Synthesis of 4-(2-(cyclopropylmethoxy)ethyl)phenol, a precursor for (*S*)-betaxolol

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Preface

This thesis "Synthesis of 4-(2-(cyclopropylmethoxy)ethyl)phenol, a precursor for (*S*)-betaxolol" was written as a master thesis of the 5-year study program Industrial Chemistry and Biotechnology at Norwegian University of Science and Technology (NTNU) under supervisor associate professor Elisabeth E. Jacobsen. The work was performed from January 2021 to June 2021.

I would like to thank my supervisor Elisabeth E. Jacobsen for all help and guidance in analyses, work in the lab and reporting results. Thanks to staff engineer Roger Aarvik for supplying all needed chemicals and equipment to the lab and to head engineer Torunn Margreta Melø for help in operating the NMR-instrument. Thanks to head engineer Odd Reidar Gautun for providing insight and equipment for reactions.

I would like to thank my fellow students at the lab, Mari Rødseth, Anna Lifen Tennfjord and Kristoffer Klungseth for advice and keeping the mood high at the lab and at weekly meetings.

A big thanks to my wife Charlene and my daughter Rebecca for supporting me and giving joy to my days, and to late nights at the lab. Thanks to all family and friends for having helped in any way.

Abstract

Enantiomerically pure drugs are synthesised and used instead of racemic mixtures. (*S*)-betaxolol ((*S*)-**1**) is one β-blocker that has shown promise in treatment of glaucoma and it has been shown that the (*S*)-enantiomer of betaxolol is more potent than the (*R*)-enantiomer in treatment of glaucoma [1] .

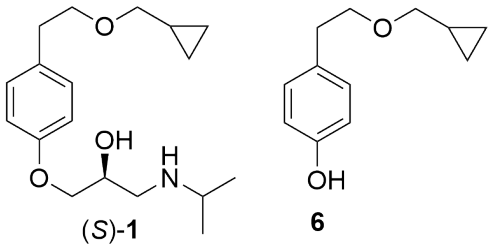
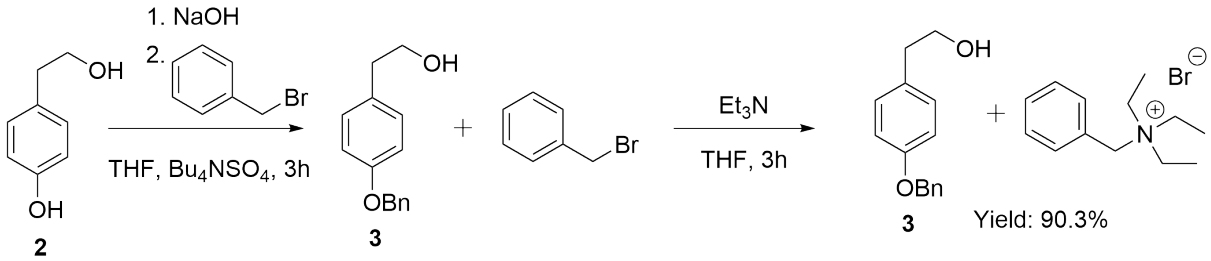


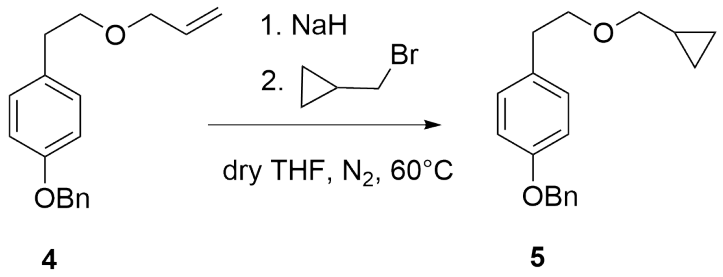
Figure 1: (*S*)-betaxolol ((*S*)-**1**) and its precursor 4-(2-cyclopropylmethoxyethyl)phenol (**6**).

This master thesis aimed to find a synthetic route to 4-(2-cyclopropylmethoxyethyl)phenol (**6**), a (*S*)-betaxolol precursor and to synthesise betaxolol by enzyme catalysed kinetic resolution. Starting from the commercially available 2-(4-hydroxyphenyl)ethanol (**2**), addition of benzylbromide was performed to form 2-(4-benzyloxyphenyl) ethanol (**3**) with a yield of 90,3 % (1,42 g, 6,22 mmol) (Scheme 1).



Scheme 1: Synthesis of 2-(4-benzyloxyphenyl) ethanol (**3**) by addition of benzylbromide to 2-(4-hydroxyphenyl) ethanol (**2**).

From the protected alcohol **3**, synthesis to form both 1-(2-(allyloxy) ethyl-4-(benzyloxy)benzene (**4**) and 1-benzyloxy-4-(2-cyclopropylmethoxyethyl) benzene (**5**) was performed. Synthesis of **5** by addition of (bromomethyl)cyclopropane was achieved in 40 % conversion of **3** into **5** after 48 h at 60 °C, but the product was not purified (Scheme 2).



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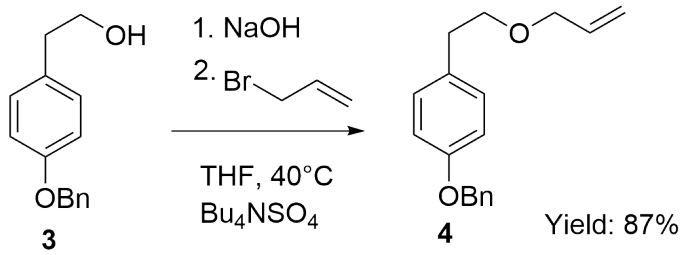
Scheme 2: Synthesis of 1-benzyloxy-4-(2-cyclopropylmethoxyethyl) benzene (**5**) by addition of (bromomethyl)cyclopropane to 2-(4-benzyloxyphenyl) ethanol (**3**).

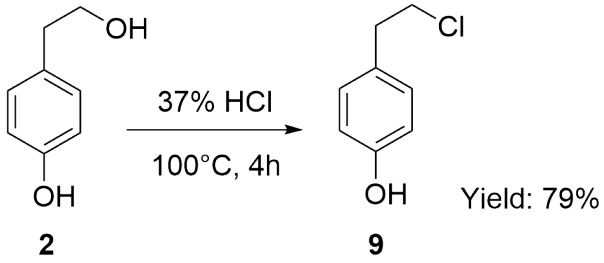
Synthesis of 1-(2-(allyloxy) ethyl-4-(benzyloxy)benzene (**4**) was performed by addition of allylbromide to **3** instead of using (bromomethyl)cyclopropane (Scheme 3). Allyl **4** was obtained in 86,8 % yield (1,1347 g, 4,23 mmol).



3 4

Scheme 3: Synthesis of 1-(2-(allyloxy) ethyl-4-(benzyloxy)benzene (**4**) by addition of allylbromide to 2-(4-benzyloxyphenyl) ethanol (**3**).

Another potential path to synthesise betaxolol phenol **6** involves synthesis of 4-(2-chloroethyl)phenol **9** by treatment of **2** with concentrated HCl at 100 °C (Scheme 4). Phenol **9** Was obtained in 79,3 % yield (0,45 g, 2,87 mmol).



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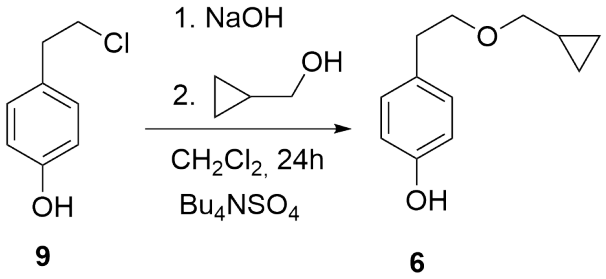
Scheme 4: Synthesis of 4-(2-chloroethyl)phenol (**9**) by treatment of **2** with HCl.

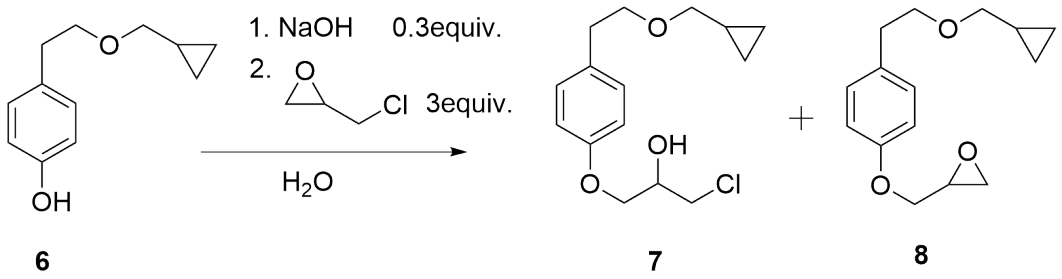
To obtain **6**, the phenol **9** can be treated with cyclopropylmethanol (Scheme 5). Phenol **6** was not isolated and purified in this thesis.

For the synthesis of betaxolol after having obtained 4-(2-cyclopropylmethoxyethyl)phenol (**6**) treatment with epichlorohydrin and catalytic amounts of base yields 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**) (Scheme 6). **7** was



Scheme 5: Synthesis of 4-(2-(cyclopropylmethoxy)ethyl)phenol (**6**) by treatment of (**9**) with cyclopropylmethanol.

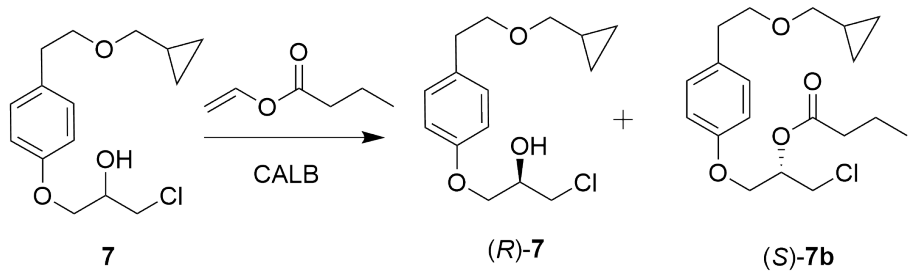
obtained in conversion of 40 %, but difficulties in purification hindered the calculation of yield.



Scheme 6: Synthesis of 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**) and by-product 2-(4-(2-(cyclopropylmethoxy)ethyl) phenoxy)methyloxirane (**8**) by addition of epichlorohydrin to 4-(2-cyclopropylmethoxyethyl)phenol (**6**).

One byproduct from the synthesis of **7** is 2-(4-(2-(cyclopropylmethoxy)ethyl) phenoxy)methyloxirane (**8**). Epoxide **8** can be removed with treatment LiCl and acetic acid. The mechanism for formation of epoxide **8** and chlorohydrin **7** can be seen in Scheme 2.9.

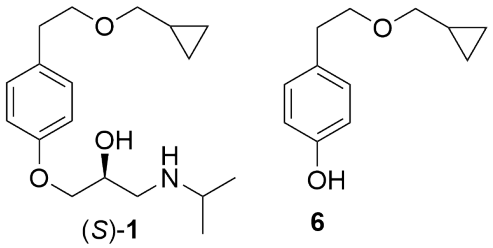
Kinetic resolution of **7** catalysed by *Candida antarctica* Lipase B (CALB) will yield (*R*)-**7** and (*S*)-1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-yl butyrate (*S*)-**7b** which can be used in the synthesis of (*S*)-betaxolol (Scheme 7).



Scheme 7: Kinetic resolution of racemic **7** catalysed by *Candida antarctica* Lipase B to yield (*S*)-**7b** and (*R*)-**7**.

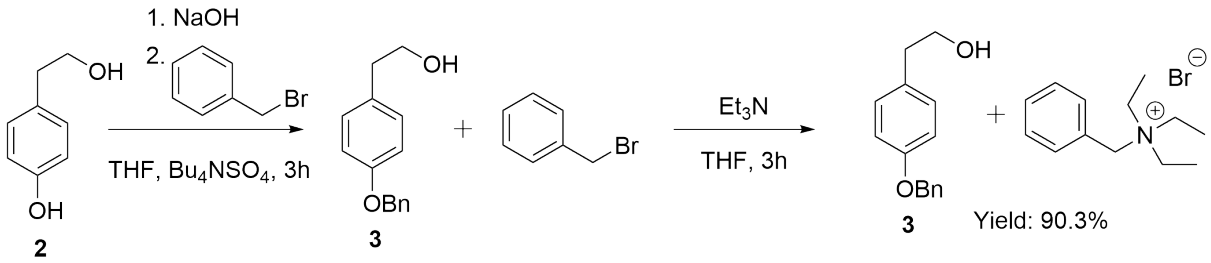
Sammendrag

Enantiomert rene legemidler blir dannet mer og mer fremfor rasemiske legemidler. (*S*)-betaksolol (*S*-**1**) er en β-blokker som har vist stort potensiale i behandling av glaukom. Det er blitt vist at (*S*)-enantiomeren av betaksolol er mye mer aktiv enn (*R*)-enantiomeren i behandlingen av glaukom [1].



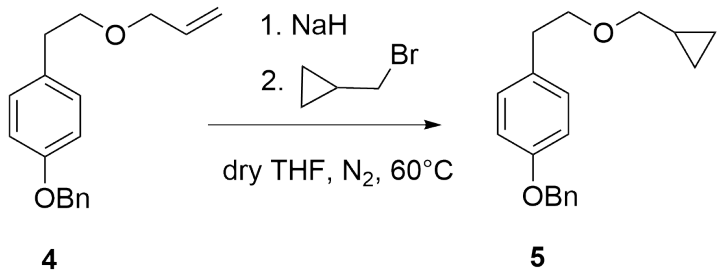
Figur 1: (*S*)-betaksolol ((*S*)-**1**) og dens byggestien 4-(2-syklopropylmetoksyetyl)fenol (**6**).

Denne masteroppgaven siktet på å finne en syntese for å danne 4-(2-syklopropylmetoksyetyl)fenol (**6**), som er en byggestein for (*S*)-betaksolol og deretter å syntetisere betaksolol ved en enzym katalysert kinetisk oppløsning. Fra det kommersielt tilgjengelige 2-(4-hydroksyfenyl)etanol (**2**) ble addisjon av bensylbromid utført for å danne 2-(4-bensyloksyfenyl)etanol (**3**) i utbytte på 90,3 % (1,42 g, 6,22 mmol) (Skjema 1).



Skjema 1: Syntese av 2-(4-bensyloksyfenyl)etanol (**3**) ved addisjon av bensylbromid til 2-(4-hydrokyfenyl)etanol (**2**.)

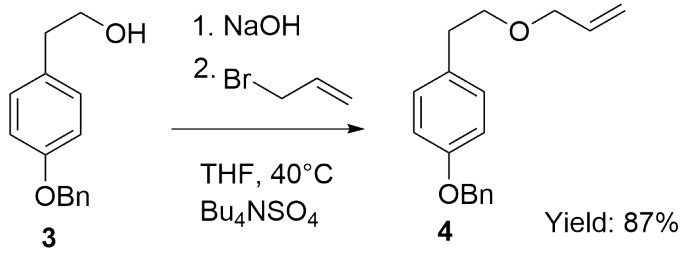
Fra den beskyttede alkoholen **3** ble det utført en syntese for å danne både 1-(2-allyloksy)etyl-4-(bensyloksy)benzen (**4**) og 1-bensyloksy-4-(2-syklopropylmetoksyetyl)benzen (**5**) utført. Syntese av **5** ved addisjon av (bromometyl)syklopropan oppnådde omsetning på 40 % av **3** til **5** etter 48 t ved 60 °C (Skjema 2).



4 **5**

Skjema 2: Syntese av 1-bensyloksy-4-(2-syklopropylmetoksyetyl)benzen (**5**) ved addisjon av (brommetyl)syklopropan til 2-(4-bensyloksyfenyl)etanol (**3**).

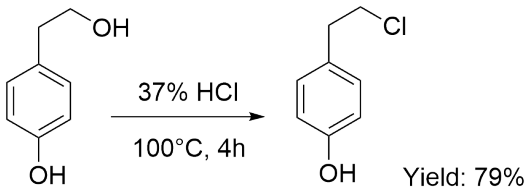
Syntese av 1-(2-allyloksy)etyl-4-(bensyloksy)benzen (**4**) ble utført ved addisjon av allylbromid til **3** istedet for addisjon av (bromometyl)syklopropan (Skjema 3). Allyl **4** ble dannet i utbytte på 86,6 % (1,1347 g, 4,23 mmol)



3 **4**

Skjema 3: Syntese av 1-(2-allyloksy)etyl-4-(bensyloksy)benzen (**4**) ved addisjon av allylbromid til 2-(4-bensyloksyfenyl)etanol (**3**).

En annen mulig rute for å danne betaksolol byggesteinen **6** var ved syntese av 4-(2-kloretyl)fenol (**9**) ved bruk av konsentrert saltsyre på **2** ved 100 °C (Skjema 4). Phenol **9** ble dannet i utbytte på 79,3 % (0,45 g, 2,87 mmol).

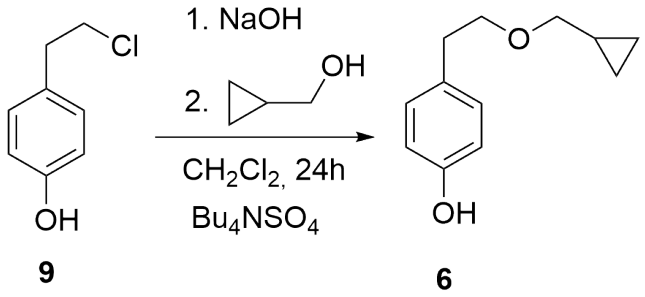


2 **9**

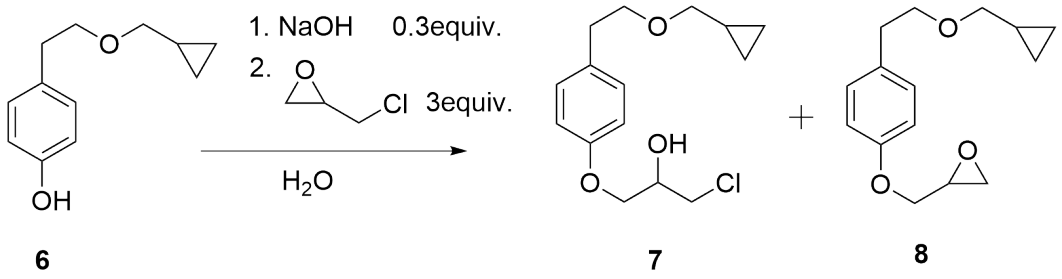
Skjema 4: Syntese av 4-(2-kloretyl)fenol (**9**) ved bruk av saltsyre på **2**.

Tilsats av Syklopropylmetanol ble brukt for å danne **6** fra fenol **9** (Skjema 5). Fenol **6** ble ikke isolert og renset i denne oppgaven.

Etter å ha dannet fenol **6**, vil behandling med epiklorhydrin og katalytisk mengde base danne 1-klor-3-(4-(2-(syklopropylmetoksy)etyl)fenoksy)propan-2-ol (**7**) (Skjema 6). Omsetning på 40 % av **6** til **7** ble oppnådd i denne oppgaven, men problemer med opparbeidelse av produkt hindret beregning av utbytte.



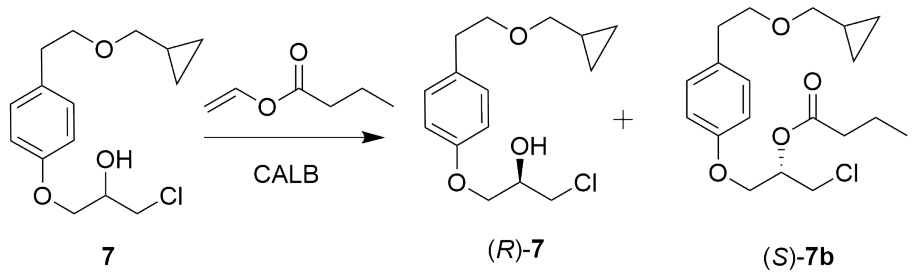
Skjema 5: Syntese av 4-(2-syklopropylmetoksyetyl)fenol (**6**) ved bruk av syklopropylmetanol på **9**.



Skjema 6: Syntese av 1-klor-3-(4-(2-(syklopropylmetoksy)etyl)fenoksy)propan-2-ol (**7**) og biprodukt 2-(4-(2-(syklopropylmetoksy)etyl)fenoksy)metyloksiran (**8**) ved addisjon av epiklorhydrin til 4-(2-syklopropylmetoksyetyl)fenol (**6**).

Et biprodukt fra syntesen av **7** er 2-(4-(2-(syklopropylmetoksy)etyl)fenoksy)metyloksiran (**8**). Epoksidet kan bli fjernet ved tilsats av LiCl og eddiksyre. Mekanisme for dannelse av epiklorhydrin **7** og epoksid **8** er vist i Skjema 2.9.

Etter at rasemisk klorhydrin **7** er dannet, vil kinetisk oppløsning katalysert av *Candida antarctica* Lipase B danne (*R*)-**7** og (**S**)-1-klor-3-(4-(2-(syklopropylmetoksy)etyl)fenoksy)propan-2-yl butyrat ((*S*)-**7b**) (Skjema 7).



Skjema 7: Dannelse av (*S*)-**7b** og (*R*)-**7** ved kinetisk oppløsning av rasemisk **7** katalysert av *Candida antarctica* Lipase B.

CONTENTS

1. INTRODUCTION

1.1. STEREOISOMERS AND ENANTIOMERS

Stereoisomers are molecules with the same molecular formula and the same constitution, that is, the same bond connections. Stereoisomers are divided into diastereomers and enantiomers. Diastereomers are defined as stereoisomers that are not mirror images, this include *cis*- and *trans*-alkenes and many compounds with more than one stereocenter. Enantiomers are stereoisomers who differ on all stereocenters, becoming mirror images of one another that can not be superimposed. No matter how the two molecules are twisted, they do not overlap correctly. Examples of both diastereomers and enantiomers are given in Figure 1.1.

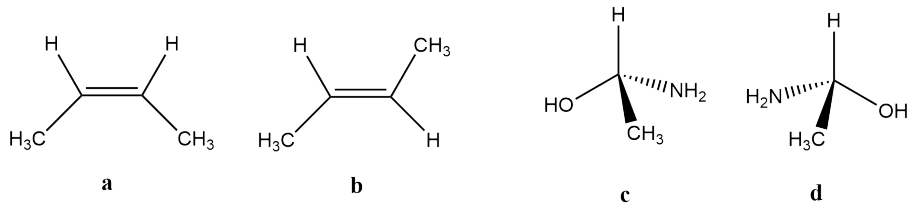


Figure 1.1: Examples of diastereomers (**a** and **b**) and enantiomers (**c** and **d**).

1.2. ENANTIOPURE COMPOUNDS IN MEDICINE

Chiral compounds are very interesting compounds in medicine because the human body contain many enzymes and receptors that are also chiral. What this means is that one enantiomer might activate a receptor, while the other does not. One way to look at this is like a hand putting on a glove. Only one of the gloves fit on each hand. With chiral compounds, the two enantiomers can have widely different effects in the body. If an enantiomer has a favourable effect it is called an eutomer, while the other is called a distomer. It is possible for both enantiomers to have the same effect and strength, although it is rare [2]. More common is the distomer having the same, but reduced activity, working as an antagonist to counteract the eutomer or having a different effect or no effect at all [3]. Bhupinder [3] presents a list of many active pharmaceutical ingredient (API) that are enantiomers and classify the distomers effect. Among these many β-blockers that are interesting to this thesis can be found. In atenolol and betaxolol, both of which have the (*S*)-enantomer as eutomer, the distomer is almost inactive. In timolol and penbutolol the distomer is active, but less potent.

The difference in activity between the eutomer and distomer is called the eudismic ratio. If the eudismic ratio is high, meaning that the distomer is less potent, inactive or an antagonist, a non-racemic drug is preferred. Having only the eutomer allows for smaller intake of medicine and generally brings about fewer side-effects.

An example of disastrous different pharmaceutical effects in eutomer and distomer is thalidomide which was licensed for sale in 1956. Originally prescribed to treat nausea, it was soon discovered that the drug also had teratogenic effects on the fetus of pregnant women. It was discovered later that only (*S*)-thalidomide has this effect [4][5]. This shows that knowing the effects of both eutomer and distomer is crucial in pharmaceutical products. For betaxolol, no unwanted effects has been reported for the distomer, but Sharif *et.al* reports that the (*S*)-enantiomer is more potent, which leads to lower doses needed for the same pharmaceutical effect[1]. After thalidomide was withdrawn from the market, tests were done and showed great promise in using it for the treatment of leprosy [2][6], although an interconversion between the two enantiomers happens in the human body, which still calls for great caution when using thalidomide.

From 2001-2010 only 9 % of new FDA approved substances worldwide was racemic [7], while a full 63 % were single enantiomers and the remaining 27 % achiral compounds. As people gets more knowledge of the difference in eutomers and distomers, it is expected that there will be less and less racemic drugs approved in the future because it is rare for both enantiomers to have the same pharmaceutical effect. The pharmaceutical market today consists of 55 % chiral drugs, 88 % of which are still sold as racemates [2]. Nguyen *et.al* also reports that among all β-blockers, the (*S*)-enantiomer is the most potent at blocking adrenoreceptors, yet most of them are sold as racemic drugs still today.

1.3. GLAUCOMA

The prevalence of glaucoma for the global population between 40 and 80 years is 3,54 % [8]. It is estimated that around 64.3 million people have glaucoma as of 2014, and it is projected to increase to around 111 million people by 2040. As glaucoma is the world leading cause of irreversible blindness having available treatment is crucial with an ageing population worldwide. Tham *et.al* [8] also reports that the highest prevalence glaucoma are found in Africa and Asia, which calls for affordable treatments as well.

Glaucoma is caused by damage to optic nerves as result of increased intraocular pressure (IOP). This damage causes the visual field to gradually reduce until the patient goes irreversibly blind. Primary open angle glaucoma (POAG) is a subset of glaucoma, where no underlying cause for raised IOP is identified. Worldwide POAG has a prevalence of 3,05 % which accounts for 86 % of all glaucoma cases [8].

The only treatment of glaucoma that has shown to be efficient is reducing IOP in the patient [9]. This can be done by applying eyedrops, laser therapy or surgery. For eyedrops there are a number of β-blockers that has shown to reduce IOP in patients. Vass *et.al* [10] compares three of these, timolol, betaxolol and carteolol, and their effect on lowering IOP and preventing loss of visual field. Vass *et.al* reports that the reduction of IOP was similar between all three β-blockers.

1.4. β-ADRENORECEPTOR ANTAGONISTS (β-BLOCKERS) AND β-AGONISTS

The first β-blockers on the market, pronethalol and propranolol were used in treatment of hypertension by lowering blood pressure [11][12]. β-Blockers binds to the cardiac β-adrenoreceptors, blocking adrenaline and noradrenaline from binding and activating the receptors. Although β-blockers are more commonly used to treat hypertension and other cardiac diseases, some are also used to treat glaucoma [13], migraine[14], hyperthyroidism and anxiety [15]. Betaxolol is one of the β-blockers that is primarily used to treat glaucoma.

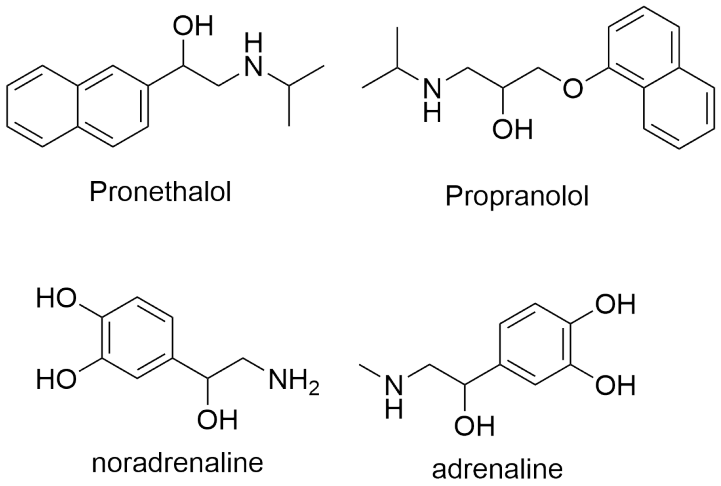


Figure 1.2: β-Antagonists pronethalol and propranolol used to treat hypertension alongside two natural β-agonists adrenaline and noradrenaline.

One side effect of β-blockers is that instead of binding to the cardiac β_1-adrenoreceptors, they bind to β_2-adrenoreceptors in the airways, resulting in bronchospasm. This side effect caused the development and usage of β_1-selective β-blockers such as betaxolol and atenolol to become more prevalent [16]. It is reported that (*S*)-betaxolol has 89 times greater affinity towards β_1-adrenoreceptors compared to β_2-adrenoreceptors, reducing the risk of bronchospasm from blocking the β_2-adrenoreceptors [17][1].

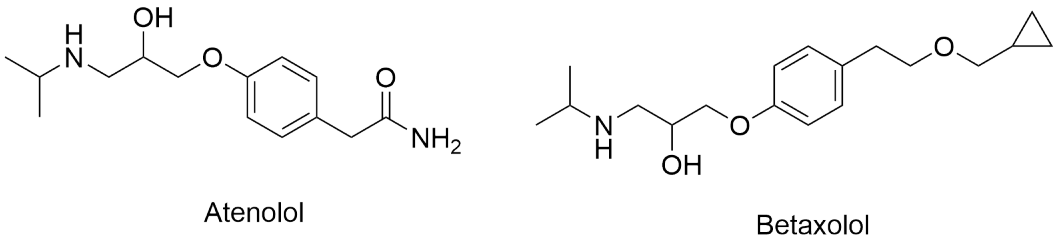
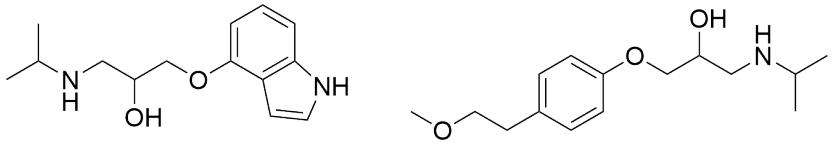


Figure 1.3: β_1-Selective β-antagonists betaxolol and atenolol.

In 2019 a number of different β-blockers were used in Norway, both in treatment of hypertension and for reducing IOP. The usage of these ranges from the non-selective pindolol used by 5 people in 2019 to β_1-selective metoprolol used by more than 287 000

people in the same year, placing it in the top 10 used in Norway. Both pindolol and metoprolol is used in treatment of hypertension [18].



Pindolol Metoprolol

Figure 1.4: Most used β_1-selective β-antagonist metoprolol, and the non-selective pindolol.

Unlike the β-antagonists which blocks a receptor to prevent other molecules from activating the receptor, a β-agonist binds to a receptor and then activates it, triggering a response from the nervous system. This means that unlike a β-antagonist that can cause bronchospasm from sudden contraction of muscles, a β-agonist can cause free airways to aid breathing. An example of a β_2-selective agonist is terbutalin, which is used in asthma medicine [19].

β-adreneric receptors are divided into 3 types, simply called β_1, β_2 and β_3. β_1-receptors are primarily found in the liver, heart and in fat cells. Their main role is sending signals to the sympathetic nervous system. The sympathetic nervous system is responsible for "flight-or-fight" responses. Activation of the sympathetic system releases adrenaline, which in turn activates β_1-receptors - increasing heart rate and cardiac output. A β_1-antagonist will prevent the activation of receptors leading to lowering of heart rate and is therefore useful in treatment of hypertension and arrhythmia [20].

β_2-receptors are found mostly in airway muscles making β_2-antagonists unviable in clinical treatment as they would disrupt breathing [21]. There are currently no FDA-approved β_2-selective antagonists. Primarily β_2-receptors can be activated by β_2-agonists such as terbutalin to ease breathing.

1.5. BETAXOLOL AS MEDICATION

Betaxolol is available as a racemic drug, Betoptic, with a strength of 0,5 % w/v and also as the pure (*S*)-enantiomer, Betoptic S, with a strength of 0,25 % w/v. These drugs were FDA approved in 1985 ad 1989 respectively [22]. Both drugs uses the hydrochloride salt of betaxolol as active pharmaceutical ingredient (API). Sharif *et.al* reports that (*S*)-betaxolol (levobetaxolol) is indeed more potent than (*R*)-betaxolol (dextrobetaxolol) in treatment of glaucoma [1]. Following this it is reasonable that the amount of API necessary in enantiomerically pure (*S*)-enantiomer would be lower than in a racemic drug. Both Betoptic and Betoptic S are given as eyedrops, meant to be used twice a day in dosage of 1 drop in the eye that has increased IOP [23].

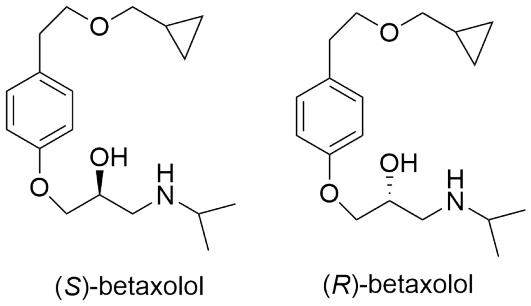


Figure 1.5: (*S*)-betaxolol (levobetaxolol) and (*R*)-betaxolol (dextrobetaxolol)

Compared to another β-antagonists, timolol, which is used widely in Norway as treatment for increased IOP, betaxolol is not used much, with only 594 persons annually, compared to timolol which was used by more than 20 000 people annually [18]. Watson *et.al* reports that stinging and uncomfortable eyes were more commonly reported in patients using betaxolol than those using carteolol or timolol [24]. He also reports that the initial effectiveness in reducing IOP were lower from betaxolol, but that over time it reached the same effectiveness as carteolol and timolol. One benefit of using betaxolol, is that unlike timolol and carteolol it is β_1-selective. This leads to lower risk of the drug binding to β_2-receptors, which has been reported to cause bronchospasm [16]. Chidlow *et.al* additionally reports that betaxolol can be a neuroprotective agents to weaken the impact of increased IOP on the retina [25][26]. They note that this may be caused by betaxolols affinity to Na^+ and Ca^{2+}-channels. Messmer *et.al* also reports that betaxolol was more potent at preserving the visual field of patients than timolol was [27].

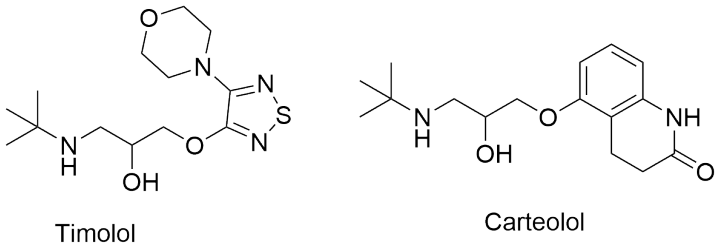


Figure 1.6: β-Antagonists timolol and carteolol used in treatment of glaucoma.

1.6. KINETIC RESOLUTION

Kinetic resolution can be used to synthesise enantiopure compounds with the help of enzymes or other chiral reagents. As have been mentioned before, enantiomers react differently in the human body. This is because our enzymes are all made out of chiral building blocks, *L*-amino acids. So in the same way a glove can only fit on one hand, sometimes only one enantiomer fit in the enzyme. The result is reaction happening solely or primarily on one of the two enantiomers. Kinetic resolution has previously been performed on a number of β-blockers similar to betaxolol by Jacobsen *et.al*[28][29]. These has been catalysed by the enzyme *Candida antarctica* Lipase B (CALB).

1.7. ENANTIOMERIC EXCESS AND ENANTIOMERIC RATIO

From a kinetic resolution the ratio between enantiomers can be calculated - the enantiomeric excess (*ee*). For this, normal analyses are not sufficient. NMR, HPLC and most other analyses does not differentiate the enantiomers. One way to differentiate the two is by chiral HPLC. With the correct composition of phases, the enantiomers can be separated and analysed. The enantiomeric excess is then calculated by Equation 1.1, where R and S are the areas of chromatography peaks for the two enantiomers (using R as the largest).

$$ee(\%) = \frac{R-S}{R+S} \times 100\% \tag{1.1}$$

.

This calculation is done for both the substrate (ee_s) and product (ee_p). These calculations can be used to find the enantiomeric ratio (E-value) given by Equation 1.2.

$$E = \frac{ln\frac{ee_p(1-ee_s)}{ee_s+ee_p}}{ln\frac{ee_p(1+ee_s)}{ee_s+ee_p}} \tag{1.2}$$

The E-value is specific for an enzyme and a substrate and a set of reaction parameters. The E-value will change if parameters like pH, temperature or solvent composition is changed. The E-value gives information about the ratio in conversion for the two enantiomers in a given reaction catalysed by the enzyme.

1.8. PREVIOUS SYNTHESIS OF (*S*)-BETAXOLOL

Two previous methods of synthesis of (*S*)-betaxolol has been studied, one of which has been relied on to some extent in the synthesis of 4-(2-cyclopropylmethoxyethyl)phenol. Joshi *et.al* [30] synthesised (*S*)-betaxolol in total yield of 24 % yield from 4-(2-hydroxyethyl)phenol with 99 %*ee*. The largest loss of yield was during the kinetic resolution of racemic 2-((4-(2-(cyclopropylmethoxy)ethyl)phenoxy)methyl)oxirane with Jacobsen catalyst to, where the yield of the synthesised (*S*)-2-((4-(2-(cyclopropylmethoxy)ethyl)phenoxy)methyl)oxirane was 43 % out of a possible 50 % which also forms a by-product which can not be used in further reactions.

Di Bono and Scilimati [31] reports synthesis of (*S*)-betaxolol in 54 % yield with 91 %ee, which is however not enough for use in pharmaceutical drugs. They report only a 4-step synthesis, but uses 4-(2-(cyclopropylmethoxy)ethyl)phenol as their starting material making the synthesis no shorter than the one reported by Joshi *et.al.* For forming (*R*)- and (*S*)-betaxolol they used lipase catalysed kinetic resolution with lipase from *Pseudomonas sp.*.

A synthetic route towards (*S*)-betaxolol, that to our knowledge has not been performed before, is the addition of epichlorohydrin to 4-(2-(cyclopropylmethoxy)ethyl)phenol to yield racemic 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol.

Addition of epichlorohydrin to a compounds similar to 4-(2-(cyclopropylmethoxy)ethyl)phenol, followed by kinetic resolution catalyzed by CALB

has been performed on many other β-blockers by Jacobsen *et.al* together with several master students [28][29][32][33]. The results are very promising with high enantiomeric excess of the β-blockers being obtained. The kinetic resolution shows great promise in forming many (*S*)-β-blockers enantioselectively.

Precursors from several other β-blockers are shown in Figure 1.7. Kinetic resolution catalyzed by CALB has been performed on these precursors to yield the respective precursors and then β-blockers in high enantiomeric excess.

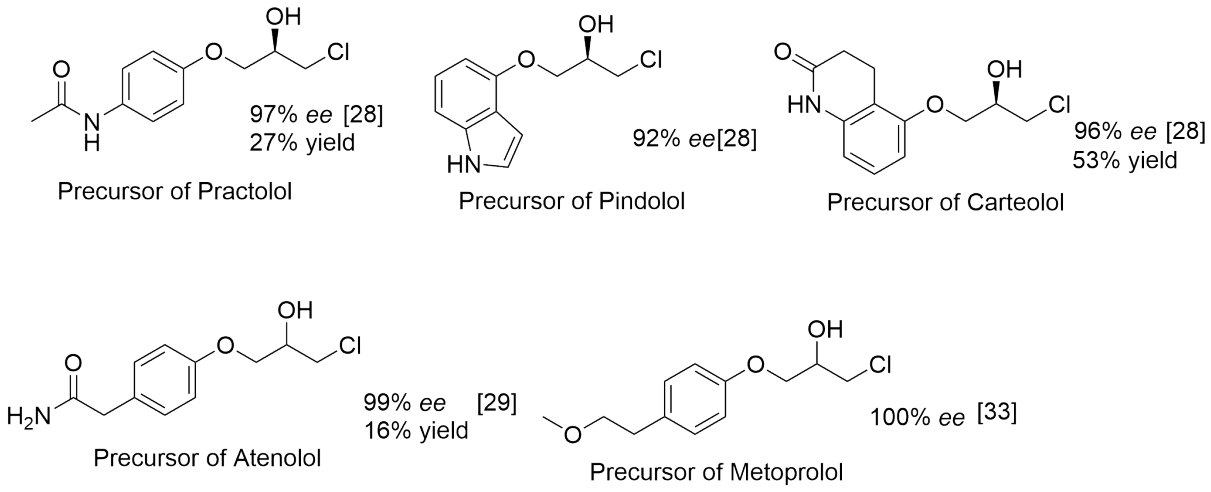


Figure 1.7: Precursors of β-blockers where kinetic resolution with CALB has been performed yielding high enantiomeric excess.

1.9. SUSTAINABLE CHEMISTRY

Paul Anastas, one of the early proponents of sustainable green chemistry in the 1990's defined the field as the "*design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances*" [34]. Later in 1998, together with John Warner, Anastas introduced 12 principles as a guiding framework for green chemistry, these where summarized in the acronym *PRODUCTIVELY* in 2005 [35]. The 12 principles are: **P**revent waste, **R**enewable materials, **O**mit derivatization steps, **D**egradable chemical products, **U**se safe synthesis methods, **C**atalytic reagents, **T**emperature and pressure ambient, **I**n-process monitoring, **V**ery few auxiliary substances, **E**-factor, maximise feed in product, **L**ow toxicity of chemical products, **Y**es, it is safe.

Anastas stresses that these principles are not meant to be independent of each other, but as a rather as a whole be the framework of synthesis design. .

A practical example of applying these principles can be seen in the synthesis of sertralin, API in Zoloft used to treat depression. In 2002 Pfizer developed a better synthetic route [34], which annually reduces waste by more than 800 tons [36]. One key step in changing the synthesis was the transition from a mixture of four organic solvents to using only a single solvent. Not only did this process reduce waste, but it is also reported to double yields [36].

2. RESULTS AND DISCUSSION

2.1. SYNTHETIC ROUTES TO (*S*)-BETAXOLOL (**1**)

This thesis aimed to synthesise the enantiopure (*S*)-betaxolol ((*S*)-**1**) (Figure 2.1). A key intermediate in the synthesis of (*S*)-betaxolol is 4-(2-(cyclopropylmethoxy)ethyl)phenol (**6**). Because of time constraints complete syntheses of *S*-betaxolol and **6** was not performed. Suggestions for a complete synthesis of **6** and (*S*)-betaxolol will be discussed in Chapter 3.

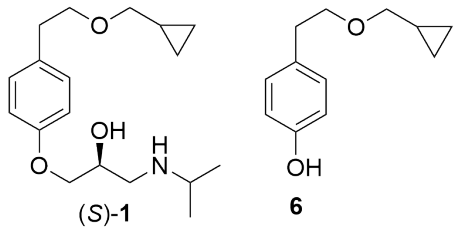
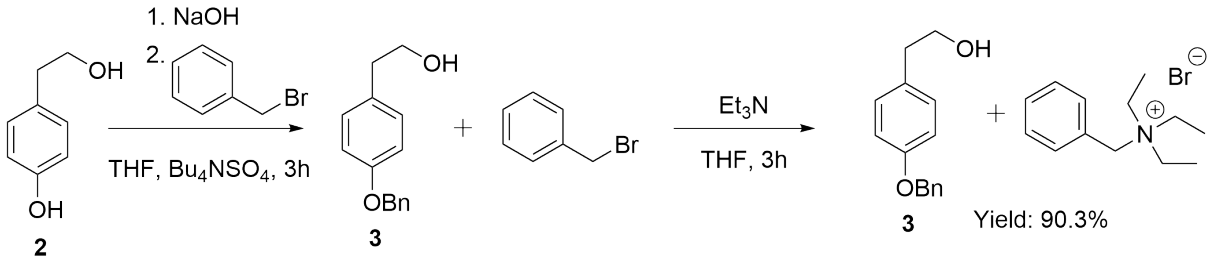


Figure 2.1: (*S*)-betaxolol ((*S*)-**1**) and its precursor 4-(2-cyclopropylmethoxyethyl)phenol (**6**).

2.2. SYNTHESIS OF 2-(4-BENZYLOXYPHENYL)ETHANOL (**3**) BY PROTECTION WITH BENZYLBROMIDE

The commercially available 4-(2-hydroxyethyl)phenol (**2**) (Scheme 2.1) was used as the starting material in the synthesis of key intermediate **6**. Before a reaction can be performed selectively on the primary alcohol, the phenol part of **2** must be protected. Chemdraw estimates the pKa of the two alcohols to be 9.8 and 15.2 for the phenol and primary alcohol respectively. Since deprotonation will occur on the phenol first, a protection group is needed before reactions can be performed on the primary alcohol.



Scheme 2.1: Synthesis of 2-(4-benzyloxyphenyl)ethanol (**3**) by addition of benzylbromide to 2-(4-hydroxyphenyl)ethanol (**2**).

Protection of phenol of **2** was achieved by using benzylbromide giving 2-(4-benzyloxyphenyl)ethanol (**3**). Deprotonation of **2** with NaOH (2 equiv.) in THF in the presence of a phase-transfer catalyst followed by addition of benzylbromide. After stirring for 4 h remaining benzylbromide was removed by addition of triethylamine which caused benzylbromide to form the water soluble benzyltriethyl ammoniumbromide which could be easily extracted. After stirring for 3 h, **3** was obtained in 90,3 % yield.

Another way to remove remaining benzylbromide that was performed in synthesis of **3** was flash chromatography in 1:2 ethylacetate (EtOAc) in petroleum spirit. This gave separation of **2**, **3** and benzylbromide with R_f values of 0.11, 0.18 and 0.75, respectively. If the reaction has not reached full conversion, a different eluent needs to be used as **2** and **3** has similar retention factors.

The advantage of using triethylamine over flash chromatography is that the amount of solvents and silica used will be reduced. It also required less work and preparation than a flash chromatography. The highest yield obtained when using flash chromatography was 45,3 %, but the reduced yield could also be affected by factors other than the method used for removing benzylbromide.

One of the key aspects taken from the synthesis of **3** is that without the use of a phase-transfer catalyst, the conversion of diol **2** into **3** was much slower. Some samples taken after 16 h showed incomplete conversion of **2** when not using a phase-transfer catalyst. Since NaOH is water soluble, a phase-transfer catalyst will help get the base in contact with the substrate, which is not water soluble, and increase the reaction rate.

^{1}H NMR analysis of **3** is shown in Figure 2.2. The aromatic signals above 7,2 ppm along with the singlet at 5,0 ppm, none of which are present in the ^{1}H NMR of **2** (Figure E.1) shows full conversion of **2** into **3**.

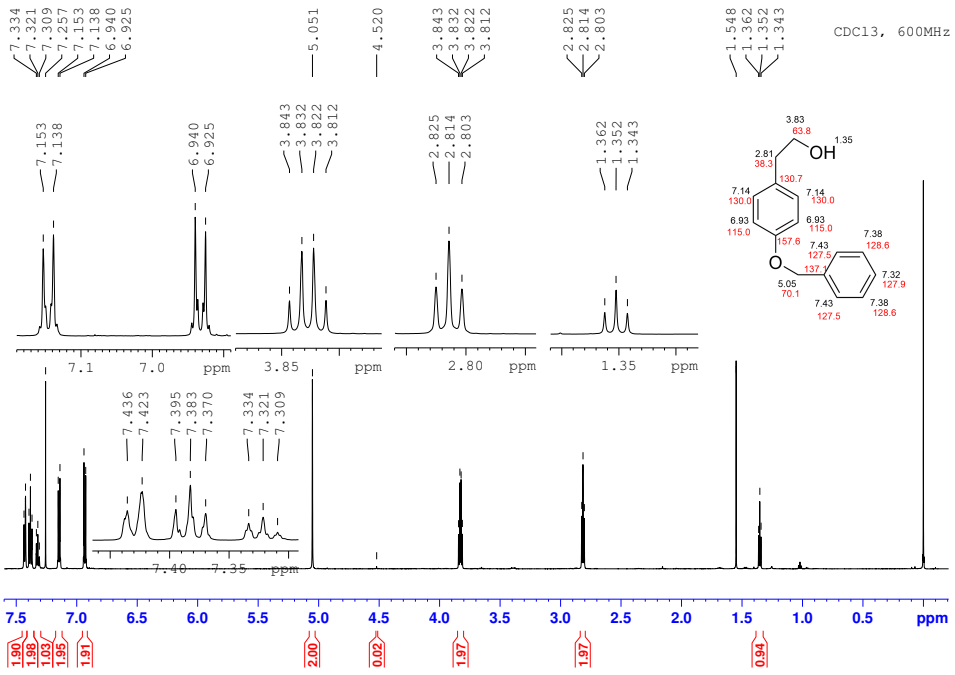


Figure 2.2: ^{1}H NMR spectra (600 MHz, $CDCl_3$) for 2-(4-benzyloxyphenyl)ethanol) (**3**).

In the ^{1}H NMR of **2** the phenol proton signal may appear around 4,7 ppm and in the ^{1}H NMR of benzylbromide (Figure E.2) the CH_2 signal will appear at 4,5 ppm. These signals must not be confused with the CH_2 signal from **3** at 5,0 ppm.

All NMR spectra for 2-(4-benzyloxyphenyl)ethanol (**3**) can be found in Appendix A. An overview from these NMR spectra is shown in Table 2.1. Assignment of shifts to **3** is shown in Figure 2.3.

Table 2.1: Compilation of data from HSQC, HMBC and COSY for 2-(4-benzyloxyphenyl)ethanol (**3**) (See Figure A.3, Figure A.4 and Figure A.5).

^{13}C shift	HSQC ^{1}H shift	HMBC ^{1}H shift	COSY ^{1}H shift
38.3	2.81 (CH_2)	3.83, 7.14	3.83
63.8	3.83 (CH_2)	2.81	1.35, 2.81
70.1	5.05 (CH_2)	7.38	-
115.0	6.93 (2xCH_{arom})	6.93	7.14
127.5	7.43 (2xCH_{arom})	5.05, 7.44, 7.32	7.32, 7.38[a]
127.9	7.32 (CH_{arom})	7.38	7.43, 7.38[a]
128.6	7.38 (2xCH_{arom})	-	7.32, 7.43[a]
130.0	7.14 (2xCH_{arom})	7.14	6.93
130.7	Cq	2.81, 3.83, 6.93	-
137.1	Cq	5.05, 7.38	-
157.6	Cq	5.05, 6.93, 7.14	-

[a]Shifts are difficult to distinguish

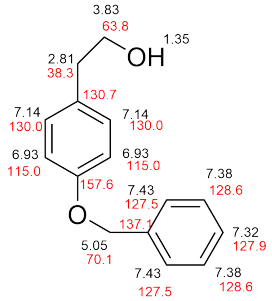


Figure 2.3: Assigned ^{1}H and ^{13}C shifts for 2-(4-benzyloxyphenyl)ethanol (**3**). NMR spectra can be found in Appendix A in Figure A.1 through Figure A.5.

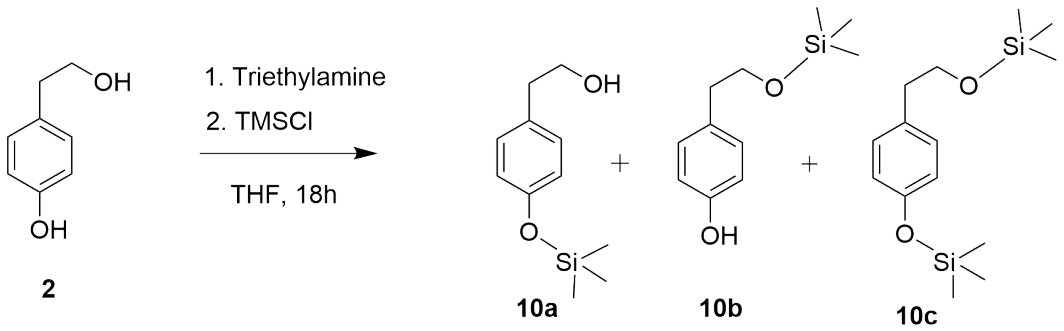
The short reaction time needed in the synthesis of **3** and the ease to remove excess reagents, makes protection with benzylbromide a good choice in the synthetic route to **6**. No protection, or other reactions, occurring on the primary alcohol was observed in any experiments when using benzylbromide with NaOH as base. Both THF and CH_2Cl_2 were used as solvents and showed the same results.

2.2.1. Protection with trimethylsilyl chloride

Protection of diol **2** was achieved with trimethylsilyl chloride (TMSCl). The main problem encountered in using TMSCl for protection of the phenol of **2**, was the reactivity of TMSCl

towards water. Protection by TMSCl needed to be performed in the absence of water and humidity, but this in itself was not a problem, however, a base suitable to selectively deprotonate the phenol was not found.

pKa values for the two alcohols in **2** were estimated by ChemDraw to be 9.8 and 15.3 in water for the phenol and primary alcohol respectively. Estimated pKa values were not found in organic solvents for **2**. One article predicts the pKa of many aromatic compounds in organic solvents [37]. While none of these match **2** exactly, 4-methoxyphenol changes pKa from 10.5 in water to 16.6 in DMSO, and a similar case is reasonable to expect for **2**. A pKa-value for triethylamine in organic solvents showed triethylamine to have pKa values of 9 in DMSO and 12.5 in THF.



Scheme 2.2: Synthesis of 2-(4-((trimethylsilyl)oxy)phenyl)ethan-1-ol (**10a**), and byproducts **10b** and **10c**, by protection of 2-(4-hydroxyphenyl)ethanol (**2**) with TMSCl.

Protection of **2** using triethylamine (2 equiv.) as base and TMSCl (2 equiv.) as protection group yielded a mixture of **10a**, **10b** and **10c** after 18 h (Scheme 2.2). ^{1}H NMR of the mixture (Figure 2.4) shows three distinct signals below 1 ppm and no alcohol peaks at 1.3 or 4,7 ppm as seen in the ^{1}H NMR of **2** (Figure E.1). The overlapping in the aromatic signals at 6.7 and 7,1 ppm as well as the superimposed multiplets at 3,7 ppm indicates the formation of more than one product. It is difficult to say whether one of these is the desired compound **10a** as no further purification was performed.

Protection of **2** using only 1 equivalent triethylamine as base and 1 equivalent TMSCl as protection group in THF gave no conversion of **2** after 24 h. Increasing the amout of base and protection group by using 3 equivalents triethylamine as base in THF and adding 2 equivalents TMSCl, protection of both alcohols in **2** was achieved yielding trimethyl(4-(2-((trimethylsilyl)oxy)ethyl)phenoxy)silane (**10c**). ^{1}H NMR of the **10c** (Figure 2.5) showed two distinct signals below 1 ppm integrating to 18. Signals from the two alcohol groups at 1.3 and 4,7 ppm seen in ^{1}H NMR of **2** (Figure E.1) are absent. While it is not uncommon for alcohol signals to not be seen in ^{1}H NMR when using $CDCl_3$, the alcohol peaks are seen frequently in other syntheses in this thesis.

The experiments show that triethylamine is too strong base to selectively deprotonate the phenol of **2** when using THF as solvent. Protection of **2** using TMSCl was not examined further. If a base suitable to selectively deprotonate the phenol of **2** is used, further examination of using TMSCl as protection group can be performed.

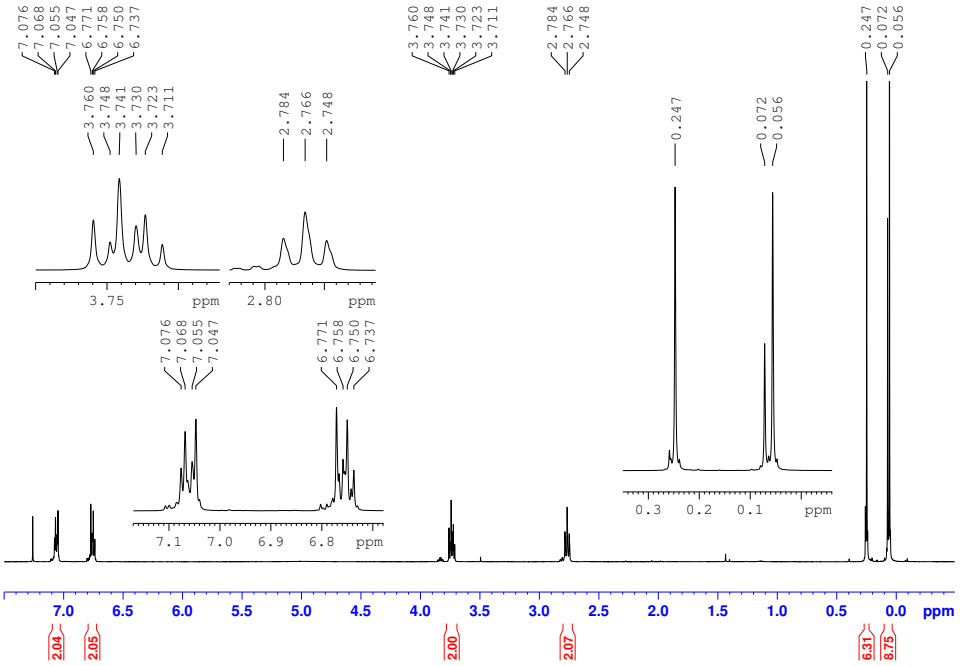


Figure 2.4: ^{1}H NMR spectra (($CDCl_3$ without TMS, 600 MHz) of a mixture of **10a**, **10b** and **10c**.

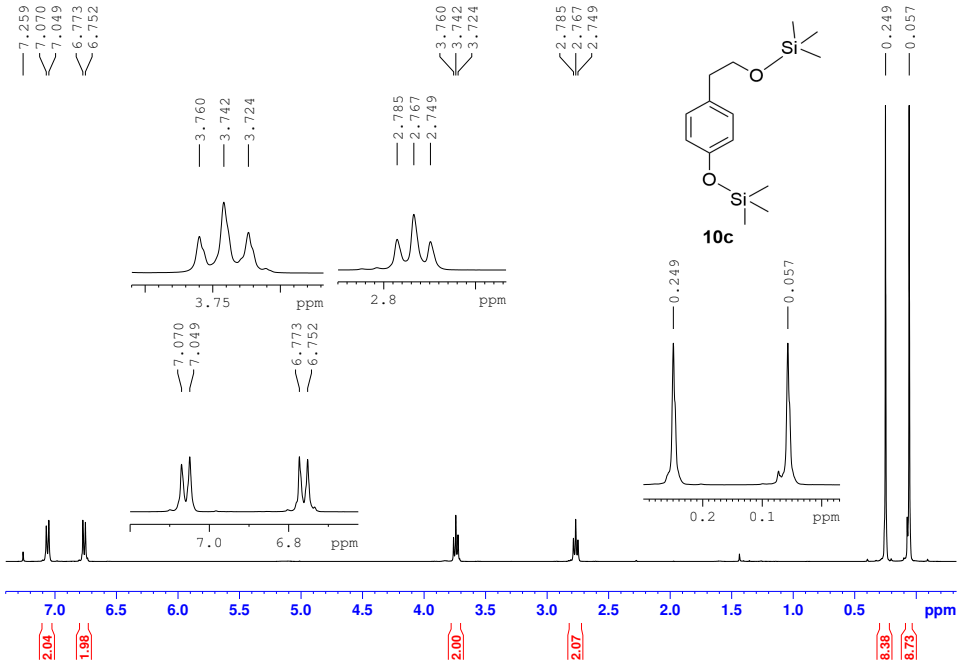
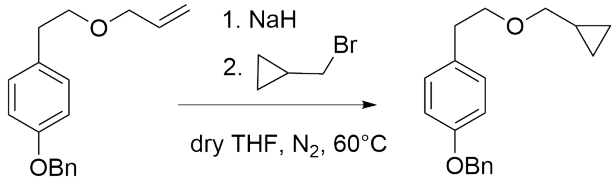


Figure 2.5: ^{1}H NMR spectra ($CDCl_3$ without TMS, 400 MHz) of the byproduct **10c**.

2.3. SYNTHESIS OF 1-BENZYLOXY-4-(2-CYCLOPROPYLMETHOXYETHYL)BENZENE (**5**)

Synthesis of 1-benzyloxy-4-(2-cyclopropylmethoxyethyl)benzene (**5**) by addition of (bromomethyl)cyclopropane to 2-(4-benzyloxyphenyl)ethanol (**3**) (Scheme 2.3) was performed by using KO^{t}Bu as base in CH_2Cl_2 in the presence of a phase-transfer catalyst resulted in conversion of 5 % of **3** into **5** after 18 h.



4 **5**

Scheme 2.3: Synthesis of 1-benzyloxy-4-(2-cyclopropylmethoxyethyl)benzene (**5**) by addition of (bromomethyl)cyclopropane to 2-(4-benzyloxyphenyl)ethanol (**3**).

To increase conversion into **5**, a stronger base was used since KO^{t}Bu may not be strong enough to deprotonate the primary alcohol due to its relatively low acidity. Using 2 equivalent NaH as base was performed at room temperature in dry THF under N_2 atmosphere. After 18 h ^{1}H NMR showed conversion of around 10 % of **3** into **5**.

NaH as base was thought to be strong enough to deprotonate the primary alcohol, which has an estimated pKa of 15. The reason for the low conversion should therefore not be due to slow or limited deprotonation. Although bromide is a good leaving group, the low conversion could be due to low reactivity of the reagent (bromomethyl)cyclopropane. Increased time and temperature was used next to increase the conversion of **3** into **5**. Using 2 equivalents NaH in dry THF in N_2 atmosphere at 60 °C. After stirring for 48 h at 60 °C, ^{1}H NMR of the mixture of **3** and **5** (Figure 2.6) showed conversion of 50 % of **3** into **5**. Due to time constraints the product was not purified further.

Synthesis of **5** was also performed using KO^{t}Bu as base in THF in the presence of a phase-transfer catalyst, stirring at 60 °C for 14 days. ^{1}H NMR showed conversion of around 20 %. Due to the harsh conditions and long reactions times needed, paired with the mediocre conversion obtained, no further attempts were made in synthesising **5** through this synthetic route. It was later found that NaOH and KO^{t}Bu is strong enough base to deprotonate the primary alcohol of **2** when heated to 40 °C. The low conversion in the synthesis of **5** is then thought to be because of the low reactivity of the reagent (bromomethyl)cyclopropane.

A synthesis of **5** from protected alcohol **3** performed by others was not found, but a similar synthesis by Claude *et.al* was examined [38]. Claude *et.al* added (bromomethyl)cyclopropane to 2-(4-bromophenyl)ethanol using NaH as base. After stirring for 16 h at room temperature 1-bromo-4-(2-(cyclopropylmethoxy)ethyl)benzene was obtained in 51 % yield.

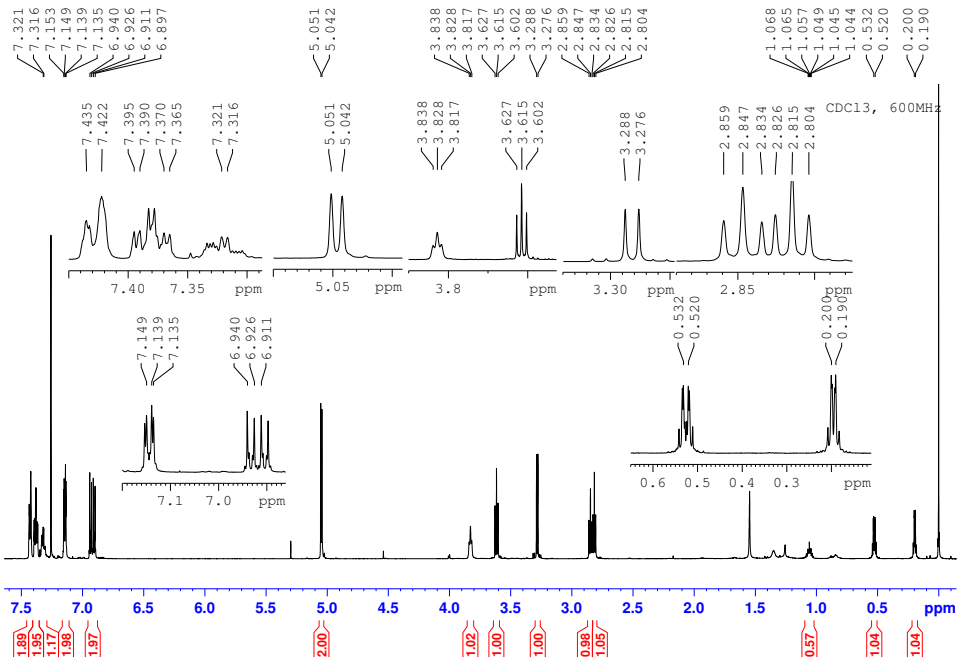
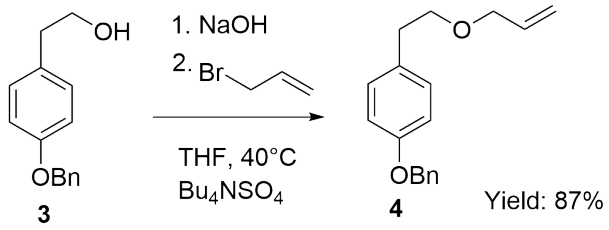


Figure 2.6: ^{1}H NMR spectra (600 MHz, $CDCl_3$) of mixture of 2-(4-benzyloxyphenyl)ethanol (**3**) and 1-(benzyloxy)-4-(2-(cyclopropylmethoxy)ethyl)benzene (**5**).

2.4. Synthesis of 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**)

Synthesis of 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**) was performed by adding allylbromide to protected phenol **3** using NaOH as base in the presence of a phase-transfer catalyst (Scheme 2.4). After stirring for 40 h at 40 °C, allyl **4** was obtained in 86,8 % yield. Assignment of ^{1}H and ^{13}C shifts for **4** is shown in Figure 2.7.



Scheme 2.4: Synthesis of 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**) by addition of allylbromide to 2-(4-benzyloxyphenyl)ethanol (**3**).

Synthesis of allyl **4** by adding allylbromide to protected phenol **3**, stirring at room temperature using NaOH as base with a phase-transfer catalyst resulted in conversion of 50 % of **3** into **4** after 7 days.

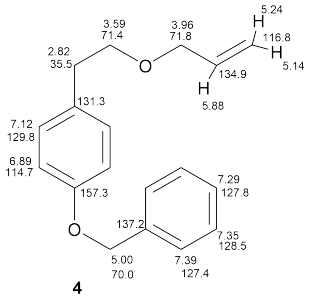


Figure 2.7: Assigned ^{1}H and ^{13}C shifts for 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**). All NMR spectra for **4** are shown in Appendix B.

The formation of **4** can be seen on TLC in 1:2 EtOAc in petroleum spirit, with R_f values of 0.18 and 0.65 for **3** and **4** respectively. The alkene peaks around 5 ppm, having coupling constants of 10 Hz and 17 Hz are also clear indication of an alkene compound (See Figure 2.8).

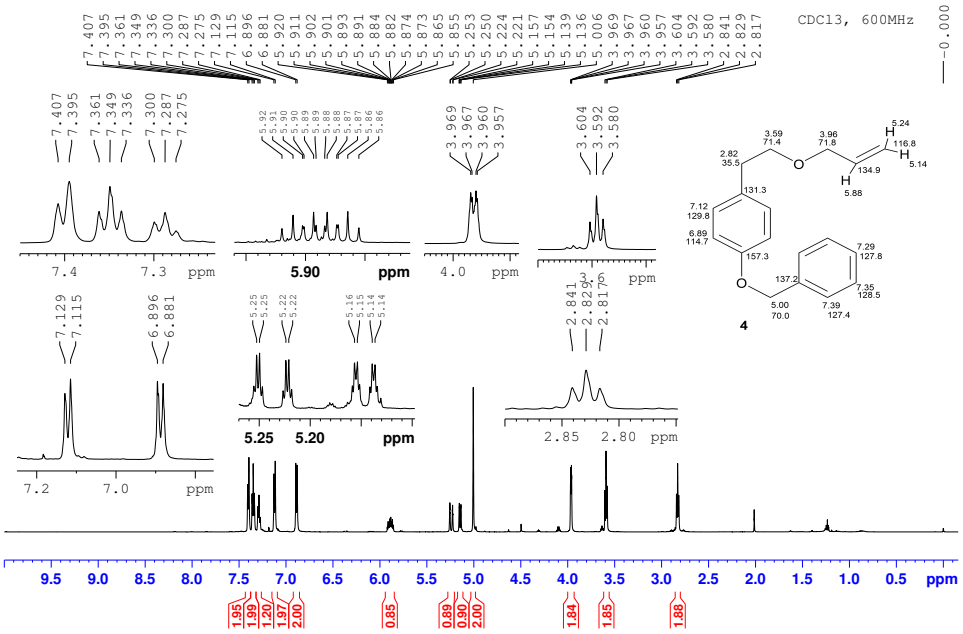


Figure 2.8: ^{1}H NMR spectra (600 MHz, $CDCl_3$) for 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**).

Data from HSQC, HMBC and COSY spectra for **4** are presented in Table 2.2. All NMR spectra for **4** are shown in Appendix B.

Table 2.2: Data from HSQC, HMBC and COSY for 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**) (See Spectra in Appendix B.

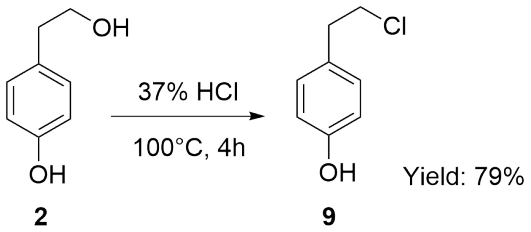
^{13}C shift	HSQC ^{1}H shift	HMBC ^{1}H shift	COSY ^{1}H shift
35.5	2.82 (CH_2)	3.59, 7.12	3.59
70.0	5.00 (CH_2)	7.39	-
71.4	3.59 (CH_2)	2.82, 3.96	2.82
71.8	3.96 (CH_2)	3.59, 5.14, 5.24	5.88
114.7	6.89 (2xCH_{arom})	6.89, 7.12	7.12
116.8	5.14, 5.24 $CH_{2alkene}$,	3.96	5.88
127.4	7.39 (2xCH_{arom})	5.00, 7.29	7.38[a]
127.8	7.29 (CH_{arom})	7.35, 7.39	7.32[a]
128.5	7.35 (2xCH_{arom})	7.38	7.38[a]
129.8	7.12 (2xCH_{arom})	2.82, 7.12	6.89
131.3	Cq	2.82, 3.59, 6.89	-
134.9	5.88 (CH_{alkene}	3.96, 5.14, 5.24	5.14, 5.24, 3.96
137.2	Cq	5.00, 7.35	-
157.3	Cq	5.00, 6.89, 7.12	-

[a]Shifts are difficult to distinguish

After synthesis of **4**, a Simmons-Smith cyclopropanation can be performed to yield **5**. This cyclopropanation was not performed in this thesis. The Simmons-Smith cyclopropanation is a well known way of forming cyclopropanes and should be suitable for synthesis of **5**. In their synthesis of betaxolol, Joshi *et.al* synthesised 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**) from **3** [30]. Joshi achieved a yield of 98 % of allyl **4** after 2 h of stirring at 40 °C using KO^{t}Bu as base. Using NaOH, this short reaction time seems unobtainable without increasing the temperature further, as samples taken after 24 h did not show full conversion. Further optimisation of the synthesis of **4** can improve reaction time, reduce the amount of chemicals needed and increase the yield of **4**.

2.5. SYNTHESIS OF 4-(2-CHLOROETHYL)PHENOL (**9**)

One synthetic route to phenol **6** attempted was adding diol **2** to concentrated HCl (37 %) and stirring at 100 °C for 4 h (Scheme 2.5). Brown oil of **9** was obtained in 79,0 % yield.



Scheme 2.5: Synthesis of 4-(2-chloroethyl)phenol (**9**) from 2-(4-hydroxyphenyl)ethanol (**2**).

While ^{1}H NMR specter of **9** (Figure 2.9) is similar to the ^{1}H NMR specter for diol **2** (Figure E.1) the formation of **9** can be seen by the change in multiplicity of the CH_2 NMR signal at 3,7 ppm and the disappearance of the primary alcohol peak at 1,3 ppm.

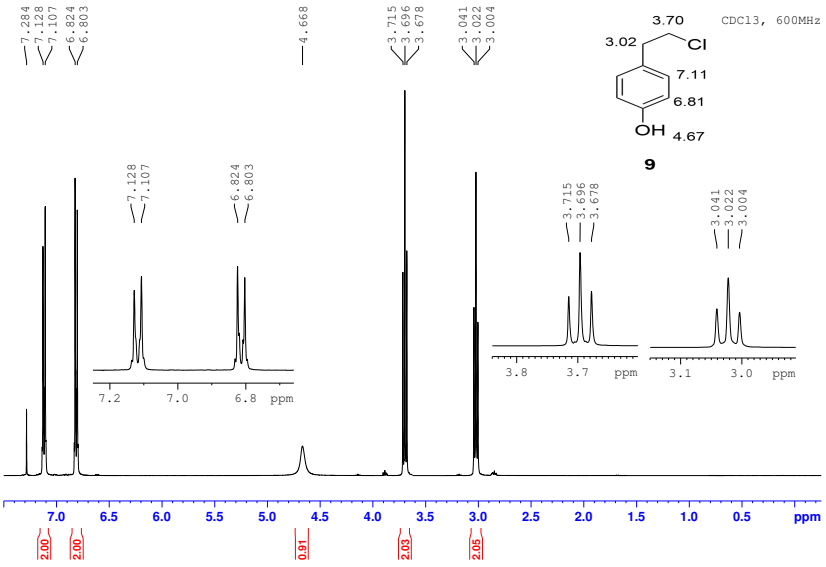


Figure 2.9: ^{1}H NMR specter (600 MHz, $CDCl_3$) of 4-(2-chloroethyl)phenol (**9**).

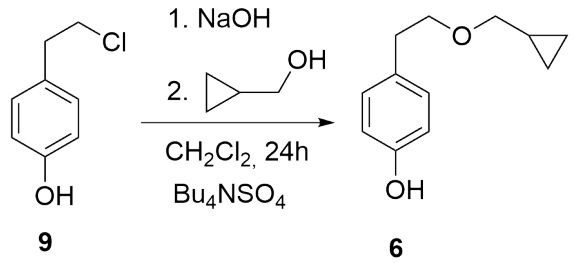
To reduce the harsh condition needed, the synthesis was also performed at 70 °C, where stirring for 18 h gave a conversion of **2** into **9** of 92 %. The product was not purified. Lower temperatures may also be possible, without reducing the high yield or conversion. It is expected that doing so will require longer reaction times.

Spivey *et.al* performed synthesis of **9** with a yield of 98 % through adding **2** to concentrated HCl, stirring for 3 h at 100 °C [39].

The advantage of using this synthetic route instead of synthesis of protected phenol **3** and allyl **4** is that to reach the key intermediate **6** neither a protection nor a deprotection step is needed, saving much time and chemicals.

2.6. Synthesis of 4-(2-(cyclopropylmethoxy)ethyl)phenol (**6**) from 4-(2-chloroethyl)phenol (**9**)

Synthesis of **6** was attempted by adding phenol **9** to a solution of cyclopropylmethanol and NaOH in the presence of a phase-transfer catalyst and stirring for 24 h (Scheme 2.6). ^{1}H NMR specter (Figure 2.10) of the obtained compound(s) showed a complex aromatic region indicating that more than one aromatic system is present.



Scheme 2.6: Synthesis of 4-(2-(cyclopropylmethoxy)ethyl)phenol (**6**) by addition of cyclopropylmethanol to 4-(2-chloroethyl)phenol (**9**).

Comparing ^{1}H NMR specter of the obtained compound (Figure 2.10) to ^{1}H NMR specter of purchased 4-(2-(cyclopropylmethoxy)ethyl)phenol (**6**) (Figure 2.11) it is clear that pure **6** has not been obtained through this synthesis.

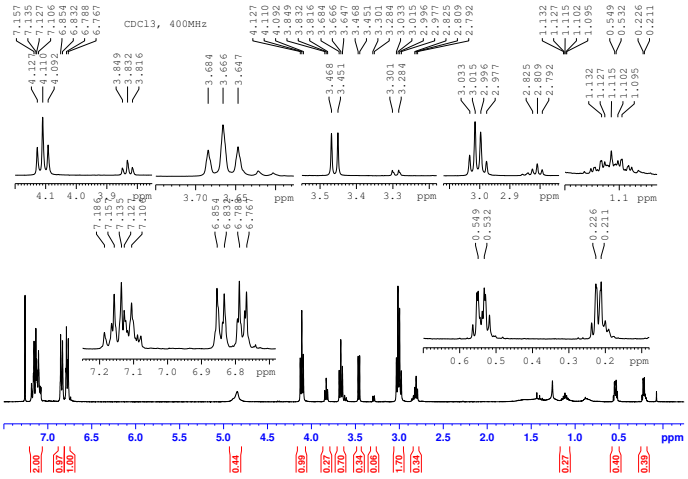


Figure 2.10: ^{1}H NMR specter (400 MHz, $CDCl_3$) of either a mixture of **6** and **9** or a di-aromatic by-product similar to the one shown in Scheme 2.7.

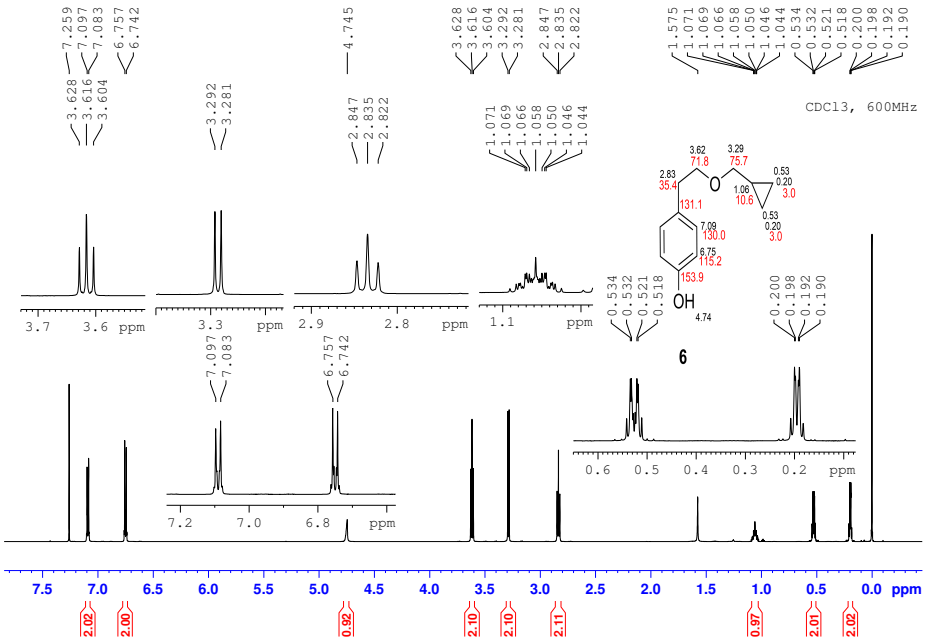


Figure 2.11: ^{1}H NMR specter (600 MHz, $CDCl_3$) of purchased 4-(2-(cyclopropylmethoxy) ethyl)phenol (**6**)

Because of the complexity of the aromatic shifts in Figure 2.10, a di-aromatic compound may have been formed. Because the phenol of **9** is deprotonated when adding NaOH as base, it may react intermolecularily with another molecule of **9**, instead of reacting with cyclopropylmethanol, forming a di-aromatic compound (Scheme 2.7).

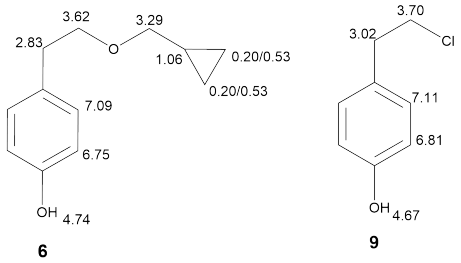
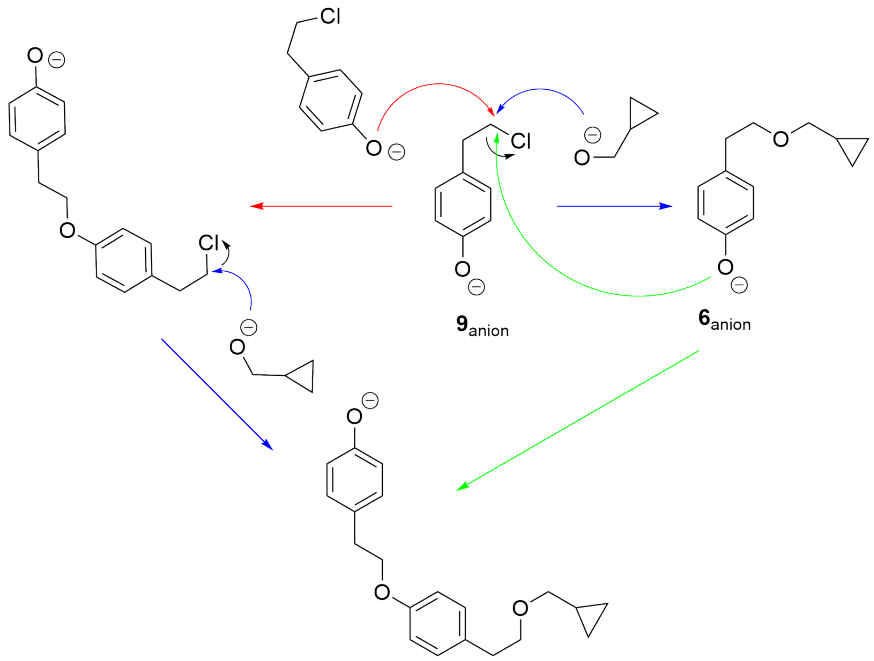


Figure 2.12: ^{1}H shift assignment to **6** and **9**. NMR spectra are shown in Figure 2.9 and Figure 2.11.



Scheme 2.7: Proposed mechanism to form **6** and possible by-products from the treatment of **9** with cyclopropylmethanol.

What ^{1}H NMR of the obtained compound (Figure 2.10) did show is the presence of a cyclopropane by the shifts at 0.2, 0.5 and 1 ppm. The ^{1}H NMR specter also showed 7 peaks between 2.7 and 4,2 ppm, while only 5 are expected if **6** and **9** are the only compounds present.

Attempts at assigning the shifts from Figure 2.10 to either **6** or **9** showed that integrals did not fit. If the ^{1}H NMR did only show **6** and **9**, it implies a conversion of 20 % of **9** into **6** seen from the shifts at 0.2 and 0,5 ppm. While the shifts at 0.2 and 0,5 ppm each integrate to 0.4, the aromatic signal at 6,78 ppm which also belongs to 2 protons, integrate to 1. The two cannot then belong to the same compound unless the aromatic shifts belong to twice as many protons. ^{1}H Shift assignment to both **6** and **9** are shown in Figure 2.12 for comparison.

Due to time constraints additional NMR spectra were not taken of the sample. It is therefore difficult to determine whether or not a di-aromatic compound or the desired **6** has indeed been formed.

To avoid the formation of the possible di-aromatic by-product proposed in Scheme 2.7, synthesis of **6** was attempted by dissolving **9** in 40 ml CH_2Cl_2 and adding it dropwise to a mixture of excess cyclopropylmethanol and triethylamine as base, before stirring for 24 h. This synthesis yielded a compound, where ^{1}H NMR specter showed contained only 5 % cyclopropyl. The compound was not purified.

Another synthesis of **6**, where **9** was dissolved in CH_2Cl_2 and added dropwise to a solution of excess cyclopropylmethanol and NaOH as base was performed.

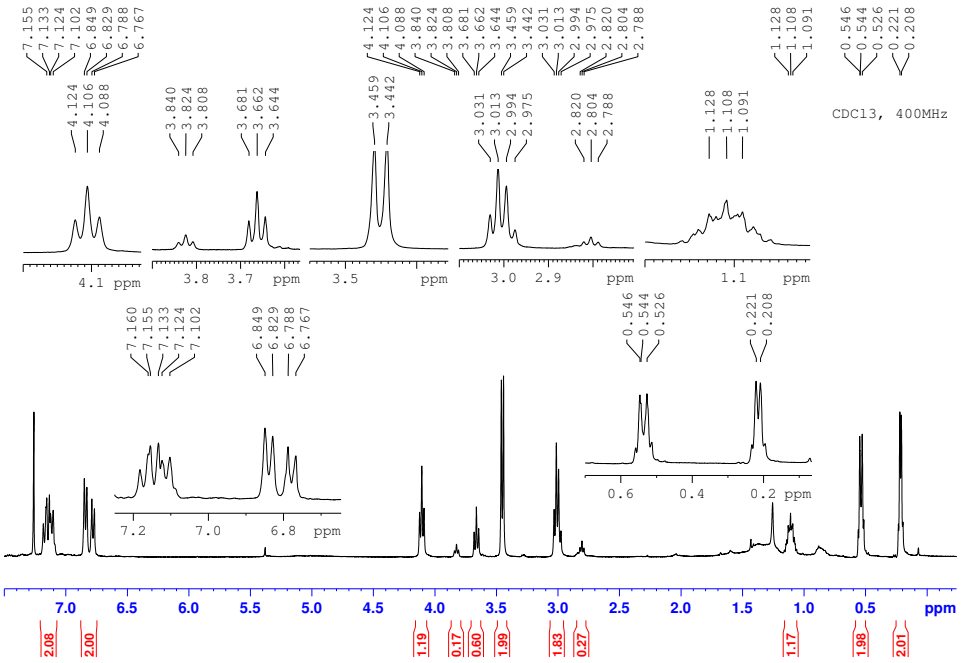
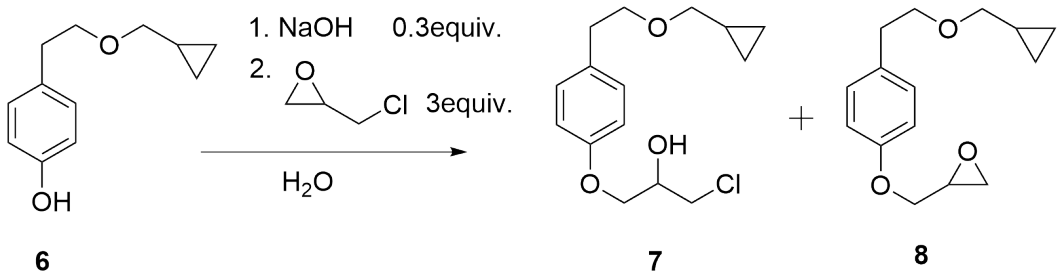


Figure 2.13: ^{1}H NMR specter (400 MHz, $CDCl_3$) likely of a mixture of **6** and **9**.

^{1}H NMR spectra (Figure 2.13) of the obtained compound showed different integrals than the previous synthesis of **6** (Figure 2.10). The cyclopropyl shifts at 0.2 and 0,5 ppm now each integrates to 2.0 instead of the previous 0.4. This implies that a larger amount of cyclopropyl-compounds has been formed. Due to their structural similarity, the reagent cyclopropylmethanol may also give signals at 0.2 and 0,5 ppm. A ^{1}H NMR specter of cyclopropylmethanol was also taken (Figure E.7). If the ^{1}H NMR of the obtained compounds contained remaining cyclopropylmethanol, its cyclopropyl signals would have to overlap perfectly with the cyclopropyl signals from **6**, but no disturbance is seen in the signals at 0.2 or 0,5 ppm in the ^{1}H NMR of the obtained compounds (Figure 2.13). Cyclopropylmethanol is water soluble and has a boiling point of 124 °C. Extraction of the possible remaining cyclopropylmethanol was performed with distilled water and the sample was left at vacuum over night. ^{1}H NMR specter afterwards showed the same peaks and integrals as before the extraction. Due to time constraints no further analysis of this sample was performed.

2.7. Synthesis of 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**)

Addition of 2 equivalents epichlorohydrin to phenol **6** dissolved in DMSO and distilled water using 0.3 equivalents NaOH as base, **7** was obtained in 40 % conversion (Scheme 2.8).



Scheme 2.8: Synthesis of 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**) and by-product 2-((4-(2-(cyclopropylmethoxy)ethyl)phenoxy)methyl)oxirane (**8**) by addition of epichlorohydrin to 4-(2-(cyclopropylmethoxy)ethyl)phenol (**6**).

Two further syntheses of chlorohydrin **7** was performed with similar reaction conditions. Table 2.3 shows an overview of some conditions and the results of the syntheses.

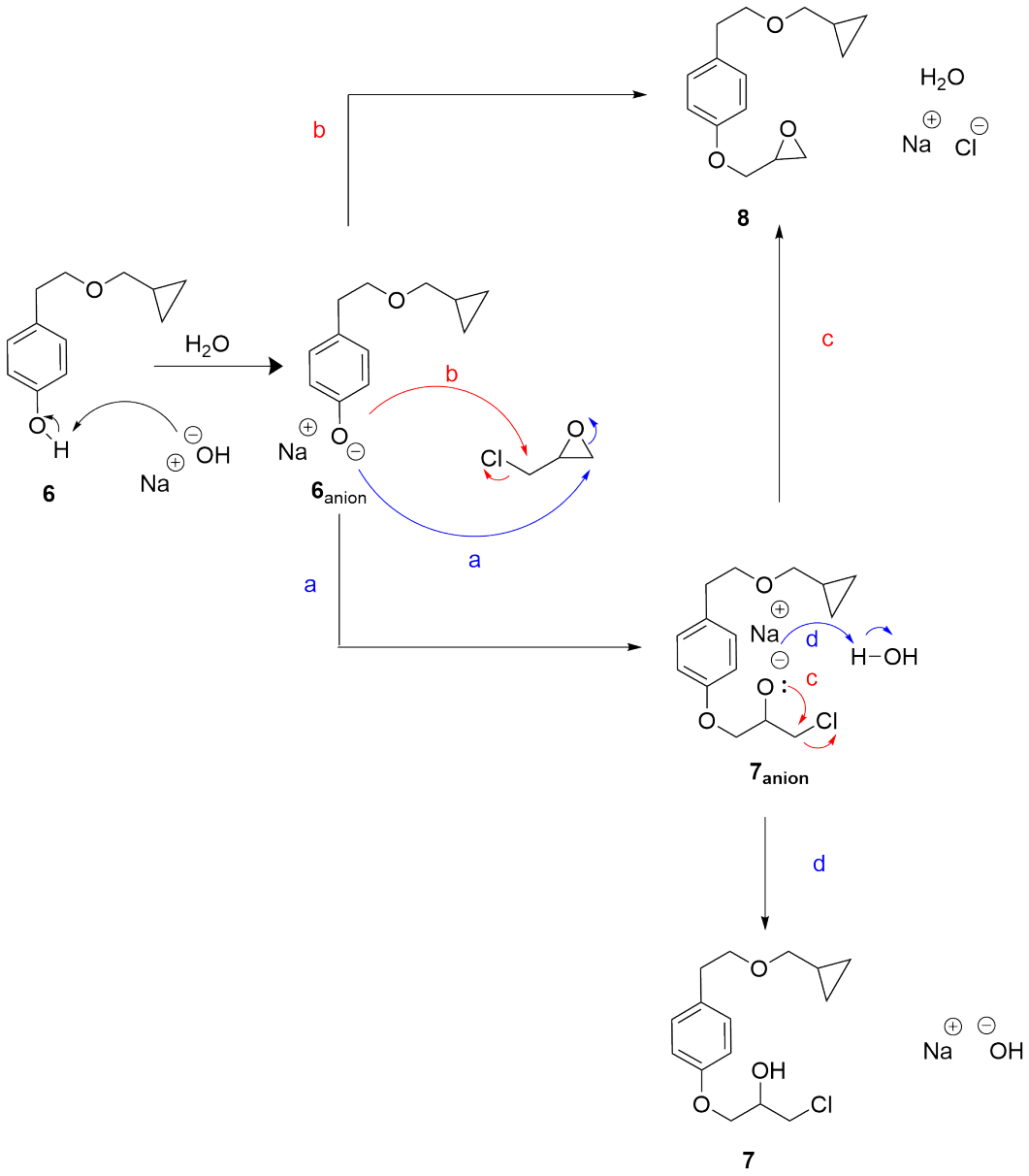
Table 2.3: Three synthesis of 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**) all using similar reaction conditions. All percentages are from ^{1}H NMR integrals.

			Composition of product (%)		
NaOH	Epichlorohydrin	Reaction time	**6**	**7**	**8**
0.3equiv.	2equiv.	72 h	60	40	<1
0.4equiv.	4equiv.	96 h	15	75	10
0.3equiv.	3equiv.	45 h	3	57	40

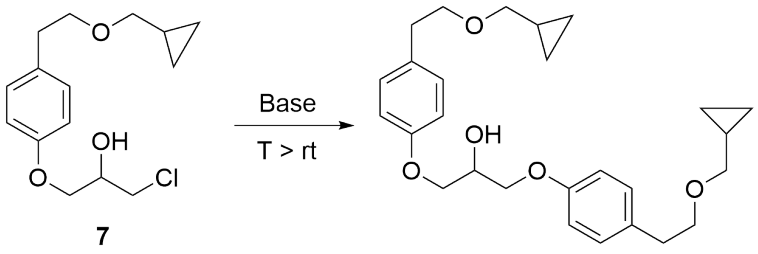
In the synthesis of compounds similar to 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl) phenoxy)propan-2-ol (**7**) from other β-blockers it has been found that formation of an epoxide from the secondary alcohol often happens when using large amounts of base [28]. The mechanism for formation of this epoxide in the synthesis of (*S*)-carteolol is presented by Gundersen *et.al* [28] and the equivalent for betaxolol precursors is shown in Scheme 2.9.

When forming **7** from $\mathbf{7}_{anion}$, the base is regenerated which allows for the use of less than 1 equivalent base. If using large amounts of base, **7** will more likely be in a deprotonated state which allows for formation of 2-((4-(2-(cyclopropylmethoxy)ethyl)phenoxy)methyl)oxirane (**8**) from the deprotonated $\mathbf{7}_{anion}$ through an internal cyclization. The formation of epoxide **8** is itself not a problem, as addition of acetic acid (5 equiv.) and LiCl (2 equiv.) will cause a ring opening of **8** to form the desired chlorohydrin **7** [28].

A better incentive to use catalytic amounts of base is seen in the synthesis of other β-blockers where dimerization of **7** has occurred similar to the one shown in Scheme 2.10. Dimerization has been showed to be more common when using larger equivalents of base, high temperatures or long reaction times [28]. Austli reports that in one experiment using 1 equivalent NaOH and 5 equivalents epichlorohydrin at 80 °C, the dimerization product was achieved with yield of 93 % in the synthesis of (*S*)-practolol [32]. In this thesis dimerization has not been observed. This may be due to the catalytic amount of base and low temperature used in all experiments.



Scheme 2.9: Mechanism for the base-catalyzed formation of 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl) phenoxy)propan-2-ol (**7**) and 2-((4-(2-(cyclopropylmethoxy)ethyl)phenoxy)methyl)oxirane (**8**) from 4-(2-(cyclopropylmethoxy)ethyl)phenol (**6**).



Scheme 2.10: A possible dimerization product from synthesis of **7** when using excess amounts of base or high temperatures.

Optimisation of the synthesis of chlorohydrin **7** to avoid the formation of epoxide **8** and dimerization products includes using catalytic amounts of base at room temperature with 2-5 equivalents of epichlorohydrin. In the synthesis of some other β-blockers, using epichlorohydrin in equivalents between 2 and 5 showed little to no effect on the overall yields and composition of the products [32][33].

Due to time constraints, the synthesis of chlorohydrin **7** remains unoptimized. The effects of different equivalents of base and epichlorohydrin has not been examined for precursors of (*S*)-betaxolol, neither have temperature-, time- or solventeffects on the formation of **7** and epoxide **8** and the possibility of a dimerization product. The thesis has however showed that the formation of chlorohydrin **7** is possible through addition of epichlorohydrin of up to 75 % conversion from **6** to **7** after 96 h.

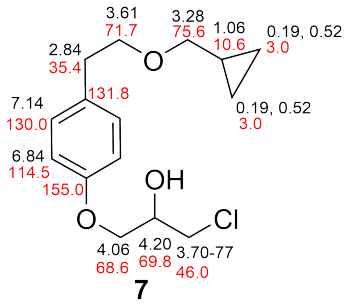


Figure 2.14: Assigned ^{1}H and ^{13}C NMR shifts to 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl) phenoxy)propan-2-ol (**7**)

No method for separating phenol **6**, chlorohydrin **7** and epoxide **8** was found during this thesis. assigned shifts to chlorohydrin **7** are shown in Figure 2.14 and data from all NMR spectra are shown in Table 2.4. All NMR spectra of the mixture of 60 % phenol **6** and 40 % chlorohydrin **7** are presented in Appendix C.

Table 2.4: Data from HSQC, HMBC and COSY for 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**) (See spectra in Appendix C).

^{13}C shift	HSQC ^{1}H shift	HMBC ^{1}H shift	COSY ^{1}H shift
3.0	0.19, 0.52	*a*	1.06
10.6	1.06	0.19, 0.52, 3.28	0.19, 0.52, 3.28
35.4	2.84	3.61, 7.14	3.61
46.0	3.70, 3.77	-	4.20
68.6	4.06	3.70, 3.77, 4.20	-
69.8	4.20	3.70, 3.77, 4.06	3.70, 3.77
71.7	3.61	2.84, 3.28	2.84
75.6	3.28	0.29, 0.52, 3.61	1.06
114.5	6.84	-	7.14
115.3	*b*	-	-
129.8	*b*	-	-
130.0	7.14	2.84, 3.61, 6.84	6.84
131.8	Cq	2.84, 3.61	-
155.0	Cq	7.14	-
156.8	*b*	-	-

*a*HMBC spectra was cut off at ^{13}C shift of 10ppm
*b*Signal belongs to compound **6**

HPLC analysis was performed of the reaction mixture (Figure 2.15) along with HPLC analysis of phenol **6** (Figure F.10). HPLC of the reaction mixture showed signals at R_t = 7,9 min which was identified as phenol **6**, R_t = 9,5 min belonging to epoxide **8**, R_t = 12 min and 14 min belonging to the two enantiomers of **7**.

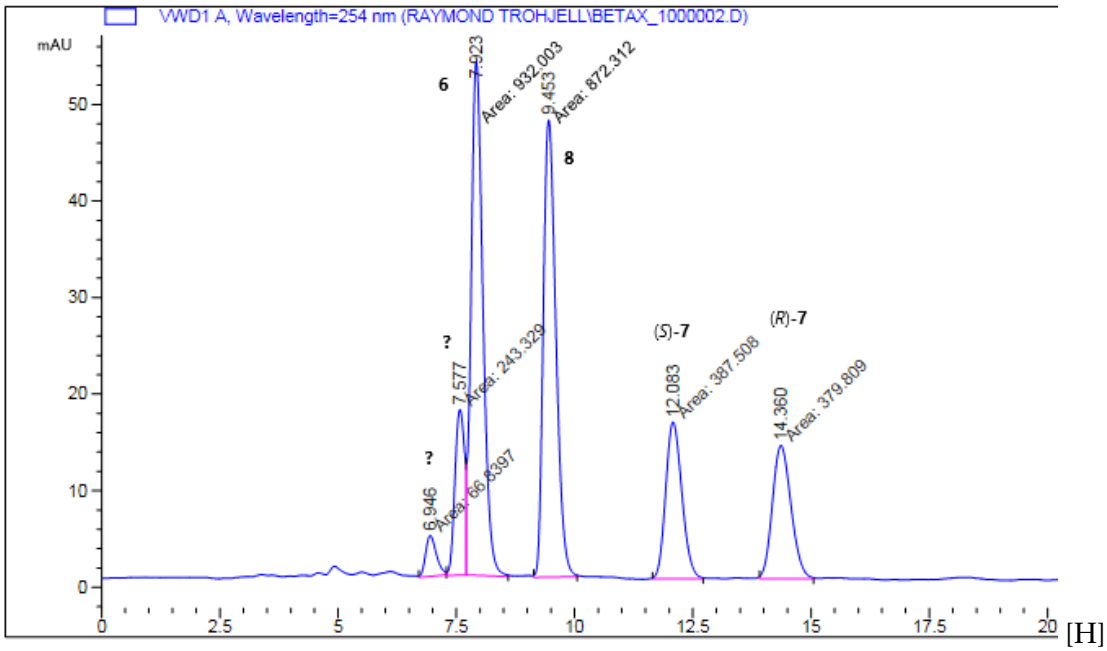


Figure 2.15: Analysis of products after reaction with epichlorohydrin. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

2.7.1. Ring opening of 2-((4-(2-(cyclopropylmethoxy)ethyl) phenoxy)methyl)oxirane (**8**)

Ring opening of **8** to form **7** was performed on a sample containing phenol **6**, chlorohydrin **7** and epoxide **8**, although only in a qualitative reaction, and was shown to be successful in converting all epoxide **8** into **7** by using acetic acid and LiCl. The samples were analysed by chiral HPLC and by comparing the chromatogram before and after ring opening identified epoxide **8** at R_t = 9,5 min (Figure 2.16 and Figure 2.17).

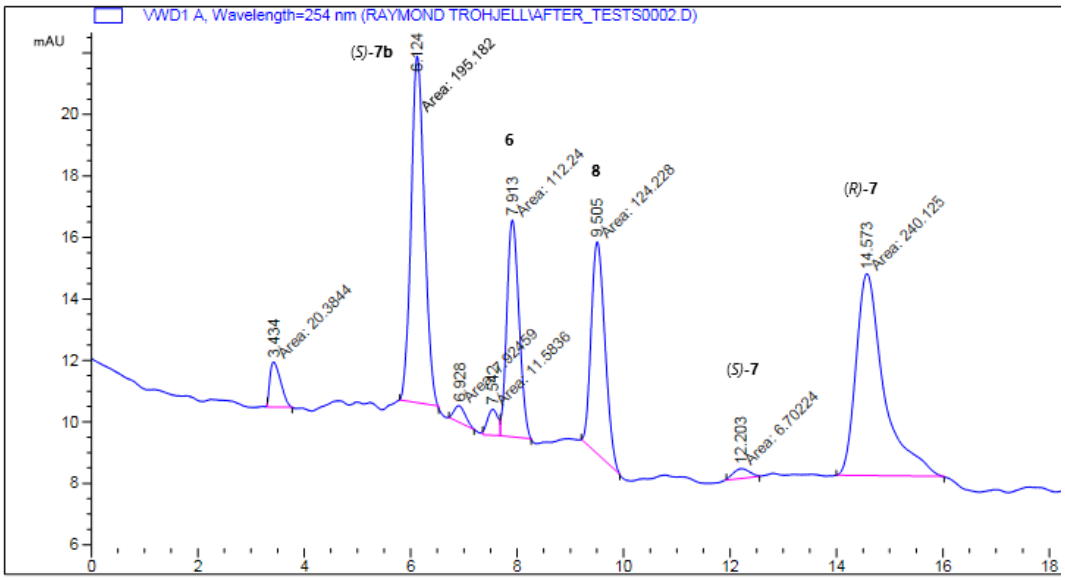


Figure 2.16: Analysis before ring opening of epoxide **8** was performed with acetic acid and LiCl. Epoxide **8** is seen at R_t = 9,5 min. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

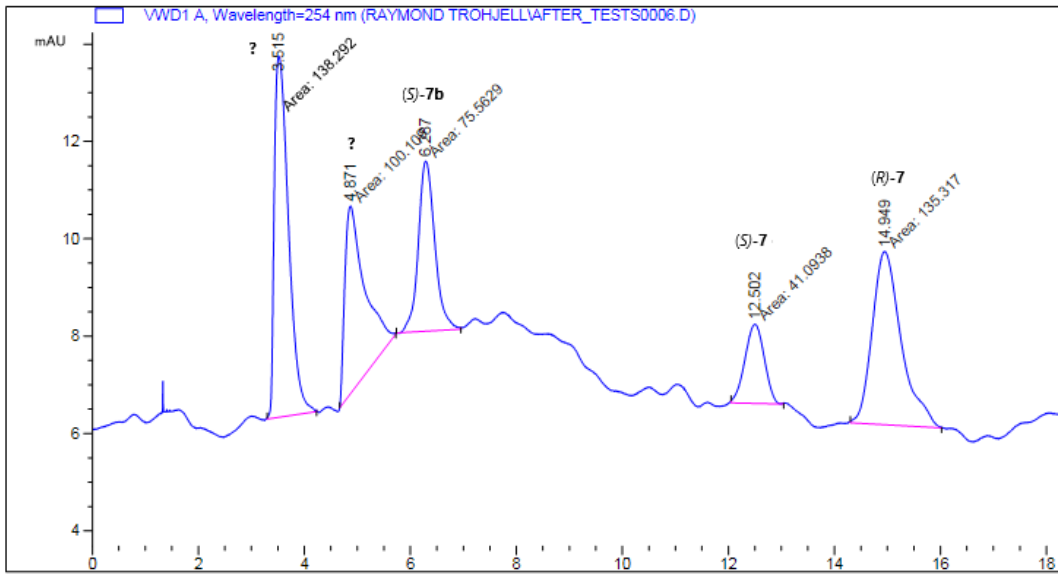


Figure 2.17: Analysis after ring opening of epoxide **8** with acetic acid and LiCl. Epoxide **8** no longer visible at R_t = 9,5 min. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

Along with the identification and removal of epoxide **8**, the synthesis gave rise to two additional signals at R_t = 3,4 min and R_t = 4,9 min. The signal at 3,4 min is not seen in any other chromatogram and may be the result of a dimerization of **6**, **7** or **8** during the ring opening. A signal at 4,9 min can be seen in derivatization of racemic **7** to form (*S*)-**7b** and (*R*)-**7b** (Scheme 2.11), however neither of these can be formed during the ring opening of **8**.

It is possible that this signal belongs to another dimerization product but no conclusion can be made for either signal.

2.7.2. Derivatisation of 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**)

Derivatization of racemic **7** (Figure 2.18) was performed by adding pyridine and butyric anhydride to racemic **7**. HPLC chromatogram (Figure 2.18) showed full conversion of **7** into **7b** as seen by the absence of chlorohydrin **7** signals at R_t = 12 and 14 min. Also seen are remaining pyridine at R_t = 7,0 min and signals at 4,9 min and 6,2 min. It is known that butyric anhydride has retention time of R_t = 4,6 min (Figure F.11) and remains of it could be present in this chromatogram at 4,9 min. More probable is that the signal at 4,9 min is one enantiomer of **7b**.

Another derivation was performed on a sample of racemic **7** by the same procedure. HPLC chromatogram (Figure 2.19) showed full conversion of **7** into **7b**.

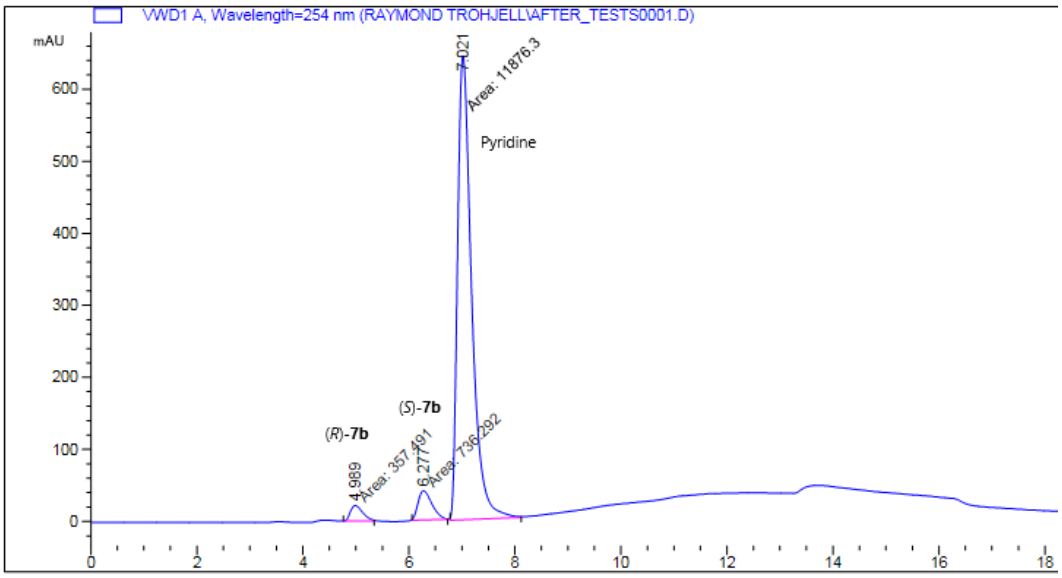


Figure 2.18: HPLC of derivatization of **7**. (*R*)-**7b** is seen at R_t = 4,9 min and (*S*)-**7b** can be seen at R_t = 6,2 min. Remaining pyridine can be seen at R_t = 7,0 min. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

As this derivation has remaining butyric anhydride is becomes clear that the signal at R_t = 4,9 min is distinct, and therefore probably belong to an enantiomer of **7b**. The signals for (*R*)-**7b** and (*S*)-**7b** has been assigned based on the kinetic resolution discussed below.

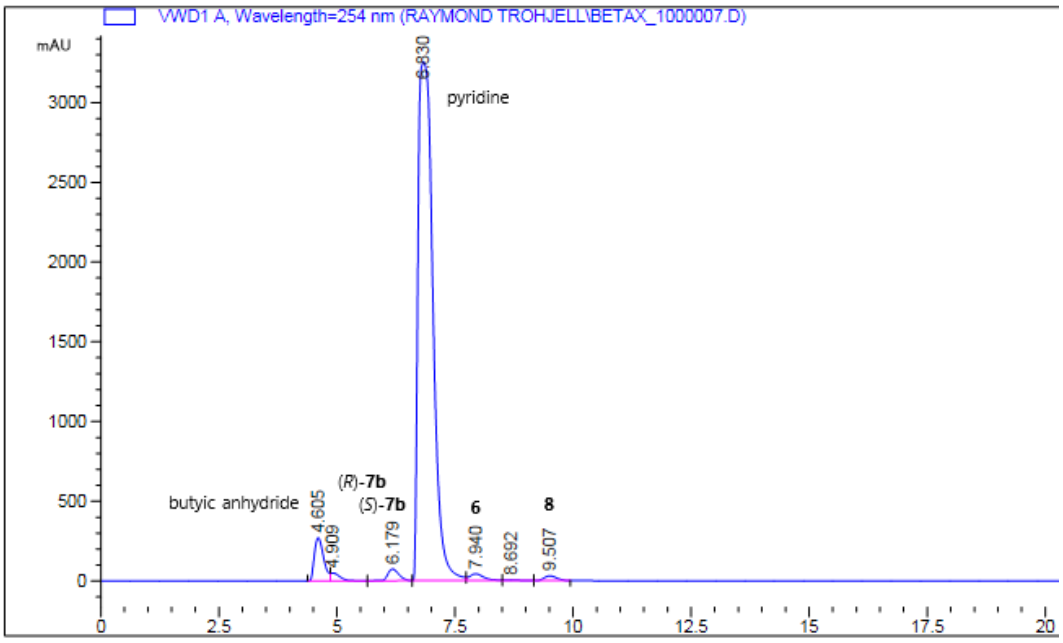
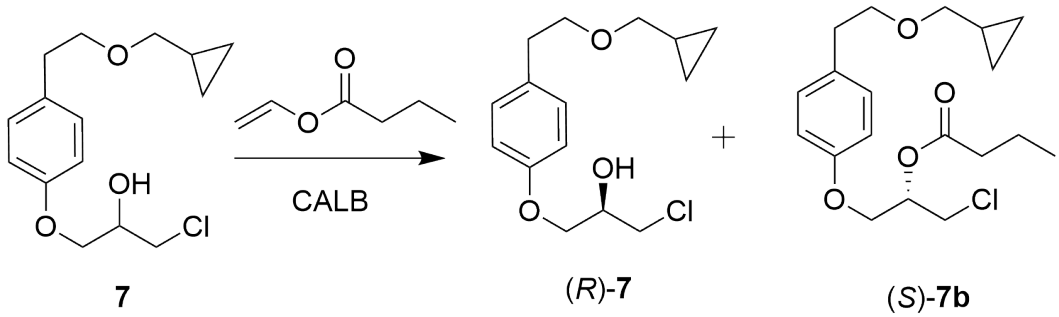


Figure 2.19: HPLC of derivatization of mixture of **6**, **7** and **8**. Remaining butyric anhydride and pyridine is seen at R_t = 4,6 min and R_t = 6,8 min. The two enantiomers of **7b** can be seen at R_t = 4.9 and 6,1 min. Phenol **6** and epoxide **8** can be seen at R_t = 7.9 and 9,5 min. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

2.8. Kinetic Resolution of 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**)

Kinetic resolution of racemic **7** catalyzed by CALB was performed (Scheme 2.11), with samples of 150 µl taken at intervals. HPLC shows formation of one enantiomer of **7b**, which is believed to be (*S*)-**7b** based on kinetic resolution of other β-blockers with CALB, and the consumption of one enantiomer of **7** ([28]).



Scheme 2.11: Kinetic resolution of **7** catalyzed by CALB to form (*S*)-**7b** and (*R*)-**7**.

Due to time constraints and difficulties in separation of compounds, the kinetic resolution of **7** was performed on a sample also containing epoxide **8** and phenol **6**. Epoxide **8** can be seen at R_t = 9,5 min and phenol **6** can be seen at R_t = 7,9 min throughout the analysis.

The kinetic resolution was only performed once due to the high price of **6** and the limited amount purchased.

Although the HPLC chromatograms contain additional peaks not originating from **7** or **7b**, the consumption of one enantiomer of **7** can be seen by the shrinking signal at R_t = 12 min, along with the growing signal at R_t = 6,1 min (See Figure 2.20 and Figure 2.21 or see all chromatograms in Appendix F).

Since CALB favours the synthesis of (*S*)-enantiomers of esters similar to **7b** above the (*R*)-enantiomers in the synthesis of other β-blockers, it is assumed to also be the case for betaxolol precursors. This places (*S*)-**7**, which is being converted into (*S*)-**7b** at R_t = 12 min and (*S*)-**7b** at R_t = 6,1 min.

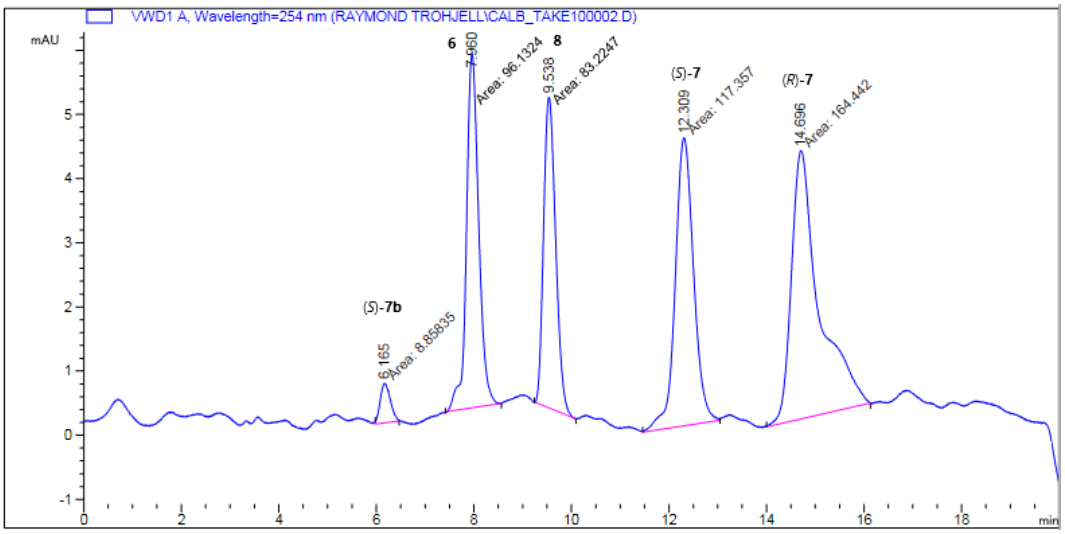


Figure 2.20: Analysis of kinetic resolution of **7** after 15 min. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

When comparing HPLC chromatogram throughout the kinetic resolution, it is observed that the signal at R_t = 12 min shrinks steadily until reaction time of 10 h. After 10 h the ee_s of the remaining chlorohydrin **7** was 94,1 % and after 22 h ee_s was 84,6 %. Because no sample was taken between 10 and 22 h it is probable that the optimal reaction time for achieving high enantiomeric excess lies between these times.

This thesis has merely scratched the surface in synthesis of enantiopure (*S*)-betaxolol by looking at the viability of using epichlorohydrin to phenol **6** followed by kinetic resolution of chlorohydrin **7** catalysed by CALB. While not proving that kinetic resolution of **7** catalysed by CALB can reach satisfyingly high *ee*, this thesis does show that the kinetic resolution of **7** of betaxolol can yield *ee* as high as 94 % in 10 h. Further optimisation is likely to achieve higher enantiomeric excess of (*R*)-**7**.

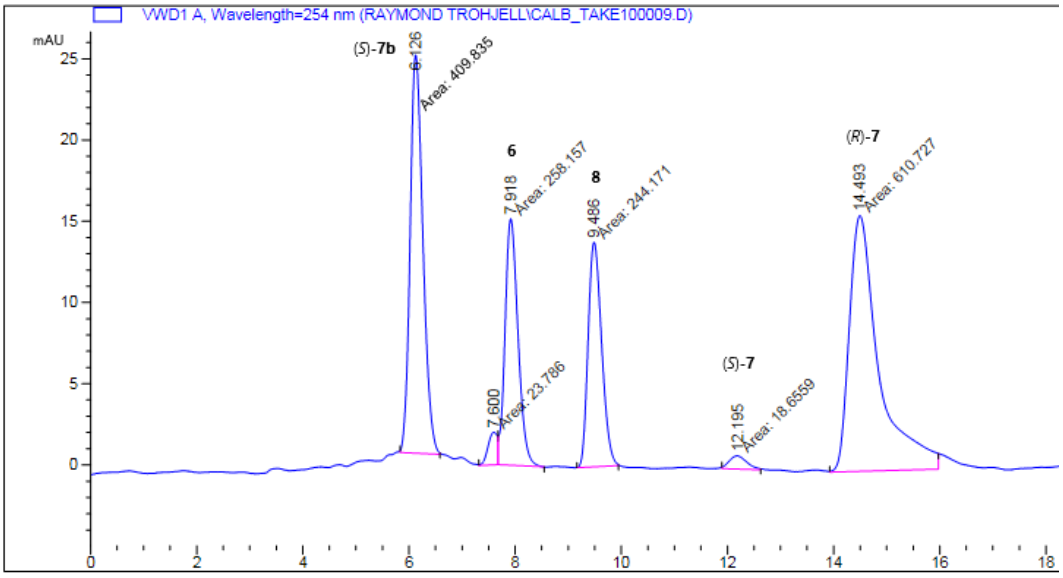
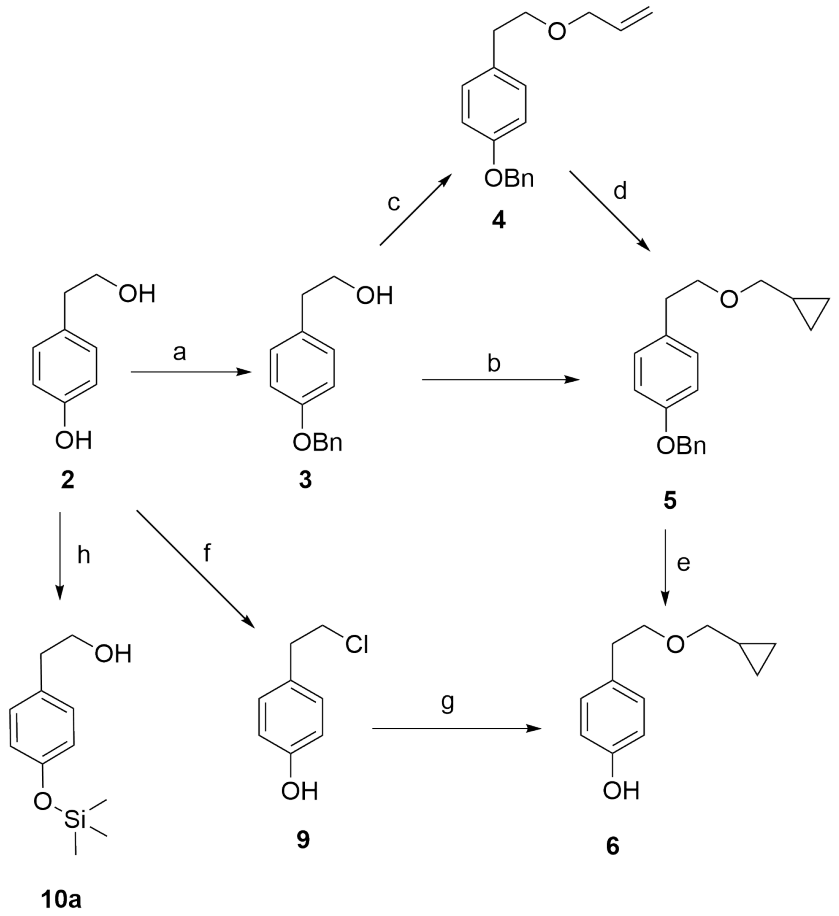


Figure 2.21: Analysis of kinetic resolution of **7** after 10 h. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

3. FUTURE WORK

This thesis has examined several different synthetic routes to the betaxolol-precursor 4-(2-(cyclopropylmethoxy)ethyl)phenol (**6**) (Scheme 3.1). Although phenol **6** was not synthesised and purified in this thesis two viable synthetic routes has been examined from diol **2**.

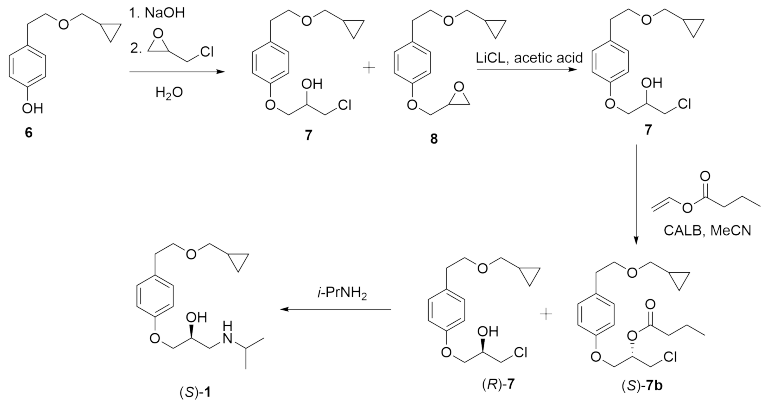


Scheme 3.1: Synthetic routes from 2-(4-hydroxyphenyl)ethanol (**2**) to 4-(2-(cyclopropylmethoxy)ethyl)phenol (**6**). Main reagents and conditions: (**a**) NaOH, benzylbromide (**b**) NaH, (bromomethyl)cyclopropane, dry conditions, 60 °C (**c**) Allylbromide, 50 °C (**d**) $ZnEt_2$, CH_2I_2 (**e**) Deprotection (**f**) Conc. HCl, 100 °C (**g**) Cyclopropanemethanol, room temperature (**h**) Triethylamine, TMSCl, dry conditions

In order to avoid unnecessary usage of chemicals, a short synthetic route to the desired product is preferred. Because of the harsh conditions needed in the synthesis of **5** from protected phenol **3** by addition of (bromomethyl)cyclopropane, this route is not encouraged further examination. If a route that achieves high conversion of **3** into **5** without the need of either NaH as base or temperatures above 50 °C is found, examining it could be beneficial.

Synthesis of phenol **9** followed by synthesis of **6** directly is the shortest synthetic route examined. If the by-products formed are identified and a way to avoid them is found, this synthetic route show great promise in the synthesis of phenol **6**.

The easiest synthetic route to **6** may be be the longest one examined. Synthesis of both **3** and **4** were achieved with yields above 85 %. A Simmon-Smith cyclopropanation similar to the one performed by Joshi *et.al* followed by a deprotection will yield phenol **6**, hopefully in high yields [30].



Scheme 3.2: Synthesis of (*S*)-betaxolol ((*S*)-**1**) by addition of epichlorohydrin to **6** 4-(2-(cyclopropylmethoxy)ethyl)phenol followed by kinetic resolution of 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol(**7**) catalysed by *Candida antarctica* Lipase B.

After obtaining phenol **6**, unless full conversion is achieved a way of separating phenol **6** and chlorohydrin **7** needs to be found. Epoxide **8** can be removed by ring opening with LiCl and acetic acid before kinetic resolution of **7** catalysed by CALB. Optimal reaction time for achieving high *ee* of (*R*)-**7** will likely be between 10 and 22 h. After obtaining high *ee* of (*R*)-**7** synthesis of (*S*)-betaxolol can be performed by addition of *i*-PrNH_2.

4. EXPERIMENTAL

4.1. MATERIALS AND METHODS

Chemicals used in this project are commercially available of analytical grade and were purchased from Sigma-Aldrich Norway (Oslo, Norway) HPLC grade of solvents were used in HPLC analyses.

4.1.1. ENZYMES

Candida antarctica Lipase B (CALB) (activity ≥ 10.000 PLU/g) immobilized at high hydrophobic macro porous resin, produced in fermentation with genetically modified *Pichia pastoris*. The enzyme is a gift from SyncoZymes Co Ltd. (Shanghai China).

4.1.2. CHIRAL HPLC ANALYSES

HPLC analyses with Chiracel OD-H column (Daicel, Chiral technologies Europe 250 x 4,6 mm ID, 5 µm particle size) were performed with an Agilent 1100 instrument with manual injection (Rheodyne 88254i/Agilent, 20 µl loop, 10 µl injection), and a variable detector set to 254 nm. Eluent: hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

4.1.3. NMR ANALYSES

NMR-analysees were recorded on a Bruker 400 MHz Avance III HD instrument, or a Bruker 600 MHz Avance III HD instrument, specified for each analysis.

4.1.4. TLC AND FLASH-CHROMATOGRAPHY ANALYSES

TLC-analyses was performed using Merck silica F_{254} (Sigma-Aldrich Norway, (Oslo, Norway)) and detection with UV at $\lambda = 254$ nm. Flash chromatography was performed using silica gel from Sigma-Aldrich Norway (Oslo, Norway) (pore size 60 Å, 230-400 mesh particle size, 40-63 µm particle size)

4.2. SYNTHESIS OF 2-(4-BENZYLOXYPHENYL)ETHANOL (**3**)

Method 1a: 2-(4-hydroxyphenyl)ethanol (**2**) (0,953 g, 6,89 mmol) was dissolved in THF (6 ml) and added phase-transfer catalyst Bu_4NSO_4 (0,11 g). NaOH (0,413 g, 10,33 mmol) dissolved in distilled water (10 ml) was then added and the solution was stirred for 20 min. To the solution was then added benzylbromide (1,30 g, 7,60 mmol) before being stirred for 4 h. The product was extracted with CH_2Cl_2 (2x10 ml) and washed with distilled water (2x15 ml). The organic phases were dried over $MgSO_4$, filtered, and solvents were evaporated at reduced pressure. TLC in 1:2 ethylacetate (EtOAc) in petroleum spirit showed the desired product **3** (R_f 0.18), remaining benzylbromide (R_f 0.75), but no remaining starting compound **2** (R_f 0.11).

Remaining benzylbromide was removed by addition of triethylamine (10 ml) in solvent of THF (8 ml) and distilled water (5 ml), stirring for 3 h. The solution was then washed with distilled water (2x10 ml) and extracted with EtOAc (2x10 ml). The organic phases were dried over $MgSO_4$, filtered, and solvents were evaporated at reduced pressure yielding white crystals of 2-(4-benzyloxyphenyl)ethanol (**3**) weighing 1,42 g (6,22 mmol) giving a total yield of 90,3 %.

^{1}H NMR (600 MHz, $CDCl_3$) of **3**: δ 7.43 (m, 2xH_{arom}), 7.38 (m, 2xH_{arom}), 7.32 (m, 1H_{arom}), 7.14 (d, 2xH_{arom}, J = 8,7 Hz), 6.93 (d, 2xH_{arom}, J = 8,7 Hz), 5.05 (s, CH_2), 3.83 (q, CH_2, J = 6,3 Hz), 2.81 (t, CH_2, 6,5 Hz), 1.35 (t, OH, J = 5,9 Hz). (See Figure A.1 in Appendix A)
^{13}C NMR (600 MHz, $CDCl_3$) of **3**: δ 38.3 (CH_2), 63.8 (CH_2), 70.1 (CH_2), 115.0 (2xCH_{arom}), 127.5 (2xCH_{arom}), 127.9 (CH_{arom}), 128.6 (2xCH_{arom}), 130.0 (2xCH_{arom}), 130.7 (C_q), 137.1 (C_q), 157.6 (C_q). (See Figure A.2 in Appendix A)

See Table 2.1 for data from NMR spectra, and see Appendix A for NMR spectra for 2-(4-benzyloxyphenyl)ethanol (**3**).

Method 1b: Similar to method 1a, 2-(4-hydroxyphenyl)ethanol (**2**) (0,582 g, 4,15 mmol) was used. Full conversion of **2** to **3** was obtained after stirring for 14 h. Remaining benzylbromide was removed by purification by flash chromatography in 1:2 EtOAc in petroleum spirit giving a yield of 45,3 % (0,428 g, 1,88 mmol) of **3**.

Method 1c: Similar to method 1a, **2** (0,793 g, 5,74 mmol) was used along with phase-transfer catalyst in THF and using NaOH (1.5equiv.) as base. White crystals of **3** weighing 1,12 g (4,89 mmol) was obtained giving a total yield of 85,2 %.

4.3. Synthesis of 2-(4-((trimethylsilyl)oxy)phenyl)ethan-1-ol (**10a**)

Method 2a:

2-(4-Hydroxyphenyl)ethanol (**2**) (0,800 g, 5,79 mmol) was dissolved in THF (35 ml) and added triethylamine ((2,41 ml, 17,4 mmol), 3equiv.). The flask was purged with N_2 before being stirred for 10 min. Trimethylsilylchloride (TMSCl) (1,46 ml, 11,59 mmol, 2equiv.) was added and the solution was stirred for 18 h. Solvents were removed under reduced pressure. The resulting residue was a mixture of trimethyl(4-(2-((trimethylsilyl)oxy)ethyl)phenoxy)silane (**10a**), 4-(2-((trimethylsilyl)oxy)ethyl)phenol (**10b**) and trimethyl(4-(2-((trimethylsilyl)oxy)ethyl)phenoxy)silane (**10c**) with a total mass of 1,22 g. The compounds were not separated and purified. (See Figure E.3)

Method 2b: Similar to method 2a, but with only 1 equivalent triethylamine and 2 equivalents of TMSCl. No conversion of **2** was observed in ^{1}H NMR.

Method 2c: Similar to method 2a, but using 2 equivalents of triethylamine and 2 equivalents of TMSCl. Product **10c** was observed in ^{1}H NMR (See Figure E.4),

4.4. SYNTHESIS OF 1-(2-ALLYLOXYETHYL)-4-BENZYLOXYBENZENE (**4**)

Method 3a 2-(4-Benzyloxyphenyl)ethanol (**3**) (1,11 g, 4,86 mmol) was dissolved in THF (6 ml), added NaOH (3 moll^{-1}, 9,0 mmol) and added phase-transfer catalyst Bu_4NSO_4. The solution was stirred for 3 h at 40 °C. Allylbromide (1,39 g, 11,5 mmol) dissolved in THF (2 ml) was then added dropwise and the solution was stirred for 40 h at 40 °C. The product was extracted with CH_2Cl_2 (2x15 ml) and washed with distilled water (3x10 ml). The organic phases were dried over $MgSO_4$, filtered, and solvents were evaporated under reduced pressure. White crystals of **4** weighing 1,14 g (4,25 mmol) was obtained, giving a yield of 87,4 %.

^{1}H NMR (600 MHz, $CDCl_3$) of **4**: δ 2.82 (t, CH_2, J = 7,1 Hz), 3.59 (t, CH_2, J = 7,3 Hz), 3.96 (dt, CH_2, J = 1,4 Hz, 5,6 Hz), 5.00 (s, CH_2), 5.14 (dq, CH_{alkene}, J = 1,3 Hz, 10,4 Hz), 5.24 (dq, CH_{alkene}, J = 1,6 Hz, 17,3 Hz), 5.88 (m, CH_{alkene}, J = 5,6 Hz, 10,4 Hz, 17,3 Hz), 6.89 (d, 2xCH_{arom}, J = 8,5 Hz), 7.12 (d, 2xCH_{arom}, J = 8,5 Hz), 7.29 (m, CH_{arom}, J = 7,5 Hz), 7.35 (m, 2xCH_{arom}, J = 7,2 Hz), 7.39 (m, 2xCH_{arom})
^{13}C NMR (600 MHz, $CDCl_3$) of **4**: δ 35.5 (CH_2), 70.0 (CH_2), 71.4 (CH_2), 71.8 (CH_2), 114.7 (2xCH_{arom}), 116.8 (CH_2), 127.4 (2xCH_{arom}), 127.8 (CH_{arom}), 128.5 (2xCH_{arom}), 129.8 (2xCH_{arom}), 131.3 (C_q), 134.9 (CH), 137.2 (C_q), 157.3 (C_q)

See Appendix B NMR spectra for **4**.

Method 3b 2-(4-Benzyloxyphenyl)ethanol (**3**) (0,617 g, 2,70 mmol) was dissolved in CH_2Cl_2 (1 ml) and added phase transfer catalyst Bu_4NSO_4 and NaOH (6 mmol, 3 moll^{-1}). The solution was stirred for 1 h and added allylbromide (0,391 g, 3,23 mmol). The solution was stirred for 7 days, after which ^{1}H NMR showed around 50 % conversion of **3** into 1-(2-allyloxyethyl)-4-benzyloxybenzene (**4**).

Purification was done by flash-chromatography in 1:2 EtOAc in petroleum spirit (R_f-values of 0.20 and 0.68 for **3** and **4** respectively from TLC). Compound weighing 0,132 g (0,492 mmol) was obtained giving a yield of 18,2 %.

4.5. SYNTHESIS OF 4-(2-CHLOROETHYL)PHENOL (**9**)

Method 4a: Concentrated HCl solution (37 %, 4 ml) was added to 2-(4-hydroxyphenyl)ethanol (**2**) (0,500 g, 3,62 mmol). The flask was linked to an oil bubbler and the solution was heated to 100 °C and stirred for 4 h. The solution was then cooled to room temperature and poured into distilled water (10 ml). The product was extracted with diethylether and dried over $MgSO_4$ before being filtered and the solvents evaporated under reduced pressure. The resulting was a brown oil of 4-(2-chloroethyl)phenol (**9**) (0,45 g, 2,87 mmol) giving a yield of 79,3 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, 2xCH_{arom}, J = 8,5 Hz), 6.80 (d, 2xCH_{arom}, J = 8,5 Hz), 4.67 (s, C-O**H**), 3.70 (t, CH_2, J = 7,5 Hz), 3.02 (t, CH_2, J = 7,5 Hz)

See Figure E.6 for ^{1}H NMR spectra)

Method 4b: Similar to method 4a, but heated to only 70 °C and stirred for 18 h. The solution was then cooled to room temperature and a conversion of 92 % into **9** was observed in ^{1}H NMR. Yield was not calculated

4.6. Synthesis of 1-benzyloxy-4-(2-cyclopropylmethoxyethyl)benzene (**5**)

Three methods of synthesising 1-benzyloxy-4-(2-cyclopropylmethoxyethyl)benzene (**5**) was proposed. Addition of (bromomethyl)cyclopropane to **3**. Simmons-Smith cyclopropanation of **4** to form **5**, both followed by a deprotection to yield **6**, and lastly addition of cyclopropylmethanol to **9** to form **6**.

4.7. Synthesis of **5** by addition of (bromomethyl)cyclopropane to **3**

Method 5a:

2-(4-Benzyloxyphenyl)ethanol (**3**) (0,426 g, 1,87 mmol) was dissolved in CH_2Cl_2 (10 ml). A solution of ^tBuOK (0,438 g, 3,90 mmol) in CH_2Cl_2 (5 ml) was added, and the solution was stirred for 2 h. (Bromomethyl)cyclopropane (0,413 g, 3,06 mmol) was then added and the solution was stirred at room temperature for 18 h.

The resulting bleached solution was washed with distilled water and extracted with CH_2Cl_2 (4x15 ml). The non-organic phase was then washed with diethylether (2x20 ml). The combined organic phases were dried over $MgSO_4$, filtered, and solvents were evaporated under reduced pressure. Integrals from ^{1}H NMR showed approximately a 5 % conversion to the desired product **5**.

Method 5b:

2-(4-Benzyloxyphenyl)ethanol (**3**) (0,260 g, 1,139 mmol) was dissolved in dry THF (2 ml) and added NaH (0,068 g, 2,83 mmol) dissolved in dry THF (2 ml) into dried equipment. The solution was stirred in N_2 atmosphere for 45 min before (bromomethyl)cyclopropane (0,130 ml, 1,34 mmol) was added. The solution was stirred for 7 h. A sample was taken and ^{1}H NMR integrals showed less than 5 % conversion to the product **5**. After 9 more hours the reaction was stopped and work up was performed similarly to method 5a. ^{1}H NMR showed around 10 % conversion into product **5**.

Method 5c:

2-(4-Benzyloxyphenyl)ethanol (**3**) (0,193 g, 0,845 mmol) was dissolved in dry THF (2 ml). NaH (0,0452 g, 1,88 mmol) dissolved in dry THF (2 ml) was added and the solution was stirred for 2 h in N_2 atmosphere. (Bromomethyl)cyclopropane (0,100 ml, 1,03 mmol) was added and the solution was stirred at in N_2 atmosphere at 60 °C for 48 h. ^{1}H NMR showed a conversion of 50 % into the desired product **5**. The crude NMR of **5** mixed with remaining **3**, can be seen in Figure E.5 in Appendix E.

4.8. Synthesis of **6** by addition of cyclopropylmethanol to **9**.

Method 6a:

A solution of cyclopropylmethanol (0,06 ml, 0,77 mmol) in CH_2Cl_2 (2 ml) was added NaOH (2,5 moll^{-1}, 5 ml) and phase-transfer catalyst benzyltrimethylammonium chloride (5 mg). 4-(2-chloroethyl)phenol (**9**) (0,100 g, 0,64 mmol) was then dissolved in CH_2Cl_2 (3 ml) and

added to the mixture. The solution was stirred for 24 h. The product was extracted with diethylether (2x10 ml) and washed with HCl (5 %, 5 ml) and washed with distilled water (2x15 ml). The organic phase was dried over $MgSO_4$, filtered and solvents were evaporated under reduced pressure. Compounds weighing 60 mg was obtained. See Figure D.1 for ^{1}H NMR spectra.

Method 6b: Similar to method 6a, but 5 equivalents of cyclopropylmethanol was used and 4-(2-chloroethyl)phenol (**9**) (0,100 g, 0,64 mmol) was dissolved in CH_2Cl_2 (7 ml) and added dropwise to the solution over 20 min before the solution was stirred for 48 h. Compounds weighing 80 mg was obtained. ^{1}H NMR spectra can be seen in Figure D.2.

Method 6c: 5 equivalents of cyclopropylmethanol was used as well as 3 equivalents of triethylamine instead of NaOH as base. 4-(2-Chloroethyl)phenol (**9**) was dissolved in CH_2Cl_2 (40 ml) and added dropwise to the solution over 40 min before the solution was stirred for 24 h. Compounds weighing 122 mg was obtained. ^{1}H NMR spectra showed around 5 % of compound with a cyclopropane ring.

4.9. Synthesis of 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**)

Method 7a

4-(2-(Cyclopropylmethoxy)ethyl)phenol (**6**) 0,238 g (1,24 mmol) was dissolved in DMSO (0,43 ml) and distilled water (2,15 ml). Epichlorohydrin (200 µl, 2,55 mmol, 2equiv.) was added along with NaOH (3 $moll^{-1}$, 0,372 mmol, 0.3equiv.) and the solution was stirred for 72 h. The product was extracted with 3x20 ml CH_2Cl_2 and washed with 2x20 ml brine. The organic phases was dried over $MgSO_4$, filtered and solvents were evaporated under reduced pressure. The obtained viscous liquid weighed 0,151 g and ^{1}H NMR showed conversion of **6** to **7** of around 40 % (See Figure C.1). A method of separating these compounds was not found. After examining a dozen eluent systems, the most promising found was 2:5 EtOAc in petroleum spirit and 1:3 acetone in hexane, both giving R_f values of 0.25 and 0.28 for **6** and **7** respectively. Due to time restraints separation could not be optimised further.

^{1}H NMR ($CDCl_3$, 600 MHz) of **7**: δ 7.14 (m, 2H), 6.84 (m, 2H), 4.20 (m, 1H), 4.06 (m, 2H), 3.77-3.70 (m, 2H), 3.61 (t, 2H), 3.28 (d, 2H), 2.84 (t, 2H), 1.06 (m, 1H), 0.52 (m, 2H), 0.19 (m, 2H) (See Figure C.1)

^{13}C NMR ($CDCl_3$, 600 MHz) of **7**: δ 155.0 (C_q), 131.8 (C_q), 130.0 (2xC_{arom}), 114.5 (2xC_{arom}), 75.6 (CH_2), 71.7 (CH_2), 69.8 (C**H**−OH), 68.6 (CH_2), 46.0 (CH_2), 35.4 (CH_2), 10.6 (CH), 3.0 (2xCH_2) (See Figure C.2)

Method 7b

4-[2-(Cyclopropylmethoxy)ethyl]phenol (**6**) (0,188 g, 0,978 mmol) was dissolved in distilled water (1 ml) and added epichlorohydrin (0,314 ml, 4,01 mmol, 4equiv. and NaOH (0,120 ml, 0,36 mmol, 0.4equiv.). The solution was stirred at room temperature for 96 h. Work-up similar to **Method 7a**. The obtained viscous liquid weighed 0,1716 g. ^{1}H NMR indicates that the sample consists of 15 % **6**, 75 % of **7** and around 10 % of **8**. The compounds were not

separated and purified.

Method 7c

4-(2-(Cyclopropylmethoxy)ethyl)phenol (**6**) (0,343 g, 1,79 mmol) was dissolved in distilled water (2 ml) and added NaOH (0,54 mmol, 0.3equiv.) and epichlorohydrin (420 µl, 5,35 mmol, 3equiv.) and stirred for 45 h. Work-up similar to **Method 7a**. A viscous liquid weighing 0,165 g was obtained. NMR showed composition of 3 % **6**, 57 % of **7** and 40 % **8**. The compounds were not separated and purified.

4.10. Kinetic resolution of **7** catalyzed by CALB

Racemic 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**) (0,033 g, 0,116 mmol) (from method 7b) was dissolved in dry acetonitrile (4 ml) and added molecular sieves. Vinyl butanoate (115 µl, 0,906 mmol) was added along with CALB enzyme (90 mg) and the sample was stirred in an incubator shaker (30 °C, 200rpm). Samples of 150 µl were collected at intervals, concentrated and dissolved in hexane before being analysed on HPLC. See Appendix F for HPLC chromatograms.

4.10.1. Derivatization of racemic 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**)

1 drop of **7** was added to 1 drop of pyridine and 5 drops of butyric anhydride. The sample was heated to 60 °C for 1 h. HPLC chromatogram is shown in Figure 2.18 and Figure 2.19.

4.10.2. Ring opening of 2-[4-(2-(cyclopropylmethoxy)ethyl)phenoxymethyl]oxirane (**8**)

Two qualitative ring openings of **8** was performed by taking a small sample of **7** and **7b** and adding it to acetic acid and LiCl, shaking for 2 h at 30 °C in an incubator shaker. HPLC chromatogram is shown in Figure 2.16 and Figure 2.17.

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APPENDIX

A. NMR SPECTRA FOR 2-(4-BENZYLOXYPHENYL)ETHANOL) (**3**)

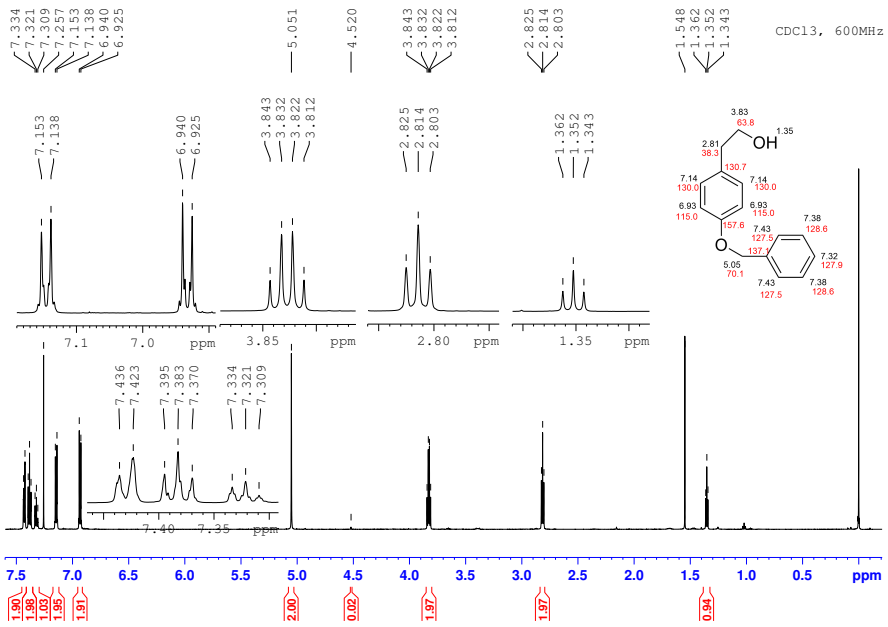


Figure A.1: ^{1}H NMR specter (600 MHz, $CDCl_3$) for 2-(4-benzyloxyphenyl)ethanol) (**3**).

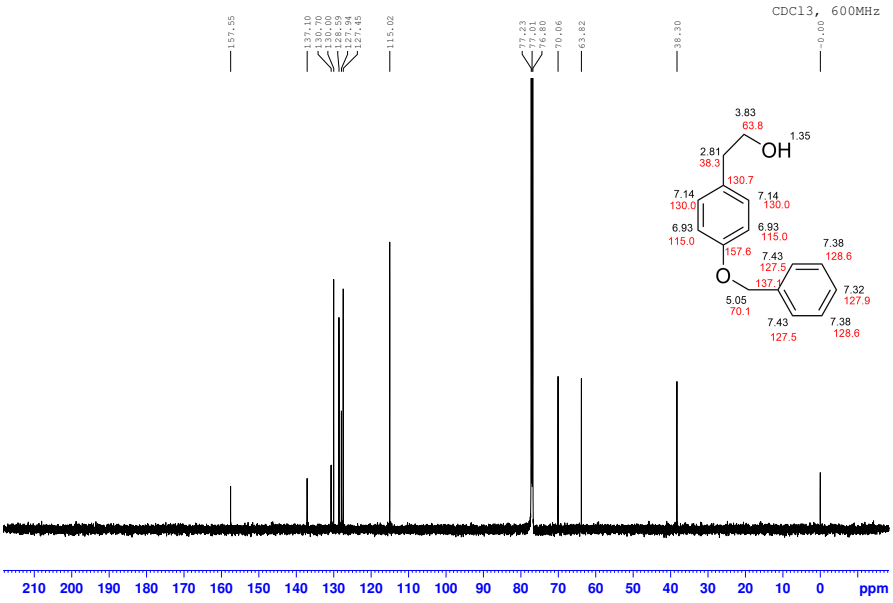


Figure A.2: ^{13}C NMR specter (600 MHz, $CDCl_3$) for 2-(4-benzyloxyphenyl)ethanol) (**3**).

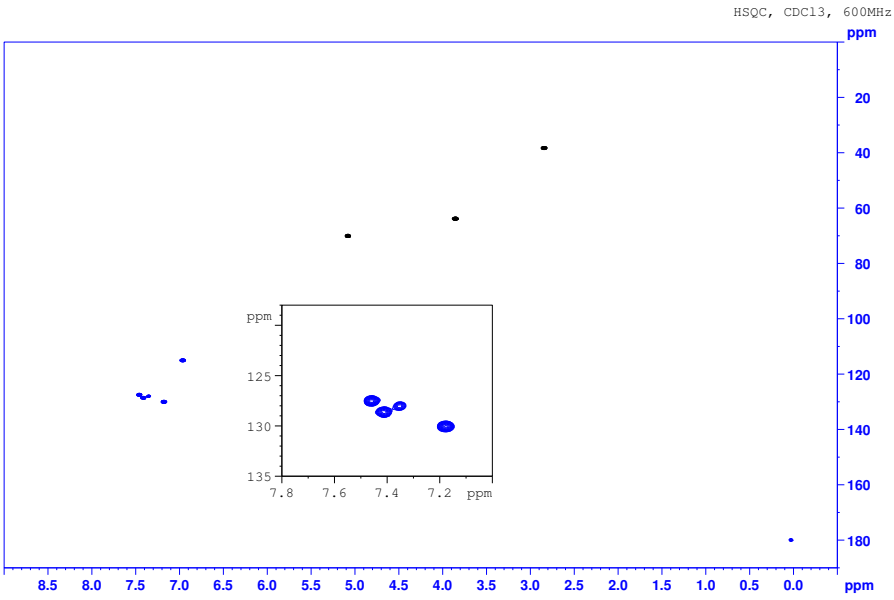


Figure A.3: HSQC NMR specter (600 MHz, $CDCl_3$) for 2-(4-benzyloxyphenyl)ethanol) (**3**).

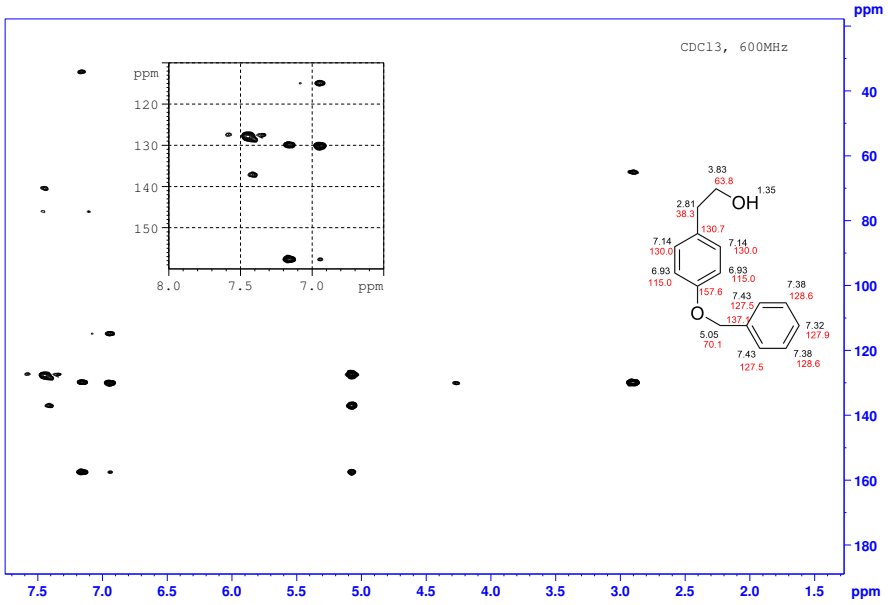


Figure A.4: HMBC NMR specter (600 MHz, $CDCl_3$) for 2-(4-benzyloxyphenyl)ethanol) (**3**).

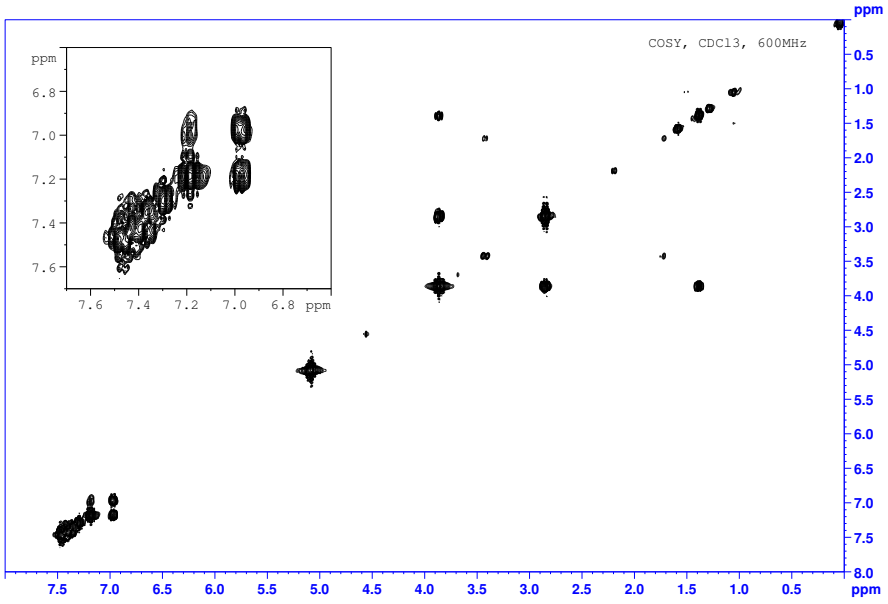


Figure A.5: COSY NMR specter (600 MHz, $CDCl_3$) for 2-(4-benzyloxyphenyl)ethanol) (**3**).

B. NMR SPECTRA FOR 1-(2-(ALLYLOXY)ETHYL)-4-(BENZYLOXY)BENZENE (**4**)

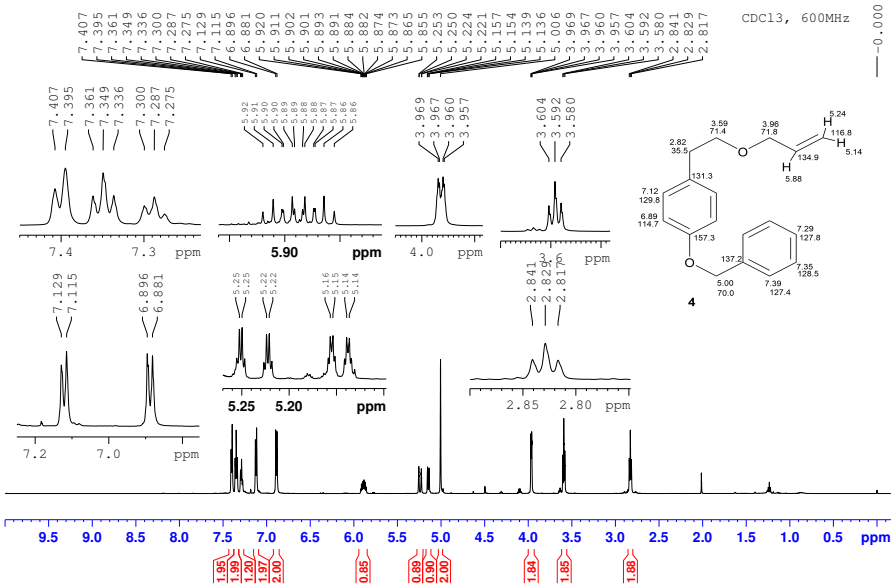


Figure B.1: ^{1}H NMR specter (600 MHz, $CDCl_3$) for 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**).

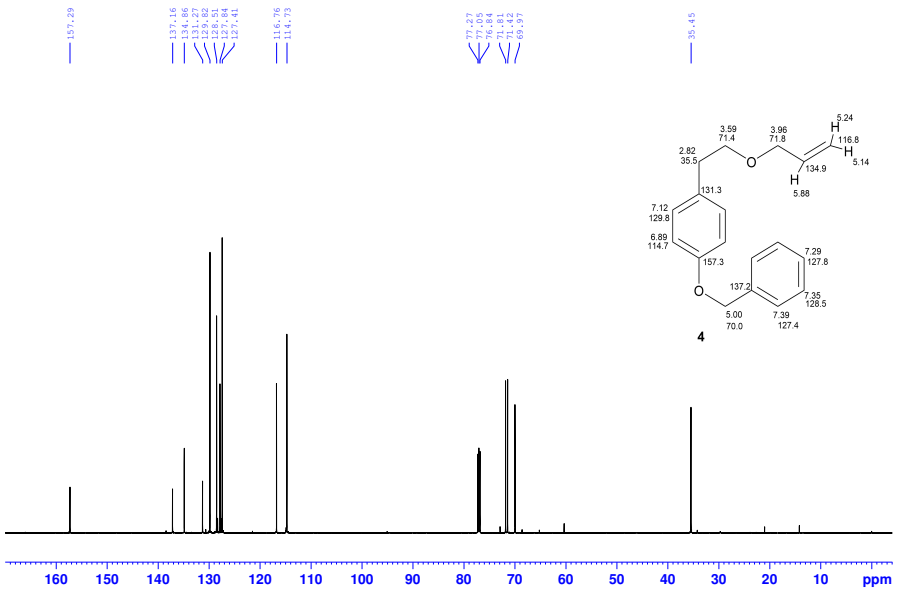


Figure B.2: ^{13}C NMR specter (600 MHz, $CDCl_3$) for 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**).

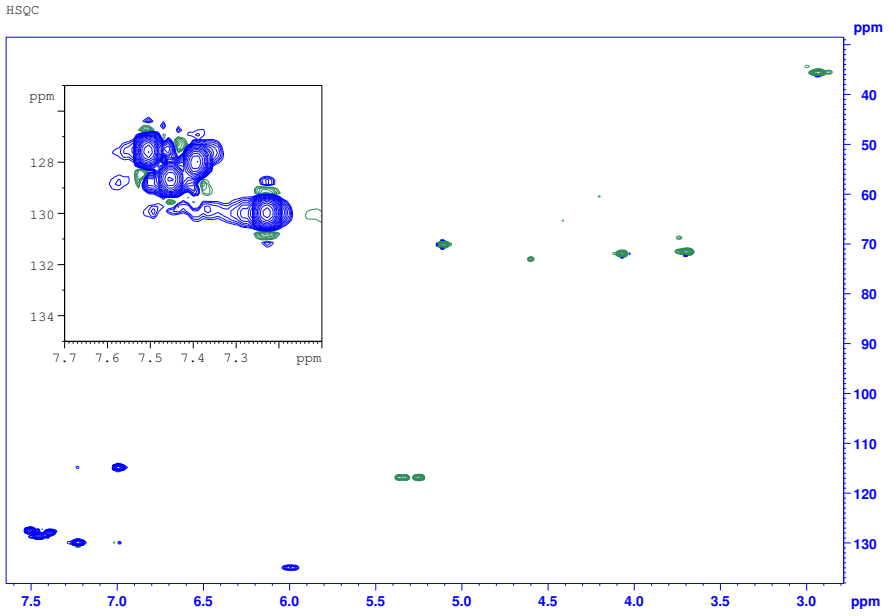


Figure B.3: HSQC NMR specter (600 MHz, $CDCl_3$) for 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**).

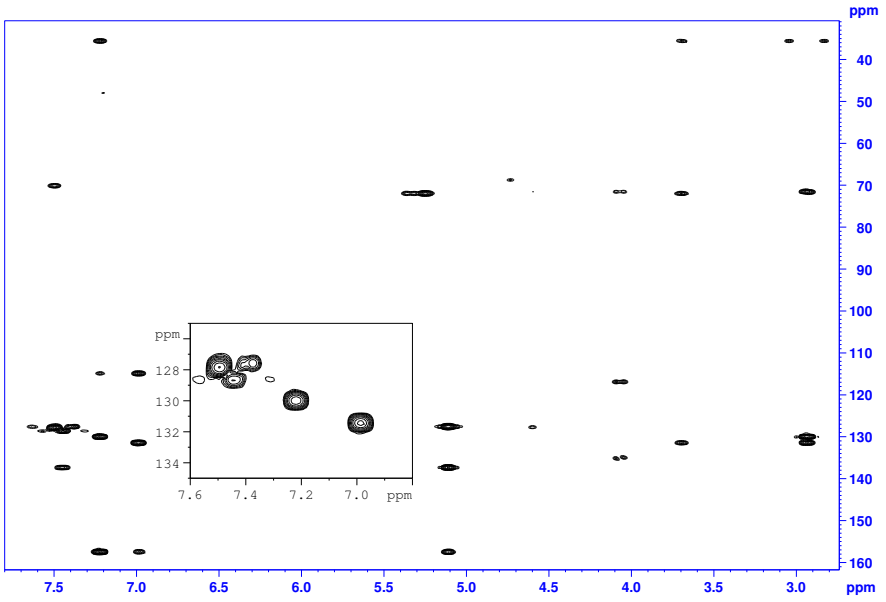


Figure B.4: HMBC NMR specter (600 MHz, $CDCl_3$) for 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**).

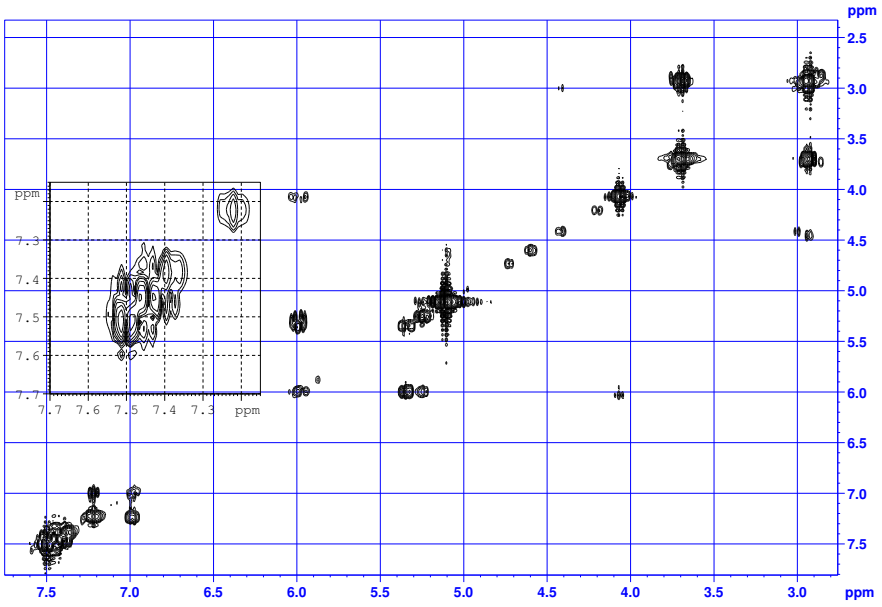


Figure B.5: COSY NMR specter (600 MHz, $CDCl_3$) for 1-(2-(allyloxy)ethyl)-4-(benzyloxy)benzene (**4**).

C. NMR SPECTRA FOR 1-CHLORO-3-(4-(2-(CYCLOPROPYLMETHOXY)ETHYL)PHENOXY)PROPAN-2-OL (**7**)

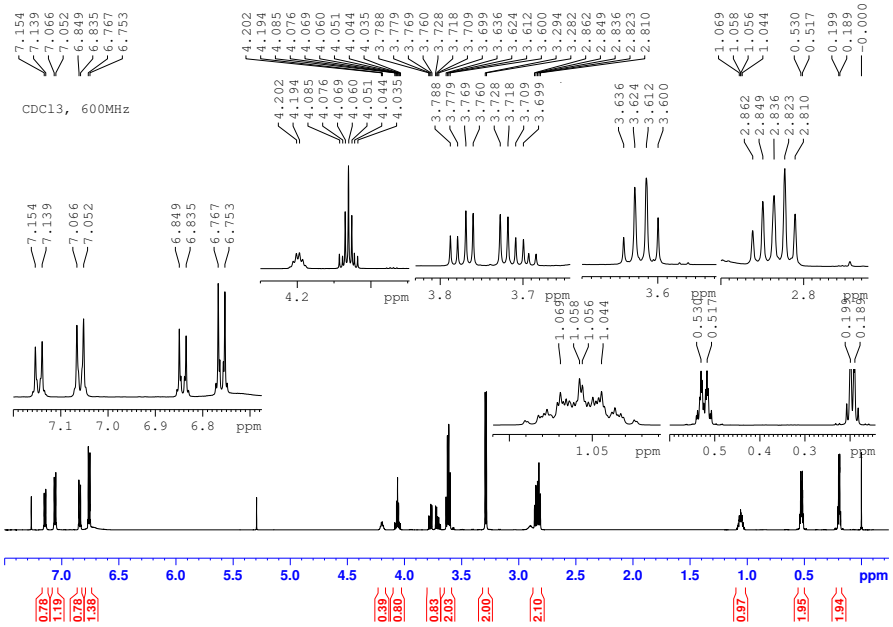


Figure C.1: ^{1}H NMR specter (600 MHz, $CDCl_3$) for 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**).

C: NMR spectra: 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**)

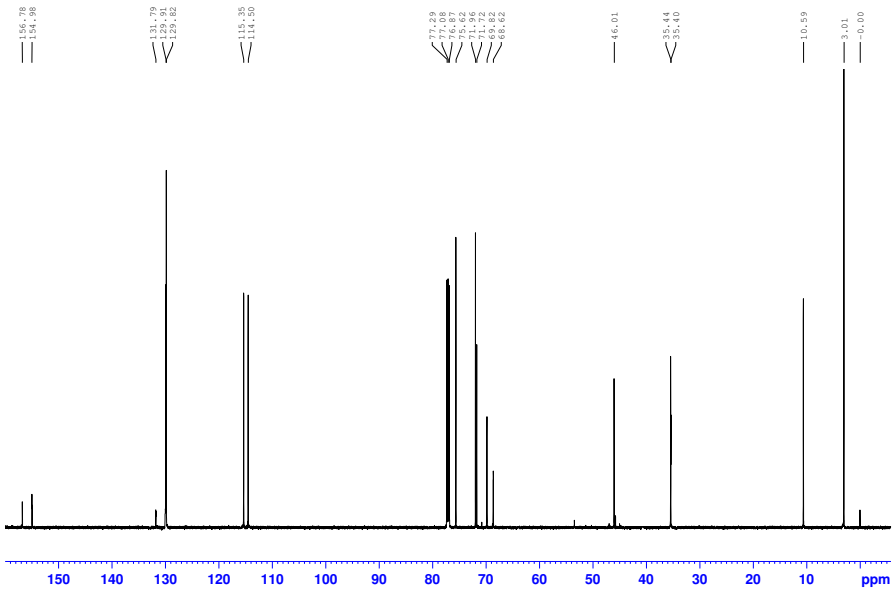


Figure C.2: ^{13}C NMR specter (600 MHz, $CDCl_3$) for 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**).

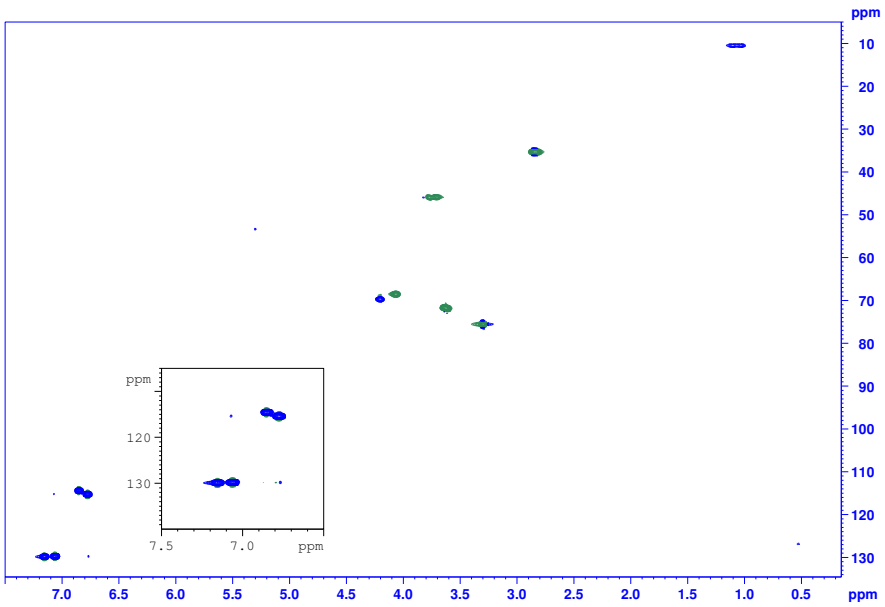


Figure C.3: HSQC NMR specter (600 MHz, $CDCl_3$) for 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**).

C: NMR spectra: 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**)

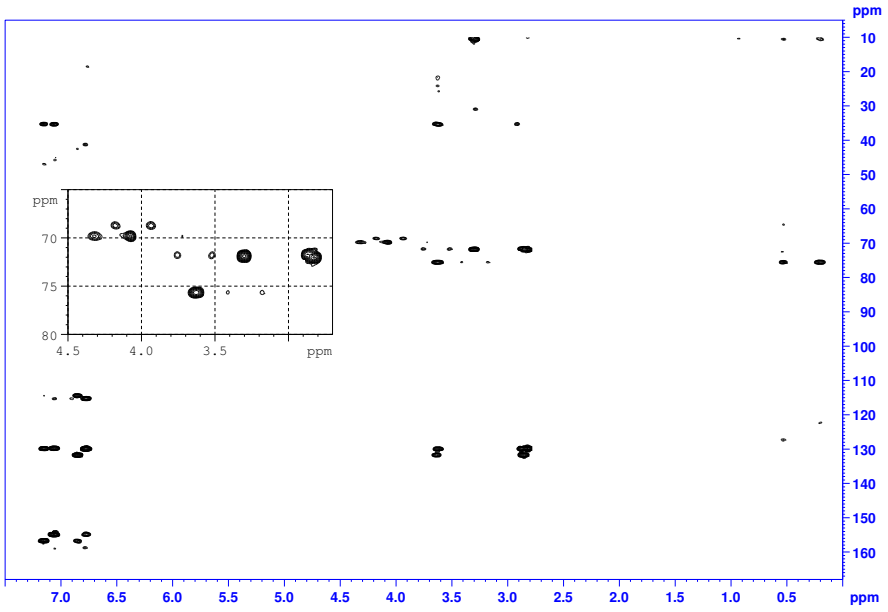


Figure C.4: HMBC NMR specter (600 MHz, $CDCl_3$) for 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**).

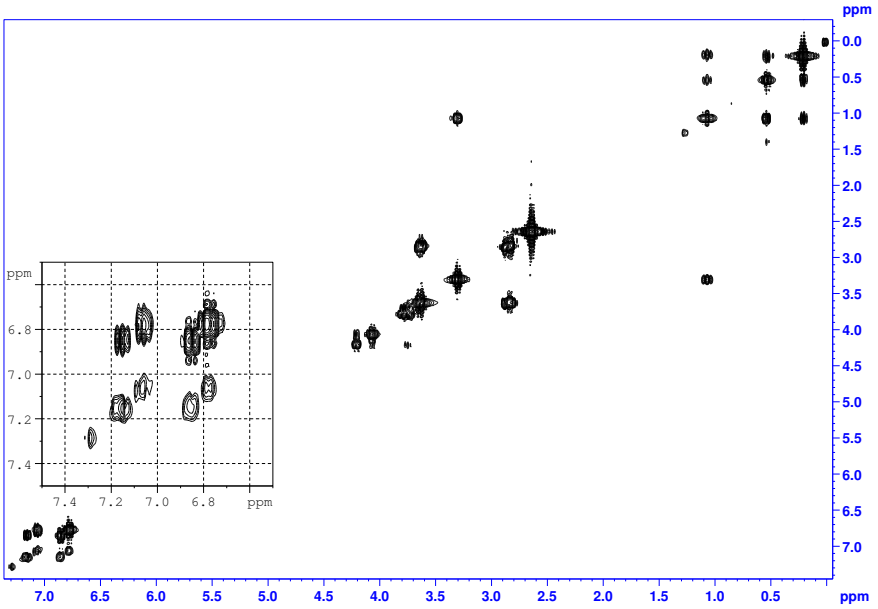


Figure C.5: COSY NMR specter (600 MHz, $CDCl_3$) for 1-chloro-3-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)propan-2-ol (**7**).

D. NMR SPECTRA OF DERIVATIVES OF 4-(2-(CYCLOPROPYLMETHOXY)ETHYL)PHENOL (**6**)

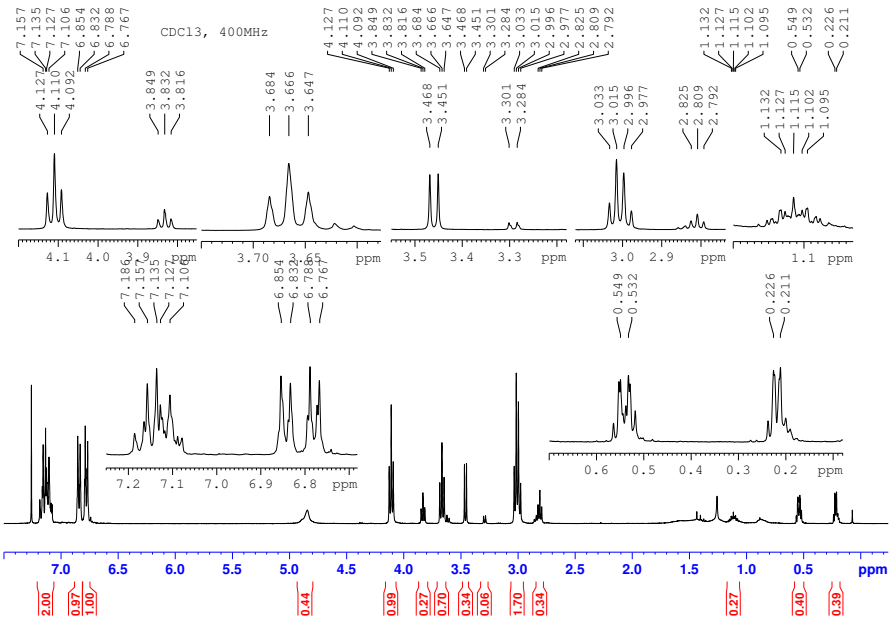


Figure D.1: ^{1}H NMR specter (600 MHz, $CDCl_3$) of

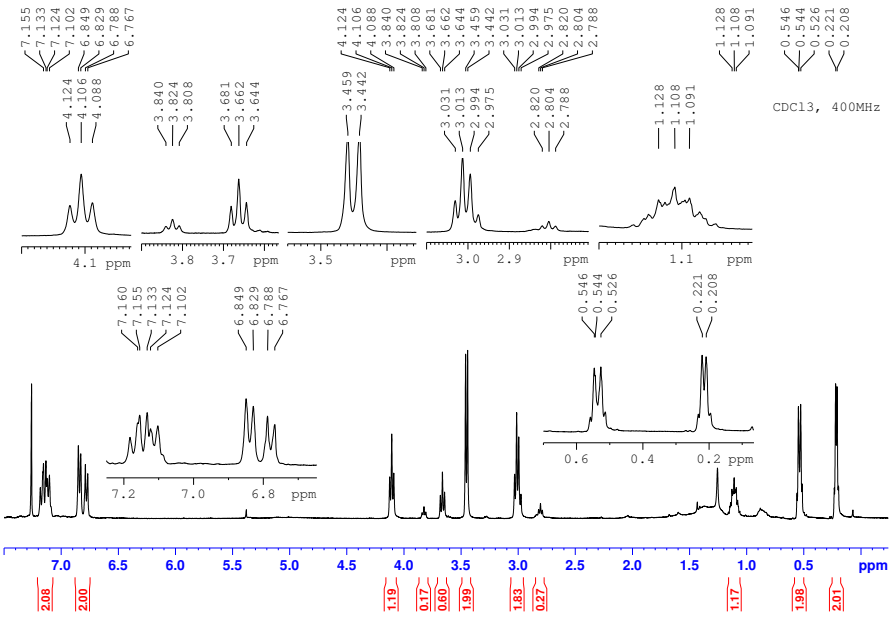


Figure D.2: ^{1}H NMR specter (600 MHz, $CDCl_3$) of

E. Additional NMR spectra

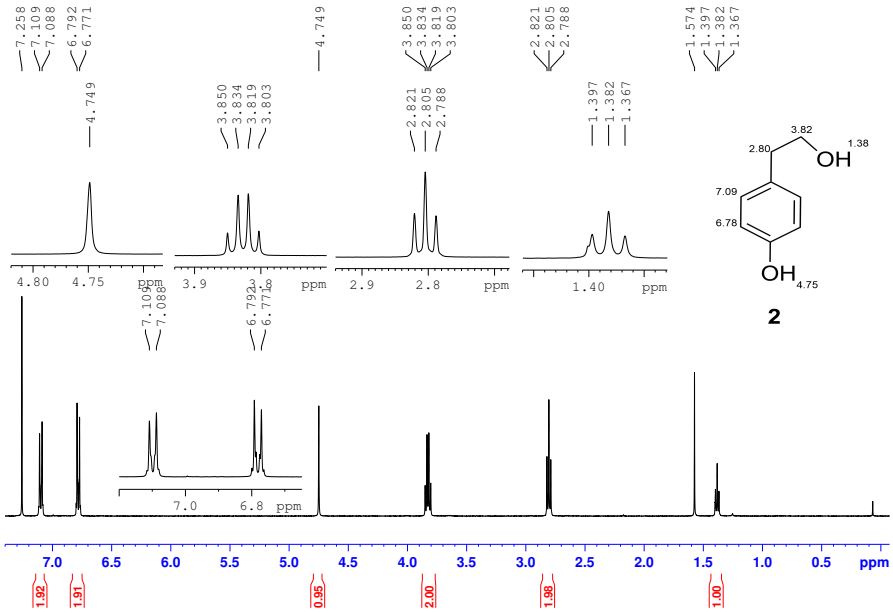


Figure E.1: ^{1}H NMR specter (600 MHz, $CDCl_3$) of 2-(4-hydroxyphenyl)ethanol (**2**).

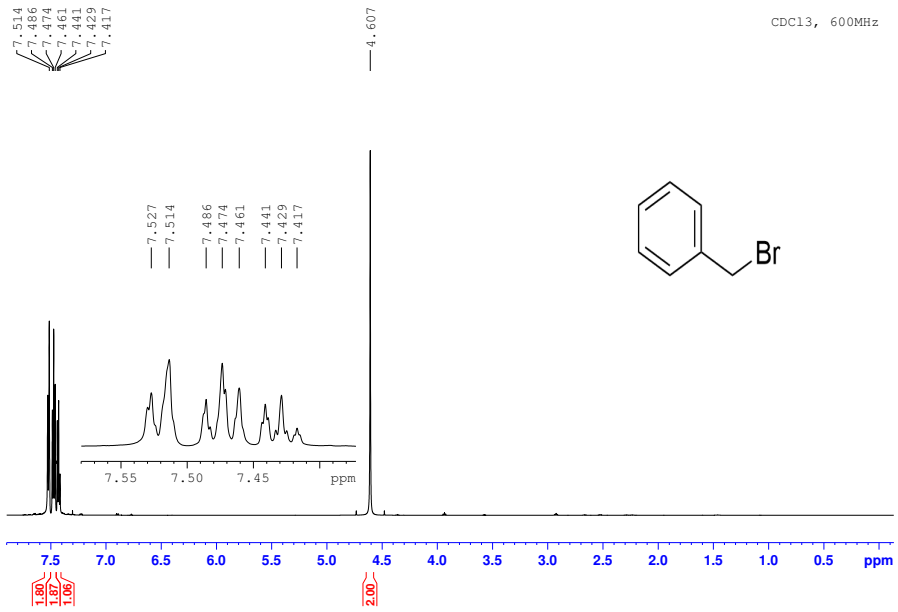


Figure E.2: ^{1}H NMR specter (600 MHz, $CDCl_3$) of benzylbromide.

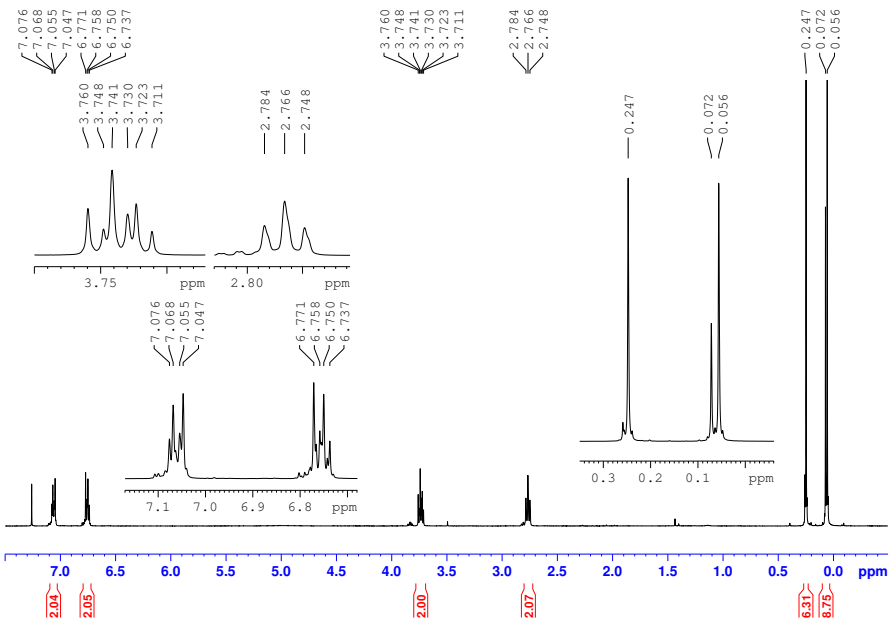


Figure E.3: ^{1}H NMR specter ((CDCl$_3$, 600 MHz) for method **2a** showing a mixture of **10a** or **10b** together with **10c**.

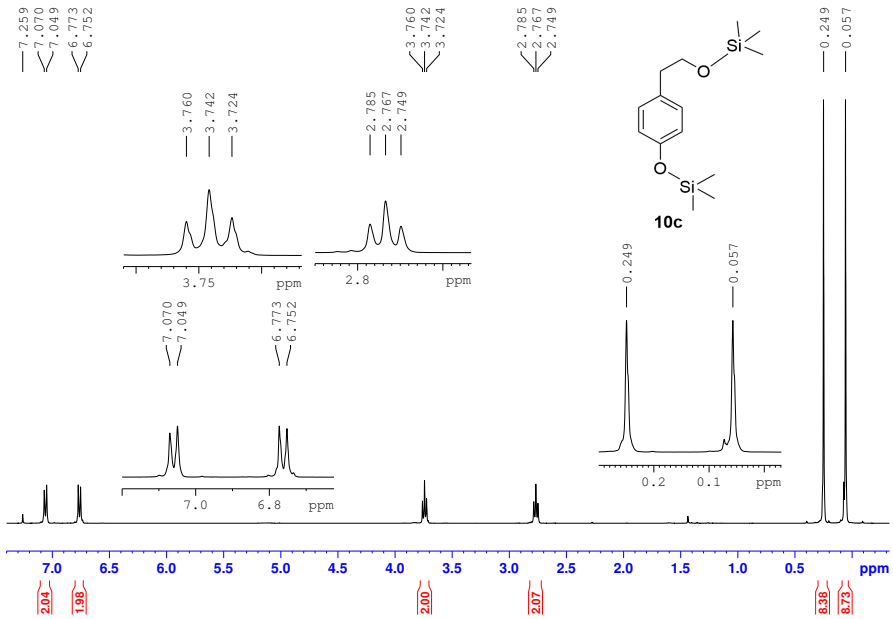


Figure E.4: ^{1}H NMR specter (600 MHz, CDCl$_3$) for method **2c**, likely from compound **10c**.

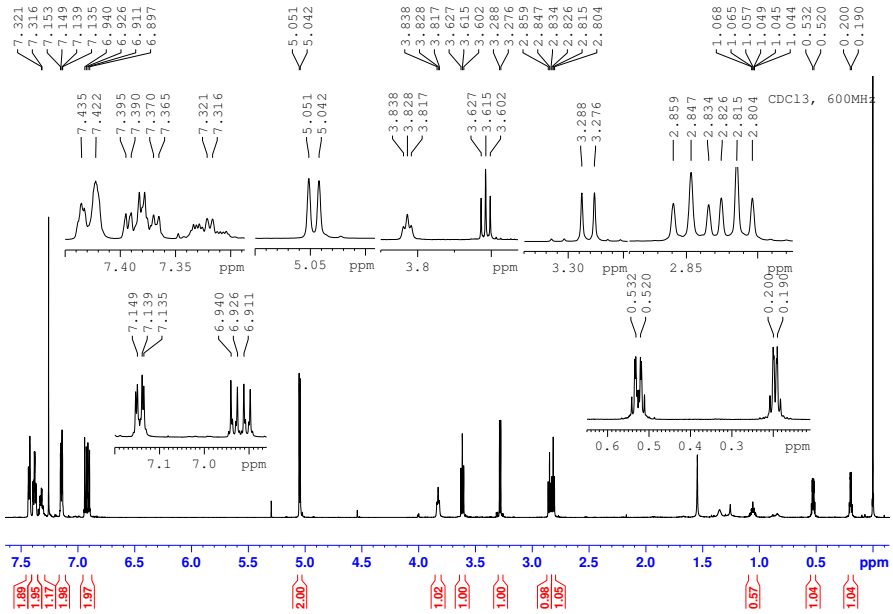


Figure E.5: ^{1}H NMR specter (600 MHz, $CDCl_3$) of mixture of 2-(4-benzyloxyphenyl)ethanol) (**3**) and 1-(benzyloxy)-4-(2-(cyclopropylmethoxy)ethyl)benzene (**5**)

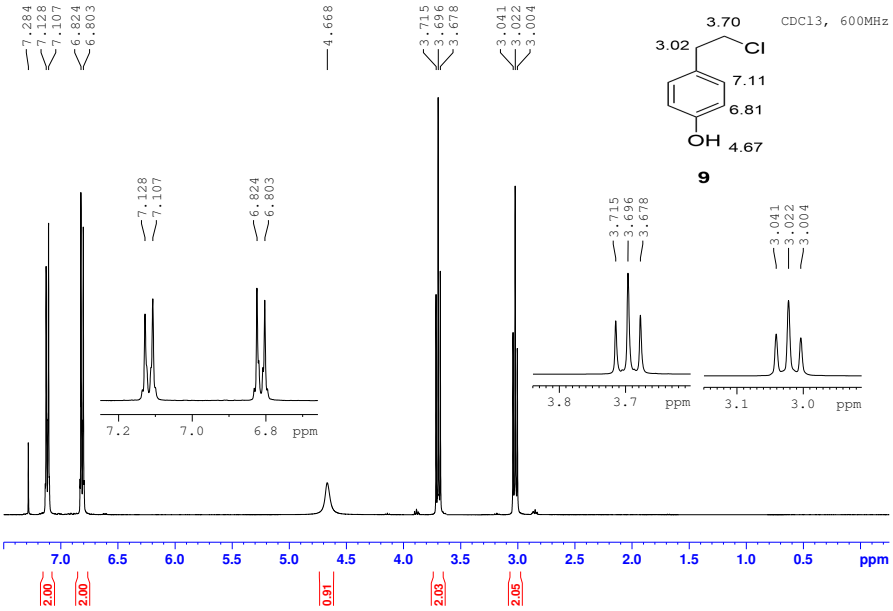


Figure E.6: ^{1}H NMR specter (600 MHz, $CDCl_3$) of 4-(2-chloroethyl)phenol (**9**).

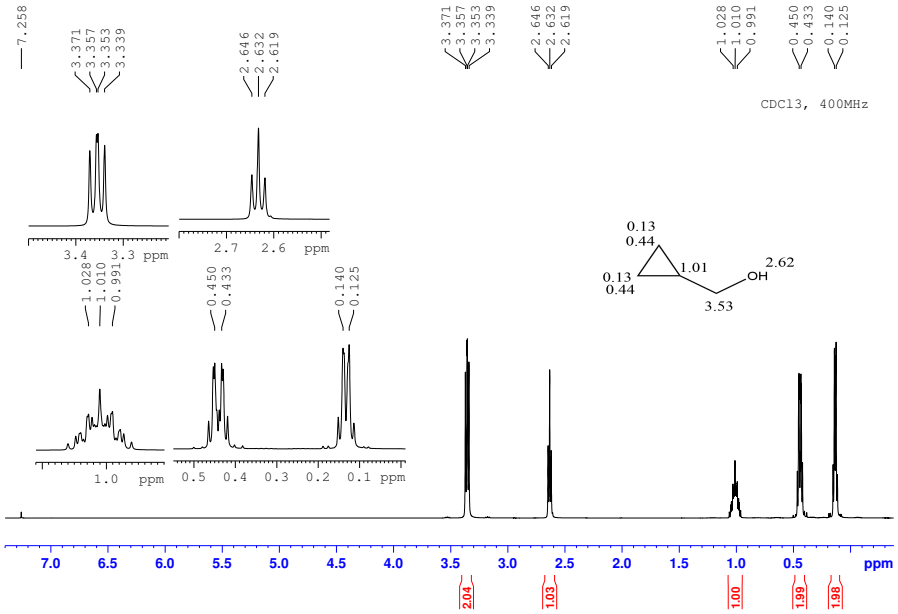


Figure E.7: ^{1}H NMR specter (400 MHz, $CDCl_3$) of cyclopropylmethanol.

F. HPLC CHROMATOGRAM FOR KINETIC RESOLUTION OF 1-CHLORO-3-(4-(2-(CYCLOPROPYLMETHOXY)ETHYL)PHENOXY)PROPAN-2-OL (**7**)

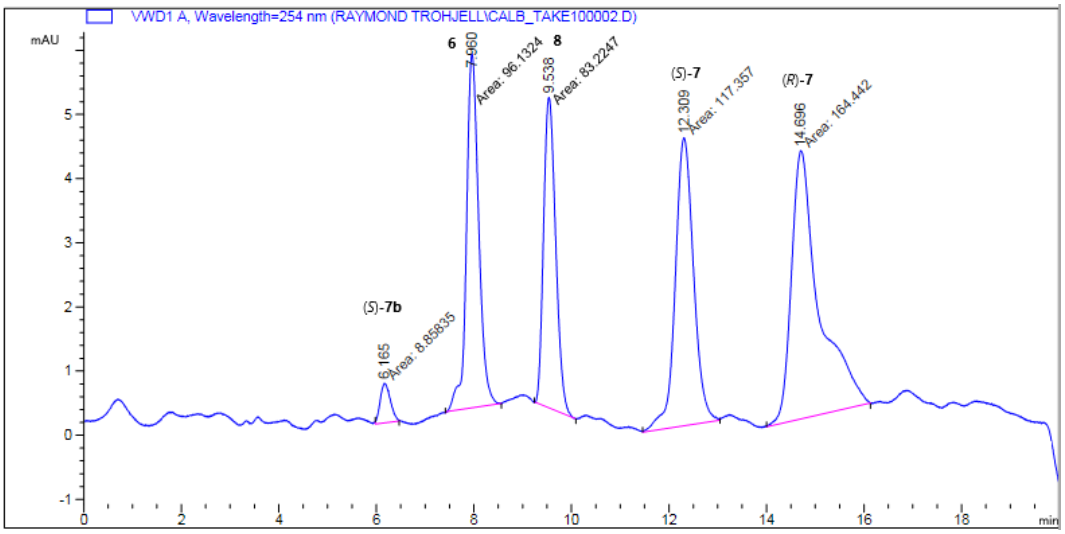


Figure F.1: HPLC of kinetic resolution of **7** after 15 min reaction time. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

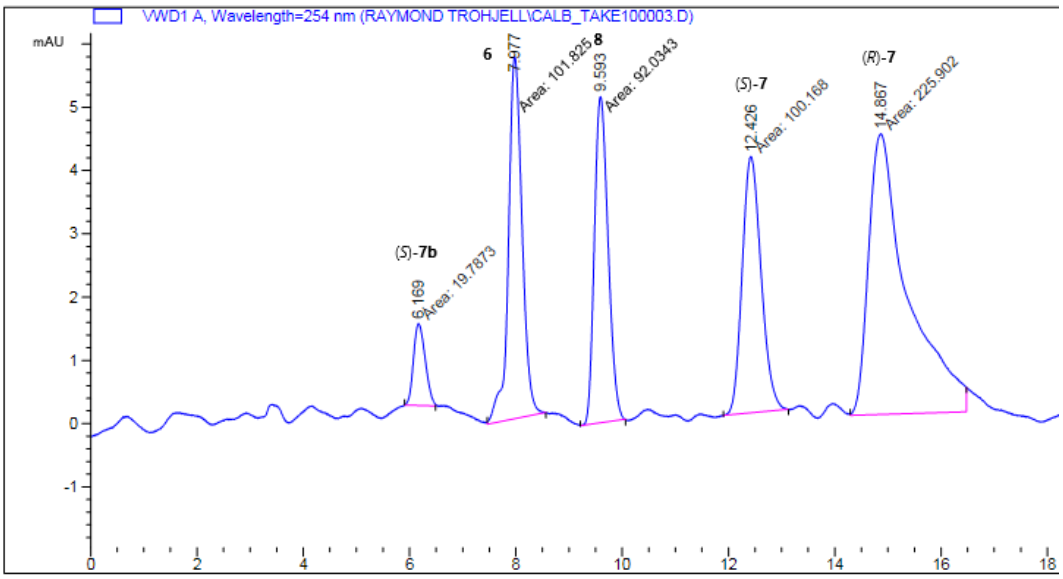


Figure F.2: HPLC of kinetic resolution of **7** after 30 min reaction time. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

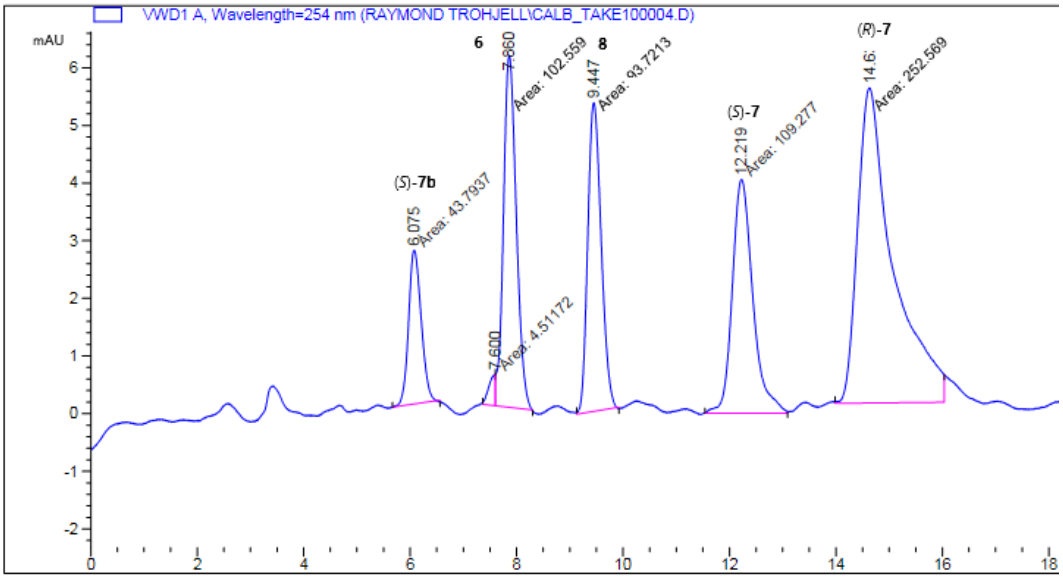


Figure F.3: HPLC of kinetic resolution of **7** after 1 h reaction time. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

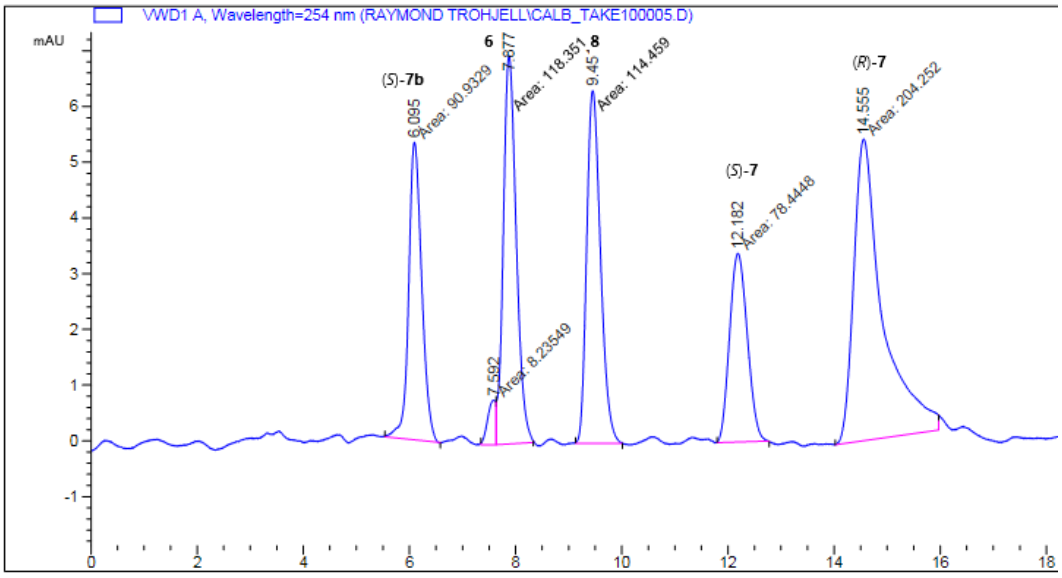


Figure F.4: HPLC of kinetic resolution of **7** after 2 h reaction time. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

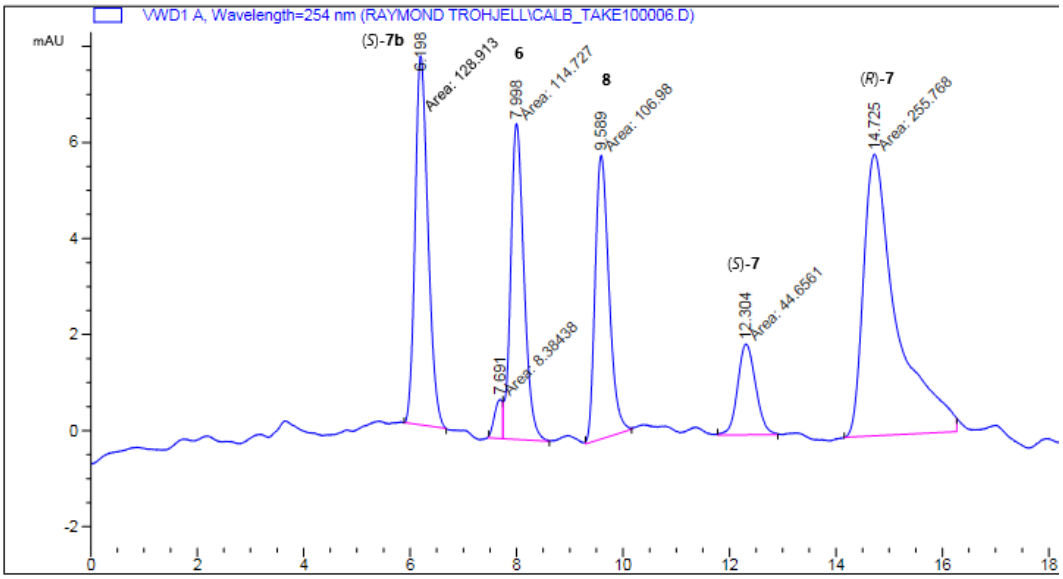


Figure F.5: HPLC of kinetic resolution of **7** after 4 h reaction time. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

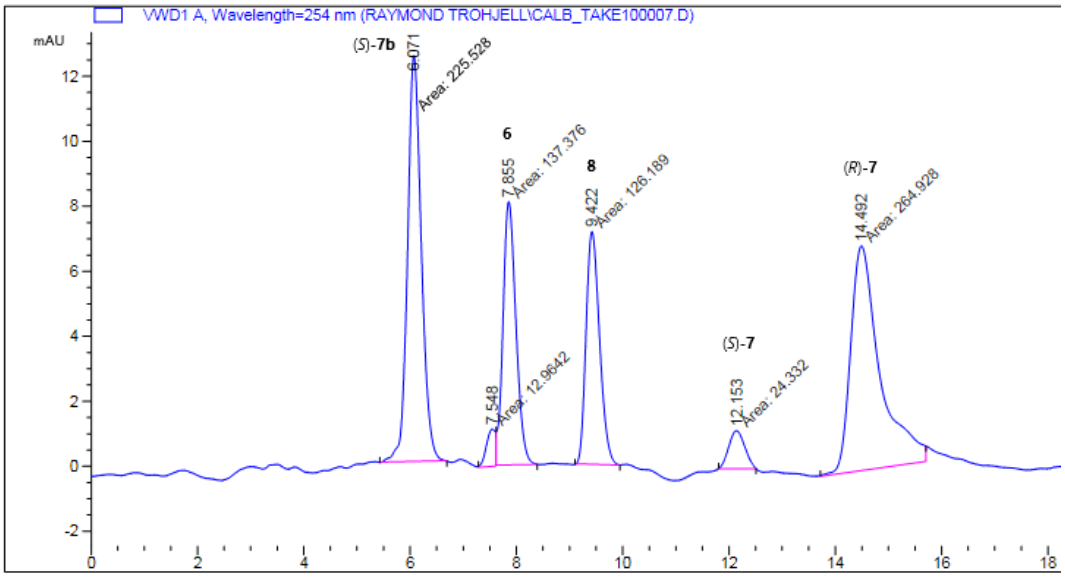


Figure F.6: HPLC of kinetic resolution of **7** after 6 h reaction time. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

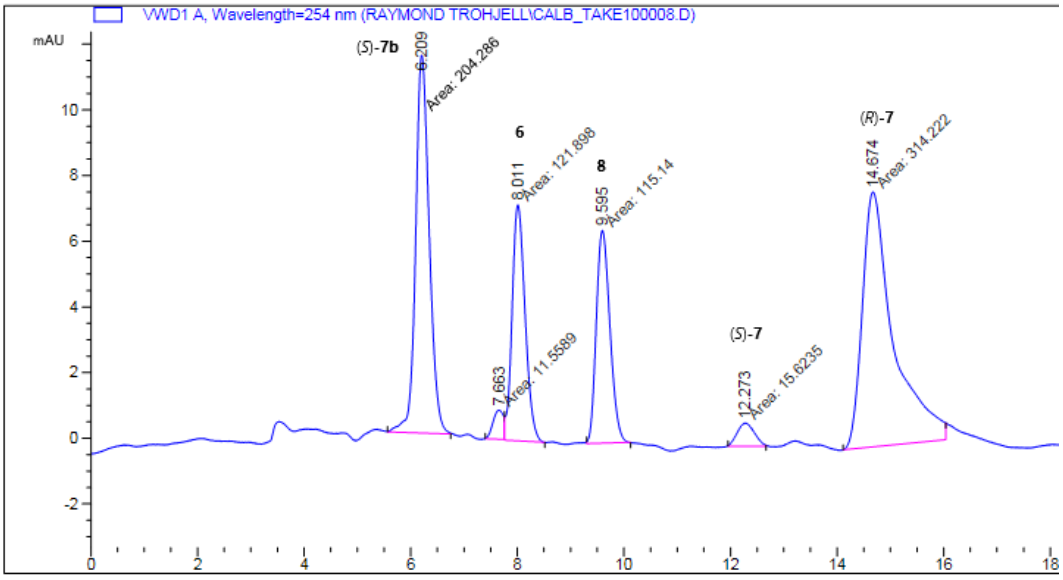


Figure F.7: HPLC of kinetic resolution of **7** after 8 h reaction time. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

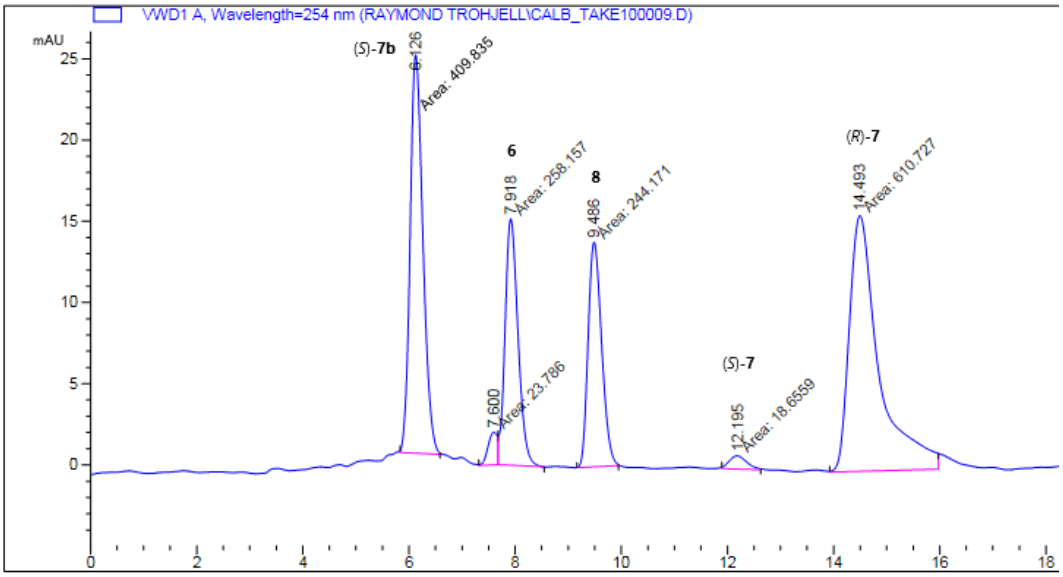


Figure F.8: HPLC of kinetic resolution of **7** after 10 h reaction time. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

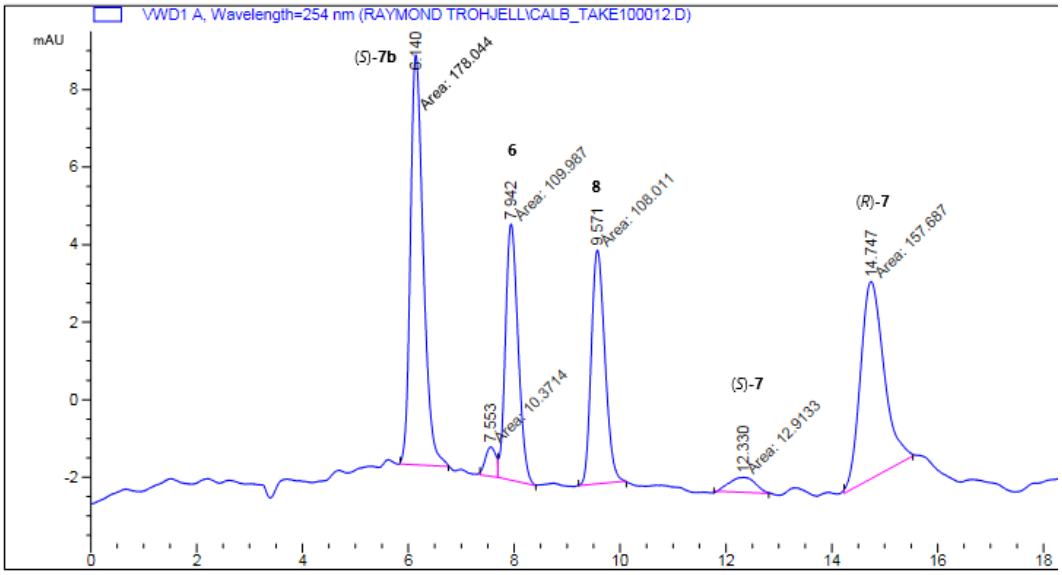
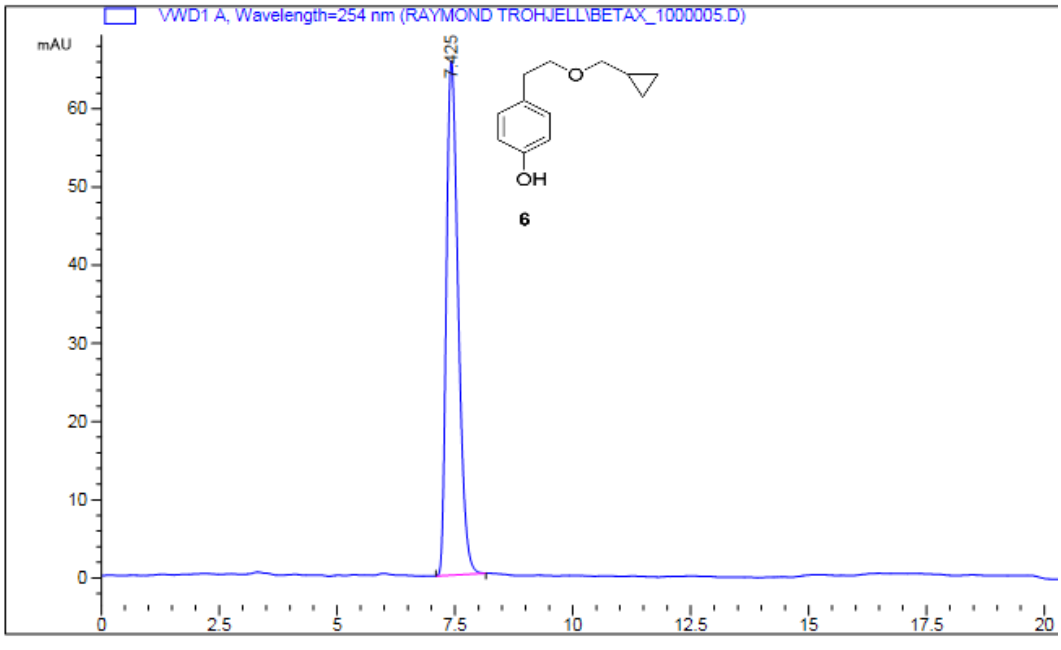


Figure F.9: HPLC of kinetic resolution of **7** after 22 h reaction time. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

F.1. Additional HPLC chromatograms



[H]

Figure F.10: Chromatogram of 4-(2-(cyclopropylmethoxy)ethyl)phenol **6**. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

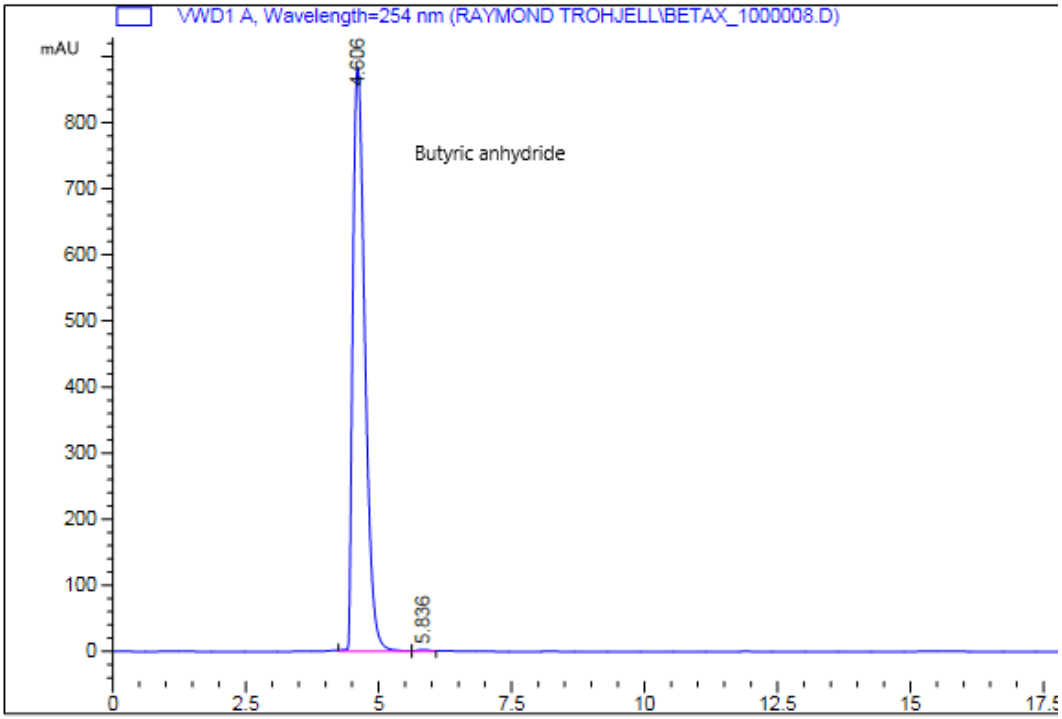


Figure F.11: HPLC of butyric anhydride used in derivatization of **7**. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

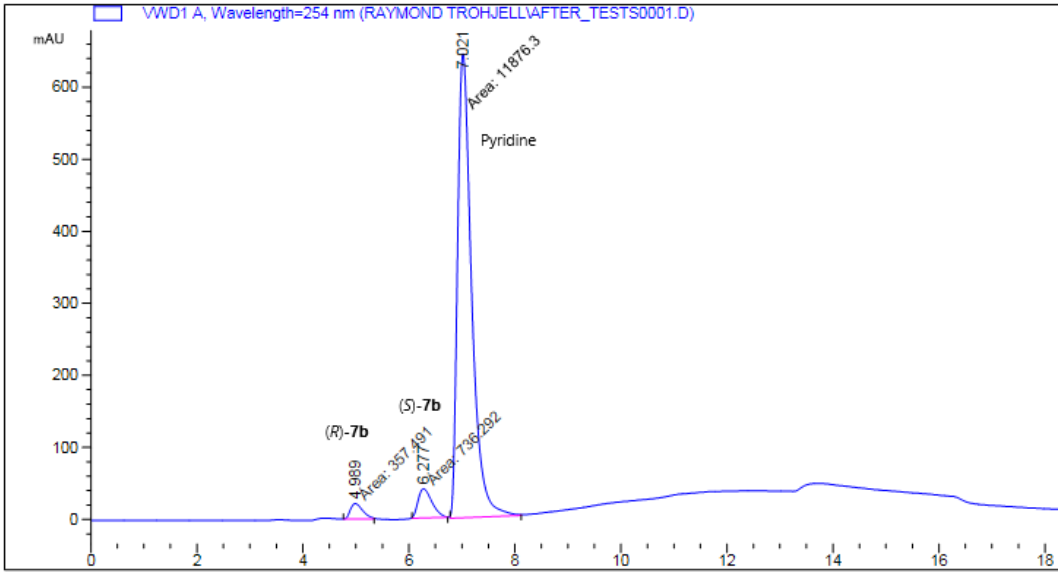


Figure F.12: HPLC of derivatized **7**. Remaining pyridine can be seen at R_t = 7,0 min. Possibly remaining butyric anhydride at R_t = 4,9 min. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

F.2. HPLC CHROMATOGRAM OF RING OPENING OF **8**.

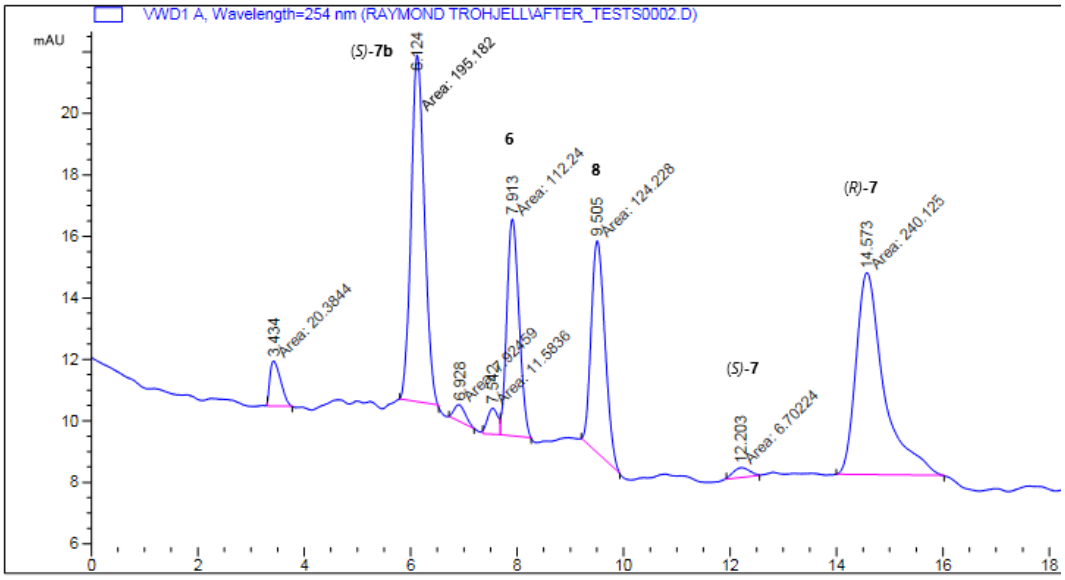


Figure F.13: HPLC before second ring opening of epoxide **8** was performed with acetic acid and LiCl. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.

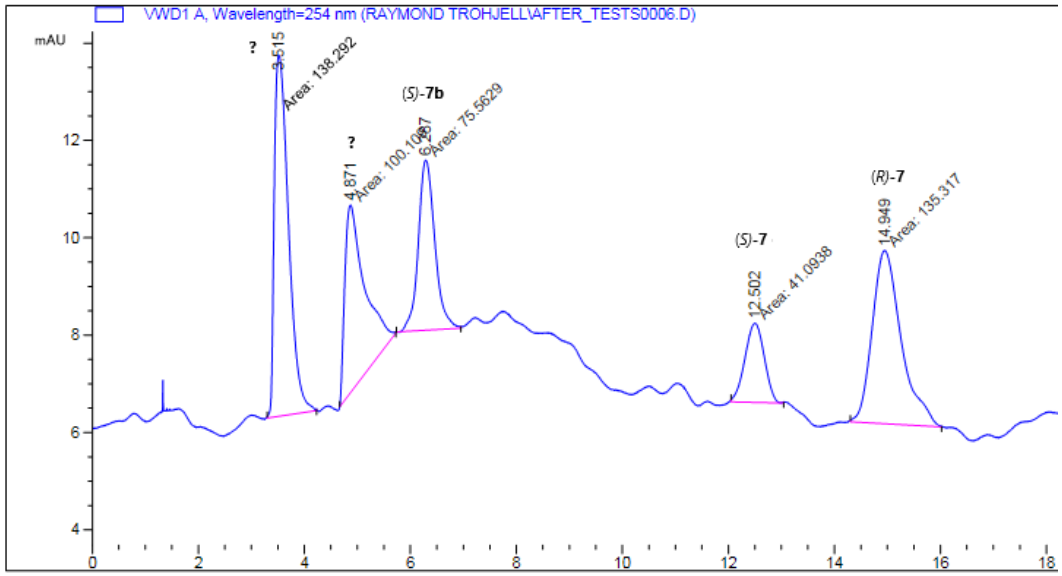


Figure F.14: HPLC after second ring opening of epoxide **8** with acetic acid and LiCl. HPLC with chiracel OD-H column hexane:isopropanol (90:10) and 1 ml min^{-1} flow.