pot Epoxidation/Epoxide Ring-Opening/Cyclization

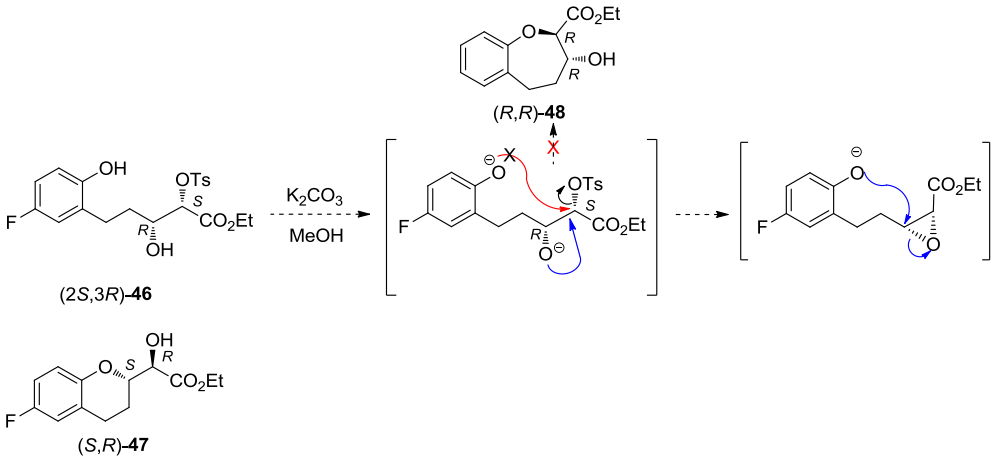
Previously, Panda et al. converted successfully a *syn*-2,3-dihydroxy ester into 2-substituted chroman derivative [27]. The above-described unfortunate failures eventually forced us to turn our attention to utilize this methodology for the synthesis 2-substituted chroman derivatives. Thus, diols (2*S*,3*R*)-**43** and (2*R*,3*S*)-**43** were subjected to the monotosylation reaction to obtain the corresponding β-hydroxy-α-tosyloxy esters (2*S*,3*R*)-**45** and (2*R*,3*S*)-**45**, respectively (Scheme 4.10) [28].



Scheme 4.10. Synthesis of β-hydroxy-α-tosyloxy esters

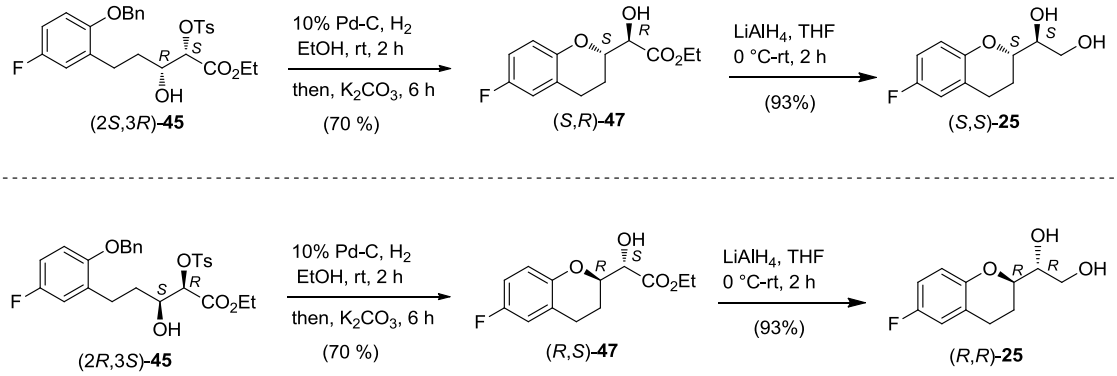
To convert a β-hydroxy-α-tosyloxy ester into the corresponding 2-substituted chroman derivative, Panda's work involved a three step reaction sequence involving epoxidation/debenzylation/epoxide ring-opening [27]. However, it has been reviewed that not only benzylic epoxides but also non-benzylic epoxides are sensitive to the standard hydrogenation/debenzylation conditions [29]. Whereas benzylic epoxides are highly sensitive to hydrogenation conditions, non-benzylic epoxides, depending on the reaction conditions, may produce traces to significant amount of side-products via hydrogenolysis. Thus, we decided to modify the Panda's synthetic route to significantly increase the overall yield. We hypothesized that this problem might be circumvented by performing the debenzylation reaction prior to the epoxide ring formation. We also

speculated that compound (2*S*,3*R*)-**46**, in the presence of a base, might undergo a sequential epoxidation-intramolecular epoxide ring opening to produce (*S*,*R*)-**47** (Scheme 4.11), and the formation of benzoxepane (*R*,*R*)-**48** via intramolecular displacement of –OTs group by ArO^- would not take place [30].



Scheme 4.11. Speculation of one-pot epoxidation/epoxide ring-opening

To test this hypothesis, first compound (2*S*,3*R*)-**45** was subjected to the debenzylation reaction with 10% Pd-C in EtOH under H_2 atmosphere (Scheme 4.12) at rt. After completion of the debenzylation process (2 h), K_2CO_3 was added to the reaction mixture in the same reaction vessel. We were happy to find that the reaction mixture, after being run for an additional 6 h, provided compound (*S*,*R*)-**47** in 70% yield which was significantly higher than the literature yield (53%) for the similar transformation [27]. Similar strategy was applied in converting (2*R*,3*S*)-**45** into chroman derivative (*R*,*S*)-**47**.

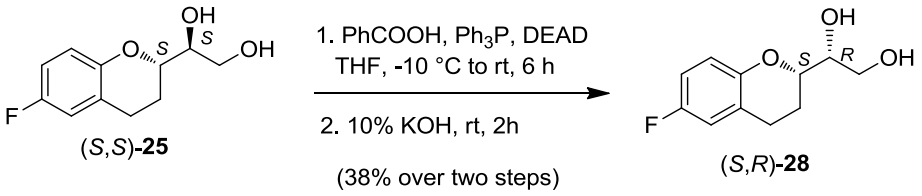


Scheme 4.12. Synthesis of chroman containing 1,2-diols

Next, $LiAlH_4$ reduction of (*S*,*R*)-**47** and (*R*,*S*)-**47** provided (*S*,*S*)-**25** and (*R*,*R*)-**25**, respectively, in 93% yield. It is to be mentioned that NMR spectra and specific rotations

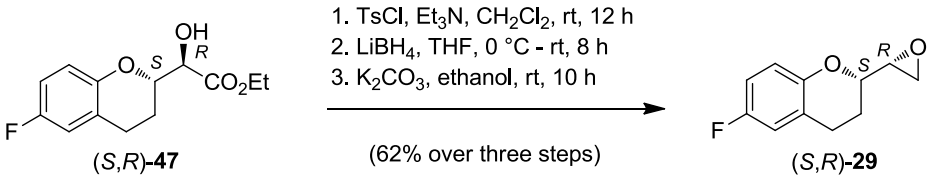
of (*S*,*S*)-**25** and (*R*,*R*)-**25** matched with those reported in the literature (see the **Experimental Section** for details).

For the synthesis of compound (*S*,*R*)-**28**, stereoisomer (*S*,*S*)-**25** was subjected to classical two-step Mitsunobu inversion protocol which was successful but poor yielding (Scheme 4.13).



Scheme 4.13. Epimerization of (*S*,*S*)-25 via Mitsunobu inversion

Not surprised with the poor yield of this transformation, we focused on the conversion of (*S*,*R*)-**47** into (*S*,*R*)-**29** which is more advanced intermediate compared to (*S*,*R*)-**28**. Thus, the tosylation of compound (*S*,*R*)-**47** followed by $LiBH_4$ reduction of resulting tosylate furnished the corresponding tosyloxy alcohol which on epoxidation with anhydrous K_2CO_3 in absolute ethanol provided compound (*S*,*R*)-**29** (Scheme 4.14). The tosylation and the reduction steps were very clean (essentially single on TLC), and hence, this three-step reaction sequence was carried out without chromatographically purifying the intermediates. NMR spectra and specific rotations of (*S*,*R*)-**29** also matched with those reported in the literature (see the **Experimental Section** for details).



Scheme 4.14. Synthesis of chroman epoxide (*S*,*R*)-29

2.5. Conclusion

In conclusion, in the context of utilizing Sharpless asymmetric dihydroxylation-derived vicinal diols in the synthesis of (*R*)-1-((*R*)-6-fluorochroman-2-yl)ethane-1,2-diol, (*R*)-1-((*S*)-6-fluorochroman-2-yl)ethane-1,2-diol, and (*S*)-6-fluoro-2-((*R*)-oxiran-2-yl)chroman, which have previously utilized as late-stage intermediates for the synthesis of (*S*,*R*,*R*,*R*)-nebivolol, we have studied there different cyclization strategies to construct the chroman ring. The construction of 2-substituted chroman derivatives using phenolic-

OH mediated intramolecular ring-opening of *syn*-2,3-diol ester-derived cyclic ortho ester or intramolecular S_NAr reaction of a triol containing a tethered 2,5-difluorophenyl substituent were ineffective. However, exposure of β-hydroxy-α-tosyloxy esters to a one-pot, three-step process (debenzylation-epoxidation-intramolecular epoxide ring opening) enabled us to achieve the target molecules. To the best of our knowledge, this is the first use of Sharpless asymmetric dihydroxylation as the sole source of chirality for the synthesis of nebivolol intermediates.

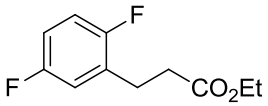
4.6. Experimental Section

4.6.1. General Remarks

Same as described in the **Chapter 2**, **Section 2.6.1** of this thesis.

4.6.2. Preparation of Compounds

Ethyl 3-(2,5-difluorophenyl)propanoate (34):



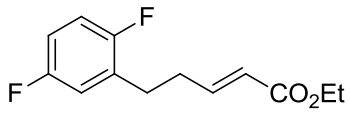
34

To a stirred solution of 2,5-difluorobenzaldehyde **33** (3.0 g, 21.11 mmol) in dichloromethane (100 mL) was added (carbethoxymethylene)triphenylphosphorane (9.2 g, 26.39 mmol) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was suspended by adding 100 mL of 10% EtOAc in hexanes and stirred vigorously. The mixture was then filtered and the filtrate was concentrated under reduced pressure to get crude ethyl 3-(2,5-difluorophenyl)acrylate as light yellow oil which was used for the next step without further purification.

A suspension of 10% Pd-C (200 mg) and the above crude material in ethanol (50 mL) was stirred for 12 h at room temperature under pressure of a hydrogen balloon. The reaction mixture was filtered through a pad of Celite® and the filter pad was well-washed with EtOAc. The filtrates were combined and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% EtOAc in hexanes) to afford **34** (4.12 g, 91% over two steps) as a colorless semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95-6.90 (m, 2H), 6.86-6.83 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.93 (t, *J* = 7.6

Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). This is a known molecule [31].

(*E*)-Ethyl 5-(2,5-difluorophenyl)pent-2-enoate (35):

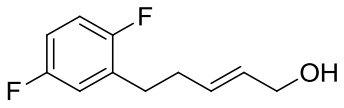


35

DIBAL-H (20 mL, 20.0 mmol, 1 M in hexanes) was added dropwise to a stirred solution of **34** (4.0 g, 18.67 mmol) in CH_2Cl_2 (50 mL) at -78 °C. The mixture was stirred for 4 h at -78°C. The reaction was quenched at -78°C by the slow addition of methanol (2 mL) and then warmed to rt. A saturated solution of Rochelle's salt (50 mL) was added and the resulting biphasic mixture was stirred vigorously for 1.5 h. After separating the organic layer, the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to get the crude aldehyde as a colorless gum which was used for the next step without further purification.

To a stirred solution of the above crude aldehyde in dichloromethane (200 mL) was added (carbethoxymethylene)triphenylphosphorane (6.97 g, 20.0 mmol) at rt. After stirring at room temperature for 4 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was suspended by adding 100 mL of 10% EtOAc in hexanes and stirred vigorously. The mixture was then filtered and the filtrate was concentrated under reduced pressure. Purification of the resulting residue by silica gel column chromatography (5% ethyl acetate in hexanes) afforded compound **35** (3.59 g, 80% over two steps) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00-6.94 (m, 2H), 6.89-6.85 (m, 2H), 5.85 (dt, 1H, *J* = 15.8, 1.5 Hz), 4.19 (q, 2H, *J* = 7.2 Hz), 2.78 (t, 2H, *J* = 7.6 Hz), 2.53-2.48 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 158.5 (d, J_{C-F} = 239.8), 156.9 (d, J_{C-F} = 237.9), 147.0, 129.2 (dd, J_{C-F} = 18.2 and 7.3 Hz), 122.2, 116.7 (dd, J_{C-F} = 23.6 and 3.6 Hz), 116.2 (dd, J_{C-F} = 25.4 and 7.3 Hz), 114.1 (dd, J_{C-F} = 23.6 and 9.1 Hz), 60.2, 32.1, 27.6, 14.2; Anal. Calcd. for $C_{13}H_{14}F_2O_2$: C, 64.99; H, 5.87, found: C, 65.12; H, 5.93.

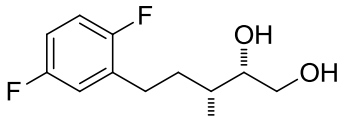
(*E*)-5-(2,5-Difluorophenyl)pent-2-en-1-ol (36):



36

DIBAL-H (15.0 mL, 15.0 mmol, 1 M in hexanes) was added dropwise to a solution of **35** (1.5 g, 6.24 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C. The reaction was quenched by adding a saturated solution of Rochelle's salt (30 mL) and the resulting biphasic mixture was stirred vigorously for 1 h. After separating the organic layer, the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexanes) to afford **36** (1.11 g, 90%) as a colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98-6.93 (m, 2H), 6.89-6.82 (m, 1H), 5.75-5.64 (m, 2H), 4.09 (t, 2 H, *J* = 5.5 Hz), 2.71 (t, 2 H, *J* = 7.6 Hz), 2.38-2.33 (m, 2 H), 1.38 (br s, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.5 (d, J_{C-F} = 243.4), 157.0 (d, J_{C-F} = 239.7), 131.2 (2C), 130.1 (dd, J_{C-F} = 19.9 and 7.2 Hz), 116.7 (dd, J_{C-F} = 23.6 and 5.5 Hz), 116.0 (dd, J_{C-F} = 25.4 and 9.1 Hz), 113.7 (dd, J_{C-F} = 25.4 and 9.1 Hz), 63.5, 32.3, 28.6; Anal. Calcd. for $C_{11}H_{12}F_2O$: C, 66.66; H, 6.10, found: C, 66.73; H, 6.24.

(2*R,3*R**)-5-(2,5-Difluorophenyl)pentane-1,2,3-triol (*rac*-32):**

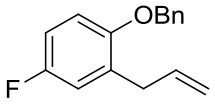


rac-**32**

To a solution of compound **36** (1.0 g, 5.04 mmol) and NMO (1.46 g, 12.5 mmol) in 60 mL acetone-H_2O (5:1) at 0 °C, was added OsO_4 (64 mg, 0.25 mmol) and the reaction mixture was stirred vigorously at the same temperature for 2 h and at rt for 12 h. The reaction was quenched with sodium bisulfite (1.0 g), diluted with water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60% ethyl acetate in hexanes) to afford **32** (1.08 g, 92%) as a colorless solid; m.p.: 68-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94-6.89 (m, 2H), 6.84-6.80 (m, 1H), 3.89 (br s, 1H), 3.75-3.55 (m, 5H),

2.84-2.63 (m, 2H), 2.46 (br s, 1H), 1.83-1.72 (m, 2 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 158.5 (d, J_{C-F} = 241.6), 157.0 (d, J_{C-F} = 239.8), 130.2 (dd, J_{C-F} = 18.1 and 7.3 Hz), 116.8 (dd, J_{C-F} = 23.6 and 5.5 Hz), 116.1 (dd, J_{C-F} = 25.4 and 7.3 Hz), 113.8 (dd, J_{C-F} = 23.6 and 9.1 Hz), 73.8, 71.6, 64.6, 33.5, 25.1; Anal. Calcd. for $C_{11}H_{14}F_2O_3$: C, 56.89; H, 6.08, found: C, 56.96; H, 6.12.

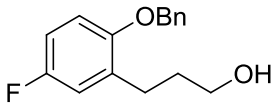
2-Allyl-1-(benzyloxy)-4-fluorobenzene (40):



40

To a solution 2-allyl-4-fluorophenol **39** (10.0 g, 65.71 mmol) in anh. acetone (150 mL) was added anhydrous K_2CO_3 (14.01 g, 101.59 mmol), benzyl chloride (7.58 mL, 65.71 mmol) and KI (500 mg). The reaction mixture was refluxed for 4 h. It was then concentrated under reduced pressure to remove acetone. The resulting residue was re-dissolved in ethyl acetate (200 mL) and water (200 mL). The organic layer was separated, washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. Solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (2% ethyl acetate in hexanes) to afford **40** (15.12 g, 95%) as a light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.35 (m, 5H), 6.97-6.84 (m, 3H), 6.08-5.98 (m, 1H), 5.16-5.11 (m, 2H), 5.08 (s, 2H), 3.47 (d, 1H, J = 6.4 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 157.1 (d, J_{C-F} = 238.6), 152.3, 137.0, 136.0,130.9 (d, J_{C-F} = 6.7), 128.5, 127.8, 127.1, 116.5 (d, J_{C-F} = 23.9), 116.2, 112.8 (d, J_{C-F} = 23.0), 112.6 (d, J_{C-F} = 7.6), 70.5 (t, J_{C-F} = 2.9), 34.2; Anal. Calcd. for $C_{16}H_{15}FO$: C, 79.32; H, 6.24, found: C, 79.28; H, 6.36. The spectral data matched with the literature data [32].

3-(2-(Benzyloxy)-5-fluorophenyl)propan-1-ol (41):

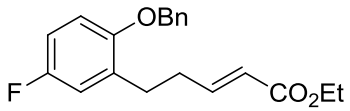


41

To a magnetically stirred solution of **40** (10.0 g, 41.27 mmol) in anhydrous THF (100 mL) was added a 0.5 M THF solution of 9-BBN (100.0 mL, 50.0 mmol) dropwise under

a nitrogen atmosphere at 0 °C. The mixture was then stirred at room temperature for 6 h. The reaction was carefully terminated by the addition of H_2O (5 mL). Next, 3N NaOH solution (50 mL) and 30% aqueous hydrogen peroxide solution (40 mL) were added to it sequentially. The reaction mixture was then stirred for an additional 2 h at 50 °C to complete the oxidation process. After cooling to rt, the mixture was extracted with ethyl acetate (2×100 mL), washed with water (150 mL) and brine (150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10% ethyl acetate in hexanes) to afford **41** (10.31 g, 96%) as a colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.33 (m, 5H), 6.92-6.84 (m, 3H), 5.05 (s, 2H), 3.60 (t, 2H, J = 6.4 Hz), 2.76 (t, 2H, J = 7.5 Hz), 1.89-1.82 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.1 (d, $J_{C–F}$ = 238.7), 152.6, 136.7,132.3 (d, $J_{C–F}$ = 7.7), 128.6, 128.0, 127.3, 116.8 (d, $J_{C–F}$ = 23.0), 112.8 (d, $J_{C–F}$ = 22.1), 112.7 (d, $J_{C–F}$ = 7.7), 70.8 (t, $J_{C–F}$ = 2.9), 61.6, 32.6, 26.0; Anal. Calcd. for $C_{16}H_{17}FO_2$: C, 73.83; H, 6.58, found: C, 73.97; H, 6.69.

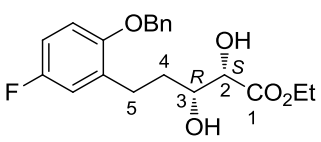
(*E*)-Ethyl 5-(2-(benzyloxy)-5-fluorophenyl)pent-2-enoate (42):



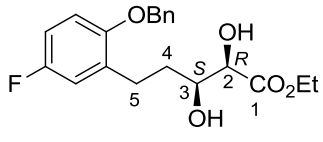
42

To an ice-cooled and stirred mixture of **41** (8.0 g, 30.73 mmol) and Celite® (4 g) in anh. CH_2Cl_2 (100 mL) was added PCC (9.93 g, 46.10 mmol) under an atmosphere of nitrogen. The reaction was stirred vigorously for 3h at rt. (Carbethoxymethylene)triphenylphosphorane (12.2 g, 35.0 mmol) was then added and the reaction was further stirred for 4h at rt. After concentrating the reaction mixture under reduced pressure, the crude product was purified by silica gel column chromatography (4% ethyl acetate in hexanes) to afford **42** (8.57 g, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.33 (m, 5H), 7.05-6.81 (m, 4H), 5.83 (d, J = 14.6), 5.06 (s, 2H), 4.19 (q, 2H, J = 7.3 Hz), 2.81 (t, 2H, J = 7.8 Hz), 2.52 (q, 2H, J = 7.8 Hz), 1.29 (t, 3H, J = 7.3 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.6, 156.9 (d, $J_{C–F}$ = 238.7), 152.5 (d, $J_{C–F}$ = 1.9), 148.1,136.9, 131.3 (d, $J_{C–F}$ = 7.7), 128.6, 127.8, 127.0, 121.7, 116.5 (d, $J_{C–F}$ = 23.0), 113.0 (d, $J_{C–F}$ = 23.0), 112.5 (d, $J_{C–F}$ = 8.6), 70.4 (t, $J_{C–F}$ = 2.9), 60.1, 32.0, 28.9, 14.2; Anal. Calcd. for $C_{20}H_{21}FO_3$: C, 73.15; H, 6.45, found: C, 73.23; H, 6.52.

(2*S*,3*R*)-Ethyl 5-(2-(benzyloxy)-5-fluorophenyl)-2,3-dihydroxypentanoate ((2*S*,3*R*)-43) and its enantiomer ((2*R*,3*S*)-43):



(2*S*,3*R*)-**43**

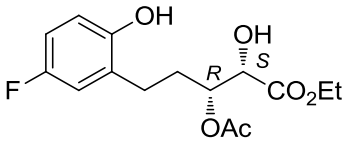


(2*R*,3*S*)-**43**

To a stirred solution of *tert*-butyl alcohol (30 mL) and water (35 mL) were added AD-mix-β (9.0 g) and methanesulfonamide (0.62 g, 6.44 mmol) at room temperature. The mixture was vigorously stirred at room temperature until both phases were clear and then cooled to 0 °C. A solution of cinnamate ester **42** (2.11 g, 6.44 mmol) in *tert*-butyl alcohol (5 mL) was added 0 °C. The reaction mixture was stirred at the same temperature for 24 h. The reaction was quenched at 0 °C by the addition of sodium bisulfite (10 g), warmed to room temperature, and further stirred for 1 h. The reaction mixture was then extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with aqueous 2 N KOH solution (50 mL), water (50 mL), and brine (50 mL). After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (30% ethyl acetate in hexanes) to afford (2*S*,3*R*)-**43** (2.07 g, 89%,) as a colorless gum. $[\alpha]^{D}_{25}$: +9.67 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.31 (m, 5H), 6.94-6.83 (m, 3H), 5.05 (s, 2H), 4.29-4.23 (m, 2H), 4.07 (s, 1H), 3.90-3.87 (m, 1H), 3.22 (s br, 1H), 2.90-2.71 (m, 2H), 2.32 (s br, 1H), 1.96-1.87 (m, 2H), 1.29 (t, 3H, *J* = 7.3 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 173.4, 157.0 (d, $J_{C–F}$ = 238.7), 152.5 (d, $J_{C–F}$ = 1.9), 136.9, 132.1 (d, $J_{C–F}$ = 7.7), 128.5, 127.9, 127.1, 116.7 (d, $J_{C–F}$ = 23.0), 112.8 (d, $J_{C–F}$ = 22.1), 112.7 (d, $J_{C–F}$ = 8.6), 73.2, 71.7, 70.7, 61.9, 33.6, 26.3, 14.0. Anal. Calcd. for $C_{20}H_{23}FO_5$: C, 66.29; H, 6.40. Found: C, 66.34; H, 6.48.

The corresponding (2*R*,3*S*) isomer (2*R*,3*S*)-**43** was synthesized using the same procedure as described above for the preparation of **(**2*S*,3*R*)-**43**, except using AD-mix-α (9.0 g) in place of AD-mix-β. Yield: 87% (2.02 g); $[\alpha]^{D}_{25}$: -9.78 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) data for (2*R*,3*S*)-**43** were identical with those of (2*S*,3*R*)-**43**.

(2*S*,3*R*)-Ethyl 3-acetoxy-5-(5-fluoro-2-hydroxyphenyl)-2-hydroxypentanoate ((2*S*,3*R*)-44):

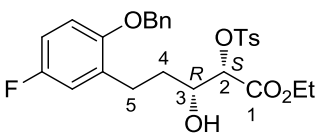


(2*S*,3*R*)-**44**

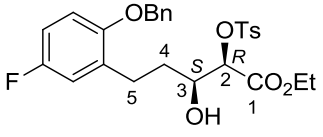
To a stirred solution of (2*S*,3*R*)-**43** (200 mg, 0.55 mmol) in ethyl acetate (10 mL) was added 10% Pd-C (10 mg). After stirring for 2 h at room temperature under pressure of a hydrogen balloon, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to get the corresponding phenolic derivative as a colorless semi-solid which was immediately used for the next step.

To a stirred solution of this crude product in anh. CH_2Cl_2 (10 mL) at 0 ºC were added sequentially trimethyl orthoacetate (54 µL, 0.58 mmol) and BF_3•Et_2O (6 µL, 0.048 mmol). The reaction mixture was stirred at rt for 1 h and then quenched with aqueous acetone. The solvent was removed under reduced pressure, and the product was purified via column chromatography (10% ethyl acetate in hexanes) to yield compound (2*S*,3*R*)-**44** as a colorless gum (49 mg, 40% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77-6.65 (m, 3H), 5.20-5.16 (m, 1H), 4.26-4.14 (m, 3H), 3.45 (s br, 1H), 2.63-2.58 (m, 2H), 2.10-1.96 (s, 5H), 1.25 (t, 3H, J = 6.87 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.3, 170.2, 156.5 (d, J_{C-F} = 237.7), 149.9 (d, J_{C-F} = 1.9), 128.7 (d, J_{C-F} = 6.7), 116.1 (d, J_{C-F} = 23.0), 115.9 (d, J_{C-F} = 7.7), 113.2 (d, J_{C-F} = 22.0), 73.8, 71.5, 62.1, 30.1, 25.7, 20.6, 13.8.

(2*S*,3*R*)-Ethyl 5-(2-(benzyloxy)-5-fluorophenyl)-3-hydroxy-2-(tosyloxy)pentanoate ((2*S*,3*R*)-45) and its enantiomer ((2*R*,3*S*)-45):



(2*S*,3*R*)-**45**

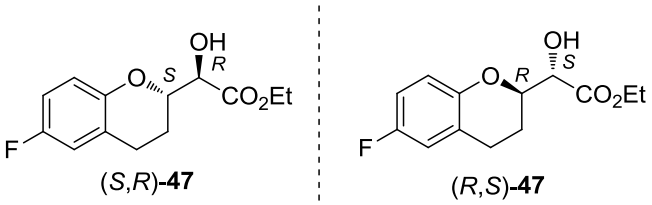


(2*R*,3*S*)-**45**

To a stirred solution of (2*S*,3*R*)-**43** (200 mg, 0.552 mmol) in anh. CH_2Cl_2 (50 mL) at 0 °C were added triethyl amine (0.115 mL, 0.827 mmol) and TsCl (109 g, 0.571 mmol), successively. The reaction mixture was then kept in the refregerator for 72 h. The reaction was quenched with a saturated aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was

concentrated under reduced pressure to get a gummy residue which was rapidly passed through a small pad of silica gel to remove the front-line and base-line impurities to obtain (2*S*,3*R*)-**45** (242 mg, 85%) in almost pure form (TLC). Compound (2*S*,3*R*)-**45** was then immediately used for the next step without further purification and characterization. Compound (2*R*,3*S*)-**45** was synthesized using the same procedure as described above for the preparation of (2*S*,3*R*)-**45**, except using (2*R*,3*S*)-**43** (200 mg, 0.552 mmol) in place of (2*S*,3*R*)-**43**.

(*R*)-Ethyl 2-((*S*)-6-fluorochroman-2-yl)-2-hydroxyacetate ((*S*,*R*)-47) and its enantiomer ((*R*,3)-47):

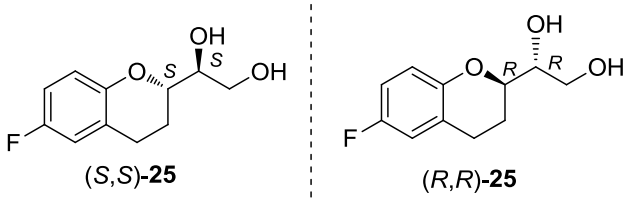


To a stirred solution of (2*S*,3*R*)-**45** (242 mg, 0.47 mmol) in absolute ethanol (20 mL) was added 10% Pd-C (40 mg). The reaction was stirred at rt for 2 h under pressure of a hydrogen balloon. Then, K_2CO_3 (305 mg, 2.20 mmol) was added to the reaction mixture and the hydrogen balloon was replaced by a drying tube ($CaCl_2$). The reaction mixture was stirred for an additional 6 h at rt. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (15% ethyl acetate in hexanes) afforded (*S*,*R*)-**47** (83 mg, 70%) as a colorless semi-solid. $[\alpha]^{D}_{25}$: +73.78 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79-6.68 (m, 3H), 4.37-4.28 (m, 3H), 4.25 (d, 1H, *J* = 1.8), 3.08 (s br, 1H), 2.93-2.77 (m, 2H), 2.18-1.96 (m, 2H), 1.32 (t, 3H, *J* = 6.9 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.3, 155.6, 150.4, 122.7 (d, J_{C-F} = 7.7), 117.6 (d, J_{C-F} = 8.6), 115.1 (d, J_{C-F} = 22.0), 113.9 (d, J_{C-F} = 23.0), 76.4, 72.8, 61.9, 24.8, 23.2, 14.1. Anal. Calcd. for $C_{13}H_{15}FO_4$: C, 61.41; H, 5.95, found: C, 61.56; H, 5.99.

The corresponding (*R*,*S*) isomer (*R*,*S*)-**47** was synthesized using the same procedure as described above for the preparation of (*S*,*R*)-**47**, except using (2*R*,3*S*)-**45** (242 mg, 0.47 mmol) in place of (2*S*,3*R*)-**45**. Yield: 70% (83 mg). $[\alpha]^{D}_{25}$ = -73.92 (*c* = 1.25,

$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) data for (*R*,*S*)-**47** were identical with those of (*S*,*R*)-**47**.

(*S*)-1-((*S*)-6-fluorochroman-2-yl)ethane-1,2-diol ((*S*,*S*)-25) and its enantiomer ((*R*,*R*)-25):

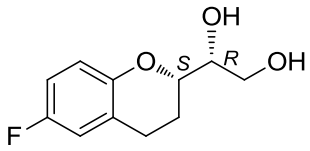


(*S*,*S*)-**25** (*R*,*R*)-**25**

To a solution of (*S*,*R*)-**47** (200 mg, 0.786 mmol) in anh. THF (10 mL) was added $LiAlH_4$ (77 mg, 1.96 mmol) portion wise at 0 °C under nitrogen atmosphere. After 1 h of stirring at room temperature, the reaction mixture was quenched by the addition of ethyl acetate (2 mL) and 1N HCl (5 mL) and then extracted with ethyl acetate (10 x 2 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (30% ethyl acetate in hexanes) to afford **(*S*,*S*)-25** (155 mg, 93%) as a colorless solid. m.p.: 101-102 °C; $[\alpha]^D_{25}$: -65.57 (*c* = 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 6.83-6.73 (m, 3H), 4.09-4.04 (m, 1H), 3.85-3.77 (m, 3 H), 2.93-2.75 (m, 2H), 2.67 (s br, 1H), 2.13 (s br, 1H), 2.04-1.91 (m, 2H); Anal. Calcd. for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17, found: C, 62.32; H, 6.25.

The corresponding (*R*,*R*) isomer (*R*,*R*)-**25** was synthesized in 93% yield using the same procedure as described above for the preparation of (*S*,*S*)-**25**, except using (*R*,*S*)-**47** (200 mg, 0.786 mmol) instead of (*S*,*R*)-**47**. $[\alpha]^D_{25}$: +65.63 (*c* = 1.0, MeOH); Lit. $[\alpha]^D_{25}$: +65.80 (*c* = 1.0 MeOH) [20] and $[\alpha]^D_{20}$: +63.08 (*c* 0.1, MeOH) [14]. ^1H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3) data for (*R*,*R*)-**25** were identical with those of (*S*,*S*)-**25**.

(*R*)-1-((*S*)-6-fluorochroman-2-yl)ethane-1,2-diol ((*S*,*R*)-28):

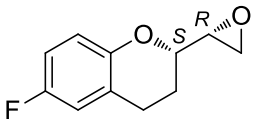


(*S*,*R*)-**28**

To a stirred solution of DEAD (966 mg, 3.53 mmol) in THF (2 mL) were added sequentially solid PPh_3 (230 mg, 3.53 mmol), a solution of (*S*,*S*)-**25** (125 mg, 0.589 mmol) in anh. THF (5 mL) and benzoic acid (431 mg, 3.53 mmol) in THF (5 mL) under an argon atmosphere at -10 °C. The resulting solution was stirred for 6 h at rt. It was then quenched with water (10 mL) and extracted with ethyl acetate (25 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was was subjected to silica gel column chromatography to remove most of the triphenyl phosphine oxide. The isolated product was not completely pure and still contained some impurities. Hence it was subjected to the next step without recording any spectral data.

To a solution of the resulting crude diester in MeOH (10 mL) was added a 10% MeOH solution of KOH (5 mL). The mixture was stirred for 2 h at rt. After removing acetone from the reaction mixture under reduced pressure, the resulting residue was dissolved in ethyl acetate (50 mL) and water (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (30% ethyl acetate in hexanes) afforded (*S*,*R*)-**28** (47 mg, 38% over two steps) as a colorless solid. m.p.: 86-87 °C; $[\alpha]^{D}_{25}$: +71.39 (*c* = 0.2, MeOH); Lit. $[\alpha]^{D}_{25}$: +71.80 (*c* = 1.0 MeOH) [20] and $[\alpha]^{D}_{20}$: +70.3 (*c* 0.1, MeOH) [14]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80–6.70 (m, 3H), 4.01–3.98 (m, 1H), 3.88-3.80 (m, 3H), 2.92 (s br, 1H), 2.87–2.74 (m, 2 H), 2.46 (s br, 1H), 2.15–2.11 (m, 1 H), 1.88-1.80 (m, 1 H); Anal. Calcd. for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17, found: C, 62.38; H, 6.21.

(*S*)-6-Fluoro-2-((*R*)-oxiran-2-yl)chroman ((*S*,*R*)-47):



(*S*,*R*)-**29**

To a stirred solution of (*S*,*R*)-**47** (100 mg, 0.393 mmol) in anh. CH_2Cl_2 (5 mL) at rt were added triethyl amine (0.075 mL, 0.654 mmol) and TsCl (74 mg, 0.393 mmol), successively. The reaction mixture was then stirred at rt for 12 h. The reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced

pressure and the resulting residue was use used for the next step without further purification.

To a solution of the obtained crude tosylate in THF (5 mL) was added 1 M $LiBH_4$ solution in THF (0.8 mL, 0.8 mmol) dropwise at 0 °C under nitrogen atmosphere. After 8 h of stirring at room temperature, the reaction mixture was quenched by the addition of ethyl acetate (2 mL) and 1N HCl (5 mL) and then extracted with ethyl acetate (10 x 2 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the corresponding hydroxyl tosylate which was then dissolved in absolute ethanol (5 mL). K_2CO_3 (70 mg, 0.50 mmol) was added to it and the reaction mixture stirred vigorously for 10 h. After removing ethanol under reduced pressur, the resulting residue *w*as redissolved in ethyl acetate (15 mL) and *w*ater (20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (15% ethyl acetate in hexanes) afforded (*S*,*R*)-**29** (47 mg, 62% over three steps) as a colorless gum. $[\alpha]^{D}_{25}$: +76.11 (*c* = 0.2, $CHCl_3$); Lit. $[\alpha]^{D}_{25}$: +72.9 (*c* = 1.0 $CHCl_3$) [33]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81-6.74 (m, 3H), 3.85-3.81 (m, 1H), 3.14-3.11 (m, 1H), 2.90-2.79 (m, 4H), 2.16-2.11 (m, 1H), 1.93-1.85 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.8 (d, J_{C-F} = 237.9), 150.0, 122.8 (d, J_{C-F} = 7.3), 117.5 (d, J_{C-F} = 9.0), 115.2 (d, J_{C-F} = 21.8), 114.1 (d, J_{C-F} = 23.6), 75.5, 52.9, 45.7, 29.6, 24.2; Anal. Calcd. for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71, found: C, 68.11; H, 5.78.

4.7. References

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4.8. NMR Spectra of Selected Compounds

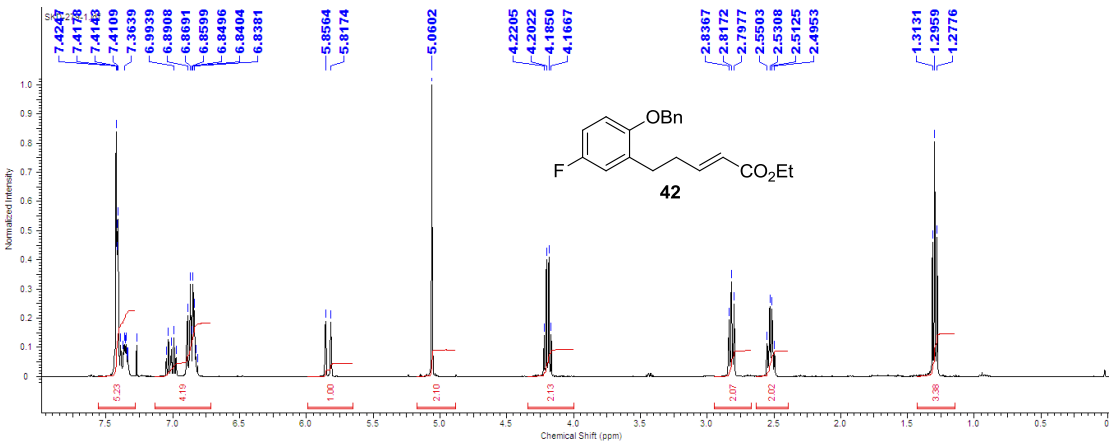

Figure 4.3. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 42

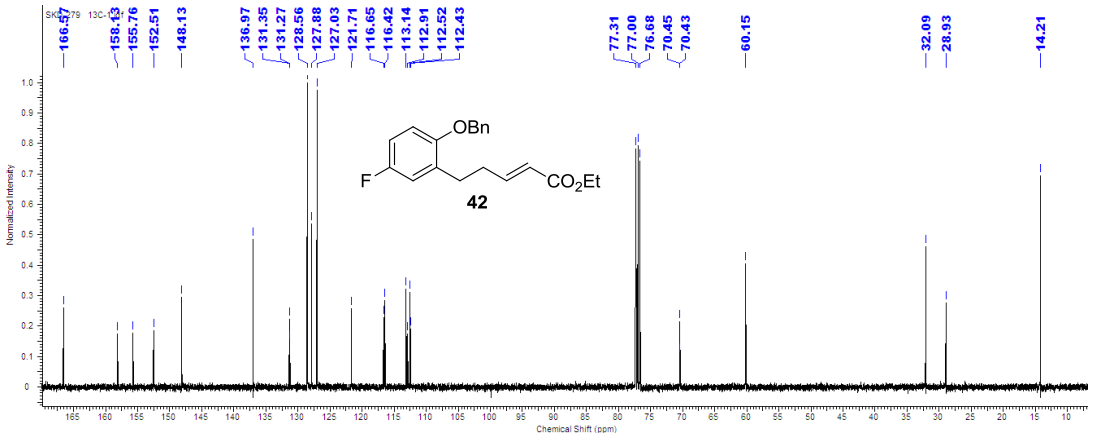

Figure 4.4. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound 42

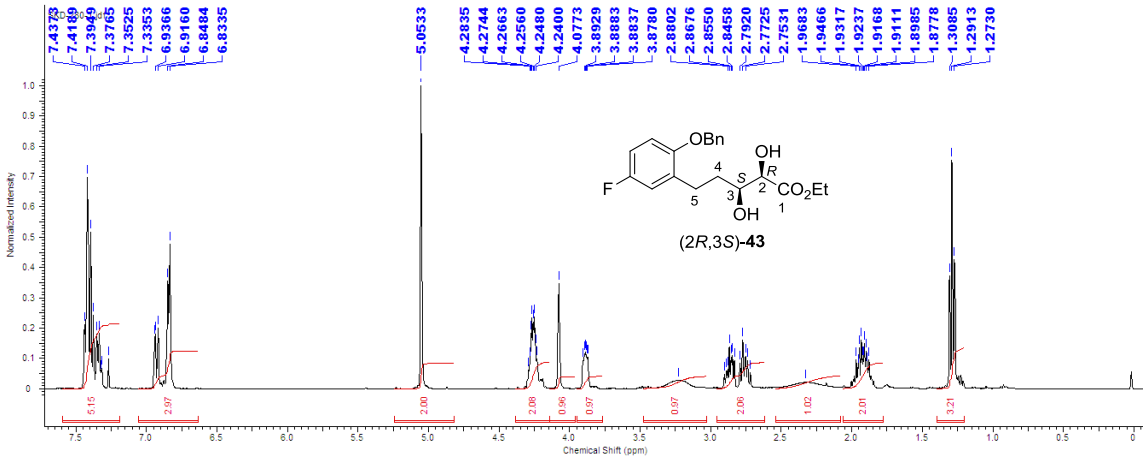

Figure 4.5. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound (2*R*,3*S*)-43

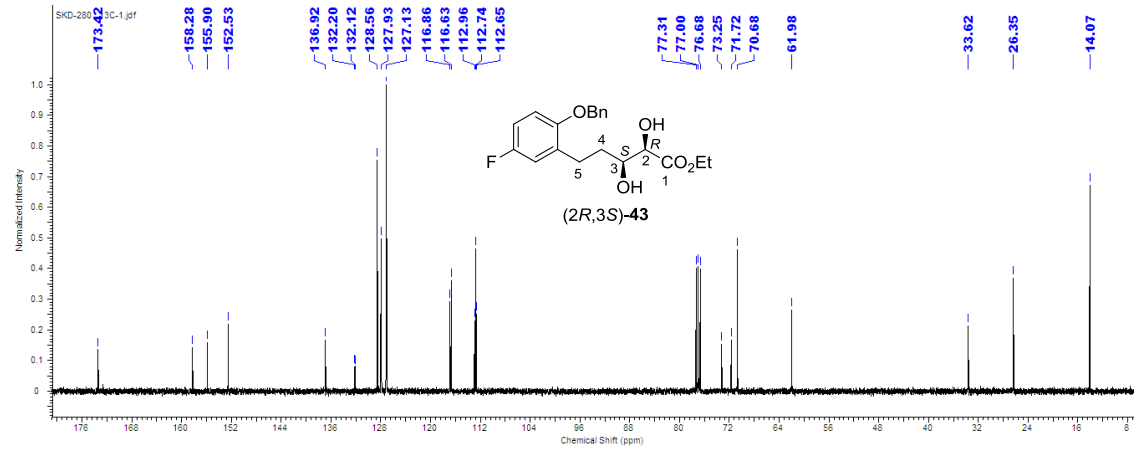

Figure 4.6. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound (2*R*,3*S*)-43

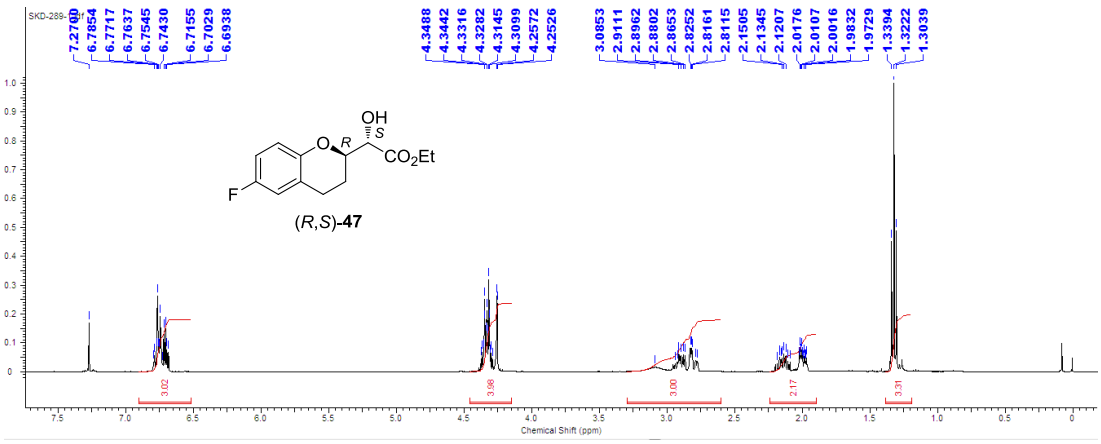

Figure 4.7. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound (*R*,*S*)-47

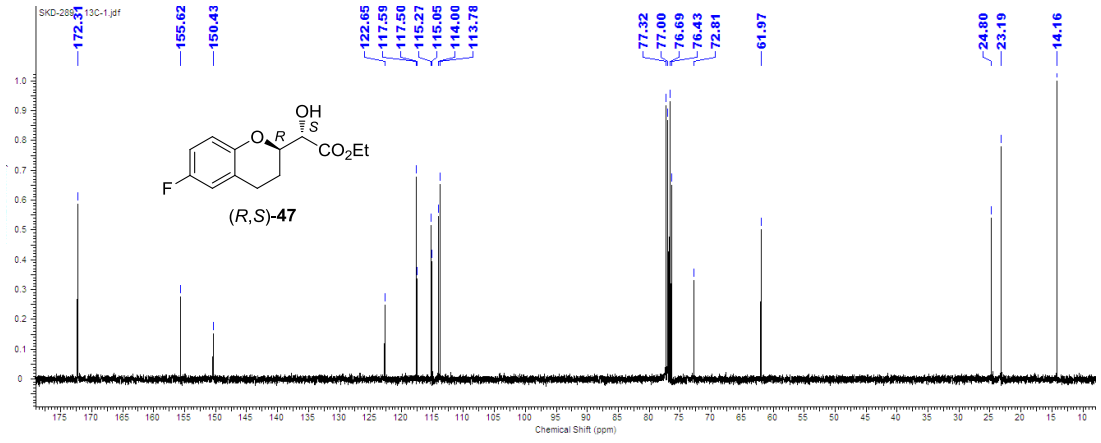

Figure 4.8. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound (*R*,*S*)-47

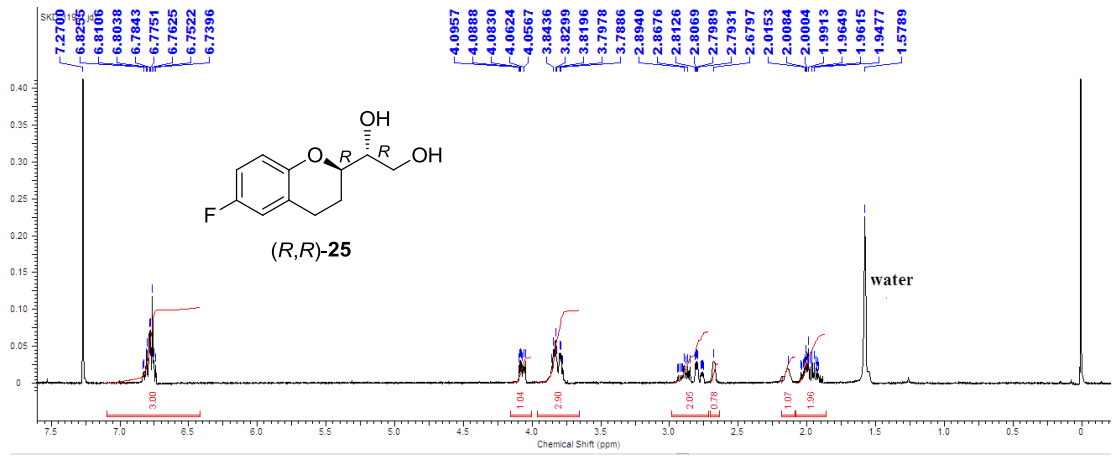

Figure 4.9. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound (*R*,*R*)-25

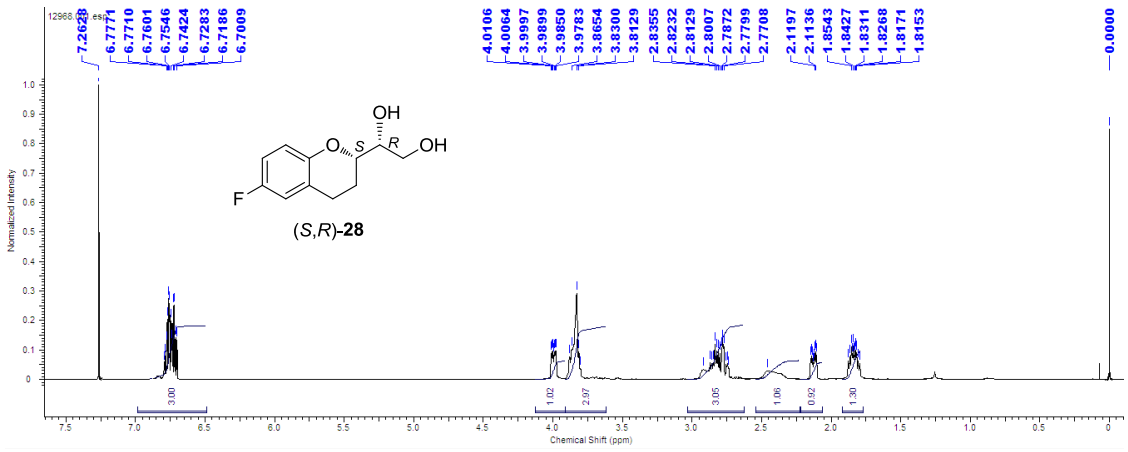

Figure 4.10. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound (*S*,*R*)-28

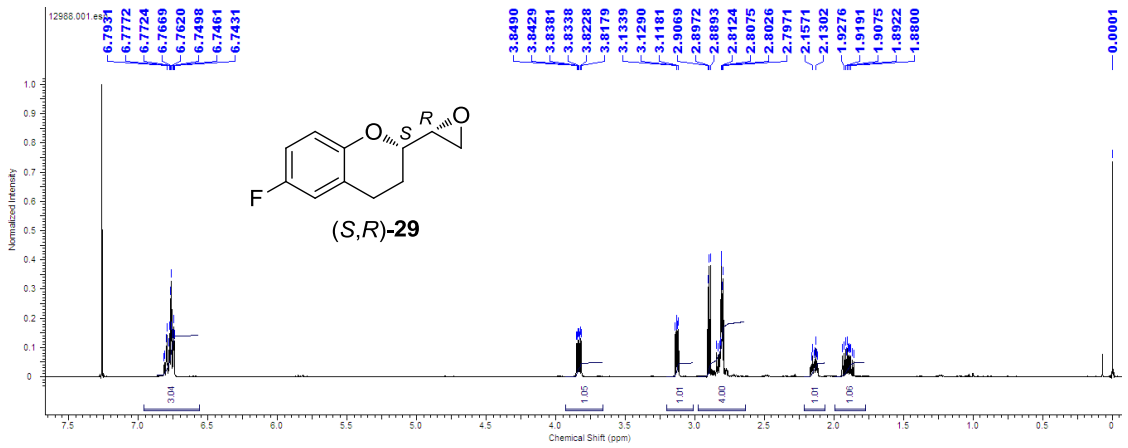

Figure 4.11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound (*S*,*R*)-29

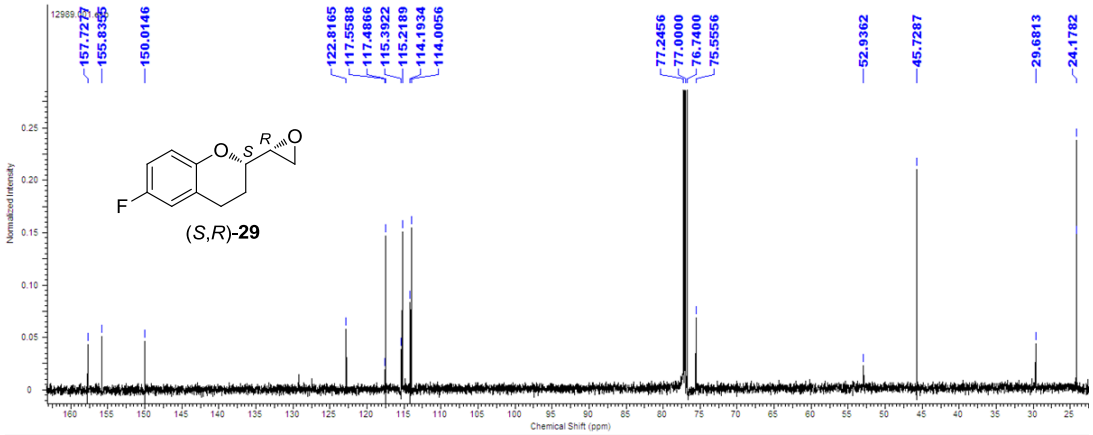

Figure 4.12. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound (*S*,*R*)-29