Synthesis and Characterization of Nebivolol: A Review of Different Synthetic Approaches and Their Efficiencies

By

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A thesis submitted to the School Of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School Of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

This project does not involve any clinical trial or human participants.

Abstract

Nebivolol is a potent beta-blocker used to treat heart failure and hypertension. With the increasing prevalence of cardiovascular diseases and the demand for effective and well-tolerated treatments, the global market for beta-blockers, including nebivolol, was worth approximately US$8.5 billion in 2020 and is projected to grow by 5.5% in the coming years. There are several techniques for synthesizing nebivolol, including Sharpless asymmetric epoxidation, Pd-, Zr-, and Mo-catalyzed processes, photochemical reconfiguration, and homochiral sulfoxide-directed reaction (Jiang et al., 2021). Among these techniques, Zr- and Mo-catalyzed processes produce the highest efficiency of 99%. However, using natural chiral starting materials and Sharpless asymmetric epoxidation is more efficient in terms of time and cost. This review article provides an in-depth analysis of the effectiveness of the various nebivolol synthesis techniques. The commercial expansion of beta-blockers and the rising need for efficient and well-tolerated medicines emphasize how critical it is to conduct further research in this area.

Keywords: (S,R,R,R)-nebivolol, Zr- and Mo-catalyzed reactions, Sharpless asymmetric epoxidation, Asymmetric dihydroxylation, chiral photochemical synthesis.

Dedication

To my family and my friends

Acknowledgement

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List of Acronyms

II	(1R,7S)-8-oxabicyclo[5.1.0] octane
III	(Z)-4-fluoro-2-(prop-1-en-1-yl)phenol
TBS-IV	tert-butyl(((1R,2R)-2-(4-fluoro-2-((Z)-prop-1-en-1-yl)phenoxy)cyclohept-3-en-1-yl)oxy)dimethylsilane
TBS-IV	tert-butyl(((1R,2R)-2-(4-fluoro-2-((Z)-prop-1-en-1-yl)phenoxy)cyclohept-3-en-1-yl)oxy)dimethylsilane
TBS-V	tert-butyl(((1R,2R)-2-(4-fluoro-2-((Z)-prop-1-en-1-yl)phenoxy)cyclohept-3-en-1-yl)oxy)dimethylsilane
TBS-VI	tert-butyl(((R)-1-((R)-6-fluoro-2H-chromen-2-yl)pent-4-en-1-yl)oxy)dimethylsilane
TBS-VII	(R)-6-((tert-butyldimethylsilyl)oxy)-6-((R)-6-fluoro-2H-chromen-2-yl)hexan-2-one
TBS-VIII	tert-butyl(((R)-1-((R)-6-fluorochroman-2-yl)allyl)oxy)dimethylsilane
(R,R)-VIII	(R)-2-((tert-butyldimethylsilyl)oxy)-2-((R)-6-fluorochroman-2-yl)ethanamine
TBS-IX	tert-butyl(((1R,2S)-2-(4-fluoro-2-((Z)-prop-1-en-1-yl)phenoxy) cyclohept-3-en-1-yl)oxy)dimethylsilane
(S,S)-XI	(S)-2-((tert-butyldimethylsilyl)oxy)-2-((S)-6-fluorochroman-2-yl)acetaldehyde
I,1	(S,R,R,R)-nebivolol
2	(R)-2-amino-1-((S)-6-fluorochroman-2-yl)ethanol
3	(R)-6-fluoro-2-((R)-oxiran-2-yl)chroman
4	4-fluorophenol

5	1-fluoro-4-methoxybenzene
5a	4-fluoro-2-methylphenol
6	(2-allyl-4-fluorophenoxy)(tert-butyl)dimethylsilane
7	2-(2-((tert-butyldimethylsilyl)oxy)-5-fluorophenyl)ethanol
8	(E)-ethyl 5-(2-((tert-butyldimethylsilyl)oxy)-5-fluorophenyl)pent-2-enoate
9	(E)-5-(2-((tert-butyldimethylsilyl)oxy)-5-fluorophenyl)pent-2-en-1-ol
9a	(E)-4-fluoro-2-(5-hydroxypent-3-en-1-yl)phenol
10	(R)-1-((S)-6-fluorochroman-2-yl)ethane-1,2-diol
12	(R)-2-azido-1-((S)-6-fluorochroman-2-yl)ethanol
13	(S)-1-((R)-6-fluorochroman-2-yl)ethane-1,2-diol
14	(R)-1-((R)-6-fluorochroman-2-yl)ethane-1,2-diyl bis(4-nitrobenzoate)
15	(R)-1-((R)-6-fluorochroman-2-yl)ethane-1,2-diol
16	(R)-2-((R)-6-fluorochroman-2-yl)-2-hydroxyethyl-4-methylbenzenesulfonate
17	6-fluoro-4-oxo-4H-chromene-2-carboxylic acid
18	6-fluorochroman-2-carboxylic acid
19	(6-fluorochroman-2-yl)methanol
20	6-fluorochroman-2-carbaldehyde
21	6-fluoro-2-(oxiran-2-yl)chroman
22	2-(benzylamino)-1-(6-fluorochroman-2-yl)ethanol
23	2,2'-(benzylazanediyl)bis(1-(6-fluorochroman-2-yl)ethanol)
24	(R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde
25	1-(5-fluoro-2-hydroxyphenyl)ethanone
(S,R)-26	(S)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-fluorochroman-4-one
(R,R)-27	(R)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-fluorochroman-4-one
(S,R)-28	(R)-2-((S)-6-fluorochroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate

(R,R)-29	(R)-2-((R)-6-fluorochroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate
(S,R)-30	(R)-2-amino-1-((S)-6-fluorochroman-2-yl)ethanol
31	6-fluorochroman-2-one
(S)-32	sulfinyl complex
(R,S)-33	Sulfoxide complex
(R)-34	(R)-6-fluorochroman-2-carbaldehyde
(R)-35	(R)-6-fluoro-2-vinylchroman
(R,R)-36	(R)-1-((R)-6-fluorochroman-2-yl)ethane-1,2-diol
(R,R)-37	(R)-2-((R)-6-fluorochroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate
(R,R)-38	(R)-6-fluoro-2-((R)-oxiran-2-yl)chroman-2-ol
(S,R)-41	(S)-2-(benzyloxy)-2-((S)-6-fluoro-2-methylchroman-2-yl)acetaldehyde
(S,R)-42	(R)-N-benzyl-2-(benzyloxy)-2-((S)-6-fluoro-2-methylchroman-2 yl)ethanamine
(S,R,R,R)-43	(R)-2-(benzyl((R)-2-(benzyloxy)-2-((S)-6-fluorochroman-2-yl)ethyl)amino)-1-((R)-6-fluorochroman-2-yl)ethanol

Chapter 1

Introduction

1.1Background of beta-blockers

Today, hypertension and hypertensive heart disease are among the major causes of death worldwide. According to the 2017 global burden of illness study, hypertensive heart disease accounts for around 12.8% of global deaths (Dai et al. 2021). There are numerous causes for this. The action of beta receptor agonists is a major contributing factor. Beta-1 (β-1), beta-2 (β-2), and beta-3 (β -3) are the three most common forms of beta receptors. Cardiac function is controlled by β-1 receptors, which are concentrated in the heart muscle. β -2 receptors, which are found in many different organ systems, cause smooth muscle to relax and are responsible for the regulation of a wide range of metabolic processes. The β -3 receptors are of marginal clinical relevance at present, as they initiate the destruction of fat cells. A wide range of disorders can be treated with β-blocking medicines, which work by preventing signals from reaching these receptors (Anon n.d.-e). β-blockers are an essential class of drugs that are often used as first therapies for a wide range of both acute and chronic conditions. β -blockers are the first line of defense against hypertensive disease. To perform its role, it works in opposite to epinephrine, also known as adrenaline. In doing so, it lowers blood pressure by making the heart beat more slowly. It helps to relax blood vessel and increase blood flow. β -blockers are an excellent treatment for high blood pressure (hypertension), heart problems (angina, arrhythmias, myocardial infarction, heart failure), overactive thyroid (hyperthyroidism), and glaucoma. They're also put to use to ward off migraine attacks (Anon n.d.-b; Quirke 2006). In general, betablockers are responsible for β -1 and β -2 antagonism; however, due to the location of β -2 in the bronchial smooth muscle, blocking this receptor may pose a major risk to asthma patients. Therefore, selectivity towards the β -1 receptor found in the heart is required.

Currently on the market are beta-blockers from three different generations: In contrast to second-generation beta-blockers, which are more cardio selective because they are more selective for β1-receptors, and third-generation beta-blockers, which are extremely selective for β1-receptors, first-generation beta-blockers are nonselective because they block both β1- and β2-receptors (Motiejunaite, Amar, and Vidal-Petiot 2021; do Vale et al. 2018). Propranolol and atenolol are examples of first-generation beta blockers, the oldest class of betablockers. The beta-1 receptor, which is mostly found in the heart, is the primary target of thesedrugs. They are commonly used to treat cardiovascular conditions such hypertension, angina, and heart failure. There are also cases of tremors and migraines that these drugs can help with.Beta blockers of the second generation, often known as "Cardio selective" beta blockers, include bisoprolol and metoprolol. These medications similarly primarily target the beta-1 receptor, but have a higher selectivity for the beta-1 receptor compared to first-generation betablockers. This indicates that their action on the beta-2 receptors, which are largely situated in the lungs, is diminished. This results in fewer adverse effects such as bronchoconstriction. Second generation beta blockers are also used to treat hypertension, angina, and other cardiovascular diseases (Oliver, Mayor Jr, and D'Ocon 2019; Weber 2005). Third generation beta blockers, also known as "vasodilating" beta blockers, include drugs such as nebivolol andcarvedilol. These drugs have a unique mechanism of action that not only block beta receptors but also have vasodilating properties. This means that they cause the blood vessels to widen, which reduces blood pressure and improves blood flow. They are less likely to have unwantedeffects since their selectivity for beta-1 and beta-2 receptors is more even (Oliver et al. 2019).

1.2 Third generation beta-blockers and uses

It is a common practice to employ beta blockers of the third generation to treat cardiovascular problems such high blood pressure and heart failure. Some of the key characteristics of third generation beta blockers include,

- Vasodilation: Vasodilating characteristics are a distinguishing feature of beta blockers of the third generation. As a result, both blood pressure and blood flow are lowered. Nitric oxide (NO) synthase enzyme activation results in increased production of nitric oxide, a powerful vasodilator, therefore the desired effect (Fisker, Grimm, and Wehland 2015; do Vale et al. 2018).
- Balanced receptor selectivity: Third generation beta blockers have a more balanced selectivity for beta-1 and beta-2 receptors compared to first-generation beta blockers. This means that they have fewer side effects such as bronchoconstriction and less impact on heart rate (Fisker et al. 2015).
- Heart failure treatment: Heart failure, which occurs when the heart cannot pump enough blood to meet the needs of the body, can be treated with nebivolol and other third-generation beta blockers. Nebivolol has been demonstrated to enhance the heart's functionality, reduce the number of times patients with heart failure must visit the hospital, and reduce the chance of death in these patients.
- Lower incidence of diabetes: In comparison to first and second-generation beta blockers, studies suggest that third-generation beta blockers such nebivolol may have a lower risk of diabetes development as a side effect (Fisker et al. 2015; do Vale et al. 2018).

1.3 Nebivolol

Nebivolol is a beta blocker of the third generation that was initially approved for treatment in hypertension and heart failure. It is a highly selective beta-1 receptor antagonist, which blocks the beta-1 receptors in the heart. Nebivolol also has a distinct mode of action that distinguishes it apart from other beta blockers. Nebivolol's vasodilating capabilities are one of its most prominent properties. It promotes the generation of Nitric oxide (NO) in blood vessels and thus leads to vasodilation and the decrease of blood pressure (Hilas, 2009). This is distinct from other beta blockers, which primarily function by decreasing the heart rate and reducing the force of the heart's contraction. Nebivolol is distinguished from other beta blockers in that it has a smaller effect on heart rate (Hilas, 2009). This is due to its balanced selectivity for β-1 and β-2 receptors, which results in fewer adverse effects such as bronchoconstriction. It has demonstrated efficacy in treating hypertension and heart failure. It has been demonstrated to lower blood pressure and increase blood flow in hypertension. It has been found to enhance cardiac function, reduce hospitalization for heart failure, and lower the chance of death in patients with heart failure. However, nebivolol is also a lipophilic molecule, which permits it to pass the blood-brain barrier and potentially damage the central nervous system (Hilas, 2009; Broeders et al. 2000; O. Go et al. 2019).

Nebivolol is a chiral chemical, which means it exists in two or more enantiomers that are mirror images of one another but cannot be superimposed. These enantiomers have diverse physical and chemical properties due to their distinct three-dimensional atomic arrangements (Grieb 1995).

Nebivolol is mostly found as two enantiomers: (1R,1'S,2S,5S) or (S,R,R,R) and (1S,1'S,2S,5S) or(S,S,S,R). One of the most common forms of nebivolol used in medicine is the (S,R,R,R) form, also known as (1R,1'S,2S,5S)-nebivolol. Now, it can be utilized to treat heart failure and excessive blood pressure. An important inactive enantiomers of nebivolol is (S,S,S,R)-

nebivolol, also known as (1S,1'S,2S,5S)-nebivolol. It has little or no effect on beta-1 receptors, the primary target of nebivolol, according to research. Notably, there are more diastereomers of nebivolol, such as the (S,S,S,S) form, but these are typically produced in minute quantities as by-products of the synthesis process (Anon n.d.-f). In addition, it should be noted that the purity of the (S,R,R,R) nebivolol form is essential for the drug's efficacy, as the presence of other stereoisomers may result in decreased activity or side effects. Manufacturers of nebivolol should ensure the drug's high purity through the use of suitable purifying processes. (S,R,R,R) nebivolol, commonly referred to as (1R,1'S,2S,5S)-nebivolol, is regarded as the most effective and therapeutically utilized variant of the medicine. Because it has the maximum activity on beta-1 receptors, the primary target of nebivolol, this is the case. (S,R,R,R) nebivolol lowers heart rate and blood pressure by binding selectively to and blocking the function of β-1 receptors in the heart. This selectivity is thought to be due to the (S,R,R,R) isomer's unique three-dimensional structure, which allows it to engage with β-1 receptors in a specialized manner (Shanghai, n.d.)(R,S,S,S) nebivolol, commonly referred to as (1S,1'S,2S,5S)-nebivolol, is one of the principal inactive stereoisomers of nebivolol. It has been determined to have minimal or no activity on beta-1 receptors and is consequently not used as an active pharmaceutical ingredient in clinical practice. However, just because nebivolol (S,R,R,R) is the most widely used therapeutic formulation of the drug does not mean that it is the most successful for every patient. Several factors, such as the patient's medical background, the presence of other medical problems, and the risk of drug interactions, can affect a medication's effectiveness (Anon n.d.-f). Typically, the synthesis of the stereoisomers of nebivolol begins with the reaction of p-bromoaniline with 2-bromoethanol to produce an intermediate molecule, which is subsequently reacted with a chiral auxiliary (Preface. Brunton L.L., 2017). The most prevalent approach forsynthesizing (S,R,R,R) nebivolol involves a chiral auxiliary, such as camphor sulfonic acid. Inthis method, the (S,R,R,R) isomer is generated by reacting an intermediate molecule with a

chiral auxiliary in the presence of a palladium catalyst. An alternative method of synthesizing (S,R,R,R) nebivolol involves employing a chiral ligand, such as a cinchona alkaloid. Using a palladium catalyst, the (S,R,R,R) isomer is generated by reacting an intermediate chemical with a chiral ligand. By adjusting the reaction conditions or using a different chiral auxiliary or ligand, (R,S,S,S) nebivolol can be synthesized. Notably, the synthesis procedures for nebivolol stereoisomers are difficult, multi-step processes that require specialist knowledge and equipment. In addition, the purity of the final product is essential to the efficacy of the medicine, as the inclusion of other stereoisomers may result in decreased activity or side effects. In pharmaceuticals and medical chemistry, the synthesis of nebivolol is a topic of great interest (Anon n.d.-f). Nebivolol is a highly selective beta-blocker used in the treatment of hypertension and heart failure. Its unique mechanism of action and favorable safety profile have made it a widely prescribed drug. In recent years, there has been a surge of research aimed at improving the synthesis of nebivolol and developing new, more efficient methods. This has led to a wealth of new knowledge and advancements in the field. In this review paper, we will summarize and discuss the current state of the art in the synthesis of nebivolol, including different methods, techniques, and optimizations. The goal of this review is to provide a comprehensive overview of the field, highlight the latest research and development, and offer a guide for future studies in the synthesis of nebivolol.

Chapter 2

Synthesis

2.1 Methodology:

Making the active pharmaceutical ingredient (API) in such a way that it can be used to manufacture the medication used to treat high blood pressure and heart failure is the aim of this review. A beta-blocker called nebivolol functions by obstructing the beta-adrenergic receptors found in the heart and blood vessels. By inhibiting these receptors, nebivolol reduces blood pressure and heart rate. This makes it an effective treatment for heart failure and excessive blood pressure. The goal of making nebivolol is to make the active pharmaceutical ingredient (API) in a pure, stable, and consistent form that can be used to make the drug in the most efficient way. The goal of the synthesis process is also to get the best product yield, keep production costs as low as possible, and make as little waste as possible.

In order to collect information on the synthesis of nebivolol, a thorough review of the relevant literature was carried out. Using databases such as PubMed, ScienceDirect, and Google Scholar, a search was conducted to find relevant patents, books, and articles that have been examined by experts. During the course of the investigation, the following terms, amongst others, served as search terms: "synthesis of nebivolol," "procedures for the synthesis of nebivolol," and "efficiencies of different methods for the synthesis of nebivolol." The information that was gathered was examined to determine the many approaches that could be taken to produce nebivolol. From those approaches, the five that proved to be the most productive and economical were chosen. The starting material, the intermediates used in the synthesis, and the important intermediates are all thoroughly evaluated, and the important intermediates are discussed in terms of their assembly and reaction efficiency.

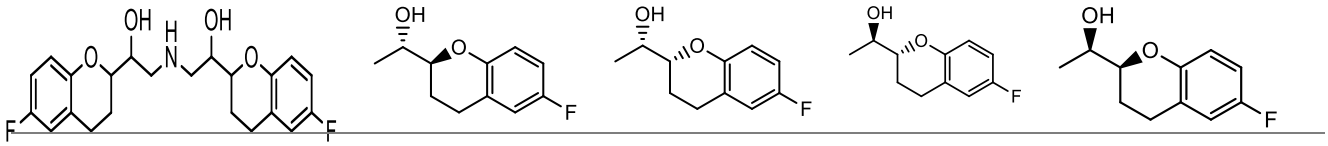
The data were also utilized to determine the difficulties and restrictions associated with each strategy. A Look at the Data and Its Interpretation: Following the collection of data, it was

examined and analyzed in order to determine the procedures for the synthesis of nebivolol that were the most productive and economical. The second synthesis method was shown to have reaction efficiencies of up to 65%, and those efficiencies can be utilized in industrial settings. This was found among all five reactions. In addition, the data were evaluated to determine the essential intermediates that were a part of the synthesis as well as the potential difficulties that were linked with each approach.

In addition, a full review of the various techniques for the synthesis of nebivolol, including their efficiencies and the intermediates that are involved in the synthesis, was derived from the data that was examined and subsequently synthesized. A conclusion was reached based on the analysis and synthesis of the data regarding the most productive and economical ways for synthesizing nebivolol, the key intermediates involved in the synthesis, the synthesis of the intermediates, and the possible new methodology for advanced synthesis. In addition to that, suggestions were offered for new lines of inquiry to be pursued in the realm of nebivolol synthesis.

2.2 (S,R,R,R)- nebivolol and stereoisomers

Nebivolol, also known as α,α′-[Iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol, is a beta-adrenergic receptor antagonist of the third generation (β-blocker). Currently, it is distributed as a blend of *d*-nebivolol consecutively *l*-nebivolol hydrochloride salts (racemic mixture). Due to the presence of four chiral centers and one sigma plane, ten different versions of nebivolol are possible (Akbarieh et al., 2008)



	SSSS	SSSR (*l*-nebivolol)	SSRR	SSRS

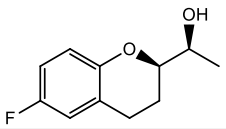
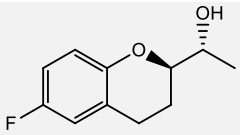
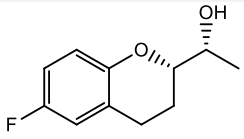
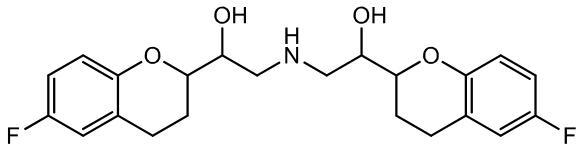
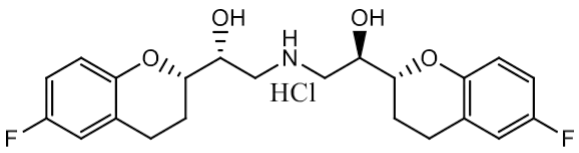
	RSSS	RSSR	RSRR	RSRS
	RRSS	RRSR	RRRR	SRRR (*d*-nebivolol)
	SRSS	SRSR	RRRS	SRRS

Figure 1: Possible stereoisomers of nebivolol

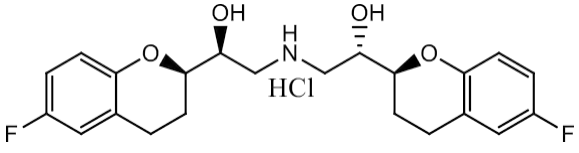
Nebivolol, in all of its ten potential stereoisomers (S,R,R,R), was discovered to be an effective blocker of β1-adrenergic receptors. However, it was discovered that the nebivolol (R,S,S,S) enantiomer lacked any β1-antagonist activity but had a sizable synergistic impact on the antihypertensive effectiveness of (S,R,R,R) -nebivolol (Anon n.d.-p). In addition, the antihypertensive effects of (R,S,S,S)-nebivolol were improved by the related beta1-blockers propranolol, and metoprolol (Akbarieh et al., 2008; Gerhard Jas et al., 2011; Sandro MAURO et al., 2012)Anon n.d.-f).



Nebivolol



(S,R,R,R)-Nebivolol
(hydrochloride salt)



(R,S,S,S)-Nebivolol
(hydrochloride salt)

Figure 2: Nebivolol and its possible active stereoisomers

2.3Materials for (S,R,R,R)-nebivolol synthesis

2.3.1 Material for synthesis 1:

The first phase of the procedure involves dissolving 80% of K_2CO_3 in acetone, after which tert-butyldimethylsilyltrifluoromethanesulphonate (TBSOTf) and 2,6-lutidine are added in CH_2Cl_2 to get a 93% yield. A yield of 44% is obtained in the second step by mixing tetrahydrofuran (THF) with zirconium derivaties of 1,1'-Bi-2-napthol ((R)-(EBTHI)Zr-binol) and ethyl magnesium cholirde (EtMgCl). Thirdly, 1 atmosphere of ethylene in benzene (C_6H_6) is used in the process, which leads to a 97% yield of kinatic TBS-V. Add $PdCl_2$ and CuCl to DMF and H_2O, followed by 1 atmosphere of O_2, and the yield increases to 87% in the fourth stage. 10% Pd/C and 1% H_2(98%) are also used in this method. The fifth stage involves filtering the mixture using a Vycor filter and then combining it with Triethylamine (Et_3N) in MeOH to obtain a 58% yield. After ozonolysis with a mixture of CH_2Cl_2 and MeOH, the addition of $NaBH_4$, and the subsequent 20-hour reaction of 1,1'-(Azodicarbonyl)dipiperidine (ADDP), Tributylphosphine (Bu_3P), and phthalimide in C_6H_6, an 85% yield of TBS-VIII is obtained. After adding Tetrakis(triphenylphosphine)palladium (Pd(PPh3)4)and n-Bu2Sn(OMe)2,-molbase and 2,6-lutidine in step 6, H_4N_2 and EtOH are added in step 7 for a 68% yield. The eighth phase of the procedure comprises adding (S)-(EBTHI)Zr-biphen and NaBH(OAc)3 in 1,2-dichloroethane, and it yields 91%. The reaction is completed by treating the product with 10% HCl in MeOH, yielding 99% (Anon n.d.-f; Johannes et al. 1998).

2.3.2 Material for synthesis 2:

First, allyl bromide and potassium carbonate (K_2CO_3) are added, which results in a yield of roughly 83% in the first step of the synthesis. Second, tert-Butyldimethylsilyl chloride

(TBDMSCl) and imidazole were added, and the resulting yield was 84%. Afterwards, in the third stage of the reaction, boron dimethyl sulfide (BH_3Me_2S) and hydrogen peroxide (H_2O_2) are applied. In the fourth phase, Dess±Martin periodinane and methylenetriphenylphosphorane (PPh_3CH-COOEt) are added, resulting in a 72% yield. Diisobutylaluminum hydride (DIBAL) and tetra-n-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) are used to reduce the reaction's bulk in the fifth stage, which yields 80%. In the sixth step, Diethylenetriamine ((2)-DET), Ti(IV)-isopropoxide, tert-butyl hydroperoxide (TBHP), and NaOH are added for sharpless epoxidation, resulting in a 65% yield of the intermediates. The seventh stage is to incorporate TsCl and Py. The eighth step involves treating the reaction with sodium azide (NaN_3) in dimethylformamide (DMF), and the ninth step involves adding Pd/C in ethyl acetate (EtOH), which together yield an impressive 81 percent. There was a 61% yield in the tenth and eleventh steps when (1)-DET, Ti(vi)-isopropoxide, NaOH, p-nitrophenol, diethyl azodicarboxylate (DEAD), and thiamin pyrophosphate (TPP) were used. The process ishandled with sodium methoxide (NaOMe) in step 12, followed by TsCl in step 13 to produce 75% of the intermediates, and finally with NaOMe in DCM to produce 62% of the intermediates. The addition reaction involving t-BuOH and $BF_3O(Et)_2$ is carried out in the 14th step (S. Chandrasekhar 2000).

2.3.3 Material for synthesis 3:

The procedure begins with the addition of hydrogen gas and ten percent palladium on carbon (Pd/C), which is then followed by the addition of acetic acid (CH_3COOH) as the first step reagent for processing the intermediates of 6-fluoro-4-(oxo-4H-chromene-2-carboxylic acid). In second step, ethyl chloroformate (ClCOOEt) and triethylamine (Et_3N) are added as catalysts. After that, sodium borohydride ($NaBH_4$) is added as a reagent to tetrahydrofuran with water (THF-H_2O). Pyridinium chlorochromate (PCC), a selective oxidizing agent, and chloroform

(CH_2Cl_2) are both utilized in the third phase. The addition of sodium hydride (NaH) and trimethylsulfoxonium iodide ($(CH_3)_3S^+I^-$) is the fourth step, which is then followed by the addition of dimethyl sulfoxide (DMSO). After that, NH_2CH_2Ph is added, which is the fifth step. EtOH comes next as the sixth step in the process. At long last, H_2 and 10% Pd-C are put in during the seventh phase (Anon 2018a; Bai and Chen n.d.).

2.3.4 Material for synthesis 4:

$SnCl_2$ is added after the addition of glyme and 2,2-dimethoxypropane in the first step of the process, which converts d-mannitol into functioning intermediate molecules. The reaction is then handled in the second phase by treating it with $NaIO_4$ in CH_2Cl_2 and $NaHCO_3$. The procedure proceeds with the third step, which involves adding pyrrolidine and PhMe to the mixture. In the fourth and fourth-to-last step of the process, 4-toluenesulfonyl chloride (TsCl), pyridine, and dry hydrochloric acid were added. This was followed by the reaction. The inclusion of NH3 and MeOH came next once the fifth step was completed. The incorporation of MeOH represents the sixth and last stage of the process (Wang et al. 2007).

2.3.5 Material for synthesis 5:

The procedure begins with the addition of LDA and THF, and then moves on to the addition of (s)-methyl p-tolyl sulfoxide in the first phase of the process. Following this, the reaction mixture is subjected to a treatment with triethylsilane (Et3SiH) and TMSOTf in CH2Cl2 in the second step. In the third phase of the process, 2,4,6-collidine, trifluoroacetic anhydride(TFAA), acetonitrile (CH3CN), and copper(II) chloride (CuCl2) are dissolved in water. This step allows the process to continue. The subsequent step, which is the addition of methyltriphenylphosphonium (Ph3PCH3Br) and n-butyllithium (nBuLi) in THF, comes immediately after this step. In the fifth stage, the reaction is then subjected to treatment with AD-mix- in an environment consisting of tBuOH and H2O. The next step in the method

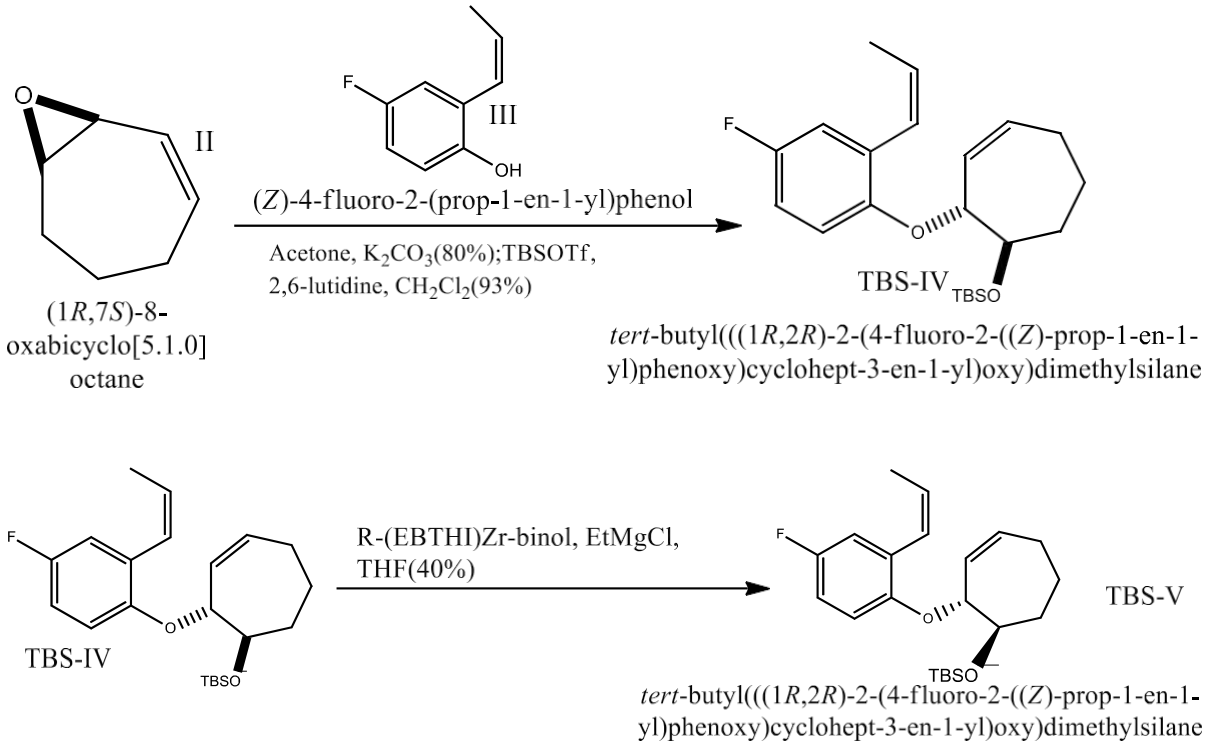
involves treating the reaction mixture with sodium hydride (NaH) that has been dissolved in THF. After that, the procedure goes back and does stages one through three again with lithium di-isopropyl amide (LDA), tetrahydrofuran (THF), triethylsilane (Et_3SiH), TMSOTf, 2,4,6-collidine, TFAA, CH_3CN, and copper chloride in water. The sixth stage of the procedure involves treating the reaction mixture with (R)-methyl-p-tolyl sulfoxide and LDA in THF. The seventh phase of the process involves adding 2,4,6-collidine, trifluoroacetic anhydride (TFAA), methyl cyanide, and copper (II) chloride to water after this step has been completed. The reaction is then treated with sodium hydroxide, bromobutane (BnBr), and tetrabutylammonium iodide (nBu_4NI) in the eighth step. The procedure is then proceeded by treating the reaction mixture with benzylamine and sodium triacetoxyborohydride in 1,2- dichloroethane. The addition of TsCl and pyridine brings the 9th and final step to a close, whichis then immediately followed by the addition of H_2 and Pd/C in ethanol and Hydrochloric acid(Carreño et al. 2008).

2.4 Synthesis Mechanism

2.4.1 Synthesis 1:

In 1998, Hoveyda and his team were successful in carrying out the first enantioselective total synthesis of (I) . A Zr-catalyzed kinetic resolution of cyclic allylic styrenyl ethers was the first significant step in this process. This was followed by their Mo-catalyzed ring-opening and ring-closing metathesis, which were the subsequent significant phases. To our knowledge, this is the very first instance in which nebivolol has been enantioselectively synthesized using total synthesis. A Regio- and stereoselective nucleophilic opening of racemic allylic epoxide (II)

was the first step in their synthesis. This opening was carried out with styrenyl phenol (III) in the presence of TBSOTf, which is utilized in the protection of ketones through the addition of the silyl group to the oxygen atom. In addition to this, 2,6-lutidine is present, which helps to speed up the oxidative cleavage of (II). (Z)-4-fluoro-2-(prop-1-en-1-yl) phenol was utilized to successfully accomplish this (III). Following this step, the newly formed secondary alcohol was subjected to TBS protection, which resulted in the formation of the (TBS-IV) molecule. The last stage was to perform a Zr-catalyzed kinetic resolution of (TBS-IV), which resulted in over 44% yields for the recovery of the starting material (TBS-V). This phase was the final one in the process. The presence of THF, which stabilizes the bromo-Zr complex and reduces the tendency of the complex to produce B-dimer, a gas that is both poisonous and explosive, is responsible for the stabilization of the Zr-catalyst. Through ring-closing metathesis that was catalyzed by molybdenum, the chroman derivative (TBS-VI) was derived from (TBS-V) (figure 2.3). The excited carbonyl compound underwent photochemical intramolecular abstraction of a α-hydrogen (a hydrogen atom three carbon positions away from the carbonyl group) to create the chroman derivative (TBS-VIII).



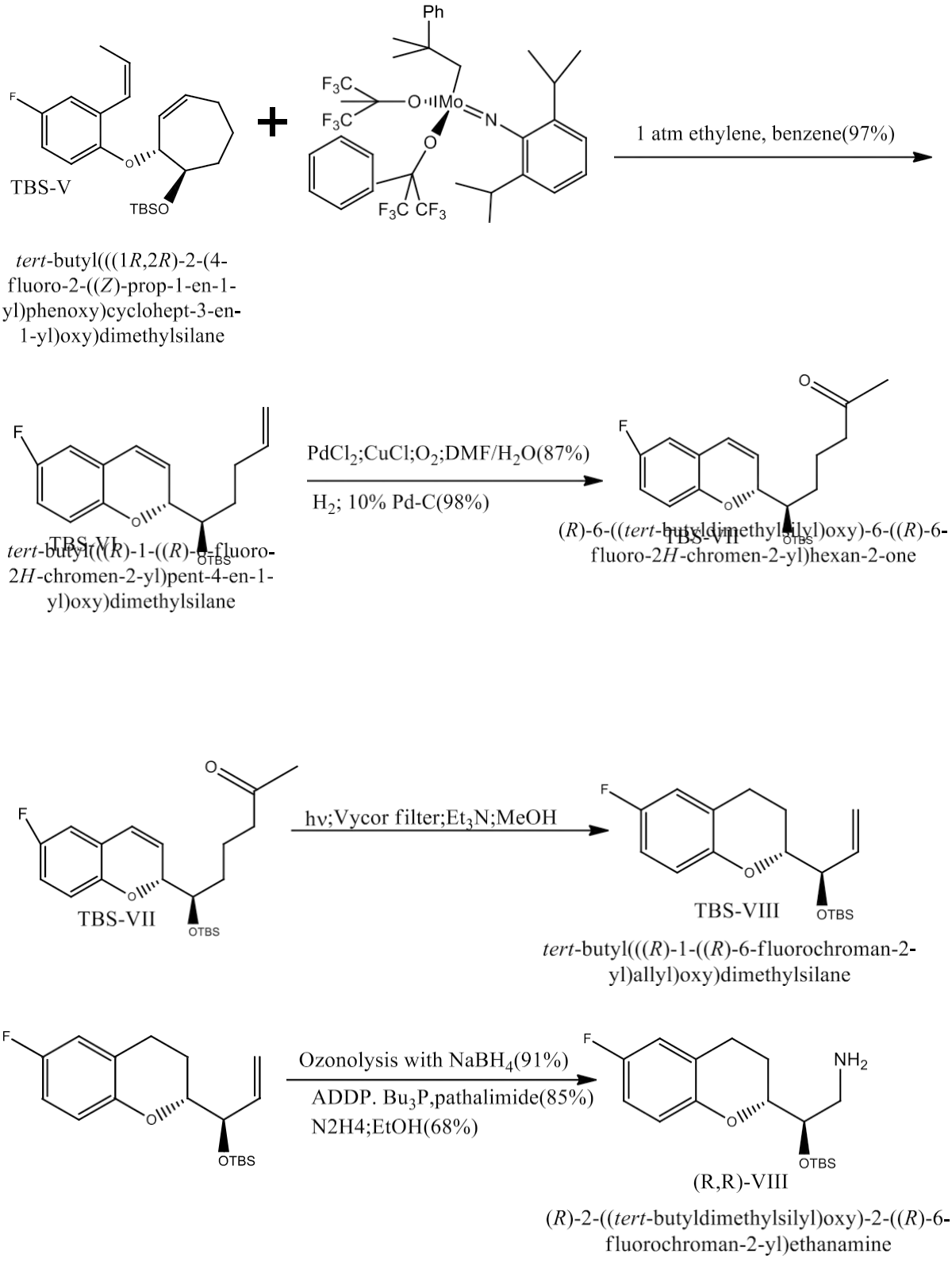


Figure 3: Mechanism for the Synthesis of (R,R)-VIII Chroman with Asymmetric Approach

This led to the production of a 1,4-biradical as a primary photoproduct (Norrish type II cleavage), which was then used to synthesize (VII). We were able to produce the chiral chroman derivative ((R,R)-VIII) by first splitting the olefin (TBS-VIII) with ozone, then reducing it, and finally converting and condensing the primary alcohol according to the Mitsunobu reaction mechanism that was left into a primary amine. This gave us the product we were looking for.(Anon 2018b; Anon n.d.-f, Anon n.d.-k; Johannes et al. 1998)

(TBS-IX) was prepared with high selectivity for both Regio isomers by a syn-selective ring-opening reaction between allylic epoxide (II) and styrenyl phenol (III). Then, using a reaction sequence very similar to that used to synthesize (TBS-VIII), (TBS-IX) was efficiently converted into ((S,R)-XI). Synthesis of the chroman-based aldehyde ((S,S)-XI) from (TBS-X) by ozonolysis. .

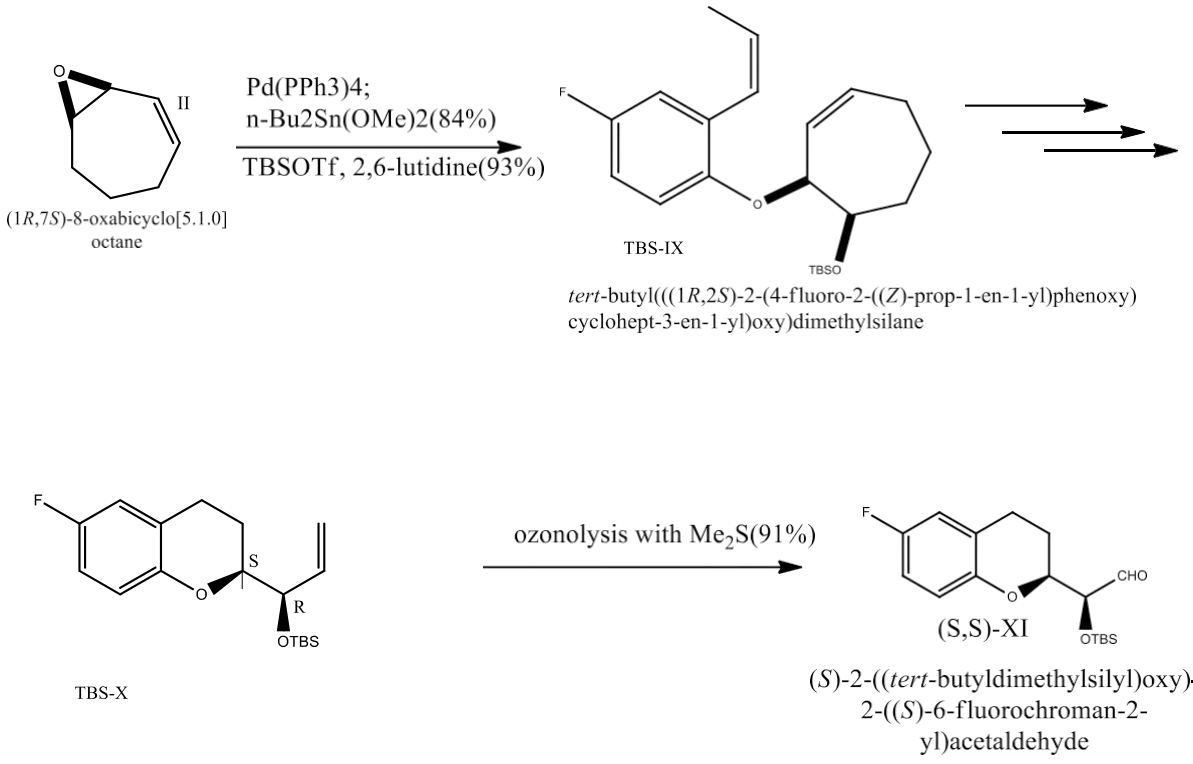


Figure 4: The conversion of the stereo intermediates of (TBS-X) through Ozonolysis for theproduction of ((S,S)-XI), a chroman-based aldehyde

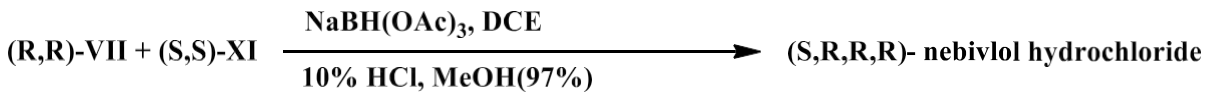


Figure 5: Synthesis of the (S,R,R,R) form of nebivolol using a method involving the utilizationof chiral compounds

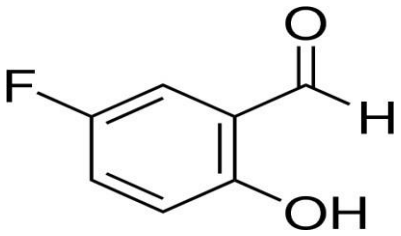
In the end, a reductive amination was utilized in order to unite a ((R,R)-VIII) and a ((S,S)-XI) in order to finish first asymmetric total synthesis of nebivolol. This was done in order to achieve the desired result of producing nebivolol. The synthesis was therefore able to be finished successfully as a result. The two reactions that are depicted in the image that can be found up top significantly contributed to the accomplishment of the entire synthesis, which wassuccessful as a whole as a result. (S,R,R,R)-nebivolol.HCl salt (99% yield for the two-step sequence) was formed as a result of the coupling of (R,R)-VIII and ((S,S)-X) by way of reductive amination (NaBH(OAc)) , which produced 91 percent of the product. After this step, the silyl ether protecting groups were cleaved away using 10% hydrochloric acid and methoxy alcohol. Overall, the two-step procedure had an 99% successful completion rate (Johannes et al. 1998)

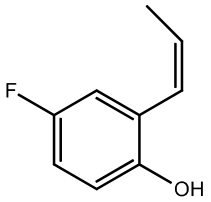
Analysis Of Synthetic Method 1:

This chemical method details the complete synthesis of the antihypertensive drug nebivolol, which was accomplished using a combination of Mo- and Zr-catalyzed chroman production and Zr-catalyzed kinetic resolution of allylic ethers. Regio- and stereoselective opening of a racemic allylic epoxide, followed by protection to generate a secondary alcohol, served as the first step in the synthesis. This secondary alcohol was then subjected to Zr-catalyzed kinetic resolution, which resulted in the formation of a chroman derivative. This chroman derivative was then subjected to ring-closing metathesis catalyzed by molybdenum, resulting in the

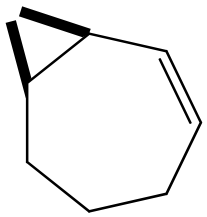
formation of a chiral chroman derivative. The final step involved a reductive amination reaction between this chroman derivative and a chroman-based aldehyde, which resulted in the formation of the desired (I) product. This synthesis highlights the versatility and efficiency of utilizing Zr-catalyzed kinetic resolution and Mo-catalyzed ring-closing metathesis for the synthesis of complex organic molecules, specifically in the pharmaceutical industry. The reaction complies of 9 steps and used a large number of different types of catalyst to yield the intermediates Here we can also see that kinetic resolution of Zr-catalyst have given a significant amount of >98% of intermediate chroman in 2nd step of the reaction. Overall, in 9th step the ozonolysis of Fluro chroman (TBS-VIII) produces 99% yield of desired product (I). The important intermediates for the synthesis and their percentage yield are described below-

Table 1: Important intermediates and their assemblage of synthesis 1:

Molecule	**Structure**	**Percentage yield**
Fluor salicylaldehyde		8.3 g (59 mmol, 22%)
Assemblage: A 30 g solution of 4-fluorophenol in 0.180 L of water was combined with 70.7 g of NaOH, and the combination was then heated to 121 °F. For an additional hour, the reaction was heated to 158 degrees Fahrenheit while chloroform was added drop by drop to a reaction volume of 0.0468L. The liquid was diluted with 0.05L of water, then acidified with 0.02L of strong hydrochloric acid, and then cooled to 71.6°F. The organic layers were rinsed three times with chloroform 50 mL, and then dried with anhydrous magnesium sulfate. After the solvent was extracted under vacuum, a red oil was recovered, and it was further refined using silica gel chromatography (Johannes et al. 1998).		

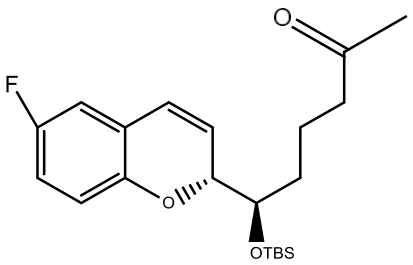
2-Propenyl-4-fluorophenol		1.02 g (6.71 mmol, 94%)

Assemblage: The operation began with the addition of 5.83 grams of ethyl triphenyl phosphonium bromide into 100 milliliters of toluene. This was followed by the addition of 1.76 grams of potassium tert-butoxide (15.7 mmol) into 24 milliliters of tetrahydrofuran at a slow rate. After stirring the resulting red solution at 71.6 degrees Fahrenheit for four hours, the temperature was lowered to -104.8 degrees Fahrenheit, and then 1.0 grams of aromatic aldehyde was added and dissolved in 16 milliliters of toluene. The mixture was then stirred once more. The mixture was then swirled for a further 14 hours as it warmed up to 71.6 degrees Fahrenheit gradually. A saturated NH_4Cl solution was added to the reaction to stop it. The solution was then rinsed with ether and diluted with water. After extracting the solvent from the solution containing the reaction's outcome, the solution was absorbed onto silica gel to create a pale yellow mixture (Johannes et al. 1998).

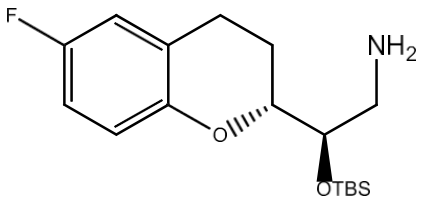
(1R,7S)-8-oxabicyclo[5.1.0] octane		5.9 g (53 mmol, 97%)

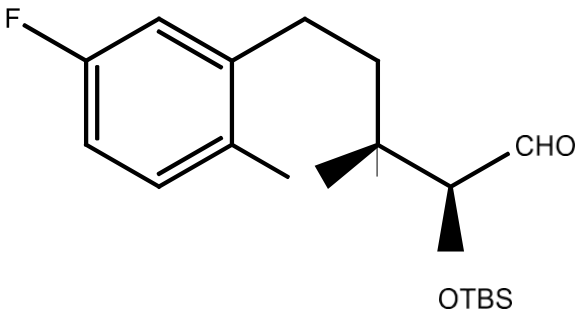
Assemblage: After suspending the two components in 100±10 mL of CH_2Cl_2 and bringing the mixture down to 32 degrees Fahrenheit, the reaction between 5 grams of cycloheptadiene and 23.4 grams of sodium carbonate was carried out. After that, 11.3 milliliters of peracetic acid were added to the mixture slowly while it was being dissolved in 20 milliliters of dichloromethane. After stirring the mixture for 14.5 hours and allowing it to reach a temperature of 71.6 degrees Fahrenheit, the Na_2CO_3 was removed using a filter. After that, the solution that had been produced was diluted with 0.1L of a saturated solution of $Na_2S_2O_3$, and it was washed

three times with parts of 0.75L of CH_2Cl_2 before the organic layers were dried over anhydrous $MgSO_4$ (Johannes et al. 1998).

(R)-6-((tert-butyldimethylsilyl)oxy)-6-((R)-6-fluoro-2H-chromen-2-yl)hexan-2-one		0.22 g (0.60 mmol; 87%)

Assemblage: In the first step, 37 milligrams of $PdCl_2$, 29 milligrams of $CuCl_2$, and 0.25 milliliters of water are combined in 5 milliliters of N, N-dimethylformamide (DMF) while being stirred for an entire hour in an oxygen-rich environment. This mixture acts as the catalyst for the reaction that is going to take place next. After that, benzopyran dissolved in 3.3 mL of DMF was added to the mixture, and the reaction was kept going by stirring it for a total of 12 hours at 71.6 degrees Fahrenheit in an oxygen-rich environment. The process was finally halted when 50 mL of a saturated solution of ammonium chloride was added in a dropwise manner. This helped to neutralize the mixture that was being produced by the reaction. After that, the mixture was diluted with 25 mL of water, and it was washed three times with parts of 50 mL ethyl ether in order to get rid of any chemicals or byproducts that were still present. Following the completion of these steps, a yellow oil was obtained by removing the solvent from the solution and then drying it over anhydrous magnesium sulfate in order to eliminate any remaining water. In the end, the yellow oil was cleaned up by employing the tried-and-true method of silica gel chromatography, which is utilized frequently in the process of organic compound cleaning. In this method, the components of a mixture are separated from one another depending on the relative extent to which they adhere to a stationary phase composed of silica gel. This leads in

the intended product being purified and the removal of any impurities that were present (Johannes et al. 1998)		
(R)-2-((tert-butyldimethylsilyl)oxy)-2-((R)-6-fluorochroman-2-yl)ethanamine		16 mg (0.05 mmol, 74%)
Assemblage: The first thing that must be done is to put thirty milligrams (0.066 millimoles) of a protected amine-phthalimide into a reaction flask with a cold finger, which is a device that is used to keep the temperature at a constant low. After that, the chemical is diluted in 0.66 mL of ethanol and combined with a little quantity of hydrogen peroxide, which serves as the reducing agent in this procedure. The reaction flask is then put into an oil bath that is heated to 75 degrees Celsius and agitated continuously for a period of six hours. This makes it possible for the reaction to take place, which results in the formation of a white solid. After that, the solvent is extracted using a vacuum, and the solid is subsequently purified by passing it through a Celite plug, which is a specific kind of filter, and then eluting it with chloroform. In the end, the residual transparent oil residue is chromatographically separated using silica gel chromatography, a method that separates various components depending on the physical and chemical properties of the components themselves. Following all of these procedures should result in the synthesis of a pure product that may then be put to use or analyzed further (Johannes et al. 1998).		

(S)-2-((tert-butyldimethylsilyl)oxy)-2-((S)-6-fluorochroman-2-yl)acetaldehyde		44.3mg (0.12 mmol, 44%)
Assemblage: In the first stage, a specified amount of racemic phenyl ether is dissolved in THF, which is a solvent. This is the beginning of the process. The combination is next subjected to the addition of a solution comprising ethylmagnesiumchloride and THF. After that, an additional reagent called (S)-(EBTHI) Zr-binol is added to the mixture, and the reaction vessel is fitted with a reflux condenser before being heated in an oil bath to 158 degrees Fahrenheit for an hour and a half. After the solution has been cooled to 32 degrees Fahrenheit, the reaction is halted by adding wet ether, water, and a solution of 2 millimeters hydrogen chloride. After that, the solution is purified by going through a series of washes with ethyl ether, and anhydrous magnesium sulfate is used to dry the organic layer once it has been separated. In the final step, the volatiles are extracted using a vacuum to generate a yellow oil, which is subsequently refined using silica gel chromatography (Johannes et al. 1998).		

In this part of the process, we can see that methanol, also known as MeOH, is utilized at multiple stages of the reaction. Throughout the process, many catalysts, including TBSOTf, 2,6-lutidine, Zr-binol complex, molybdenum complex, palladium chloride, ADDP, benzene, and N2H4, are utilized. TBSOTf is a flammable liquid that has dangerous properties, such as the ability to cause severe skin burns and corrosion of the skin as well as harm to the eyes. Because there is no data regarding the substance's toxicity, it is unclear which class of TBSOTf was utilized in the synthesis. However, it should be handled with care and the appropriate protective gear at all times (Sigma-Aldrich 2021).

Ingestion of 2,6-lutidine is not only dangerous but also dangerous since it is a combustible liquid and vapor. It is moderately hazardous, with an oral LD50 of 400 mg/kg and an inhalation LD50 of 33.42 mg/l, and it irritates the skin as well as the eyes very severely. In this reaction, 2,6-lutidine is employed as an analytical standard; however, in industry, 98% of this component is utilized so that the reaction can be carried out more successfully (Anon 2020).

The acute oral toxicity of palladium complex is estimated to be between 500 and 1 mg/kg, although there are no data available about its inhalation toxicity (sigma-aldrich 2022). It does not aggravate the condition of the skin. ADDP has a moderate propensity to irritate both the skin and the eyes, although there is currently no information available regarding its toxicity. Caution is required when working with it (Iwabuchi 2013).

In this particular reaction, N_2H_4 is the catalyst that poses the greatest risk. It is a combustible liquid that has a high risk of catching fire quickly and has the capacity to catch fire readily. Additionally, it has a significant potential for acute toxicity when exposed to it orally, topically, or by inhalation; this can cause skin corrosion, damage to the eyes, skin sensitization, and harm to aquatic life. Because of N_2H_4's potential toxicity, which has been calculated to have an oral LD50 of 262 mg/kg and an inhalation LC50 of 0.76 mg/l, only trained specialists should handle the compound (Ketchen and Porter n.d.).

Benzene is also used in this reaction, and it possesses dangerous properties such as a moderate potential to ignite and cause skin and eye irritation, a high potential to cause genetic mutations and cancer, damage to the respiratory system, aspiration toxicity, and an acute toxicity of LD50 greater than 2,000 mg/kg oral. In addition, it has a moderate potential to ignite and cause skin and eye irritation (Choi et al. 2019).

2.4.2 synthesis 2:

According to the findings of Chandrasekhar's research team, the chromans (2) and (3) would unite through the nucleophilic opening of epoxide (3) and amine (2). The chromans (2) and (3) might be derived from an appropriate allyl alcohol 9a by means of a one-pot Sharpless asymmetric epoxidation (SAE) involving ring closure. The Claisen rearrangement of the required allylic ether (5) was utilized to produce allyl alcohol, which was then employed to produce allyl chloride (S. Chandrasekhar 2000).

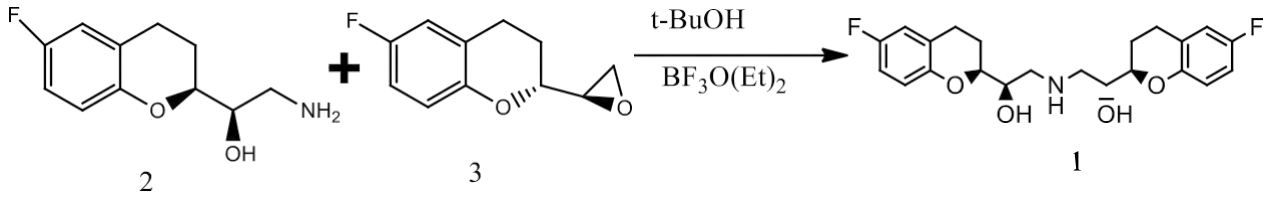


Figure 6: (S,R,R,R)-nebivolol synthesis. The final step of one-pot SAE (1)

The synthesis began with p-fluorophenol 4, which could be purchased, and continued with the manufacture of O-allyl ether 5 through the treatment of acetone, K2CO3, and allyl bromide in a reflux environment. This was done in order to achieve the desired end product. In order to

complete the Claisen rearrangement, O-allyl ether 5 was necessary.

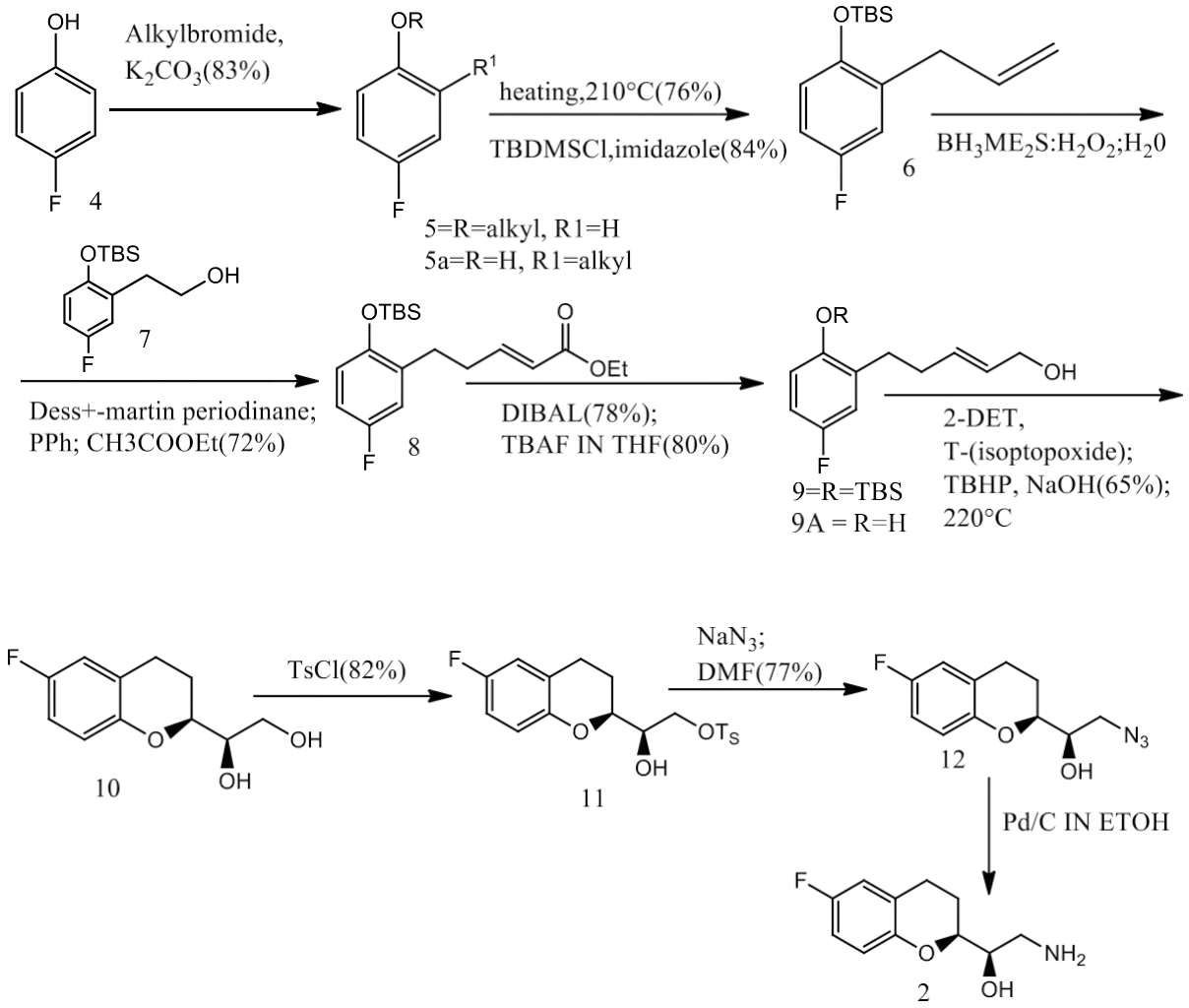


Figure 7:The Production of (R)-2-amino-1-((S)-6-fluorochroman-2-yl)ethanol (2), anintermediate product by one pot SAE (S. Chandrasekhar 2000).

After being heated, O-allyl ether (5) underwent a rearrangement that resulted in the synthesis of 2-allyl-4-fluoro phenol (5a). This was the product of the reaction. The preservation of the phenol group 6 was achieved by using TBDMS-Cl and imidazole as the two active ingredients. Compound (6) ($BH_3.Me_2S$) was hydroborated, and then it was treated with hydrogen peroxide (H_2O_2), which resulted in the formation of primary alcohol (7). This primary alcohol (7) was then subjected to one-pot oxidation with Dess-Martin periodinane and Wittig olefination with ethyltriphenylphosporane, which resulted in the formation of alpha, beta-unsaturated ester The reduction of ester (8) by DIBAL-H resulted in the synthesis of the matching alcohol, which

was subsequently desilylated (with TBAF) in order to make allyl alcohol (9a), which preparedthe path for Sharpless asymmetric epoxidation. The two requisite chromans (10), and (13) were generated from (9a)a in "one pot" after being treated with (-)-DET and (+)-DET, respectively, and then being worked up with sodium hydroxide. (7) Chroman (10), when subjected to a treatment in dimethylformamide (DMF) involving first tosylchloride and subsequently sodium nitrate, formed azido alcohol (12). The synthesis of the left segment of nebivolol was completed by reducing the azide to the amine (2) that corresponds to it. This operation completed the reaction and brought it full circle. In a way analogous to this, chroman (13) wassubjected to the Mitsunobu conditions (p-NO2C6H4COOH, TPP, and DEAD), which resulted in the formation of benzoate derivative 14 with an inversion at (C2). The standard deprotectionof di-PNB ester 14 (NaOMe, MeOH) results in the synthesis of diol (15), monotosylation results in the formation of (16)

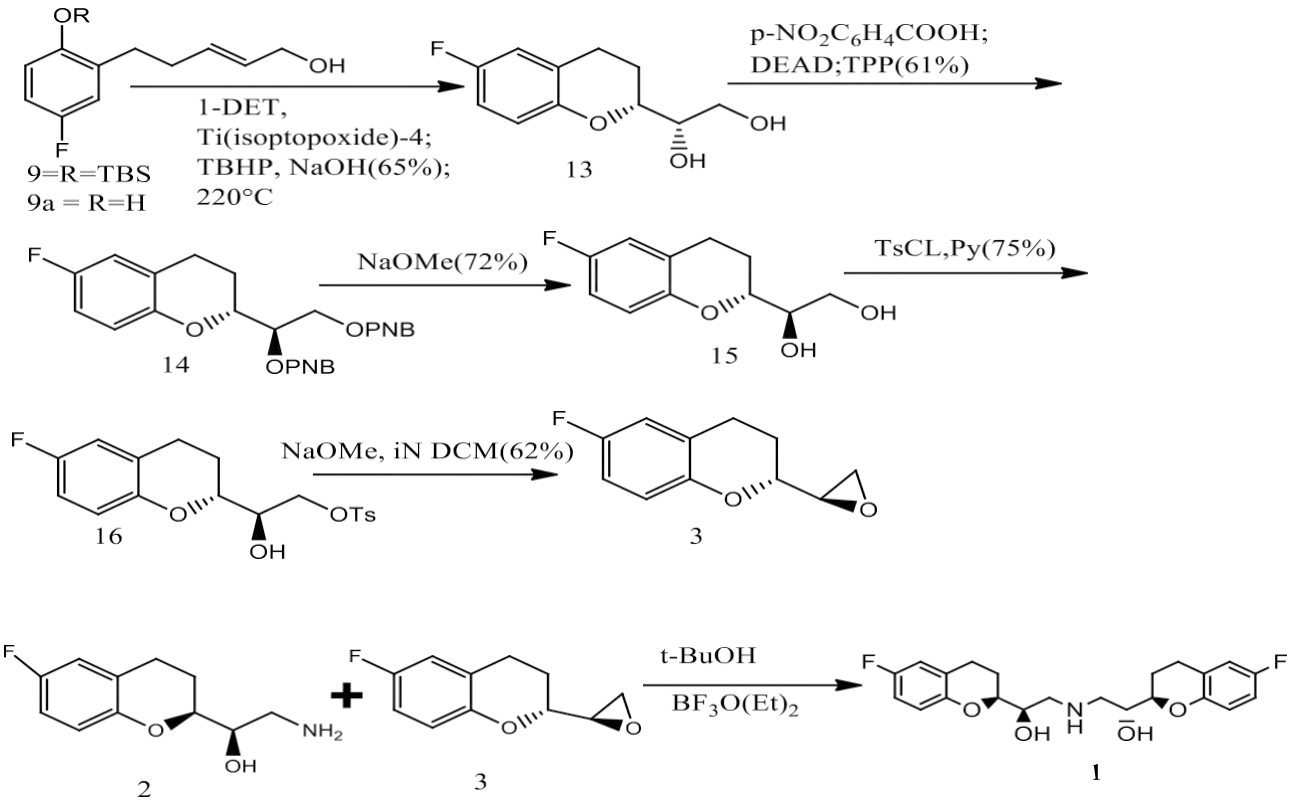


Figure 8: The mechanism of synthesizing the chroman intermediates of (R)-6-fluoro-2-((R)-oxiran-2-yl)chroman (3) and its core synthesis (S. Chandrasekhar 2000).

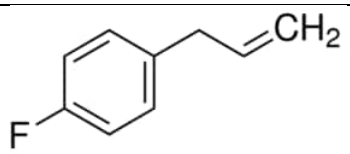
and formation of epoxide (3) via base (NaOMe, Dichloromethane) After performing the nucleophilic opening of epoxide (3) with hydroxy amine (2), which was required for the coupling of the two fragments, the entire synthesis of (1) was completed by derivatizing the product as the hydrochloride salt. The results that have been published for (1) are totally in line with the measurements that have been made of its spectrum. The chiral chroman, the Claisen rearrangement, and a one-pot reaction are produced via an intramolecular epoxide opening in conjunction with an internal phenoxide anion. The most important steps in this synthesis are called Sharpless asymmetric epoxidation (Anon n.d.-f; S. Chandrasekhar 2000)

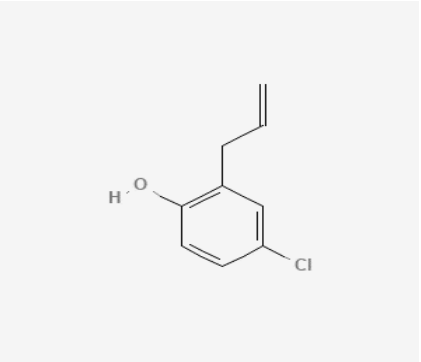
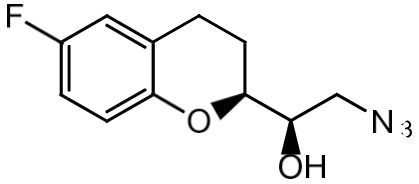
Analysis of synthetic method 2:

A chemical synthesis of the molecule (1) is described in the text. The synthesis begins with p-fluorophenol as the starting point. There are a total of 14 stages involved in the process, and many stages deserve special attention. One such stage is the Claisen rearrangement of (5), which results in the production of (5a). The yield of the rearrangement reaction is approximately 43%. The hydroboration of primary alcohol with boron dimethyl sulfide and the oxidation of primary alcohol (7) with Dess Martin periodinane and methylenetriphenylphosphorane to generate alpha, beta-unsaturated ester (E)-ethyl 5-(2-(tert-butyldimethyl the reduction of ester 8 with diisobutylaluminum hydride to make the allyl alcohol (9a), followed by the Sharpless asymmetric epoxidation of (9a) to generate the chromans (R)-1-((S)-6-fluorochroman-2-y. The synthesis continues with the generation of azido alcohol (R)-2-azido-1-((S)-6-fluorochroman-2-yl) ethanol (12) from chroman 10, followed by the formation of diol (R)-1-((R)-6-fluorochroman-2-yl) ethane-1,2-diol (15) from chroman (13). In the presence of TsCl, chroman (15) was transformed into chroman (16), which

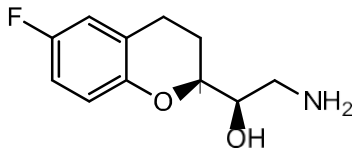
resulted in an approximate 75% increase in the yield of intermediates. The completion of the synthesis of compound (1) occurs as a result of the nucleophilic opening of epoxide (3) with hydroxy amine (2), which results in the compound being derivatized as the hydrochloride salt. The researchers who carried out this study point out that the outcomes of the synthesis are consistent with the spectral analyses that were performed on the chemical.

Table 2: Important intermediates and their assemblage of synthesis 2:

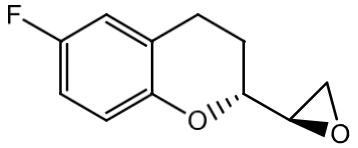
Molecule	**Structure**	**Percentage yield**
1-Allyloxy-4-fluoro-benzene		(34 g, 83%)
Assemblage: The synthesis of allyl phenyl ether of 1-allyloxy-4-fluorobenzene started with the addition of p-fluorophenol in the amount of 30 grams, anhydrous potassium carbonate in the amount of 64.6 grams, and allyl bromide in the amount of 38.8 grams to a solution of acetone that was 250 milliliters in volume. After heating the combination and allowing it to reflux for a total of 8 hours, it was subsequently cooled to room temperature before being poured into 0.5 liters of cold water. Following the extraction of the aqueous layer with three portions of ether, the mixed organic layers were washed with 0.1 liters of a solution containing sodium hydroxide at a concentration of 2 M and then dried with anhydrous potassium carbonate. In the end, the solvents were extracted using a vacuum, resulting in the completion of the product (S. Chandrasekhar 2000)		

2-Allyl-4-fluoro-phenol		(19 g, 76%)
Assemblage: In order to produce 2-allyl phenol, 25 grams of 1-allyloxy-4-fluorobenzene were subjected to a six-hour heating process at 410 degrees Fahrenheit. After observing the reaction with TLC, the mixture was allowed to cool, and then it was dissolved in 0.1 liter of a solution containing sodium hydroxide. The mixture was extracted using two different proportions of light petroleum ether in order to get rid of trace amounts of the by-product 2-methyl dihydrobenzofuran. After that, the aqueous solution was made more acidic by adding 2M hydrochloric acid while it was being cooled, and the aqueous layer was then extracted with ether and dried over sodium sulfate. In the end, the volatiles were extracted under lower pressure, which resulted in the production of allyl phenol (S. Chandrasekhar 2000)		
(R)-2-azido-1-((S)-6-fluorochroman-2-yl) ethanol		(1.7 g, 82%)
Assemblage: A solution of 6-Fluoro-2-[1-hydroxy-2-(4-methylphenylsulfonyloxy)- (1R)-ethyl] -(2S)-3H,4H-chromene After stirring for ten hours at 176 degrees Fahrenheit, 1.25 grams of sodium azide was combined with 1.05 grams of sodium azide in dry N,N-dimethylformamide. After bringing the mixture down to room temperature, it was further diluted with twenty milliliters of water. After this, two sections of 0.05 liters of ether were used to extract the substance. The		

solution was then washed with 0.25 liters of water and 0.25 liters of brine before being dried with sodium hydroxide and concentrated. The end product of azide was obtained after the crude product was subjected to column chromatography in which hexane and ethyl acetate were used as solvents (S. Chandrasekhar 2000).

(R)-2-amino-1-((S)-6-fluorochroman-2-yl) ethanol		(0.155 g, 75% yield);

Assemblage: he synthesis of (R)-2-amino-1-((S)-6-fluorochroman-2-yl) ethanol salt is discussed in the book. This reaction is carried out by reducing 2-Azido-1-[6-fluoro-(2S)-3H,4H-2-chromenyl]. -(1R)-ethan-1-ol in a solution of dry methanol by employing a catalyst composed of 10% platinum and charcoal and utilizing hydrogen gas as the reducing agent. In order to obtain the desired chemical with a yield of 81%, the reaction was agitated for a total of eight hours, and the resultant mixture was filtered and concentrated while being subjected to a vacuum. After that, the chemical was treated with dry HCl gas while it was dissolved in dry ether in order to produce its hydrochloride salt (S. Chandrasekhar 2000).

(R)-6-fluoro-2-((R)-oxiran-2-yl) chroman	 .	(0.165 g, 62%)

Assemblage: 0.5 grams of (R)-2-((R)-6-fluorochroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate was dissolved in 0.02 liters of CH2Cl2 and then combined with 0.144 grams of sodium methoxide that had been recently synthesized. After that, the mixture was mixed continuously for a period of six hours at room temperature. After that, the reaction was stopped by adding a solution of saturated ammonium chloride, and the organic layer was washed with water and brine before being extracted with 50 mL of CH2Cl2. In order to obtain (R)-6-fluoro-2-

((R)-oxiran-2-yl) chroman, the solvent was first extracted under low pressure, and then the crude product was refined using column chromatography using a mixture of 95:5 hexane and ethyl acetate (S. Chandrasekhar 2000).

Alkyl bromide have been utilized in the Claisen Rearrangement process. This material is a flammable liquid, it is toxic and skin corrosive qualities, it can damage eye and can inflict permanent damage to the eye, it is also harmful for aquatic life, and it is a compound that has a higher potential for causing harm. Acute toxicity estimation Oral - 200 mg/kg Acute toxicity estimation Inhalation for four hours yielded a concentration of 2.41 mg/l, indicating that it is a very dangerous substance. Therefore, the safety protocol must to be adhered to with extreme caution and care (Zanganeh et al. 2018). Following that, Dess-Martin periodinane was utilized so that the primary alcohol could be oxidized. It has a low hazardous potential but can induce eye irritation and skin irritation following exposure for a short length of time. However, it also has a moderate hazardous potential and has the potential to cause damage to certain target organs after a single exposure (Hessam et al. n.d.). Ester reduction has been accomplished through the utilization of diisobutylaluminum hydride. According to the safety data sheet, diisobytylaluminum hydride is combustible (Pyr. Liq. 1), can react with water (Water-react 1), is a skin irritant (Skin Corr. 1B), and is harmful to the eyes (Eye Dam. 1) Additionally, it may cause skin damage if it comes into contact with the skin, is hazardous if it is breathed in, and is harmful to the eyes (Lu and Ralph 1998). Diethylenetriamine ((2)-DET), tert-butyl hydroperoxide (TBHP), and titanium (IV)-isopropoxide (Ti(IV)-isopropoxide) have been utilized in the Sharpless epoxidation procedure. In this instance, Diethylenetriamine ((2)-DET) has a skin corrosion rating of 1B, an acute toxicity level of 4 (extremely toxic), an acute toxicity level of 2 (moderately toxic), and an acute toxicity level of 1 (very toxic). In addition to that, it has the potential to irritate the skin and create major health problems if it is breathed in (STOT

SE 3). The substance is harmful to one's health and comes with a variety of warning labels, some of which are as follows: H302- harmful if swallowed; H330- fatal if inhaled; H312- harmful in contact with the skin; H314- causes severe skin burns and eye damage; H318- causes severe eye damage; H317- causes an allergic skin reaction; H335- causes respiratory irritation. After four hours of inhalation, the estimated concentration of the chemical in the air is 0.51 mg/l when it is in the form of vapor. The estimated lethal dose (LD50) of the substance when it is consumed by rats is 1.080 mg/kg (Laird 2004). Diethyl azodicarboxylate has been utilized as the primary catalyst in the manufacture of azaide alcohol. On the scale that rates how flammable a material is, the substance that has the label "Flam. Liq. 2" is a flammable liquid with a rating of 2. In addition, it has a rating of 2 for both the irritation of the skin and the toxicity to reproductive systems. It is categorized as both STOT RE 2 and STOT SE 3, which stands for "specific target organ toxicity - single exposure" (specific target organ toxicity - repeated exposure). It has a toxicity rating of 1 for inhalation and a grade of 3 for chronic toxicity in aquatic environments. H225 (very flammable liquid and vapor), H315 (skin irritant), H361d (possibly detrimental to fertility or the unborn child), H336 (may cause drowsiness or dizziness), H373 (may cause organ damage through prolonged or repeated exposure), H304 (may be lethal if eaten and enters airways), and H412 are all hazard codes associated with the material (harmful to aquatic life with long-lasting effects). The maximum allowable concentration of this chemical, according to STOT SE 3 and H336, is 20%. Oral administration results LD50 of 5.580 mg/kg, which is the median lethal dose (Iwabuchi 2013).

2.4.3 synthesis 3:

In the course of our most recent synthesis, (1) was produced via a coupling reaction involving two different segments. These segments were epoxide (21) and hydroxy amine (22). Epoxide (23) was created by performing a nucleophilic opening on benzylamine. As illustrated in the image, the essential epoxide (21) was generated from the aldehyde (20) by reacting it with the

necessary amount of sulfur ylide. In the process described in the patent EP334429, the essential intermediate (21) was made by starting with the appropriate acid (18) and subjecting it to extremely severe (unusual) processing conditions. To make the procedure

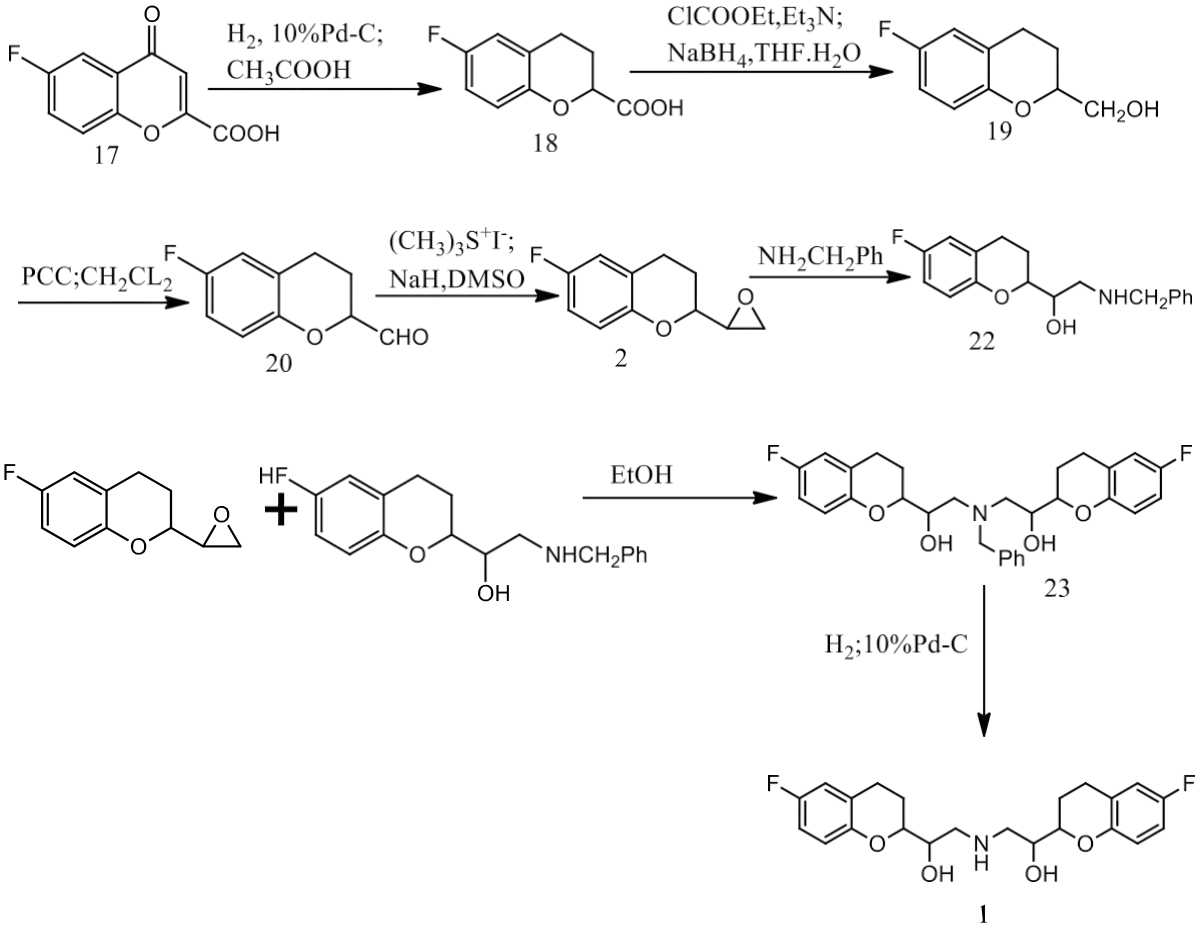


Figure 9: Synthesis of (1): A Mild Approach to Producing the (S,R,R,R) Isomer of 2,2'- azanediylbis(1-(6-fluorochroman-2-yl)ethanol)(Bai and Chen n.d.)

outlined in EP334429 more effective, we looked for a technique that was both straightforward and applicable in industrial settings (Anon 2009). The alcohol (19), which was produced by reducing the mixed anhydride of (17) with $NaBH_4$ to achieve a high yield of 90%, was selected by us as the product that piqued our curiosity because of its production method. A typical oxidation of the alcohol (18) using PCC and additives produced the aldehyde (20) with a 78% yield; both steps were performed at room temperature and normal pressure for an overall yield of 67%, which is more than that of the method described in EP334429 (58%). The epoxidation

of the double bond, which was produced by the Wittig reaction of (5), is the conventional technique for producing the oxirane (21) from the corresponding aldehyde. This reaction was carried out by the Wittig group (20) (Anon 2009; Bai and Chen n.d.; Wang et al. 2007).

This action is taken in order to obtain the product that is wanted. In contrast to the trimethylsulfoxonium iodide used in EP334429, we discovered that a far higher quantitative yield of product (21) was achieved by using the direct epoxidation reagent trimethylsulfonium iodide. Overall yield was increased by 33% due to the majority of reactions being performed at ambient temperature and normal pressure. In conclusion, we have been successful in establishing a new approach for the synthesis of (1) by employing efficient synthetic processes. This was accomplished through the course of our research (Bai and Chen n.d.).

Analysis of synthesis 3:

This article details the process of synthesis for the chemical (1), which is generated by joining together two distinct segments. A nucleophilic reaction was used to open benzylamine, which resulted in the formation of the first segment, epoxide (21). This intermediate was generated from acid (18) using the initial method described in patent EP334429. The processing conditions at that time were extremely harsh. On the other hand, the authors of this work attempted to establish a method that was both more effective and more applicable by making use of the alcohol (19) that was formed through the reduction of mixed anhydride (17) with NaBH4 (Anon n.d.-i). Bromide of sodium has potentially dangerous properties, such as the fact that it has a low reactivity with water. It produces severe burns to the skin as well as damage to the eyes and has an acute toxicity level of three. Additionally, it is hazardous to reproduction and poses a potential risk to the health of the unborn child. If the chemical is allowed to come into contact with air, it will spontaneously catch fire and will be toxic if it is ingested. The concentration limit for this drug is more than or equal to 34%, and it may cause damage to fertility in addition to having an acute toxicity estimate of 162 mg/kg when taken orally.

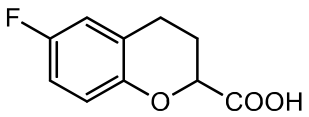
Though Taking this strategy led to a higher yield of aldehyde (20), reaching up to 78%; nonetheless, extreme caution is required when working with this material. It is also possible to produce a high yield through the oxidation of the alcohol (18) with the help of PCC and additions. PCC is a harmful oxidizer, and its hazard profile suggests that it behaves similarly to an oxidizing solid, earning a grade of two on the scale that rates oxidizing characteristics. It can cause sensitization of the skin and has the potential to cause cancer in humans. This substance has a rating of one for both its acute and chronic toxicity to aquatic life. It also has the potential to start a fire or an explosion, may provoke an allergic reaction on the skin, and may lead to cancer. Additionally, it is extremely toxic to aquatic life and its effects are long-lasting. Therefore, all of the precautionary measures should be taken either after use or while it is being used (Luzzio and Guziec 1988).

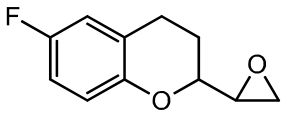
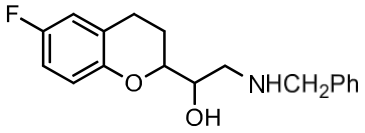
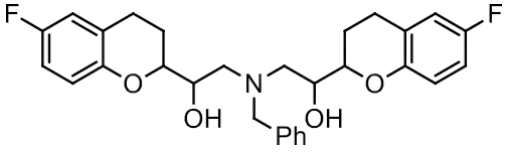
After that, the authors utilized a typical Wittig reaction in order to convert the aldehyde (20) into the desired product, the epoxide (21). The Wittig group (20) was used to carry out this reaction since, according to the basic mechanism, the Wittig group is the one responsible for converting the carbonyl group into alkenes. The Wittig group is composed of dimethyl sulfoxide, sodium hydride (NaH), trimethylsulfoxonium iodide ($(CH_3)_3S+I$), and then sodium hydride again. In the process of organic synthesis, sodium hydride is a chemical that is solid and very reactive. It is also combustible. This substance has the hazard codes H228 (flammable solid), H260 (in contact with water releases flammable gases), H290 (may be corrosive to metals), H314 (causes severe skin burns and eye damage), and H318. H228 describes the substance as being flammable while H260 describes how it releases flammable gases when it comes into contact with water (causes serious eye damage) (Anon n.d.-h). They discovered that a direct epoxidation reagent called trimethylsulfonium iodide, which has an acute toxicity estimate of oral 2,500 mg/kg, generated a better yield of the product 21 (100%) in comparison

to the approach described in EP334429, which employed trimethylsulfoxonium iodide (selker & Kemp, n.d.)

The vast majority of the reactions in the synthesis of (1) were carried out under mild circumstances, at room temperature and under standard pressure, which contributed to an increase in the total yield of the compound. The authors came to the conclusion that they had been successful in developing a new method that was both more effective and more straightforward for the synthesis of (1). In this reaction, the frequent use of 10% Pd-C and H_2 rather than MeOH and EtOH makes the reaction much more efficient, and the total number of steps is reduced to seven.

Table 3: Important intermediates and their assemblage of synthesis 3:

Molecule	**Structure**	**Percentage yield**
6-fluorochroman-2-carboxylic acid		8.1 g (86%)
Assemblage: The palladium-on-charcoal catalyst at a 10% concentration was added to a solution containing 0.1 liter of acetic acid and 10 grams of 6-fluoro-4-oxo-4H-chromene-2-carboxylic acid. After placing the mixture in an autoclave, it was subjected to hydrogenation at a pressure of 2 MPa and a temperature ranging from 158-176 degrees Fahrenheit. After the required quantity of hydrogen had been taken up, the catalyst was strained out, and the solution that was left behind was put into cold water, which resulted in the formation of a white solid. The unrefined product was filtered, recrystallized from toluene, and dried under vacuum at 158 degrees Fahrenheit, which resulted in the production of 8.1 grams of colorless 6-fluorochroman-2-carboxylic acid (Bai and Chen n.d.).		

6-fluoro-2-(oxiran-2-yl) chroman		1.06g (100%)
Assemblage: A mixture that was chilled in an ice-salt bath consisted of 0.2 grams of sodium hydride that was suspended in 0.005 liters of dimethyl sulfoxide. While stirring, a solution of trimethylsulfonium iodide containing 1.2 grams dissolved in 0.001 liters of DMSO was added bit by bit over the course of a half an hour. After another twenty minutes of stirring, the concoction was finally finished. A solution of 6-fluorochroman-2-carbaldehyde 1.0 g in DMSO 5 ml was added dropwise to the mixture and agitated for an additional hour. The mixture was then given time to reach room temperature. The reaction mixture was then put into cold water, the product was extracted with hexane, washed three times with water, dried, and filtered, and the solvents were then evaporated (Bai and Chen n.d.).		
2-(benzylamino)-1-(6-fluorochroman-2-yl) ethanol		0.71 g (92%)
Assemblage: At room temperature, a mixture of 0.5 grams of 6-fluoro-2-(oxiran-2-yl)chroman, 1.67 grams of benzenemethanamine, and 10 milliliters of methanol was swirled throughout the entirety of one night. After that, the reaction mixture was sent through a rotary evaporator in order to be evaporated and concentrated. In order to get 92 percent of the product, which was a white solid, the residue was first diluted with 25 milliliters of hexane, and then the precipitated product was filtered, crystallized from ethanol, and dried (Bai and Chen n.d.).		
2,2'-(benzylazanediyl)bis(1-(6-fluorochroman-2-yl)ethanol)		0.69 g (82%)
Assemblage: At normal temperature, a mixture containing 0.5 grams of 2-(benzylamino)-1-(6-fluorochroman-2-yl) ethanol, 1.67 grams of benzenemethanamine, and 0.001 liters of methanol was swirled continuously for an entire night. After that, the reaction mixture was sent through		

a rotary evaporator in order to be evaporated and concentrated. The residue was diluted with 0.025 liters of hexane, and the product that precipitated was filtered, crystallized from ethanol, and dried so that 82% of the product, which was a white solid, could be obtained (Anon 2009; Bai and Chen n.d.).

2.4.4 synthesis 4:

The chirality of (1) was obtained from (24), which can be easily produced from D-mannitol using chiral pool synthesis. Chiral pool synthesis refers to a collection of molecules that are enantiomerically pure and are found in nature. Wang and his team synthesized (S Here, the production of both enantiomers of (24) is facilitated by natural D-sugar mannitol (Agustian, Kamaruddin, and Bhatia 2010; Wang et al. 2007).

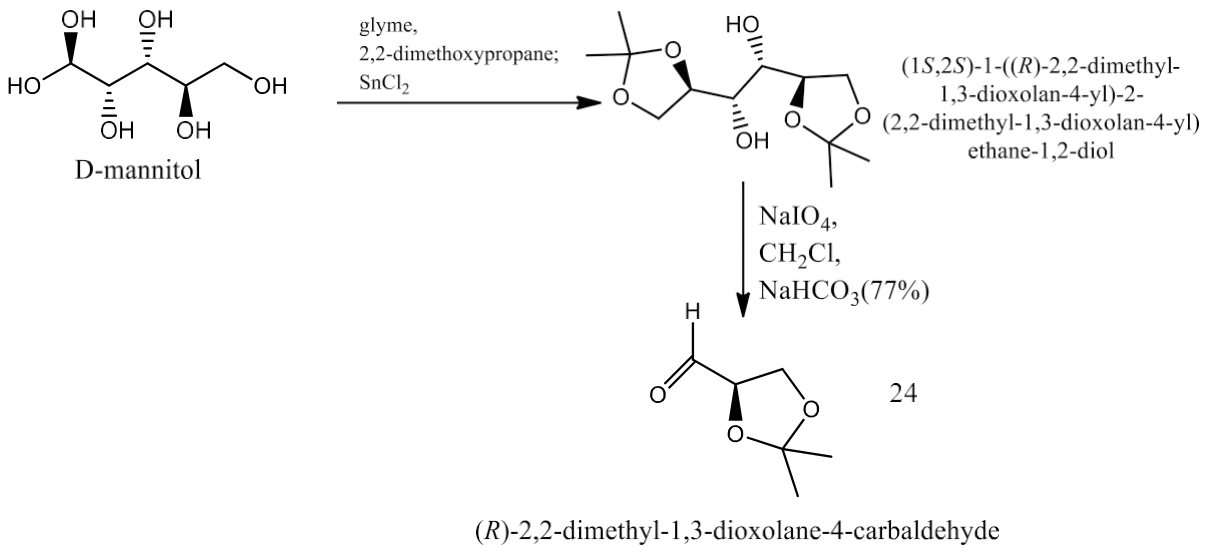


Figure 10: 2,3-isopropylideneglyceraldehyde (24) formation from d-mannitol(Agustian et al. 2010)

Using pyrrole as a catalyst, the Kabbe reactions of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (24) and (25) yielded the major building components about 60proportion to 40

diastereomeric mixture of chromanones (S,R)-26 and (R,R)-27 with a 40% yield (Wang et al. 2007).

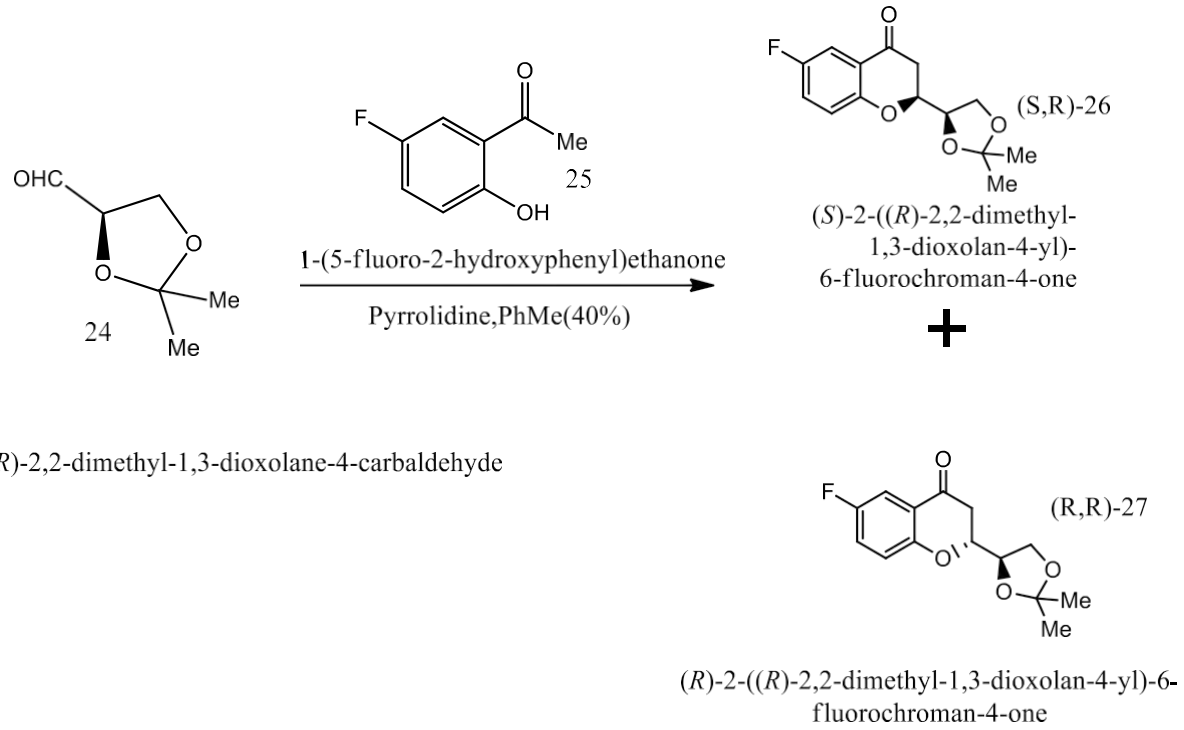


Figure 11: kabbe reaction procedure for ((R,R)-27, ((S,R)-26) production from (R)-2,2- dimethyl-1,3-dioxolane-4-carbaldehyde (24) and 1-(5-fluro-2-hydroxyphenyl)ethanone (25)

Subsequently, using zinc powder in HCl and Clemmensen reduction to create (S,R)-28 and (R,R)-29, respectively, the diols that correspond to (S,R)-26 and (R,R)-27 were created. These compounds were then tosylated. Ammonia was the catalyst for the transformation of (S,R)-28 into (S,R)-30, the amino alcohol. In the end, the required molecule of (1) was synthesized by N-alkylating (S,R)-30 with tosylate (R,R)-29. This process took a very long time. The synthesis of this kind, however, is not only economical but also does not imply any kind of industrial use.

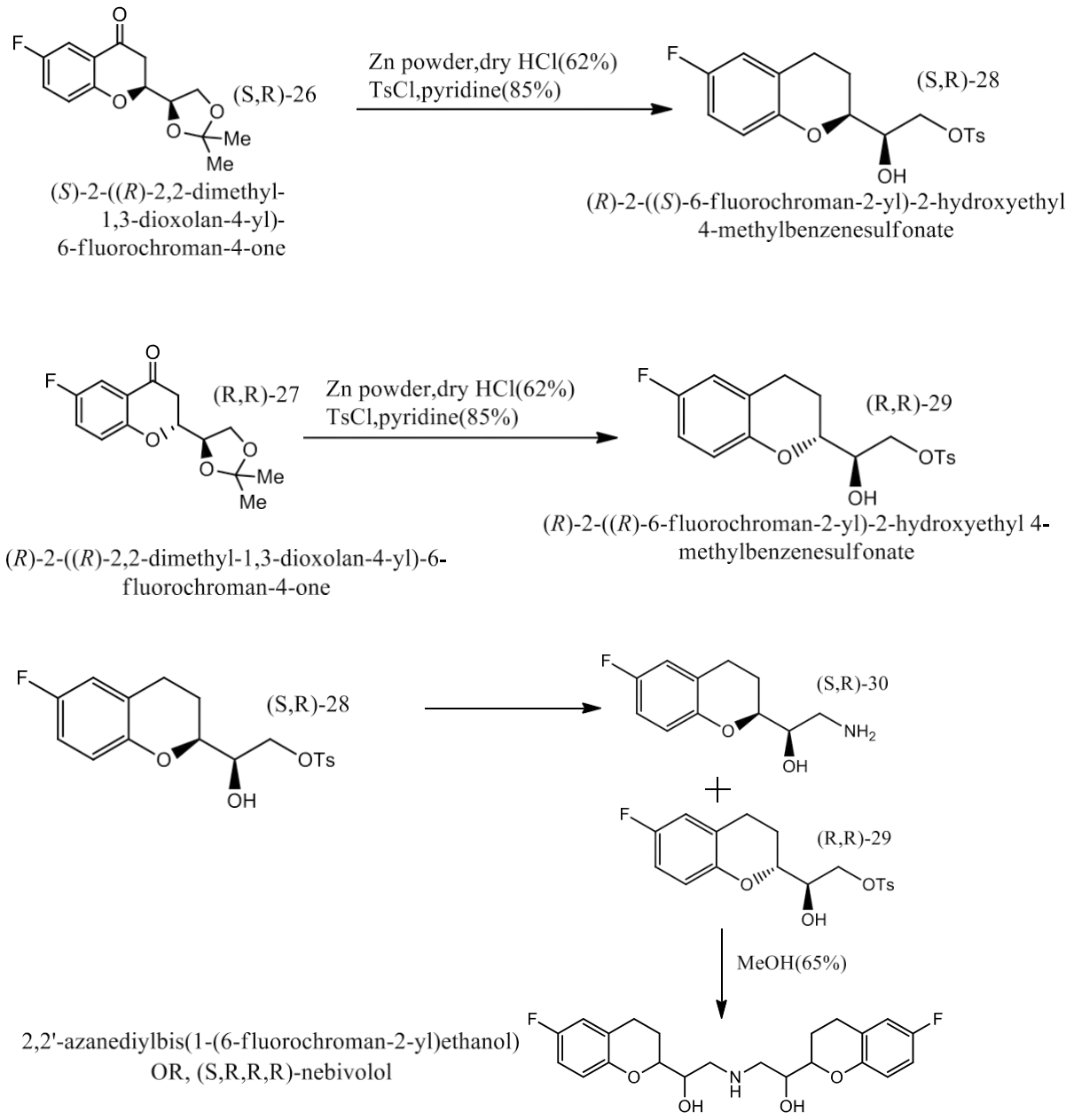


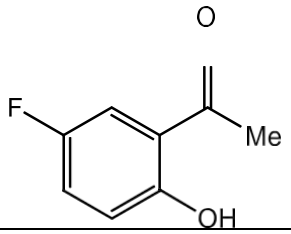
Figure 12: Asymmetric synthesis through chiral pool mechanism for (1).

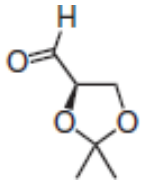
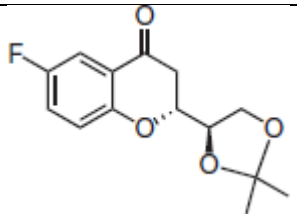
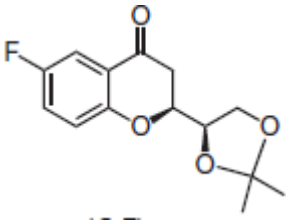
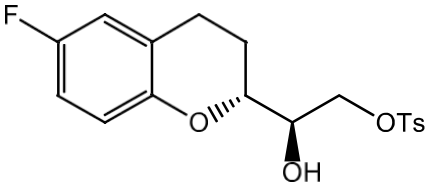
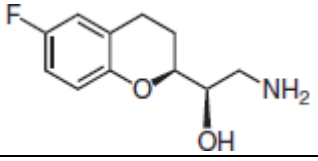
Analysis of synthesis 4:

The paper provides an explanation of a synthetic method for the production of the chiral medicine (1). Through a process known as chiral pool synthesis, the starting material (24) can

be obtained from D-mannitol. The initial material is subjected to a succession of reactions, such as the Kabbe reaction, the Clemmensen reduction, and the N-alkylation, which are then carried out in order to transform it into the final product, which is known as (1). In those reactions, the catalyst was utilized specifically for the creation of chiral pools. The overall product has a yield of 65%, while the important intermediate, which is a mixture of chromanones (S,R)-26 and (R,R)-27 in a ratio of 60 proportion to 40, is obtained with a yield of 40%. The synthesis that has been described is efficient in terms of cost, but no claims are made about its potential use in industrial settings. Below is a list of important intermediate chromans, along with their respective percentage yields.

Table 4: Important intermediates and their assemblage of synthesis 4:

Molecule	**Structure**	**Percentage yield**
1-(5-fluoro-2-hydroxyphenyl) ethenone		(89%)
Assemblage: At room temperature, 83 grams of 4-fluorophenol and 0.079 liters of acetyl chloride were combined, and the mixture was agitated for a period of thirty minutes. After that, 178 g of AlCl3 was added to the mixture, and it was heated and stirred for a total of 2 hours at a temperature of 130 °C. After allowing the mixture to cool down, one hundred fifty milliliters of water were added to it, and then the solid was filtered out. After that, the solid was rinsed with three separate batches of water, each containing 100 mL. In the end, the unfinished product was crystallized from the petroleum ether, which led to the creation of 1-(5-fluoro-2-hydroxyphenyl) ethenone as a solid crystalline substance (Wang et al. 2007)		

(*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde		(77%)
Assemblage: At room temperature, 33 grams of D-mannitol were dissolved in 0.3 liters of CH2Cl2 to produce a solution. After adding 11.9 mL of sodium bicarbonate, the next step was the gradual addition of 52.8 g of sodium periodate over the course of 20 minutes while the mixture was vigorously stirred. After stirring the mixture for two hours at 77 degrees Fahrenheit, the solid was separated from the liquid using filtering. In order to get a pure chemical, the filter was distilled at an air pressure of 131 degrees Fahrenheit, and the leftover oil was then moved to a smaller container and distilled (Wang et al. 2007).		
(R)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-fluorochroman-4-one		(16%)
(S)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-fluorochroman-4-one		(24%)
(R)-2-((R)-6-fluorochroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate		(62%)
(R)-2-amino-1-((S)-6-fluorochroman-2-yl)ethanol		(80%)

Assemblage: A reaction was carried out using a Parr bottle that had 1.5 grams of (R)-2-((S)-6-fluorochroman-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate and 25 milliliters of dry methanol added to it. The reaction was allowed to take place at room temperature. A record was kept of the weight. After that, ammonia was added to the solution until a total of 0.14 g had been dissolved. After being heated to 176 degrees Fahrenheit and having its seal broken, the bottle was allowed to cool. Following that, the solvent was extracted by evaporating it while the pressure was lowered (Wang et al. 2007).

When sodium metaperiodate is exposed to the skin for the first time, it has the potential to cause skin corrosion and serious eye damage. When sodium metaperiodate is repeatedly exposed to the skin, it has the potential to cause damage to organs such as the thymus gland. Sodium metaperiodate is an important catalyst for the chiral pool synthesis of D-mannitol (Gawande et al. 2008). It is a relatively dangerous oxidative solid. The precise amount of this chemical that was used in this process was not specified; nonetheless, for safe use, the concentration should be lower than 72%. Pyrrolidine is employed as the principal catalyst in the kabbe reaction. It is a very flammable catalyst; thus, you should keep it away from heat while you utilize it. Pyrrolidine is also poisonous, with an LD50 value of 430 milligrams per kilogram (Farzam & Han, 2022). If it is breathed in, it can do major damage to the respiratory system, and it can also cause damage to the eyes. When doing the Clemmensen reduction, 4- tolunesulfonyl chloride is utilized; while it is perfectly safe to do so, prolonged contact with itmay result in irritation of the skin (Bell et al. 2020). N-alkylation process is catalyzed mostly by pyridine, which can exist as a flammable liquid or as a vapor and, if inhaled, can irritate theeyes. Because it only has an acute toxicity of 1.5 g/kg (Young 2009), it is a much safer reactantto use in this synthesis than the others. The fact that the synthesis does not require any kind ofheavy metal or metal complex, which are both notoriously difficult to remove from the

reaction, is one of the most significant aspects of it. The total synthesis may be completed in six steps, making it the simplest and most efficient synthesis reaction for nebivolol.

2.4.5 Synthesis 5:

The synthesis of the right segment of Nebivolol (14), was carried out with a stereoselective manner, starting from the lactone (31), which was known. The first process involved reacting lactone (31) with sulfoxide ((S)-32) to create the sulfinyl complex ((S)-32), a combination of epimers that is an intermediary of (C-2). Using Et3SiH/TMSOTf, the reductive degassing procedure produced an epimer mixture with an 89 to 11 ratio. With a 70% yield, pure (33) was separated from the mixture. This result showed that by changing the absolute orientation of sulfur in the sulfinyl complex, it was possible to synthesize both stereoisomers of the 2H-chroman ingredient (Carreño et al. 2008). Sulfoxide (33) was then converted into vinyl derivative 35 by use of two reactions that were carried out on the first generated aldehyde (34): a Pummerer reaction about 86% yield and a Wittig reaction about 78% yield. In three stereoselective stages, the final product, epoxide (38), was produced from vinyl chroman (35). From the 91:9 combination of the diastereoisomeric diols produced by the Sharpless asymmetric dihydroxylation of the double bond of (35) with AD-mix, the major (36) could be purified with an 88% yield. About 70% of the yield of carbinol (37) was produced when the primary OH of (36) was selectively tosylated. Then, using NaH in THF, this carbinol was converted into epoxy chroman ((R,R)-38) in around 93% of the yield. It took seven stages and a total yield of 23% to complete the stereoselective synthesis of the right segment of (S,R,R,R)-Nebivolol, (38), starting with fluorochroman-2-one (31) (Carreño et al. 2008).

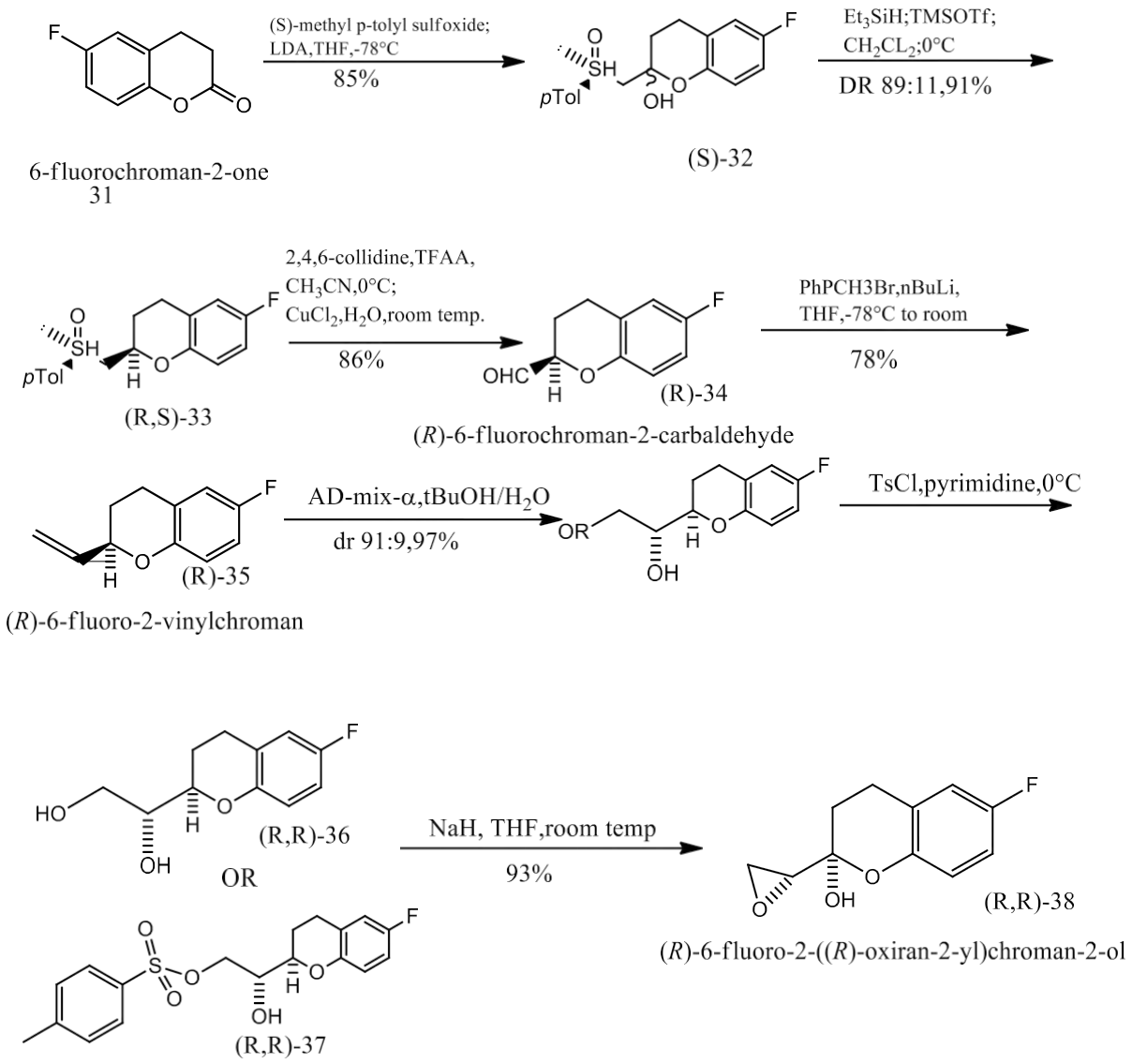


Figure 13: Stereoselective Preparation of (S,R,R,R)-Nebivolol Right Fragment, EpoxyChroman (R,R)-38

On the left fragment of nebivolol, a number of chemical processes resulted in the creation of the second chiral carbinol. First, a Pummerer reaction was used to transform sulfoxide (S,R)-33 into aldehyde ((S)-34) with a 90% yield. Aldehyde ((S)-34) was then given a lithium anion from (S)-methyl p-tolyl sulfoxide, which produced compound ((S,S,S)-39), which was purified in 75% of the samples following chromatographic separation. Strong diastereoselectivity was considered to be caused by the double asymmetric induction between aldehyde ((S)-34) and the nucleophile created from sulfoxide ((S)-2) (Anon 2018b; Carreño et al. 2008).

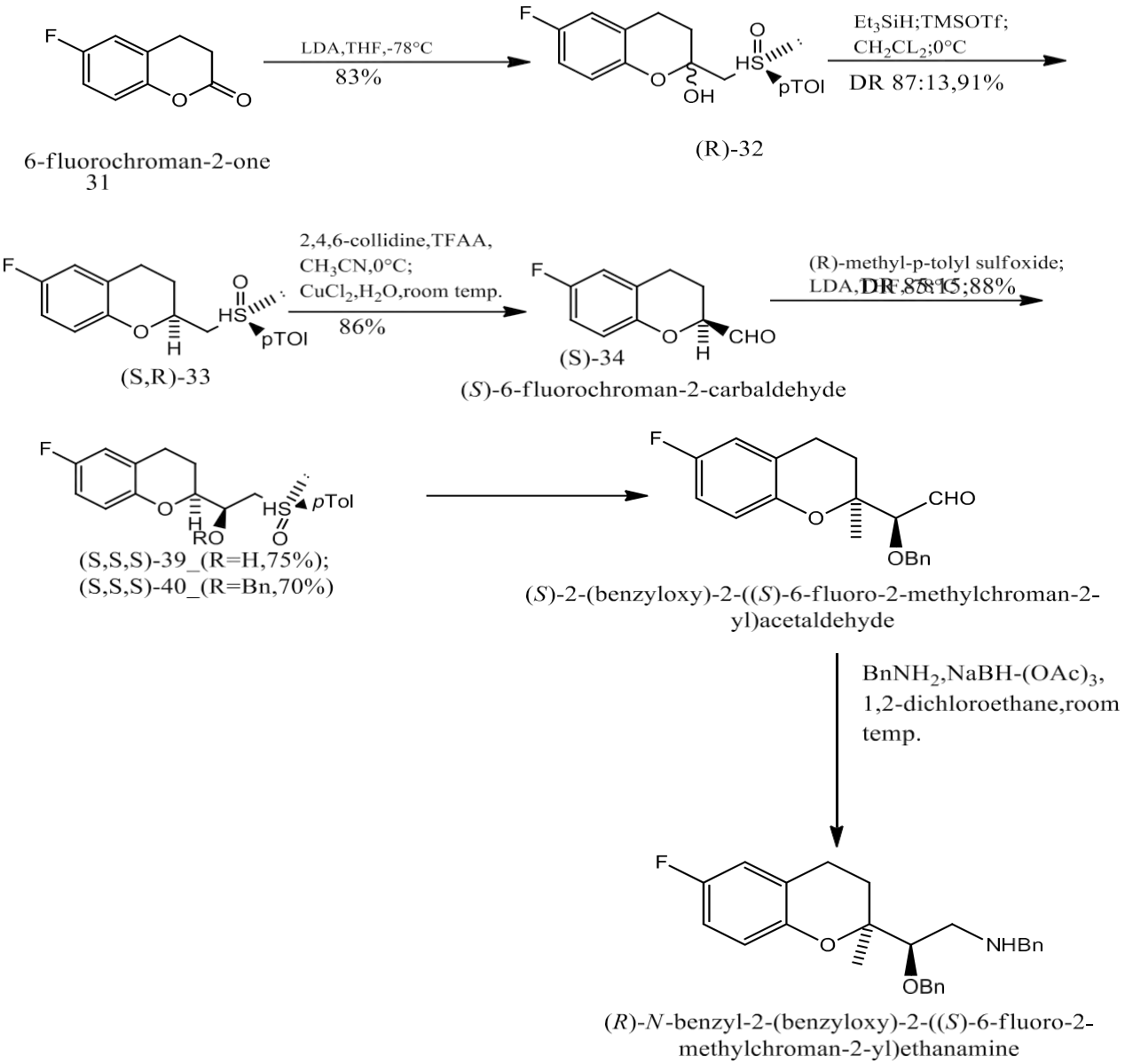


Figure 14: sulfoxide transformation into amine intermediate of right segment of nebivolol((R,S)-42) with assistance with O-benzyl derivatives (Anon n.d.-f)

After preserving the carbinol as the O-benzyl derivative ((S,S,S)-40) and turning sulfoxide 8 into aldehyde ((S,S)-41) via a Pummerer reaction (83% yield), sulfoxide (39) was then converted into the amine in the intermediate ((S,R)-42). Aldehyde (9) was finally converted with a 73% yield via reductive amination producing the dibenzyl-protected amino alcohol ((S,R)-42). From the known lactone fluorochroman-2-one (31), the stereoselective synthesis of

the left portion of (S,R,R,R)-Nebivolol, ((S,R)-42), was completed in 7 states with an overall yield of 18% (Anon n.d.-f; Carreño et al. 2008).

By heating the mixture at reflux in ethanol, the two stereoselectively produced fragments benzylamine ((R,S)-42) and epoxide ((R,R)-38) were combined to create the O,N-dibenzylated Nebivolol ((S,R,R,R)-43) with a 90% yield. With a combined yield of 69% for these two procedures, the benzyl protecting groups were removed using hydrogenolysis and then subjected to an acidic treatment to produce the final product, nebivolol hydrochloride. It was determined that the artificial substance and a real sample of racemic nebivolol hydrochloride were similar (Carreño et al. 2008).

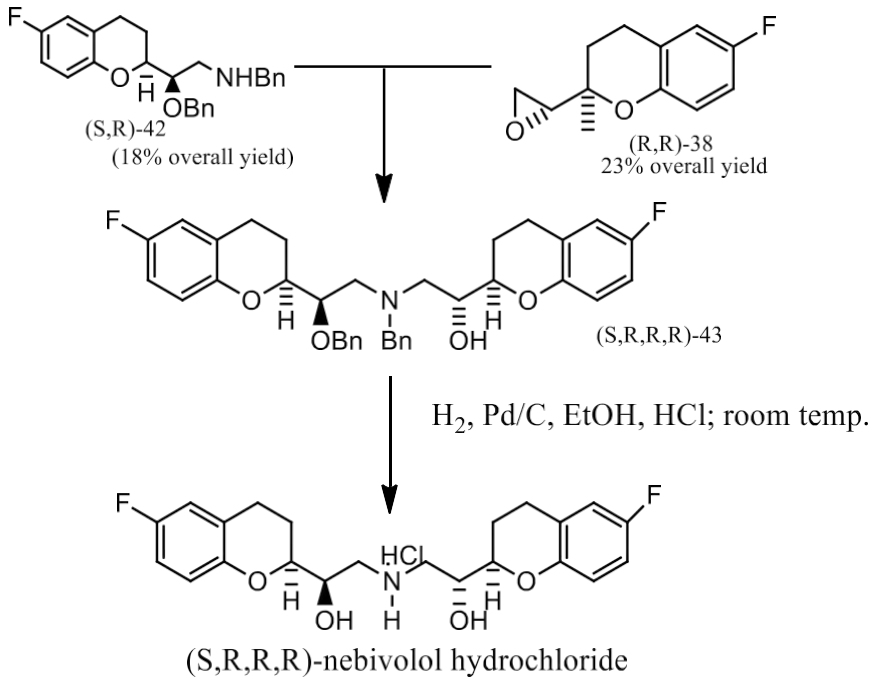


Figure 15: End product synthesis for (1) by epoxy chroman and benzylamine forming of (S,R,R,R)-43

Analysis of synthesis 5:

In the synthetic reaction it facilitates the synthesis of the right and left fragments of the beta-blocker drug, (1). The synthesis of the right fragment, (R)-6-fluoro-2-((R)-oxiran-2-yl) chroman-2-ol, starts from a known lactone 6-fluorochroman-2-one and involves seven steps

with an overall yield of 23%. The process involves forming a sulfinyl complex ((S)-32) from lactone 6-fluorochroman-2-one and (S)-methyl p-tolyl sulfoxide, which results in a mixture of C-2 epimers. The mixture is then purified to obtain the pure (R)-6-fluorochroman-2-carbaldehyde. Vinyl derivative (R)-6-fluoro-2-vinylchroman is obtained from ((R)-34) through Pummerer and Wittig reactions. The final product, epoxide (R)-6-fluoro-2-((R)-oxiran-2-yl) chroman-2-ol ((R,R)-38), is obtained through Sharpless asymmetric dihydroxylation and tosylation processes. The synthesis of the left fragment ((S,R)-42), starts from the same lactone and involves seven steps with an overall yield of 18%. The process involves transforming sulfoxide ((S,R)-33) into ((S)-34), adding lithium anion to it, and protecting the carbinol as the O-benzyl derivative ((S,S,S)-40). The final product, the dibenzyl-protected amino alcohol ((S,R)-42), is obtained through reductive amination. Finally, the two stereoselectivity synthesized fragments, ((S,R)-42) and ((R,R)-38), are combined to form the final product, Nebivolol hydrochloride, with a yield of 69%. The final product was confirmed to be identical to an authentic sample of racemic Nebivolol hydrochloride. In conclusion, the synthesis of Nebivolol hydrochloride was accomplished through the stereoselective synthesis of the right and left fragments, which were then combined to form the final product. The final product was confirmed to be identical to an authentic sample of the drug.

Chapter 3

Discussion

We have successfully synthesized (1) using five distinct synthesis methods, as described above. During the course of those synthesis, we were able to acquire varying amounts of the nebivolol that was anticipated. We concentrated only on (1) because it is the only molecule that is responsible for the beta-adrenergic activity. At the same time, (R,S,S,S) is working on the vasodilation activity. In synthesis 1, Hoveyda and his team disclose the first enantioselective total synthesis of the antihypertensive medication (1). This synthesis was performed by using four different enantiomers. Benzopyran and 2(S)-(2'-tert-Butyldimethylsiloxy-5-hexenyl)-6-fluoro-2H-benzopyran are the chiral nonracemic 2-substituted chromans that are synthesized by the use of effective Zr- and Mo-catalyzed processes during the synthesis. In order to acquire the two chiral catalysts that are necessary, the racemic $ZrCl_2$ catalyst must first be resolved using the Buchwald procedure. In addition to this, the synthesis includes a Pd-catalyzed reaction that is both highly efficient and selective, as well as a photochemical modification of the chroman side chain.(Anon n.d.-f; Johannes et al. 1998). After that, in synthesis 2, Chandrasekhar and his team were able to effectively synthesize the anti-hypertensive drug known as (S,R,R,R)-Nebivolol by utilizing a combination of a Claisen rearrangement and a one-pot Sharpless asymmetric epoxidation. By using this method, they were successful in producing the optically pure form of the molecule that they had been aiming for. This synthesis is thought to be effective because it makes use of Sharpless asymmetric epoxidation chemicals that are readily available for purchase, as well as because it allows for the simple preparation of allyl alcohols. The utilization of reactions that only required a single pot was another factor that contributed to the overall efficacy of the synthesis. (S. Chandrasekhar 2000). In addition, the authors Yihui Bai and Xinzhi Chen present a new technique of synthesis in their work titled

"Synthesis 3." This approach is for the chemical known as (1). The synthesis was performed at conditions of normal pressure and room temperature, and the result was a yield of 33% overall. This new synthesis approach helps contribute to the development of a scalable synthesis process for the related medicinal molecule known as nebivolol (Anon 2018a; Bai and Chen n.d.). Then, in Synthesis 4, Wang and his team detail how they used natural chiral starting materials and an efficient and convergent synthesis approach to create the beta-adrenergic antagonist (S,R,R,R)-a,a'-iminobis(methylene)bis(6-fluoro-3H,4H-dihydro-2H-1-benzopyran-2-methanol (Wang et al. 2007). In Synthesis 5, the group led by Colobert and Carreo describes a unique method for synthesizing the hypertension medicine known as Nebivolol. This approach involves a homochiral sulfoxide-directed reductive deoxygenation of 2-(p-tolyl sulfinyl) methyl-2-chromanols. This deoxygenation process enables the synthesis of 2H-chromans with a high degree of stereoselectivity, with a diastereoisomeric ratio of up to 95:5. The enantioselective synthesis of the (S,R,R,R)-enantiomer of nebivolol was carried out using this technology, which resulted in a rapid and effective procedure (Carreño et al. 2008). There are also several different synthetic methods that have been developed for the synthesis of nebivolol, each with its own set of advantages and disadvantages. Some of the most common synthesis methods include:

Alkylation of aniline: This method involves the reaction of p-bromoaniline with 2-bromoethanol to form an intermediate compound, which is then reacted with a chiral auxiliary to form the final product.

Condensation of aniline and aldehyde: This method involves the condensation of p-bromoaniline and formaldehyde to form an intermediate compound, which is then reacted with a chiral auxiliary to form the final product.

Wittig reaction: This method involves the use of a Wittig reagent to form an intermediate compound, which is then reacted with a chiral auxiliary to form the final product.

Palladium-catalyzed reaction: This method involves the use of a palladium catalyst to form an intermediate compound, which is then reacted with a chiral auxiliary to form the finalproduct (Motaleb, Moustapha, and Ibrahim 2011).

Table 5: Amount of fluctuation in overall yield of (S,R,R,R)-nebivolol of five consecutive synthesis has been observed above

Synthesis number	**Yield (0.05 mmol)**
Synthesis 1	7 mg, (99%)
Synthesis 2	0.025g or 25mg (20%)
Synthesis 3	0.107g or 107mg (65%)
Synthesis 4	0.13g or 130mg (65%)
Synthesis 5	23%

Here in the chart, we can see that synthesis 1 or synthesis of Hoveyada and his group's gives the maximum amount of end product about 99% of desired amount. The yield percentage is a measure of the efficiency of a chemical reaction, and is calculated as the ratio of the amount of product obtained to the amount of starting material used, expressed as a percentage. So, in this case, the reaction resulted in the synthesis of 7 milligrams of product, which is 99% of the expected or theoretical yield based on the amount of starting material used.

(R)-1-((R)-6-fluorochroman-2-yl) According to studies, the 2-substituted chroman derivatives ethane-1,2-diol and (R)-1-((S)-6-fluorochroman-2-yl) ethane-1,2-diol can be employed as

intermediate steps in the production of (S,R,R,R)-nebivolol. The intramolecular ring-opening of enantiomerically pure chroman epoxides caused by the phenolic hydroxy group is commonly used to produce (R)-1-((S)-6-fluorochroman-2-yl) ethane-1,2-diol. This procedure has been tried and tested. By using either the Sharpless asymmetric epoxidation or the Wittig reaction with 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde, the necessaryepoxide can be produced from the E-allylic alcohol. Both of these methods require the presenceof the 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxalde However, it would appear that theZ-allylic alcohol is not an appropriate choice for the production of the R-epoxide by either theSharpless asymmetric epoxidation or the Wittig reaction. Neither of these two processes requirean R-epoxide. So, 1-[6-Fluoro-(2S)-3H,4H-dihydro-2H-2-chromenyl] Mitsunobu inversion is an alternate approach. The enantiomeric epoxide, -(1R)-1,2-ethanediol, was employed to createthe enantiomer, (R)-1-((R)-6-fluorochroman-2-yl) ethane-1,2-diol (Anon n.d.-f; Devi and Das 2017).

The Sharpless asymmetric dihydroxylation method was utilized in a more recent and substantial attempt to synthesize the substances (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) (SAD). The SAD reaction is a technique that is frequently used for the stereoselective synthesis of vicinal diols. Vicinal diols are molecules that contain two hydroxyl functions that are situated on nearby carbon atoms. In order to generate a vicinal diol that has exceptionally highlevels of stereoselectivity, the reaction must make use of a chiral titanium complex catalyst andan olefin substrate. SAD was used as a starting material in order to produce vicinal diols, whichwere then used in the synthesis of the target compounds (Devi and Das 2017).

The process of synthesizing compounds (24) and (25), (27) and its enantiomer (28), (2), and (29) was carried out by performing various chemical reactions. The first step was the debenzylation of compound (24) with 10% Pd-C in ethanol under hydrogen atmosphere.

Following completion of the reaction, the mixture was subjected to further treatment with K_2CO_3, which resulted in the production of compound 27 with a yield of 70%, which was higher than the previously reported yield of 53%.

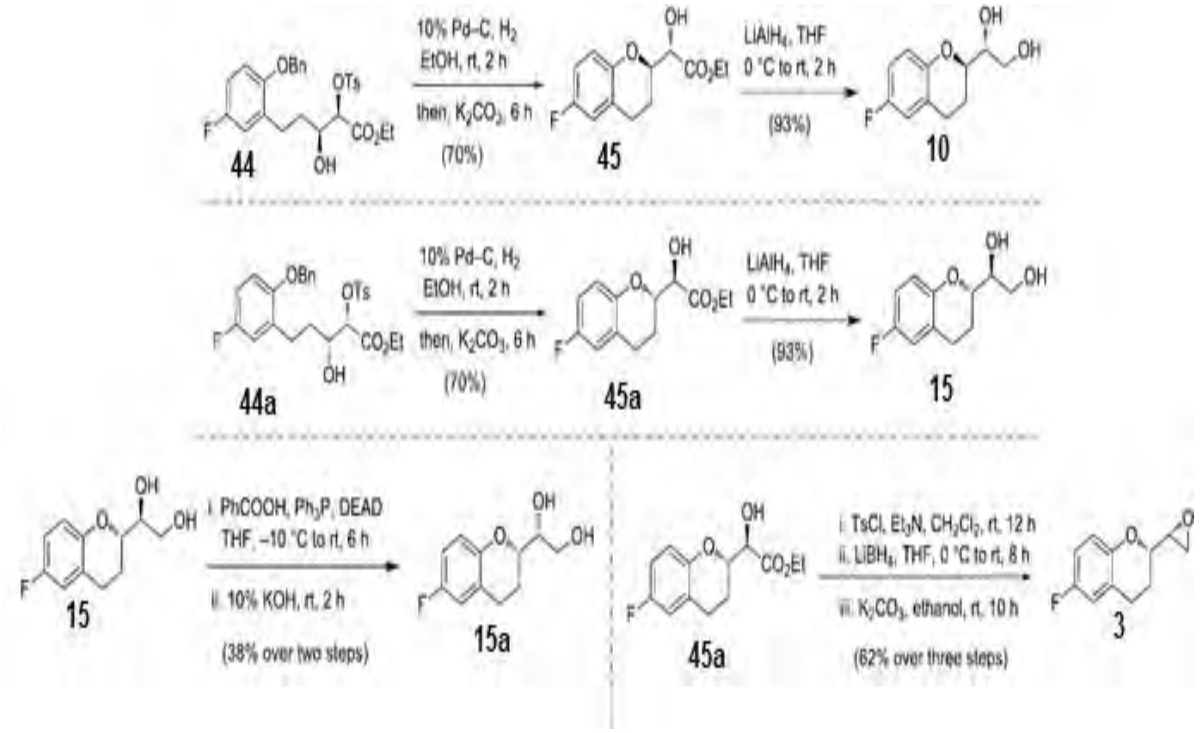


Figure 16: synthesis mechanism of (3); of (R)-1-((S)-6-fluorochroman-2-yl)ethane-1,2-diol (15) and its enantiomer (15a) by SAD process (Anon n.d.-f)

The number (25) was converted into the number (28) using the same method. After that, the reduction of compound (27) with compound (28) using $LiAlH_4$ yielded product (2) and compound (29), respectively, with a yield of 93%. It was discovered that the NMR spectra and particular rotations of (2) and (29) correspond to the values found in the literature. In the end, molecule (29) was successfully transformed into an enantiomer (3) of S)-1-((S)-6-fluorochroman-2-yl) ethane-1,2-diol by following a traditional two-step Mitsunobu inversion technique (Devi and Das 2017) It is essential to emphasize the significance of the R and S configurations, as well as the fact that the stereochemistry of the compounds to be targeted has been defined in detail. In order to understand the significance of the stereoselectivity obtained

from the Sharpless SAD reaction in the creation of these compounds, it is helpful to consider the preceding information (Mitsunobu, 1981).

In general, the Sharpless asymmetric dihydroxylation-derived vicinal diols played an important part in the stereoselective synthesis of the target compounds, and the application of this method enabled the effective creation of the stereoisomers that were required.

Chapter 4

4.1 Conclusion

In the treatment of hypertension, generally known as high blood pressure, as well as heart failure, a beta-1 selective receptor blocker medication called nebivolol has been found to be effective. The discovery of nebivolol is notable because it represents a new class of beta-blockers that is capable of nitric oxide (NO) donation. This makes the manufacture of nebivolol significant. Because of this, the synthesis of nebivolol is an important process. Because of this property, it is distinct from other beta-blockers and exhibits a mechanism of action that is unique, both of which are useful in the treatment of cardiovascular problems. In addition, it has the potential to reduce the side effects of other beta-blockers. In addition to its effects on beta-blockade, nebivolol has been shown to increase the synthesis of nitric oxide (NO) in the vascular system. This action is independent of the beta-blockade effects. [Further citation is required] This increased production of NO causes vasodilation, which means the blood vessels relax and become wider as a result of the increased blood flow. This occurs as a direct result of the increased generation of NO. This results in both a reduction in blood pressure and an improvement in the circulation of blood to the heart and other organs in the body. Both of these benefits lead to a healthier lifestyle. It has also been shown that nebivolol exhibits anti-inflammatory qualities, which contribute to the benefits that it offers in the treatment of cardiovascular illnesses. Nebivolol's antioxidant capabilities also contribute to the benefits that

it offers in the treatment of cardiovascular illnesses. Because it has been discovered to have a lower risk of adverse effects than other beta-blockers do, nebivolol is a feasible therapeutic choice for persons who are unable to tolerate other beta-blockers. This makes it an option for people who are looking for an alternative treatment option. Because of this, it is an excellent choice for patients who are unable to tolerate the effects of other beta-blockers. In conclusion, the manufacture of nebivolol has significant implications for the medical management of cardiovascular diseases. It is a very valuable addition to the drug arsenal that is already being used to treat these problems due to its one-of-a-kind method of action and relatively limited risk for unpleasant side effects. For the synthesis of (1), five distinct approaches have been described so far. These approaches include Zr- and Mo-catalyzed reactions, Cliasen rearrangement, normal pressure and room temperature conditions, the utilization of naturally occurring chiral starting materials, and homochiral sulfoxide-directed reductive deoxygenation. These many syntheses have resulted in varying percentages of nebivolol being produced; however, synthesis 1 has produced the highest percentage, 99%. In addition to this, nebivolol can also be synthesized using the alkylation of aniline, the condensation of aniline and aldehyde, the Wittig reaction, or the palladium-catalyzed reaction. In this case, thesynthesis of (1) requires the utilization of intermediate molecules such as (R)-1-((S)-6-fluorochroman-2-yl) ethane-1,2-diol or (R)-1-((S)-6-fluorochroman-2-yl) ethane-1,2-diol. In the production of (R)-1-((S)-6-fluorochroman-2-yl) ethane-1,2-diol, the intramolecular ring- opening of chroman epoxides is a standard approach. However, (R)-1-((R)-6-fluorochroman- 2-yl) ethane-1,2-diol was obtained using an alternate method involving the Mitsunobu inversion of (1). A variety of chemical processes, such as debenzylation, treatment with K_2CO_3,reduction with $LiAlH_4$, and the traditional two-step Mitsunobu inversion, were utilized in orderto successfully synthesize the target compounds. The utilization of Sharpless asymmetric dihydroxylation (SAD) was an essential component in the stereoselective synthesis of the target

compounds. This was due to the fact that the SAD-derived vicinal diols made it possible for the effective creation of the stereoisomers that were required. Due to the fact that the stereochemistry of the target compounds has been described, the significance of the stereoselectivity produced through the Sharpless SAD reaction has been brought to light.

In addition, there have been a number of developments in the technology used to synthesize nebivolol over the course of the past few years. The utilization of continuous flow synthesis is one of the most cutting-edge methods that have recently been developed for synthesizing nebivolol.

The process of continuous flow synthesis is a method in which the reactants are constantly supplied into a reactor and the reaction products are continually withdrawn, without any intermediate stages for the purification or isolation of the products of the reaction (Zhong et al. 2021). When compared to conventional methods of batch synthesis, this technology offers a number of benefits, the most notable of which are increased reaction yields, enhanced reaction kinetics, and a reduction in the amount of time needed for the reaction (Anon n.d.-m).

Utilizing the principles of green chemistry is another step forward in the technological process of producing nebivolol. In chemical synthesis, reducing waste and using as few potentially harmful chemicals and solvents as possible are two of the primary goals of green chemistry concepts. The use of this methodology contributes to the synthesis of nebivolol becoming more sustainable and friendly to the environment (Bandichhor n.d.).

Additionally, the development of more effective routes for the synthesis of nebivolol has been made possible by recent leaps in the fields of computational chemistry and molecular modeling. Researchers are able to make accurate predictions about the results of various reactionpathways and better understand how to optimize the conditions for the synthesis of nebivolol by using computer simulations (Sebastian et al. 2022).

The overall goal of the most recent technological advancements in the synthesis of nebivolol is to improve the process's efficacy, sustainability, and safety. Researchers are able to produce nebivolol in a manner that is both more efficient and less damaging to the surrounding environment if they make use of these technologies.

4.2 Impact

In this paper, a detailed description of the various methods for the synthesis of nebivolol, including their efficiencies as well as the intermediates that are involved in the synthesis, is provided. Natural chiral photochemical reconfiguration of the chroman side chain and Sharpless epoxidation are both better and more cost-efficient ways to synthesize the desired product. However, the most recent method for synthesizing intermediates, Sharpless asymmetric dihydroxylation, opens up new perspectives and makes the process of synthesis more efficient. However, the usage of dangerous catalysts in industrial settings, such as diethyl azodicarboxylate and triphenylphosphine, should be replaced with more safer reagents. A one-pot Sharpless asymmetric epoxidation and a homochiral sulfoxide-directed reaction are also included in this review as some ways that have been reported to be very cost-effective. These procedures include photochemical reconfiguration of the chroman side chain. In comparison to Zr- and Mo-catalyzed processes, which are more effective but also more time-consuming and costly, the aforementioned procedures are typically less expensive and more expedient overall. The final decision regarding which method will be the most cost-effective will be influenced by a number of factors, including the level of purity that is desired in the end product. Chiral photochemical reconfiguration yields about 65% of the final product after six consecutive steps, whereas the most efficient process yields about 99% of the final product after more than nine steps of production, but the cost of the starting materials and catalysts is extremely high and dangerous to work with. The important intermediates involved in the synthesis, such as (R)-2-((tert-butyldimethylsilyl)oxy)-2-((R)-6-fluorochroman-2-

yl)ethanamine and 6-fluoro-2-(oxiran-2-yl)chroman, as well as the potential problems connected with each technique, are listed below. In addition, the chiral photochemical reconfiguration of the chroman side chain requires the production of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde from D-mannitol. This is done in order to get the desired configuration. Utilizing the natural enantiomer of S-serine is an alternative method that can be used instead of this technique. Because of this, the number of intermediate catalysts that would be used would be kept to a minimal while remaining non-toxic. This enantiomer can be purchased for a reasonable price and has the potential to have an industrial application; however, this application is not currently being carried out in an efficient manner. Therefore, additional research can be done to make the chiral photochemical reconfiguration more practical for use in commercial settings.

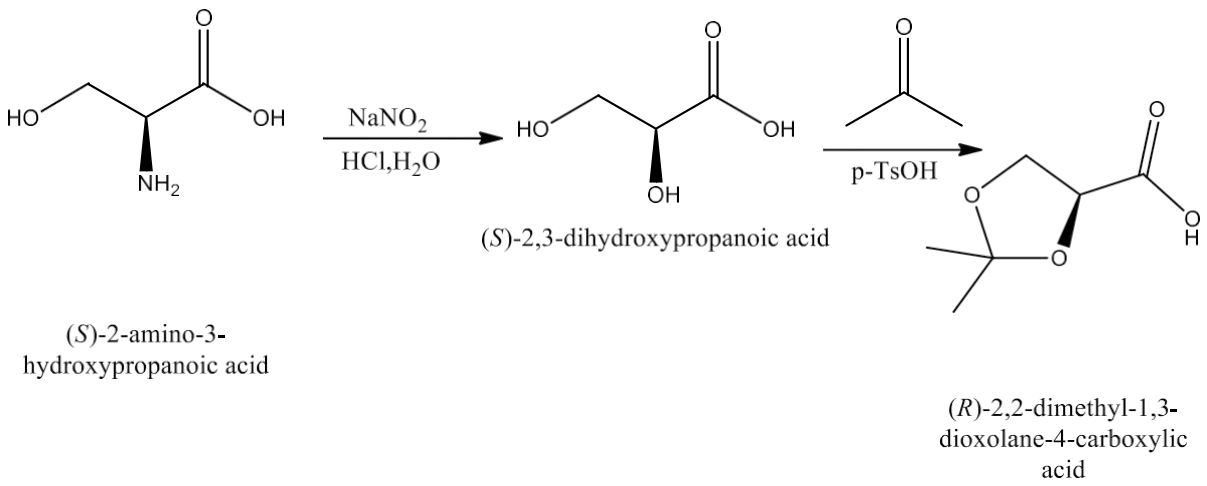


Figure 17: synthesis of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde enantiomers from(S)-2-amino-3-hydroxypropanoic acid(Reider, 1987)

The development of improved technologies for the synthesis of nebivolol could lead to the creation of therapeutic options that are superior in both quality and efficiency for the conditions of hypertension and heart failure. Patients who are afflicted with these illnesses may have improvements in their health and general well-being as a result of this.

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