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Synthesis of Bifunctional Alkenes for Nucleophile-Controlled Selenocyclizations

A thesis submitted for the degree of
Doctor of Philosophy at
Cardiff University

by

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Abstract

Synthesis of an olefin containing two functional groups, a hydroxy and an acid functionality has been successfully achieved. A methodology for highly selective cyclizations with phenylselenenyl electrophiles has been developed. The exclusive formation of substituted tetrahydrofurans can be achieved using triflate as the counterion and with the addition of acetic acid, whereas cyclizations can also be directed towards complete formation of lactones using hexafluorophosphate or sulfate as the counterion and methanol as an additive. A series of chiral diselenides were synthesized and employed in cyclization of bifunctional olefins. Highest selectivity was obtained with a chiral methoxy substituted alcohol diselenide.

A comparison of *endo*- versus *exo*- cyclization was estimated using dihydroxy olefins with selenium and iodine electrophiles. The obtained results showed highest diastereomeric ratios in the *endo*-cyclization compared to *exo*-cyclization.

Summary

Cyclization reactions of olefins can lead to heterocycles, which serve as essential building blocks for the synthesis of useful natural products. The most common building blocks are based on lactone and substituted tetrahydrofuran structures and are commonly obtained from individual substrates.

The aim was to synthesize an olefin that contained two functional groups: a hydroxy and an acid functional group. 5-*exo* Cyclization via the hydroxy group of this olefin with an electrophile resulted in substituted tetrahydrofurans while the cyclization via the acid functionality resulted in the formation of lactones. A series of reactions using different additives and a variety of counterions with selenium electrophiles led to the discovery of selective cyclization conditions of each cyclized product. Using phenylselenenyl triflate in the presence of acetic acid the reaction led exclusively to the formation of substituted tetrahydrofurans while lactones could be obtained using hexafluorophosphate or sulfate as a counterion and methanol as an additive. The selective synthesis of each cyclized product indicated the influence of additives on the course of cyclization. The additives (alcohol and the acid) were than incorporated into the selenium reagents. The expected coordination of the selenium electrophile to internal heteroatoms or to the substrate led to independent cyclization and there was no influence of additives on the course of cyclization. As expected, these modified achiral selenium reagents produced a 1:1 mixture of substituted tetrahydrofurans and lactones.

The enantioselectivity of known chiral selenium electrophiles containing the heteroatom in a 1,3-relation to the selenium was studied in the reaction with this olefin and the highest selectivity was found with the methoxy substituted alcohol diselenide. To increase the selectivity the synthesis of new chiral selenium reagents were attempted. The synthesis of modified sulfur selenium reagents was carried out according to the reference of *Tiecco et al.* but showed a lower selectivity in reaction with this substrate.

To investigate the results between 5-*endo* and 5-*exo* cyclization other bifunctional olefins containing a dihydroxy functionality were synthesized. The reaction of these olefins with selenium and iodine electrophiles gave a comparison of *endo*- versus *exo*-cyclization. The major isomer from *exo*-cyclization was the *cis* isomer while in *endo*-cyclization it was the *trans* isomer.

Dedicated to my parents,
for their support and encouragement...

Contents

List of Abbreviations.....XII

1. Introduction

1.1 The importance of selenium in organic synthesis.....1

1.2 Organoselenium compounds.....1

1.3 Selenium nucleophiles.....2

1.4 Selenium electrophiles.....3

1.4.1 Asymmetric oxyselenenylation reaction.....4

1.4.2 Cyclization reactions.....5

1.5 Selenium precursors in radical reactions.....6

1.5.1 Deselenenylation via tin mediated reactions.....7

1.6 Selenium-stabilized carbanions.....8

2. Selective cyclization to lactones and furans

2.1 Selenocyclization reaction.....9

2.2 Recent discoveries on the effect of additives in selenocyclization.....10

2.3 Influence of counterions.....11

2.4 Research Targets.....12

2.5 Synthesis of substrate **41**.....13

2.6 Selective synthesis of tetrahydrofurans and lactones.....15

2.7 Stereochemical assignment of **44/45**.....18

2.8 Reaction of **41** with phenylselenenyltriflate and influence of additives.....19

2.9 Reaction of **41** with different counterions.....22

2.10 Reaction of **41** under different temperature conditions.....22

2.11 Stability of selenofuran **42b/43b** and selenolactone **44b/45b**.....24

2.12 Conclusions.....25

3. Achiral selenium reagents

3.1 Selenium reagents with an internal heteroatom.....26

3.2 Synthesis of alcohol diselenide.....27

3.2.1 Reaction of **41** with alcohol diselenide.....27

3.3 Synthesis of acid diselenide....28
3.3.1 Reaction of acid diselenide with **41**....29
3.4 Synthesis of ester diselenide....30
3.4.1 Reaction of ester diselenide with **41**....31
3.5 Diastereomeric ratio of tetrahydrofuran **56** from selective cyclization....32
3.6 Conclusions....32

4. Chiral selenium reagents

4.1 Chiral selenium reagents with a heteroatom-containing moiety in the *ortho*–position....33
4.2 Chiral selenium reagent with oxygen as the heteroatom....34
4.2.1 Synthesis of chiral alcohol diselenide....34
4.2.2 Synthesis of chiral MOM diselenide....35
4.2.3 Synthesis of chiral methoxy substituted diselenide....35
4.2.4 Synthesis of chiral diol diselenide....36
4.3 Chiral selenium reagents with sulfur as the heteroatom....39
4.3.1 Synthesis of chiral sulfur diselenide....39
4.3.2 Synthesis of chiral sulfur methoxy diselenide....40
4.4 Chiral selenium reagents with selenium as the heteroatom....41
4.5 Reaction of **41** with chiral selenium reagents....41
4.5.1 Reaction of **51** with chiral selenium reagents....44
4.6 Selectivity of chiral selenium reagents....46
4.7 Kinetic resolution of substrate **41**....51
4.8 Conclusions....52

5. 5-*exo* versus 5-*endo* cyclization

5.1 Synthesis of a new bifunctional olefin for *endo*-cyclizations....53
5.2 Synthetic strategies towards **101**....53
5.3 Synthesis of diol **116**....56
5.4 Cyclization reaction of **116**....57
5.4.1 Reaction of **116** with achiral electrophilic reagents....58
5.4.2 Selectivity of chiral selenium reagents with **116**....59
5.5 Synthesis and cyclization of *exo* diol **121**....60

5.5.1 Reaction of **121** with achiral electrophilic reagents.....61
5.5.2 Selectivity of chiral selenium reagents with **121**.....62
5.6 Other attempts for comparison of *exo*- versus *endo*-cyclization.....62
5.7 Conclusions.....63

6. Double cyclization reactions

6.1 Cyclization reactions of tetrahydrofurans and lactones compounds.....64
6.2 Cyclization from selenolactone and substituted tetrahydrofuran.....65
6.3 Cyclization from iodolactone.....66
6.4 Cyclization from substituted iodo tetrahydrofuran.....68
6.5 Conclusions.....68

7. Conclusion & Outlook

7.1 Conclusions.....69
7.2 Outlook.....70

8. Experimental

8.1 General reactions details.....72
8.2 Physical Data.....73
8.3 General procedures.....75
8.3.1 Cyclization reaction of olefins with generated selenium electrophiles (GP 1).....75
8.3.2 Cyclization reaction of olefins with iodine monochloride (GP 2).....75
8.3.3 Ester hydrolysis (GP 3).....76
8.3.4 Chiral reduction with (+)DIPCl (GP 4).....76
8.3.5 Reduction with $LiAlH_4$ (GP 5).....76
8.3.6 Introduction of sulfur moiety (GP 6).....76
8.3.7 Synthesis of sulfur diselenides (GP 7).....77
8.3.8 Deselenenylation by radical cleavage of arylselenides (GP 8).....77
8.4 Spectroscopic data.....78

References.....127

Appendix 1.....132

Appendix 2.....135

Conferences, Presentations & Publications (2001-2004).....138

List of Abbreviations

$[\alpha]_D$	specific optical rotation
AIBN	2,2´-Azobis(2-methyl-propionitrile)
APCI	atmospheric pressure chemical ionization
Ar	aromatic substituent
δ	chemical shift
DCM	dichloromethane
DEPT	dissortionless enhancement by polarisation transfer
DIPCl	(+)-B-chlorodiisopinocampheylborane
d.r.	diastereomeric ratio
EI	electronic ionization
eq.	equivalent
ee	enantiomeric excess
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
GC	gas chromatography
GC-MS	gas chromatography-mass spectroscopy
GP	general procedure
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
Hr	hour
IR	infrared spectroscopy
J	NMR coupling constant
LDA	lithium diisopropyl amine
M^+	molecular ion
MCPBA	*meta*-chloro perbenzoic acid
MOM	methoxy methyl
MS	mass spectrometry
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
ppm	part per million
R*f*	retention factor

red	reduction
rt	room temperature
S_N2	nucleophilic substitution
THF	tetrahydrofuran
TMEDA	tetra methyl ethylenediamine
TBDMS	*tert*-butyldimethylsilyl

Chapter 1

1. Introduction

1.1 The importance of selenium in organic synthesis

Organoselenium compounds are very useful reagents, which are commonly employed in synthetic chemistry. They offer the possibility of introducing new functional groups into complex organic substrates under mild reaction conditions with a high degree of chemo-, regio- and stereoselectivity. When incorporated, they can be directly converted into different functional groups.

1.2 Organoselenium compounds

The various structures of organoselenium compounds are closely related to their sulfur analogs as they appear in the same group (main group VI) in the periodic table, but their properties observed in reactions are often quite different. Different bond lengths[1] C–S = 1.82 Å, C–Se = 1.96 Å and bond energies[2] C–S = 69.7 kcal/mol, C–Se = 59.9 kcal/mol as well as a different electronic behavior lead to a difference in reactivity. Reactions like the introduction of a heteroatom, the manipulation of the resulting molecules and, in particular, the removal of the selenium containing moieties via oxidative elimination occurs under more simple and mild conditions (reaction at room temperature) than those described for the corresponding sulfur compounds.[3]

Selenium containing moieties can be employed in organic reactions in different forms, as an electrophile, as a nucleophile or as a radical. A further characteristic of organoselenium species involves the reaction of the selenoacetal with a suitable organolithium compound, which allows the formation of a stable carbanion by cleavage of one C–Se bond of seleno acetals.[4]

Subsequent manipulation of selenium containing compounds (often achieved under milder conditions than their sulfur analogues) particularily oxidative elimination of the selenium moiety, a characteristic that dominates the use of selenium in organic chemistry.[5]

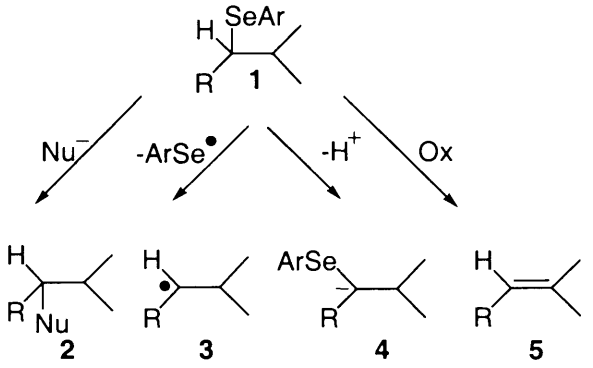


Figure 1-1: Typical reactions of selenium containing compounds.

The arylseleno group in **1** can be removed in several ways: Substitution of the selenium moiety with a suitable nucleophile will yield compounds of type **2**. By treatment with tin hydrides in the presence of AIBN, the homolytic cleavage of the carbon–selenium bond takes place and carbon radicals **3** are generated. Selenium stabilized carbanions **4** are valuable intermediates in organic synthesis. Oxidation of the selenide **1** gives rise to selenoxides **6** from which products **5** are obtained by elimination (Figure 1-2).[6] The elimination via selenoxides is several orders of magnitude faster than the elimination of the corresponding sulfoxides.

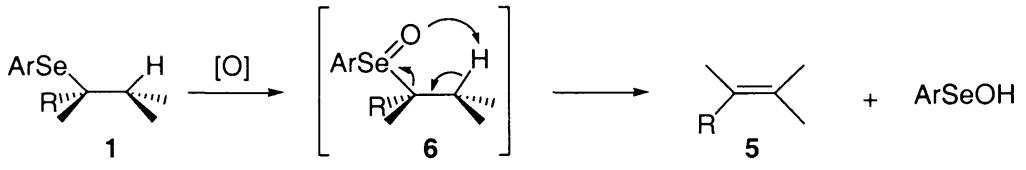


Figure 1-2: Synthesis of alkenes by selenoxide elimination.

1.3 Selenium nucleophiles

Since Sharpless's application of a nucleophilic selenolate[7] to the ring opening of epoxides, various nucleophilic selenium species have been widely used in organic synthesis. Advantages of the use of selenolates are rationalised in their high reactivity and selectivity as well as in the easy removal of the selenium moiety from the reaction products.

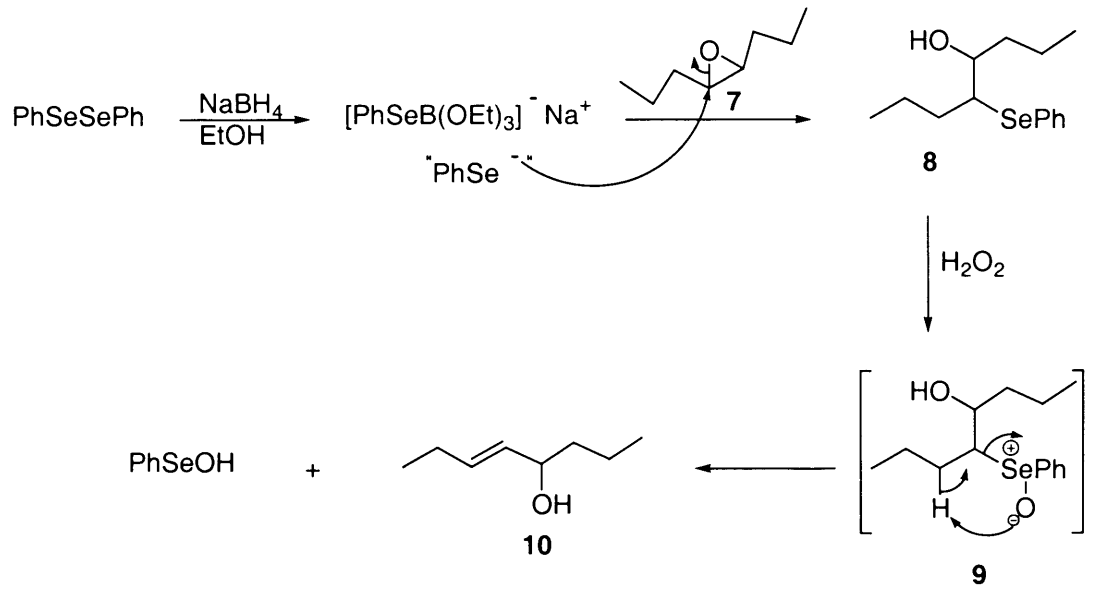


Figure 1-3: Allylic alcohols from epoxides by Sharpless.

Its usefulness in the nucleophilic ring opening of various epoxides and the subsequent oxidative elimination of the phenylseleno group led to allylic alcohols under mild conditions. Sodium borohydride ($NaBH_4$) was employed as a reducing agent to generate the nucleophilic selenium moiety $PhSe^-$ from diphenyl diselenide (PhSeSePh) in ethanol. The structure of this mild nucleophilic selenium species is the sodium phenylseleno(triethoxy)borate complex $[PhSeB(OEt)_3Na]$.[8] Oxidative elimination of selenium moiety **9** from **8** at room temperature resulted in allylic alcohol **10**. Since Sharpless' discovery a number of nucleophilic reactions using diphenyl diselenide have been developed, including substitution reactions with halides[9], addition reactions to cyclic ethers[10], nucleophilic reductions of α,β-epoxy carbonyl compounds[11], etc. These reactions are useful in organic synthesis as well as in the preparation of biologically active organoselenium compounds.[12]

1.4 Selenium electrophiles

Electrophilic selenenylation reactions of alkenes have been used successfully to functionalize non activated carbon–carbon double bonds.[13] Stereoselective variants of this reaction with chiral selenium electrophiles have been performed by numerous research groups.[14,15]

Selenium halides are often used as electrophilic selenium reagents. They can easily be prepared from the corresponding diselenides by addition of molecular bromine or thionyl chloride. Other counter anions (e.g. hexafluorophospate, tetrafluoroborate) to the selenium electrophile can be introduced by treatment of the selenium halide with an appropriate silver

salt[16] (e.g. treatment of aryl selenenyl bromide with silver triflate generates the corresponding aryl selenenyl triflate). These reagents are potent electrophiles in addition reactions to alkenes. Although both species (arylselenenylbromide and arylselenenyltriflate) are a good source of selenium in comparison to bromide the triflate counterion is often preferred due to its low nucleophilicity.

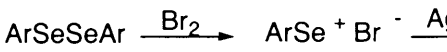


Figure 1-4: Selenium electrophile generated from diaryl diselenide.

The mechanism of the addition reaction of selenium electrophiles with alkenes is a two-step process. In the first step the double bond is activated by the selenium electrophile to form a three-membered intermediate, the seleniranium cation **11** (Figure 1-5). In the second step a nucleophile attacks the substrate from the *anti*-side, leading to the *trans*-addition product **12**. The reaction shows Markovnikov-selectivity, as the attack of the nucleophile occurs on the higher substituted carbon atom. [17]

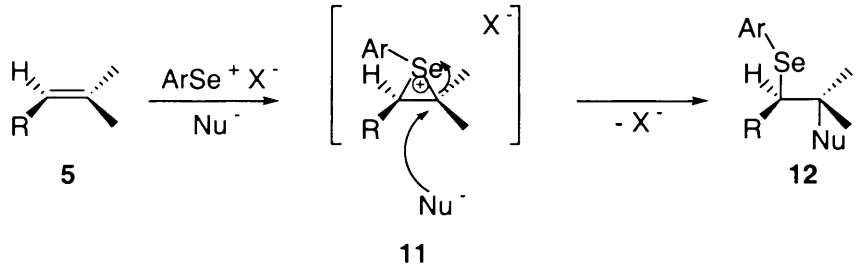


Figure 1-5: Reaction of a selenium electrophile with alkenes.

1.4.1 Asymmetric oxyselenenylation reactions

A number of new addition reactions have been described in recent years. These mainly concern reactions carried out in the presence of external oxygen (oxyselenenylations) or nitrogen nucleophiles (aminoselenenylations). The oxyselenenylation reactions, i.e. the stereospecific *anti* addition of an organoseleno group and an oxygen nucleophile (such as OH, OR and OCOR group) to an olefin are very useful and widely used procedures for the preparation of simple as well as complex molecules.

Asymmetric oxyselenenylation reactions have been extensively employed to investigate the efficiency of the various chiral non-racemic selenenylating agents. In particular the methoxyselenenylation of styrene has been studied with a variety of chiral selenium reagents. The mechanistic course of methoxyselenenylation of styrene has been investigated in some detail by Wirth[18] using the selenyl triflate of a chiral hydroxy diselenide.

Starting from the electrophilic selenium reagent with the *S*-configuration two diastereomeric addition products **15** and **16** were formed in a ratio of up to 96:4 and it was demonstrated that the newly generated stereocentre of the major diastereomer (Figure 1-6) had the *(R)*-configuration. This corresponds to a favoured *re* attack of styrene. [19]

The stereochemistry of the addition reaction is dictated by the selenium reagent. Since nucleophilic attack on the seleniranium ion **13** or **14**, which is generated from the attack of electrophile on *re* or *si* side of styrene, is exclusively *anti* to the selenium atom, the placement of a chiral moiety with *(S)* configuration on the selenium reagent will create two possible diastereomeric products **15** with *(R)*, *(S)* and **16** with *(S)*, *(S)* configuration.

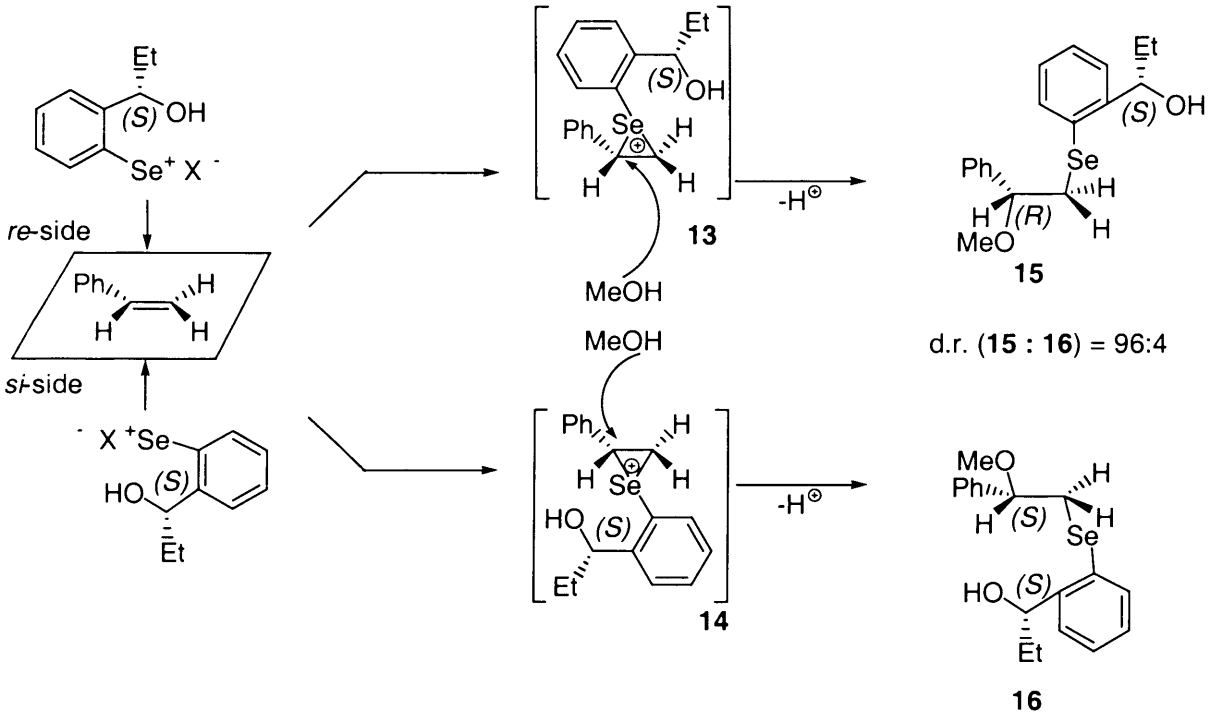


Figure 1-6: Origin of diastereomers during enantiotopic attacks of selenium electrophile.

The selection of the substrate, having two different substituents on the carbon where nucleophilic attack (e.g. from MeOH) takes place, enables the formation of a new chiral centre e.g. on **15** *(R)* and **16** *(S)* configuration.

1.4.2 Cyclization reactions

The selenium reagents can also be employed in cyclization reactions for the stereoselective synthesis of interesting heterocyclic compounds. For the elaboration of highly functionalized heterocyclic compounds this methodology continues to receive methodological as well as synthetic attention.

When selenium electrophiles react with alkenes of type **17**, bearing an internal nucleophile, ring formation can occur. The seleniranium cation can be opened by the intramolecular nucleophile either via an *exo* or *endo* attack, depending on ring size or substituent effects to form the products **18** or **19**, respectively (Figure 1-7).

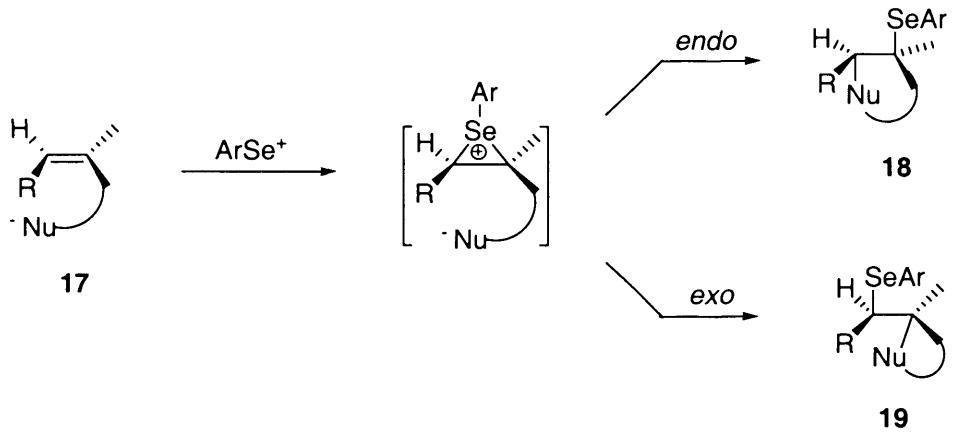


Figure 1-7: Cyclization of alkenes bearing an internal nucleophile.

1.5 Selenium precursors in radical reactions

Oganoselenium compounds are very versatile radical precursors, which are widely used. Due to their stability and ease of preparation, they offer unique advantages over organic halides as radical precursors. The important advantages involve homolytic cleavage of carbon–selenium bonds and selenium–selenium bonds which is an easy process that can be initiated thermally or photochemically. Secondly, radical substitution at selenium is very effective with stannyl and silyl radicals. Divalent and tetravalent selenium species can also be involved in reductive and oxidative electron-transfer processes.

Organoselenium compounds can be utilized in tin mediated radical reactions as well as in group transfer reactions[20] (Figure 1-8) for the formation of carbon–carbon bonds and carbon–heteroatom bonds.

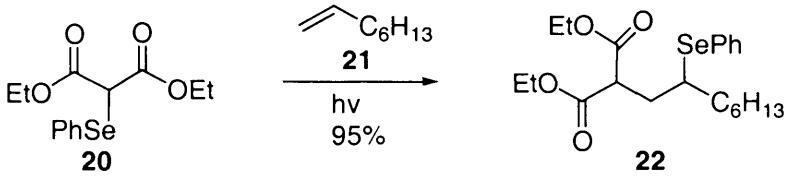


Figure 1-8: Group transfer reaction of organoselenium compounds.

Irradiation of the selenomalonate **20** gives the malonyl radical which adds efficiently to the olefin **21**[20]. The abstraction of the phenyl selenogroup results in the addition product **22**.

1.5.1 Deselenenylation via tin mediated reactions

The great importance of electrophilic addition of phenylselenyl reagents to olefins is due to the fact that, because of the versatility of the selenium containing moiety, they can be used as precursors for a series of useful transformations. Alkyl or aryl selenides are routinely applied as radical precursors for the generation of a wide range of radicals. The homolysis of the carbon–selenium bond (similar to a carbon–bromine bond) is extremely easy leading to interesting derivatives in each case.

Deselenenylation of **23** with tributyltin hydride in the presence of a catalytic amount of AIBN lead to formation of **24**. This resulting radical **24** can effect hydrogen abstraction to afford the reduction product **25** (Figure 1-9).

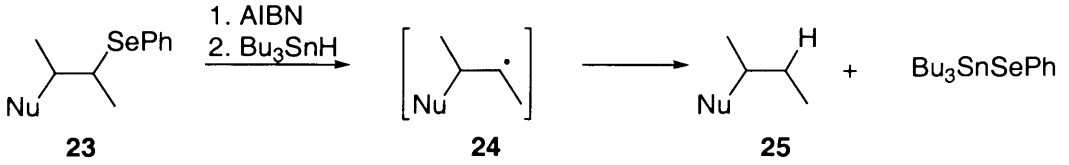


Figure 1-9: Deselenenylation via radical cleavage.

The reduction product can also be used to determine the selectivity of the chiral non-racemic selenium reagents. The organoselenium lactone **26** generated from the reaction of an olefin with a chiral selenium electrophile can influence the preference for formation of one stereoisomer. After deselenenylation the reduction product consists of enantiomers **27a** and **27b**. The ratio of enantiomers and thereby the selectivity of the employed chiral selenium reagent can be accurately determined by HPLC analyses using a chiral phase column (Figure 1-10).

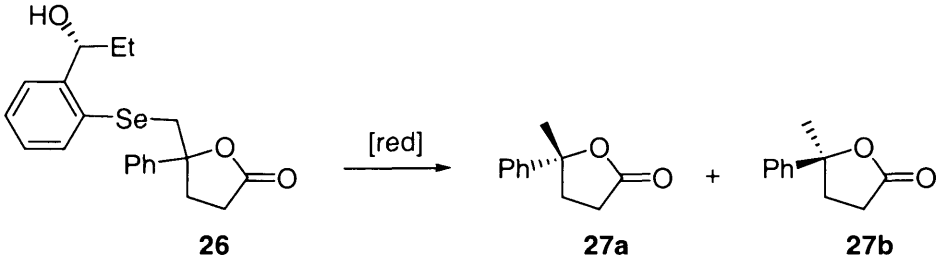
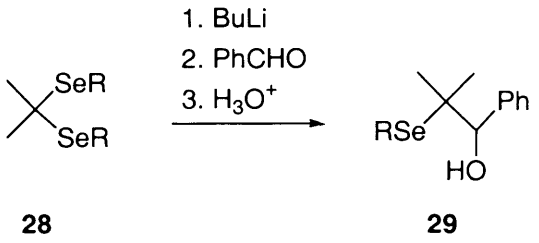


Figure 1-10: Formation of enantiomers.

1.6 Selenium-stabilized carbanions

Selenium-stabilized carbanions are now recognized as very important intermediates in organic synthesis. One of the main properties of selenides is their aptitude for attack by

various nucleophilic reagents. Alkyllithiums, which are not reactive with sulfides, have a marked selenophilic character (Figure 1-11).

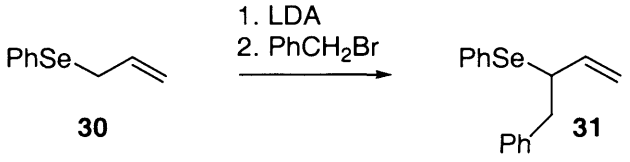


28 **29**

Figure 1-11: Formation of **29** via selenium stabilised carbanion.

Treatment of selenoacetal **28** with an organolithium reagent at –78 °C generates a carbanion by cleavage of one seleno group. The α-selanylalkyllithium was trapped at low temperature with benzaldehyde to give a β-hydroxyselenide **29**. [21]

Strong non-nucleophilic bases such as LDA, NaH, KH etc can deprotonate the α-carbon of selenides and the resulting carbanion can be alkylated (Figure 1-12).



30 **31**

Figure 1-12: Formation of **31** via α-deprotonation of selenide **30**.

The lithiated anion was generated by treatment of an allyl selenide **30** with LDA. Subsequent alkylation of the anion with benzylbromide gave the product **31**.[22]

Chapter 2

2. Selective cyclization to lactones and furans

2.1 Selenocyclization reaction

Alkenes bearing an internal oxygen nucleophile are the first and most thoroughly investigated substrates in cyclization reactions and have been found to be most suitable as substrates for these reactions.[23] In most cases the oxygen atom was from an alcohol or a carboxylic acid functional group. The corresponding cyclization reactions are usually referred to as selenoetherification or selenolactonizations.

The cyclization of **32** to **33** and **34** to **35** (Figure 2-1) represent the simple case in which the internal nucleophile is the oxygen of an alcohol.[24]

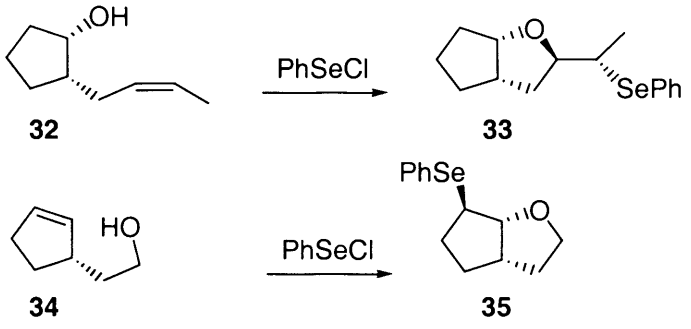


Figure 2-1: Cyclization of alkenes.

2.2 Recent discoveries on the effect of additives in selenocyclizations

Several observations on the effect of counterions in selenenylation reactions have already been reported, but they do not yet allow for a conclusive picture. From recent investigations by the Wirth Group (PhD work of Lars Uehlin)[19] on selective cyclizations, it was observed that the addition of external nucleophiles to the reaction lead to either selenolactonization (via addition of acetic acid) or to methoxyselenenylation (addition of methanol) as shown in Figure 2-3.

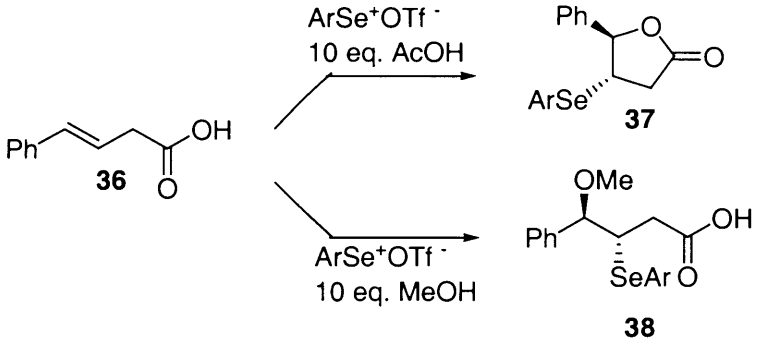


Figure 2-3: Selenenylation of unsaturated carboxylic acid **36** under different reaction conditions.

It was observed that the nature of cyclized products is influenced by the nature of the selenium electrophile used. The interaction between the selenium electrophile and the external nucleophile is dependent upon the nature of the internal nucleophile (present in the substrate) and the reactivity of the selenium electrophile, which, in turn, depends on the nature of the selenium counterion. The coordination of the selenium electrophile to a carboxylic acid is stronger than to an alcohol, selenium coordination to the carboxylic acid moiety in the substrate decreases the nucleophilicity of the acid function and intermolecular methoxyselenenylation is favoured over intramolecular lactonization, if methanol is present in the reaction. An excess of external nucleophilic acetic acid, which then competes in coordinating to the selenium electrophile is less nucleophilic, and leads to exclusive intramolecular lactonization (see Figure 2-4).

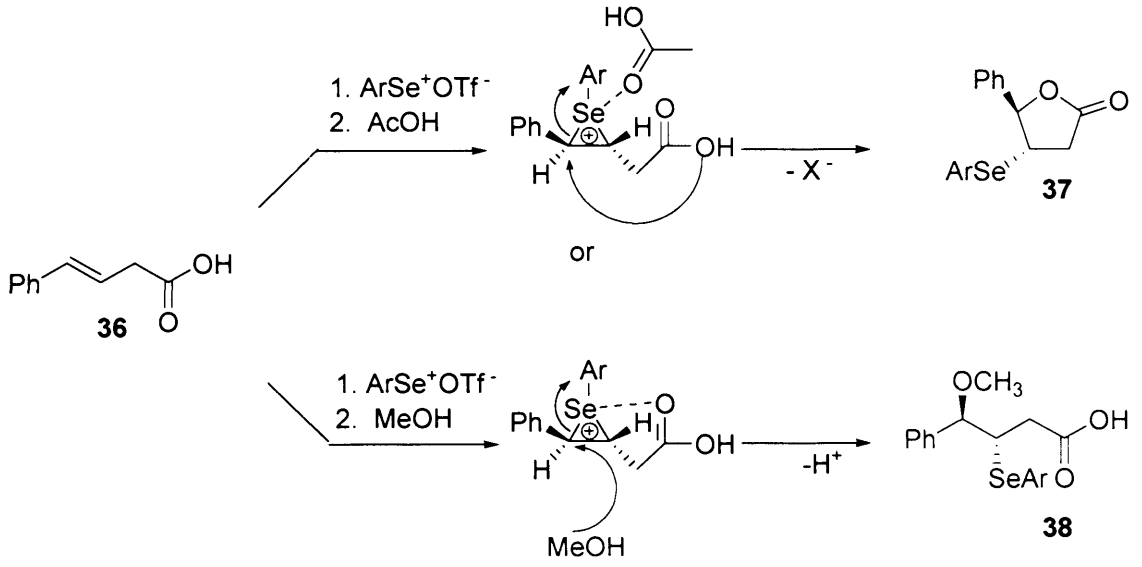


Figure 2-4: Proposed mechanism for methoxyselenenylation and selenocyclization.

2.3 Influence of counterions

The influence of counterions on the selectivity and yields of selenenylation reactions is considerable and has been investigated by different research groups.[25] The information gained from these experiments shows that stereoselectivity is always dependant on the alkene, the selenium electrophile, the nucleophile, counterion, the solvent, and the temperature.

The results of counterions were studied by Tomoda[26] by employing a chiral diselenide in reactions with β-methylstyrene (Figure 2-5), in methylene chloride and methanol at -100°C.

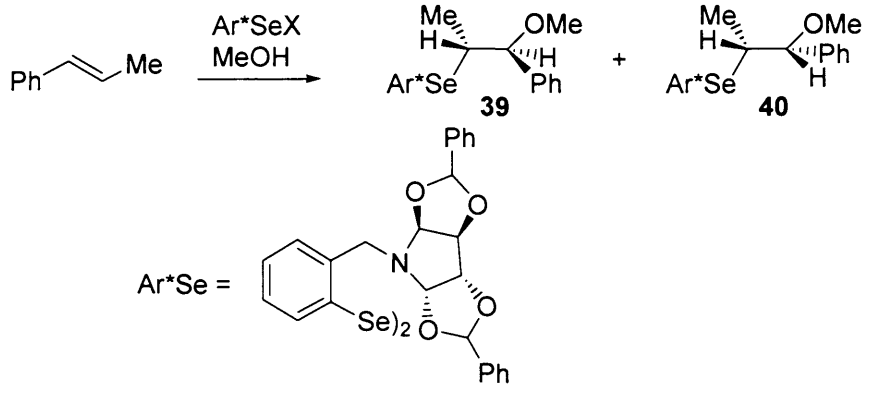


Figure 2-5: Reaction of β-methylstyrene with Tomoda's chiral diselenide.

The result of addition product **39** and **40** obtained from the reaction of β-methylstyrene with the diselenide are summarised in Table 2-1.

Table 2-1: Addition results of β-methylstyrene with chiral diselenide

Entry	Counterion	**39:40**	*d.e* [%]	Yield [%]
1	Br^-	3.2:1	52	85
2	ClO_4^-	9.0:1	80	47
3	TfO^-	17:1	89	68
4	BF_4^-	18:1	90	67
5	SbF_6^-	31:1	94	64
6	PF_6^-	37:1	95	58

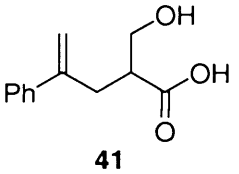
Although there is no common optimal counterion for the majority of cases on the base of these results it can still be generalised that counterions with lower nucleophilicity (such as triflate, tetrafluoraborate or hexafluorophosphate) increase the electrophilicity of the selenium reagent and therefore yield higher diastereomeric ratios than the corresponding selenenyl chlorides or bromides.

2.4 Research Targets

The research described in this thesis involves most previously described concepts: selenium nucleophiles, selenium electrophiles (influence of solvents, counterions, additives, and internal nucleophile on selenocyclizations) and deselenenylation via radical cleavage. Although the effect of counterions in selenenylations and the interactions of selenium electrophiles with nearby heteroatoms have been reported previously, these observations do not yet allow for a conclusive picture.

In order to understand the selenium electrophilic cyclization with two different internal nucleophiles (an alcohol and a carboxylic acid) the synthesis of the novel bifunctional olefin **41** was attempted. The investigation was further broadened on how different nucleophiles, solvents, and counterions affect selenocyclizations, of **41**.

Alkenes with an aromatic substituent have been chosen for all cyclization reaction due to the low volatility of the cleavage products, which are obtained after deselenenylation.



41

Target substrate.

Compound **41** presents the seleniranium ion with two options for cyclization (Figure 2-6). When the electrophile created is attacked by the hydroxy moiety the formation of tetrahydrofurans **42/43** can be observed, while the nucleophilic attack of the carboxylic acid functionality leads to formation of the lactones **44/45** as described in Figure 2-6. This compound, therefore, was then reacted under a variety of reaction conditions, varying solvent, additive, temperature, reaction time, etc. to optimize the reaction yield. Levels of selectivity with respect to the different products (lactones or tetrahydrofurans) were then measured and correlations determined.

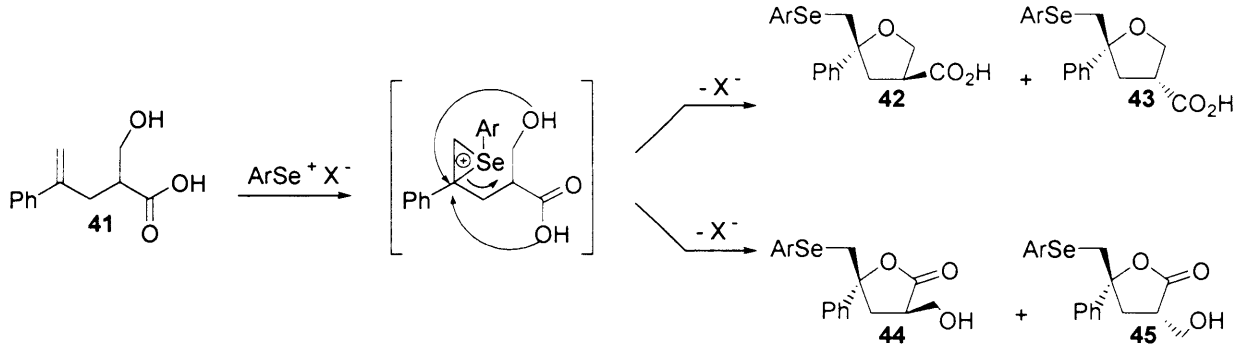
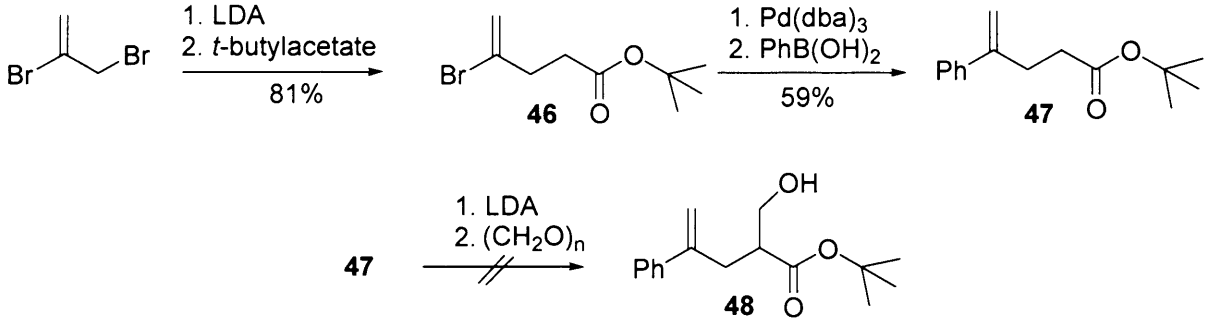


Figure 2-6: Modes of cyclization of the target substrate.

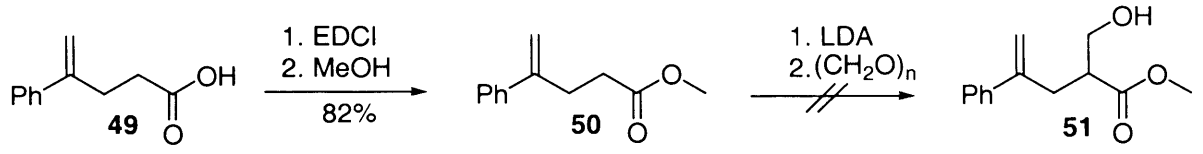
2.5 Synthesis of substrate 41

Several attempts were made to synthesise the target substrate. The first attempt as shown in Scheme 2-1 was made by treating tertiary butylacetate with LDA to form an enolate which was then allowed to react with dibromopropene to obtain tertiary butylester **46**[27] in 81% yield. Ester **46** was treated with phenylboronic acid in the presence of a palladium catalyst to obtain tertiary butyl ester **47**[28]. When the enolate of **47** was treated with paraformaldehyde in various forms [as vapour or as a solid] to obtain the hydroxymethylation product **48**, this could result in **41** after cleavage of the ester moiety. The reaction resulted in a complex mixture of compounds, along with a high yield of starting material.



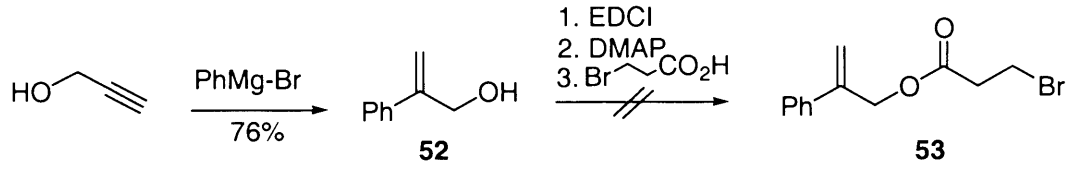
Scheme 2-1: First attempt toward the synthesis of the substrate.

The tertiary butyl group was thought to be obstacle in the alkylation of the enolate due to steric hindrance. This problem was resolved by choosing an alternative substrate with a smaller subsituent (methylester, see Scheme 2-2) and the route was followed based on a similar strategy. The unsaturated acid **49**[29] was converted into methylester **50**[30] by treatment with EDCI and MeOH in 82 % yield. The hydroxymethylation using paraformaldehyde in different forms [as vapour and as solid] was again attempted with the enolate of **50** but again it failed to give the required product **51**.



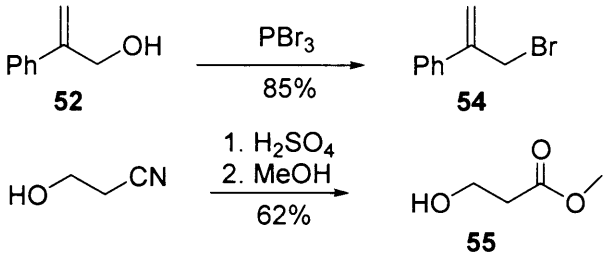
Scheme 2-2: Second route for the synthesis of required olefin.

A different strategy (Scheme 2-3) was then sought. Allyl alcohol **52**, which was formed by reaction of propargylic alcohol with phenyl magnesium bromide in 76 % yield[31], was treated with 3-bromopropionic acid to obtain compound **53**. However the reaction failed and only starting material was recovered. The idea was to obtain the desired compound from the Claisen [3,3] sigmatropic rearrangement of the bromoester followed by substitution with a hydroxy nucleophile but this was not formed despite many attempts under different reaction conditions.



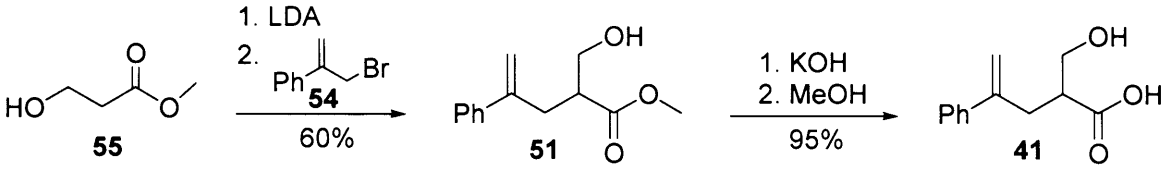
Scheme 2-3: Third strategy for the synthesis of required substrate.

Another enolate-chemistry route was applied. The allyl alcohol **52** was treated with phosphorous tribromide to form **54**[32] in good yield. Hydroxy propionitrile was treated with methanol in the presence of an acid and the hydroxy methylester **55**[33] was formed (Scheme 2-4).



Scheme 2-4: Synthesis of **54** and **55**.

The enolate of this hydroxy ester **55** was alkylated with the bromo precursor **54**, to form the hydroxy ester **51**. The hydrolysis of ester **51** gave the desired product **41** in excellent yield (Scheme 2-5).



Scheme 2-5: Successful strategy towards the synthesis of **41**.

2.6 Selective synthesis of tetrahydrofurans and lactones

The formation of the tetrahydrofurans or the lactones is dependent on the cyclizing nucleophile. Electrophilic 5-*exo*-cyclization[34] of **41** can lead to either tetrahydrofurans **42/43** or to lactones **44/45** as shown in Figure 2-7.

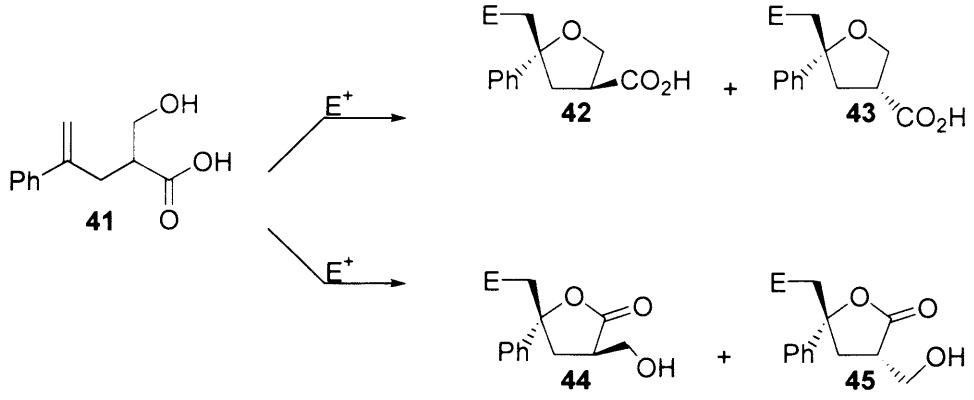
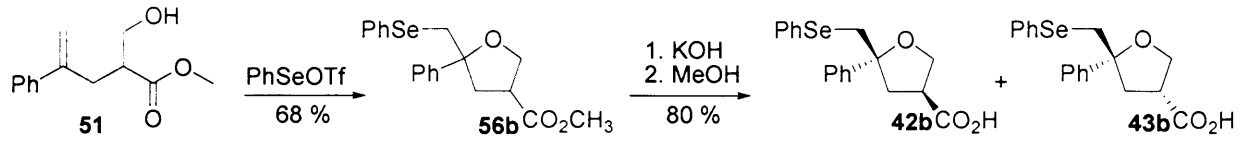


Figure 2-7: Selenenylation of **41** to the tetrahydrofuran and/or lactone.

The reaction of **41** with phenyl selenyl triflate resulted in a mixture of substituted tetrahydrofurans and lactones. Each cyclized product (substituted tetrahydrofurans and lactones) consists of two isomers: *cis* and *trans* (Figure 2-7). The NMR-spectrum contained signals of four compounds which were overlapping. To distinguish between the tetrahydrofurans and lactones by NMR spectral data and to determine the stereochemistry of

the products, each compound (lactones and tetrahydrofurans) was cyclized independently. The cyclization of hydroxyl ester **51** with phenylselenenyl triflate under standard reaction conditions (3 hr –78°C followed by 90 minutes at room temperature) led selectively to the formation of tetrahydrofurans **56b** in 68% yield. The hydrolysis of **56b** resulted in the reference compounds **42b/43b** in 80 % combined yield (Scheme 2-6) with a *cis*:*trans* (**42b:43b**) ratio of 37:63.Low temperature is important for obtaining efficient asymmetric induction from chiral selenium reagents to the olefins. The stereochemistry of **56b** compound could be resolved from the COSY-spectra of **42b/43b**, which distinguished *cis* and *trans* isomers signals by showing correlation between **b** and **a** protons and correlation between **e**, **f** and **h** protons (see Figure 2-8). Proton **b** has characteristic multiplicity and appearance (correlated from corresponding lactone spectrum, see Figure 2.9) around 3.00 ppm allowed ambigious assignment of *cis* and *trans* isomers signals. The diasteromeric ratio of *cis* to *trans* in **56b** was determined from the ^{1}H-NMR-spectrum.



Scheme 2-6: Selective synthesis of **42b** and **43b.**

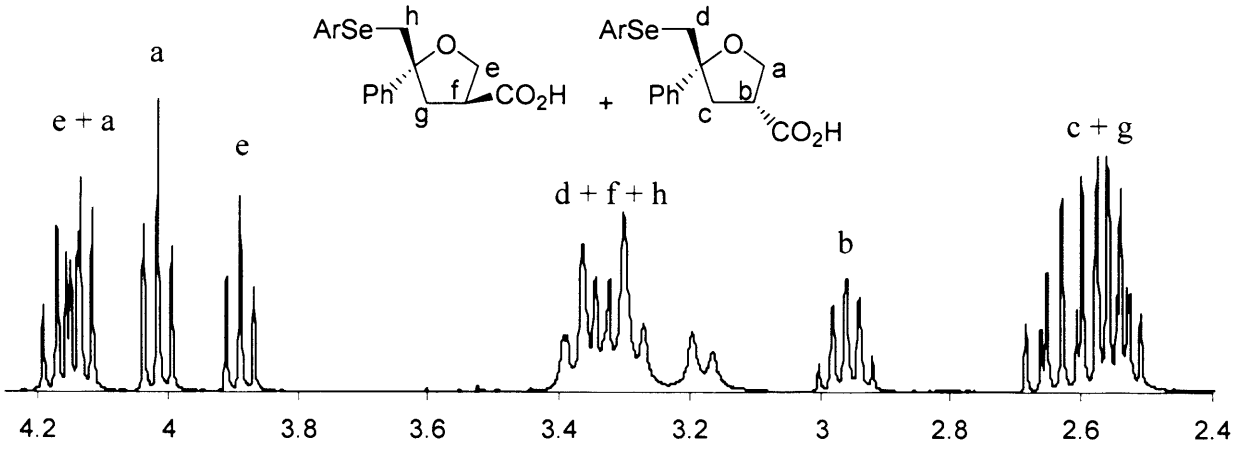
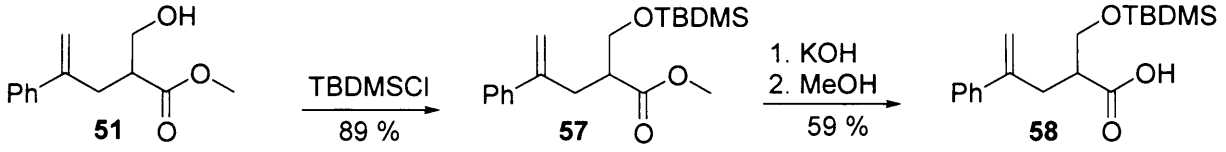


Figure 2-8: Aliphatic region of **42b/43b** in ^{1}H-NMR spectrum.

Protons **g** and protons **c** are near two chiral centers and appear as multiplets between 2.43-2.70 ppm. While proton **b** of *trans* isomer is on the chiral center and appear like a quintet in the region 2.90-3.01 ppm. For *cis* isomer this proton **f** appear like a quintet between 3.30-3.42 ppm. In the same region diastereotopic protons **h** for *cis* and **d** for *trans* show overlapping

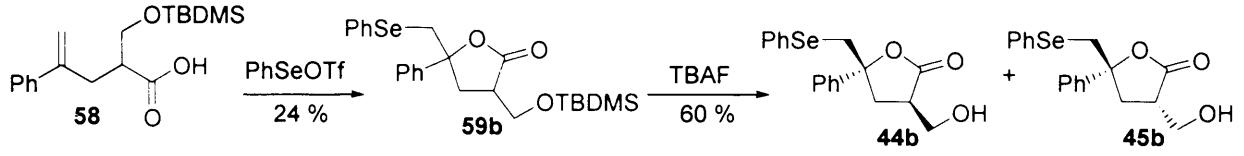
signals and appear like doublet of doublet (region: 3.10-3.41 ppm). Protons **e** for *cis* and **a** for *trans* isomers are near another chiral center and appear like a apparent triplet of triplet in the region of 3.81-4.21 ppm.

To obtain exclusively the lactone, substrate **41** needed to be protected at the hydroxy functionality, to be able to perform the cyclization exclusively via the acid moiety. The hydroxy group was first protected as its silyl ether by treating **51** with *tert*-butyldimethylsilylchloride in the presence of a base. This silyl protected substrate **57** was then treated under basic condition to cleave the ester and the silyl substituted acid **58** was formed (scheme 2-7).



Scheme 2-7: Synthesis of the substrate for independent formation of **44b/45b**.

The cyclization of this silyl protected acid with phenylselenenyl triflate under standard reaction conditions gave the protected lactone **59b** in poor yield. The silyl moiety was cleaved by treatment with TBAF to obtain the reference compounds **44b/45b** (Scheme 2-8).



Scheme 2-8: Selective synthesis of **44b/45b**.

The *cis* to *trans* ratio for the selenolactones were determined from the ^{1}H-NMR data (see Figure 2-9).

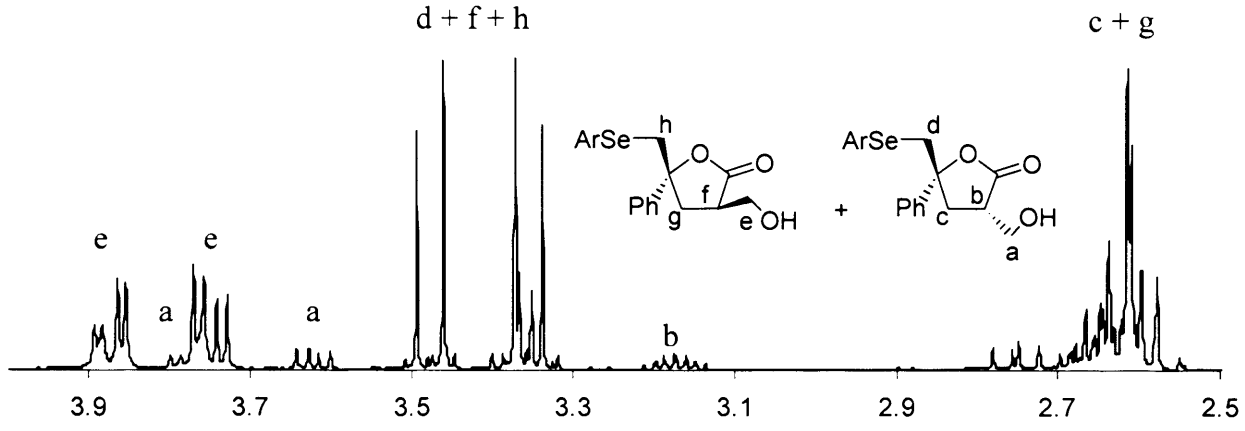


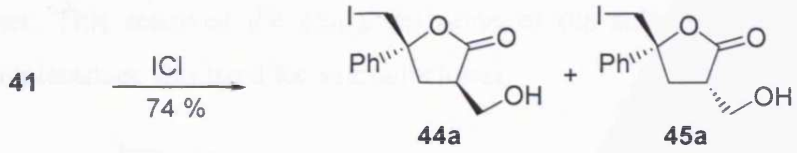
Figure 2-9: Partial ^{1}H-NMR spectrum of compounds **44b/45b**.

Protons **g** of *cis* and **c** of *trans* isomers are near a chiral center and appear like a multiplet between the region 2.51-2.78 ppm. Also proton **b** of *trans* isomer, which is on a chiral center, appears like a quintet around 3.12-3.20 ppm. While for *cis* isomer this proton **f** appears in overlapping region of **d** and **h** protons. They (**d** and **h**) are diastereotopic protons and appear as doublet of doublet between 3.30-3.52 ppm for *cis* and for *trans* isomers. Protons **a** and **e** are also near a chiral center and appear like doublet of doublet for *cis* and *trans* isomer in the region of 3.58-3.91 ppm.

2.7 Stereochemical assignment of 44/45

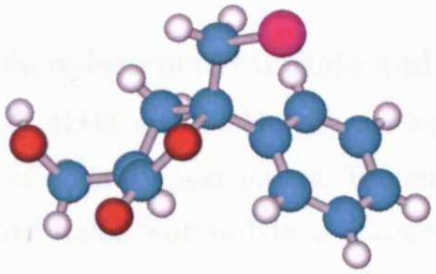
Even after the separate synthesis of tetrahydrofurans **42/43** and lactones **44/45**, the stereochemical assignment was not possible for **44/45**. Unfortunately, even nOe experiments could not clarify the relative stereochemistry because of overlapping signals for the lactones, which were obtained as mixture of *cis* and *trans* isomer.

However other electrophiles were employed in the cyclization reaction of substrate **41**. Treatment of **41** with iodine monochloride led exclusively to the formation of iodolactones **44a/45a** (E = I) and the tetrahydrofurans **42a/43a** could not be detected.



Scheme 2-9: Synthesis of iodolactones **44a/45a**.

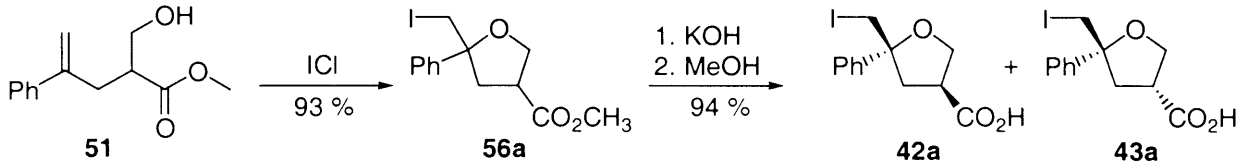
The mixture of diastereoisomers generated in such an iodocyclization could be separated by flash chromatography on silica gel. The major isomer **44a** separated by flash chromatography on silica gel was recrystallized and X-ray analysis [Appendix 1, pg. 132] finally allowed an unambiguous assignment of the NMR signals.[35]



Crystal structure of iodolactone **44a**.

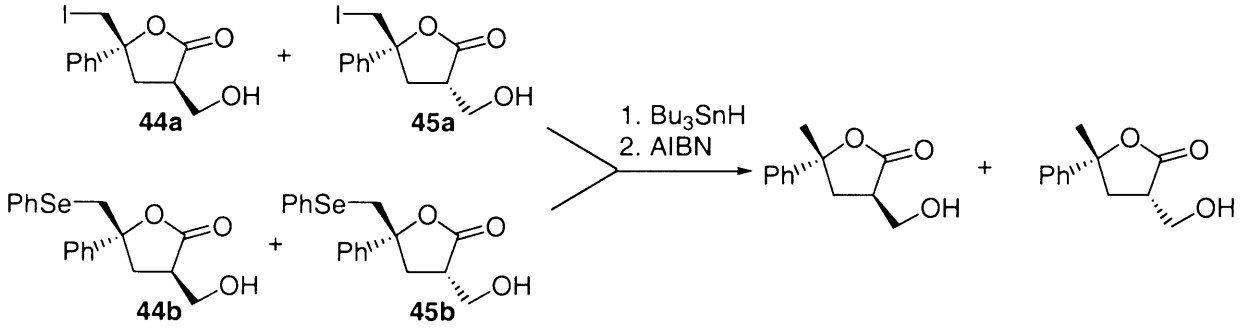
The diastereomeric ratio of the iodolactones was calculated from the NMR-spectra of the crude reaction mixture, which contained both *cis* and *trans* isomers.

To determine the relative stereochemistry of tetrahydrofurans **42a/43a** (E = I) the tetrahydrofuran **56a** was obtained from the iodocyclization of **51** (93% yield). The diasteromeric ratio *cis*:*trans* of the iodotetrahydrofuran esters was 42:58. Subsequent ester hydrolysis of **56a** led to **42a/43a** in 94% yield as shown in Scheme 2-10.



Scheme 2-10: Formation of **42a** and **43a** from **51**.

To correlate the assignment of selenolactones **44b/45b** with iodolactones **44a/45a** the selenium moiety from the selenolactone and the iodine moiety from the iodolactone were cleaved radically by treatment with tributyltin hydride in the presence of AIBN. The corresponding deiodinated and deselenenylated lactones showed identical NMR spectra. The retention time for both isomers was detected by HPLC and found to be similar for the major and minor isomer. This resolved the characterization of the selenolactones and the NMR assignment of iodolactones was used for selenolactones.



Scheme 2-11: Reduction product of lactones from radical cleavage.

2.8 Reaction of 41 with phenylselenenyl triflate and influence of additives

Once the reference compounds **42/43** and **44/45** were synthesized and characterized, the investigation of the influence of additives was started. The reaction of **41** to form lactones and/or tetrahydrofurans was first tested with triflate as a counterion and in the presence of alcohol and acid additives. The reaction was also performed without the presence of any additive and in the presence of water as an additive. The results of selenocyclizations in

diethyl ether with phenylselenenyl triflate as an electrophile and in the presence and absence of additives are shown in Table 2-2.

Table 2-2: Cyclization of **41** with and without use of additive in the presence of phenylselenenyl triflate.

Entry	Additive (10 eq.)	**42b : 43b** (*cis:trans*)	**44b : 45b** (*cis:trans*)	**42b,43b : 44b,45b**	Yield [%]
1	MeOH	13:87	81:19	63:37	67
2	BnOH	27:73	64:36	89:11	76
3	$PhCO_2H$	53:47	100:0	88:12	69
4	AcOH	47:53	-	100:0	90
5	-	49:51	72:28	75:25	83
6	H_2O	0:100	77:23	27:73	58

From the results obtained we observed a trend: two main interactions influence the cyclization. First, the selenium electrophile can interact with the internal nucleophile of the unsaturated substrate; with the hydroxy group or with the acid moiety. Secondly, there are associations between the electrophile and the external nucleophile / additives.

Strong influenced by additives, as shown in Table 2-2 is partially overridden in cyclizations involving the triflate counterion. For example, using a weakly coordinating counter ion, such as triflate (Table 2-2, entry 1), which influence additionally previously described interactions, gave a mixture of furan and lactone products among which the formation of tetrahydrofurans was favoured over the formation of lactones (Figure 2-10). Only if the electrophile-acid group (from the additive) interaction is disturbed by the addition of water, lactones were formed preferentially (Table 2-2 entry 6, Figure 2-10).

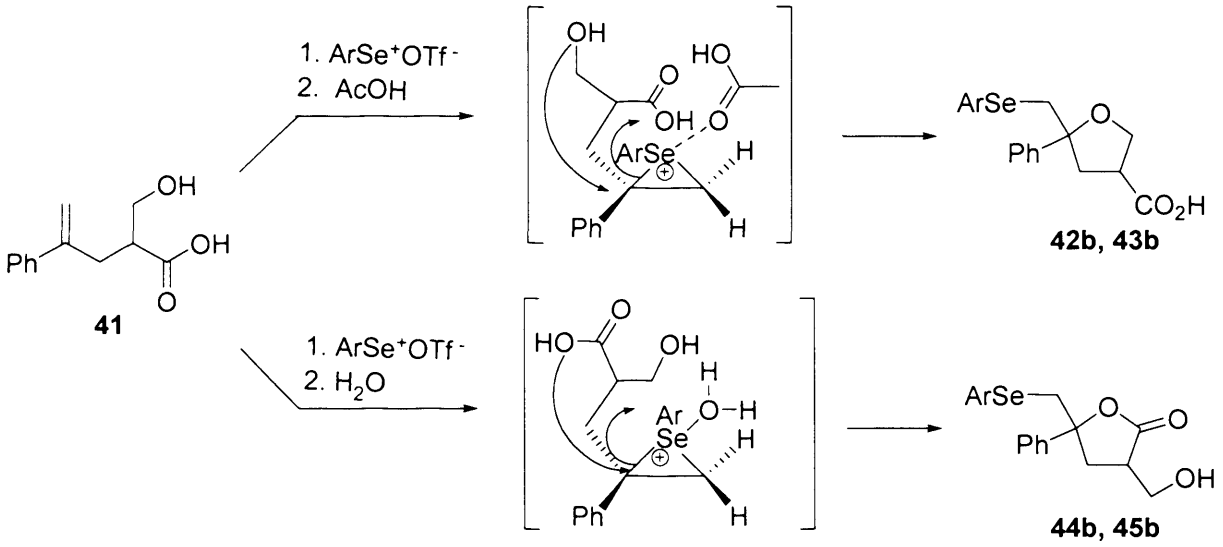


Figure 2-10: Proposed mechanism of influence of additives on cyclization.

On the other hand, from the results with acid as external nucleophile / additive it was observed that acetic acid, as a weakly coordinating additive, tunes the reactivity of the electrophile and a highly selective formation of the tetrahydrofurans **42b/43b** can be achieved (Table 2-2, Entry 5 and Figure 2-10).

This seems to be a quite unique combination, as benzoic acid (Table 2-2, Entry 4) led to the formation of a considerable amount of lactones **44b/45b**. In these examples there seems to be almost no coordination of the electrophile to the carboxylic acid moiety of the substrate, as the *cis*- and *trans*-isomers of the tetrahydrofurans **42b/43b** are formed in similar amounts. A coordination to the carboxylic acid moiety should have led to a preferential formation of the *cis*-isomer **42b**.[36] An alcohol has a higher nucleophilicity than a carboxylic acid, and the selenium electrophile coordinates to the hydroxy group rather than to a carboxylic acid moiety of the substrate **41**.

The influence of solvents was also investigated with phenylselenenyl triflate in the presence of alcohol and acid additives. The results obtained are shown in Table 2-3.

Table 2-3: Cyclization of **41** with phenylselenenyl triflate and with acid, alcohol as additive with different solvents.

Entry	Solvent	Additive (10 eq.)	**42b : 43b**	**44b : 45b**	**42b, 43b : 44b, 45b**	Yield [%]
1	CH_2Cl_2	MeOH	33:67	73:28	43:57	85
2	MeCN	MeOH	46:54	50:50	84:16	90
3	CH_2Cl_2	AcOH	41:59	76:24	75:25	92
4	MeCN	AcOH	49:51	65:35	63:37	88

The solvent seemed to also have some effect on the cyclization. From these results it can be seen that methanol as an additive in acetonitrile favours the cyclization to tetrahydrofurans **42b/43b**, while in dichloromethane a nearly equal mixture of tetrahydrofurans **42b/44b** and lactones **44b/45b** was formed. This is probably due to the high polarity of the reaction mixture, which causes better coordination of the acid moiety of the substrate to the selenium moiety and thereby making it more likely to cyclize via the alcohol functionality of the substrate leading to **42b/43b** as the major product.

This seems to be in agreement when employing acetic acid as an additive in these solvents (acetonitrile, and dichloromethane). With acetic acid as additive and acetonitrile or dichloromethane as solvent the cyclization reaction to the tetrahydrofurans were favoured in both cases.

2.9 Reaction of 41 with different counterions

The outcome of the competing selenocyclizations is different when other counterions are involved. A series of counterions with low nucleophilicity were employed in cyclizations of substrate **41** and the results are shown in Table 2-4.

Table 2-4: Cyclizations of **41** with phenylselenenyl electrophile in diethyl ether with various counterions.

Entry	Reagent	Additive (10 eq.)	**42b : 43b**	**44b : 45b**	**42b, 43b : 44b, 45b**	Yield [%]
1	PhSeBr	-	20:80	63:37	54:46	74
2	PhSeOTf	-	49:51	72:28	75:25	83
3	PhSeOTf	MeOH	13:87	81:19	63:37	67
4	$PhSeBF_4$	MeOH	0:100	84:16	14:86	70
5	$PhSePF_6$	MeOH	-	78:22	0:100	50
6	$PhSePF_6$	MeOH	0:100	73:27	30:70	85
7	$PhSePF_6$	AcOH	42:58	100:0	92:8	11
8	$PhSeSO_4$	MeOH	-	67:33	0:100	42
9	$PhSeSO_4$	AcOH	0:100	62:38	21:79	52

It was seen that whereas phenylselenenyl bromide and -triflate yield mixtures of tetrahydrofurans **42b/43b** and lactones **44b/45b** (Table 2-4, Entries 1-3), the corresponding hexafluorophosphate (Table 2-4, Entry 5) or sulfate (Table 2-4, Entry 8) can be used to synthesise exclusively the lactones **44b/45b** under the standard reaction conditions (3 hr –78 °C followed by 90 min. at room temperature). Only a prolonged reaction time with phenylselenenyl hexafluorophosphate (Table 2-4, Entry 6) led to the formation of some tetrahydrofurans **42b/43b**. The addition of methanol (10 eq.) in these reactions is important as its replacement with acetic acid (10 eq.) led to the formation of a mixture of **42b/43b** and **44b/45b** in very low yield (Table 2-4, Entry 7). As has already been mentioned, the coordination of the selenium electrophile to the hydroxy group of the substrate is stronger than that to the carboxylic acid moiety. Irrespective of the additive used, this behaviour is reflected in the *cis*:*trans* ratio (**44b**:**45b**) as a coordination to the alcohol moiety of **41** leads to the *cis*-lactone **44b** as the major isomer.

2.10 Reaction of 41 under different temperature conditions

The temperature also seemed to have a strong influence on the course of cyclization reactions. Different temperature conditions varying from room temperature (28 °C) to –78 °C

2	40 °C overnight	PhSeOTf[a]	0	63:37	0
	3 hr –78 °C & 3/2 hr rt	PhSeOTf[b]	13:87	81:19	6
3	6 hr rt	PhSeOTf[b]	0:100	64:36	2
	3 hr –78 °C & 3/2 hr rt	PhSeBr	20:80	63:37	5
4	5 hr –78 °C & 0.5 hr rt	PhSeBr	21:79	62:38	6
	15 min rt	ICl	0	76:24	0
5	2 hr –78 °C	ICl	33:67	80:20	2
6	2 hr rt	I_2	50:50	82:18	3

[a] = H_2O (additive), [b] = MeOH (additive).

At standard reaction conditions (3 hr, –78 °C and 90 min at room temp cyclization of **41** with selenium as an electophile, triflate as counter ion and additive the ratio of formation of **42b/43b** to **44b/45b** was 27:73. Prolonging time at room temperature (1hr at –78 °C and 5 hr at room temperature) did not i selectivity of the reaction. But when changing the reaction conditions to 40 there is clear difference in the course of cyclization. The reaction proceed towards **44b/45b**.

Similar influence of temperature was also seen with methanol as additive. With an additive under standard reaction conditions the cyclization of **41** gave a **42b/43b** and **44b/45b** in a ratio of 63:37. When applying ambient reaction condi reaction (6 hour at room temperature) the same trend was observed. The course o was preferential towards the lactones.

The exchange of counterion from triflate to bromine did not alter the results When using bromine as a counter ion in the presence of methanol under stanc conditions a mixture of **42b/43b** and **44b/45b** was observed. Using lower conditions (5 hr –78 °C and 30 min room temperature) did not result in much dif gave an indication that at lower temperature (-78 °C) the reaction does not have for cyclization of **41**. There is no strong coordination of the acid or alcohol mo selenium electrophile thus leading to a mixture of **42b/43b** and **44b/45b** in

amounts.

Higher temperature influences the cyclization towards lactones, probably due to lower reactivity of the alcohol functionality at ambient to higher temperature. This results in better coordination of the alcohol moiety to the selenium electrophile and leads to the cyclization of **41** via the acid functionality thus giving lactones as products.

Cyclization of **41** with iodine electrophile showed the same influence of temperature on the course of cyclization. When performing the reaction at ambient temperature with iodine monochloride a selective formation of iodolactones **44a/45a** was observed. When performing this reaction at low temperature (-78 °C) a mixture of **42a/43a** and **44a/45a** was formed.

Reaction of **41** with electrophilic iodine, generated from iodine also gave a mixture of **42a/43a** and **44a/45a**. It is probably due to the fact that in iodine monochloride chlorine is more electronegative than iodine so the iodine electrophile is generated faster and, subsequently, the reaction take place faster. With molecular iodine there is obviously no difference in electronegativity, so the generation of the corresponding iodine electrophile from this reagent is slower for this reaction.

2.11 Stability of selenofuran 42b/43b and selenolactone 44b/45b

To check the stability of the cyclization products **42b/43b** and **44b/45b** another cyclization reaction under standard reaction conditions with phenylselenenyl triflate and acetic acid was carried out on the mixture of **42b/43b** and **44b/45b**.

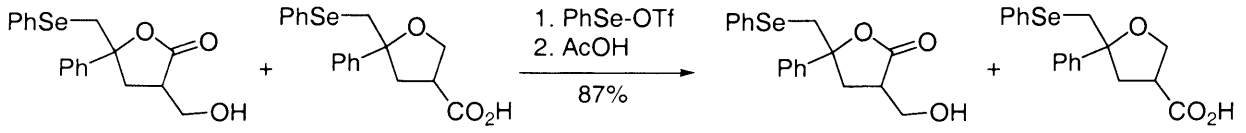


Figure 2-12: Reaction for the stability control of **42b/43b** and **44b/45b**.

The use of acetic acid could have led to the ring opening reaction of both cyclized products, the presence of phenylselenenyl triflate could cause the cyclization to occur again and a different ratio of lactone and tetrahydrofurans would be observed (Figure 2-13).

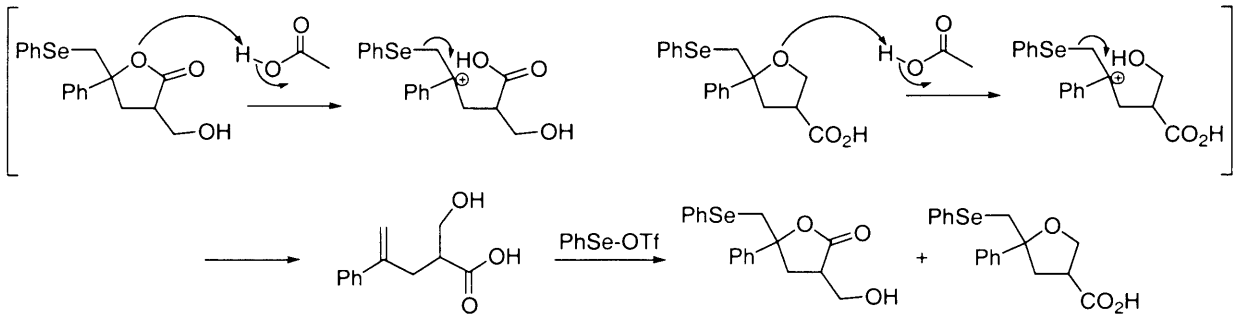


Figure 2-13: Proposed mechanism of recyclization of **41**.

The ratio of lactones and tetrahydrofurans remained the same as before the reaction. This result proved the stability of both cyclized products.

2.12 Conclusions

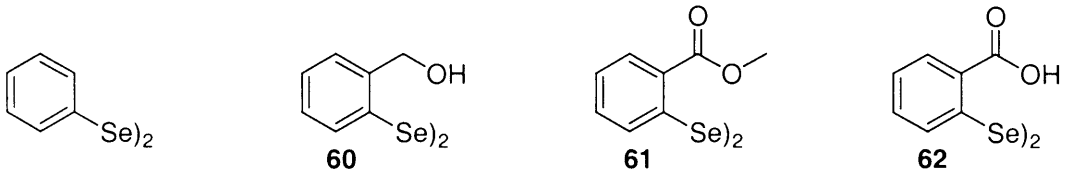
From the obtained results for the cyclization reaction of **41** with phenylselenenyl triflate under different reaction conditions (different counterions and additives) it was observed that the use of counterions and additives influence selective formation of tetrahydrofurans **42/43** and lactones **44/45**. [37] The exclusive formation of the tetrahydrofurans **42/43** could be achieved with the triflate counter ion and with the addition of acetic acid whereas formation of the lactones **44/45** could be achieved with the use of hexafluorophosphate or sulfate as counterions and with additional methanol.

Chapter 3

3. Achiral selenium reagents

3.1 Selenium reagents with an internal heteroatom

Forcing the additive to coordinate to the selenium electrophile can also be achieved in an intramolecular fashion, which has already been investigated. [38] It was decided to incorporate the functionality of the employed additives (acid and alcohol moieties) into the selenium reagents, which could lead to the coordination of the selenium electrophile with internal heteroatoms instead of the substrate or additives, thereby omitting the use and influence of external additives. The achiral selenium electrophiles, generated from the corresponding diselenides **60-62** with alcohol, ester and acid functionalities, were synthesized while diphenyl diselenide was commercially available (see Figure 3-1). The cyclization behaviour of **41** towards these modified reagents was studied. The reactivity of **41** with phenylselenenyl triflate has already been discussed in Chapter 2.



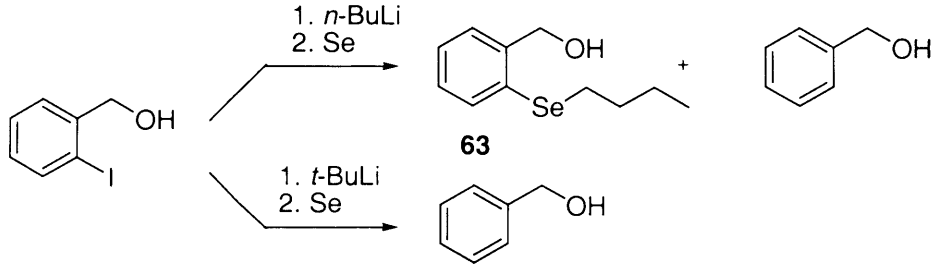
60 **61** **62**

Figure 3-1: Achiral diselenide with the internal nucleophiles.

3.2 Synthesis of alcohol diselenide

Several routes have already been used for the synthesis of racemic diselenides with an alcohol functionality at the *ortho*-position from the selenium atom.

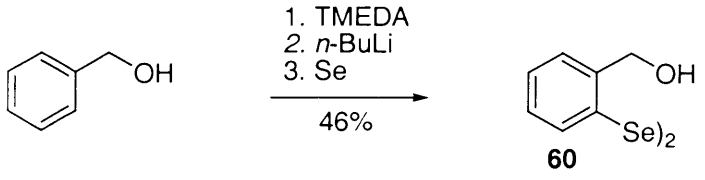
Lithiation followed by introduction of selenium was carried out on 2-iodobenzylalcohol. The mixture of products obtained from this reaction consisted mainly of benzylalcohol and traces of the butylselenenylated alcohol **63** when using *n*-butyllithium (Scheme 3-1).



Scheme 3-1: First attempt towards the synthesis of alcohol diselenide.

The same strategy was used with 2-iodobenzylalcohol, treating it first with *t*-butyllithium to produce the anion followed by selenenylation resulted in mainly deiodinated product (benzylalcohol).

The diselenide with an alcohol group in the *ortho*-position to the selenium was synthesized by deprotonating benzylalcohol with *n*-butyllithium in the presence of TMEDA, which led to the formation of the corresponding carbanion. This was subsequently allowed to react with selenium to form a selenolate. Acidic workup led to the formation of diselenide **60**[39] in 46% yield (Scheme 3-2).



Scheme 3-2: Successful route to the formation of alcohol diselenide.

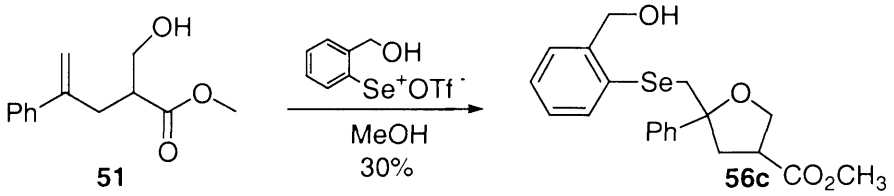
3.2.1 Reaction of 41 with alcohol diselenide

The cyclization reactions of **41** with **60** were performed with and without the use of additives and the results obtained are shown in Table 3-1.

Table 3-1: Cyclization of **41** to **42c/43c** and **44c/45c** with selenium electrophile generated from alcohol diselenide **60**.

Entry	Additive	**42c : 43c**	**44c : 45c**	**42c, 43c : 44c, 45c**	Yield [%]
1	-	-	80:20	0:100	51
2	MeOH	-	80:20	0:100	40
3	AcOH	-	80:20	0:100	45

From the results shown in Table 3-1 it is obvious that the use of additives indeed led to no great influence on the cyclization of **41** because of strong coordination of the internal oxygen-atom with the selenium electrophile. Due to this strong coordination exclusive formation of lactones **44c/45c**, irrespective of any additives, was observed and the *cis*-isomer was mainly formed[37] (Table 3-1, Entries 1-3). To investigate the *cis*- to *trans*-ratio of the tetrahydrofurans with this selenium reagent, the tetrahydrofurans were synthesized selectively by reaction of substrate **51** with this selenium reagent leading to the tetrahydrofuran compound **56c** (see Scheme 3-3).



Scheme 3-3: Selective cyclization of tetrahydrofurans from alcohol diselenide.

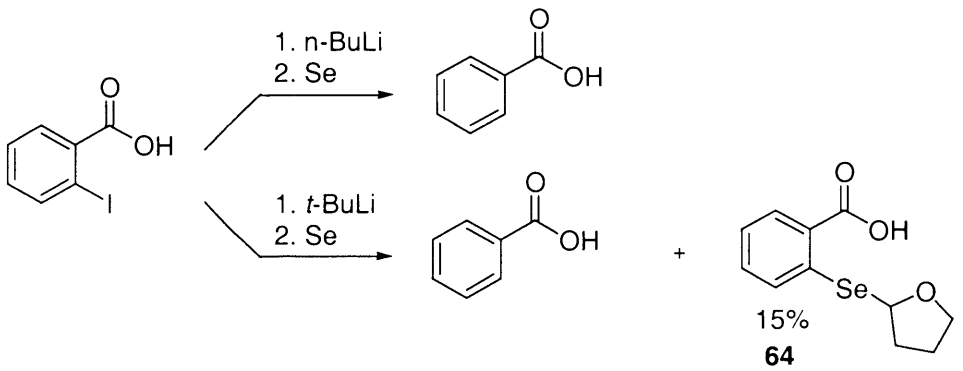
The results of *cis* to *trans* ratio of **56c** are summarised in Table 3-4 and discussed later in paragraph 3.4 along with other substituted tetrahydrofuran products **56d** and **56e** derived from the cyclization of **41** with the electrophiles of **61** and **62**.

3.3 Synthesis of acid diselenide

The synthesis of an acid diselenide was attempted in order to investigate its reactivity with substrate **41**. Several strategies were used for the synthesis.

The same strategy as that used for the synthesis of the alcohol diselenide, lithiation with *n*-butyllithium followed by treatment with selenium, was first tried, but failed to give any desired product.

Similarly using 2-iodobenzoic acid for lithiation with *n*-butyllithium, followed by selenenylation, was attempted, but resulted only in deiodination and in the formation of benzoic acid (Scheme 3-5).

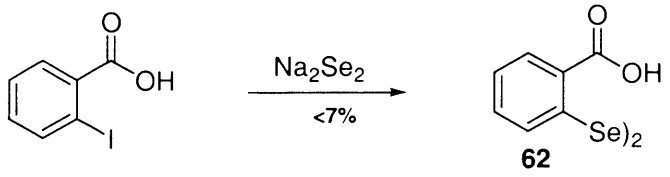


Scheme 3-5: Second attempt on the synthesis of acid diselenide.

When employing *t*-butyllithium instead of *n*-butyllithium under different reaction conditions (using different temperature conditions and different equivalents of *t*-butyllithium), small amounts (15%) of selenenylated furan **64** and mainly benzoic acid were formed.

The lithiation of 2-iodobenzoic acid and tetrahydrofuran with *t*-butyllithium has probably in small amount taken place. The lithiated species of 2-iodobenzoic acid reacted with selenium to form the electrophilic selenium species. Nucleophilic attack from the lithiated tetrahydrofuran with the selenium electrophile has possibly given compound **64**.

A different strategy was adopted for the synthesis of the acid diselenide. Use of disodium diselenide in the presence of 2-iodobenzoicacid led to traces of the desired product (Scheme 3-6), but sufficient quantities were obtained to carry out our study.



Scheme 3-6: Another attempt of selenenylation with disodium diselenide.

3.3.1 Reaction of acid diselenide with 41

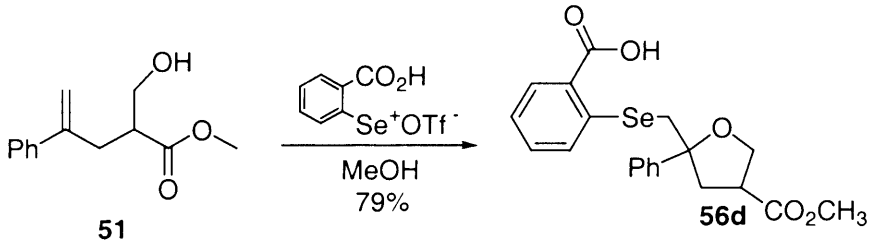
The reaction of **41** with the selenium electrophile generated from **62** was tested with and without the use of additives and the results obtained are shown in Table 3-2.

Table 3-2: Cyclization of **41** with selenium electrophile generated from acid diselenide **62**.

Entry	Additive	**42d : 43d**	**44d : 45d**	**42d, 43d : 44d, 45d**	Yield [%]
1	-	32:68	82:18	46:54	89
2	MeOH	33:67	84:16	52:48	99
3	AcOH	52:48	83:17	49:51	45

A mixture of **42d/43d** and **44d/45d** under all reaction conditions was observed. The use of additives did again not play any role in the selectivity of cyclization to furan or lactone. They are formed in nearly 1:1 ratio. The selectivity was not influenced either. For the lactones **44d/45d** the *cis* isomer was formed preferentially while weak coordination of acid (from the substrate) gave nearly an equal amount of the *cis* and *trans* isomer of **42d/43d**.

Compound **42d/43d** and **44d/45d** could only be separated with great difficulty due to the high polarity of these compounds. Only the lactones were partially separated by flash chromatography on silica gel. To be able to interpret the signal of the NMR-spectra and fully characterise the acid substituted **42d/43d** compounds were independently cyclized from **51** with acid diselenide yielding **56d** in good yield (see Scheme 3-7).

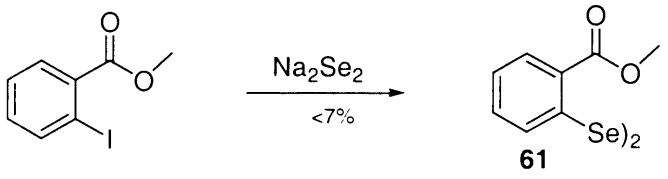


Scheme 3-7: Selective formation of **56d**.

3.4 Synthesis of ester diselenide

The reaction of **41** was also investigated with the ester diselenide. The synthesis of the ester diselenide was approached via several routes.

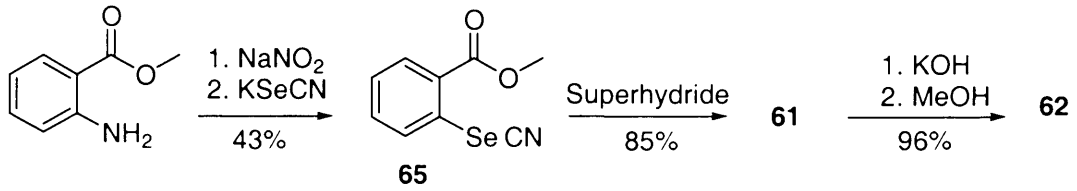
The first attempt towards the synthesis of ester diselenide **61** was attempted using the disodium diselenide procedure. The aryl iodoester when treating with disodium diselenide resulted in only traces of desired product **61** (Scheme 3-8).



Scheme 3-8: Selenenylation of aryl iodo-ester.

Due to the low yield of this reaction an alternate route for the synthesis of this reagent was sought. The organoselenocyanate was formed via a Sandmeyer reaction from the amino ester. The treatment of amine with sodium nitrite resulted in the diazonium precursor which was in the same pot reacted further with potassium selenocyanate to obtain compound **65**. [40] The

selenocyanate was further treated with superhydride to produce the ester diselenide **61**[40] in 85% yield (Scheme 3-9). The yield of acid diselenide **62** was also improved by hydrolysis of **61** giving **62** in 96 % yield.



Scheme 3-9: Synthesis of ester diselenide.

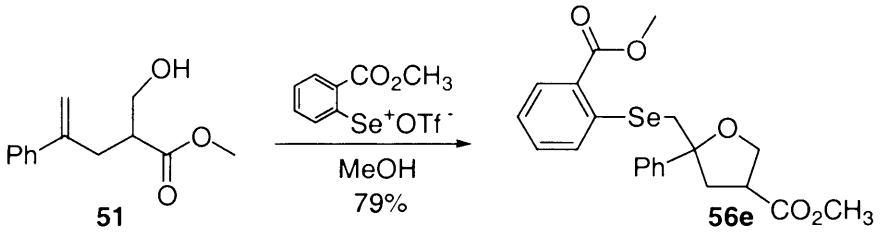
3.4.1 Reaction of ester diselenide with 41

The reaction of **41** in the formation of **42e/43e** and **44e/45e** was also investigated under the same reaction conditions as those used with the alcohol and acid diselenide. The results obtained are shown in Table 3-3.

Table 3-3: Cyclization reaction of **41** with ester diselenide.

Entry	Additive	**42e : 43e**	**44e : 45e**	**42e, 43e : 44e, 45e**	Yield [%]
1	-	50:50	82:18	46:54	74
2	MeOH	25:75	81:19	52:48	79
3	AcOH	24:76	84:16	49:51	91

Polarity problem as those seen with the cyclized acid substituted product **42d/43d** and **44d/45d** were observed with the cyclized ester product **42e/43e** and **44e/45e**. Again the lactones were partially separated by flash chromatography on silica gel. To fully characterise and compare the NMR-spectral data the ester substituted tetrahydrofurans were cyclized from **51** with the electrophile generated from the ester diselenide yielding the product **56e** in 79% yield (Scheme 3-10).



Scheme 3-10: Exclusive formation of ester substituted tetrahydrofurans from **51**.

3.5 Diastereomeric ratio of tetrahydrofuran 56 from selective cyclization

Due to the high polarity of the tetrahydrofurans products **42d/43d** and **44e/45e**, their purification was difficult. To correctly assign the NMR spectra, ester **51** was subjected to cyclization with electrophiles **61** and **62**. The *cis:trans* ratio of about 1:1 in the products **56d** and **56e** is similar to that observed in the reactions mentioned in paragraph 3-1. The results of the cyclizations of **51** are summarized in Table 3-4.

Table 3-4: Cyclization reaction of **51** with achiral selenium reagents **60**, **61** and **62**.

Entry	Electrophiles	Products	*Cis:trans*	Yield [%]
1	**60**	**56c**	48:52	30
2	**61**	**56d**	48:52	79
3	**62**	**56e**	50:50	79

Electrophiles with acid or ester functionality give almost equal mixtures of tetrahydrofurans and lactones with low (tetrahydrofuran) to moderate (lactones) *cis:trans* selectivities. No additive influence was observed, due to internal coordination of carboxylic acid/ester moiety to the selenium electrophile. [37]

The cyclized products showed that the carboxylic acid moiety of the substrate coordinate less strongly to the selenium electrophile and thereby giving a mixture of tetrahydrofuran diastereoisomers in equal ratios. A coordination of the carboxylic acid functionality of the substrate with the selenium electrophile would have led to preferential formation of the *cis* isomer.

3.6 Conclusions

From the results obtained it was clear that the use of additives indeed led to no great influence on the course of cyclization of **41**. It is due to efficient coordination of the internal oxygen atoms from **60-62** to the selenium electrophile. The coordination of acid and ester moities in **61** and **62** is weaker, which results in mixtures of furans and lactones. While strong coordination of the hydroxy group of **60** lead to exclusively formation of lactone.

Chapter 4

4. Chiral selenium reagents

4-1 Chiral selenium reagents with a heteroatom-containing moiety in the *ortho*–position

Chiral selenium electrophiles can be employed in many addition reactions with high levels of enantioselectivity.[14, 27, 41] Their application in organic synthesis has been limited due to their long and often difficult synthesis. Wirth et al. has developed structurally simple selenium reagents, which are accessible in high yield in only a few steps.[42]

The structures of most chiral selenium compounds show one common feature: the presence of a functional group containing heteroatom in a 1, 3-relationship to the selenium, as shown in Figure 4-1.

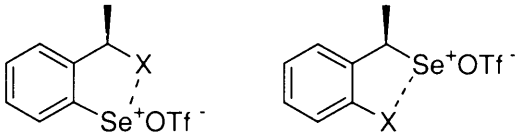


Figure 4-1: Selenium 1, 3-relation with the heteroatom.

The presence of a heteroatom containing functional group in the *ortho*-position is essential to the stereoselectivity as intramolecular coordination of this heteroatom to the lone pair of the positively charged selenium results in the fixed conformation. This, in turn, draws the chiral centre closer to the reaction centre that is important for a more efficient transfer of chiral information.[43] The existence of these interactions has been verified by NMR spectroscopic measurements, as well as by X-ray structure determinations and theoretical calculations.[44]

The reaction of alkene **41** with several chiral selenium reagents was studied in an attempt to find the high selectivity of each isomers of substituted tetrahydrofuran or lactone with certain chiral selenium reagents. These reagents were synthesized according to the procedures of Wirth *et al.*[19, 45] and Tiecco *et al.*[46] The selectivity in the cyclization reaction was determined by deselenenylation of **56**, **44** and **45** with tributyltin hydride in the presence of AIBN which were then analysed using chiral column on GC and HPLC.

In addition to testing known chiral selenium reagents, a number of new selenium reagents were prepared, with a chiral moiety in the *ortho*-position, thus placing the selenium electrophile in a pseudo five-membered ring.

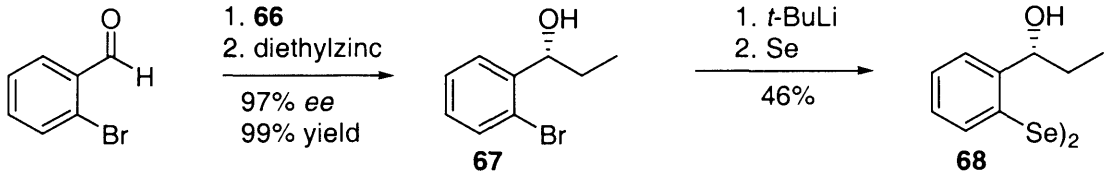
4.2 Chiral selenium reagent with oxygen as the heteroatom

It has recently been determined that in the case of the oxygen containing diselenide **68** better diasteroselectvities could be obtained by introducing an appropriate substituent in the 6-position of the aromatic ring.[19]

Initially easily synthesized selenium reagents were prepared and tested. These reagents with oxygen as a heteroatom in a 1,3 relationship to the selenium were employed to explore the selectivity of selenium reagents and reactivity of **41**.

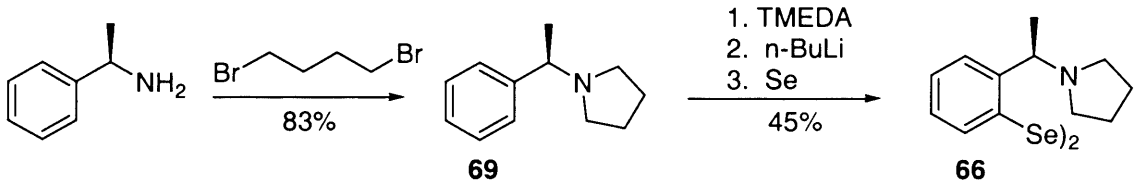
4.2.1 Synthesis of chiral alcohol diselenide

The synthesis of this reagent was made following the procedure of Wirth *et al.*[19, 45] An asymmetric addition to 2-bromobenzaldehyde, in the presence of a selenium catalyst **66** and diethylzinc, led to the formation of enantiomerically enriched alcohol **67** (97 % *ee*) in quantitative yield.[19, 47] In order to determine the HPLC conditions necessary for analysing the product **67**, the racemic alcohol was synthesized by lithium aluminium hydride reduction of ketone at room temperature. Chiral alcohol **67** was then treated with *t*-butyllithium followed by selenium to obtain the corresponding diselenide **68** (46 %).



Scheme 4-1: Synthesis route of enantiomerically rich alcohol diselenide.

The selenium catalyst **66** used in this addition was synthesized by treating the enantiomerically pure primary amine with dibromobutane in the presence of a base to obtain pyrrolidine **69** in good yield. The selenenylation of **69** in the presence of *n*-butyllithium and TMEDA gave the desired diselenide **66**. [45]

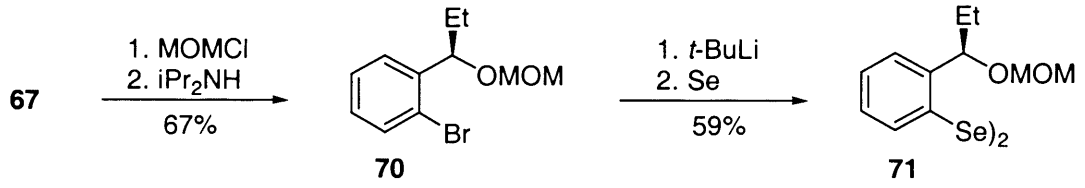


69 **66**

Scheme 4-2: Synthesis of selenium catalyst.

4.2.2 Synthesis of chiral MOM diselenide

Considering a possible coordination of a second oxygen atom to the selenium cation, which could yield to a better transfer of chiral information and thereby lead to better selectivity, the synthesis of MOM diselenide **71** was carried out according to the procedure of Wirth et al. [19, 46] Thus, bromo benzylalcohol **67** was treated with chloromethyl methylether in the presence of diisopropylamine to obtain the methoxymethylated derivative **70**[19] in 67 % yield. This MOM-protected compound was selenenylated by treatment with *t*-butyllithium followed by selenium to form **71**. [19]



70 **71**

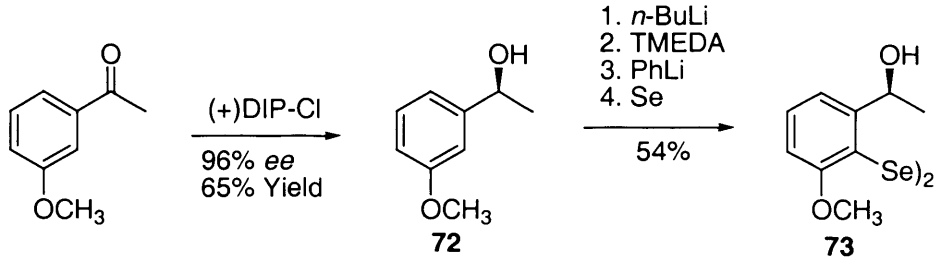
Scheme 4.3: Synthesis of MOM-protected benzyl alcohol.

4.2.3 Synthesis of chiral methoxy substituted diselenide

The presence of another subsituent in the *ortho*-position to the selenium atom could induce a greater conformational rigidity to the chiral selenium reagent and a more efficient transfer of chirality should be observed.

To investigate the effect of two sided coordination of heteroatoms to the selenium electrophile the synthesis of such selenium reagents was attempted. One *ortho*-position of the selenium atom was occupied by the alcohol functionality while the other *ortho* subsituent was a methoxy group.

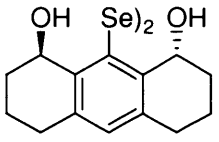
Thus, *m*-methoxy acetophenone was reduced to the chiral alcohol **72**[48] (65 % yield) with high enantiomeric excess (96% *ee*). Chiral substrate **72** was selenenylated using standard methods to give the diselenide **73**[19] (54 %).



Scheme 4-4: Synthesis of methoxy-substituted diselenide.

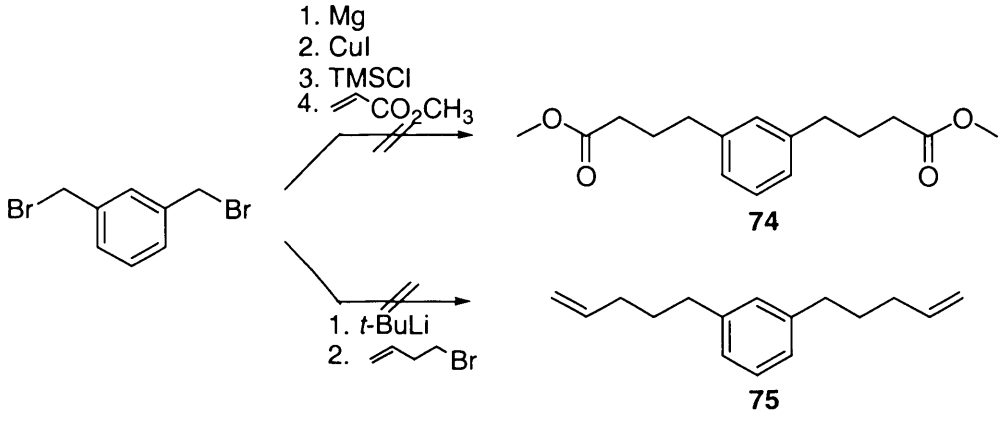
4.2.4 Synthesis of chiral diol diselenide

The synthesis of a structurally different chiral selenium reagent was also attempted. Diol diselenide was chosen due to its possible bis-coordination to selenium and because of the bi-cyclic structure on the benzene ring. The high level of substitution was expected to lead to high conformational rigidity and therefore greater selectivity.



Diol diselenide.

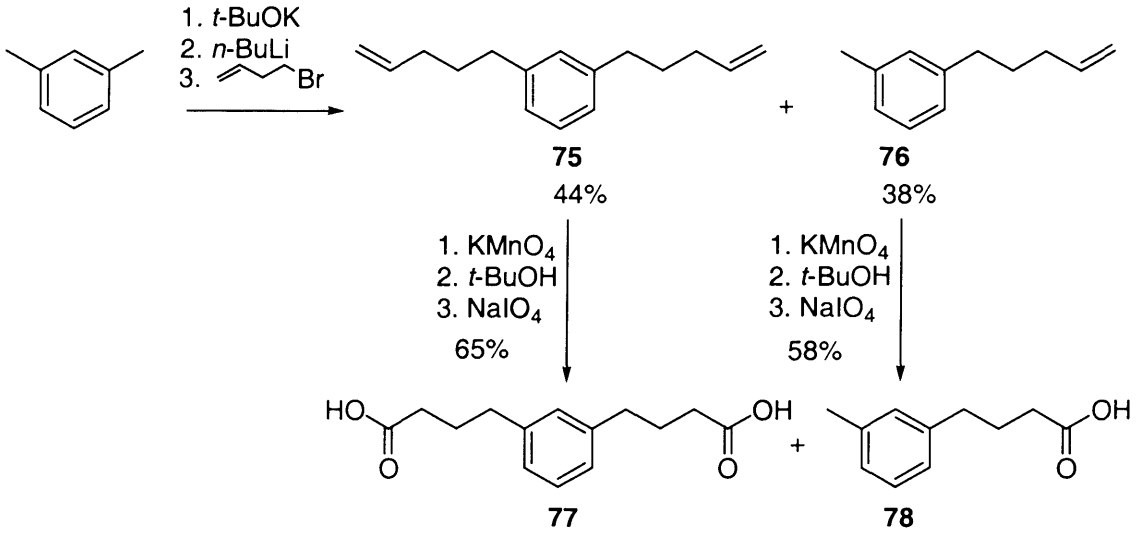
Several routes were attempted for the synthesis of this selenium reagent (diol diselenide). The first attempt was made by treating a dibromo precursor with a Grignard reagent in the presence of CuI and TMSCl to produce the dianion, which was further treated with methylacrylate to form the dimethoxy ester **74**. The reaction failed to give product **74**.



Scheme 4-5: First attempt towards the synthesis of di-alcohol diselenide.

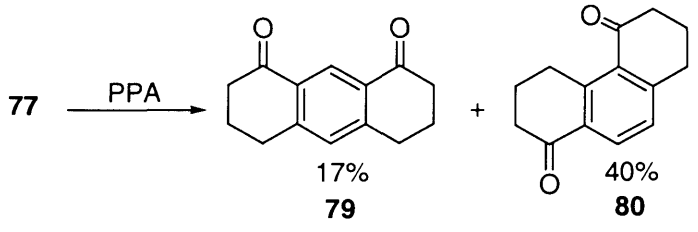
A similar strategy to produce the dianion was followed by treating the dibromo compound with *t*-butyllithium and then treatment with bromo precursor, but the reaction failed to give the required product **75**.

Treating *m*-xylene with potassium tertiary butoxide and *n*-butyllithium produced the dianionic species. This was alkylated with bromobutene to form compound **75** [49] and the mono compound **76** as a side product. Compound **75** was purified by Kugelrohr distillation under reduced pressure and was further oxidized in the presence of potassium permanganate and sodium metaperiodate to obtain **77** [49] (65%).



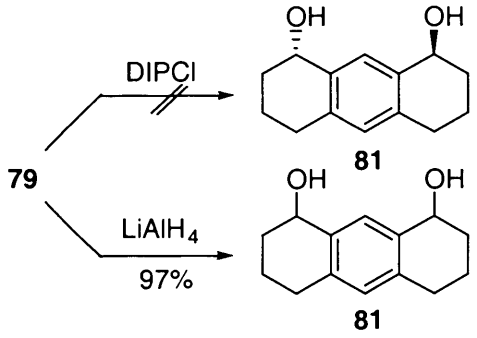
Scheme 4-6: Synthesis strategy of di-alcohol diselenide.

The desired diketone **79**[49] was obtained as a minor product when the diacid **77** was treated with polyphosphoric acid; the major product of this reaction was diketone **80**. [50]



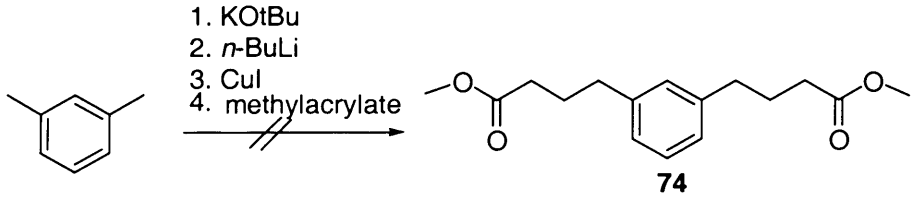
Scheme 4-7: Synthesis of diketone.

The chiral reduction to form chiral diol **81** with (+) DIP-Cl failed. However, the racemic reduction with lithium aluminium hydride gave the racemic diol **81** in quantitative yield.



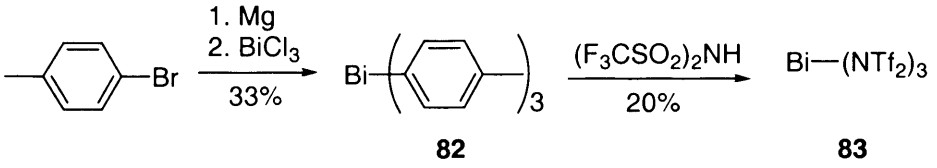
Scheme 4-8: Diol synthesis.

To avoid the use of the expensive reagent bromobutene in the first step of this synthesis, another route was sought which would also shorten the synthetic route. Subsequent attempts to obtain the dianion, by treating *m*-xylene with potassium tertiary butoxide and *n*-butyllithium, followed by alkylation with methylacrylate failed.



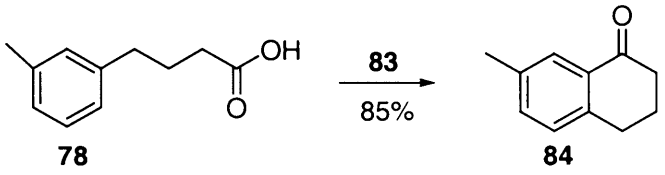
Scheme 4-9: A route for the synthesis of di-ester **74**.

To overcome the low yield of the diketone in the key step of the synthesis of the diselenide, an alternative reaction for the double cyclization was sought. A relevant strategy was found using Lewis acid catalyst **83** to cyclize **77** (instead of polyphosphoric acid). The bismuth Lewis acid catalyst **83**, was synthesized by first preparing the Grignard of bromotoluene followed by treatment with bismuthtrichloride. The tris (*para*-tolyl) bismuth compound **82**[51] was formed in 33 % yield. This was then treated with Tf_2NH under an anhydrous atmosphere to obtain catalyst **83**[52] (20%).



Scheme 4-10: Synthesis of the Lewis acid catalyst.

This bismuth catalyst was first tested on the cyclization of the monoacid, which was formed by oxidation of 4-(*m*-tolyl) butanoic acid (side product from the compound **75**). The cyclized product **84**[53] was obtained in good yield (85 %).



78 **84**

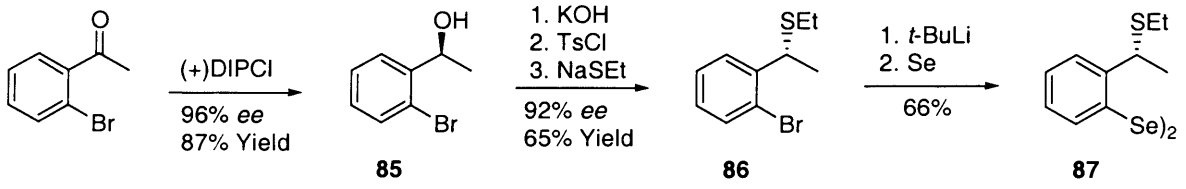
Scheme 4-11: Cyclization with the use of the synthesized Lewis acid catalyst.

4.3 Chiral selenium reagents with sulfur as the heteroatom

A recent investigation with sulfur containing diselenide by Tiecco *et al.*[14i] has shown good results in asymmetric addition to alkenes. The suggestion was made that the interaction of selenium with sulfur was probably more significant than those with oxygen or nitrogen. This new class of reagents was synthesized with slight variation in the structure to investigate their reactivity with substrate **41**.

4.3.1 Synthesis of chiral sulfur diselenide

In order to compare diselenides with oxygen or sulfate as heteroatoms, at first chiral sulfur diselenide **87** was synthesized. It is similar in structure to chiral alcohol diselenide **68**. The cyclization of **41** with this reagent would give a good comparison.



85 **86** **87**

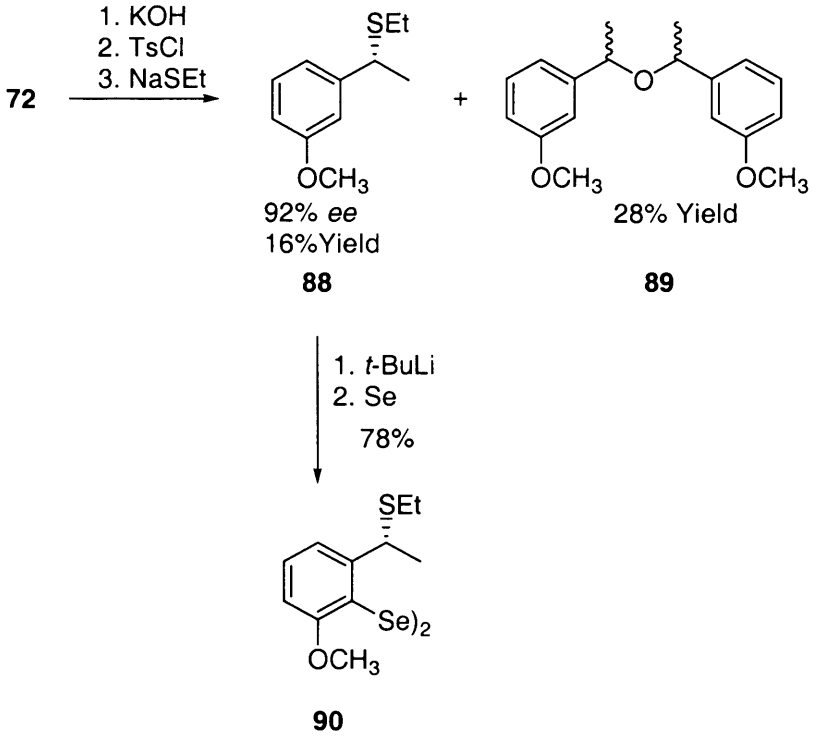
Scheme 4-12: Synthesis of sulfur diselenide.

The known chiral reduction of 2-bromo acetophenone led to the enantiomarically enriched alcohol **85** in good yield. The introduction of the sulfur moiety via an S_N2 reaction with the tosylated precursor gave **86** in 65 % yield and 92% enantiomeric excess (The corresponding racemate was obtained from reduction of the ketone with sodium borohydride followed by tosylation and introducing the sulfur moiety at room temperature). The routine lithiation of **86** with *t*-butyllithium followed by selenenylation gave the diselenide **87**.

4.3.2 Synthesis of chiral sulfur methoxy diselenide

From the result with the methoxy substituted diselenide **73**, the cyclized product derived from the selenium electrophile (generated from diselenide **73**) showed higher enantioselectivity (e.g. **95**: % *e.e.* = 76) in comparison to chiral alcohol diselenide **68** (**95**: % *e.e.* = 38). To investigate the same trend of high selectivity with **90** the synthesis of sulfur methoxy diselenide **90** was performed.

Enantiomerically enriched alcohol **72** (97% *ee*) was tosylated in the presence of a base and the tosylated moiety was replaced with a sulfur group via an S_N2 reaction to form **88** with high enantioselectivity (92% *ee*). This step resulted mainly in dimer **89** as side product. This compound showed optical rotation but the absolute configuration of this compound is not yet determined. The high reactivity of the benzyl tosylate probably resulted in a fast reaction of **72** with the tosylated precursor to form **89**. The racemate **88** was synthesized from racemic alcohol **72** by tosylation followed by treatment with the sulfur substrate at room temperature. Chiral sulfur precursor **88** was additionally lithiated at the *ortho*-position and treated with selenium resulting in target diselenide **90**.[54]

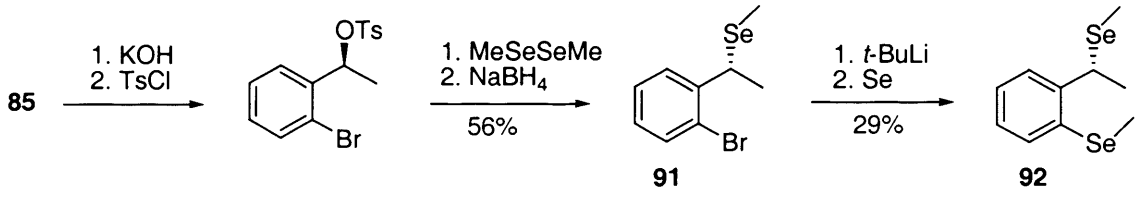


Scheme 4-13: Synthesis of sulfur-methoxy diselenide.

4.4 Chiral selenium reagents with selenium as the heteroatom

The synthesis of another selenium reagent with selenium as a heteroatom was attempted. The attempt to synthesise a selenol diselenide was made because it has the same relative structure (heterosubsituent at *ortho*-position from selenium) as the previously used diselenides (chiral alcohol **68** diselenide and chiral sulfur diselenides **87**) and as the properties of selenium and sulfur are similar it would be interesting to compare these two classes of reagents. Thus, chiral alcohol **85** was tosylated in the presence of a base. Various attempts (prolonging the reaction time of tosylation up to 48 hours and increasing the amount of base and tosylchloride up to 2.2 eq.) were made to selenylate the tosylated precursor in most cases it decomposed to the chiral alcohol **85** and in some cases no reaction was taken place.

Compound **91** could only be formed when the tosylated precursor was first isolated and then allowed to react with the nucleophilic methylselenenyl species (nucleophilic methylselenenyl anion[55] was generated by treating dimethyldiselenide with sodium borohydride in absolute ethanol). The selenium precursor **91** was allowed to react under usual selenenylation conditions, but instead of selenium diselenide being formed, the bismethylselenenylated species **92** was formed.



Scheme 4-14: Synthesis route for selenium diselenide.

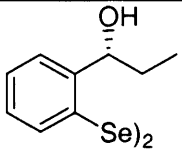
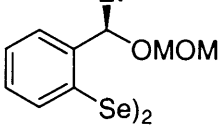
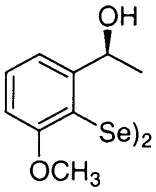
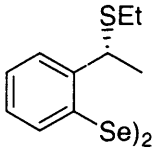
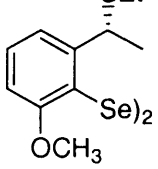
4.5 Reaction of 41 with chiral selenium reagents

The cyclization reaction of **41** with chiral selenium reagents will produce diastereomeric ratio and enantioselectivity results. To avoid the confusion between these two results they are divided in two parts. The results of diastereomeric ratios of substituted tetrahydrofurans and lactones are discussed in this paragraph while the results of enantioselectivity of employed chiral electrophiles are discussed in paragraph 4.6 (pg. 48 and pg 49) and listed in Table 4-3 and Table 4-4.

The synthesized chiral selenium reagents (**68**, **71**, **73**, **87** and **90**) were employed in the cyclization reaction of compound **41** under standard reaction conditions (3 hr at -78 °C,

followed by 90 minutes at room temperature) and the outcomes of the reaction are shown in Table 4-1.

Table 4-1: Cyclization reaction of **41** with selenium electrophile generated from corresponding diselenides.

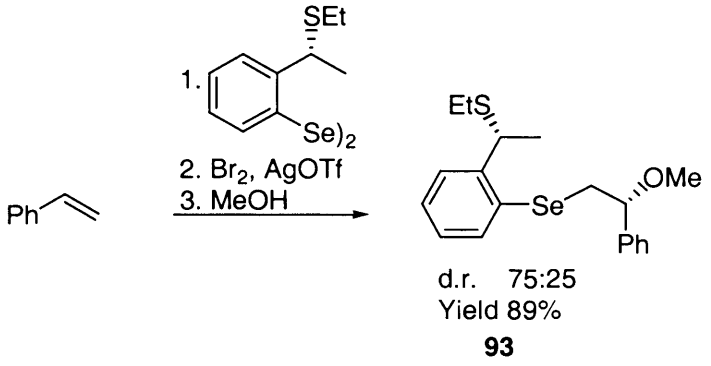
Entry	Diselenide	Products	Solvent	**42 : 43**	**44 : 45**	**42, 43 : 44, 45**	Yield [%]
1	 **68**	**44f, 45f**	Et_2O	-	79:21	0:100	40
2	 **71**	**44g, 45g**	Et_2O	-	82:18	0:100	68
3	 **73**	**56h, 44h, 45h**	Et_2O	30:70	85:15	50:50	77
4	 **87**	**42i, 43i, 44i, 45i**	THF	38:62	87:13	55:45	55
5	 **90**	**42j, 43j, 44j, 45j**	THF	41:59	70:30	60:40	48

The cyclization of **41** was at first carried out with **68**. It led to exclusive formation of lactones **44f/45f** again we observed the same trend[37] as in our previous result described in Chapter 2 and Chapter 3. The strong coordination of alcohol moiety (of the substrate and of the selenium reagent) with the selenium electrophile led to cyclization via the acid functionality yielding exclusively lactones. The reaction of **41** with the selenium electrophile generated from MOM-protected diselenide **71** under standard reaction conditions led to the formation of

only lactones products **44g/45g**. Again strong internal coordination of the MOM-group and of alcohol functionality of the substrate with the selenium electrophile influences the cyclization exclusively via the acid functionality giving the lactones with preferential formation of the *cis*-isomer.

With methoxy diselenide **73** substrate **41** yielded a 50:50 mixture of cyclized products, **56h**, **44h/45h** and interestingly the tetrahydrofurans were isolated as the methylester **56h**. In this case due to the strong coordination of selenium species with heteroatoms there was no selective coordination with the functional groups (the alcohol or the carboxylic acid functionality) of the substrate and therefore a mixture of cyclized products (tetrahydrofurans and lactones) was obtained. [54]

The selectivity of sulfur reagent **87** was at first tested with the reference compound styrene as described in the literature of Tiecco *et al.*[14i] The reaction with styrene gave the addition product **93** as major isomer with a diastereomeric ratio of 75:25 estimated by NMR data. Literature quotes, however, a diastereomeric ratio of 98:2 in favour of the major isomer when using the analogue sulfur reagent (methyl instead of ethyl) in the same reaction.



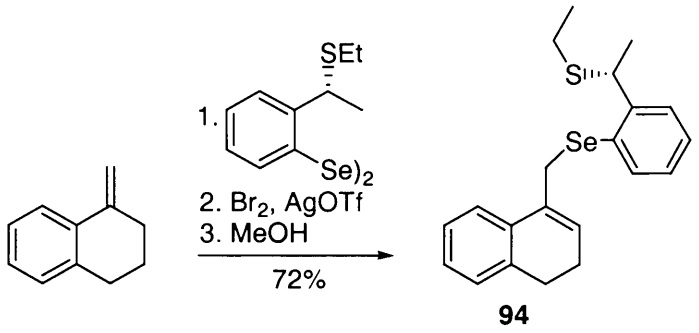
Scheme 4-15: Addition product from styrene.

Employing sulfur reagent **87** in the cyclization reaction under standard reaction conditions with substrate **41** gave a mixture of lactones products, which could not be purified by flash chromatography on silica gel. They could not be identified due to the small amount of each fraction.

However, in this reaction an interesting solvent effect was observed. When the sulfur diselenide **87** was treated with bromine to form the selenenylbromide, the reaction mixture turned into a yellow precipitate while with other selenium reagents a deep red solution was observed. To solubilise the precipiate, THF was added to the reaction mixture. From this point onward the reaction was carried on under usual reaction conditions. The result of this

reaction was now a mixture of tetrahydrofurans **42i/43i** and lactones **44i/45i** in nearly 1:1 ratio.[54]

Another substrate with *exo*-cyclic functionality was tested with sulfur reagent **87**. The tetralon-olefin (synthesized by S. Bissmire) with **87** under standard reaction conditions gave compound **94** in 72% instead of giving the addition product. The quaternary carbon (addition) was presumably formed but was unstable and resulted in β-elimination yielding in **94**.



Scheme 4-16: Elimination product **94** formation from the tetralon-olefin.

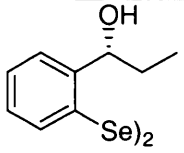
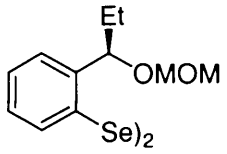
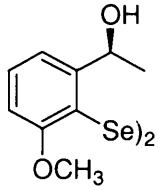
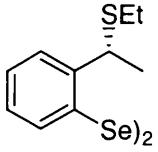
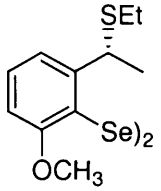
The selectivity of the *ortho*-methoxy substituted sulfur diselenide **90** was tested with **41** under the standard reaction conditions and *exo*-cyclized product **56j** was obtained. It was again isolated as the methylester as observed when using chiral methoxy substituted selenium reagent **73**. The ester formation observed in reactions with chiral methoxy diselenide **73** and chiral sulfur methoxy diselenide **90** is probably due to catalysis by the triflic acid generated *in situ* in this reaction.

To investigate the solvent effect with **90** this reaction was performed in THF and diethyl ether. However regardless of the solubility problem under standard reaction conditions with diethyl ether clean reaction product **56j** was obtained. When using THF, a mixture of **42j/43j** and **44j/45j** were observed.[54]

4.5.1 Reaction of 51 with chiral selenium reagents

The reactivity of substituted tetrahydrofurans with chiral selenium reagents, **68**, **71** and **87** was also investigated via independent cyclization of **51**. The reactivity of tetrahydrofurans with **73** and **90** was determined from the recovered methyl ester products recovered from the reaction with substrate **41**. The results of tetrahydrofurans **56** with the selenium electrophile generated from chiral selenium reagents (**68**, **71**, **73**, **87** and **90**) are listed in Table 4-2.

Table 4-2: Reaction of **51** with chiral selenium reagents.

Entry	Diselenide	Products	*Cis* : *Trans*	Yield [%]
1	 **68**	**56f**	30:70	78
2	 **71**	**56g**	44:56	41
3	 **73**	**56h**	30:70	38
4	 **87**	**56i**	33:67	40
5	 **90**	**56j**	42:58	38

By reacting the alkene **51** with chiral alcohol **68** diselenide compound **56f** was formed exclusively in 78% yield. The ester of **56f** was hydrolysed under basic conditions leading to the formation of **42f/43f** in 70% yield. The influence on diastereomeric ratio of substituted terahydrofuran by selenium electrophile generated from MOM-protected diselenide **71** was investigated by selective synthesis of **56g** under standard reaction conditions.

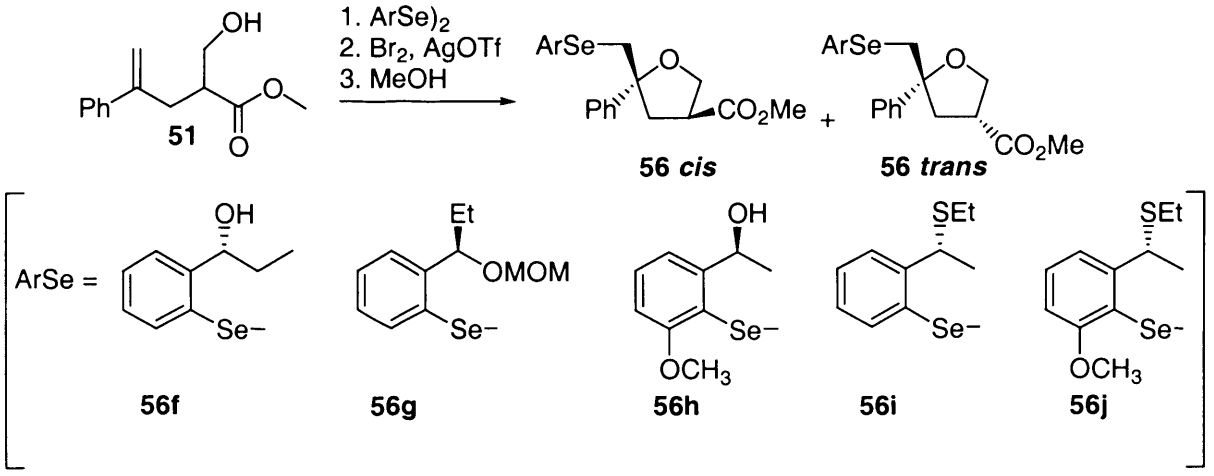


Figure 4-2: Cyclized products **56** derived from chiral selenium reagents.

Preliminary results with sulfur reagent **87** under standard reaction conditions (diethyl ether as solvent) gave a mixture of lactones products, which could not be identified. To investigate whether the synthesis of substituted tetrahydrofurans under these reaction conditions also results in mixture of (furans) products the reaction towards the exclusive synthesis of **56i** was carried out. In this case a clean reaction product **56i** was formed.

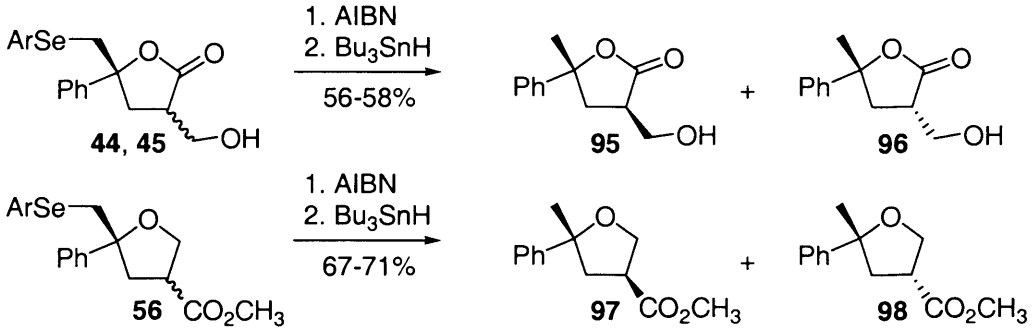
Compounds **56h** and **56j** were recovered from the reaction of **73** and **90** with **41** and the influence of the employed chiral selenium reagents on diastereomeric ratio was estimated from the NMR-spectra.

Cyclization products **56f**, **56h** and **56i** obtained from chiral selenium reagents **68**, **73** and **87** give slightly favourable reactivity towards *trans* isomer while **56g** and **56j** obtained from chiral reagents **71** and **90** give nearly identical reactivity. [54] In all cases the *trans*-isomer is the major isomer in all these reactions. The coordination of the ester moiety of the substrate to the selenium electrophile is probably not so strong and thus resulting in a diasteromeric ratio of around 35:65. A strong coordination of the ester functionality would have resulted in a preferential isomer.

4.6 Selectivity of chiral selenium reagents

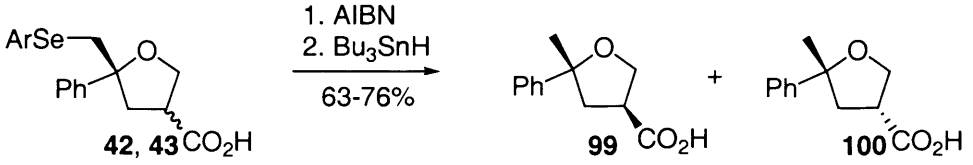
The selectivity of chiral selenium reagents was accurately determined by cleaving the selenium moiety from substituted tetrahydrofurans **56** and **42/43** and lactones **44/45** followed by HPLC analyses on a chiral phase column. In some cases the selectivity was estimated by NMR-data. The racemic deselenenylated product was obtained from the cleavage of racemic seleno compound. Treating the seleno compounds with tributyltin hydride and AIBN carried

out all deselenenylation reactions. [56] The yield of deselenenylated lactone ranged from 56-58 % while for the furan ester deselenenylation was between 67-71%.



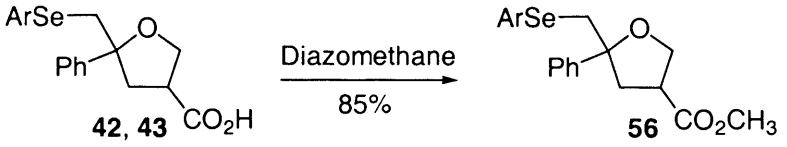
Scheme 4-17: Deselenenylated products of seleno lactones and -furans.

For the selectivity of acid substituted furans a similar strategy of deselenenylation by treatment of the substrate with AIBN and tributyltin hydride was employed. Due to high polarity the condition for the resolution of this compound could not be found on the HPLC columns available.



Scheme 4-18: Deselenenylation of **42/43**.

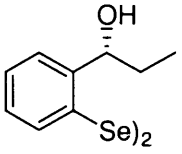
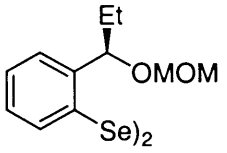
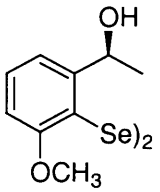
In order to investigate the enantiomeric ratio of selenofurans they were converted to the corresponding esters. Compound **42/43** was treated with diazomethane[57] (which was generated *in situ* by treating diazald with a base) under an inert atmosphere at room temperature for 15 minutes to yield **56** in 85% yield.



Scheme 4-19: Esterfication of **42/43**.

Analyses by HPLC on a chiral phase column indicated the enantiomeric ratio of the *cis* and *trans* isomers. The selectivity of **44/45** from chiral selenium reagents **68**, **71** and **73** are shown in Table 4-3.

Table 4-3: Selectivity of employed chiral selenium reagents with **41**.

Entry	Diselenide	**95**	**96**
1	 **68**	69:31	78:22
2	 **71**	79:21	83:17
3	 **73**	88:12	89:11

The selectivity with **71** was slightly higher compared to that of the corresponding alcohol diselenide **68** probably due to the second coordination to the oxygen of the MOM group.

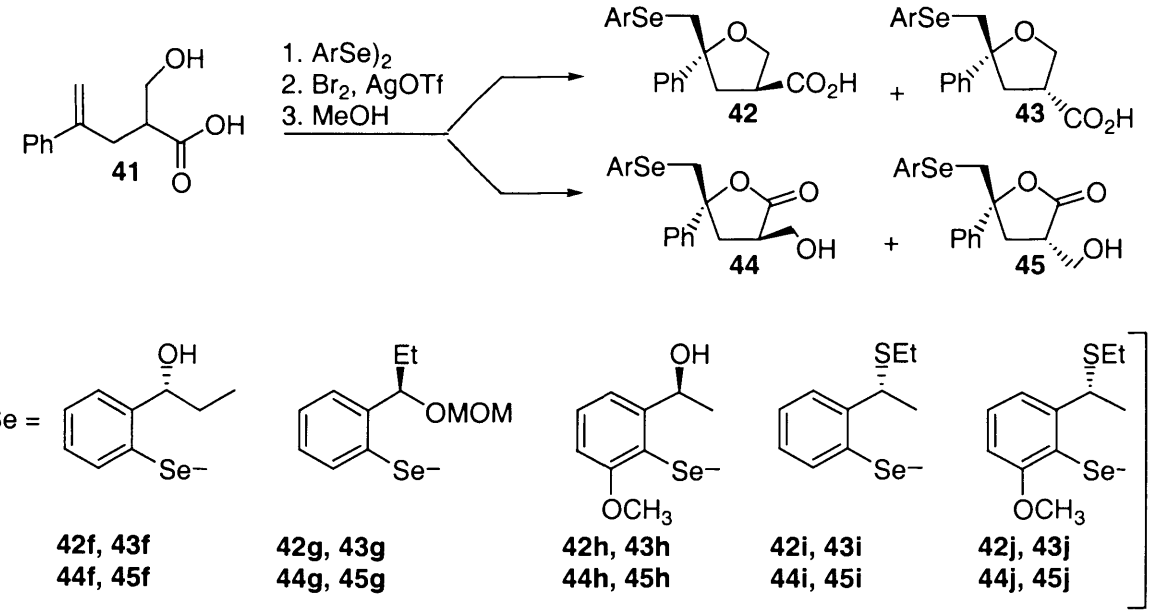
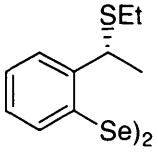
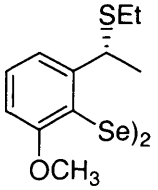


Figure 4-3: Cyclized products **42/43** and **44/45** derived from chiral selenium reagents.

The stereoselectivities of the compounds **42h/43h** and **44h/45h** from **73** as expected was higher due to the two-side coordination of selenium reagent with the heteroatoms which result in the attack of the nucleophile exclusively from one face (*re* or *si*) and thereby

efficient transfer of chiral information.[54] The selectivity for the *cis* and *trans* isomer of **42h/43h** was estimated by NMR-spectroscopy. The stereoselectivity of lactones **44h/45h** was determined after radical cleavage of selenium moiety followed by analyses in HPLC on a chiral phase column. The selectivity result of cyclization with **87** and **90** are listed in Table 4-4.

Table 4-4: Selectivity of employed chiral selenium reagents with **41**.

Entry	Diselenide	**95**	**96**	d.r [**42j**] *cis*	d.r [**43j**] *trans*
1	 **87**	60:40	87:13	-	-
2	 **90**	73:27	88:12	66:34	62:38

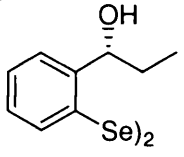
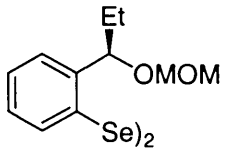
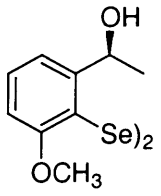
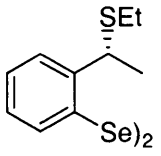
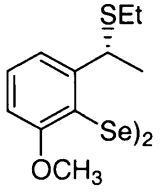
The enantiomeric ratio of the lactone from **87** was determined by deselenenylation followed by HPLC analysis. Compared to the chiral alcohol diselenide **68** [Table 4-3, entry 1] the enantiomeric ratio of the *trans*-isomer **96** was higher [Table 4-4, entry 1]. The selectivity of cyclized products (tetrahydrofurans **56j** and **42j/43j** and lactones **44j/45j** from **90** was determined by ^{1}H-NMR spectra. The diastereomeric ratio of **42j/43j** [Table 4-4, entry 2] was lower than that observed for selective formation of **56j** [Table 4-5, entry 5]. The reason for this phenomenon remains unclear, as one would expect better selectivity in this case due to higher solubility. Also deselenenylated products **95/96** [Table 4-4, entry 3] of lactones show higher diastereomeric ratio than **42j/43j** [Table 4-4, entry 3] but lower selectivity compared with **95/96** [Table 4-3, entry 3] obtained from reaction of **41** with **71**. [54]

Neither of the sulfur reagents performed better than their oxygen analogs towards the selectivity of lactones. [54] They did not result in much higher selectivity than previously used chiral selenium reagents (**68, 71, 73**). Substrate **41** did not seem to be suitable for sulfur reagents towards lactonization.

To investigate the selectivity of chiral selenium reagents, **68**, **71**, and **87** towards the formation of tetrahydrofurans it was independently cyclized from alkene **51**. The methyl ester

tetrahydrofurans from **73** and **90** were recovered from the reaction with substrate **41**. The selectivites observed in **56** from chiral selenium reagents are listed in Table 4-5.

Table 4-5: Selectivity of employed chiral selenium reagents with **51**.

Entry	Electrophile	d.r.[**56** *cis*]	d.r. [**56** *trans*]
1	 **68**	76:24[a]	71:29[a]
2	 **71**	80:20	83:17
3	 **73**	86:14	82:18
4	 **87**	83:17	75:25
5	 **90**	89:11	72:28

[a] *e.r.* (enantiomeric ratio) of **97** and **98** calculated on chiral phace column by HPLC after radical cleavage of the selenium moiety.

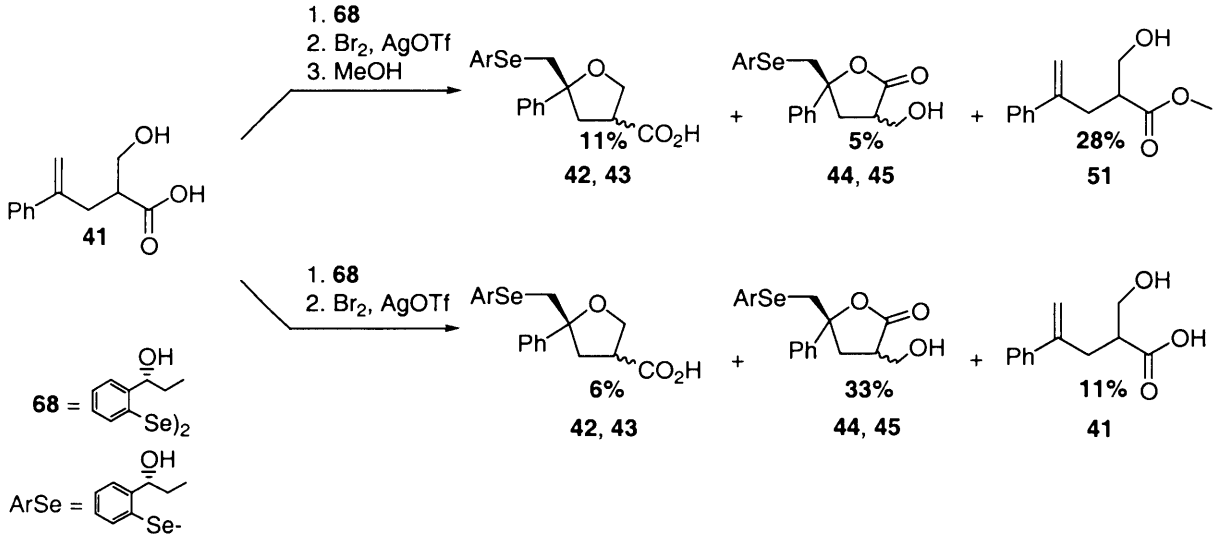
The selectivity for **56f** with **68** was determined by HPLC after deselenenylation. For all other tetrahydrofurans products **56g**, **56h**, **56i** and **56j** the selectivity was estimated from diastereomeric ratio in the NMR-spectra.

There was no significant difference in selectivities between selenium reagents with oxygen as heteroatom (**68**, **71** and **73**) and selenium reagents with sulfur as heteroatom (**87** and **90**). Probably similar coordination of **51** with the selenium electrophiles with oxygen and sulfur

heteroatom has taken place, which resulted in the same efficiency in transferring the chiral information and thus resulting in similar selectivity.[54] The absolute configuration of deselenenylated products **95-100** is not yet resolved.

4.7 Kinetic resolution of substrate 41

To perform the kinetic resolution of alkene **41** it was treated with 0.25 equivalent of the selenium reagent **68**. The reaction mixture led to the formation of cyclized products **42f/43f** in 11% yield, **44f/45f** in 5% yield and **51** in 28% yield. An interesting effect of additive was observed when performing this reaction in the presence of methanol where formation of **51** was observed and substituted tetrahydrofuran had the preference over lactone formation. This was not the case when performing this reaction under standard reaction conditions (instead of 0.25 equivalent 0.50 equivalent of selenium reagent **68** was used).



Scheme 4-20: Racemic resolution of substrate **41**.

When no methanol was added the percentage of tetrahydrofurans **42f/43f** to lactones **44f/45f** changed dramatically. Without methanol, lactones were formed preferentially as the major product. Furans were obtained in only 6% yield while the lactones were formed in 33% yield and the starting material **41** was recovered in 11% yield.

In both cases, the substrates **51** and **41**, which were recovered from the reaction, turned out to be racemic so no enantiomeric resolution was obtained. For the analysis of **41** by HPLC it was first esterified by treatment with diazomethane resulting in compound **51** in quantitative yield.

4.8 Conclusions

Employing chiral selenium reagents with oxygen as heteroatom at 1,3 relation to selenium gave best selectivity with methoxydiselenide **73**.

New chiral sulfur selenium reagents **87** and **90** were synthesized and employed in the cyclization of **41**. They showed low selectivity compared to their oxygen analogue.

Chapter 5

5. 5-*exo*- versus 5-*endo*-cyclization

5.1 Synthesis of a new bifunctional olefin for *endo*-cyclizations

The 5-*exo*-cyclization of compound **41** has extensively been investigated under different reaction conditions with a variety of electrophilic reagents producing conclusive results for selective cyclization conditions.

The synthesis of a new substrate **101** was now targeted. This substrate was designed to give a good comparison between 5-*endo* and 5-*exo* cyclizations of bifunctional olefins. The cyclization of **101** via the acid nucleophile would generate lactone **102** while the cyclization via the hydroxy functionality would result in a substituted tetrahydrofuran **103**. The cyclization products, lactone and furan, from the 5-*endo* cyclizations of **101** can also serve as useful substructures for important heterocycles.

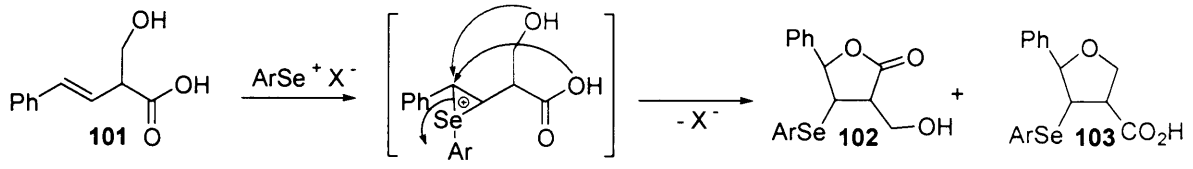
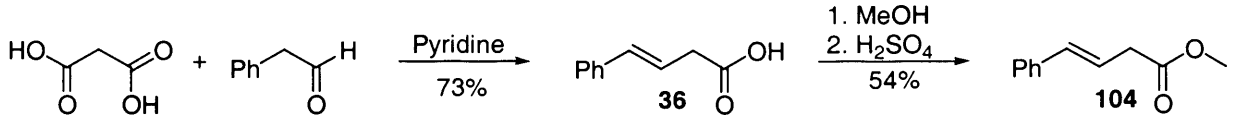


Figure 6-1: 5-*endo*-cyclization with olefin **101**.

5.2 Synthetic strategies towards 101

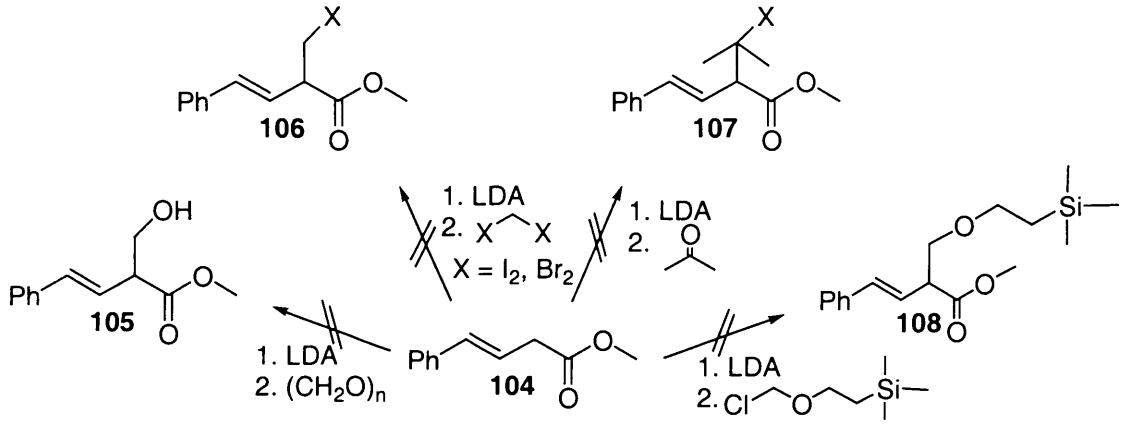
The attempts towards the synthesis of new olefin were mainly carried out based on enolate chemistry. First synthetic route was attempted using the enolate of **104**.

Malonic acid was first treated with phenyl acetaldehyde in the presence of a base to yield the acid **36** via Knoevenagel condensation this was esterified by treatment with acid in the presence of methanol to yield **104**. [58].



Scheme 6-1: Synthesis route of **104**.

Substrate **104** was deprotonated at the α-position from the carbonyl with LDA and the enolate was used to perform alkylation with different alkylating reagents. At first hydroxymethylation with paraformaldehyde [as vapour and as solid] was carried out. The reaction resulted mainly in starting material with a complex mixture of impurities.



Scheme 6-2: First synthetic route for the synthesis of **101**.

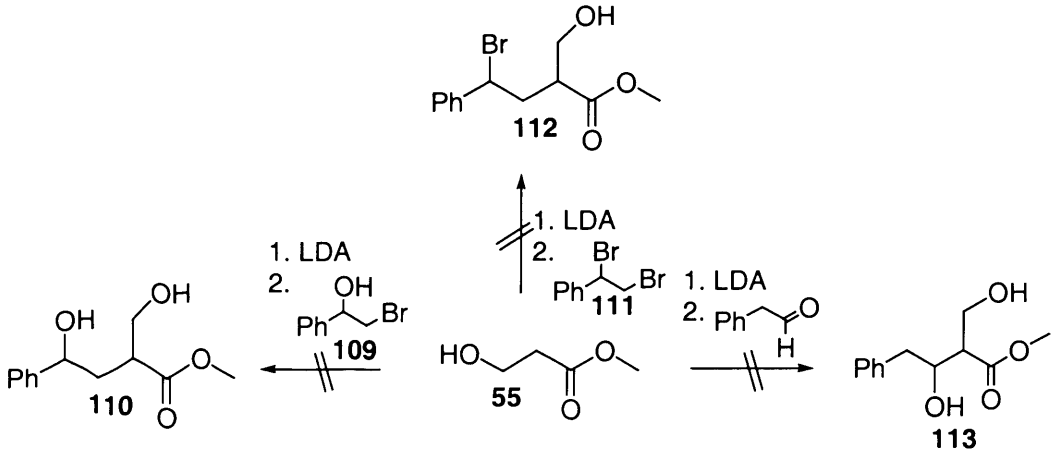
Hydroxymethylation using paraformaldehyde was neither successful for the synthesis of **41** and it was thought to be not good alkylating unit. Therefore it was replaced by dihalo-methane the reaction was performed with diiodo- and dibromomethane in an attempt to obtain **106**. Again no reaction was observed and mainly starting material **104** was recovered from the reaction mixture.

A possible explanation for this result was that the dihalomethane act as a solvent rather than a reagent, therefore another source of hydroxymethylation was attempted by using anhydrous acetone. Also this resulted in recovery of starting material.

As the introduction of a functionalised one carbon electrophile turned challenging, a different source of electrophile was employed. The use of silylchloro ether in an attempt to form **108** resulted in several compounds, which were purified by flash chromatography on silica gel. The main fraction contained two compounds, which could not be separated by flash chromatography although the crude NMR of this mixture indicated the possibility of the presence of the expected reaction product **108**. This fraction was further treated with *tert-*

butyl ammonium fluoride in the hope of obtaining the desired product. Instead this reaction step resulted in a range of side products, which could not be dentified due to separation problems.

The reaction of enols of **104** with a variety of electrophiles did not show any promising results. Now a different source of electrophile and nucleophile was investigated for the formation of **101**. Another synthetic route based on the enolate of **55** with a variety of alkylating reagents was carried out.



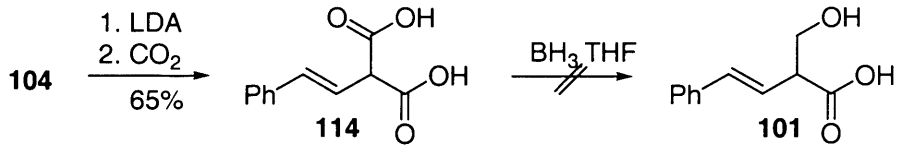
Scheme 6-3: Second route for the synthesis of new olefin.

Hydroxypropionic ester **55** was treated with LDA to form the enolate. This nucleophile was treated with styrene oxide in an attempt to open the epoxide, resulting in the desired reaction product **110**. Unfortunately this gave no reaction and after several hours only starting material (styrene oxide) was recovered. The problem of epoxide opening was resolved by using **109**[59] as alkylating reagent for the enolate of hydroxypropionic ester **55**. In this case also no reaction was observed for formation of **110** and styreneoxide was isolated from the reaction mixture.

The basic reaction conditions were thought to be the reason for this phenomenon. The deprotonation of the hydroxy group of **109** would result in the rapid formation of this epoxide.

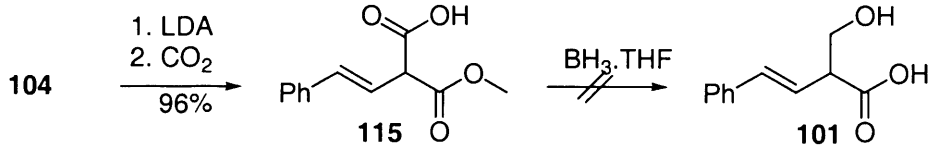
An alternative was to use the dibromo precursor for this reaction. This would overcome the problem of epoxide formation. The use of **111**[60] with the enolate of hydroxypropionic ester also failed to give product **112**. Even use of phenyl acetaldehyde with the enolate of hydroxy propionic acid resulted in a variety of side products that could not be separated and hence were not identified.

Introduction of one carbon unit (in the α-position to the carbonyl of compound **104**) in the form of an acid or ester moiety is known in literature. [58] The synthesis of this compound followed by partial reduction of the ester was chosen as a new route for the synthesis of **101**. Compound **104** was lithiated and the anion produced was now treated with carbon dioxide. An acid base workup was performed and led to the cleavage of ester group resulting in diacid **114** product. It was very unstable at room temperature and had the tendency to decompose to the starting material **104** via 1,3 decarboxylation. The diacid **114** was treated with borane tetrahydrofuran complex to partially reduce the acid moiety and to obtain **101** but it decomposed to **104**.



Scheme 6-4: The synthesis of **101** via reduction of acid.

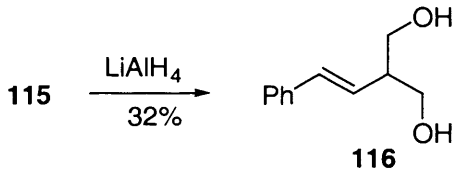
The tendency of the diacid **114** to decompose was thought to be an obstacle for partial reduction. This was resolved by synthesizing compound **115**, which had both an ester and an acid moiety and was thought to be more stable to partial reduction. Compound **115** was obtained according to the same procedure as for the diacid only in the workup of this reaction acid base workup was omitted. This resulted in **115** (this compound was also unstable at room temperature and decomposed to **104**). The reduction of **115** with the borane-tetrahydrofuran complex led to the same result (decomposition product **104** was recovered).



Scheme 6-5: Second attempt via reduction towards the synthesis of **101**.

5.3 Synthesis of diol 116

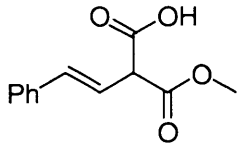
Borane tetrahydrofuran complex is a very mild reducing reagent, which results in slow reactions. The substrate **115** tended to decompose during a long reaction time. This problem was overcome by using lithium aluminium hydride. The use of this reducing reagent with compound **115** resulted in formation of diol **116**. Now the reaction had occurred too fast and instead of partial reduction both, acid and ester–moieties, were reduced.



Scheme 6-6: Complete reduction of **101** leading to the formation of diol **116**.

The amount of lithium aluminium hydride in the reaction was varied to find the conditions for partial reduction. A series of conditions were used and the results are described in Table 5-1.

Table 5-1: Partial reduction conditions for the synthesis of hydroxy-ester.



$LiAlH_4$ (eq.)	Compound.	Yield [%]
0.5	**104**	85
0.7	**104**	79
1.0	**104**	75
2.0	**116**	28

Despite all of the variations in reaction conditions none of the reactions gave the desired product. The use of lithium aluminium hydride up until one equivalent resulted in decomposition product **104** while using more than one equivalent lithium aluminium hydride led to the formation of diol **116**. No further attempts were made to synthesise this product.

5.4 Cyclization reaction of 116

Compound **116** contained also two functional groups the reaction of **116** with achiral electrophiles and chiral selenium electrophiles was now studied in an attempt to find the influence of dihydroxy group on course of cyclization and thereby on the formation of **117** and **118**. Two kinds of achiral electrophiles; phenylselenium and iodine electrophiles, were employed in the cyclization reaction of **116**. To investigate and compare the selectivity of chiral selenium electrophile with **116**, two chiral selenium reagents were selected for the cyclization reactions. Reagents **68** and **87** were chosen as chiral selenium electrophilic precursors for the cyclization reaction of **116**.

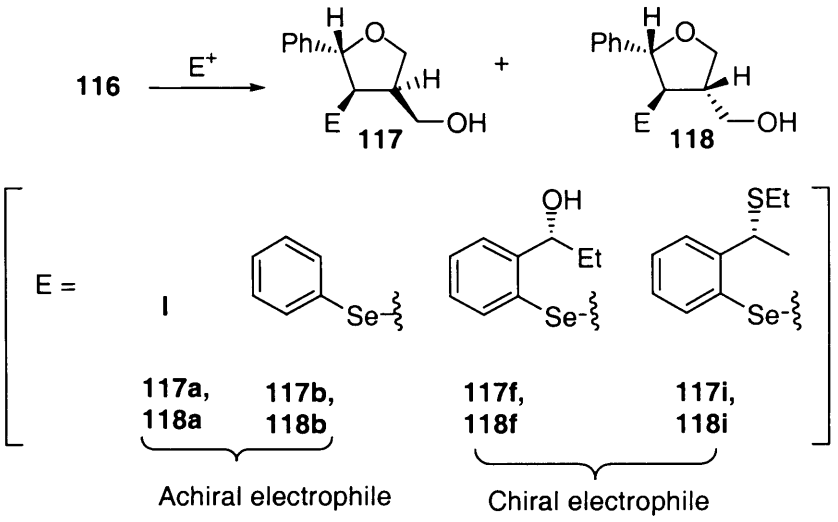


Figure 6-2: Cyclization of **116**.

5.4.1 Reaction of 116 with achiral electrophilic reagents

At first the cyclization reactions of **116** were performed with achiral electrophiles (pheneylselenenyl electrophile and iodine electrophile). The use of phenylselenenyl triflate under standard reaction conditions (3 hr –78 °C followed by 90 minutes at room temperature) resulted in the corresponding *endo* cyclized product **117b/118b**. The cyclization with iodine monochloride under standard reaction conditions (10 minutes at rt) gave the products **117a/118a**. Compound **117** has *trans* relation between the protons **b** and **e** while compound **118** has *cis* relation between the protons **g** and **j**.

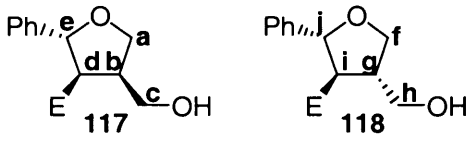


Figure 6-3: *Cis* and *trans* isomers.

The result obtained from these reactions gave a mixture of *cis*- and *trans*-isomers and are shown in Table 5-2. The stereochemistry of these isomers was resolved by nOe-experiments. Proton **j** was irradiated and an enhancement [2.71 %] in the signal of **g** was observed showing a cis relation between **j** and **g** protons. This resolved the assignment of the stereoisomers. The ratio of *cis* to *trans*-isomers was determined by NMR-spectroscopy.

Table 5-2: Cyclization result of **116** with achiral electrophilic reagents.

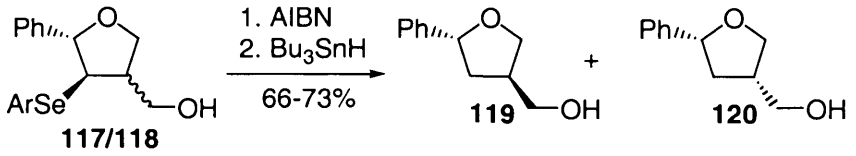
E^+	Products	**117:118** *trans*:cis	Yield [%]
I^+	**117a**, **118a**	88:12	79
$PhSe^+$	**117b**, **118b**	94:6	50

With selenium and iodine electrophiles the influence on the diasteromeric ratio of **117:118** was highly in the favor of the *trans*-isomer (was the major product). The effect on low yield of the reaction with the phenylselenenyl electrophile is probably due to small reaction scale. The cyclized products **117/118** have very low UV visibility (204 nm, part from that these compound are also not clearly visible from cerium, permanganese, iodine or vaniline dip) and small reaction scale results in low concentration.which lead to great impact on loss of part of the product during purification.

5.4.2 Selectivity of chiral selenium reagents with 116

The reaction of **116** with the chiral selenium reagent **68** having oxygen as a heteroatom was performed under standard reaction condition and the products **117f/118f** were obtained. The sulfur-selenium reagent **87** was also employed for the reaction with **116**. This gave the cyclized products **117i/118i** under standard reaction conditions.

The enantiomeric ratio of the cyclized products with chiral selenium electrophile was accurately determined after cleavage of the selenium moiety. The corresponding racemates for estabilishing the conditions for HPLC separation were obtained by cleavage of the selenium moiety of compounds **117b/118b**. The deselenenylation of the cyclization products was carried out by treatment with tributyltin hydride and AIBN and were obtained in yields between 66-73 %.



Scheme 6-7: Deselenenylation of **117/118**.

The results obtained from cyclization of **116** with the selenium electrophile generated from corresponding diselenides **68** and **87** are summarized in Table 5-3.

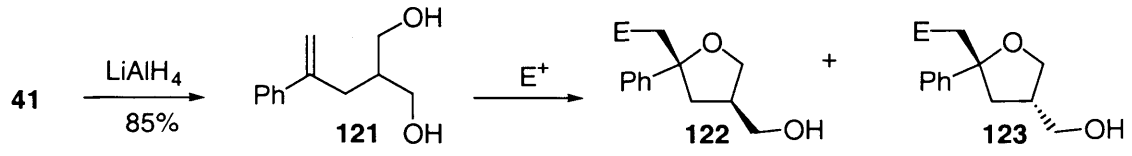
Table 5-3: The selectivity result of **117/118** with selenium reagent **68** and **87**.

Diselenide	**117 : 118** *trans* : *cis*	**119** [*trans*] e.r	**120** [*cis*] e.r	Yield [%]
68	93:7	77:23	72:28	64
87	86:14	77:23	88:12	30

The influence of selenium electrophiles generated from **68** and **87** on the diastereomeric ratio of **117**:**118** was found to be in the favour of **117** which was the major isomer. [54] The selectivity with these reagents was determined after deselenenylation by HPLC analyses. There was no significant difference in the selectivity between **68** and **87** compared with the results obtained with substrate **41**. Cyclized products **117/118** has low yields due to small reaction scales this resulted in detection difficulties as described in 5.4.1 and thereby in possible loss of the product after purification.

5.5 Synthesis and cyclization of *exo* diol 121

Despite of all the attempts to synthesise the bifunctional alkene for *endo*-cyclization no synthetic strategy was discovered to compare the *endo*- versus *exo*-cyclization. Another comparison of *endo*- versus *exo*-cyclization was sought by synthesis of *exo*-diol.[54] This would give the *exo*-cyclization products, which can be compared with the *endo*-cyclization products of **116**. The treatment of **41** with lithium aluminium hydride gave compound **121**.



Scheme 6-8: Synthesis and subsequent cyclization of *exo* diol **121**.

The same selection of achiral electrophilic reagents, which were used for the *endo*-cyclization reaction, was also employed with the *exo*-cyclization reaction of **121**.

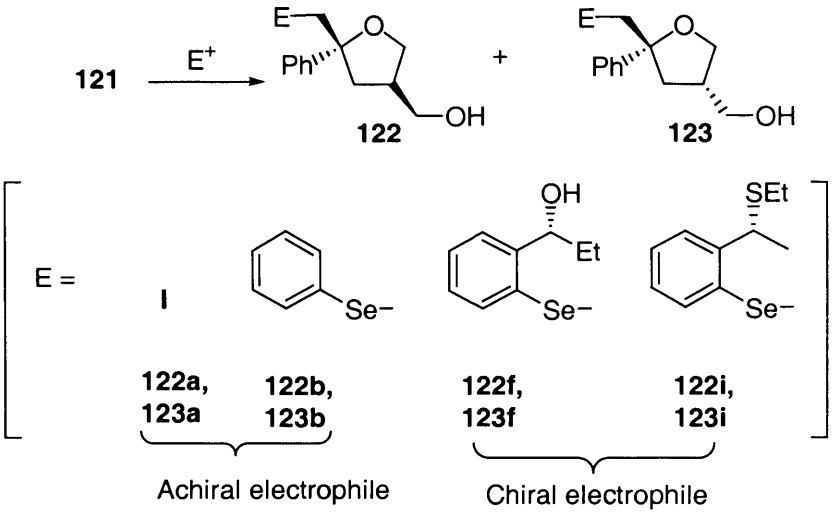


Figure 6-4: Cylized products **122/123** from corresponding electrophile.

5.5.1 Reaction of 121 with achiral electrophilic reagents

Cyclization of **121** with phenylselenenyl triflate yielded compound **122b/123b**. Treatment of **121** with iodine monochloride gave iodocyclized products **122a/123a** under standard reaction conditions. The results for seleno- and iodocyclization with **121** are summarised in Table 5-4.

Table 5-4: Cyclization result of **122/123** with achiral electrophiles.

E^+	Products	**122:123** *cis* : *trans*	Yield [%]
I^+	**122a**, **123a**	66:34	43
$PhSe^+$	**122b**, **123b**	70:30	74

The resulting compounds **122b/123b** from the cyclization with achiral selenium reagent phenylselenenyl triflate gave a mixture of *cis*- and *trans*-isomers. The diastereomeric ratio of *cis*:*trans* isomer was calculated by ^{1}H-NMR spectra. Comparing *endo*- versus *exo* - cyclization reactions the *cis* isomer is the dominant isomer in *exo*-cyclization reactions, while in the *endo*-cyclization reactions the *trans* isomer is the major product.[54]

The coordination of the second hydroxy group with the selenium electrophile appears to be stronger for the *endo*-cyclization products compared to the *exo* products and was probably the reason for high selectivity for the major isomer (*trans* isomer).

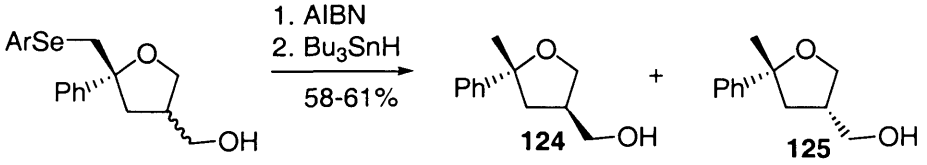
5.5.2 Selectivity of chiral selenium reagents with 121

The selections of chiral selenium reagents used for substrate **116** were also used for **121**. The chiral selenium reagent **68** with oxygen as heteroatom was tested in the cyclization reaction and resulted in products **122f/123f**. The diastereoisomeric ratio **122f:123f** was determined by ^{1}H-NMR-spectroscopy and was found to be 59:41. Finally, the chiral selenium reagent **87** with sulfur as heteroatom was employed in the cyclization reaction and the products **122i/123i** were formed in 33% yield. The selectivities for these reactions are shown in Table 5-5.

Table 5-5: Selectivity and reactivity results with **68** and **87**.

Diselenide	**122f : 123f** cis:trans	**124** *Cis* d.r	**125** *Trans* d.r	Yield [%]
68	59:41	61:39	59:41	28
87	81:19	78:22	-	33

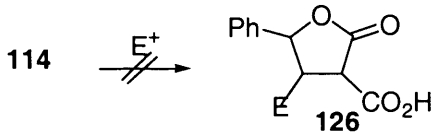
An attempt was made to accurately determine the selectivity of the *exo*-cyclized products obtained from chiral selenium reagents by cleaving the selenium moiety. The deselenenylation of seleno compounds was carried out by treatment with tributyltin hydride and AIBN. The yield for **124/125** was determined as 58-61%. Despite the deselenenylation an accurate enatiomeric ratio could not be determined by HPLC due to poor separation of the enantiomers. Many attempts on a variety of columns and under various HPLC conditions were made but conditions for a successful separation could not be found. The selectivity of employed chiral selenium reagents could therefore be only estimated by the diastereomeric ratio of each isomer by ^{1}H-NMR spectra.



Scheme 6-9: Deselenenylation of *exo* seleno-product.

5.6 Other attempts for comparison of *exo*- versus *endo*-cyclization

The *endo*-versus *exo*-cyclization was tested with the diols. To have a further comparison of *endo*-versus *exo*- other substrates were sought to investigate this phenomenon. Compound **114** with the two acid moieties was chosen it would not only give a comparison of *endo*-versus *exo*- but also the reactivity of acid versus alcohol moiety with the electrophile and thereby the influence on each diastereomeric ratio could be investigated.

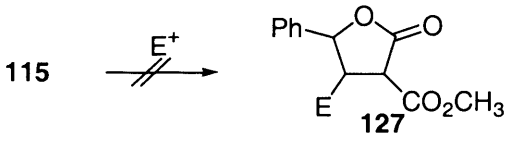


Scheme 6-10: Cyclization with diacid **114** as substrate.

The diacid was at first treated with an achiral selenium reagent, phenylselenenyl triflate, under standard reaction conditions. After stirring the reaction mixture for 3 hours at -78°C followed by 90 minutes at room temperature, the reaction showed no traces of product (decomposition product **36** was isolated).

The long reaction time under standard reaction conditions was presumed to be the problem considering the instability of diacid **114**. The iodocyclization is much faster than the selenocyclization and was therefore carried out. However, the reaction with iodine as electrophile did not change the outcome of the reaction. Again decomposition product **104** was isolated from the reaction mixture.

Keeping in mind the instability of diacid due its tendency to decarboxylate, the cyclizations were attempted with the acidester substrate **115**.



Scheme 6-11: Cyclization with **79**.

When performing the cyclization reaction of **115** with phenylselenenyl triflate no reaction was observed under standard reaction conditions and starting material was recovered. Also the use of additive (MeOH) did not influence the reaction to occur and starting material was recovered. A final attempt was made to carry out the iodocyclization of **115**. As expected no reaction was observed and again the starting material was recovered. The instability of **114/115** prevented the cyclization reaction to take place.

5.7 Conclusions

Despite of many attempts new olefin **101** could not be synthesized. The comparison between *endo* and *exo*-cyclization was obtained by employing diol **116** and **121** in reaction with different electrophiles. The obtained results showed higher diastereomeric ratio with *endo*-cyclized products containing *trans* as major isomer.

Chapter 6

6. Double cyclization reactions

6.1 Cyclization reactions of tetrahydrofurans and lactones compounds

Substituted tetrahydrofurans and lactones are useful building blocks for natural products. A second cyclization of these compounds (Figure 6-1) would lead to a bicyclic skeleton, which might be of interest in the synthesis of various natural products. Several strategies were adapted to obtain this target.

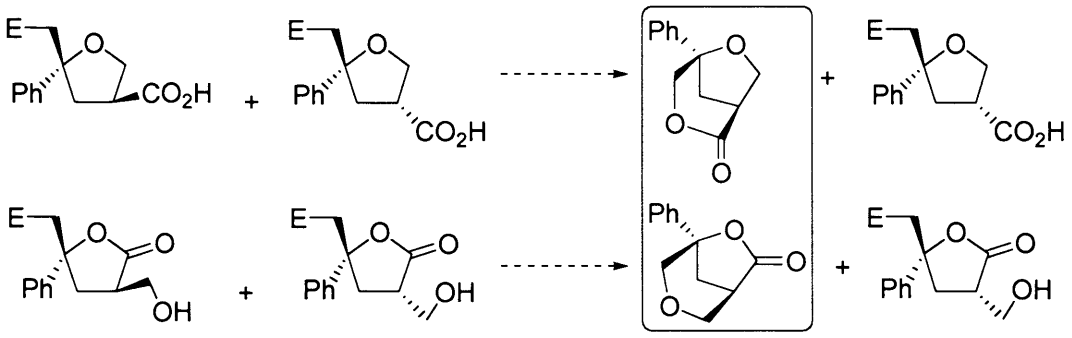
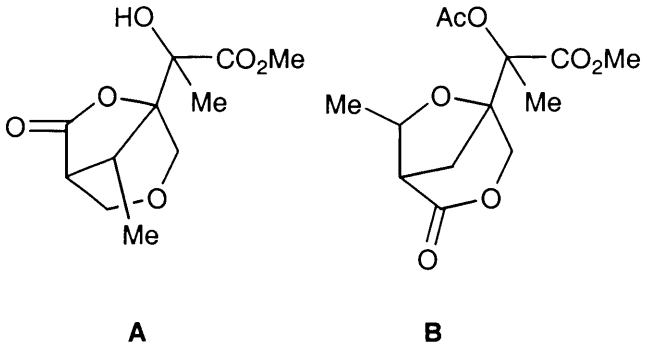


Figure 6-1: Planned double cyclization of substituted tetrahydrofurans and lactones.

The double cyclized product can be used as important skeleton for several alkaloid (Alkaloids have been defined in various ways, but one definition comes fairly close to actuality. An alkaloid is a plant-derived compound that is toxic or physiologically active, contains a nitrogen in a heterocyclic ring, is basic, has a complex structure, and is of limited distribution in the plant kingdom.) e.g. **A** is skeleton of swazine alkaloid and is a natural product [61], **B** is skeleton of natural product erucifolinecic acid senecio alkaloid. [62]



6.2 Cyclization from selenolactone and substituted tetrahydrofuran

The *cis*-isomer **44b** predominant formed in the selenolactonization could result in a second cyclization due to the *cis* arrangement of the hydroxy group and the selenium moiety. Treatment of **44b/45b** with an oxidant would convert the selenium moiety into a good leaving group and a nucleophilic attack from the hydroxy group to the electrophilic carbon bound to the selenone would give the desired product **128** together with the unreacted *trans* isomer. A series of reactions under various conditions using different reagents were conducted. At first the selenium moiety was attempted to convert into a better leaving group by treating **44b/45b** with *n*-bromosuccinimide[63] at room temperature. The reaction failed to give the desired product. Employing *m*-chloroperoxybenzoic acid[64,65,66] and Meerwein's salt[63] under mild reaction conditions did not change the outcome of the reaction and a complex mixture was isolated.

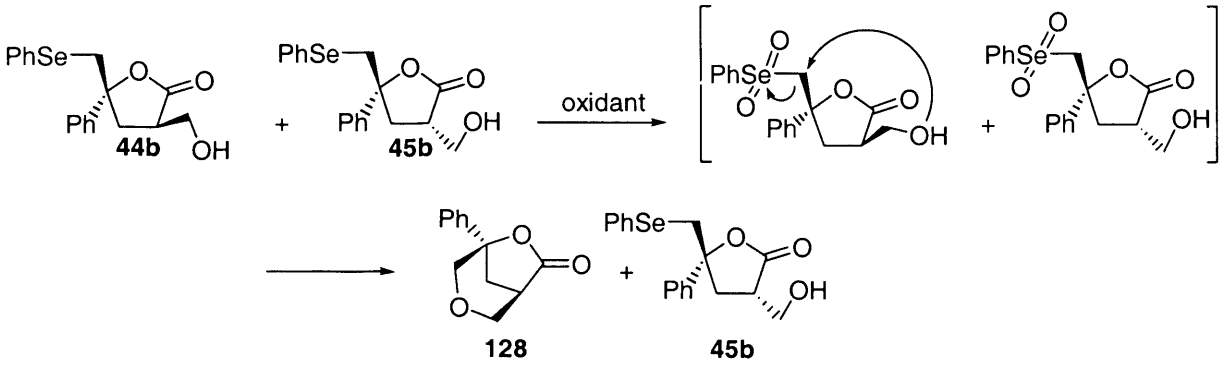


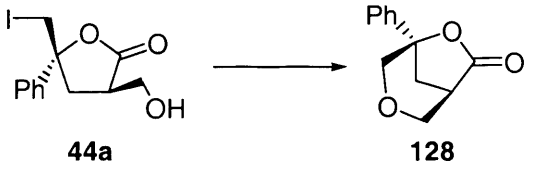
Figure 6-2: Expected cyclization from selenolactones.

Similar reactions were attempted with the substituted tetrahydrofuran **42b/43b**. Treatment with *m*-chloroperoxybenzoic acid failed to give the desired product. While with *n*-bromosuccinimide and Meerwein's salt no reaction was observed and starting material was recovered from the reaction mixture.

6.3 Cyclization from iodolactone

Attempts to synthesise the cyclization products of selenium precursors resulted in either no reaction or mixture of impurities. The oxidation of the seleno moiety to obtain a good selenone leaving group was assumed to be the obstacle in these reactions. To overcome this problem it was decided to use the iodo substituted tetrahydrofurans and lactones instead of seleno substituted tetrahydrofurans and lactones as iodine its self is a good leaving group.

The cyclization of **41** with iodine monochloride led exclusively formation of the lactones. The diastereomeric ratio of *cis*:*trans* isomers was around 76:24. Again the *cis*-isomer was the major product. Treatment with a base would deprotonate the hydroxy group leading to an activated nucleophile which would attack the electrophilic carbon bond to the iodine. This would result in substitution of the iodine and formation of the product together with the unreacted *trans*-isomer.

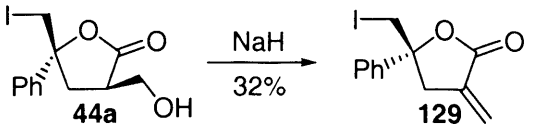


44a **128**

Figure 6-3: Expected cyclization from cis iodo-lactone

A range of reactions were performed with the following mild bases[67,68]; sodium hydrogen carbonate, silver carbonate, collidine and diisopropylamine.

The result of all reactions was negative. Lengthening of the reaction time from 4 to 24 hours and temperature from room temperature to 45 °C had no effect. In all cases no product was formed and complete recovery of the starting material was possible. Therefore it was decided to employ stronger bases. In these reactions the *cis*-isomer **44a** of the iodolactone was used. Again no reaction was observed with sodium hydroxide. However when sodiumhydride was used as a base another interesting compound was isolated (Figue 6-4).

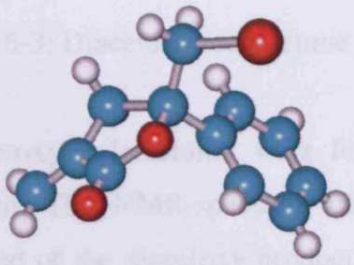


44a **129**

Scheme 6-1: Elimination product from *cis* iodo-lactone

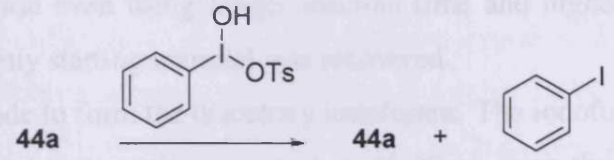
The elimination product **129** was obtained from the *cis* isomer of iodolactone with sodiumhydride at room temperature as a white solid. This product can also serve as an important building block for some natural products some of which can serve as anticancer

agents. [69,70,71] The product was recrystallised and the structure of **129** was further confirmed by X-ray crystallography [Appendix 2, pg 135].



Crystal structure of **129**.

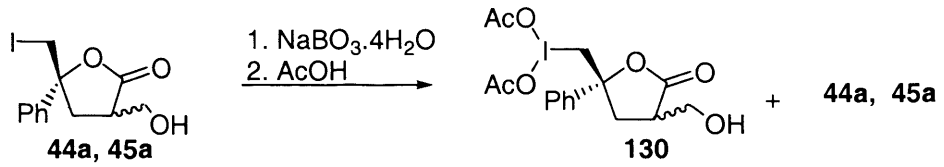
Since mild bases led to no reaction and a strong base resulted in elimination product it was decided to convert the iodine into a better leaving group. The iodolactones **44a**/**45a** were treated with Koser's Reagent[72,73] in an attempt to perform a ligand exchange. The iodine moiety of the iodolactone would be exchanged with the iodine moiety of the Koser reagent {[hydroxy(tosyloxy)iodo]benzene}. The iodine moiety of the iodolactone would now be converted into an iodine(III)-atom. This was expected to rapidly recyclize to give the double cyclized product.



Scheme 6-2: Cyclization attempt via ligand exchange.

Instead of the expected result just starting material was recovered from the reaction mixture. However when analysing this reaction mixture with GC-MS two peaks were detected. One peak gave the mass spectrum of iodolactones while the other peak gave the mass of iodobenzene. Most probably the ligand exchange of the iodine moiety has occurred but due to the instability of the iodine(III)-atom instead of resulting in a second cyclization it tended to decompose to the starting material.

The iodolactones were treated with sodium perborate in the presence of acetic acid to form diacetoxy iodolactone **130**[74], which was expected to cyclize to form the desired product.



Scheme 6-3: Diacetoxy iodolactone formation.

Against expectations the diacetoxy iodolactones were found to be stable and no further cyclized product was observed. The NMR-spectrum of the crude product showed the presence of the iodolactones and of the diacetoxy product. This hypervalent iodine product could not be purified by flash chromtagraphy as it decomposed to the iodolactones.

6.4 Cyclization from substituted iodo tetrahydrofuran

The iodotetrahydrofurans **42a/43a** were formed from the cyclization of **51** with iodine monochloride followed by ester hydrolysis under basic conditions. The diastereomeric ratio of *cis*:*trans* isomer is comparable with selenofurans (45:55).

The use of mild bases such as silver carbonate and sodium hydrogencarbonate with reaction time changing from 4-24 hours and temperature from ambient to 45 °C resulted only in starting material. The use of strong bases such as sodium hydroxide and sodiumhydride led to no reactions. In this case even using longer reaction time and higher temperature gave no elimination product. Only starting material was recovered.

Attempts were also made to form the diacetoxy iodofurans. The iodofurans **42a** and **43a** were treated with sodium perborate and acetic acid at 45 °C to form the diacetoxy iodofurans, which was expected to result in a second cyclization due to instability of hyper iodofuran. Even increasing the reaction time from 4 to 48 hour and temperature from 45 to 65 °C did not result in the diacetoxy furans. Only starting material was recovered.

6.5 Conclusions

Attempts towards cyclization of furans and lactones under different reaction conditions lead in most cases to no reaction. Using sodiumhydride on iodolactone **44a** led interestingly to elimination product **129**, which is of high interest for synthesis of certain anti-cancer reagents.

Chapter 7

7. Conclusions & Outlook

7.1 Conclusions

Cyclization reactions of olefins containing one functional group have been studied with different electrophiles. In most cases the functional group contain an oxygen atom (e.g. OH, CO_2H etc.) and the cyclized product obtained from these reactions gave heterocycles, which are essential building blocks for the synthesis of useful natural products. The most commonly applied buildings block contains the structure of lactones and substituted tetrahydrofurans. So far these cyclized products were mostly obtained from individual substrates.

The synthesis of an olefin from which both cyclized products could be achieved was synthesized. This substrate contained two functional groups: hydroxy and acid functional groups. 5-*exo* Cyclization via the hydroxy functionality of this substrate with an electrophile resulted in tetrahydrofurans while cyclization via the acid functionality led to the formation of lactones. First reactions with phenylselenenyl triflate and a variety of additives revealed the selective cyclization condition of tetrahydrofurans. The use of phenylselenenyl triflate in the presence of acetic acid gave exclusive formation of tetrahydrofurans. The study of the influence of counterions on selenium electrophile gave the reaction condition for exclusive formation of lactones. Using hexafluorophospate or sulphate as counterion and methanol as additive gave solely lactones.

Resolving the stereochemistry of these compounds was challenging as the crude reaction mixture consisted of two cyclized products that additionally consisted of two isomers; *cis* and *trans* isomers.

This problem was resolved by crystallization of *cis*-isomer of iodolactone that was separated by flash chromatography on silica gel. The X-ray analysis of this isomer allowed an unambiguous assignment of the NMR signals.

The reaction conditions for selective synthesis of tetrahydrofurans and lactones pointed out the influence of additives on the course of cyclization. The additives (alcohol and carboxylic acid) were now incorporated into the selenium reagents and the reaction of the olefin was now studied with these modified achiral selenium reagents. The results obtained from the reactions confirmed impartialness of additives they do not influence the course of cyclization. The cyclized products, substituted tetrahydrofurans and lactones, were formed in nearly 1:1 ratio.

Chiral selenium electrophiles containing the heteroatom at 1,3 relation to the selenium was employed in reaction with this substrate and the highest enantioselectivity was found with methoxy substituted alcohol diselenide. To increase the selectivity the synthesis of new chiral selenium reagents was aimed. The synthesized selenium reagent with sulfur as heteroatom gave in reaction with the olefin lower selectivity.

To investigate the results between 5-*exo* and 5-*endo* cyclization and to obtain other interesting heterocycles the synthesis of other bifunctional olefin was aimed. New olefins containing diol functionality were synthesized and applied in reaction with selenium and iodine electrophiles. This gave a comparison of *endo*- versus *exo*-cyclization. The major product from *exo*-cyclization was found to be the *cis* isomer while in *endo*-cyclization the main isomer was the *trans* isomer. The diastereomeric ratio in *endo*-cyclization was higher [d.r.(*cis*:*trans*) = 6:94] than that found with *exo*-cyclization [d.r. (*cis*:*trans*) = 70:30] probably due to the stronger coordination of the functional groups of the substrate with the selenium electrophile.

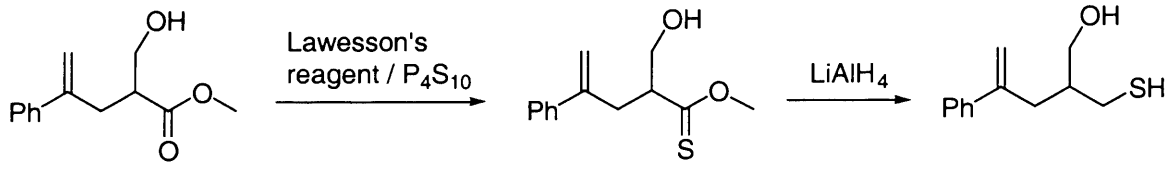
Cyclization of lactones obtained from first olefin would results in a bicyclic product, which is an important building block of important alkaloids; despite of many attempts the conditions for desired bicyclic products were not yet achieved.

7.2 Outlook

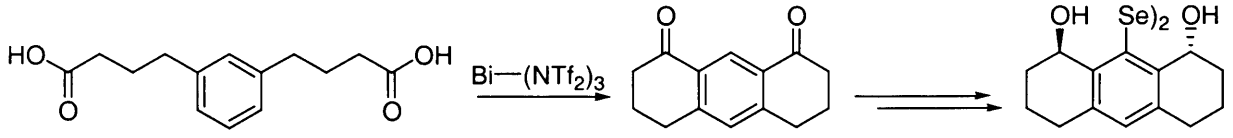
5-*exo* Cyclization of substrate **41** with a variety of electrophiles has been studied in some depth and conclusive results for selective cyclization have been successfully obtained. This study can be broaden by exploring synthetic strategies to other substrates containing two

functional groups, which can lead to other interesting heterocycles via 5-*endo* or 5-*exo* cyclization.

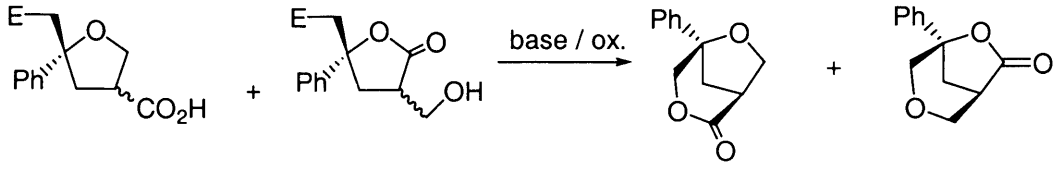
The synthesis of a thiol would generate an interesting olefin. The cyclization of this olefin with an electrophile can lead to important heterocycles: substituted tetrahydrofurans and substituted tetrahydrothiophens. A possible route for the synthesis of this thiosubstrate is the conversion of the ester moiety of hydroxyester into corresponding thioester by treatment with appropriate sulfur source e.g. Lawesson's reagent[75] or P_4S_{10}[76] followed by reduction using lithium aluminium hydride[77].



Another important matter is to increase the enantioselectvity by synthesizing chiral selenium reagents, which are easy to prepare. The dialcohol-diselenide has high level of substitution this is expected to lead to high conformational rigidity and therefore greater selectivity. Main work on the synthesis of this reagent has already been carried out. The crucial bicyclization step can be carried out with the synthesized Lewis acid catalyst. Chiral reduction followed by routine selenenylation should give the possible efficient chiral selenium reagent.



Cyclization of tetrahydrofurans or the lactones can generate useful skeleton for some alkaloid. Preliminary work on the synthesis of this bicyclic compound has been done. Other reaction conditions involving searching for a suitable base and/ or converting the electrophile into a good leaving group should reveal the conditions for this essential step.



Chapter 8

8. Experimental

8.1 General reactions details

Most reactions were carried out using standard laboratory equipment. Inert reactions conditions are applied by vacuum dried or oven dried (120 °C) apparatus under an argon atmosphere. Reactions requiring constant working temperature were performed using hotplates with temperature probe control in silicon oil. The solvent evaporation was performed with Büchi R-124 rotary evaporator (vacuum upto ca. 15 mbar). Further drying was obtained in high vacuum at ca. 0.05 mbar.

Vacuum distillation was performed in a Büchi *GKR-50* Kugelrohr distillation apparatus. Anhyrous solvents were freshly distilled: THF and diethyl ether were distilled over sodium / benzophenone under inert atmosphere. Diisopropylamine was distilled over KOH and CH_2Cl_2 was distilled from CaH_2 while toluene was distilled over sodium at inert atmosphere. All other high purity solvents employed in reactions were purchased from Fluka in septum bottles and handled under argon.

The temperature –78 °C for certain reactions is achieved by preparing a cooling bath with acetone and dry ice while for the temperature –20 °C or longer reaction time experiments a *Haake EK 90* Kryostate was employed.

8.2 Physical data

^{1}H NMR-spectroscopy

Bruker DPX 400 (400 MHz)

The chemical shifts δ are given in ppm relative to an internal standard. Tetramethylsilane was used in deutrated chloroform. All coupling constants *J* are reported in Hertz. The multiplicity of a signal is designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = unresolved multiplet, br = broad. Signals that have not been assigned to a specific proton on an aromatic ring are labelled as aromatic.

^{13}C NMR-spectroscopy

Bruker DPX 400 *(100 MHz)*

The chemical shifts δ are given in ppm relative to the solvent signal of deutrated chloroform (δ = 77.0 t). Peaks were assigned based on DEPT (dissortionless enhancement by polarisation transfer) sequences as required.

^{77}Se NMR-spectroscopy

Jeol Eclipse 300 (57.3 MHz)

The chemical shifts are given in ppm relative to diphenyl diselenide (δ = 475 t).

Mass Spectrometry

Fisons VG Platform

The analyses were performed by R. Jenkins and by S. Ali in the mass spectrometry laboratory of the Department of Chemistry (Cardiff University). Ions were generated using atmospheric pressure chemical ionisation (APCI) or by GC-MS (column: DB 5-MS) using electronical ionisation (EI).

In both cases the masses of the fragments are given in atomic mass unit per elementary charge ratio (m/z). The intensity relative to the strongest signal (molecular peak) is quoted in brackets (in %).

Accurate high resolution mass spectral data of these compounds were carried out by the EPSRC mass spectrometry service centre at University of Swansea.

All molecular formulas are values quoted for either molecular ions (M^+), molecular + hydrogen ($M + H^+$) or molecular + ammonium ion ($M + NH_4^+$). All values are given in atomic

mass units per elementary charge (m/z). The intensity relative to the strongest signal is quoted in brackets (in %).

Gas Chromatography Mass Spectrometry

Varian Saturn 3400 GC/MS

DB 5-MS, 30 m, column 0.5 mm inner diameter and helium at 12 psi used as the carrier gas. Injector was set to 230 °C, ions were generated by Electronic Ionisation and detected in a *Varian Ultratrace* ion trap, and column conditions were varied between experiments.

IR-Spectroscopy

Perkin Elmer 1600 FTIR spectrometer

Wave numbers quoted in cm^{-1}. All samples were measured as a liquid film on sodium chloride plates as a solution in chloroform ($CHCl_3$).

Optical Rotation

Measurements were carried out using an *Optical Activity Ltd. AA-1000* Polarimeter at a wavelength of 589 nm, cell length 5 cm, concentrations c given in g / 100 ml.

Melting point

Electrothermal melting apparatus

Melting points of all compounds were measured in an open capillary tube on this apparatus and are uncorrected.

Chromatography

Thin layer chromatography was performed on *Merck silica gel 60 F 254* precoated aluminium backed plates. The plates were visualised by ultraviolet-fluoroscence or developed iodine vapour or basic potassium permanganate solution in water or 5wt % phosphomolibdic acid solution in ethanol.

Flash chromatography

Flash chromatography was carried out using *Fisher* silica gel 60 (35-70 mesh) the eluent is given for each product in volume percentage.

High performance liquid chromatography

a) *Merck-Hitachi L6200* gradient pump with *Merck-Hitachi L4200 UV/Vis* detector and *Merck-Hitachi L2500* integrator.

b) *Shimadzu LC-10AT-VP* solvent delivery system, *Shimadzu SPD-M10A-VP DAD* detector, *Shimadzu Class VP* software.

Analytical columns used for separations were the *Chiralcel* (OB, OB-H, OD, OD-H, AD, OD-OJ) from Daicel Chemical Industries column length 25 cm, diameter 0.46 mm. Solvent flow rate was fixed at 0.5 ml/min for all separations.

8.3 General procedures

Following general procedures were applied for certain reactions.

8.3.1 Cyclization reaction of olefins with generated selenium electrophiles (GP 1)[34]

In inert atmosphere the diselenide (0.085 mmol) was dissolved in diethyl ether (3.5 mL), cooled to –78 °C and treated with bromine (0.085 mmol, 0.085 mL of a 1 M solution in CCl_4). After 10 min a solution of silver triflate (0.24 mmol, 61 mg) in MeOH (2 mmol, 80 µL) (or the corresponding amount of a silver salt dissolved in 10 eq. of the additive used) was added at –78 °C and stirred for 10 min. The mixture was treated with the substrate (0.17 mmol) and stirred at –78 °C for 3 h followed by 1 hr at rt. The mixture was treated with *sym*-collidine (0.13 mmol, 17 µL) followed by water (3 mL). After extraction with *tert.*-butyl methyl ether, the organic extracts are combined, dried with $MgSO_4$ and the solvent was evaporated to produce a crude product which was purified by flash chromatography on silica gel.

8.3.2 Cyclization reaction of olefins with iodine monochloride (GP 2)[78]

In inert atmosphere the substrate (0.24 mmol) was dissolved in dichloromethane (8.0 ml), treated with iodinemonochloride (0.39 mmol, 1M solution in dichloromethane) and stirred at rt for 15 min. The reaction quenched with saturated solution of sodium thiosulphate and extracted with dichloromethane. The collected organic extracts were dried over magnesium sulphate and the solvent was evaporated to produce crude product, which was further purified by flash chromatography on silica gel.

8.3.3 Ester hydrolysis (GP 3)[79]

The substrate (2.73 mmol) was dissolved in MeOH (25 mL) and treated at 0 °C with aq. 30% KOH (13 mL) and stirred overnight at rt. Water (30 mL) was added and the solution washed with diethyl ether (25 mL). The aqueous layer was cooled to 0°C and CH_2Cl_2 (25 mL) was added followed by 5 N HCl until pH < 5. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated.

8.3.4 Chiral reduction with (+) DIPCl (GP 4)[80]

In a dry flask (+) DIPCl (0.036mol, 11.5 g) was dissolved in THF (20 ml) and the ketone (0.033 mol) was dropswise added to this mixture at –20 °C. This reaction mixture was stirred at –20 °C for 24 hr. The solvent was evaporated and the oily solid was treated with ether (60 ml) followed by diethanol amine (0.074 mol, 7.78 g). This reaction mixture was stirred at rt for approximately 2 hr (reaction mixture turned from pale yellow emulsion to white solid emulsion). The reaction mixture was filtered over celite and the solvent was evaporated from the filtrate to produce colourless oil, which was further purified by chromatography on silica gel.

8.3.5 Reduction with $LiAlH_4$ (GP 5)[81]

Lithium aluminium hydride (11 mmol) was dissolved in dry THF (10 mL). To this mixture the substrate (11 mmol), dissolved in THF (5 mL) was added at 0°C and stirred at rt overnight. The reaction was quenched at 0°C with ethanol (20 mL) and the solvents were evaporated. The solid was dissolved in water (15 mL), extracted with diethyl ether (3 x 15 mL), the combined organic phases were dried over $MgSO_4$ and the solvent was evaporated to produce crude product.

8.3.6 Introduction of sulfur moiety (GP 6) [14i]

In dry flask at –20°C the alcohol (9.86 mmol), potassium hydroxide (19.7 mmol, 1.104 g) and tosylchloride (10.8 mmol, 2.12 g) were dissolved in ether (20 ml) & THF (20 ml) and this reaction mixture was stirred at –20°C for 24 hr. At–20°C sodium ethanethiolate (19.7 mmol, 1.66 g) was added to this mixture and it was warmed up to rt and stirred for additional approximately 14 hr. The reaction was quenched with water and extracted with ether (3x 25

ml). The collected organic extracts were dried over $MgSO_4$ and the solvent was evaporated to produce yellow oil, which was further purified by flash chromatography on silica gel.

8.3.7 Synthesis of sulfur diselenides (GP 7) [14i]

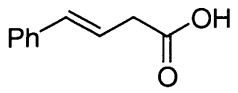
In dry atmosphere at –78°C the bromo precursor (4.1 mmol) was slowly treated with *t*-BuLi (6.1 mmol, 4.07 ml). This reaction mixture stirred at –78°C for approximately 15 mins. the reaction mixture turned from oil to precipitated mixture. The reaction mixture warmed up to rt and stirred for additional 30 mins (reaction mixture is still precipitated mixture) than it was again cooled down to –78°C and treated with THF (10 ml) (reaction mixture turn from emulsion into solution) followed by selenium powder (8.2 mmol, 648 mg). The reaction mixture warmed up to rt and stirred for 24 hr. The reaction was quenched with HCl (1M) and extracted with ether (3x 10 ml). The collected organic extracts were dried over $MgSO_4$ and the solvent was evaporated to produce deep red oil, which was purified by flash chromatography on silica gel.

8.3.8 Deselenenylation by radical cleavage of arylselenides (GP 8)[56]

AIBN (0.25 mmol, 41 mg) and tributyltin hydride (0.25 mmol, 73 mg) were added to a solution of the substrate (83 μmol) in refluxing toluene (3 mL) and the mixture was refluxed for 45 min. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel.

8.4 Spectroscopic data

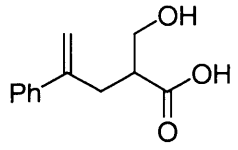
4-Phenyl-but-3-enoic acid (36)



Synthesized according to the reference[58] to obtain pale yellow solid with 73% yield (6.0 g, 0.037 mol).

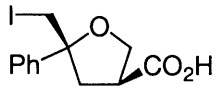
^{1}H NMR (400 MHz, $CDCl_3$,): δ = 3.10 (d, *J* = 6.4 Hz, 2H, CH_2), 6.04-6.13 (dt, *J* = 6.4, 16.0 Hz, 1H, =CH), 6.32 (d, *J* = 16.0 Hz, 1H, CH=), 7.00-7.20 (m, 5H, CH-Ar).

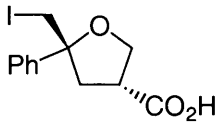
2-Hydroxymethyl-4-phenylpent-4-enoic acid (41)



Compound **51** (600 mg, 2.73 mmol) was dissolved in MeOH (25 mL) and treated at 0 °C with aq. 30% KOH (13 mL) and stirred overnight at rt. Water (30 mL) was added and the solution washed with diethyl ether (25 mL). The aqueous layer was cooled to 0°C and CH_2Cl_2 (25 mL) was added followed by 5 N HCl until pH < 5. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated The product was obtained as a yellow solid in 95% yield (534 mg, 2.59 mmol). No further purification was necessary. m.p.: 59-61 °C; IR (thin film on NaCl): ν = 3436, 1704, 1495, 1444, 1207, 1028, 904, 780, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.60-2.72 (m, 2H, CH_2), 2.93-3.04 (m, 1H, CH), 3.64-3.81 (m, 2H, CH_2OH), 5.11 (s, 1H, $=CH_2$), 5.30 (s, 1H, $=CH_2$), 7.20-7.35 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.2 (CH_2), 45.9 (CH), 62.4 (CH_2OH), 115.6 ($=CH_2$), 126.6 (CH-Ar), 128.3 (CH-Ar), 128.9 (CH-Ar), 140.2 (C), 145.3 (C-Ar), 180.2 (C=O); *m/z* (%): 207 (37) $[M+H]^+$, 191 (100), 173 (65), 159 (58); HRMS calcd for $C_{12}H_{14}O_3$ 207.1021, found 207.1019.

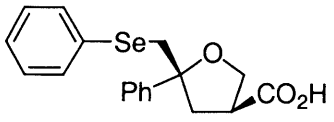
5-Iodomethyl-5-phenyl-tetrahydrofuran-3-carboxylic acid (42a, 43a)

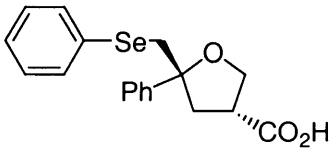




Synthesized from **56a** according to GP 3. Yield: 94 % (112 mg, 0.34 mmol), white solid need no purification; m.p.: 108-110°C; d.r. (**42a**:**43a**) 43:57; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.63 (dd, *J* = 8.8, 18.8 Hz, 4H, CH_2), 3.03 (quint, *J* = 8.0 Hz, 1H, 43a-CH), 3.33-3.45 (m, 1H, 42a-CH) 3.41 (d, *J* = 10.4 Hz, 1H, 42a-CH_2I), 3.46 (d, *J* = 10.8 Hz, 1H, 42a-CH_2I), 3.50 (d, *J* = 10.8 Hz, 1H, 43a-CH_2I), 3.54 (d, *J* = 10.4 Hz, 1H, 43a-CH_2I), 3.93 (t, *J* = 8.8 Hz, 1H, 42a-CH_2O), 4.09 (t, *J* = 8.8 Hz, 1H, 43a-CH_2O), 4.19 (t, *J* = 8.2. Hz, 1H, 43a-CH_2O), 4.27 (t, *J* = 8.4 Hz, 1H, 42a-CH_2O), 7.15-7.40 (m, 10H, Ar); **43a**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (CH_2), 40.8 (CH_2O), 44.4 (CH), 69.7 (CH_2I), 86.0 (C), 125.7 (CH-Ar), 128.3 (CH-Ar), 128.9 (CH-Ar), 142.5 (C-Ar), 179.4 (C=O); IR (NaCl): ν = 3440, 1707, 1447, 1188, 1057, 762, 702 cm^{-1}; MS (EI): *m/z* (%) 350 (3) $[M+NH_4]^+$, 224 (100), 208 (37), 191 (15), 152 (16), 134 (10), 119 (20), 106 (9), 78 (6), 52 (55); HRMS calcd for $C_{12}H_{13}O_3I$ 350.0253, found 350.0256.

5-Phenyl-5-phenylselanylmethyl-tetrahydrofuran-3-carboxylic acid (42b, 43b)

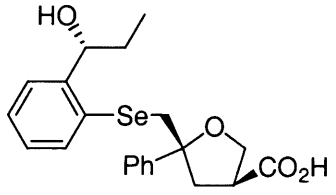


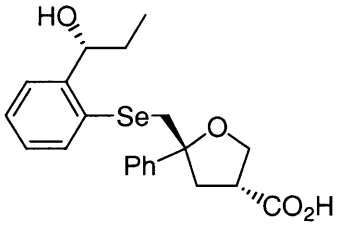


Synthesized from **56b** according to GP 1. Yield 80% (205 mg, 0.58 mmol) product needed no purification; white solid; d.r. (**42b**:**43b**) 37:63; m.p.: 52-55 °C; **42b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50-2.70 (m, 2H, CH_2), 3.18 (d, *J* = 12.4 Hz, 1H, CH_2Se), 3.30-3.38 (m, 1H, CH), 3.32 (d, *J* = 11.6 Hz, 1H, CH_2Se), 3.89 (t, *J* = 8.4 Hz, 1H, CH_2O), 4.18 (t, *J* = 8.4 Hz, 1H, CH_2O), 7.00-7.40 (m, 10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.3 (CH_2), 40.7 (CH_2 Se), 43.9 (CH), 68.1 (CH_2O), 85.9 (C), 124.1 (CH-Ar), 125.8 (CH-Ar), 126.3 (CH-Ar), 127.3 (CH-Ar), 128.0 (CH-Ar), 129.9 (C-Ar), 131.6 (CH-Ar), 143.8 (C-Ar), 177.7 (C=O); ^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 255.3; **43b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50-2.70 (m, 2H, CH_2C), 2.97 (quint, *J* = 8.4 Hz, 1H, CH), 3.29 (d, *J* = 12.0 Hz, 1H, CH_2Se), 3.39 (d, *J* = 12.0 Hz, 1H, CH_2Se), 4.02 (t, *J* = 8.4 Hz, 1H, CH_2O), 4.14 (t, *J* = 7.2 Hz, 1H, CH_2O), 7.00-7.40 (m, 10H, 2xAr); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.5 (CH_2), 39.8 (CH_2 Se), 42.8 (CH), 68.0 (CH_2O), 86.2 (C), 124.1 (CH-Ar), 125.7 (CH-Ar), 126.4 (CH-Ar), 127.4 (CH-Ar),

128.0 (CH-Ar), 130.0 (C-Ar), 131.6 (CH-Ar), 142.7 (CH-Ar), 178.4 (C=O); ^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 257.5; IR (thin film on NaCl): ν = 3477, 1705, 1643, 1579, 1478, 1437, 1236, 1058, 738, 702 cm^{-1}; *m/z* (%): 362 (2) $[M+H]^+$, 331 (1), 191 (76), 173 (12), 157 (20), 145 (22), 128 (18), 115 (32), 105 (70), 91 (69), 77 (100), 65 (25), 51 (72), 45 (91); HRMS calcd for $C_{18}H_{18}O_3Se$ 363.0499, found 363.0495.

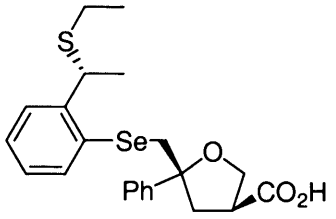
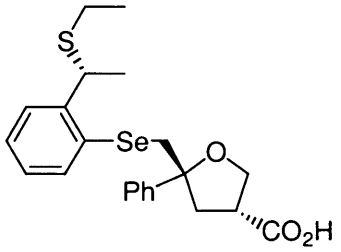
5-{2[(*S*)-1-Hydroxypropyl]-phenylselanylmethyl}5-phenyl-tetrahydrofuran-3-carboxylic acid (42f, 43f)





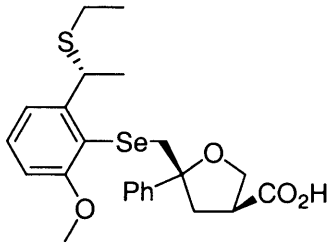
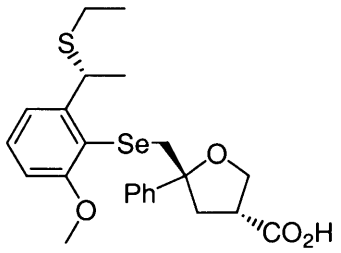
Synthesized from **56f** according to GP 3. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 1:1. Yield: 70% (64 mg, 0.2 mmol), colorless oil, d.r. (**42f**:**43f**) 48:52; $[\alpha]^{23}_D$ = +5.04 (c = 0.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ =0.82 (t, *J* = 6.4 Hz, 3H, 43f-CH_3), 0.84 (t, *J* = 7.6 Hz, 3H, 42f-CH_3), 1.53-1.70 (m, 4H, CH_2CH_3), 2.48-2.70 (m, 4H, CH_2), 2.98 (quint, *J* = 8.4 Hz, 1H, 43f-CH), 3.26 (d, *J* = 12.4 Hz, 1H, 42f-CH_2Se), 3.27 (d, *J* = 12.4 Hz, 1H, 43f-CH_2Se), 3.29-3.34 (m, 1H, 42f-CH), 3.32 (d, *J* = 13.2 Hz, 1H, 42f-CH_2Se), 3.34 (d, *J* = 12.4 Hz, 1H, 43f-CH_2Se), 3.94 (t, *J* = 8.4 Hz, 1H, 42f-CH_2O), 3.99-4.10 (m, 2H, 43f-CH_2O), 4.20 (t, *J* = 8.4 Hz, 1H, 42f-CH_2O), 4.85 (t, *J* = 6.8 Hz, 1H, 43f-CHOH-Ar), 4.88 (t, *J* = 6.8 Hz, 1H, 42f-CHOH), 6.90-7.4 (m, 18H, Ar); **43f**: ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.3 (CH_3), 30.1 (CH_2CH_3), 39.9 (CH_2), 40.7 (CH), 43.7 (CH_2Se), 68.1 (CH_2O), 73.3 (CHOH-Ar), 85.8 (C), 124.2 (CH-Ar), 125.2 (CH-Ar), 126.3 (CH-Ar), 126.6 (CH-Ar), 126.9 (CH-Ar), 127.3 (CH-Ar), 128.9 (C-Ar), 133.3 (CH-Ar), 142.9 (C-Ar), 145.0 (C-Ar), 176.6 (C=O); IR (NaCl): ν = 3217, 1710, 1447, 1199, 1050, 758, 703 cm^{-1}; *m/z* (%): 402 (100) $[M-H_2O]^+$, 391 (38), 216 (22), 208 (99), 197 (50), 152 (6), 118 (96); HRMS for $C_{21}H_{24}O_4Se$ calcd 420.0834, found 420.0834.

5-[2-(*R*)-(1-Ethylsulfanylethyl)-phenylselanylmethyl]-5-phenyl-tetrahydrofuran-3-carboxylic acid (42i, 43i)

Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 2:1. Yield 28% (19 mg, 0.042 mmol), colourless oil; d.r. (**42i**:**43i**) 38:62; $[\alpha]^{23}_D$= –18.1 (c = 0.21, $CHCl_3$); **43i**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.2 Hz, 3H, CH_3), 1.45 (d, *J* = 7.2 Hz, 3H, CH_3), 2.25 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 2.58 (d, *J* = 7.6 Hz, 1H, CH_2), 2.62 (d, *J* = 7.6 Hz, 1H, CH_2), 2.95-3.05 (quint, *J* = 8.4 Hz, 1H, CH), 3.28 (d, *J* = 12.0 Hz, 1H, CH_2Se), 3.38 (d, *J* = 11.6 Hz, 1H, CH_2Se), 4.05 (t, *J* = 8.8 Hz, 1H, CH_2O), 4.18 (t, *J* = 7.2 Hz, 1H, CH_2O), 4.60 (q, *J* = 7.2 Hz, 1H, CH-Ar), 6.90-7.48 (m, 9H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (CH_3CH_2), 22.8 (CH_2CH_3), 25.6 (CH_3), 41.0 (CH-Ar), 41.8 (CH), 42.9 (CH_2), 44.0 (CH_2Se), 69.6 (CH_2O), 87.7 (C), 125.5 (CH-Ar), 127.5 (CH-Ar), 127.8 (CH-Ar), 127.9 (CH-Ar), 128.0 (CH-Ar), 128.8 (CH-Ar), 132.0 (C-Ar), 134.1 (CH-Ar), 144.2 (C-Ar), 146.0 (C-Ar), 178.5 (C=O); IR (NaCl): ν = 3367, 3046, 2956, 2915, 1725, 1711, 1594, 1489, 1464, 1448, 1368, 1333, 1263, 1217, 1157, 1101, 1049, 1027, 761, 700, 650 cm^{-1}; *m/z* (%): 398 (2) $[M+NH_4]^+$, 468 (100), 451 (33), 433 (9), 422 (38); HRMS calcd for $C_{22}H_{26}O_3SSe$ 468.1106, found 468.1109.

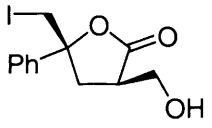
5-[2-(*R*)-(1-Ethylsulfanylethyl)-6-methoxy-phenylselanylmethyl]-5-phenyl-tetrahydrofuran-3-carboxylic acid (42j, 43j)

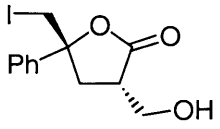



Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 2:1. Yield 23% (17 mg, 0.035 mmol), colorless oil, d.r. (**42j**:**43j**) 47:53; $[\alpha]^{23}_D$= –26.96 (c = 0.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t,

J = 7.6 Hz, 3H, 42j-CH_3), 1.08 (t, J = 7.6 Hz, 3H, 43j-CH_3), 1.34 (d, J = 7.2 Hz, 3H, 42j-CH_3), 1.44 (d, J = 7.2 Hz, 3H, 43j-CH_3), 2.25 (q, J = 7.2 Hz, 2H, 42j-CH_2CH$_3$), 2.29 (q, J = 8.4 Hz, 2H, 43j-CH_2CH$_3$), 2.49-2.57 (m, 2H, CH_2), 2.70-2.90 (m, 2H, CH_2), 2.98 (quint, J = 8.4 Hz, 1H, 43j-CH), 3.21 (d, J = 11.6 Hz, 1H, 42j-CH_2Se), 3.23 (d, J = 11.6 Hz, 1H, 43j-CH_2Se), 3.28 (d, J = 12.0 Hz, 1H, 43j-CH_2Se), 3.30 (d, J = 12.0 Hz, 1H, 42j-CH_2Se), 3.38-3.45 (m, 1H, 42j-CH), 3.76 (s, 3H, 43j-OCH_3), 3.79 (s, 3H, 42j-OCH_3), 3.88 (t, J = 8.8 Hz, 1H, 42j-CH_2O), 4.04 (t, J = 8.4 Hz, 1H, 43j-CH_2O), 4.13 (t, J = 8.4 Hz, 1H, 43j-CH_2O), 4.21 (t, J = 8.4 Hz, 1H, 42j-CH_2O), 4.76 (q, J = 6.8 Hz, 1H, 43j-CH-Ar), 4.89 (q, J = 7.2 Hz, 1H, 42j-CH-Ar), 6.60-7.40 (m, 18H, Ar); **43j**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (CH_3), 22.9 (*C*H_2CH$_3$), 25.6 (*C*H$_3$CH), 40.6 (CH), 41.3 (CH_2), 44.0 (CHOH-Ar), 45.4 (CH_2Se), 56.4 (OCH_3), 69.5 (CH_2O), 87.9 (C), 109.3 (CH-Ar), 120.0 (CH-Ar), 120.1 (CH-Ar), 127.7 (CH-Ar), 128.6 (CH-Ar), 129.7 (CH-Ar), 144.5 (C-Ar), 146.1 (C-Ar), 150.1 (C-Ar), 159.7 (C-Ar), 178.3 (C=O); IR (NaCl): ν = 3364, 2962, 2922, 2360, 1707, 1569, 1463, 1423, 1260, 1057, 771, 695 cm^{-1}; *m/z* (%): 398 (2) [M+NH_4]$^+$, 503 (1), 275 (22), 245 (16), 213 (42), 183 (100), 145 (23), 102 (36); HRMS calcd for $C_{23}H_{28}O_4SSe$ 503.0766, found 503.0763.

3-Hydroxymethyl-5-iodomethyl-5-phenyldihydro-3*H*-furan-2-one (44a, 45a)



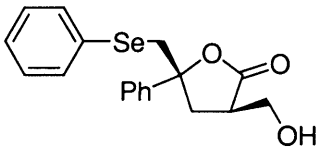


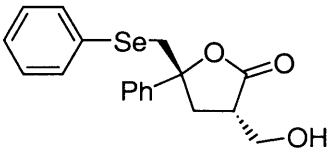
Synthesized from **41** according to GP 2. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 1:1. Yield 74% (63 mg, 0.18 mmol), white solid; m.p.: 108-110 °C; d.r. (**44a**:**45a**) 76:24. The mixture was further purified by flash chromatography on silica gel using *tert.*-butyl methyl ether:petrol ether (1:1) as eluent to obtain 56% (45 mg, 0.134 mmol) of the *cis* isomer (**44a**) and 18% (15 mg, 0.045 mmol) of a mixture of **44a** and **45a**. A X-ray structure of the isomer **44a** clarified the stereochemistry; **44a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56-2.77 (m, 3H, CH_2, CH), 3.58 (d, J = 11.2 Hz, 1H, CH_2I), 3.63 (d, J = 11.2 Hz, 1H, CH_2I), 3.77 (dd, J = 4.8, 11.2 Hz, 1H, CH_2OH), 3.92 (dd, J = 4.0, 11.2 Hz, 1H, CH_2OH), 7.25-7.40 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1 (CH_2I), 37.1 (CH_2C), 43.3 (CH); 61.1 (CH_2OH), 85.1 (C), 125.4 (CH-Ar), 129.2 (CH-Ar), 129.3 (CH-Ar), 140.0 (C-Ar), 176.9 (C=O); **45a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48-2.55 (m, 1H, CH_2), 2.80-2.89 (m, 1H, CH_2), 3.24 (q, J = 5.2 Hz, 1H, CH), 3.53-3.65 (m, 2H,

CH_2I), 3.65 (dd, J = 5.6, 10.8 Hz, 1H, CH_2OH), 3.83 (dd, J = 4.8, 11.2 Hz, 1H, CH_2OH), 7.20-7.45 (m, 5H, Ar);

IR (thin film on NaCl): ν = 3437, 1768, 1644, 1448, 1152, 699, 650 cm^{-1}; *m/z* (%): 350 (27) $[M+NH_4]^+$, 332 (11), 302 (3), 258 (3), 224 (75), 206 (100), 178 (26), 161 (16), 145 (13), 119 (11), 91 (5); HRMS calcd for $C_{12}H_{13}O_3I$ 350.0253, found 350.0250.

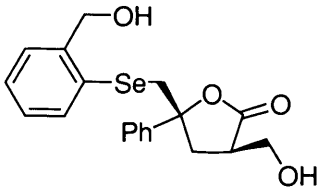
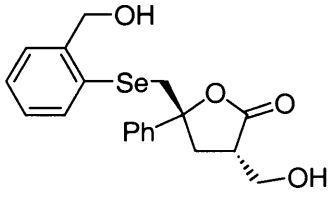
3-Hydroxymethyl-5-phenyl-5-phenylselanylmethyldihydro-3*H*-furan-2-one (44b, 45b)





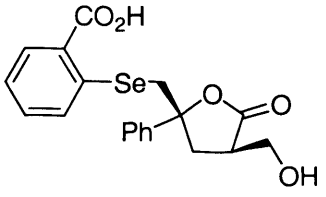
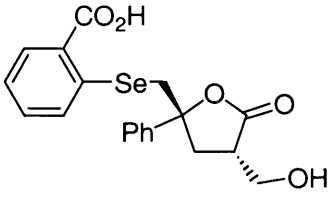
Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 1:1. Yield 60% (52 mg, 0.144 mmol), white solid; m.p.: 50-52 °C; d.r. (**44b**:**45b**) 83:17; **44b**: ^1H NMR (400 MHz, $CDCl_3$): δ = 2.54-2.71 (m, 3H, CH_2, CH), 3.35 (d, J = 13.2 Hz, 1H, CH_2Se), 3.48 (d, J = 13.2 Hz, 1H, CH_2Se), 3.75 (dd, J = 5.2, 11.2 Hz, 1H, CH_2OH), 3.88 (dd, J = 4.0, 11.2 Hz, 1H, CH_2OH), 7.10-7.40 (m, 10H, 2xAr); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.3 (CH_2), 40.0 (CH_2Se), 41.5 (CH), 59.8 (CH_2OH), 85.9 (C), 123.8 (CH-Ar), 126.4 (CH-Ar), 127.3 (CH-Ar), 128.1 (CH-Ar), 128.3 (CH-Ar), 129.1 (C-Ar), 132.2 (CH-Ar), 140.4 (C-Ar), 176.1 (C=O); ^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 259.7; **45b**: ^1H NMR (400 MHz, $CDCl_3$): δ = 2.33-2.41 (m, 1H, CH_2), 2.71-2.80 (m, 1H, CH), 3.17 (quint, J = 5.6 Hz, 1H, CH), 3.34 (d, J = 13.6 Hz, 1H, CH_2Se), 3.38 (d, J = 13.2 Hz, 1H, CH_2Se), 3.62 (dd, J = 6.0, 11.2 Hz, 1H, CH_2OH), 3.78 (dd, J = 5.2, 11.6 Hz, 1H, CH_2OH), 7.10-7.40 (m, 10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.9 (CH_2), 40.3 (CH_2Se); 42.5 (CH), 60.5 (CH_2OH), 86.0 (C), 123.6 (CH-Ar), 126.5 (CH-Ar), 127.1 (CH-Ar), 127.6 (CH-Ar), 128.3 (CH-Ar), 128.9 (C-Ar), 132.0 (C-Ar), 142.2 (CH-Ar), 176.0 (C=O); ^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 258.5; IR (thin film on NaCl): ν = 3426, 3068, 2932, 1771, 1579, 1478, 1448, 1314, 1155, 1022, 969, 738, 701 cm^{-1}; *m/z* (%): 380 (12) $[M+NH_4]^+$, 362 (13), 224 (81), 206 (100), 194 (32), 178 (37), 161 (28), 119 (35), 96 (20), 78 (20); HRMS calcd for $C_{18}H_{18}O_3Se$ 380.0765, found 380.0766.

3-Hydroxymethyl-5-(2-hydroxymethyl-phenylselanylmethyl)-5-phenyldihydro-3*H*-furan-2-one (44c, 45c)

Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 2:1. Yield 51% (30 mg, 0.077 mmol), colorless oil; d.r. (**44c**:**45c**) 80:20; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50-2.80 (m, 5H, 44c-CH, CH_2), 3.09-3.16 (m, 1H, 45c-CH), 3.35 (d, *J* = 13.2 Hz, 2H, CH_2Se), 3.50 (d, *J* = 13.2 Hz, 2H, CH_2Se), 3.63 (dd, *J* = 6.0, 11.2 Hz, 1H, 45c-CH_2OH), 3.68 (dd, *J* = 4.4, 11.2 Hz, 1H, 44c-CH_2OH), 3.76 (dd, *J* = 5.2, 11.2 Hz, 1H, 45c-CH_2OH), 3.92 (dd, *J* = 3.6, 11.2 Hz, 1H, 44c-CH_2OH), 4.66 (q, *J* = 12.8 Hz, 4H, CH_2OH-Ar), 7.05-7.58 (m, 18H, Ar); **44c**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.6 (CH_2), 41.7 (CH_2Se), 43.1 (CH), 60.7 (CH_2OH), 65.7 (*C*H_2OH-Ar), 87.2 (C), 125.0 (C-Ar), 125.2 (CH-Ar), 128.6 (CH-Ar), 128.7 (CH-Ar), 129.0 (CH-Ar), 129.2 (CH-Ar), 130.6 (C-Ar), 135.2 (CH-Ar), 141.9 (CH-Ar), 143.1 (C-Ar), 177.5 (C=O); IR (NaCl): ν = 3376, 2359, 1758, 1643, 1446, 1236, 1145, 952, 766, 700 cm^{-1}; *m/z* (%): 410 (2) $[M+NH_4]^+$, 166 (9), 128 (30), 105 (49), 91 (73), 79 (31), 42 (47); HRMS calcd for $C_{19}H_{20}O_4Se$ 410.0865, found 410.0866.

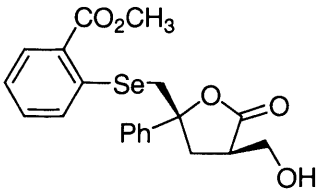
2-(4-Hydroxymethyl-5-oxo-2-phenyl-tetrahydrofuran-2-ylmethylselanyl)-benzoic acid (44d, 45d)

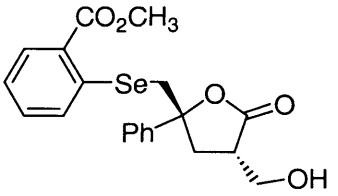



Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:1. Yield 23% (9 mg, 0.022 mmol), colorless oil; d.r. (**44d**:**45d**) 80:20; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40-2.98 (m, 5H, 44d-CH, CH_2), 3.27 (quint, *J* = 4.8 Hz, 1H, 45d-CH), 3.61-3.69 (m, 2H, 45d-CH_2Se), 3.66 (d, *J* = 11.2 Hz, 1H, 44d-CH_2Se), 3.69-3.74 (m, 1H, 45d-CH_2OH), 3.73 (d, *J* = 11.2 Hz, 1H, 44d-CH_2Se), 3.79 (dd, *J* = 4.4, 11.6 Hz, 1H, 44d-CH_2OH), 3.86 (dd, *J* = 4.8, 11.2 Hz, 1H, 45d-CH_2OH), 3.92

(dd, J = 4.0, 11.6 Hz, 1H, 44d-CH_2OH), 7.22-8.10 (m, 18H, Ar); **44d**; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.3 (CH_2), 40.4 (CH_2Se), 42.9 (CH), 61.1 (CH_2OH), 85.6 (*C*), 125.5 (CH-Ar), 128.9 (CH-Ar), 129.1 (C-Ar), 129.2 (CH-Ar), 129.3 (CH-Ar), 129.4 (CH-Ar), 129.7 (CH-Ar), 130.6 (CH-Ar), 134.2 (C-Ar), 140.0 (CH-Ar), 172.0 (O=CAr), 177.1 (C=O); IR (NaCl): ν = 3428, 1770, 1688, 1599, 1579, 1453, 1423, 1328, 1292, 1157, 1097, 1067, 1032, 926, 766, 706 cm^{-1}.

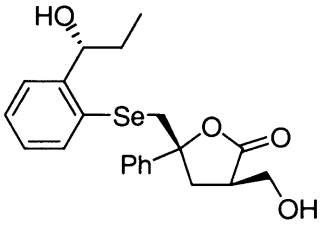
2-(4-Hydroxymethyl-5-oxo-2-phenyl-tetrahydrofuran-2-ylmethylselanyl)-benzoic acid methyl ester (44e, 45e)

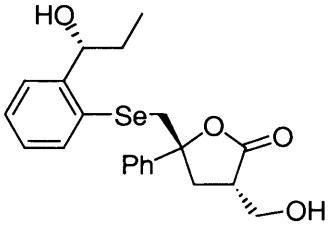




Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:2. Yield 31% (22 mg, 0.052 mmol), colorless oil, d.r. (**44e**:**45e**) 84:16; m.p.: 140-142 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40-2.59 (m, 1H, 45e-CH_2), 2.59-2.76 (m, 3H, 44e-CH_2, CH), 2.88-2.98 (m, 1H, 45e-CH_2), 3.22 (quint, J = 8.4 Hz, 1H, 45e-CH), 3.38 (d, J = 12.4 Hz, 2H, CH_2Se), 3.47 (d, J = 12.4 Hz, 2H, CH_2Se), 3.64 (dd, J = 4.9, 11.6 Hz, 1H, 45e-CH_2OH), 3.68-3.77 (m, 1H, 45e-CH_2OH), 3.75 (dd, J = 5.2, 11.2 Hz, 1H, 44e-CH_2OH), 3.84 (s, 3H, 44e-OCH_3), 3.85 (s, 3H, 45e-OCH_3), 3.87 (dd, J = 3.9, 11.4 Hz, 1H, 44e-CH_2OH), 7.10-7.95 (m, 18H, Ar); **44e**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.0 (CH_2), 38.2 (CH_2Se), 43.0 (CH), 52.8 (OCH_3), 61.2 (CH_2OH), 87.2 (C), 125.3 (CH-Ar), 124.9 (CH-Ar), 125.5 (CH-Ar), 128.9 (CH-Ar), 129.0 (CH-Ar), 129.2 (CH-Ar), 131.8 (CH-Ar), 133.1 (C-Ar), 136.9 (C-Ar), 141.9 (C-Ar), 167.7 (C=O-Ar), 177.5 (C=O); IR (NaCl): ν = 3458, 2925, 1767, 1708, 1579, 1433, 1303, 1273, 1256, 1147, 1097, 1032, 750, 698 cm^{-1}; *m/z* (%): 421 (9) $[M+H]^+$, 288 (9), 215 (100), 191 (12), 159 (6), 143 (6), 100 (5); HRMS for $C_{20}H_{20}O_5Se$ calcd 421.0549, found 421.0546.

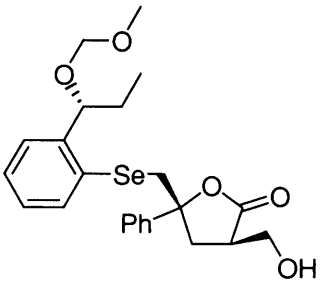
3-Hydroxymethyl-5[2-(*R*)-(1-hydroxypropyl)-phenylselanylmethyl]-5-phenyl-dihydro-*3H*-furan-2-one (44f, 45f)

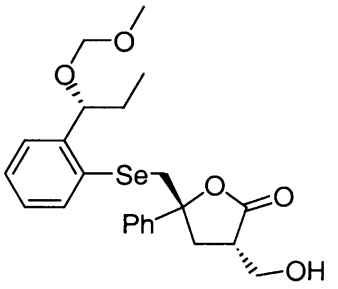




Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 2:1. Yield 40% (27 mg, 0.064 mmol), colorless oil; d.r. (**44f**:**45f**) 79:21; $[\alpha]^{22}_D$ = –8.0 (c = 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.6 Hz, 3H, 45f-CH_3), 0.85 (t, *J* = 7.6 Hz, 3H, 44f-CH_3), 1.49-1.76 (m, 5H, 44f-CH, CH_2CH_3), 2.35-2.67 (m, 2H, 45f-CH_2), 2.57 (t, *J* = 11.6 Hz, 1H, 44f-CH_2), 2.85 (t, *J* = 11.6 Hz, 1H, 44f-CH_2), 2.58-2.67 (m, 1H, CH), 3.32 (d, *J* = 13.6 Hz, 1H, 45f-CH_2Se), 3.35 (d, *J* = 13.6 Hz, 1H, 44f-CH_2Se), 3.45 (d, *J* = 14.0 Hz, 1H, 44f-CH_2Se), 3.51 (d, *J* = 13.2 Hz, 1H, 45f-CH_2Se), 3.62 (dd, *J* = 3.6, 11.6 Hz, 1H, 45f-CH_2OH), 3.73 (dd, *J* = 4.8, 11.6 Hz, 1H, 44f-CH_2OH), 3.92 (dd, *J* = 5.2, 11.6 Hz, 1H, 45f-CH_2OH), 3.96 (dd, *J* = 4.0, 11.6 Hz, 1H, 44f-CH_2OH), 4.98 (dd, *J* = 6.0, 13.2 Hz, 1H, 44f-ArCHOH), 5.18 (t, *J* = 5.6 Hz, 1H, 45f-ArCHOH), 7.05-7.55 (m, 18H, Ar); **44f**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.7 (CH_3), 32.2 (CH_2CH_3), 36.5 (CH_2), 42.6 (CH_2Se), 43.1 (CH), 60.7 (CH_2OH), 74.6 (CHOH), 87.5 (C), 125.1 (CH-Ar), 126.7 (CH-Ar), 128.5 (CH-Ar), 128.7 (CH-Ar), 129.1 (CH-Ar), 129.2 (CH-Ar), 129.8 (C-Ar), 135.3 (CH-Ar), 142.1 (C-Ar), 147.5 (C-Ar), 178.0 (C=O); IR (NaCl): ν = 3390, 3055, 2928, 1770, 1448, 1315, 1260, 1159, 1029, 970, 759, 701 cm^{-1}; *m/z* (%): 420 (9) $[M]^+$, 403 (2), 224 (100), 206 (26), 136 (53); HRMS calcd for $C_{21}H_{34}O_4Se$ 420.0834, found 420.0838.

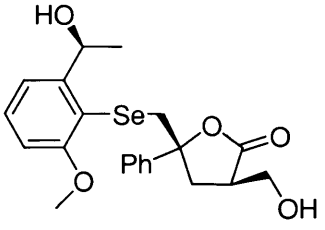
3-Hydroxymethyl-5-[2-(*S*)-(1-methoxymethoxypropyl)-phenylselanylmethyl]-5-phenyl-dihydrofuran-2-one (44g, 45g)

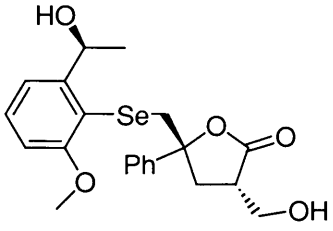




Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether / petrol 2:1. Yield 68% (47 mg, 0.101 mmol), colorless oil; d.r. (**44g**:**45g**) 85:15; $[\alpha]^{21}_D$ = –49.2 (c = 0.065, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.6 Hz, 3H, 45g-CH_3), 0.91 (t, *J* = 7.2 Hz, 3H, 44g-CH_3), 1.49-1.72 (m, 4H, CH_2CH_3), 2.30-2.94 (m, 5H, 45g-CH, CH_2), 3.05-3.16 (m, 1H, 45g-CH), 3.30 (s, 3H, 45g-OCH_3), 3.31 (d, *J* = 11.2 Hz, 1H, 44g-CH_2Se), 3.32-3.38 (m, 2H, 45g-CH_2Se), 3.36 (s, 3H, 44g-OCH_3), 3.53 (d, *J* = 13.2 Hz, 1H, 44g-CH_2Se), 3.63 (dd, *J* = 4.4, 12.8 Hz, 1H, 44g-CH_2OH), 3.65-3.68 (m, 1H, 45g-CH_2OH), 3.73 (dd, *J* = 4.8, 11.2 Hz, 1H, 45g-CH_2OH), 3.95 (dd, *J* =4.0, 11.6 Hz, 1H, 44g-CH_2OH), 4.42-4.47 (m, 1H, 45g-OCH_2O), 4.48 (dd, *J* = 6.8, 10.0 Hz, 2H, 44g-OCH_2O), 4.49-4.54 (m, 1H, 45g-OCH_2O), 4.99 (dd, *J* = 4.8, 8.0 Hz, 1H, 44g-CHO), 5.07 (dd, *J* = 4.8, 8.0 Hz, 1H, 45g-CHO), 7.05-7.42 (m, 18H, Ar); **44g**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9 (CH_3), 31.8 (CH_2CH_3), 35.5 (CH_2), 41.1 (CH_2Se), 43.3 (CH), 56.0 (OCH_3), 60.3 (CH_2OH), 78.3 (CHO), 86.9 (C), 94.7 (OCH_2O), 125.1 (CH-Ar), 125.2 (CH-Ar), 127.1 (CH-Ar), 128.4 (C-Ar), 128.5 (CH-Ar), 129.0 (CH-Ar), 130.2 (CH-Ar), 133.8 (CH-Ar), 142.4 (C-Ar), 144.4 (C-Ar), 177.2 (C=O); IR (NaCl): *ν* = 3472, 2922, 1770, 1644, 1448, 1158, 1104, 1029, 916, 756, 701 cm^{-1}; *m/z* (%): 482 (55) $[M+NH_4]^+$, 464 (21), 456(29), 433 (91), 420 (55), 403 (68), 391 (100), 377 (26), 359 (47); HRMS calcd for $C_{23}H_{28}O_5Se$ 482.1440, found 482.1438.

5{-[2-[(*S*)-1-Hydroxyethyl]-6-methoxyphenylselanylmethyl}-3-hydroxymethyl-5-phenyl-dihydro-*3H*-furan-2-one (44h, 45h)

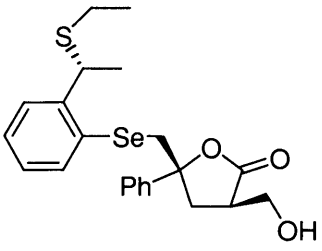


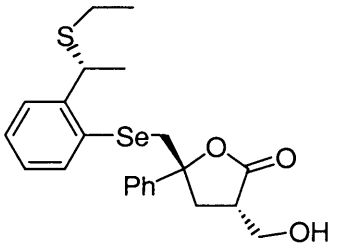


Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:1. Yield 35% (23 mg, 0.053 mmol), colorless oil, d.r. (**44h**:**45h**) 85:15; $[\alpha]^{22}_D$ = –62.2 (c = 0.45, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.8 Hz, 3H, 44h-CH_3), 1.30 (d, *J* = 6.8 Hz, 3H, 45h-CH_3), 2.30-2.52 (m, 2H, 44h-CH_2), 2.56-2.65 (m, 3H, 44h-CH, 45h-CH_2), 2.82-3.00 (m, 1H, 45h-CH), 3.18 (d, *J* = 14.0 Hz, 1H, 44h-CH_2Se), 3.35 (d, *J* = 14.0 Hz, 1H, 45h-CH_2Se), 3.43 (d, *J* = 14.0 Hz, 1H, 45h-CH_2Se), 3.58 (d, *J* = 14.0 Hz, 1H, 44h-CH_2Se), 3.70 (dd, *J* = 4.8, 11.6 Hz, 1H, 44h-CH_2OH), 3.78-

3.82 (m, 1H, 45h-CH_2OH), 3.80 (s, 3H, 44h-OCH_3), 3.82 (s, 3H, 45h-OCH_3), 3.93 (dd, J = 3.6, 11.6 Hz, 1H, 45h-CH_2OH), 3.95 (dd, J = 4.0, 11.6 Hz, 1H, 44h-CH_2OH), 5.36 (q, J = 6.4 Hz, 1H, 44h-CHOH-Ar), 5.56 (q, J = 6.4 Hz, 1H, 45h-CHOH-Ar), 6.70-7.40 (m, 16H, Ar); **44h:** ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 (CH_3), 36.5 (CH_2), 39.3 (CH_2Se), 43.2 (CH), 56.5 (OCH_3), 60.4 (CH_2OH), 69.7 (CHOH-Ar), 87.8 (*C*), 109.9 (CH-Ar), 116.7 (C-Ar), 118.5 (CH-Ar), 125.1 (CH-Ar), 128.6 (CH-Ar), 128.9 (CH-Ar), 129.0 (CH-Ar), 142.4 (C-Ar), 151.1 (C-Ar), 159.3 (C-Ar), 178.2 (C=O); IR (NaCl): ν = 3447, 2937, 1760, 1637, 1564, 1464, 1261, 1157, 1054, 916, 846, 786, 705 cm^{-1}; *m/z* (%): 454 (12) $[M+NH_4]^+$, 436 (15), 419 (23), 312 (6), 286 (12), 260 (12), 254 (27), 246 (36); HRMS calcd for $C_{21}H_{24}O_5Se$ 454.1127, found 454.1131.

5-[2-(*R*)-(1-Ethylsulfanylethyl)-phenylselanylmethyl]-3-hydroxymethyl-5-phenyldihydro-*3H*-furan-2-one (44i, 45i)

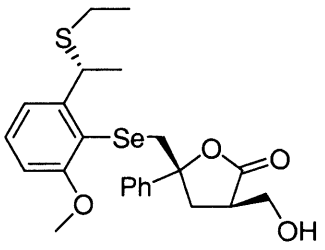


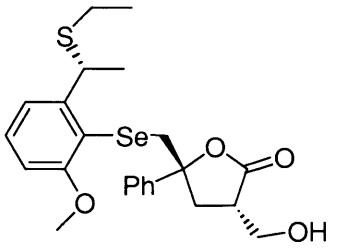


Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 2:1. Yield 28% (19 mg, 0.042 mmol), colorless oil, d.r (cis to trans) = 85:15; $[\alpha]^{21}_D$ = −11.7 (c = 0.29, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.2 Hz, 3H, 44i-CH_3), 1.10 (t, J = 7.2 Hz, 3H, 45i-CH_3), 1.44 (d, J = 7.2 Hz, 3H, 45i-CH_3), 1.48 (d, J = 7.2 Hz, 3H, 44i-CH_3), 2.31 (q, J = 7.6 Hz, 4H, CH_2CH_3), 2.56-2.70 (m, 5H,44i-CH, CH_2), 3.15-3.24 (m, 1H, 45i-CH), 3.36 (d, J = 13.2 Hz, 1H, 45i-CH_2Se), 3.38 (d, J = 12.4 Hz, 1H, 44i-CH_2Se), 3.48 (d, J = 12.8 Hz, 1H, 44i-CH_2Se), 3.49 (d, J = 13.2 Hz, 1H, 45i-CH_2Se), 3.65 (dd, J = 4.8, 12.0 Hz, 1H, 45i-CH_2OH), 3.73 (dd, J = 4.8, 11.6 Hz, 1H, 44i-CH_2OH), 3.79 (dd, J = 4.0, 12.0 Hz, 1H, 45i-CH_2OH), 3.88 (dd, J = 3.6, 11.6 Hz, 1H, 44i-CH_2OH), 4.48 (q, J = 6.8 Hz, 1H, 45i-CH), 4.57 (q, J = 6.8 Hz, 1H, 44i-CH), 7.00-7.50 (m, 18H, Ar); **44i**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (CH_3CH_2), 22.6 (CH_2CH_3), 25.6 (CH_3), 30.7 (CH), 41.5 (CH), 43.0 (CH_2Se), 61.2 (CH_2OH), 87.2 (C), 125.3 (CH-Ar), 127.7 (CH-Ar), 128.0 (CH-Ar), 128.5 (CH-Ar), 128.6 (CH-Ar), 129.0 (CH-Ar), 129.1 (CH-Ar), 131.2 (C-Ar), 134.8 (C-Ar), 141.8 (C-Ar), 146.2 (C-Ar), 177.5 (C=O); IR (NaCl): ν = 3453,

2961, 2915, 1776, 1464, 1442, 1261, 1157, 1025, 762, 701, 650 cm^{-1}; *m/z* (%): 468 (4) $[M+NH_4]^+$, 245 (64), 206 (83), 194 (32), 180 (47), 167 (100), 145 (38), 136 (42), 119 (98), 108 (39), 78 (36); HRMS calcd for $C_{22}H_{26}O_3SSe$ 468.1106, found 468.1104.

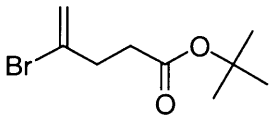
5-[2-(*R*)-(1-Ethylsulfanylethyl)-6-methoxyphenylselanylmethyl]-3-hydroxymethyl-5-phenyldihydro-*3H*-furan-2-one (44j, 45j)





Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 2:1. Yield 21% (15 mg, 0.031 mmol), colorless oil, d.r. (**44j**:**45j**) 82:18; $[\alpha]^{23}_D$= –49.2 (c = 0.59, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.6 Hz, 3H, 45j-CH_3), 1.12 (t, *J* = 7.2 Hz, 3H, 44j-CH_3), 1.39 (d, *J* = 7.2 Hz, 3H, 44j-CH_3), 1.59 (d, *J* = 7.2 Hz, 3H, 45j-CH_3), 2.19-2.37 (m, 4H, CH_2CH_3), 2.49-2.62 (m, 5H, 44j-CH, CH_2), 2.98 (quintet, *J* = 8.4 Hz, 1H, 45j-CH), 3.10 (dd, *J* = 3.2, 11.6 Hz, 1H, 45j-CH_2OH), 3.23 (d, *J* = 12.4 Hz, 2H, CH_2Se), 3.26 (d, *J* = 12.0 Hz, 2H, CH_2Se), 3.30 (dd, *J* = 4.0, 12.0 Hz, 1H, 44j-CH_2OH), 3.77 (s, 3H, 44j-OCH_3), 3.78 (dd, *J* = 4.0, 9.2 Hz, 1H, 44j-CH_2OH) 3.79 (s, 3H, 45j-OCH_3), 3.97 (dd, *J* = 4.0, 9.2 Hz, 1H, 45j-CH_2OH), 4.56 (q, *J* = 6.8 Hz, 1H, 45j-CH-Ar), 4.73 (q, *J* = 8.4 Hz, 1H, 44j-CH-Ar), 6.60-7.40 (m, 18H, Ar); **44j**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7 (CH_3CH_2), 22.9 (CH_2S), 23.2 (CH_3), 40.4 (CH-Ar), 40.8 (CH_2), 48.0 (CH), 48.4 (CH_2Se), 53.7 (OCH_3), 60.9 (CH_2OH), 85.2 (C), 106.7 (CH-Ar), 117.3 (CH-Ar), 124.9 (CH-Ar), 125.8 (C-Ar), 127.1 (CH-Ar), 130.5 (CH-Ar), 137.6 (CH-Ar), 142.0 (C-Ar), 144.0 (C-Ar), 157.1 (C-Ar), 177.8 (C=O); IR (NaCl): ν = 3427, 2966, 2915, 2363, 1734, 1564, 1464, 1373, 1261, 1047, 1032, 755, 695, 650 cm^{-1}; *m/z* (%): 398 (2) $[M+NH_4]^+$, 503 (23), 275 (38), 245 (16), 213 (100), 159 (26); HRMS calcd for $C_{23}H_{28}O_4SSe$ 503.0766, found 503.0767.

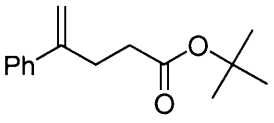
4-Bromo pent-4-enoic acid *tert*-butyl ester (46)



Synthesized according to the reference[27] and purified by flash chromatography with the eluent ether / petrol (1:4) to obtain colorless oil with 81 % yield (3.06 g, 0.013 mol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.38 (s, 9H, $CH_3)_3$, 2.42 (t, *J* = 7.8 Hz, 2H, CH_2CO), 2.63 (t, *J* = 7.8 Hz, 2H, CH_2C), 5.38 (s, 1H, $=CH_2$), 5.58 (s, 1H, $=CH_2$), 7.18-7.38 (m, 5H, Ar).

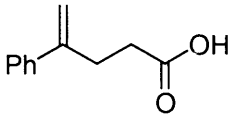
4-Phenyl pent-4-enoic acid *tert*-butyl ester (47)



Synthesized from **46** according to the reference[28] and purified by flash chromatography with the eluent diethyl ether / petrol (1:2) to obtain colorless oil with 59 % yield (1.51 g, 6.49 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.38 (s, 9H, $CH_3)_3$, 2.32 (t, *J* = 7.8 Hz, 2H, CH_2CO), 2.73 (t, *J* = 7.8 Hz, 2H, CH_2C), 5.01 (s, 1H, $=CH_2$), 5.21 (s, 1H, $=CH_2$), 7.18-7.38 (m, 5H, Ar).

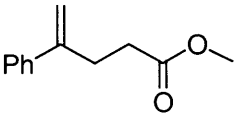
4-Phenyl pent-4-enoic acid (49)



Synthesized according to the reference[29] and purified by flash chromatography with the eluent diethyl ether to obtain white solid with 79 % yield (506 mg, 2.87 mmol).

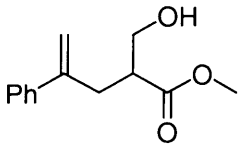
^{1}H NMR (400 MHz, $CDCl_3$,): δ = 2.54 (t, *J* = 8.1 Hz 2H, CH_2C), 2.84 (t, *J* = 7.6 Hz, 2H, CH_2CO), 5.07 (s, 1H, $=CH_2$), 5.31 (s, 1H, $=CH_2$), 7.18-7.38 (m, 5H, Ar).

4-Phenyl pent-4-enoic acid methyl ester (50)



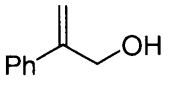
Synthesized from **49** according to the reference[30] and purified by flash chromatography with the eluent ether / petrol (1:2) to obtain colorless oil with 82 % yield (448 mg, 2.36mmol). ^{1}H NMR (400 MHz, $CDCl_3$,): δ = 2.40 (t, *J* = 7.6 Hz 2H, CH_2C), 2.79 (t, *J* = 8.0 Hz, 2H, CH_2CO), 3.59 (s, 3H, OCH_3), 5.02 (s, 1H, $=CH_2$), 5.26 (s, 1H, $=CH_2$), 7.12-7.32 (m, 5H, Ar).

2-Hydroxymethyl-4-phenyl pent-4-enoic acid methyl ester (51)



Lithium diisopropyl amide (LDA), prepared from *n*-BuLi (21.2 mmol, 8.48 mL, 2.5 M in hexane) and dry diisopropylamine (21.2 mmol, 3 mL) in THF (60 mL), was added at –78 °C to 3-hydroxy propionic acid methyl ester (1.0 g, 9.62 mmol) in THF (60 mL) and stirred for 1 h while warming up to rt. The reaction mixture was cooled to –78°C and 3-bromo-2-phenyl propene (1.90 g, 9.62 mmol) was added dropwise. This mixture was stirred for 4 h at –78°C and then for 1 h at rt. The reaction was quenched with sat. aq. NH_4Cl and extracted with diethyl ether (3 x 50 mL). The combined organic phases were dried with $MgSO_4$ and after evaporation of the solvent the crude reaction mixture was purified by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether (1:2) as eluent to give a yellow oil in 60% yield (1.27 g, 5.0 mmol). HPLC-conditions: Chiracel OD-H, flow rate: 0.5 ml•min^{-1}, 2-propanol:n-hexane 10:90, 10°C, $R_f(1)$ = 17.8 min, $R_f(2)$ = 22.4 min; IR (thin film on NaCl): ν = 3408, 2952, 1714, 1628, 1495, 1437, 1379, 1170, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56-2.67 (m, 2H, CH_2), 2.80-2.90 (m, 1H, CH), 3.54 (s, 3H, CH_3), 3.62 (d, *J* = 5.2 Hz, 2H, CH_2OH), 5.04 (d, *J* = 0.8 Hz, 1H, $=CH_2$), 5.23 (d, *J* = 1.2 Hz, 1H, $=CH_2$), 7.15-7.33 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.6 (CH_2), 46.4 (CH_2OH), 52.2 (CH), 62.8 (OCH_3), 115.4 ($=CH_2$), 126.3 (CH-Ar), 126.6 (CH-Ar), 128.2 (CH-Ar), 128.9 (CH-Ar), 140.4 (C), 145.7 (C-Ar), 175.6 (C=O); *m/z* (%): 221 (100) $[M+H]^+$, 203 (4), 143 (2), 118 (13), 52 (7); HRMS calcd for $C_{13}H_{16}O_3$ 221.1177, found 221.1178.

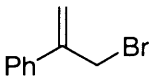
2-phenyl-prop-2-en-1-ol (52)



Synthesized according to the reference[31] and purified by flash chromatography with the eluent ether / petrol (1:2) to obtain colorless oil with 76 % yield (8.13 g, 0.060 mol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 4.45 (s, 2H, CH_2), 5.26 (d, *J* = 1.0 Hz, 1H, =CH_2), 5.38 (d, *J* = 1.0 Hz 1H, C=CH_2), 7.18-7.38 (m, 5H, Ar).

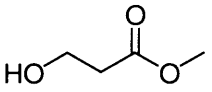
3-bromo-2-phenyl propene (54)



Synthesized from **52** according to the reference[32] as pure product to obtain pale yellow oil with 85 % yield (6.37 g, 0.032 mol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 4.31 (s, 2H, CH_2Br), 5.41 (d, *J* = 0.5 Hz,1H, =CH_2), 5.48 (d, *J* = 0.5 Hz,1H, =CH_2), 7.21-7.45 (m, 5H, Ar).

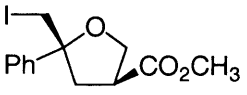
3-hydroxy-propionic acid methyl ester (55)

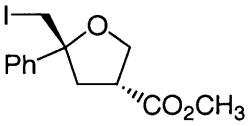


Synthesized according to the reference[33] and purified by kugelrohr to obtain colourless oil with 62 % yield (3.31 g, 0.032 mol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 2.52 (t, *J* = 5.6 Hz, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.80 (t, *J* = 5.6 Hz, 2H, CH_2OH).

5-Iodomethyl-5-phenyltetrahydrofuran-3-carboxylic acid methyl ester (56a)

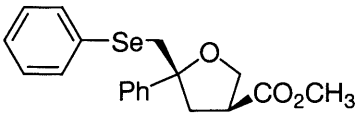


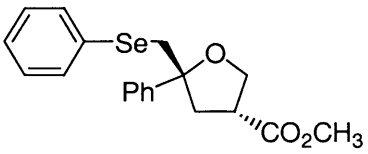


Synthesized from **51** according to GP 2. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 1:2. Yield 93% (236 mg, 0.68 mmol), white solid; m.p.: 69-71 °C; d.r. (*cis*:*trans*) 42:58; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58 (d, *J* = 8.8 Hz, 2H, CH_2C), 2.63 (d, *J* = 8.6 Hz, 2H, CH_2C), 3.00 (quint, *J* = 8.4 Hz, 1H, *cis*-CH), 3.35 (quint, *J* = 8.4 Hz, 1H, *trans*-CH), 3.40 (d, *J* = 10.8 Hz, 1H, *cis*-CH_2I), 3.45 (d, *J* = 11.2 Hz, 1H, *cis*-CH_2I), 3.47 (s, 3H, *cis*-OCH_3), 3.49 (d, *J* = 10.8 Hz, 1H, *trans*-CH_2I), 3.55 (d, *J* = 10.8 Hz, 1H, *trans*-CH_2I), 3.64 (s, 3H, *trans*-OCH_3), 3.93 (t, *J* = 8.4 Hz, 1H, *cis*-CH_2O), 4.08 (t, *J* =

8.4 Hz, 1H, *trans*-CH_2O), 4.16 (t, J = 8.4 Hz, 1H, *trans*-CH_2O), 4.24 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 7.15-7.45 (m, 10H, Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (CH_2), 39.6 (CH_2O), 43.0 (OCH_3), 51.2 (CH), 68.5 (CH_2I), 84.4 (C), 124.2 (CH-Ar), 126.6 (CH-Ar), 127.4 (CH-Ar), 141.4 (C-Ar), 171.4 (C=O); IR (NaCl): ν = 3449, 2952, 1735, 1447, 1200, 1027, 763, 702 cm^{-1}; MS (EI): *m/z* (%): 364 (28) $[M+NH_4]^+$, 347 (5), 238 (100), 221 (56), 205 (29), 152 (14), 136 (10), 119 (21), 110 (10), 98 (13), 90 (18), 52 (60), 44 (65); HRMS calcd for $C_{13}H_{15}O_3I$ 364.0410, found 364.0414.

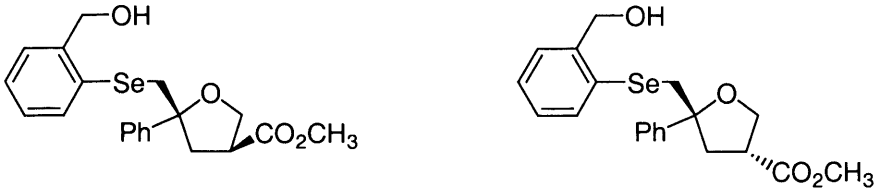
5-Phenyl-5-(phenylselanylmethyl)-tetrahydrofuran-3-carboxylic acid methyl ester (56b)





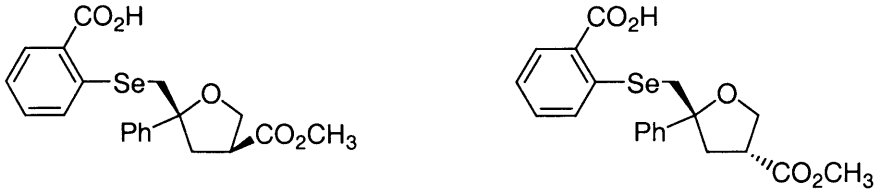
Synthesized from **51** according to GP 1. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 1:10. Yield: 68% (318 mg, 085 mmol), white solid, m.p.: 44-46 °C; d.r. (*cis*:*trans*) 39:61; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.49-2.70 (m, 4H, CH_2), 2.96 (quint, J = 8.4 Hz, 1H, *trans*-CH), 3.20 (d, J = 12.4 Hz, 1H, *cis*-CH_2Se), 3.29-3.36 (m, 1H, *cis*-CH), 3.31 (d, J = 12.0 Hz, 1H, *trans*-CH_2Se), 3.34 (d, J = 12.4 Hz, 1H, *cis*-CH_2Se), 3.40 (d, J = 12.0 Hz, 1H, *trans*-CH_2Se), 3.47 (s, 3H, *cis*-OCH_3), 3.62 (s, 3H, *trans*-OCH_3), 3.91 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 4.04 (t, J = 8.4 Hz, 1H, *trans*-CH_2O), 4.13 (t, J = 8.4 Hz, 1H, *trans*-CH_2O), 4.18 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 7.00-7.40 (m, 20H, Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.3 (CH_2), 42.3 (CH_2 Se), 44.2 (CH), 52.6 (OCH_3), 69.8 (CH_2O), 87.5 (C), 125.6 (CH-Ar), 127.1 (CH-Ar), 127.8 (CH-Ar), 128.8 (CH-Ar), 129.3 (CH-Ar), 131.6 (C-Ar), 133.1 (CH-Ar), 144.5 (C-Ar), 173.8 (C=O); IR (thin film on NaCl): ν = 3440, 1735, 1644, 1578, 1478, 1436, 1200, 1061, 1022, 737, 703 cm^{-1}; *m/z* (%): 377 (56) $[M+H]^+$, 238 (56), 221 (37), 205 (63), 52 (39); HRMS calcd for $C_{19}H_{20}O_3Se$ 377.0656, found 377.0660.

5-(2-Hydroxymethyl phenylselanylmethyl)-5-phenyltetrahydrofuran-3-carboxylic acid methyl ester (56c)



Synthesized from **51** according to GP 1. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 1:4. Yield 30% (11 mg, 0.027 mmol), colorless oil, d.r. (*cis*:*trans*) 48:52; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (dd, *J* = 8.4 Hz, 2H, *cis*-CH_2), 2.58 (d, *J* = 8.4 Hz, 2H, *trans*-CH_2), 2.97 (q, *J* = 8.4 Hz, 1H, *trans*-CH), 3.21 (d, *J* = 12.4 Hz, 1H, *trans*-CH_2Se), 3.28-3.34 (m, 1H, *cis*-CH), 3.31 (d, *J* = 10.8 Hz, 1H, *cis*-CH_2Se), 3.36 (d, *J* = 10.8 Hz, 1H, *trans*-CH_2Se), 3.39 (d, *J* = 12.4 Hz, 1H, *cis*-CH_2Se), 3.46 (s, 3H, *trans*-OCH_3), 3.62 (s, 3H, *cis*-OCH_3), 3.95 (t, *J* = 8.8 Hz, 1H, *cis*-CH_2O), 4.06 (t, *J* = 8.0 Hz, 1H, *trans*-CH_2O), 4.08 (t, *J* = 8.0 Hz, 1H, *trans*-CH_2O), 4.10 (t, *J* = 8.4 Hz, 1H, *cis*-CH_2O), 4.58 (d, *J* = 12.4 Hz, 1H, *cis*-CH_2OH-Ar), 4.59 (d, *J* = 12.4 Hz, 1H, *trans*-CH_2OH-Ar), 4.66 (d, *J* = 12.4 Hz, 1H, *trans*-CH_2OH-Ar), 4.69 (d, *J* = 12.4 Hz, 1H, *cis*-CH_2OH-Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.6 (CH_2), 42.9 (CH_2Se), 45.2 (CH), 52.4 (CH_2O), 66.2 (CH_2OH-Ar), 69.8 (OCH_3), 87.2 (C), 125.5 (CH-Ar), 127.7 (CH-Ar), 127.9 (CH-Ar), 128.3 (CH-Ar), 128.7 (CH-Ar), 129.0 (CH-Ar), 129.2 (CH-Ar), 135.5 (C-Ar), 143.2 (C-Ar), 145.0 (C-Ar), 173.0 (C=O); IR (NaCl): ν = 3430, 3056, 2946, 1732, 1584, 1446, 1373, 1333, 1273, 1200, 1122, 1027, 931, 755, 704 cm^{-1}; *m/z* (%): 424 (2) $[M+NH_4]^+$, 389 (5), 238 (100), 221 (74), 205 (20), 143 (11), 108 (20); HRMS calcd for $C_{20}H_{22}O_4Se$ 424.1022, found 424.1020.

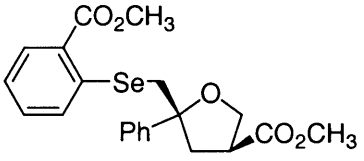
5-(2-Carboxyphenylselanylmethyl)-5-phenyltetrahydrofuran-3-carboxylic acid methyl ester (56d)

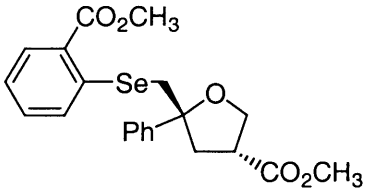


Synthesized from **51** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:1. Yield 79% (30 mg, 0.072 mmol); white solid, m.p.: 146-148 °C; d.r. (*cis*:*trans*) 50:50; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62-2.78 (m, 4H, CH_2), 2.98

(quint, J = 7.6 Hz, 1H, *trans*-CH), 3.21 (d, J = 12.0 Hz, 1H, *cis*-CH_2Se), 3.29-3.39 (m, 1H, *cis*-CH), 3.31 (d, J = 12.0 Hz, 1H, *cis*-CH_2Se), 3.33 (d, J = 12.0 Hz, 1H, *trans*-CH_2Se), 3.37 (d, J = 11.6 Hz, 1H, *trans*-CH_2Se), 3.46 (s, 3H, *cis*-OCH_3), 3.63 (s, 3H, *trans*-OCH_3), 3.94 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 4.05 (t, J = 8.4 Hz, 1H, *trans*-CH_2O), 4.17 (t, J = 7.6 Hz, 1H, *trans*-CH_2O), 4.22 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 7.10-8.10 (m, 18H, Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.9 (CH_2), 39.8 (CH_2Se), 42.8 (CH), 50.9 (OCH_3), 68.4 (CH_2O), 85.9 (C), 123.7 (CH-Ar), 124.0 (CH-Ar), 126.3 (CH-Ar), 126.6 (CH-Ar), 127.4 (CH-Ar), 131.4 (CH-Ar), 132.1 (CH-Ar), 137.9 (C-Ar), 143.1 (C-Ar), 144.3 (C-Ar), 170.4 (O=CAr), 171.8 (C=O); IR (NaCl): ν = 2946, 1732, 1584, 1558, 1462, 1428, 1373, 1256, 1207, 1142, 1033, 741, 703 cm^{-1}; *m/z* (%): 438 (19) $[M+NH_4]^+$, 318 (19), 238 (100), 221 (74), 205 (18), 143 (8), 105 (6), 78 (5); HRMS calcd for $C_{20}H_{20}O_5Se$ 438.0814, found 438.0815.

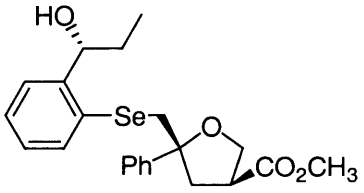
5-(2-Methoxycarbonylphenylselanylmethyl)-5-phenyltetrahydrofuran-3-carboxylic acid methyl ester (56e)

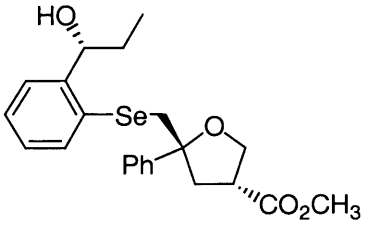




Synthesized from **51** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:2. Yield 79% (31 mg, 0.072 mmol); white solid, m.p.: 140-142 °C; d.r. (*cis*:*trans*) 48:52; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.60-2.80 (m, 2H, CH_2), 2.97 (quint, J = 7.6 Hz, 1H, *trans*-CH), 3.19 (d, J = 11.6 Hz, 1H, *cis*-CH_2Se), 3.29 (d, J = 12.0 Hz, 1H, *cis*-CH_2Se), 3.30 (d, J = 11.6 Hz, 1H, *trans*-CH_2Se), 3.32-3.39 9m, 1H, *cis*-CH), 3.34 (d, J = 11.6 Hz, 1H, *trans*-CH_2Se), 3.46 (s, 3H, *cis*-OCH_3), 3.62 (s, 3H, *trans*-OCH_3), 3.83 (s, 3H, *cis*-OCH_3-Ar), 3.85 (s, 3H, *trans*-OCH_3-Ar), 3.92 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 4.05 (t, J = 8.4 Hz, 1H, *trans*-CH_2O), 4.15 (t, J = 7.6 Hz, 1H, *trans*-CH_2O), 4.20 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 7.05-7.95 (m, 18H, Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.2 (CH_2), 39.3 (CH_2Se), 41.5 (CH), 44.1 (OCH_3-Ar), 52.7 (OCH_3), 69.7 (CH_2O), 86.9 (C), 125.0 (CH-Ar), 125.5 (CH-Ar), 127.8 (CH-Ar), 128.9 (CH-Ar), 129.0 (CH-Ar), 131.8 (CH-Ar), 132.9 (CH-Ar), 138.5 (C-Ar), 144.6 (C-Ar), 145.9 (C-Ar), 167.7 (O=CAr), 173.2 (C=O); IR (NaCl): ν = 3428, 2946, 1735, 1710, 1579, 1458, 1434, 1273, 1253, 1202, 1052, 1027, 740 cm^{-1}; *m/z* (%): 452 (100) $[M+NH_4]^+$, 435 (30), 403 (3), 391 (5); HRMS calcd for $C_{21}H_{22}O_5Se$ 452.0971, found 452.0971.

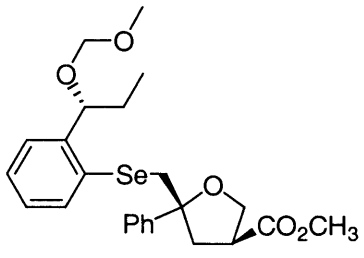
5-{2-[(*S*)-1-Hydroxypropyl]-phenylselanyl}-methyl-5-phenyltetrahydrofuran-3-carboxylic acid methyl ester (56f)

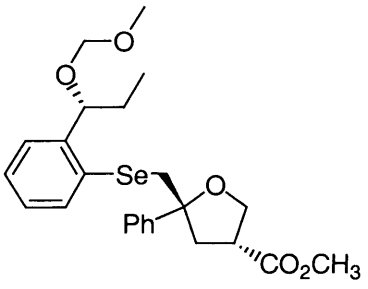




Synthesized from **51** according to GP 1. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 1:2. Yield 78% (37 mg, 0.11mmol), colorless oil; d.r. (*cis*:*trans*) 30:70; $[\alpha]^{23}_{D}$ = -6.71 (c = 0.69, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ =0.85 (t, *J* = 7.2 Hz, 3H, *trans*-CH_3), 0.83 (t, *J* = 7.2 Hz, 3H, *cis*-CH_3), 1.55-1.70 (m, 4H, CH_2CH_3), 2.35-2.41 (m, 1H, *trans*-CH_2), 2.47-2.66 (m, 3H, *cis*-CH_2, *trans*-CH_2), 2.86-3.02 (quint, *J* = 8.4 Hz, 1H, *trans*-CH), 3.25 (d, *J* = 12.4 Hz, 1H, *trans*-CH_2Se), 3.27-3.31 (m, 1H, *cis*-CH), 3.29 (d, *J* = 12.4 Hz, 1H, *trans*-CH_2Se), 3.32 (d, *J* = 12.4 Hz, 1H, *cis*-CH_2Se), 3.38 (d, *J* = 12.0 Hz, 1H, *cis*-CH_2Se), 3.46 (s, 3H, *trans*-OCH_3), 3.62 (s, 3H, *cis*-OCH_3), 3.90 (t, *J* = 8.4 Hz, 1H, *cis*-CH_2O), 4.00-4.11 (m, 2H, *trans*-CH_2O), 4.19 (t, *J* = 8.0 Hz, 1H, *cis*-CH_2O), 4.89 (t, *J* = 6.4 Hz, 2H, CH-Ar), 6.95-7.40 (m, 18H, Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.33 (CH_3), 30.2 (CH_2CH_3), 40.1 (CH_2), 42.8 (CH), 43.9 (CH_2Se), 51.2 (OCH_3), 68.4 (CH_2O), 73.1 (CHOH-Ar), 85.7 (C), 124.2 (CH-Ar), 125.1 (CH-Ar), 126.2 (CH-Ar), 126.8 (CH-Ar), 127.2 (CH-Ar), 127.3 (CH-Ar), 129.0 (C-Ar), 133.1 (CH-Ar), 143.8 (C-Ar), 145.2 (C-Ar), 171.6 (C=O); IR (NaCl): ν = 3478, 2958, 2876, 1736, 1585, 1446, 1200, 1052, 1027, 977, 756, 703 cm^{-1}; *m/z* (%): 433 (1) $[M]^+$, 416 (67), 391 (2), 222 (100), 198 (35); HRMS calcd for $C_{22}H_{26}O_4Se$ 434.0991, found 434.0999.

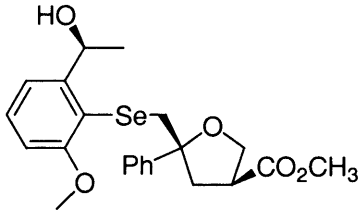
5-{|2-[(*S*)-1-Methoxymethoxypropyl]-phenylselanylmethyl}-5-phenyltetrahydrofuran-3-carboxylic acid methyl ester (56g)

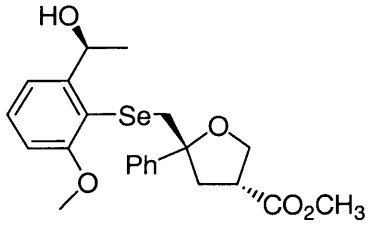




Synthesized from **51** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:1. Yield 41% (18 mg, 0.038 mmol), colorless oil; d.r. (*cis*:*trans*) 44:56; $[\alpha]^{21}_D$ = –81.8 (c = 0.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.6 Hz, 6H, CH_3), 1.55-1.70 (m, 4H, CH_2CH_3), 2.53-2.73 (m, 4H, CH_2), 2.97 (quint, *J* = 7.6 Hz, 1H, *trans*-CH), 3.18 (d, *J* = 12.0 Hz, 1H, *cis*-CH_2Se), 3.29 (d, *J* = 12.0 Hz, 1H, *trans*-CH_2Se), 3.30 (s, 3H, *trans*-OCH_3-Ar), 3.31 (s, 3H, *cis*-OCH_3-Ar), 3.32 (d, *J* = 12.4 Hz, 1H, *trans*-CH_2Se), 3.33-3.38 (m, 1H, *cis*-CH), 3.40 (d, *J* = 12.0 Hz, 1H, *cis*-CH_2Se), 3.48 (s, 3H, *cis*-OCH_3), 3.62 (s, 3H, *trans*-OCH_3), 3.92 (t, *J* = 8.4 Hz, 1H, *cis*-CH_2O), 4.05 (t, *J* = 8.4 Hz, 1H, *trans*-CH_2O), 4.11 (t, *J* = 8.0 Hz, 1H, *trans*-CH_2O), 4.17 (t, *J* = 8.4 Hz, 1H, *cis*-CH_2O), 4.38 (dd, *J* = 3.6, 6.4 Hz, 2H, OCH_2O), 4.45 (dd, *J* = 3.6, 6.8 Hz, 2H, OCH_2O), 4.90 (t, *J* = 7.6 Hz, 1H, *cis*-ArCHOH), 4.92 (t, *J* = 7.6 Hz, 1H, *trans*-ArCHOH), 7.00-7.40 (m, 18H, Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9 (CH_3), 31.0 (CH_2CH_3), 41.1 (CH_2), 41.6 (CH_2Se), 45.3 (CH), 52.3 (OCH_3), 56.0 (OCH_3-Ar), 69.7 (CH_2O), 78.6 (ArCHOH), 87.1 (C), 95.0 (OCH_2O), 125.6 (CH-Ar), 126.9 (CH-Ar), 127.6 (CH-Ar), 127.8 (CH-Ar), 127.9 (CH-Ar), 128.2(C-Ar), 128.7 (CH-Ar), 130.9 (CH-Ar), 134.1 (C-Ar), 144.5 (C-Ar), 173.2 (C=O); IR (NaCl): *ν* = 3377, 2948, 2360, 1737, 1567, 1501, 1439, 1404, 1346, 1240, 1201, 1175, 1102, 1032, 958, 911, 807 cm^{-1}; *m/z* (%): 496 (100) $[M+NH_4]^+$, 447 (55), 417 (86), 358 (91), 340 (32), 312 (26); HRMS calcd for $C_{24}H_{30}O_5SSe$ 496.1597, found 496.1599.

5-{2-[(*S*)1-Hydroxyethyl]-6-methoxy-phenylselanylmethyl}-5-phenyltetrahydrofuran-3-carboxylic acid (56h)

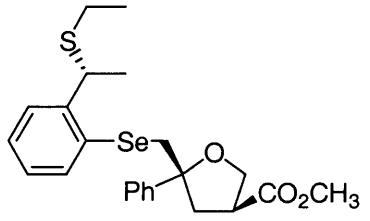


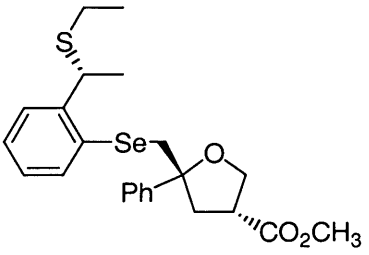


Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:1. Yield 38% (21 mg, 0.047 mmol), colorless oil, d.r. (*cis*:*trans*) 30:70; $[\alpha]^{23}_D$ = +55 (c = 0.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.8 Hz, 3H, *cis*-CH_3), 1.30 (d, *J* = 6.8 Hz, 3H, *trans*-CH_3), 2.30-2.72 (m, 4H, CH_2), 2.94 (quint, *J* = 6.8 Hz, 1H, *trans*-CH), 3.16-3.20 (m, 1H, cis-CH_2-Se), 3.29 (d, *J* = 12.4 Hz, 1H, *cis*-CH_2Se), 3.30-3.38 (m, 1H, *cis*-CH), 3.31-3.34 (m, 1H, *cis*-CH_2Se), 3.35 (d, *J* = 12.8 Hz, 1H, *cis*-CH_2Se), 3.48 (s, 3H, *cis*-OCH_3), 3.62 (s, 3H, *trans*-OCH_3), 3.80 (s, 3H, *trans*-

$ArOCH_3$), 3.81 (s, 3H, *cis*-$ArOCH_3$), 3.96 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 3.98 (t, J = 8.0 Hz, 1H, *trans*-CH_2O), 4.04 (t, J = 8.0 Hz, 1H, *trans*-CH_2O), 4.21 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 5.18 (d, J = 6.4 Hz, 1H, *trans*-ArCHOH), 5.22 (d, J = 6.8 Hz, 1H, *cis*-ArCHOH), 6.60-7.30 (m, 16H, Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (CH_3), 40.0 (CH_2C), 41.8 (CH_2Se), 44.1 (CH), 52.6 (OCH_3), 56.4 (CHOH), 69.7 (CH_2O), 88.0 (CCH_2Se), 109.8 (CH-Ar), 118.2 (CH-Ar), 118.3 (C-Ar), 125.5 (CH-Ar), 127.4 (CH-Ar), 128.5 (CH-Ar), 129.9 (CH-Ar), 130.1 (CH-Ar), 145.4 (C-Ar), 150.6 (C-Ar), 159.7 (C-Ar), 174.0 (C=O); IR (NaCl): ν = 3440, 1730, 1644, 1463, 1260, 1057 cm^{-1}; *m/z* (%): 446 (27) $[M]^+$, 432 (20), 246 (74), 228 (100); HRMS calcd for $C_{22}H_{26}O_5Se$ 446.0967, found 446.0956.

5-{2-[(*R*)-1-Ethylsulfanylethyl]-phenylselanylmethyl}-5-phenyltetrahydrofuran-3-carboxylic acid methyl ester (56i)

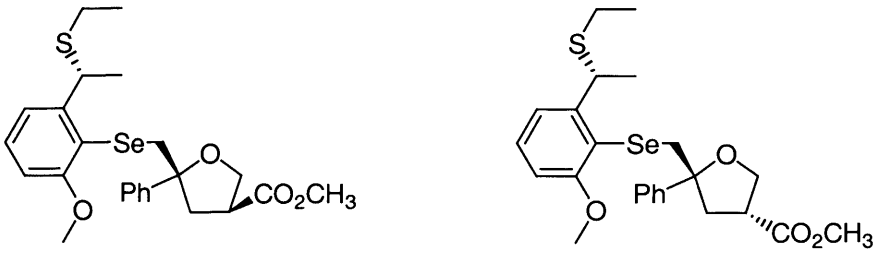




Synthesized from **51** according to GP 1. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 1:2. Yield 40% (26 mg, 0.056 mmol), colorless oil; d.r. (*cis*:*trans*) 33:67; $[\alpha]^{23}_D$ = –8.08 (c = 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, J = 7.2 Hz, 3H, *trans*-CH_3), 1.07 (t, J = 7.2 Hz, 3H, *cis*-CH_3), 1.40 (d, J = 7.2 Hz, 3H, *cis*-CH_3),1.45 (d, J = 7.2 Hz, 3H, *trans*-CH_3), 2.27 (q, J = 7.2 Hz, 1H, CH), 2.50-2.71 (m, 4H, CH_2), 2.97 (q, J = 8.4 Hz, 1H, *trans*-CH), 3.20 (d, J = 12.0 Hz, 1H, *cis*-CH_2Se), 3.30-3.39 (m, 1H, *cis*-CH), 3.31 (d, J = 12.0 Hz, 1H, *trans*-CH_2Se), 3.32 (d, J = 12.0 Hz, 1H, *trans*-CH_2Se), 3.37 (d, J = 12.0 Hz, 1H, *cis*-CH_2Se), 3.48 (s, 3H, *cis*-OCH_3), 3.63 (s, 3H, *trans*-OCH_3), 3.92 (t, J = 8.8 Hz, 1H, *cis*-CH_2O), 4.05 (t, J = 8.8 Hz, 1H, *trans*-CH_2O), 4.13 (t, J = 8.0 Hz, 1H, *trans*-CH_2O), 4.17 (t, J = 8.4 Hz, 1H, *cis*-CH_2O), 4.52 (q, J = 6.8 Hz, 1H, *cis*-ArCH), 4.59 (q, J = 6.8 Hz, 1H, *trans*-ArCH), 6.90-7.40 (m, 18H, Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7 (CH_3CH_2), 21.4 (CH_2CH_3), 24.2 (CH_3), 28.7 (ArCH), 40.4 (CH_2), 42.8 (CH_2Se), 44.0 (CH), 51.1 (OCH_3), 68.4 (CH_2O), 86.1 (C), 124.1 (CH-Ar), 126.0 (CH-Ar), 126.3 (CH-Ar), 126.6 (CH-Ar), 127.3 (CH-Ar), 130.6 (CH-Ar), 132.6 (C-Ar), 143.0 (C-Ar), 144.0 (CH-Ar), 144.5 (C-Ar), 172.4 (C=O); IR (NaCl): ν = 3046, 2966, 2925, 2865, 1737, 1584, 1494, 1446, 1368, 1268, 1199, 1057, 1022, 761, 705 cm^{-1}; *m/z* (%): 482 (18) $[M+NH_4]^+$, 403 (58), 238

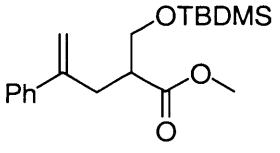
(100), 221 (68), 205 (27), 167 (11), 122 (8); HRMS calcd for $C_{23}H_{28}O_3SSe$ 482.1263, found 482.1270.

5-{2-[(*R*)-1-Ethylsulfanylethyl]-6-methoxy-phenylselanylmethyl}-5-phenyltetrahydrofuran-3-carboxylic acid methyl ester (56j)



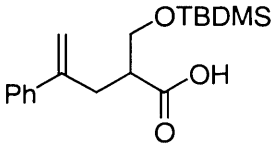
Synthesized from **41** according to GP 1. Purification by flash chromatography on silica gel with ether / petrol ether 1:1. Yield 38% (24 mg, 0.046 mmol), colorless oil; d.r. (*cis*:*trans*) 42:58; $[\alpha]^{23}_D$ = –9.56 (c = 0.126, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.6 Hz, 3H, *cis*-CH_3), 1.10 (t, *J* = 7.6 Hz, 3H, *trans*-CH_3), 1.36 (d, *J* = 6.4 Hz, 6H, CH_3), 1.42 (q, *J* = 6.8 Hz, 4H, CH_2CH_3), 2.47-2.57 (m, 2H, CH_2), 2.67-2.74 (m, 2H, CH_2), 2.95 (quint *J* = 8.4 Hz, 1H, *trans*-CH), 3.20-3.36 (m, 1H, *cis*-CH), 3.49 (s, 3H, *cis*-OCH_3), 3.62 (s, 3H, *trans*-OCH_3), 3.76 (d, *J* = 12.0 Hz, 2H, CH_2Se), 3.77 (s, 3H, *trans*-OCH_3-Ar), 3.80 (d, *J* = 12.8 Hz, 2H, CH_2Se), 3.81 (s, 3H, *cis*-OCH_3-Ar), 3.91 (t, *J* = 8.4 Hz, 1H, *cis*-CH_2O), 4.03 (t, *J* = 8.4 Hz, 1H, *trans*-CH_2O), 4.11 (t, *J* = 8.0 Hz, 1H, *trans*-CH_2O), 4.20 (t, *J* = 8.0 Hz, 1H, *cis*-CH_2O), 4.87 (q, *J* = 6.8 Hz, 2H, ArCH), 6.60-7.40 (m, 18H, Ar); ***trans***: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (CH_3CH_2), 23.1 (CH_3) 25.6 (CH_2), 40.9 (ArCH), 43.4 (CH_2C), 44.1 (CH), 45.6 (CH_2Se), 52.5 (OCH_3), 56.4 ($ArOCH_3$), 69.7 (CH_2O), 87.3 (C), 109.3 (CH-Ar), 119.9 (C-Ar), 125.5 (CH-Ar), 127.6 (CH-Ar), 128.6 (CH-Ar), 128.7 (CH-Ar), 129.8 (CH-Ar), 144.2 (C-Ar), 146.5 (C-Ar), 159.1 (C-Ar), 173.8 (C=O); IR (NaCl): ν = 3418, 2950, 1736, 1568, 1464, 1373, 1261, 1202, 1050, 1022, 786, 761, 730, 704 cm^{-1}; *m/z* (%): 511 (15) $[M+NH_4]^+$, 433 (34), 275 (23), 238 (100), 221 (71), 205 (30), 152 (18); HRMS calcd for $C_{24}H_{30}O_4SSe$ 511.1030, found 511.1053.

2-(*tert.*-Butyl-dimethylsilanyloxymethyl)-4-phenylpent-4-enoic acid methyl ester(57)



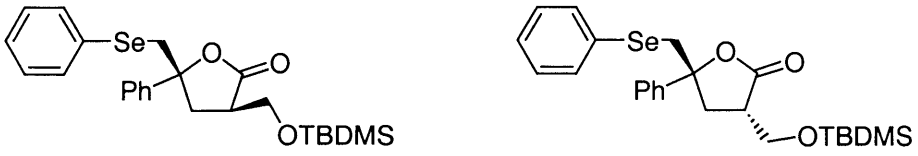
Compound **51** (250 mg, 1.14 mmol) was dissolved in DMF (6.5 mL) and treated with *tert.*-butyldimethylsilyl chloride (196 mg, 1.3 mmol) and imidazole (176 mg, 2.6 mmol) and stirred at rt overnight. The mixture was diluted with diethyl ether (25 mL) and washed with sat. aq. NaCl. The organic layer was dried with $MgSO_4$ and after evaporation of the solvent the crude product was purified by flash chromatography on silica gel using *tert.*-butyl methyl ether:petrol ether (1:4) as eluent. The product (yellow oil) was isolated in 89% yield (340 mg, 1.02 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6H, $Si(CH_3)_2$), 0.85 (s, 9H, $C(CH_3)_3$), 2.65-2.75 (m, 1H, CH), 2.75-2.88 (m, 2H, CH_2), 3.60 (s, 3H, OCH_3), 3.64-3.78 (m, 2H, CH_2O), 5.03 (d, *J* = 1.2 Hz, 1H, $=CH_2$), 5.22 (d, *J* = 0.8 Hz, 1H, $=CH_2$), 7.23-7.40 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = -0.50 ($SiMe_2$), 18.6 (CMe_3), 26.1 $C(CH_3)_3$), 34.3 (CH_2), 47.4 (CH), 51.8 (OCH_3), 63.7 (CH_2O), 114.9 ($=CH_2$), 126.6 (CH-Ar), 128.0 (CH-Ar), 128.8 (CH-Ar), 140.7 (C), 146.0 (C-Ar), 174.9 (C=O); IR (thin film on NaCl): ν = 3420, 2954, 2857, 1739, 1629, 1495, 1472, 1435, 1387, 1361, 1256, 1205, 1169, 1106, 1006, 901, 837, 777, 707 cm^{-1}; *m/z* (%): 335 (100) $[M+H]^+$, 277 (11), 245 (4), 220 (3), 203 (9), 159 (2), 132 (2), 106 (3), 91 (3), 76 (2), 58 (2), 52 (19), 44 (2); HRMS calcd for $C_{19}H_{30}O_3Si$ 335.2042, found 335.2040.

2-(*tert.*butyl dimethylsilanyloxymethyl)-4-phenylpent-4-enoic acid(58)



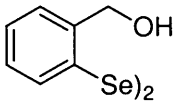
Synthesized from **57** according to GP 3. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 1:4. Yield 59%, (150 mg, 0.47 mmol); yellow solid; m.p.: 46-48 °C; The side product recovered from this reaction was **41** (30%, 49 mg, 0.24 mmol). m.p.: 46-48 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6H, $SiCH_3)_2$), 0.85 (s, 9H, $CH_3)_3$), 2.62-2.79 (m, 2H, CH_2), 2.91 (dd, *J* = 7.0, 14.4 Hz, 1H, CH), 3.75 (d, *J* = 5.6 Hz, 2H, CH_2O), 5.13 (s, 1H, $=CH_2$), 5.32 (s, 1H, $=CH_2$), 7.22-7.42 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.00 ($SiCH_3)_2$), 17.1 ($CCH_3)_3$), 24.7 ($CCH_3)_3$), 32.5 (CH_2), 45.4 (CH), 61.8 (CH_2O), 113.7 ($C=CH_2$), 125.2 (CH-Ar), 126.7 (CH-Ar), 127.4 (CH-Ar), 139.1 ($C=CH_2$), 144.2 (C-Ar), 178.7 (C=O); IR (thin film on NaCl): ν = 3386, 2955, 1709, 1638, 1470, 1256, 1110, 835, 777 cm^{-1}; *m/z* (%): 321 (58) $[M+H]^+$, 263 (30), 245 (4), 224 (5), 189 (3), 171 (2), 143 (3), 118 (2), 91 (5), 75 (2); HRMS calcd for $C_{18}H_{28}O_3Si$ 321.1886, found 321.1882.

3-(*tert.* butyl dimethylsilanyloxymethyl)-5-phenyl-5-phenylselanylmethyl-dihydrofuran-2-one (59b)



Synthesized from **58** according to GP1. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 1:4. Yield 24%, (18 mg, 0.04 mmol); white solid; m.p.: 41-43 °C; d.r. (*cis*:*trans*) 68:32; ^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.85 (d, *J* = 3.2 Hz, 6H, *trans*-$SiCH_3)_2$), 0.00 (d, *J* = 3.2 Hz, 6H, *cis*-$SiCH_3)_2$), 0.60 (s, 9H, *trans*-$CH_3)_3$), 0.80 (s, 9H, *cis*-$CH_3)_3$), 2.52-2.75 (m, 5H, CH_2, *cis*-CH), 3.05-3.13 (m, 1H, *trans*-CH), 3.37 (d, *J* = 12.8 Hz, 2H, CH_2Se), 3.46 (d, *J* = 12.8 Hz, 2H CH_2Se), 3.63 (dd, J = 3.2, 10.0 Hz, 1H, *trans*-CH_2OSi), 3.72 (dd, *J* = 3.2, 10.4 Hz, 1H, *cis*-CH_2OSi), 3.80 (dd, *J* = 4.8, 10.0 Hz, 1H, *trans*-CH_2OSi), 3.91 (dd, *J* = 4.4, 10.0 Hz, 1H, *cis*-CH_2OSi), 7.10-7.50 (m, 20H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.00 $(SiCH_3)_2$), 17.3 $(CCH_3)_3$), 24.8 $(CCH_3)_3$), 35.7 (CH_2), 40.1 (CH_2Se), 42.1 (CH), 59.8 (CH_2OSi), 85.2 (C), 123.6 (CH-Ar), 124.0 (CH-Ar), 126.2 (CH-Ar), 127.1 (CH-Ar), 127.5 (CH-Ar), 128.2 (CH-Ar), 132.2 (CH-Ar), 141.1 (C-Ar), 175.0 (C=O); IR (thin film on NaCl): ν = 3443, 2976, 2855, 1778, 1649, 1463, 1258, 1112, 740 cm^{-1}; *m/z* (%): 477 (35) $[M+H]^+$, 419 (7), 338 (84), 321 (100), 263 (23), 222 (36), 206 (23), 164 (15), 132 (44), 119 (37), 91 (22), 78 (13); HRMS calcd for $C_{24}H_{32}O_3SeSi$ 477.1364, found 477.1365.

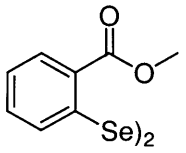
2,2'-diselenobisbenzyl alcohol (60)



Synthesized from 2-iodo benzyl alcohol according to the procedure of reference[40] and purified by flash chromatography with the eluent ethylacetate/petrol (1:4) to obtain pale yellow solid with 46 % yield (1.6g, 4.30 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 4.70 (s, 4H, CH_2OH), 7.20 (t, *J* = 7.6 Hz, 2H, CH-Ar), 7.30 (t, *J* = 7.2 Hz, 2H, CH-Ar), 7.68 (d, *J* = 7.6 Hz, 4H, CH-Ar).

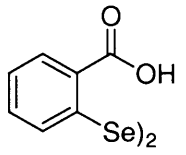
2,2'-diselenobisbenzoic acid methyl ester (61)



Synthesized from **65** according to the reference[40] and purified by flash chromatography with the eluent ethylacetate/petrol (1:10) to obtain pale yellow solid with 85 % yield (378 mg, 0.88 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 3.92 (s, 6H, OCH_3), 7.17 (t, *J* = 7.6 Hz, 2H, CH-Ar), 7.25 (dt, *J* = 1.2, 8.0 Hz, 2H, CH-Ar), 7.73 (d, *J* = 8.0 Hz, 2H, CH-Ar), 7.97 (dd, *J* = 1.2, 8.0 Hz, 2H, CH-Ar).

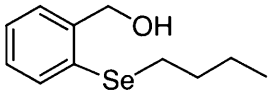
2,2'-diselenobisbenzoic acid (62)



Synthesized from **61** according to GP 3. Pure product was pale yellow solid with 96 % yield (134 mg, 0.33 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 7.42 (t, *J* = 8.0 Hz, 2H, CH-Ar), 7.56 (t, *J* = 7.6 Hz, 2H, CH-Ar), 8.06 (d, *J* = 8.0 Hz, 4H, CH-Ar).

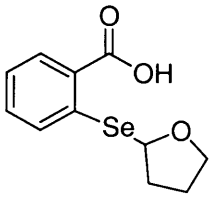
(2-Butylselanyl-phenyl)-methanol (63)



Synthesized from 2-iodo benzyl alcohol in traces.

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 0.84 (t, *J* = 7.2 Hz, 3H, CH_3), 1.36 (q, *J* = 7.6 Hz, 2H, CH_2), 1.59 (q, *J* = 7.6 Hz 2H, CH2), 2.84 (t, *J* = 7.6 Hz, 2H, CH_2Se), 4.70 (s, 2H, CH_2OH), 7.10-7.22 (m, 2H, CH-Ar), 7.31 (dd, *J* = 1.2, 7.2 Hz, 1H, CH-Ar), 7.44 (dd, *J* = 1.2, 7.6 Hz, 1H, CH-Ar).

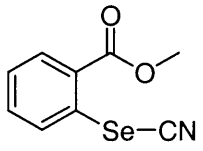
2-(Tetrahydrofuran-2-ylselanyl)-benzoic acid (64)



Synthesized from 2-iodo benzoic acid. Purified by flash chromatography with the eluent ethylacetate/petrol (1:10) to obtain pale yellow oil with 15 % yield (325 mg, 1.2 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.89 (t, *J* = 6.8 Hz, 2H, CH_2), 2.00-2.10 (m, 1H, CH_2CH), 2.17-2.27 (m, 1H, CH_2CH), 3.85-3.99 (m, 2H, OCH_2), 5.18 (dd, *J* = 6.0, 8.4 Hz, 1H, CHSe), 7.39 (t, *J* = 7.6 Hz, 2H, CH-Ar), 7.49 (t, *J* = 7. Hz, 1H, CH-Ar), 7.91 (dd, *J* = 1.2, 7.2 Hz, 1H, CH-Ar).

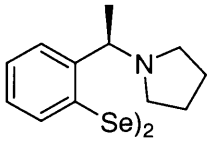
2-Selenocyanato-benzoic acid methyl ester (65)



Synthesized according to the reference[40] and purified by flash chromatography with the eluent ethylacetate/petro (1:4) to obtain orange solid with 43 % yield (360 mg, 1.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 3.93 (s, 3H, OCH_3), 7.37 (dt, *J* = 0.8, 8.0 Hz, 1H, CH-Ar), 7.55 (t, *J* = 1.6, 8.4 Hz, 1H, CH-Ar), 7.98 (d, *J* = 8.0 Hz, 1H, CH-Ar), 8.05 (dd, *J* = 1.2, 8.0 Hz, 1H, CH-Ar).

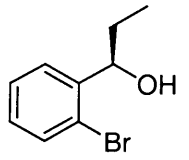
(R, R)-Bis{2-[1-(pyrrolidin-1-yl)ethyl]phenyl}diselenide (66)



Synthesized from **69** according to the reference[45] and purified by flash chromatography with the eluent aceton/petrol (1:5) to obtain orange solid with 45 % yield (379 mg, 1.04 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.44 (d, *J* = 6.6 Hz, 6H, CH_3), 1.80 (m, 8H, CH_2), 2.58 (m, 8H, CH_2N), 3.74 (q, *J* = 6.6 Hz, 2H, CH), 7.06 (t, *J* = 7.5 Hz, 2H, CH-Ar), 7.13 (t, *J* = 7.2 Hz, 2H, CH-Ar), 7.23 (d, *J* = 7.5 Hz, 2H, CH-Ar), 7.79 (d, *J* = 7.8 Hz, 2H, CH-Ar).

(S)-(-)-(2-Bromo phenyl)-propan-1-ol (67)

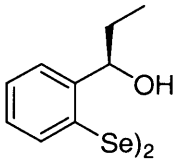


Synthesized according to the reference[19,48] and purified by flash chromatography with the eluent diethyl ether/petrol (1:2) to obtain colourless oil with 99% yield (1.94 g, 9.02 mmol) and 97 % *ee*.

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 0.90 (t, *J* = 7.2 Hz, 3H, CH_3), 1.52-1.79 (m, 2H, CH_2), 2.74 (s, 1H, OH), 4.90 (dd, *J* = 4.8, 7.6 Hz, 1H, CH), 7.01 (dt, *J* = 1.6, 8.0 Hz, 1H, CH-Ar), 7.22 (t, *J* = 7.6 Hz, 1H, CH-Ar), 7.38-7.45 (m, 2H, CH-Ar).

Seperation of the enantiomers on the GC: 90 °C-160 °C, slope 3 °C/min, 90kpa.

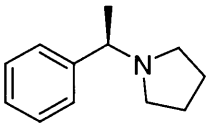
(S,S)-Bis-[2-(1-hydroxypropyl)phenyl]-diselenide(68)



Synthesized from **67** according to the reference[19,48] and purified by flash chromatography with the eluent diethyl ether/petrol (1:2) to obtain yellow solid with 46% yield (463 mg, 1.08 mmol).

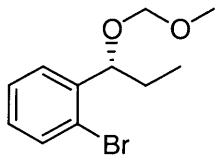
^{1}H NMR (400 MHz, $CDCl_3$,): δ = 0.75 (t, *J* = 7.2 Hz, 3H, CH_3), 1.53-1.63 (m, 2H, CH_2), 4.68 (t, *J* = 6.8 Hz, 1H, CH), 7.13 (dt, *J* = 1.2, 7.6 Hz, 1H, CH-Ar), 7.28 (dt, *J* = 1.2, 7.6 Hz, 1H, CH-Ar), 7.38 (dd, *J* = 1.2, 7.6 Hz, 1H, CH-Ar), 7.69 (dd, *J* = 1.2, 7.6 Hz, 1H, CH-Ar).

(R) 1-[(Pyrrolidin-1-yl) ethyl] benzene (69)



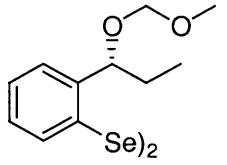
^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.43 (d, *J* = 6.8 Hz, 3H, CH_3), 1.72-1.83 (m, 4H, 2xCH_2), 2.33-2.42 (m, 2H, CH_2N), 2.52-2.62 (m, 2H, CH_2N), 3.19 (q, *J* = 6.8 Hz, 1H, CH), 7.20-7.40 (m, 5H, CH-Ar).

(S)-1-Bromo-2-(1-methoxymethoxypropyl)-benzene (70)



Synthesized from **67** according to the reference[19] and purified by flash chromatography with eluent diethyl ether/petrol (1:20) to obtain colourless oil with 67 % yield (4.07 g, 15.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$,): δ = 0.94 (t, *J* = 7.2 Hz, 3H, CH_3), 1.60-1.83 (m, 2H, CH_2), 3.34 (s, 3H, OCH_3), 4.54 (d, *J* = 6.7 Hz, 1H, OCH_2O), 4.57 (d, *J* = 7.4 Hz, 1H, OCH_2O), 4.95 (dd, *J* = 4.0, 7.6 Hz, 1H, CH), 7.06 (dt, *J* = 1.6, 7.6 Hz, 1H, CH-Ar), 7.27 (dt, *J* = 0.8, 7.6 Hz, 1H, CH-Ar), 7.44 (dd, *J* = 1.2, 8.4 Hz, 1H, CH-Ar), 7.47 (dd, *J* = 1.2, 8.0 Hz, 1H, CH-Ar).

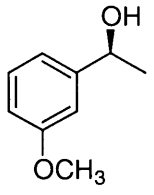
(S,S)-Bis-[2-(1-methoxymethoxypropyl)phenyl] diselenide (71)



Synthesized from **70** according to the reference[19] and purified by flash chromatography with the eluent diethyl ether/petrol (1:10) to obtain deep yellow oil with 59 % yield (1.54 g, 2.98 mmol)

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 0.90 (t, *J* = 7.2 Hz, 3H, CH_3), 1.62-1.84 (m, 2H, CH_2), 3.32 (s, 3H, OCH_3), 4.42 (d, *J* = 6.4 Hz, 1H, OCH_2O), 4.49 (d, *J* = 6.4 Hz, 1H, OCH_2O), 4.88 (dd, *J* = 5.2, 8.0 Hz, 1H, CH), 6.98 (dt, *J* = 0.8, 7.6 Hz, 1H, CH-Ar), 7.17 (dt, *J* = 0.8, 7.6 Hz, 1H, CH-Ar), 7.25 (dd, *J* = 1.2, 7.6 Hz, 1H, CH-Ar), 7.62 (dd, *J* = 0.8, 7.6 Hz, 1H, CH-Ar).

(S)-1-(3-Methoxyphenyl)ethanol (72)

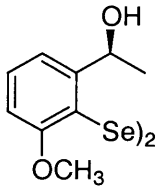


Synthesized according to the GP 4 and purified by flash chromatography with the eluent ethylacetate/petrol (1:4) to obtain colourless oil with 65% yield (3.23 g, 21.4 mmol) and 96 % *ee*.

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.38 (d, *J* = 6.4 Hz, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.75 (q, *J* = 6.4 Hz, 1H, CH), 6.72 (dd, *J* = 1.6, 8.0 Hz, 1H, CH-Ar), 6.84 (d, *J* = 6.4 Hz, 2H, CH-Ar), 7.17 (t, *J* = 8.0 Hz, 1H, CH-Ar).

Separation of the enantiomers on the HPLC-conditions: Chiracel OD-H, flow rate: 0.5 ml•min^{-1}, 2-propanol:n-hexane 10:90, 25°C, $R_f(S)$ = 56.6 min, $R_f(R)$ = 64.3 min.

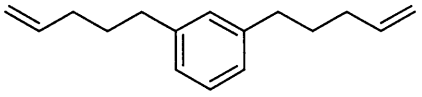
(S,S)-Bis[2-(1-hydroxyethyl)-6-methoxyphenyl]diselenide (73)



Synthesized from **72** according to the reference[19] and purified by flash chromatography with the eluent ethylacetate/petrol (1:4) to obtain orange solid with 54% yield (966 mg, 2.1 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.26 (d, *J* = 6.5 Hz, 6H, CH_3), 3.83 (s, 6H, OCH_3), 5.06 (q, *J* = 6.5 Hz, 2H, CH), 6.84 (d, *J* = 8.0 Hz, 2H, CH-Ar), 7.18 (d, *J* = 7.8 Hz, 2H, CH-Ar), 7.36 (t, *J* = 8.0 Hz, 2H, CH-Ar).

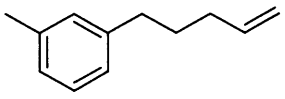
1,3-Bis(4-pentenyl)benzene (75)



Synthesized according to the reference[49] and purified by kugelrohr to obtain colourless oil with 44% yield (615 mg, 2.87 mmol). A side product from this reaction was **76** (colourless oil) formed with 38% yield (397 mg, 2.48 mmol)

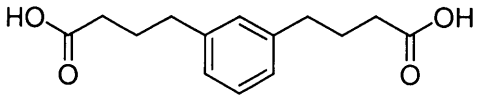
^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.58-1.69 (m, 4H, CH_2), 1.97-2.06 (m, 4H, CH_2), 2.47-2.56 (m, 4H, CH_2), 4.90 (d, *J* = 10.0 Hz, 2H, =CH_2), 4.92 (d, *J* = 6.0 Hz, 2H, =CH_2), 5.70-5.84 (m, 2H, -CH=), 6.88-6.96 (m, 3H, CH-Ar), 7.05-7.14 (m, 1H, CH-Ar).

1-Methyl-3-pent-4-enyl-benzene (76)[49]



^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.58-1.70 (m, 2H, CH_2), 1.97-2.08 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.48-2.58 (m, 2H, CH_2), 4.90 (d, *J* = 10.0 Hz, 1H, =CH_2), 4.95 (d, *J* = 17.6 Hz, 1H, =CH_2), 5.72-5.84 (m, 1H, -CH=), 6.88-6.96 (m, 3H, CH-Ar), 7.05-7.14 (m, 1H, CH-Ar).

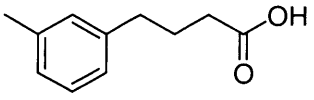
1,3-Bis(3-carboxypropyl)benzene (77)



Synthesized from **75** according to the reference[49] to obtain white solid with 65% yield (453 mg, 1.81 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.71-1.84 (m, 4H, CH_2), 2.15-2.25 (m, 4H, CH_2), 2.45-2.57 (m, 4H, CH_2), 6.84-7.13 (m, 4H, CH-Ar).

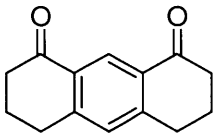
4-*m*-Tolyl-butyric acid (78)



Synthesized from **76** according to the reference[49] to obtain white solid with 58% yield (257 mg, 1.44 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.71-1.84 (m, 2H, CH_2), 2.15-2.23 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.45-2.57 (m, 2H, CH_2), 6.84-7.13 (m, 4H, CH-Ar).

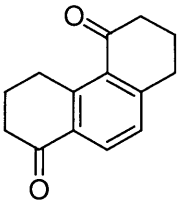
3, 4, 5, 6-Tetrahydro-1 (2H), 8(7H)-anthracenedione (79)



Synthesized from **77** according to the reference[49] and purified by flash chromatography with the eluent ethylacetate/petrol (1:4) to obtain white solid with 17% yield (146 mg, 0.68 mmol). The main side product from this reaction was compound **80** formed in 40 % yield.

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 2.02-2.16 (m, 4H, CH_2), 2.60 (t, *J* = 6.0 Hz, 4H, CH_2C), 2.91 (t, *J* = 6.0 Hz, 4H, CH_2C=O), 7.09 (s, 1H, CH-Ar), 8.63 (s, 1H, CH-Ar).

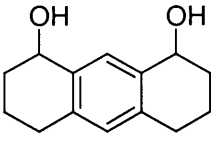
2, 3, 4, 5, 7, 8-Hexahydro-phenanthrene-1,6-dione (80)[50]



Purification by flash chromatography with the eluent ethylacetate:petrol 1:4 Yield white solid with 40 % yield (342 mg, 1.60 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.95-2.09 (m, 4H, CH_2), 2.56 (t, *J* = 6.4 Hz, 2H, CH_2C), 2.62 (t, *J* = 6.4 Hz, 2H, CH_2C), 2.93 (t, *J* = 6.0 Hz, 2H, CH_2C=O), 3.32 (t, *J* = 6.0 Hz, 2H, CH_2C=O), 7.15 (d, *J* = 8.0 Hz, 1H, CH-Ar), 8.09 (d, *J* = 8.4 Hz, 1H, CH-Ar).

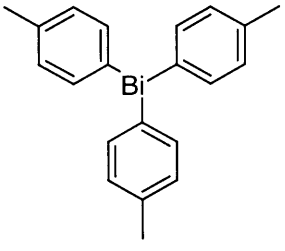
1, 2, 3, 4, 5, 6, 7, 8-Octahydroanthracene-1,8-diol (81)



Synthesized from **79** according to the GP 5 to obtain white solid with 97 % yield (69 mg, 0.32 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.60-1.75 (m, 4H, CH_2), 1.78-1.98 (m, 4H, CH_2C), 2.56-2.78 (m, 4H, C*H*$_2$CH), 4.71 (t, *J* = 4.4 Hz, 2H, CH), 6.80 (s, 1H, CH-Ar),7.43 (s, 1H, CH-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0 (CH_2), 28.8 (*C*H_2-C), 32.4 (*C*H_2-CH), 67.4 (CH), 128.5 (CH-Ar), 129.1 (C-Ar), 136.0 (CH-Ar), 136.5 (C-Ar).

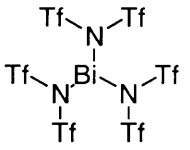
Tri-*p*-tolyl-bismuthane (82)



Synthesized according to the reference[51] to obtain yellow solid with 33 % yield (3.72 g, 7.72 mmol).

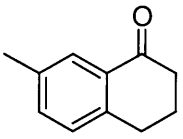
^{1}H NMR (400 MHz, $CDCl_3$,): δ = 2.24 (s, 9H, CH_3), 7.11 (d, *J* = 7.6 Hz, 6H, CH-Ar), 7.54 (d, *J* = 7.6 Hz, 6H, CH-Ar).

Bismuth (III) bis(trifluoromethanesulfonyl)amide (83)



Synthesized from **82** according to the reference[52] to obtain light brown solid with 20% yield (107 mg, 0.10 mmol). ^{13}C-NMR (100 MHz, $CDCl_3$,): δ = 120 ppm (quad., $^1J_{13C/19F}$ = 321 Hz).

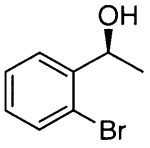
7-Methyl-3, 4-dihydro-2H-naphtalen-1-one (84)



Synthesized from **78** according to the reference[53] and purified by flash chromatography with the eluent ethyl acetate:petrol 1:4 to obtain pale yellow solid with 85 % yield (153 mg, 0.95 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.88-2.10 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.56 (t, *J* = 6.4 Hz, 2H, CH_2C), 2.85 (t, *J* = 6.0 Hz, 2H, CH_2C=O), 6.99 (s, 1H, CH-Ar), 7.04 (d, *J* = 8.0 Hz, 1H, CH-Ar), 7.86 (d, *J* = 8.0 Hz, 1H, CH-Ar).

(S)-2-(2-Bromophenyl) ethanol (85)

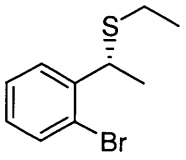


Synthesized according to the GP 4 and purified by flash chromatography with the eluent ethylacetate/petrol (1:5) to obtain colourless oil with 87 % yield (4.33 g, 0.022 mmol) and 96 % *ee*.

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.41 (d, *J* = 6.8 Hz, 3H, CH_3), 5.18 (q, *J* = 6.4 Hz, 1H, CH), 7.05 (dt, *J* = 1.6, 7.6 Hz, 1H, CH-Ar), 7.27 (dt, *J* = 0.8, 7.6 Hz, 1H, CH-Ar), 7.44 (dd, *J* = 1.2, 8.0 Hz, 1H, CH-Ar), 7.52 (dd, *J* = 1.6, 8.0 Hz, 1H, CH-Ar).

Seperation of the enantiomers on the HPLC-conditions: Chiracel OD-H, flow rate: 0.5 ml.min^{-1}, 2-propanol:n-hexane 1:99, 25°C, $R_f(S)$ = 25.4 min, $R_f(R)$ = 28.5 min.

(R) 1- Bromo-2(1-ethylsulfanylethyl)-benzene (86)

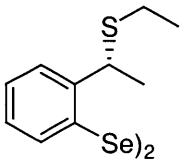


Synthesized from **85** according to GP 6 and purified by flash chromatography on silica gel with the eluent petrol to obtain colourless oil with 65% yield (1.59 g, 6.44 mmol) and 92 % *ee*.

Seperation of the enantiomers on the HPLC-conditions: Chiracel OD-H, flow rate: 0.5 ml•min^{-1}, 2-propanol:n-hexane 2:98, 25°C, R_f(major) = 8.20 min, R_f(minor) = 9.29 min.

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.12 (t, *J* = 7.4 Hz, 3H, CH_3), 1.43 (d, *J* = 7.2 Hz, 3H, CH_3), 2.20-2.38 (m, 2H, CH_2), 4.49 (q, *J* = 7.2 Hz, 1H, CH), 6.99 (dt, *J* = 1.6, 8.0 Hz, 1H, CH-Ar), 7.23 (t, *J* = 8.0 Hz, 1H, CH-Ar), 7.43 (d, *J* = 8.0 Hz, 1H, CH-Ar), 7.54 (dd, *J* = 1.6, 8.0 Hz, 1H, CH-Ar).

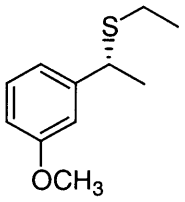
(R, R)-Bis-[2-(1-ethylsulphanyl)-ethylphenyl]diselenide (87)



Synthesized from **86** according to GP 7 and purified by flash chromatography on silica gel with the eluent diethyl ether/petrol (1:20) to obtain deep yellow oil with 66% yield (659 mg, 1.35 mmol).

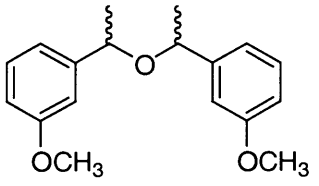
^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.12 (t, *J* = 7.4 Hz, 3H, CH_3), 1.45 (d, *J* = 7.2 Hz, 3H, CH_3), 2.25-2.38 (m, 2H, CH_2), 4.42 (q, *J* = 6.8 Hz, 1H, CH), 7.04 (dt, *J* = 1.2, 7.6 Hz, 1H, CH-Ar), 7.17 (dt, *J* = 1.6, 8.0 Hz, 1H, CH-Ar), 7.34 (dd, *J* = 1.2, 8.0 Hz, 1H, CH-Ar), 7.68 (dd, *J* = 1.2, 8.0 Hz, 1H, CH-Ar).

(*R*)-1-(1-Ethylsulfanylethyl)-3-methoxybenzene (88)



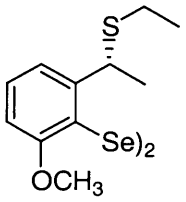
Synthesized from **72** according to GP 6. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:4. Yield 16%, (310 mg, 1.58 mmol); colorless oil; A side product, bis(1-methoxy-3-(1-methoxyethyl)benzene), was also isolated in 28% yield as a colorless oil. HPLC-conditions: Chiracel OD-H, flow rate: 0.5 ml•min^{-1}, 2-propanol:n-hexane 1:99, 25°C, R_f(*R*) = 11.2 min, R_f(*S*) = 12.9 min; e.r. 96:4; $[\alpha]^{21}_D$ = –84.8 (c = 0.125, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.6 Hz, 3H, CH_3), 1.58 (d, *J* = 7.2 Hz, 3H, CH_3), 2.37 (q, *J* = 5.2 Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.99 (q, *J* = 7.2 Hz, 1H, CH), 6.78 (d, *J* = 8.0 Hz, 1H, Ar), 6.95 (d, *J* = 10.4 Hz, 2H, Ar), 7.24(dd, *J* = 8.0 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (CH_3CH_2), 23.0 (CH_3), 25.6 (CH_2), 44.1 (CH), 55.6 (OCH_3), 112.6 (CH-Ar), 113.2 (CH-Ar), 120.1 (CH-Ar), 129.8 (CH-Ar), 146.3 (C-Ar), 160.1 (C-Ar); IR (NaCl): ν = 2967, 2917, 1600, 1485, 1454, 1369, 1318, 1259, 1203, 1154, 1044, 874, 781, 701 cm^{-1}; *m/z* (%): 197 (56) $[M]^+$, 152 (100), 135 (25), 72 (12); HRMS calcd for $C_{11}H_{16}OS$ 197.0995, found 197.0994.

Bis-1-(3-methoxyphenyl)diethyl ether (89)



$[\alpha]^{23}_D$= +44.63 (c = 2.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 6.4 Hz, 3H, CH_3), 1.51 (d, *J* = 6.4 Hz, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.28 (q, *J* = 6.4 Hz, 1H, CH), 4.56 (q, *J* = 6.4 Hz, 1H, CH), 6.78-6.93 (m, 6H, Ar), 7.21-7.35 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (CH_3), 25.1 (CH_3) 55.6 (CH), 75.0 (OCH_3), 111.7 (CH-Ar), 112.8 (CH-Ar), 119.0 (CH-Ar), 129.9 (CH-Ar), 146.4 (C-Ar), 160.2 (C-Ar); IR (NaCl): ν = 2972, 2925, 2825, 1723, 1601, 1579, 1486, 1455, 1433, 1368, 1317, 1282, 1257, 1158, 1093, 1047, 956, 874, 782, 700 cm^{-1}; *m/z* (%): 304 (49) $[M+NH_4]^+$, 286 (9), 269 (12), 168 (8), 152 (100), 136 (18), 74 (11); HRMS calcd for $C_{18}H_{22}O_3$ 304.1907, found 304.1903.

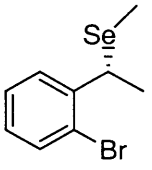
(*R*,*R*)-Bis [2-(1-Ethylsulfanylethyl)-6-methoxyphenyl] diselenide (90)



Synthesized according to GP 7. Purifiaction by flash chromatography on silica gel with the eluent diethyl ether:petrol ether 1:10. Yield 78 % (142 mg, 0.26 mmol), yellow oil.

$[\alpha]^{21}_D$ = –173.8 (c = 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.6 Hz, 6H, CH_3), 1.22 (d, *J* = 6.8 Hz, 6H, CH_3), 2.23 (q, *J* = 7.2 Hz, 4H, CH_2), 3.65 (s, 6H, OCH_3), 4.52 (q, *J* = 6.8 Hz, 2H, CH), 6.67 (d, *J* = 8.0 Hz, 2H, Ar), 7.01 (d, *J* = 7.6 Hz, 2H, Ar) 7.18 (dd, *J* = 8.0, 10.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_3CH_2), 20.9 (CH_2), 24.1 (CH_3), 42.0 (CH), 55.0 (OCH_3), 108.0 (CH-Ar), 118.0 (CH-Ar), 120.6 (CH-Ar), 129.4 (C-Ar), 148.0 (C-Ar), 159.0 (C-Ar); IR (NaCl): ν = 3427, 2970, 2920, 1562, 1462, 1262, 1045, 781, 650 cm^{-1}; *m/z* (%): 573 (7) $[M+NH_4]^+$, 275 (58), 213 (100), 181 (10), 151 (20), 135 (17), 119 (8), 100 (15); HRMS calcd for $C_{22}H_{30}O_2S_2Se_2$ 572.9910, found 572.9905.

(R)-1-Bromo-2-(1-methylselnaylethyl)-benzene(91)

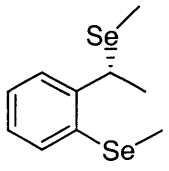


In a dry flask the alcohol **85** (650 mg, 3.23 mmol), potassium hydroxide (362 mg, 6.46 mmol) and tosylchloride (760 mg, 3.88 mmol) were dissolved in THF and this reaction mixture was stirred at–20 °C for 24 hr. The solvent was evaporated and crude tosylated product was obtained as white solid.

In another dry flask sodiumborohydride (306 mg, 8.1 mmol) was dissolved in ethanol (20 ml) and this reaction mixture was at 0 °C dropswise treated with dimethyldiselenide (305 mg, 1.62 mmol). The reaction mixture changed from yellow solution to colourless solution. This reaction mixture stirred from 0 °C to rt for approximately 20 mins. This solution was at -20 °C dropwise added to the tosylated product and the reaction mixture was stirred for 24 hr from -20 °C to rt. The reaction was quenched with water and extracted with ether (3x 15 ml). The collected organic extracts were dried over magnesium sulphate and the solvent was

evaporated to produce pale yellow oil which was further purified by flash chromatography on silica gel with the eluent petrol to obtain colourless oil with 56 % yield (501 mg, 1.80 mmol). ^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.63 (d, *J* = 7.2 Hz, 3H, CH_3), 1.82 (s, 3H, $SeCH_3$), 4.56 (q, *J* = 7.2 Hz, 1H, CH), 6.99 (dt, *J* = 1.6, 7.6 Hz, 1H, CH-Ar), 7.23 (dt, *J* = 1.2, 7.6 Hz, 1H, CH-Ar), 7.41 (dd, *J* = 1.6, 8.0 Hz, 1H, CH-Ar), 7.45 (dd, *J* = 1.2, 8.0 Hz, 1H, CH-Ar).

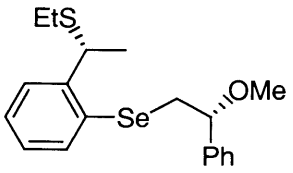
(R) 1-Methylselanyl-2-(1-methylselanylethyl)-benzene (92)



In dry atmosphere at –78°C compound **91** (150 mg, 0.54 mmol) was slowly treated with *t*-BuLi (0.81 mmol, 0.54 ml) and pale yellow precipitated was formed. This reaction mixture stirred at –78°C for approximately 15 mins. the reaction mixture turned from pale yellow precipitated to orange precipitated mixture. The reaction mixture warmed up to rt and stirred for additional 30 mins than it was again cooled down to –78°C and treated with THF (1.5 ml) (reaction mixture turn from deep orange precipitate into red solution) followed by selenium powder (85.3 mg, 1.08 mmol). The reaction mixture warmed up to rt and stirred for 6 hr. The reaction was quenched with HCl (1M) and extracted with diethyl ether (3x 5 ml). The collected organic extracts were dried over magnesium sulphate and the solvent was evaporated to produce deep red oil which was further purified by flash chromatography on silica gel with the eluent diethyl ether/petrol (1:20) to obtain colourless oil with 29 % yield (45 mg, 0.15 mmol).

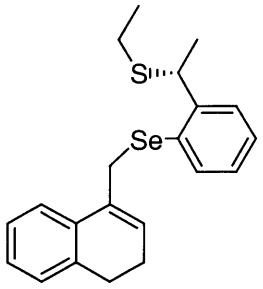
$[\alpha]^{23}_D$ = +17 (c = 0.24, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.69 (d, *J* = 7.2 Hz, 3H, CH_3), 1.83 (s, 3H, $SeCH_3$), 2.26 (s, 3H, $SeCH_3$), 4.55 (q, *J* = 7.2 Hz, 1H, CH), 7.07 (dt, *J* = 1.2, 7.6 Hz, 1H, CH-Ar), 7.15 (dt, *J* = 1.2, 7.6 Hz, 1H, CH-Ar), 7.44 (d, *J* = 7.6 Hz, 2H, CH-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.24 (CH_3), 8.22 (Ar-$SeCH_3$), 22.3 ($SeCH_3$), 36.3 (CH), 126.9 (CH-Ar), 127.1 (CH-Ar), 127.7 (CH-Ar), 132.8 (CH-Ar), 135.1 (C-Ar), 144.5 (C-Ar); IR (NaCl): ν = 3056, 2966, 2923, 1584, 1559, 1465, 1428, 1373, 1266, 1195, 1165, 1053, 1030, 901, 799, 754 cm^{-1}; *m/z* (%): 294 (3) $[M]^+$, 199 (26), 183 (44), 117 (18), 104 (100), 93 (68), 77 (63), 63 (21), 51 (52), 40 (42); HRMS calcd for $C_{10}H_{14}Se_2$ 293.9420, found 293.9421.

1-[(S)-1-Ethylsulfanylethyl]-2-[(R)-(2-methoxy-2-phenyl)ethyl]selenobenzene (93)



Synthesized from styrene according to GP 1. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 1:2. Yield 89% (21 mg, 0.055 mmol), colorless oil, $[\alpha]^{23}_D$ = -18.95 (c = 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 6.6 Hz, 3H, CH_3), 1.48 (d, *J* = 7.2 Hz, 3H, CH_3), 2.32 (q, *J* = 7.2 Hz, 2H, CH_2S), 3.01 (dd, *J* = 4.8, 12.0 Hz, 1H, CH_2Se), 3.17 (s, 3H, OCH_3), 3.21 (dd, *J* = 8.4, 12.0 Hz, 1H, CH_2Se), 4.27 (dd, *J* = 4.8, 8.8 Hz, 1H, CH), 4.59 (q, *J* = 6.8 Hz, 1H, CHS), 6.98-7.48 (m, 9H, CH-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (CH_2CH_3), 22.8 (CH_2), 25.6 (CH_3), 36.4 (CH_2Se), 42.9 (CHS), 57.4 (OCH_3), 83.4 (CHO), 127.1 (CH-Ar), 128.0 (CH-Ar), 128.5 (CH-Ar), 128.6 (CH-Ar), 129.0 (CH-Ar), 131.5 (C-Ar), 133.7 (CH-Ar), 141.3 (C-Ar), 146.0 (C-Ar); IR (NaCl): ν = 3518, 2966, 2927, 1453, 1261, 1182, 1104, 1030, 951, 758, 700 cm^{-1}; *m/z* (%):8 (2)[$M+NH_4]^+$, 319 (20), 289 (21), 245 (100), 167 (5), 135 (11), 121 (8), 104 (5); HRMS for $C_{19}H_{24}OSSe$ calcd 398.1051, found 398.1056.

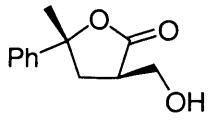
(S) 4-[2-(1-Ethylsulfanylethyl)phenylselanylmethyl]-1,2-dihydronaphthalene (94)

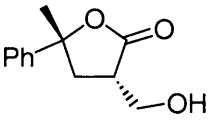


Synthesized according to GP 1. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 1:20 Yield 72% (39 mg, 0.10 mmol), colorless oil, $[\alpha]^{23}_D$ = -6.81 (c = 0.24, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.2 Hz, 3H, CH_3), 1.40 (d, *J* = 7.2 Hz, 3H, CH_3), 2.07-2.15 (m, 2H, CH_2C), 2.28 (q, *J* = 7.2 Hz, 2H, CH_2S), 2.61 (dt, *J* = 3.6, 8.4 Hz, 2H, CH_2), 3.82 (s, 2H, CH_2Se), 4.57 (q, *J* = 6.8 Hz, 1H, CH), 5.76 (t, *J* = 4.4 Hz, 1H, CH=), 7.03-7.25 (m, 6H, CH-Ar), 7.31 (d, *J* = 7.2 Hz, 1H, CH-Ar), 7.42 (dd, *J* = 1.2, 7.6 Hz, 1H, CH-Ar), 7.46 (dd, *J* = 1.2, 7.6 Hz,, 1H, CH-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6

(CH_3), 21.5 (CH_3), ($CHCH_3$), 22.2 (CH_2), 24.2 (CH_2CH), 26.9 (CH_2), 30.0 (CH_2Se), 41.6 (CHS), 122.1 (CH=), 125.3 (CH-Ar), 126.07 (CH-Ar), 126.09 (CH-Ar), 126.2 (CH-Ar), 126.7 (CH-Ar), 127.1 (CH-Ar), 127.5 (CH-Ar), 130.2 (C-Ar), 131.5 (C-Ar), 132.2 (C-Ar), 133.9 (CH-Ar), 135.5 (C), 145.3 (C-Ar); IR (NaCl): ν = 3207, 2966, 2915, 1667, 1619, 1549, 1489, 1458, 1429, 1373, 1264, 1197, 1087, 1029, 926, 801, 766, 735 cm^{-1}; *m/z* (%): 388 (93) $[M]^+$, 340 (78), 326 (56), 279 (100); HRMS calcd for $C_{21}H_{24}SSe$ 388.0758, found 388.0749.

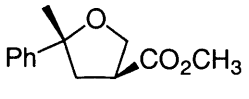
3-Hydroxymethyl-5-methyl-5-phenyldihydrofuran-2-one (95, 96)

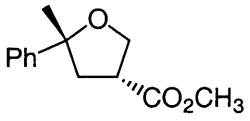




Synthesized from **44/45** according to GP 8. Purification by flash chromatography on silica gel with ethyl acetate: petrol ether 2:1. Yield 56% (10 mg, 0.049 mmol), colorless oil; **95**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.70 (s, 3H, CH_3), 2.29 (t, *J* = 11.2 Hz, 1H, CH_2), 2.59 (t, *J* = 11.2 Hz, 1H, CH_2), 2.59-2.69 (m, 1H, CH), 3.69 (dd, *J* = 5.2, 11.2 Hz, 1H, CH_2OH), 3.89 (dd, *J* = 4.0, 11.2 Hz, 1H, CH_2OH), 7.20-7.40 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.6 (CH_3), 39.4 (CH_2), 43.1 (CH), 61.2 (CH_2OH), 86.1 (C), 124.6 (CH-Ar), 128.2 (CH-Ar), 129.1 (CH-Ar), 144.1 (C-Ar), 178.4 (C=O); HPLC-conditions: Chiracel OD-H, flow rate: 0.5 ml•min^{-1}, 2-propanol:n-hexane 3:97, 10°C, $R_f(1)$ = 68.0 min, $R_f(2)$ = 81.4 min; **96**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 3H, CH_3), 2.51-2.65 (m, 2H, CH_2), 3.02-3.12 (m, 1H, CH), 3.72 (dd, *J* = 6.0, 10.8 Hz, 1H, CH_2OH), 3.88 (dd, *J* = 5.2, 11.2 Hz, 1H, CH_2OH), 7.10-7.30 (m, 5H, Ar); HPLC-conditions: Chiracel OD-H, flow rate: 0.5 ml•min^{-1}, 2-propanol:n-hexane 3:97, 10°C, $R_f(1)$ = 98.2 min, $R_f(2)$ = 190.9 min; IR (NaCl): ν = 3394, 2359, 1758, 1643, 1446, 1236, 1145 cm^{-1}; *m/z* (%): 207 (100) $[M+H]^+$, 190 (46), 160 (7), 147 (22), 124 (13), 113 (14), 91 (66); HRMS calcd for $C_{12}H_{14}O_3$ 207.1016, found 207.1013.

5-Methyl-5-phenyltetrahydrofuran-3-carboxylic acid methyl ester (97, 98)

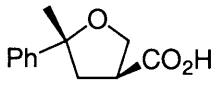


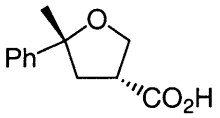


Synthesized from **56** according to GP 8. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:10. Yield 68 % (28.8 mg, 0.13 mmol); **97**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 3H, CH_3), 2.35 (dd, *J* = 8.9, 12.6 Hz, 1H, CH_2), 2.50 (dd, *J* = 8.1,

12.6 Hz, 1H, CH_2), 3.28 (quint, *J* = 8.1 Hz, 1H, CH), 3.50 (s, 3H, OCH_3), 4.00 (t, *J* = 8.5 Hz, 1H, CH_2O), 4.20 (t, *J* = 8.4 Hz, 1H, CH_2O), 7.10-7.35 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2 (CH_3), 42.9 (CH_2), 44.9 (CH), 52.3 (OCH_3), 69.4 (CH_2O), 85.3 (C), 125.0 (CH-Ar), 127.0 (CH-Ar), 128.6 (CH-Ar), 147.5 (C-Ar), 173.6 (C=O); GC-conditions: Chirasil-Dex CB (25 m), 75-110°C at 0.5°C min^{-1}, R_f(major) = 54.9 min, R_f(minor) = 56.0 min; **98**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 3H, CH_3), 2.27 (dd, *J* = 9.4, 12.3 Hz, 1H, CH_2), 2.53 (dd, *J* = 8.1, 12.4 Hz, 1H, CH_2), 2.96 (quint, *J* = 8.2 Hz, 1H, CH), 3.62 (s, 3H, OCH_3), 4.02 (t, *J* = 8.7 Hz, 1H, CH_2O), 4.11 (t, *J* = 8.7 Hz, 1H, CH_2O), 7.12-7.32 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (CH_3), 43.1 (CH_2), 44.3 (CH), 52.5 (OCH_3), 69.5 (CH_2O), 85.8 (C), 124.9 (CH-Ar), 127.2 (CH-Ar), 128.7 (CH-Ar), 146.9 (C-Ar), 174.4 (C=O); HPLC-conditions: Chiracel OD-H, flow rate: 0.5 ml•min^{-1}, 2-propanol:n-hexane 3:97, 10°C, R_f(minor) = 17.5 min, R_f(major) = 19.7 min; IR (thin film on NaCl): ν = 3466, 2966, 1736, 1629, 1489, 1445, 1373, 1328, 1268, 1199, 1167, 1062, 1022, 761, 702 cm^{-1}; *m/z* (%): 221 (11) $[M]^+$, 205 (100), 173 (10), 159 (4), 145 (49), 131 (6), 117 (16), 105 (36), 91 (7), 77 (11), 65 (4), 51 (8), 43 (12); HRMS calcd for $C_{13}H_{16}O_3$+NH_4^+ 238.1438, found 238.1438.

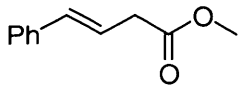
5-Methyl-5-phenyltetrahydrofuran-3-carboxylic acid (99, 100)





Synthesized from **42/43** according to GP 8. Purification by flash chromatography on silica gel with diethyl ether : petrol ether 2:1 Yield 76 % (13 mg, 0.063 mmol); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 3H, trans-CH_3), 1.51 (s, 3H, cis-CH_3), 2.26 (dd, *J* = 9.2, 12.4 Hz, 1H, cis-CH_2), 2.35 (dd, *J* = 9.2, 12.8 Hz, 1H, trans-CH_2), 2.49 (dd, *J* = 8.4, 12.4 Hz, 1H, trans-CH_2), 2.54 (dd, *J* = 8.4, 12.4 Hz, 1H, *cis*-CH_2), 2.97 (quint, *J* = 7.2 Hz, 1H, trans-CH), 3.28 (quint, *J* = 8.4 Hz, 1H, cis-CH), 4.00 (t, *J* = 8.4 Hz, 1H, cis-CH_2O), 4.02 (t, *J* = 8.4 Hz, 1H, trans-CH_2O), 4.12 (t, *J* = 7.2 Hz, 1H, trans-CH_2O), 4.19 (t, *J* = 8.4 Hz, 1H, cis-CH_2O), 7.08-7.35 (m, 10H, CH-Ar); ***trans***-^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (CH_3), 42.9 (CH_2), 44.1 (CH), 69.1 (CH_2O), 86.5 (C), 124.9 (CH-Ar), 127.2 (CH-Ar), 128.6 (CH-Ar), 146.8 (C-Ar), 178.4 (C=O); IR (thin film on NaCl): ν = 3136, 2956, 2915, 1711, 1494, 1446, 1273, 1072, 1037, 766, 701 cm^{-1}; *m/z* (%): 224 (100) $[M+NH_4]^+$, 207 (8), 191 (12); HRMS calcd for $C_{12}H_{14}O_3$ 224.1281, found 224.1281.

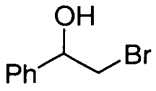
4-Phenyl-but-3-enoic acid methyl ester (104)



Synthesized from **36** according to the reference[58] and purified by kugelrohr distillation to obtain colourless oil with 54% yield (4.78 g, 0.027 mol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 3.19 (d, *J* = 7.2 Hz, 2H, CH_2), 3.65 (s, 3H, OCH_3), 6.18-6.28 (m, 1H, =CH), 6.42 (d, *J* = 16.0 Hz, 1H, CH=), 7.20-7.40 (m, 5H, CH-Ar).

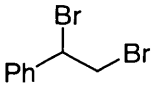
2-Bromo-1-phenylethanol (109)



Synthesized according to the reference[59] and purified by flash chromatography on silica gel with the eluent ethylacetate/petrol (1:4) to obtain colourless oil with 37% yield (613 mg, 3.0 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 3.54-3.68 (m, 2H, CH_2), 4.95 (dd, *J* = 3.2, 9.2 Hz, 1H, CH), 7.39-7.43 (m, 5H, CH-Ar).

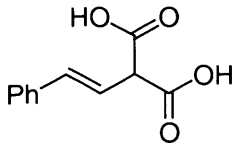
(1, 2-Dibromoethyl)benzene (111)



Synthesized by treating styrene with bromine[60]. Purified by flash chromatography with the eluent petrol to obtain colourless oil with 79 % yield (1.1 g, 0.38 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 3.98-4.15(m, 2H, CH_2), 5.12-5.20 (dd, *J* = 6.0, 6.0 Hz, 1H, CH), 7.40-7.46 (m, 5H, CH-Ar).

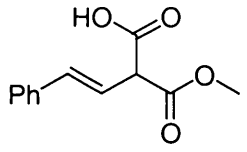
2-Styryl-malonic acid (114)



Synthesized from **104** according to the reference[58] to obtain yellow solid with 65% yield (1.53 g, 7.42 mmol).

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 4.12 (d, *J* = 9.04 Hz, 1H, CH), 6.35 (dd, *J* = 8.8, 16.0 Hz, 1H, =CH), 6.53 (d, *J* = 16.0 Hz, 1H, CH=), 7.12-7.38 (m, 5H, CH-Ar).

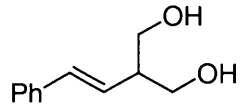
(*E*)-2-(methoxycarbonyl)-4-phenylbut-3-enoic acid (115)



Synthesized from **104** according to the reference[58] to obtain pale yellow solid with 96 % yield (2.53 g, 0.12 mol).

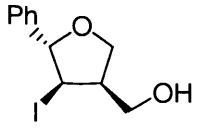
^{1}H NMR (400 MHz, $CDCl_3$,): δ = 3.72 (s, 3H, OCH_3), 4.18 (d, *J* = 9.2 Hz, 1H, CH), 6.31 (dd, *J* = 8.8, 16.0 Hz, 1H, =CH), 6.55 (d, *J* = 16.0 Hz, 1H, CH=), 7.16-7.36 (m, 5H, CH-Ar).

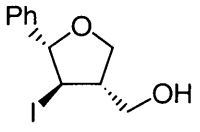
2-Styryl-propane-1,3-diol (116)



Synthesized from **115** according to GP5 (using 2.5 equivalent of $LiAlH_4$ towards 1 equivalent of substrate). Purification by flash chromatography on silica gel with diethyl ether Yield 32 % (260 mg, 1.46 mmol) pale yellow solid; m.p.: 76-78°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51-2.54 (m, 1H, CH), 3.77 (d, *J* = 6.0 Hz, 4H, CH_2OH), 6.03 (dd, *J* = 8.4, 16.0 Hz, 1H, =CH), 6.50 (d, *J* = 16.0 Hz, 1H, =CH), 7.12-7.35 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.6 (CH), 65.5 (CH_2OH), 126.6 (CH-Ar), 127.2 (=CH), 128.0 (CH-Ar), 128.7 (CH-Ar), 129.0 (CH-Ar), 133.6 (CH=), 137.2 (C-Ar); IR (NaCl): ν = 3408, 2925, 2885, 1647, 1494, 1449, 1031, 967, 748, 694 cm^{-1}; *m/z* (%): 196 (100) $[M+NH_4]^+$, 178 (8), 161 (16), 130 (24); HRMS calcd for $C_{11}H_{14}O_2$ 196.1332, found 196.1333.

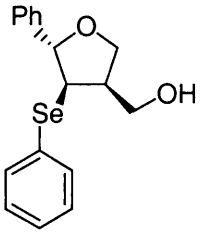
(4-Iodo-5-phenyl tetrahydrofuran-3-yl)-methanol (117a, 118a)

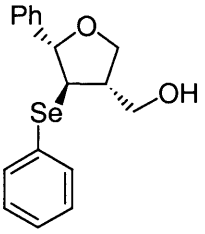




Synthesized from **116** according to GP2. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 1:2. Yield 79% (34 mg, 0.11 mmol), colorless oil, d.r. (**117a**:**118a**) 88:12; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73-2.83 (m, 2H, CH), 3.67-3.74 (m, 4H, CH_2O), 3.77 (dd, *J* = 4.8, 10.8 Hz, 2H, CHI), 3.98 (dd, *J* = 6.8, 8.8 Hz, 1H, 117a-CH_2OH), 4.07 (t, *J* = 8.8 Hz, 1H, 117a-CH_2OH), 4.26 (dd, *J* = 6.8, 9.2 Hz, 2H, 118a-CH_2OH), 4.94 (d, *J* = 8.8 Hz, 1H, 117a-OCH), 5.28 (d, *J* = 5.2 Hz, 1H, 118a-OCH), 7.18-7.42 (m, 10H, Ar); **117a**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8 (CH), 52.0 (CHI), 60.8 (CH_2OH), 68.6 (CH_2), 88.6 (OCH), 124.8 (C-Ar), 125.6 (CH-Ar), 127.5 (CH-Ar), 137.1 (CH-Ar); IR (NaCl): ν = 3364, 3032, 2938, 1602, 1494, 1454, 1377, 1312, 1216, 1150, 1052, 966, 914, 759 cm^{-1}; *m/z* (%): 305 (33) $[M+H]^+$, 178 (13), 151 (15), 117 (100), 99 (14), 85 (44), 79 (11), 60 (42); HRMS calcd for $C_{11}H_{13}O_2I+NH_4^+$ 322.0298, found 322.0301.

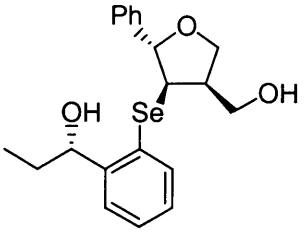
(5-Phenyl-4-phenylselanyl-tetrahydrofuran-3-yl)-methanol (117b, 118b)

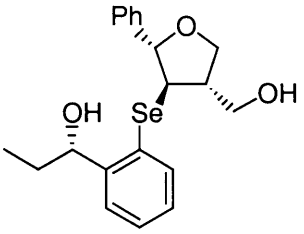




Synthesized from **116** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrolether 1:4. Yield 50% (30 mg, 0.091 mmol), colorless oil, d.r. (**117b**:**118b**) 94:6; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45-2.56 (m, 2H, CH), 3.10 (t, *J* = 7.6 Hz, 2H, CHSe), 3.58-3.72 (m, 4H, CH_2), 3.93 (dd, *J* = 2.8, 5.6 Hz, 2H, 117b-CH_2OH), 4.24 (dd, *J* = 4.3, 6.0 Hz, 2H, 118b-CH_2OH), 4.67 (d, *J* = 8.8 Hz, 1H, 117-OCH), 4.86 (d, *J* = 6.8 Hz, 1H, 118-OCH), 7.05-7.44 (m, 20H, Ar); **117b**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.3 (CHSe), 48.8 (CH), 62.3 (CH_2OH), 69.0 (CH_2OH), 85.8 (OCH), 125.4 (CH-Ar), 126.7 (CH-Ar), 127.0 (CH-Ar), 127.4 (CH-Ar), 128.1 (CH-Ar), 132.8 (CH-Ar), 134.4 (C-Ar), 138.9 (C-Ar); IR (NaCl): ν = 3405, 3059, 2869, 1732, 1578, 1494, 1476, 1437, 1376, 1302, 1176, 1048, 1023, 739, 697 cm^{-1}; *m/z* (%): 335 (100) $[M+H]^+$, 317 (22), 178 (100), 160 (12); HRMS calcd for $C_{17}H_{18}O_2Se$ 335.0545, found 335.0552.

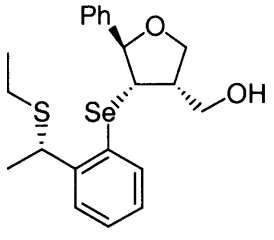
(*1S*)-*1*-[2-(4-Hydroxymethyl-2-phenyl tetrahydrofuran-3-yl)-phenylselanyl]-propan-1-ol (117f, 118f)

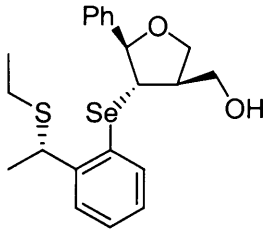




Synthesized from **116** according to GP 1. Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether:petrol ether 2:1. Yield 64% (35 mg, 0.11 mmol), colorless oil, d.r. (**117f**:**118f**) 93:7; $[\alpha]^{22}_{D}$ = +70.6 (c = 0.60, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.6 Hz, 6H, CH_3), 152-1.72 (m, 4H, CH_2), 2.48-2.62 (m, 1H, 117f-CH), 2.63-2.70 (m, 1H, 118f-CH), 3.17 (dd, *J* = 6.8, 8.4 Hz, 1H, 117f-CHSe), 3.19-3.23 (m, 1H, 118f-CH-Se), 3.43 (dd, *J* = 6.0, 10.8 Hz, 1H, 117f-CH_2O), 3.49-3.53 (m, 1H, 118f-CH_2O), 3.58 (dd, *J* = 6.4, 10.8 Hz, 1H, 117f-CH_2O), 3.68-3.73 (m, 1H, 118f-CH_2O), 3.89 (dd, *J* = 4.8, 9.2 Hz, 1H, 117f-CH_2OH), 3.97 (dd, *J* = 7.6, 8.8 Hz, 1H, 117f-CH_2OH), 4.18-4.31 (m, 2H, 118f-CH_2OH), 4.68 (d, *J* = 8.8 Hz, 1H, 117f-OCH), 4.87 (d, *J* = 8.8 Hz, 1H, 118f-OCH), 4.98 (q, *J* = 6.0 Hz, 1H, 117f-ArCHOH), 5.09 (q, *J* = 6.0 Hz, 1H, 117f-ArCHOH), 6.80-7.44 (m, 18H, Ar); **117f**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.7 (CH_3), 31.7 (CH_2), 51.0 (CHSe), 51.5 (CH), 63.3 (CH_2OH), 67.5 (CH_2O), 71.0 (ArCHOH), 87.5 (OCH), 121.8 (C-Ar), 128.2 (CH-Ar), 128.3 (CH-Ar), 128.5 (CH-Ar), 128.8 (CH-Ar), 129.2 (CH-Ar), 131.8 (CH-Ar), 136.8 (CH-Ar), 140.2 (C-Ar), 147.4 (C-Ar); IR (NaCl): ν = 3358, 3056, 2962, 2880, 1615, 1456, 1378, 1263, 1192, 1048, 972, 911, 754, 699 cm^{-1}; *m/z* (%): 392 (36) $[M]^+$, 187 (11), 149 (10), 122 (12), 107 (100), 85 (48), 61 (15); HRMS calcd for $C_{20}H_{24}O_3Se$ 392.0885, found 392.0887.

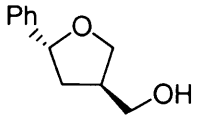
{4-[2-(*R*)-2-Ethylsulfanylethyl)-phenylselanyl]-5-phenyl-tetrahydrofuran-3-yl}-methanol (117i, 118i)

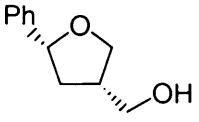




Synthesized from **116** according to GP 1. Purification by flash chromatography on silica gel with diethyl ether:petrol ether 2:1. Yield 30% (14 mg, 0.032 mmol), colorless oil, d.r. (**117i**:**118i**) 86:14; $[\alpha]^{23}_D$ = -30.5 (c = 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.6 Hz, 3H, 118i-CH_3), 1.11 (t, *J* = 7.6 Hz, 3H, 117i-CH_3), 1.39 (d, *J* = 6.8 Hz, 3H, 117i-CH_3), 1.43 (d, *J* = 6.8 Hz, 3H, 118i-CH_3), 2.32 (q, *J* = 7.6 Hz, 4H, SCH_2), 2.48-2.62 (m, 1H, CH), 2.71-2.80 (m, 1H, 118i-CH), 3.20 (dd, *J* = 6.8, 8.4 Hz, 1H, 117i-CH_2O), 3.29 (dd, *J* = 6.4, 9.2 Hz, 1H, 118i-CH_2O), 3.52-3.66 (m, 1H, 117i-CH_2O), 3.72-3.78 (m, 1H, 118i-CH_2O), 3.89-3.94 (m, 1H, 118i-CH_2OH), 3.97 (dd, *J* = 5.2, 8.8 Hz, 1H, CH_2OH), 4.03 (dd, *J* = 7.6, 8.8 Hz, 1H, 117i-CH_2OH), 4.26 (dd, *J* = 7.6, 8.4 Hz, 1H, 118i-CH_2OH) 4.43 (q, *J* = 6.8 Hz, 1H, 118i-SCH), 4.56 (q, *J* = 6.8 Hz, 1H, 117i-SCH), 4.72 (d, *J* = 8.4 Hz, 1H, 117i-OCH), 4.82 (d, *J* = 7.2 Hz, 1H, 118i-OCH), 6.75-7.44 (m, 18H, Ar); **117i**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (CH_3), 22.6 (CH_2), 25.6 (CH_3), 43.0 (CHS), 50.7 (CH), 51.1 (CH-Se), 63.6 (CH_2OH), 70.4 (CH_2O), 87.8 (C), 126.6 (CH-Ar), 126.8 (CH-Ar), 127.8 (CH-Ar), 128.4 (CH-Ar), 128.8 (CH-Ar), 129.1 (CH-Ar), 129.6 (CH-Ar), 136.6 (C-Ar), 140.3 (C-Ar), 146.8 (C-Ar); IR (NaCl): ν = 3428, 3056, 2956, 2915, 2855, 1589, 1494, 1454, 1373, 1263, 1212, 1157, 1041, 1027, 754, 699, 650 cm^{-1}; *m/z* (%): 398 (2) $[M+NH_4]^+$, 440 (8), 391 (15), 376 (25), 363 (100), 344 (12), 335 (8); HRMS calcd for $C_{21}H_{26}O_2SSe$ 440.1157, found 440.1161.

(5-Phenyl-tetrahydrofuran-3-yl)-methanol (119, 120)

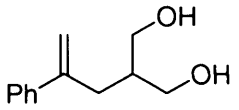




Synthesized from **117/118** according to GP 8. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:2. Yield 73% (3 mg, 0.02 mmol), colorless oil, d.r. (*trans*:*cis*) 92:8; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42-1.51 (m, 2H, CH_2), 2.41 (dd, *J* = 6.4, 12.4 Hz, 2H, CH_2), 2.58 (quint, *J* = 7.2 Hz, 2H, CH), 3.59 (dd, *J* = 2.4, 6.4 Hz, 2H, CH_2O), 3.73-3.77 (m, 1H, 120-CH_2O), 3.87 (dd, *J* = 5.6, 8.8 Hz, 1H, CH_2OH), 3.95 (t, *J* = 8.8 Hz, 1H, CH_2OH), 4.14-4.18 (m, 2H, 120-CH_2OH), 4.79 (dd, *J* = 6.4, 9.6 Hz, 1H, *trans*-CHO), 4.92 (t, *J* = 7.6 Hz, 1H, *cis*-CHO), 7.15-7.35 (m, 10H, Ar); ***trans***-isomer: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7 (CH_2), 41.3 (CH), 64.3 (CH_2OH), 70.0 (CH_2O), 80.2 (OCH), 124.7 (CH-Ar), 126.4 (CH-Ar), 127.4 (CH-Ar), 141.3 (C-Ar); IR (NaCl): ν = 3428, 3016, 2918, 2845, 1652, 1453, 1373, 1265, 1217, 1053, 909, 758, 700 cm^{-1}; m/z (%): 196 (100)

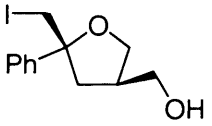
$[M+NH4]^+$, 179 (8); HRMS calcd for $C_{11}H_{14}O_2$ 196.1332, found 196.1331. HPLC-conditions: Chiracel OD-H, flow rate: 0.5 ml•min^{-1}, 2-propanol:n-hexane 3:97, 10°C, R_f(*cis-1*) = 91.4 min, R_f(*cis-2*) = 99.0 min, R_f(*trans-1*) = 112.3 min, R_f(*trans-2*) = 126.1 min.

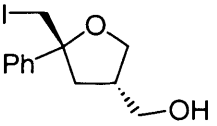
2-(2-Phenylallyl)-propane-1,3-diol (121)



Synthesized from **41** according to GP 5 (using 2 equivalent of $LiAlH_4$ towards 1 equivalent of substrate). Purification by flash chromatography on silica gel with *tert.*-butyl methyl ether Yield 85% (144 mg, 0.75 mmol), white solid; m.p. 55-56 °C; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 1.75-1.85 (m, 1H, CH), 2.47 (d, *J* = 7.6 Hz, 2H, CH_2), 3.58 (dd, *J* = 7.2, 10.8 Hz, 2H, CH_2OH), 3.72 (dd, *J* = 3.6, 10.4 Hz, 2H, CH_2OH), 5.04 (d, *J* = 0.8 Hz, 1H, $=CH_2$), 5.26 (d, *J* = 1.2 Hz, 1H, $=CH_2$), 7.15-7.45 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.3 (CH_2), 40.5 (CH), 66.2 (CH_2OH), 114.8 ($=CH_2$), 126.6 (CH-Ar), 128.1 (CH-Ar), 128.9 (CH-Ar), 140.9 (C=), 146.6 (C-Ar); IR (NaCl): ν = 3374, 2927, 2882, 1626, 1494, 1444, 1092, 1028, 971, 898, 779, 709 cm^{-1}; *m/z* (%): 192 (10), 174 (31), 157 (76), 150 (23), 143 (30), 128 (27), 117 (100), 103 (17), 91 (10); HRMS calcd for $C_{12}H_{16}O_2$ 193.1223, found 193.1222.

(5-Iodomethyl-5-phenyl-tetrahydrofuran-3-yl)-methanol (122a, 123a)

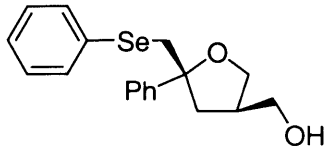


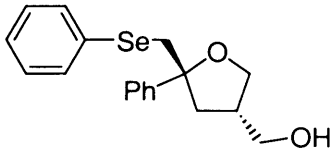


Synthesized from **121** according to GP2. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:1. Yield 43% (29 mg, 0.091 mmol), colorless oil, d.r. (**122a**:**123a**) 70:30; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95-2.15 (m, 2H, 122a-CH_2), 2.30-2.58 (m, 3H, 123a-CH_2, 122a-CH), 2.70 (quint, *J* = 7.6 Hz, 1H, 123a-CH), 3.42 (d, *J* = 10.4 Hz, 1H, 123a-CH_2I), 3.47 (t, *J* = 10.4 Hz, 1H, 123a-CH_2I), 3.49 (d, *J* = 10.4 Hz, 1H, 122a-CH_2I), 3.50 (d, *J* = 10.4 Hz, 1H, 122a-CH_2I), 3.59-3.64 (m, 2H, 122a-CH_2O), 3.63 (d, *J* = 6.4 Hz, 2H, CH_2O), 3.80 (t, *J* = 8.0 Hz, 1H, 122a-CH_2OH), 3.97 (t, *J* = 8.0 Hz, 1H, 122a-CH_2OH), 4.04 (t, *J* = 7.2 Hz, 1H, 123a-CH_2OH), 4.18 (t, *J* = 8.4 Hz, 1H, 123a-CH_2OH), 7.10-7.45 (m, 10H, Ar); **122a**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3 (CH_2), 40.9 (CH_2O), 42.2 (CH), 64.8 (CH_2OH), 70.9 (CH_2I), 85.5 (C), 125.8 (CH-Ar), 127.9 (CH-Ar), 128.8 (CH-

Ar), 143.3 (C-Ar); IR (NaCl): ν = 3438, 2931, 2875, 1644, 1446, 1188, 1048, 763, 702 cm^{-1}; *m/z* (%): 319 (6) $[M+H]^+$, 301 (100), 283 (5), 206 (14), 192 (23), 174 (4), 156 (6); HRMS calcd for $C_{12}H_{15}O_2I$ 336.0455, found 336.0456.

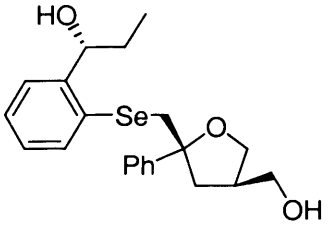
(5-Phenyl-5-phenylselanylmethyl-tetrahydrofuran-3-yl)-methanol (122b, 123b)

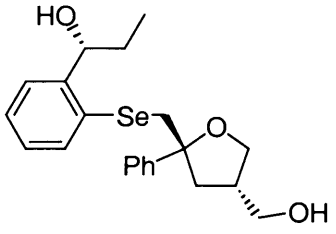




Synthesized from **121** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:2. Yield 74% (46 mg, 0.13 mmol), colorless oil, d.r. (**122b**:**123b**) 66:34; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.01 (dd, *J* = 6.8, 12.8 Hz, 1H, 123b-CH_2), 2.08 (dd, *J* = 8.4, 11.6 Hz, 1H, 122b-CH_2), 2.33 (quint, *J* = 7.2 Hz, 1H, 122b-CH), 2.38-2.44 (m, 1H, 122b-CH_2), 2.52 (dd, *J* = 8.8, 12.8 Hz, 1H, 123b-CH_2), 2.67 (quint, *J* = 7.2 Hz, 1H, 123b-CH), 3.25 (d, *J* = 12.0 Hz, 1H, 123b-CH_2Se), 3.26 (d, *J* = 12.0 Hz, 1H, 122b-CH_2Se), 3.33 (d, *J* = 12.0 Hz, 1H, 123b-CH_2Se), 3.42 (d, *J* = 12.4 Hz, 1H, 122b-CH_2Se), 3.57-3.59 (m, 2H, 122b-CH_2O), 3.60 (d, *J* = 6.8 Hz, 2H, CH_2O), 3.76 (dd, *J* = 6.4, 8.8 Hz, 1H, 122b-CH_2OH), 3.94 (t, *J* = 8.4 Hz, 1H, 122b-CH_2OH), 4.04 (t, *J* = 7.2 Hz, 1H, 123b-CH_2OH), 4.12 (t, *J* = 7.2 Hz, 1H, 123b-CH_2OH), 7.01-7.40 (m, 20H, Ar); **122b**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.3 (CH_2), 40.6 (CH_2Se); 41.9 (CH), 63.6 (CH_2OH), 69.3 (CH_2O), 85.7 (C), 124.2 (CH-Ar), 125.6 (CH-Ar), 126.1 (CH-Ar), 127.3 (CH-Ar), 127.9 (CH-Ar), 130.3 (C-Ar), 131.4 (CH-Ar), 143.9 (C-Ar); IR (NaCl): *ν* = 3414, 3060, 2930, 2876, 1642, 1579, 1478, 1446, 1202, 1049, 1022, 764, 737, 703 cm^{-1}; *m/z* (%): 349 $[M]^+$ (17), 331 (29), 220 (7), 192 (100), 178 (22), 174 (7), 144 (8), 108 (20), 84 (7); HRMS calcd for $C_{18}H_{20}O_2Se$ 366.0967, found 366.0962.

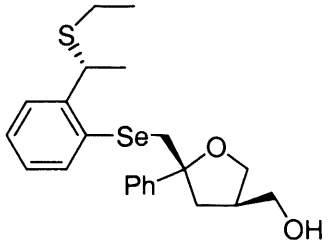
1-{2-[(*S*)-4-Hydroxymethyl-2-phenyl-tetrahydrofuran-2yl-methylselanyl]-phenyl}-propan-1-ol (122f, 123f)

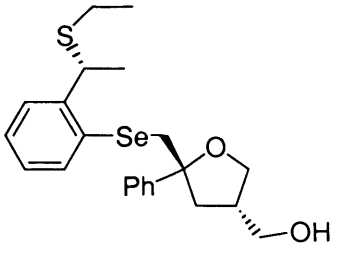




Synthesized from **121** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:2. Yield 28% (20 mg, 0.05 mmol), colorless oil, d.r. (**122f**:**123f**) 59:41; $[\alpha]^{22}_D$ = +8.0 (c = 0.075, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.2 Hz, 3H, 123f-CH_3), 0.86 (t, *J* = 7.6 Hz, 3H, 122f-CH_3), 153-1.74 (m, 4H, CH_2CH_3), 1.92-2.15 (m, 2H, CH_2), 2.30 (quint, *J* = 6.8 Hz, 1H, 122f-CH), 2.35-2.52 (m, 2H, CH_2), 2.66 (quint, *J* = 7.2 Hz, 1H, 123f-CH), 3.23 (d, *J* = 12.0 Hz, 1H, 123f-CH_2Se), 3.30 (d, *J* = 12.0 Hz, 1H, 122f-CH_2Se), 3.35 (d, *J* = 12.4 Hz, 1H, 122f-CH_2Se), 3.36 (d, *J* = 11.2 Hz, 1H, 123f-CH_2Se), 3.60 (d, *J* = 9.6 Hz, 2H, CH_2O), 3.61-3.63 (m, 2H, 122f-CH_2O), 3.76 (dd, *J* = 6.4 Hz, 1H, 122f-CH_2OH), 3.96 (t, *J* = 8.0 Hz, 1H, 122f-CH_2OH), 4.05 (t, *J* = 7.2 Hz, 1H, 123f-CH_2OH), 4.13 (t, *J* = 7.2 Hz, 1H, 123f-CH_2OH), 4.86 (q, *J* = 6.8 Hz, 1H, 122f-CH-Ar), 5.02-5.10 (m, 1H, CH-Ar), 6.90-7.44 (m, 18H, Ar); **122f**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8 (CH_3), 31.4 (CH_2CH_3), 41.2 (CH), 41.9 (CH_2Se), 43.2 (CH_2), 64.8 (CH_2OH), 70.6 (CH_2O), 74.8 (CHOH-Ar), 87.3 (C), 125.7 (CH-Ar), 126.5 (CH-Ar), 127.3 (CH-Ar), 127.6 (CH-Ar), 128.3 (CH-Ar), 128.4 (CH-Ar), 130.7 (C-Ar), 134.8 (CH-Ar), 146.6 (C-Ar); IR (NaCl): ν = 3418, 2928, 2865, 1632, 1446, 1268, 1197, 1047, 753, 703 cm^{-1}; *m/z* (%): 389 (43) $[M-H_2O]^+$, 371 (22), 197 (31), 176 (36), 158 (36), 108 (100), 100 (7); HRMS calcd for $C_{21}H_{26}O_3Se+NH_4^+$ 424.1385, found 424.1389.

{5-[2-(*R*)-1-Ethylsulfanylethyl-phenylselanylmethyl]-5-phenyl-tetrahydrofuran-3-yl}-methanol (122i, 123i)

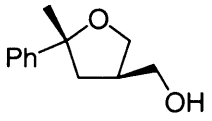


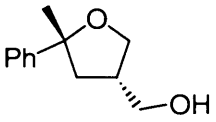


Synthesized from **121** according to GP 1. Purification by flash chromatography on silica gel with ethyl acetate:petrol ether 1:2. Yield 33% (28 mg, 0.06 mmol), colorless oil, d.r. (**122i**:**123i**) 81:19; $[\alpha]^{22}_D$ = -7.71 (c = 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.2 Hz, 3H, 122i-CH_3), 1.10 (t, *J* = 7.6 Hz, 3H, 123i-CH_3), 1.41 (d, *J* = 7.2 Hz, 3H, 123i-CH_3), 1.45 (d, *J* = 7.2 Hz, 3H, 122i-CH_3), 2.06-2.14 (m, 2H, CH_2), 2.24-2.45 (m, 5H, CH_2S, CH), 2.50-2.56 (m, 2H, 123i-CH_2), 2.68 (quint, *J* = 7.6 Hz, 1H, 123i-CH), 3.24 (d, *J* = 12.0 Hz, 1H, 122i-CH_2Se), 3.27 (d, *J* = 12.0 Hz, 1H, 123i-CH_2Se), 3.36 (d, *J* = 12.0 Hz, 1H, 123i-

CH_2Se), 3.38 (d, J = 12.0 Hz, 1H, 122i-CH_2Se), 3.62 (d, J = 6.8 Hz, 1H, 122i-CH_2O), 3.63 (d, J = 6.4 Hz, 2H, 123i-CH_2O), 3.77 (t, J = 8.4 Hz, 1H, 122i-CH_2OH), 3.78 (t, J = 6.8 Hz, 1H, 122i-CH_2OH), 3.95 (t, J = 8.0 Hz, 2H, 123i-CH_2OH), 4.54 (q, J = 6.8 Hz, 1H, 123i-CH-Ar), 4.58 (q, J = 6.8 Hz, 1H, 122i-CH-Ar), 6.90-7.40 (m, 18H, Ar); **122i**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (CH_3), 23.0 (CH_3CH), 25.6 (CH_2S), 40.8 (CH_2), 42.0 (CH), 42.6 (CH_2Se), 42.9 (CH-Ar), 65.1 (CH_2O), 70.7 (CH_2OH), 87.2 (C), 125.6 (CH-Ar), 127.5 (CH-Ar), 127.7 (CH-Ar), 127.9 (CH-Ar), 128.0 (CH-Ar), 128.7 (CH-Ar), 132.1 (C-Ar), 133.9 (CH-Ar), 145.4 (C-Ar), 145.9 (C-Ar); IR (NaCl): ν = 3396, 3056, 2928, 2869, 1599, 1584, 1494, 1464, 1446, 1378, 1262, 1202, 1047, 806, 763, 730, 704 cm^{-1}; *m/z* (%): 436 (100) $[M]^+$, 407 (24); HRMS calcd for $C_{22}H_{28}O_2SSe$ 436.0970, found 436.0975.

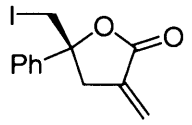
(5-Methyl-5-phenyl-tetrahydrofuran-3-yl)-methanol (124, 125)





Synthesized from **122/123** according to GP 8. Purification by flash chromatography on silica gel with ethyl acetate:petrolether 1:2. Yield 61% (7 mg, 0.039 mmol), colorless oil, d.r. (*cis*:*trans*) 80:20; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 3H, *trans*-CH_3), 1.49 (s, 3H, *cis*-CH_3), 1.70 (dd, J = 8.8, 12.0 Hz, 1H, *cis*-CH_2), 1.89 (dd, J = 7.2, 12.4 Hz, 1H, *trans*-CH_2), 2.22 (dd, J = 8.4, 12.8 Hz, 1H, *trans*-CH_2), 2.30 (quint, J = 8.0 Hz, 1H, *cis*-CH), 2.41 (dd, J = 7.6, 12.0 Hz, 1H, *cis*-CH_2), 2.63 (quint, J = 7.6 Hz, 1H, *trans*-CH), 3.38 (dd, J = 7.6, 10.8 Hz, 1H, *trans*-CH_2O), 3.44 (dd, J = 6.4, 10.4 Hz, 1H, *trans*-CH_2O), 3.59 (dd, J = 2.4, 6.8 Hz, 2H, *cis*-CH_2O), 3.73 (dd, J = 6.4, 8.8 Hz, 1H, *cis*-CH_2OH), 3.92 (t, J = 8.8 Hz, 1H, *cis*-CH_2OH), 4.20 (t, J = 7.6 Hz, 2H, *trans*-CH_2OH), 7.10-7.35 (m, 10H, Ar); ***cis***-isomer: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4 (CH_3), 40.8 (CH), 41.5 (CH_2), 64.1 (CH_2OH), 68.7 (CH_2O), 84.0 (C), 123.6 (CH-Ar), 125.5 (CH-Ar), 127.2 (CH-Ar), 146.4 (C-Ar); IR (NaCl): ν = 3397, 2976, 2925, 2875, 1489, 1446, 1373, 1263, 1127, 1097, 1037, 906, 850, 801, 761, 700 cm^{-1}; m/z (%): 210 (100) $[M+NH_4]^+$, 193 (16), 177 (8), 136 (8), 115 (7), 74 (10); HRMS calcd for $C_{12}H_{16}O_2$ 210.1489, found 210.1490.

5-Iodomethyl-3-methylene-5-phenyl-dihydrofuran-2-one (129)



Sodium hydride (18.6 mg, 0.15 mmol) was suspended in THF (5 mL) and **44a** (0.056 mmol, 18.6 mg) was added. This reaction mixture was stirred at rt for 5 h, quenched with water and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated to produce pale yellow solid which was purified by flash chromatography on silica gel with ethyl acetate: petrol ether 1:2 to produce a pale yellow solid in 32% yield (16 mg, 0.018 mmol). m.p.: 66-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.03 (tt, *J* = 2.8, 2.8 Hz, 1H, CH_2), 3.47 (tt, *J* = 2.8, 2.8 Hz, 1H, CH_2), 3.66 (dd, *J* = 7.2, 12.0 Hz, 1H, CH_2I), 3.81 (dd, *J* = 3.6, 12.4 Hz, 1H, CH_2I), 5.59 (t, *J* = 2.8 Hz, 1H, $=CH_2$), 6.18 (t, *J* = 2.8 Hz, 1H, $=CH_2$), 7.22-7.38 (m, 5H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.0 (CH_2), 69.7 (CH_2I), 86.5 (C), 122.9 ($HC=\underline{C}H_2$), 125.3 (CH-Ar), 128.7 (CH-Ar), 129.2 (CH-Ar), 135.0 ($\underline{C}H=CH_2$), 140.9 (C-Ar), 170.1 (C=O); IR (NaCl): ν = 2931, 2853, 1767, 1456, 1270, 1116, 1011, 808 cm^{-1}; *m/z* (%): 315 (35) $[M]^+$, 187 (34), 173 (100), 141 (21), 128 (12), 115 (19), 105 (60), 91 (25), 77 (14), 51 (17), 40 (25); HRMS calcd for $C_{12}H_{11}O_2I$ 332.0142, found 332.0147.

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[35] CCDC 214760 contains the supplementary crystallographic data for this Thesis. These

data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk).

[36] The energies of the tetrahydrofurans **42b** and **43b** and of the lactones **44b** and **45b** are almost identical as *ab-initio* calculations on different levels (6-31G*, 6-311G*) have shown.

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Appendix 1

Crystallographic data of lactone 44a

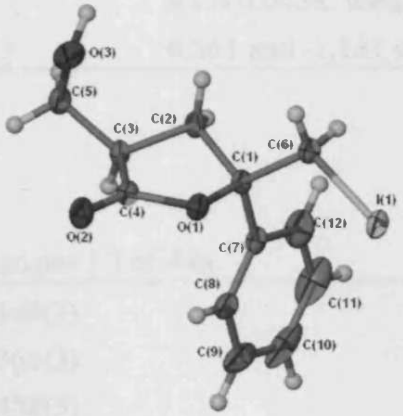

Table 1: Crystal data and structure refinement

Identification code	iodolactone	
Empirical formula	C12 H13 I O3	
Formula weight	332.12	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 12.8185(5) Å	α= 90°.
	b = 15.8609(7) Å	β= 93.0690(15)°.
	c = 5.9362(3) Å	γ = 90°.
Volume	1205.18(9) Å^3	

Z	4
Density (calculated)	1.830 Mg/m^3
Absorption coefficient	2.646 mm^-1
F(000)	648
Crystal size	0.20 x 0.18 x 0.16 mm^3
Theta range for data collection	3.02 to 27.50°
Index ranges	-16<=h<=16, -20<=k<=20, -7<=l<=7
Reflections collected	14967
Independent reflections	2743 [R(int) = 0.0638]
Max. and min. transmission	0.6768 and 0.6196
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2743 / 1 / 149
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0717
R indices (all data)	R1 = 0.0438, wR2 = 0.0773
Largest diff. peak and hole	0.561 and -1.111 $e.Å^{-3}$

Table 2: Bond lengths [Å] and angles [°] of **44a**.

I(1)-C(6)	2.149(3)
O(1)-C(4)	1.361(3)
O(1)-C(1)	1.458(3)
O(2)-C(4)	1.205(4)
O(3)-C(5)	1.412(4)
C(1)-C(7)	1.515(4)
C(1)-C(6)	1.518(4)
C(1)-C(2)	1.542(4)
C(2)-C(3)	1.532(4)
C(3)-C(4)	1.508(4)
C(3)-C(5)	1.518(4)
C(7)-C(8)	1.387(5)
C(7)-C(12)	1.390(5)
C(8)-C(9)	1.384(5)
C(9)-C(10)	1.379(8)
C(10)-C(11)	1.361(8)
C(11)-C(12)	1.385(7)
C(4)-O(1)-C(1)	110.1(2)

C(5)-O(3)-H(3)	105(4)
C(5)-C(1)-C(7)	110.1(2)
O(1)-C(1)-C(6)	107.3(2)
C(7)-C(1)-C(6)	113.4(2)
O(1)-C(1)-C(2)	103.2(2)
C(7)-C(1)-C(2)	112.3(3)
C(6)-C(1)-C(2)	110.0(3)
C(3)-C(2)-C(1)	101.8(2)
C(4)-C(3)-C(5)	111.8(3)
C(4)-C(3)-C(2)	102.0(2)
C(5)-C(3)-C(2)	116.9(3)
O(2)-C(4)-O(1)	121.0(3)
O(2)-C(4)-C(3)	128.7(3)
O(1)-C(4)-C(3)	110.2(2)
O(3)-C(5)-C(3)	110.9(3)
C(1)-C(6)-I(1)	114.6(2)
C(8)-C(7)-C(12)	118.3(3)
C(8)-C(7)-C(1)	122.1(3)
C(12)-C(7)-C(1)	119.6(3)
C(9)-C(8)-C(7)	120.6(4)
C(10)-C(9)-C(8)	120.2(5)
C(11)-C(10)-C(9)	119.8(4)
C(10)-C(11)-C(12)	120.5(4)
C(11)-C(12)-C(7)	120.6(4)

Appendix 2

Crystallographic data of lactone 129

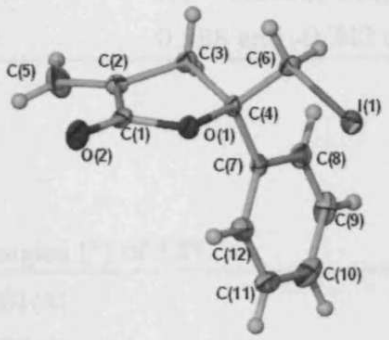

Table 1. Crystal data and structure refinement of **129**.

Identification code	iodo elimination product	
Empirical formula	C12 H11 I O2	
Formula weight	314.11	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/a	
Unit cell dimensions	a = 5.8858(2) Å	α= 90°.
	b = 23.8926(8) Å	β= 97.903(3)°.
	c = 8.3423(3) Å	γ = 90°.
Volume	1162.01(7) $Å^3$	
Z	4	
Density (calculated)	1.795 Mg/m^3	

Absorption coefficient	2.733 mm^{-1}
F(000)	608
Crystal size	0.23 x 0.09 x 0.08 mm^3
Theta range for data collection	3.00 to 27.45°
Index ranges	-7<=h<=7, -30<=k<=31, -10<=l<=10
Reflections collected	8596
Independent reflections	2648 [R(int) = 0.0569]
Completeness to theta = 27.45°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8110 and 0.5721
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2648 / 0 / 136
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0358, wR2 = 0.0638
R indices (all data)	R1 = 0.0596, wR2 = 0.0705
Largest diff. peak and hole	0.588 and -0.742 e.$Å^{-3}$

Table 2: Bond lengths [Å] and angles [°] of **129**.

C(1)-O(2)	1.201(4)
C(1)-O(1)	1.359(4)
C(1)-C(2)	1.473(5)
C(2)-C(5)	1.319(6)
C(2)-C(3)	1.493(5)
C(3)-C(4)	1.562(5)
C(4)-O(1)	1.459(4)
C(4)-C(6)	1.514(5)
C(4)-C(7)	1.517(5)
C(6)-I(1)	2.167(4)
C(7)-C(8)	1.382(5)
C(7)-C(12)	1.397(5)
C(8)-C(9)	1.393(6)
C(9)-C(10)	1.385(7)
C(10)-C(11)	1.363(6)
C(11)-C(12)	1.391(5)
O(2)-C(1)-O(1)	121.0(4)
O(2)-C(1)-C(2)	129.7(4)

O(1)-C(1)-C(2)	109.3(3)
C(5)-C(2)-C(1)	121.6(4)
C(5)-C(2)-C(3)	131.0(4)
C(1)-C(2)-C(3)	107.3(3)
C(2)-C(3)-C(4)	102.3(3)
O(1)-C(4)-C(6)	106.9(3)
O(1)-C(4)-C(7)	109.9(3)
C(6)-C(4)-C(7)	113.1(3)
O(1)-C(4)-C(3)	104.4(3)
C(6)-C(4)-C(3)	110.3(3)
C(7)-C(4)-C(3)	111.7(3)
C(4)-C(6)-I(1)	112.5(2)
C(8)-C(7)-C(12)	118.8(4)
C(8)-C(7)-C(4)	119.2(3)
C(12)-C(7)-C(4)	122.0(3)
C(7)-C(8)-C(9)	120.5(4)
C(10)-C(9)-C(8)	119.8(4)
C(11)-C(10)-C(9)	120.3(4)
C(10)-C(11)-C(12)	120.2(4)
C(11)-C(12)-C(7)	120.4(4)
C(1)-O(1)-C(4)	111.3(3)

CONFERENCES, PRESENTATIONS & PUBLICATIONS (2001-2004)

Conference presentations

- ORCHEM 2004 of GDCh (Gesellschaft Deutscher Chemikar) at Bad Nauheim, Germany, 9^{th}-11^{th} September 2004.

Poster presented entitled: Selenocyclisation Controlled by Nucleophiles.

- Cardiff Easter Conference at Cardiff University, UK, 6^{th} April 2004.

Oral presentation entitled: Nucleophile Controlled Selenocyclisation.

- International Conference on the Chemistry of Selenium and Tellurium (ICCST 9) at Indian Institute of Technology (IIT) in Bombay India, 23^{rd}-27^{th} February 2004.

Poster presented entitled: Chemoselective Control of Selenocyclisation.

- Conference of Chemistry at University of Bath, 15^{th} December 2003.

Poster presented entitled: Control of Selenocyclisation with Competing Nucleophiles.

Publications

1) S. S. Khokhar, T. Wirth, *European Journal of Organic Chemistry*, *24*, **2004**, 4567-4581.

2) S. S. Khokhar, T. Wirth, *Angewandte Chemie, International Edition*, *43*, **2004**, 631-633.