

**Ring-Closing Metathesis:
A Gateway to Medium Size Ring Ethers**

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“Where nature finishes producing its own species, man begins, using natural things and in harmony with this very nature, to create an infinity of species”

-Leonardo da Vinci (1452-1519)

Dedicated to my family

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Chapter A

Regioselectivity in the Formation of Small- and Medium-Sized Cyclic Ethers by Diene-Ene Ring-Closing Metathesis

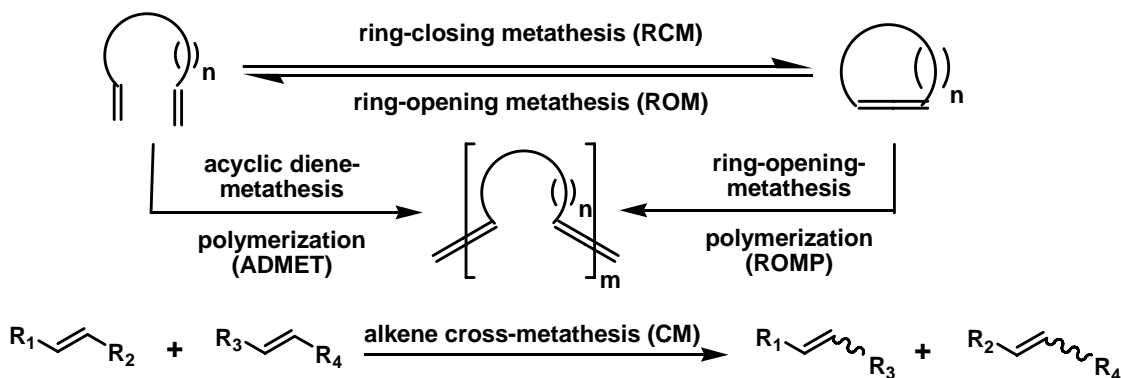
1. Background:

1.1 Introduction:

The Diels-Alder, Aldol, Grignard and Wittig reactions are four most important carbon-carbon bond forming reactions which played decisive roles in shaping today's science of chemical synthesis. During the last three decades two more reactions came in the play as complementary of the aforementioned carbon-carbon bond forming reactions. They are (i) the palladium-catalyzed cross coupling reactions¹ and (ii) metathesis reactions.² Olefin metathesis reactions unambiguously influenced and shaped the new horizon of synthetic organic chemistry more than any other single chemical reaction over the last 15 years.

1.1.2 Olefin metathesis. A short historical account:

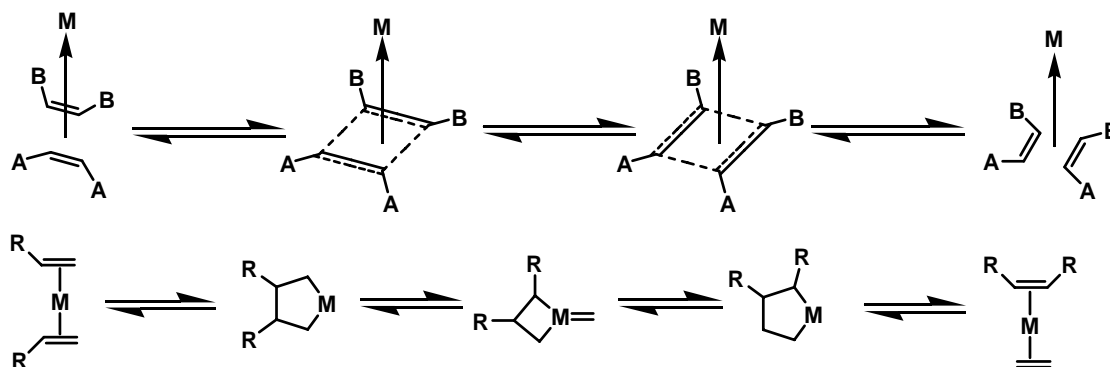
Derived from the Greek words *meta* (change) and *thesis* (position), olefin metathesis is the exchange of the parts of the two substances, $AB + CD$ to $AC + BD$, where the reactants are olefins (Scheme 1.1).



Scheme 1.1. The most commonly employed alkene-metathesis reactions in organic synthesis.

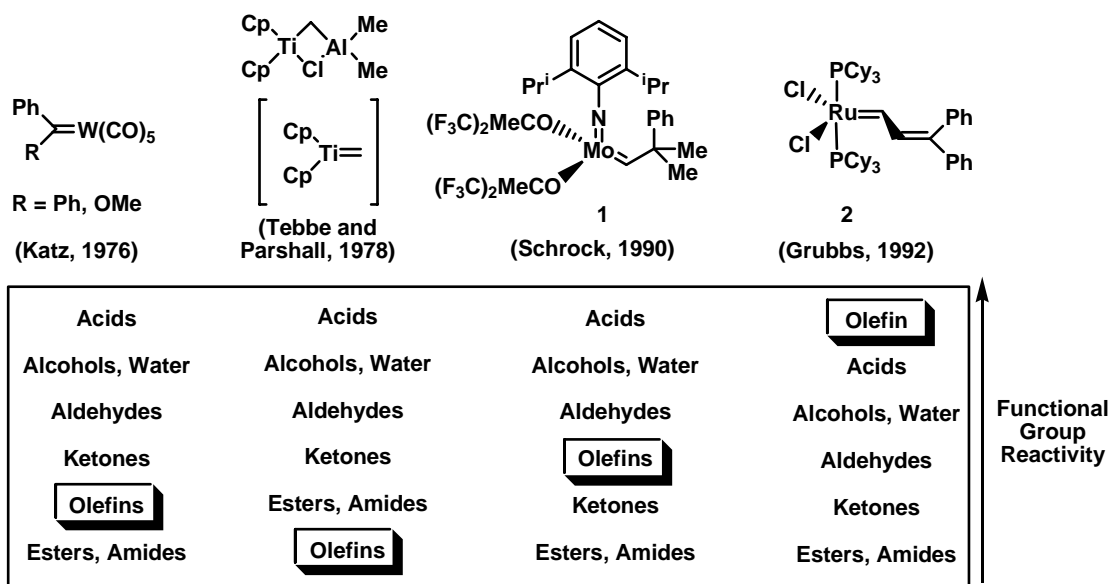
The history of olefin metathesis is fascinating. It started nearly 50 years ago through to the design and application of the latest catalyst (initiator) available today. The generally

accepted mechanism was first proposed by Hérisson and Chauvin in 1971,³ with key experimental evidences provided by the Casey,⁴ Katz⁵ and Grubbs groups⁶ (Scheme 1.2).



Scheme 1.2. Mechanism for the olefin metathesis.

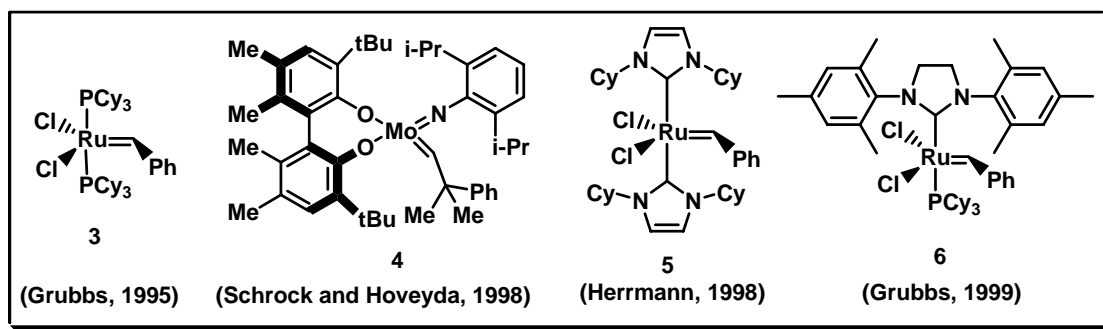
A key milestone in the evolution of olefin metathesis was demonstrated by Katz and co-workers in 1976 that, single component, well defined tungsten carbenes could initiate olefin metathesis without added coactivators (Scheme 1.3).⁷



Scheme 1.3. The evolution of single-component olefin metathesis catalyst and their functional group tolerance.

Thus from 1976 onwards, the use of multi-component catalyst systems gradually lost its importance and the field of olefin metathesis catalyst development emerged. The evolution of single-component olefin metathesis catalysts developed by different groups and their functional group tolerance is shown in Scheme 1.3.^{8,9}

The drawback of the catalyst **1** family is its sensitivity to both oxygen and moisture, since the “Mo” metal center is highly oxophilic. So both the preparation and handling of **1** require glove box techniques to establish an inert atmosphere as well as purified, dried and degassed solvents. In 1992, Grubbs and co-workers discovered an alternative catalyst **2** that can overcome many of those shortcomings.¹⁰ Over time catalyst **2** has been optimized to **3** which is far easier to prepare (Scheme 1.4).¹¹



Scheme 1.4. Recent development in olefin metathesis catalyst.

Catalyst **4** is a variation of **1**, developed by Schrock and Hoveyda; in which the molybdenum center is coordinated to a chiral derivative of BINOL, creating a homochiral environment that can induce catalytic asymmetric olefin metathesis.¹² As the activity of ruthenium based catalysts is due to the presence of a strong electron donating ligand, Herrmann and co-workers in 1998 developed catalyst **5** bearing more strongly σ -donating *N*-heterocyclic carbene ligands.¹³ Despite this potential beneficial feature, the overall activity of the catalyst **5** is only a slight improvement over **3** because the *N*-heterocyclic carbenes are strongly σ -donating; they are far less labile, thus leading to a more sluggish initiator. Based on this behaviour Grubbs and co-workers anticipated that a highly powerful catalyst for metathesis could be obtained by combining the beneficial properties of **3** and **5** into a single system **6**, in which the phosphine ligand can dissociate, while the

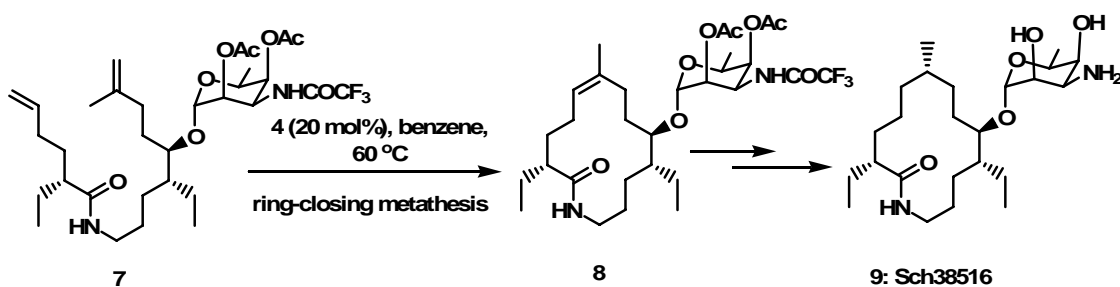
better σ -donating imidazoline type ligand remains attached to the ruthenium core.¹⁴ Moreover unlike catalyst **2** and **3** which are less thermally stable, catalyst **6** remains active even at elevated temperatures. In this regard, the bulky mesityl ligands likely shield the metal center from reaction with air, thus decrease the rate of catalyst decomposition.

1.1.3 Olefin metathesis in total synthesis:

Olefin ring-closing metathesis reaction has become one of the most powerful and reliable methods for ring formation in the natural product synthesis. A countless array of ring systems including medium or large, carbocyclic or heterocyclic has been synthesized by this sharp tool.¹⁵

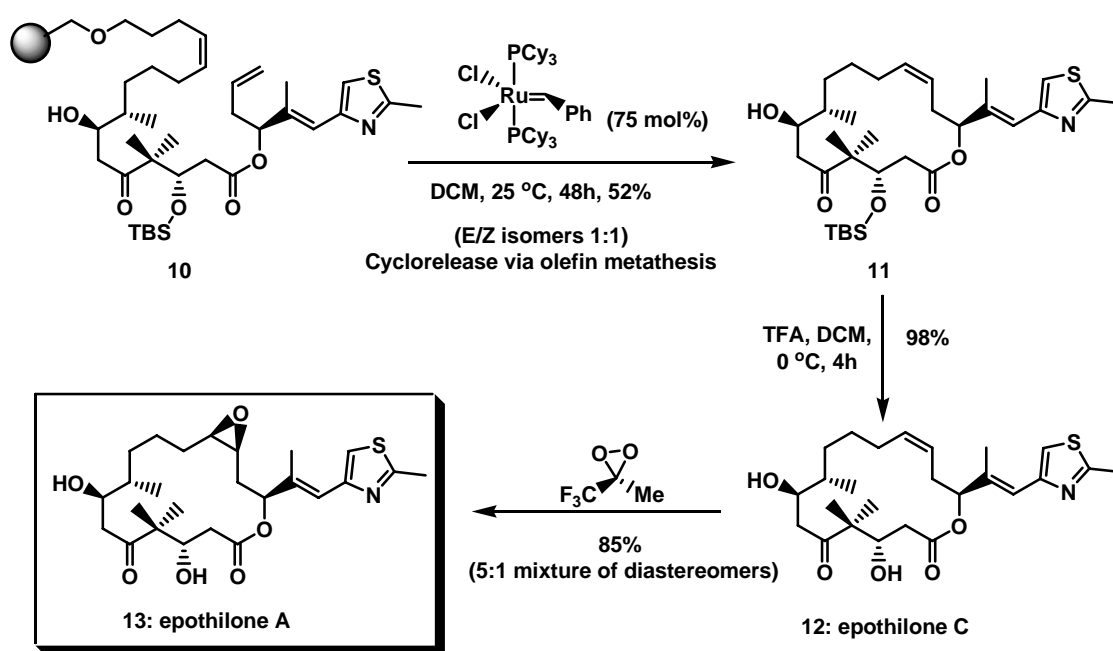
1.1.3.1 Ring-closing metathesis in the total synthesis of natural products:

Amir Hoveyda and co-workers were the first to report a successful ring-closing metathesis reaction as part of the total synthesis of a complex molecule. Targeting the natural product Sch38516 (**9**), having activity against the Influenza A virus, they showed that the trisubstituted olefinic compound **7** can be formed from a ring-closing metathesis reaction of **7** upon exposure to a 20 mol% loading of Schrock's catalyst **4** in benzene (60 °C) in 90% yield (Scheme 1.2).¹⁶



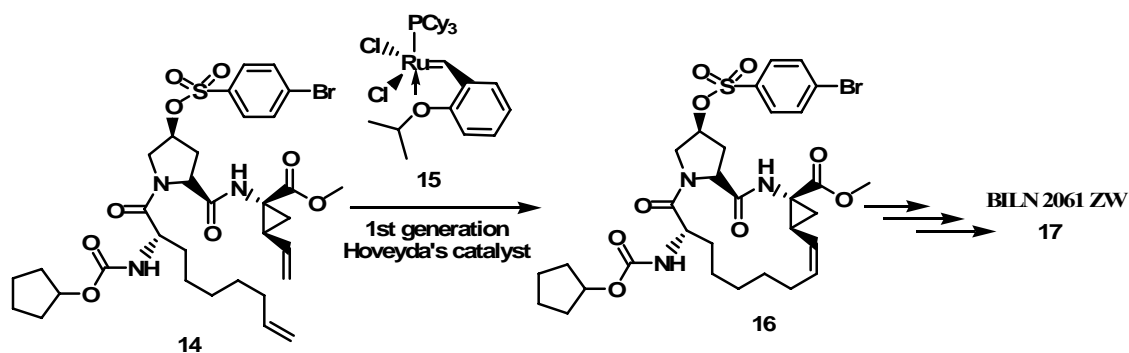
Scheme 1.5. Application of RCM in the total synthesis of Sch38516.

The Nicolaou group investigated solid phase synthesis to epothilone A (**13**), keeping in mind the metathesis technology in the context of combinatorial chemistry. The designed strategy worked remarkably well, as upon treatment of precursor **10** with the catalyst **3** under slightly longer reaction time, cycloreleased from the resin leading to epothilone C (**12**) macrocycles as an expected mixture of four products in 52% combined yield (Scheme 1.6).¹⁷ Those isomers could then be separated by high pressure liquid chromatography (HPLC).



Scheme 1.6. Application of RCM in the solid phase total synthesis of epothilone A and C.

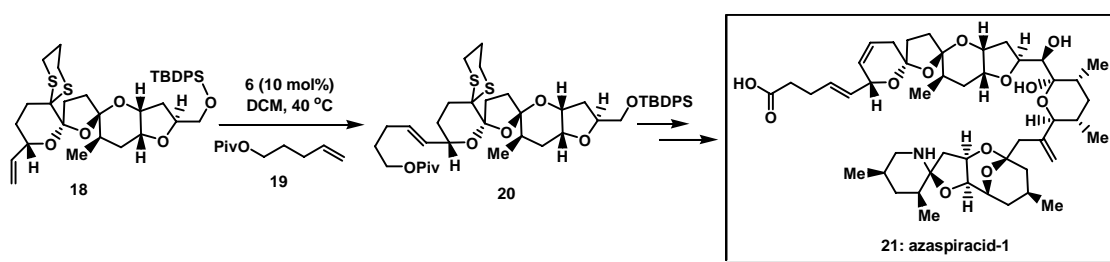
Recently Boehringer Ingelheim pharmaceutical company in Germany has used olefin metathesis for the commercial preparation of 400 kg of BILN 2061 ZW (**17**), which has promising results against the Hepatitis C virus (Scheme 1.7). The key step of the synthetic route is the conversion of the diene **14** to the 15-membered macrocycle **16** by the ring-closing metathesis reaction using 1st generation Hoveyda's catalyst **15**. The most important issue in the synthetic route is the first scale-up of a ring-closing metathesis reaction to form a 15-membered macrocycle in the industrial set up.¹⁸



Scheme 1.7. Commercial application of ring-closing metathesis to synthesize BILN 2061 ZW.

1.1.3.2 Alkene cross metathesis:

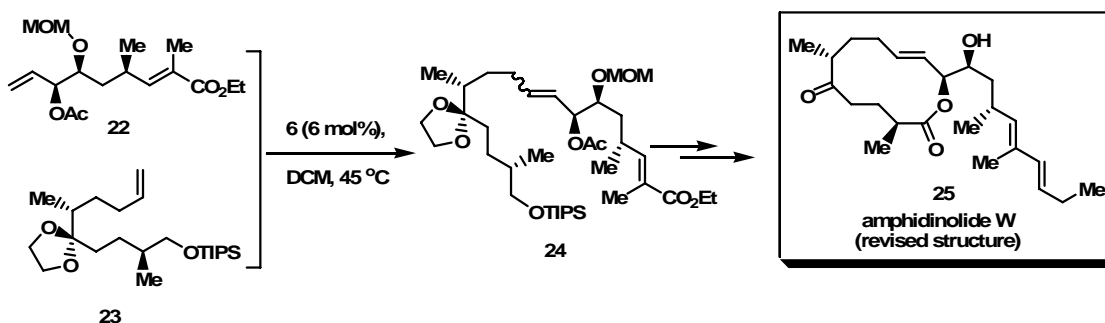
Alkene cross metathesis has long been of great importance in the industrial field. In industry the cross metathesis has been applied to convert propene into ethylene and butene and polymers to improve durability. But use of cross metathesis in the total synthesis as a viable methodology is a very much recent affair.¹⁹ The biggest challenge in cross metathesis is the chemo- and stereoselective formation of the desired compound from the mixture of potential reaction products. Applications of cross metathesis reaction in total synthesis can be divided into two classes mainly-(i) chain elongation process and (ii) fragment coupling reactions including the dimerization process. Alkene cross metathesis was efficiently used in chain elongation in the total synthesis of azaspiracid-1 (**21**, Scheme 1.8) by the Nicolaou group.²⁰



Scheme 1.8. Application of alkene cross metathesis in the total synthesis of azaspiracid-1.

When the tetracyclic compound **18** was treated with alkene **19** in presence of catalyst **6** (10 mol%) in refluxing DCM, the desired cross metathesis product **20** was formed in 60% yield and with good stereoselectivity ($E/Z = 10:1$).

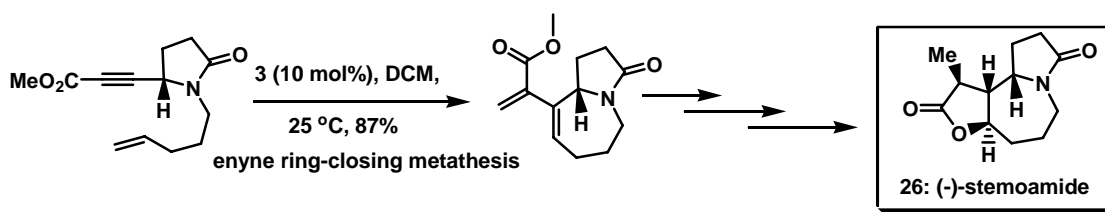
An excellent use of cross metathesis has been demonstrated by the Ghosh group in the total synthesis and structure revision of amphidinolide W (**25**, Scheme 1.9).²¹ When the advanced intermediates **22** and **23** were exposed with catalyst **6** (6 mol%) in refluxing DCM for 15h, the cross metathesis product **24** was formed in 85% yield in good E selectivity ($E/Z = 11:1$).



Scheme 1.9. Cross metathesis in total synthesis of amphidinolide W.

1.1.3.3 Enyne ring-closing metathesis:

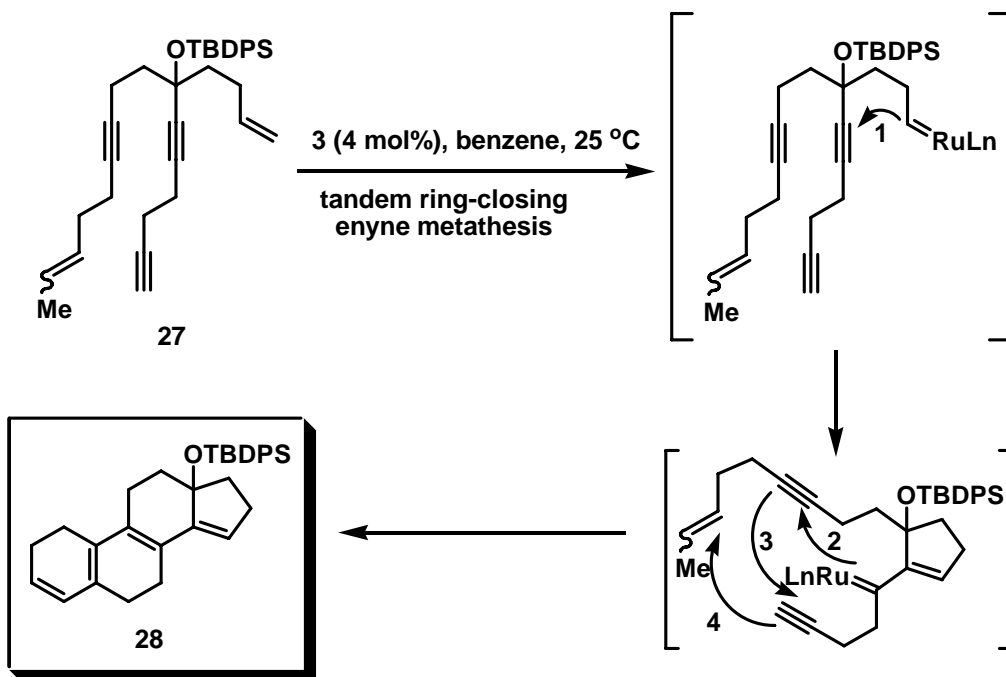
The use of ruthenium carbene complexes in the enyne metathesis chemistry was first introduced by the Mori group, demonstrating its utility in the formation of five-, six- and seven-membered nitrogen containing heterocyclic rings.²²



Scheme 1.10. Application of enyne ring-closing metathesis in the total synthesis of (-)-stemoamide.

The same group reported the first application of an enyne metathesis reaction in a total synthesis of the tricyclic alkaloid (-)-stemoamide (**26**, Scheme 1.10) in 1996.²³

One of the most exciting and powerful applications of enyne metathesis reaction is its use in the cascade reaction to generate complex polycyclic structures from simple open chain precursor. Grubbs and co-workers reported the first example of tandem enyne metathesis reaction to generate the polycyclic frame work **28** (Scheme 1.11).²⁴ The exposure of the acyclic compound **27** to the catalyst **3** (4 mol%) in benzene at ambient temperature triggered a cascade reaction resulting the formation of steroid-type compound **28** in 70% yield. In this cascade sequence four new carbon-carbon bonds and four new rings were formed in a regioselective manner.

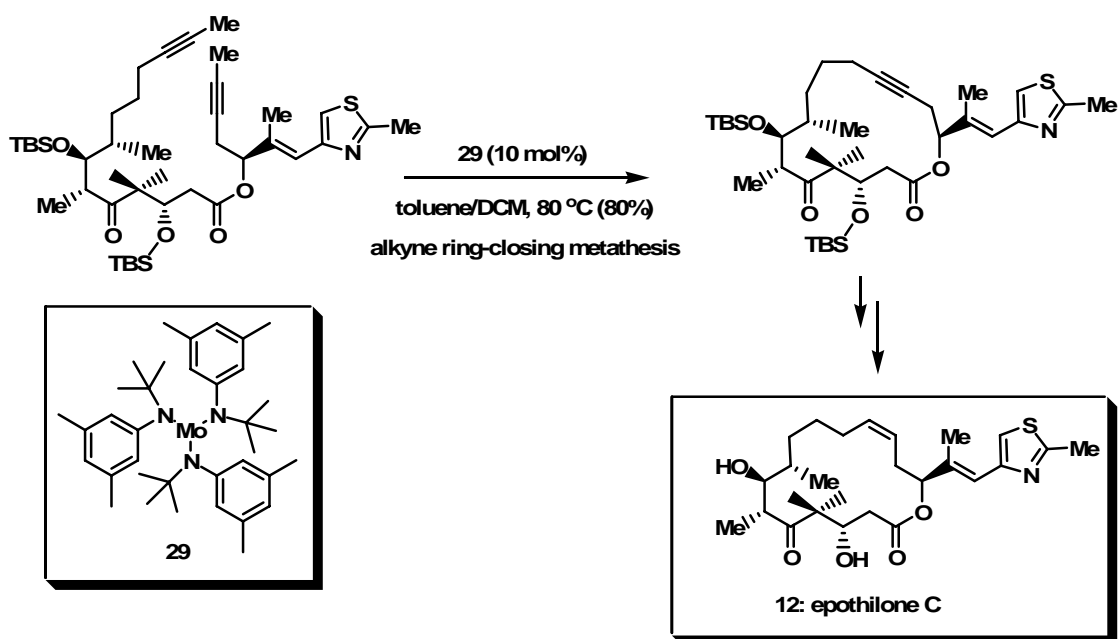


Scheme 1.11. Application of domino enyne ring-closing metathesis sequence for the construction of a steroid-type polycyclic **28**.

1.1.3.4 Alkyne ring-closing metathesis:

Since its discovery, alkyne metathesis has found very limited application in organic synthesis. However a ground breaking work was reported by the Fürstner group to show

the power of alkyne ring-closing metathesis. One of the very few shortcomings of olefin ring-closing metathesis reactions is the lack of control over the configuration of the newly formed double bond if the reaction is applied to the macrocycles. The products formed are usually obtained as mixtures of the *E* and *Z* isomers, with the former dominating in most of the recorded cases. The Fürstner group showed the strength of alkyne ring-closing metathesis reaction in the total synthesis of epothilone C (**12**) as a single isomer (Scheme 1.12).²⁵

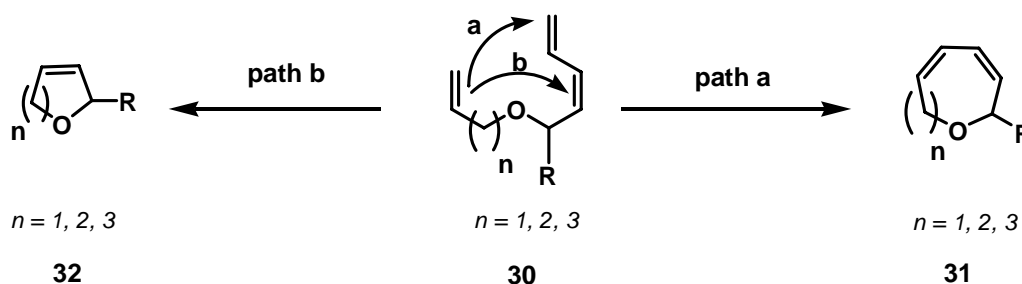


Scheme 1.12. Alkyne ring-closing metathesis in the total synthesis of epothilone C.

2. Aim of the project:

Seven-, eight- and nine-membered oxygen heterocycles with one or two double bonds embedded into the heterocyclic ring systems are characteristic structural frameworks of various natural products.²⁶ This project aimed at the synthesis of such natural product frameworks employing the ring-closing metathesis (RCM) reaction as key transformation.^{2a} Since the last couple of decades the ring-closing metathesis reaction has rapidly become an important tool to form carbon-carbon bonds.²⁷ Intramolecular diene-

ene ring closing metathesis has been used extensively to prepare many macrocyclic natural products with mostly large ring sizes very efficiently.²⁸ In the formation of small to medium ring ethers the behaviour of conjugated diene and olefin under ring-closing metathesis conditions has not yet been explored. Open chain conjugated diene-ene ethers show a very different and interesting reactivity in ring-closing metathesis to synthesize small and medium rings.



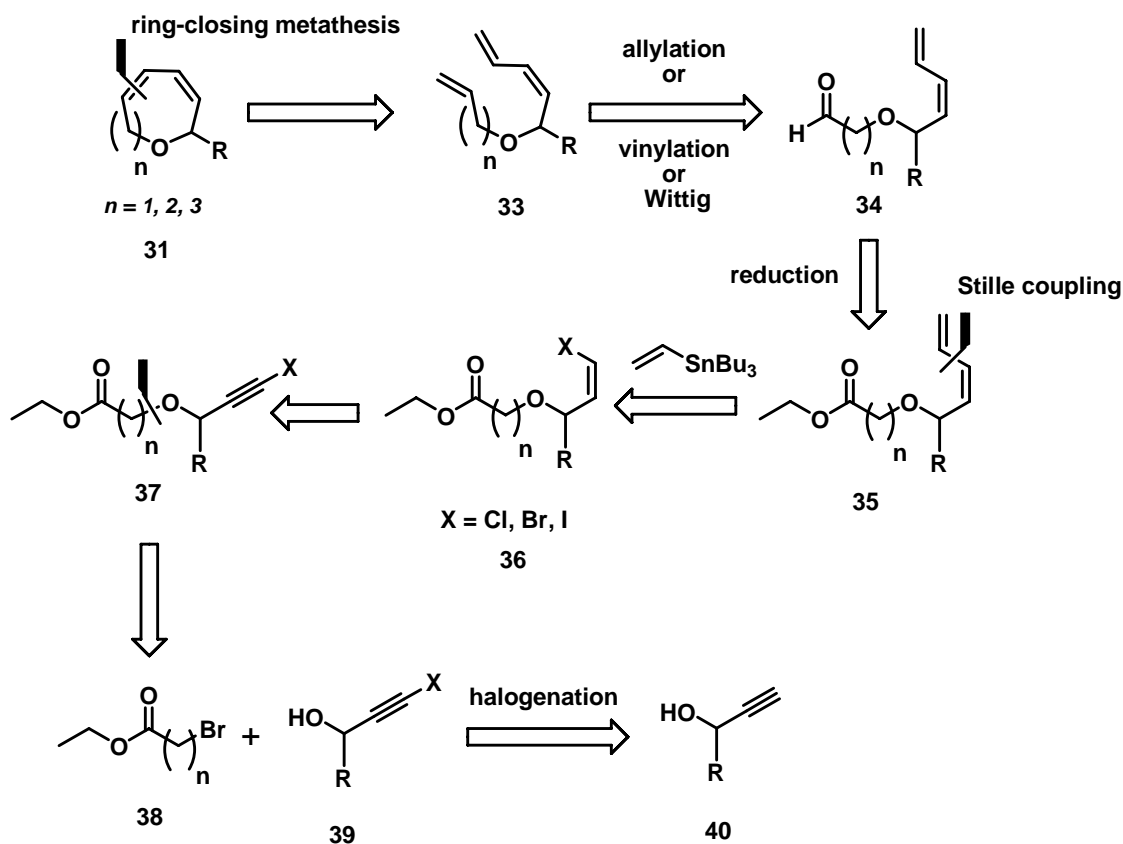
Scheme 2. Strategy for the synthesis of medium sized cyclic ethers by means of diene-ene ring-closing metathesis employing differently substituted pentadienyl ethers as substrates.

In particular, the diene-ene ring-closing metathesis reaction employing pentadienyl ethers **30** as substrates (Scheme 2) attracted immense interest since it would give rise to seven- to nine-membered cyclic dienes that would be amenable to substantial structural variation by means of various transformations. In this context the regioselectivity of the ring-closing metathesis reaction giving either rise to the larger dienyl ethers **31** or the smaller monounsaturated ethers **32** was of particular interest. The main aim of this project in one hand is to explore the regioselectivity between conjugated diene and olefin under the ring-closing metathesis conditions on the pentadienyl ether to explore either it gives the small rings or the larger ring ethers exclusively. In this regard the competition between the formation of smaller and larger rings in this metathesis condition will also be surveyed. On the other hand the aim of this project is to determine the underlying conditions which could guide the regioselectivity in this conjugated diene-ene metathesis reactions. In this perspective how the regioselectivity upon introduction of the bulk in one part of the olefin changes the course of the reactivity of the precursor in ring-closing metathesis was also investigated.

3. Results and discussions:

3.1 Retrosynthetic analysis:

The precursor of the decisive ring-closing metathesis **33** was intended to be synthesized from the commercially available propargyl alcohol **40**. The retrosynthetic analysis is shown in Scheme 3.1.



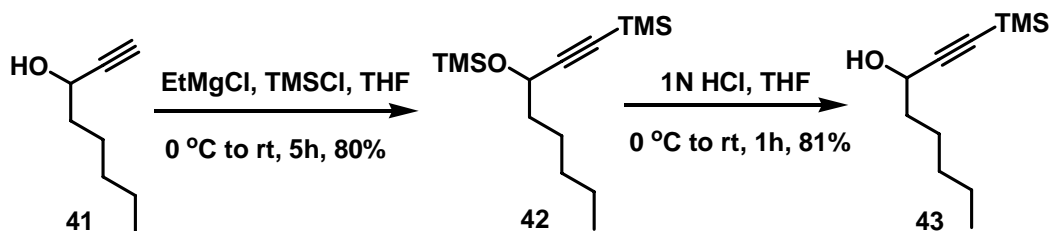
Scheme 3.1. Retrosynthetic analysis of the targeted small and medium dienylic cyclic ethers.

The dienylic cyclic ethers **31** can be envisioned to be synthesized by ring-closing metathesis from the open chain triene precursor **33**. The latter can be synthesized from the key diene aldehyde **34** by means of allylation or vinylation by allyl or vinyl Grignard reagents or by Wittig olefination. The aldehyde **34** can be obtained from the diene ester **35** by reduction, whereas the diene moiety in **35** can be obtained by the Pd catalyzed

Stille cross coupling reaction from the vinyl halide **36**, which in turn can be synthesized from the acetylinic halide **37** by means of selective reduction of alkyne to the *Z*-olefin. The ether moiety in **37** intermediate can be tethered by the etherification of the substituted halogenated propargyl alcohol **39** and bromoethyl acetate **38**. The commercially available substituted propargyl alcohol **40** can be halogenated to synthesize **39**. Based on this blue print journey was commenced to synthesize the ring-closing metathesis precursors **33** from commercially available substituted propargyl alcohol **40**.

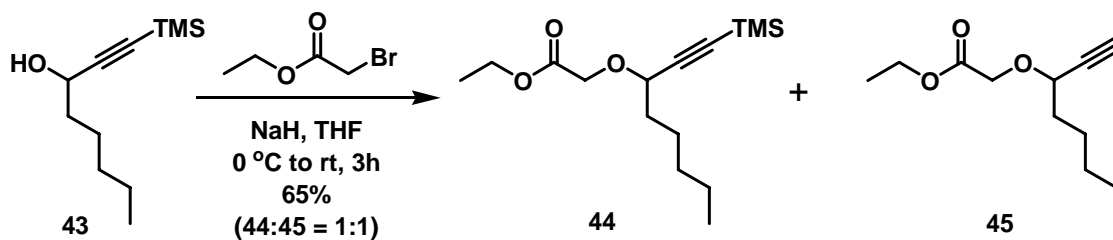
3.2 Synthesis of the ether moiety:

The synthetic strategy proceeded from the commercially available substituted propargyl alcohol **41**. Compound **41** was first doubly protected by trimethyl silyl (TMS) group using ethyl magnesium chloride, trimethyl silyl chloride (TMSCl) in THF from 0 °C to room temperature for 5h, giving rise to **42** in 80% yield. The alcohol in compound **42** was then selectively deprotected by using 1N HCl in THF to produce **43** in 81% yield (Scheme 3.2).²⁹



Scheme 3.2. Synthesis of **43** from **41**.

Ether formation of compound **43** by ethyl bromo acetate in the presence of sodium hydride (NaH) as a base in THF at 0 °C to room temperature for 3h, yielded along with desired product **44**, an undesired product **45** in 1:1 mixture in total 65% yield (Scheme 3.3).³⁰



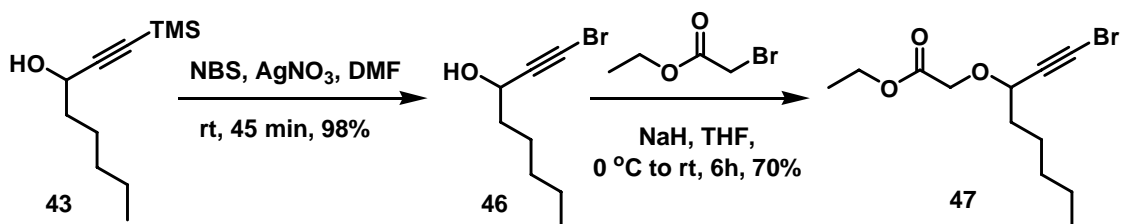
Scheme 3.3. Ether formation reaction.

Compound **45** was treated with ethyl magnesium chloride and trimethylsilyl chloride (TMSCl) in THF at 0 °C to room temperature to produce **44** again. Different reaction conditions (Table 3.1) were tested changing the temperature for protecting the alkyne in **45**, but in all cases decomposition of the starting material was observed with no trace of **44**.

Table 3.1. Use of different base and temperature to convert **45** to **44**.

Entry	Base	Temperature	Product
1	EtMgCl	-78 °C to rt	Decomposition of 45
2	<i>n</i> BuLi	-78 °C to rt	Decomposition of 45
3	NaHMDS	-78 °C to rt	Decomposition of 45

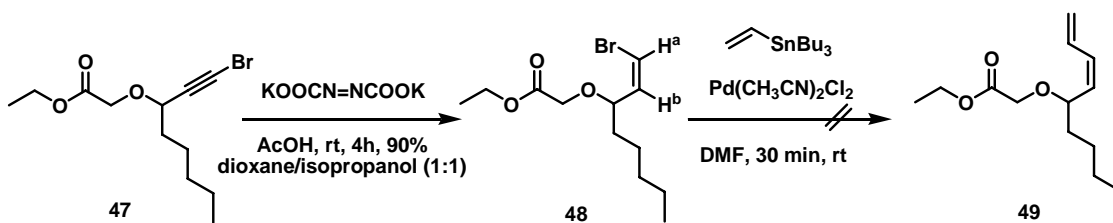
Since the trimethylsilyl group (TMS) was not stable enough in the presence of a base such as sodium hydride and half of the product was lost, it was decided to halogenate the alkyne first and then to carry out the ether formation reaction. Thus **43** was treated with *N*-bromosuccinimide (NBS) in the presence of catalytic amounts (20 mol%) of silver nitrate in DMF at room temperature for 45 minutes.³¹ The bromo derivative **46** was formed in nearly quantitative yield (98%). Then the ether formation reaction set off very smoothly when **46** was deprotonated with sodium hydride and treated with ethyl bromoacetate in THF at 0 °C to room temperature for 6h to afford the ether **47** in 70% yield (Scheme 3.4).



Scheme 3.4. Synthesis of ether **47**.

3.3 Stille cross coupling:

The subsequent step was to reduce the alkyne moiety in **47** to form the *Z*-vinyl bromide **48**. The reduction of **47** was accomplished by *in situ* formation of the diimide from the dipotassium salt of aza dicarboxylic acid in the presence of acetic acid in 1:1 solvent mixture of 1,4-dioxane and isopropanol at room temperature for 4h to afford the *Z*-vinyl bromide **48** in 90% yield (Scheme 3.5).^{32a, b} The *Z*-geometry was determined by the small coupling constant ($J_{\text{H}^{\text{a}}-\text{H}^{\text{b}}} = 7.2 \text{ Hz}$) between H^{a} and H^{b} by ^1H NMR spectroscopy.

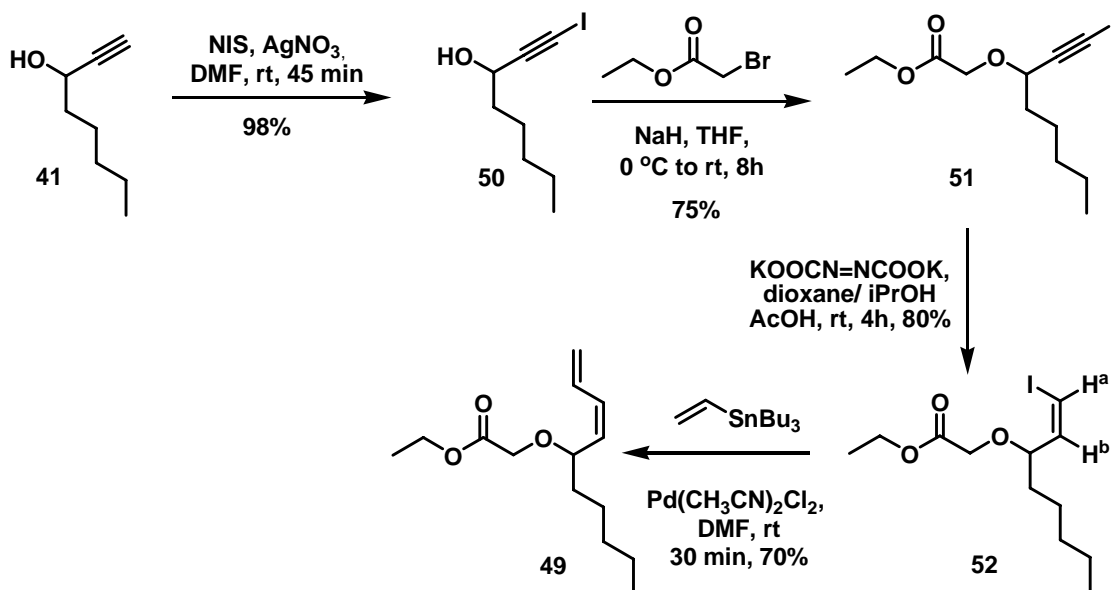


Scheme 3.5. Attempted synthesis of **49**.

The decisive palladium catalyzed Stille cross coupling reaction was endeavored with *Z*-vinyl bromide **48** and tributyl vinyl tin in presence of 5 mol% of $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ catalyst in DMF at room temperature to afford the diene **49**.³³ But the Stille cross coupling reaction did not yield the desired diene compound **49** and decomposition of the starting material **48** was observed.

It materialized that the vinyl bromide **48** was not the best substrate for the attempted palladium catalyzed Stille cross coupling to generate the diene **49**. Keeping the idea in

mind that the vinyl iodide analogue of **48** could give rise to **49** by Stille cross coupling, the synthesis of vinyl iodide was set off from the same commercially available oct-1-yn-3-ol **41**. Instead of treating **41** with NBS, it was then treated with *N*-iodosuccinimide (NIS) in the same reaction condition in presence of 20 mol% of AgNO₃ in DMF at room temperature for 45 minutes to afford the iodo derivative **50** in 98% yield (Scheme 3.6).^{32a, b, 34} Ether **51** was prepared in 75% yield using ethyl bromoacetate and NaH. The alkyne moiety in **51** was reduced to *Z*-vinyl iodide **52** in 80% yield using the reduction protocol discussed before. In compound **52** the *Z*-geometry of the olefin was confirmed by the small coupling constant ($J_{\text{H}^a\text{-H}^b} = 7.6$ Hz) between H^a and H^b by ¹H NMR spectroscopy. When the vinyl iodide **52** was treated with tributyl vinyl tin in presence of 5 mol% of Pd(CH₃CN)₂Cl₂ catalyst in DMF at room temperature, the diene **49** was achieved in 70% yield (Scheme 3.6).³³

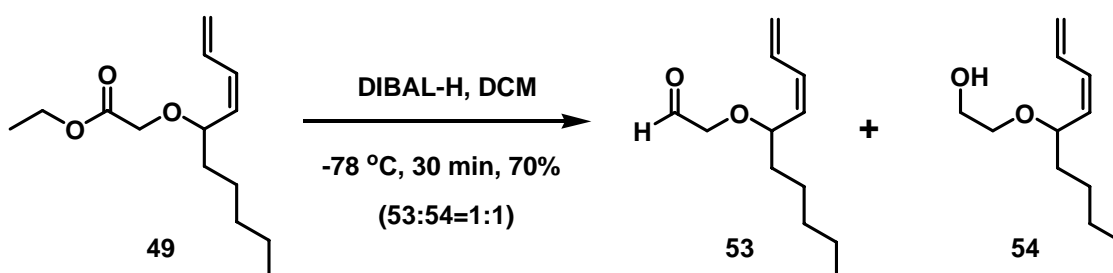


Scheme 3.6. Synthesis of the diene **49**.

3.4 Synthesis of the aldehyde intermediate **53**:

Achieving diene **49** in a smooth way, the following step was to reduce the ethyl ester to the aldehyde to acquire the key intermediate **53**. The diene ethyl ester **49** was treated with

diisobutylaluminiumhydride (DIBAL-H) in DCM at -78 °C temperature for 30 minutes to afford the 1:1 mixture of both the desired aldehyde **53** and undesired over reduced alcohol **54** in 70% yield (Scheme 3.7).³⁵ The products ratio was determined based on the isolated yield.



Scheme 3.7. Attempted reduction of **49** to **53**.

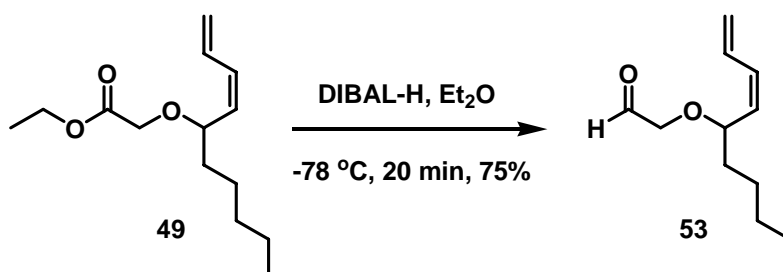
After chromatographic separation, the oxidation of alcohol **54** to aldehyde **53** was attempted under different reaction conditions (Table 3.2) but not a single procedure gave the desired aldehyde **53**.

Table 3.2. Different oxidizing agents and conditions to convert **54** to **53**.

Entry	Starting material	Conditions	Product
1	54	PCC ³⁶ DCM, rt, 3h	decomposition
2	54	IBX ³⁷ DMSO, 0 °C to rt, 3h	decomposition
3	54	TEMPO ³⁸ NaOCl, KBr, DCM, -10 °C, 5h	decomposition
4	54	(CO) ₂ Cl ₂ , DMSO, Et ₃ N ³⁹ DCM, -78 °C, 2h	decomposition

It appeared from the above table, that in all the cases the starting alcohol **54** was sensitive to both the acidic and basic conditions and it decomposed.

Thus the remedy of the above mentioned problem was to reduce the ethyl ester moiety to aldehyde selectively. Changing the solvent from DCM to diethyl ether and using high dilution solved the problem. Hence treating **49** with diisobutylaluminiumhydride in diethyl ether in very diluted solution under vigorous stirring and slow addition of DIBAL-H at $-78\text{ }^{\circ}\text{C}$ temperature, the aldehyde **53** was obtained exclusively in 75% yield without any trace of the alcohol **54** (Scheme 3.8).

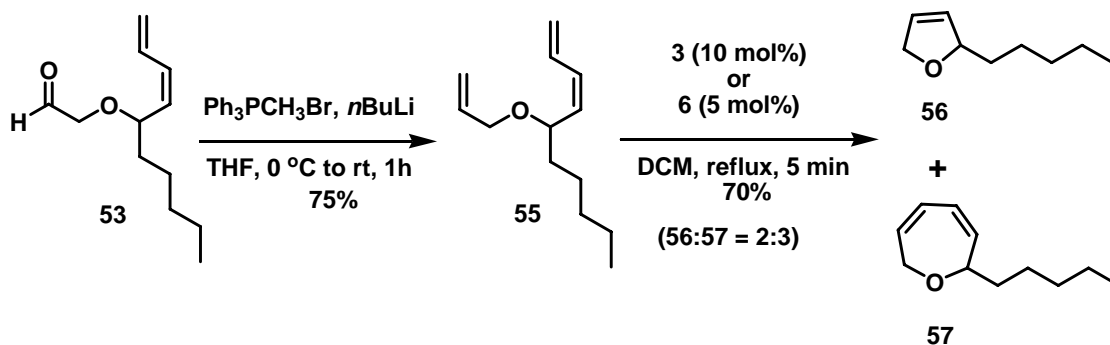


Scheme 3.8. Synthesis of **53** from **49** by DIBAL-H reduction.

3.5 Regioselectivity between five- and seven-membered ring formations:

With the key aldehyde intermediate **53** in hand, the path was set to synthesize different diene-ene precursor to investigate the metathesis reactions on them to get the idea about their regioselectivity. To explore the regioselectivity between the five-membered and seven-membered ring, the precursor **55** was synthesized by the Wittig olefination of the aldehyde **53**. The Wittig salt was generated *in situ* by treatment of triphenylmethyl phosphonium bromide in the presence of *n*-butyl lithium as a base in THF at $0\text{ }^{\circ}\text{C}$ for 30 minutes. The Wittig ylide was then treated with the aldehyde **53** at $0\text{ }^{\circ}\text{C}$ to room temperature for 1h to get the diene-ene precursor **55** in 75% yield (Scheme 3.9).⁴⁰ When **55** was exposed separately with either 10 mol% of Grubbs 1st generation catalyst **3** or 5 mol% of 2nd generation Grubbs catalyst **6** in refluxing DCM, a mixture of five- and

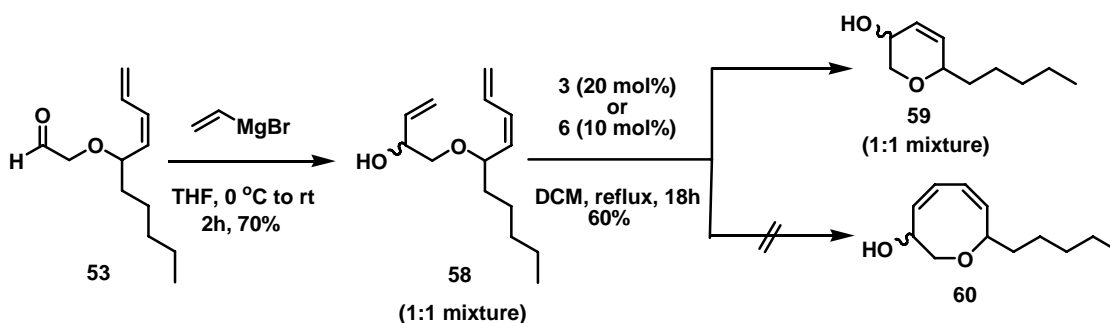
seven-membered ring ethers **56** and **57** in 2:3 ratio in 28% and 42% yield respectively in 5 minutes. The products ratio was based on isolated yield.



Scheme 3.9. Competition between the five and seven membered ring ethers **56** and **57**.

3.6 Regioselectivity between six- and eight-membered ring formations:

Next the competition between the six-membered and the eight-membered ring ethers was explored. The requisite precursor was directly synthesized from the intermediate **53** by treating it with vinylmagnesiumbromide in THF at $0\text{ }^\circ\text{C}$ to room temperature for 2h to furnish the allylic alcohol **58** as 1:1 inseparable mixture of two isomers in 70% yield (Scheme 3.10). The isomeric ratio was determined by the ^1H NMR spectroscopy.

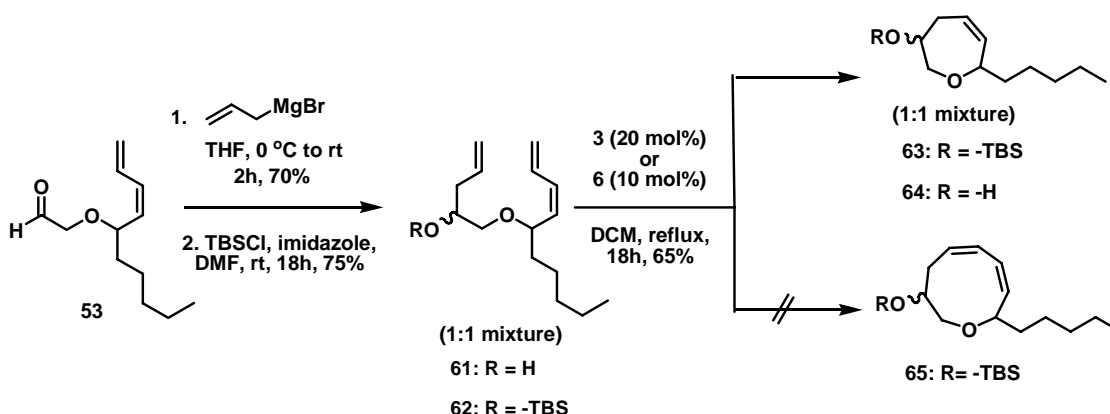


Scheme 3.10. Competition between the six and eight membered ring ethers **59** and **60**.

When 1:1 isomeric mixture of **58** was treated with Grubbs 1st generation catalyst **3** (20 mol%) in refluxing DCM for 18h, only the six membered cyclic ether **59** was formed exclusively in 60% yield as 1:1 inseparable mixture of two isomers (ratio determined by ¹H NMR spectroscopy) without any trace of the eight membered cyclic diene ether **60**. The same result was found when compound **58** was treated with 10 mol% of 2nd generation Grubbs catalyst **6** in refluxing DCM.

3.7 Regioselectivity between seven- and nine-membered ring formations:

The aldehyde **53** was treated with allylmagnesiumbromide in THF at 0 °C to room temperature for 2h to afford the homoallyl alcohol **61** as 1:1 mixture of two diastereomers in 70% yield (Scheme 3.11). The diastereomeric mixture was determined by ¹H NMR spectroscopy.



Scheme 3.11. Competition between the seven- and nine-membered ring ethers **63** and **65**.

The homoallyl alcohol **61** was then protected as tertiary butyl dimethylsilyl ether **62** by treatment with tertiary butyl dimethyl silylchloride (TBSCl) in the presence of imidazole as base in DMF at room temperature for 18h in 75% yield. Ring-closing metathesis of this TBS-protected homoallyl alcohol **62** using 20 mol% of **3** in refluxing DCM for 18h afforded the seven-membered mono olefinic cyclic ether **63** as 1:1 inseparable mixture of two isomers in 65% yield devoid of any trace of the doubly unsaturated nine-membered

cyclic ether **65**. The same result was observed using 10 mol% of **6** as the metathesis catalyst.

From the above study about the regioselectivity in ring-closing metathesis it could be concluded that in all the cases the generation of the ruthenium carbene complex initiated in the isolated olefin moiety and then terminated in the diene moiety to generate the smaller possible rings. The only exception observed was in the case of the competition between the five- and seven-membered ring formations, where both were formed. To investigate whether the ring-closing metathesis reaction was kinetically or thermodynamically controlled two further experiments were carried out.

On one hand, the formation of five- and seven-membered ethers **56** and **57** was followed by means of GC-MS. The treatment of dienyl ether **55** with first generation Grubbs catalyst **3** in refluxing DCM within 5 min led to complete consumption of the starting material, and the initially determined product ratio did not change if the refluxing was continued for 1h. At room temperature, the reaction required 2 h to proceed to completion with the product ratio showing the same distribution. On the other hand, if the seven-membered cyclic dienyl ether **57** was subjected to the conditions of the ring-closing metathesis, that is, refluxing in DCM in presence of 10 mol% of **3** and ethylene for 3h, formation of the five-membered cyclic ether **56** was detected by GC-MS.⁴¹ Assuming that the five-membered ring ether is more stable than the seven-membered cyclic ring ether, these results indicate that this ring-closing metathesis reaction is thermodynamically controlled.

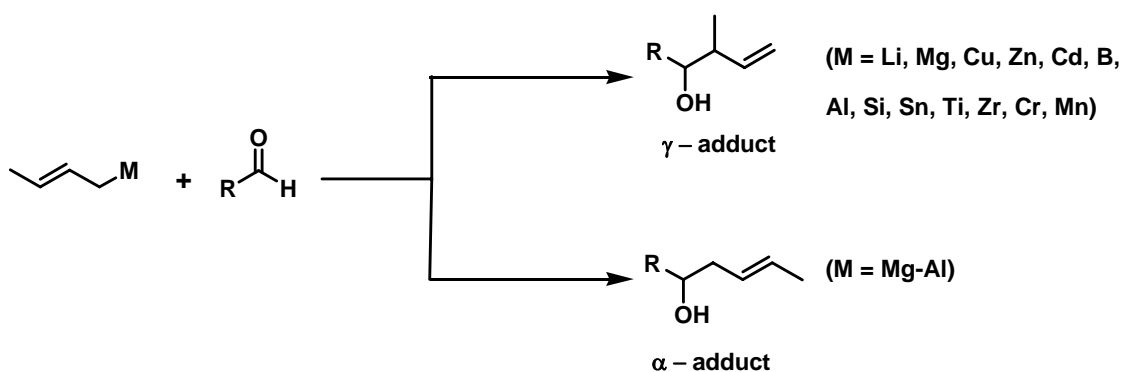
3.8 Introduction of bulk in the isolated olefin moiety:

3.8.1 Crotylation of aldehyde **53:**

As it was speculated from the behavior of the regioselectivity in the ring-closing reactions in the diene-ene ethers that the metathesis reaction initiated by the formation of the ruthenium carbene in the isolated olefin followed by the termination in the diene-moiety, the investigations were directed towards the formation of the initial ruthenium carbene at the diene moiety, so that the termination can happen in the isolated olefin to give rise to the larger ring ethers. The initial ruthenium carbene can only be formed in the diene

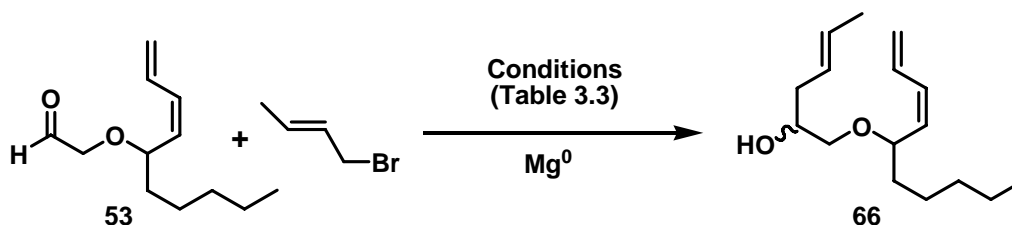
moiety if its formation can be prevented in the isolated olefin moiety. This can be done by increasing the bulk in the isolated olefin.

One methyl group was chosen as the smallest bulky group to be introduced in the isolated olefin moiety. The reaction of unhindered carbonyl compounds with substituted allylic organometallic reagents such as $M = \text{Li, Mg, Cu, Zn, Cd, B, Al, Si, Sn, Ti, Zr, Cr}$ and Mn , generally results in products where the allylic group is attached at the more highly substituted position forming the γ -adduct. On the other hand the regioversed addition is one of the difficult problems in the organic synthesis (Scheme 3.12). But the reaction of carbonyl compounds with crotylmagnesiumchloride in the presence of AlCl_3 at -78°C gives predominantly products in which the allylic group is attached at the less substituted position (α -adduct).⁴²



Scheme 3.12. Regioselectivity of crotylation.

The aldehyde **53** was treated with 1-bromo-2,3-butene and Mg metal in THF to synthesize the homoallyl alcohol **66** (Scheme 3.13), in different conditions (Table 3.3).



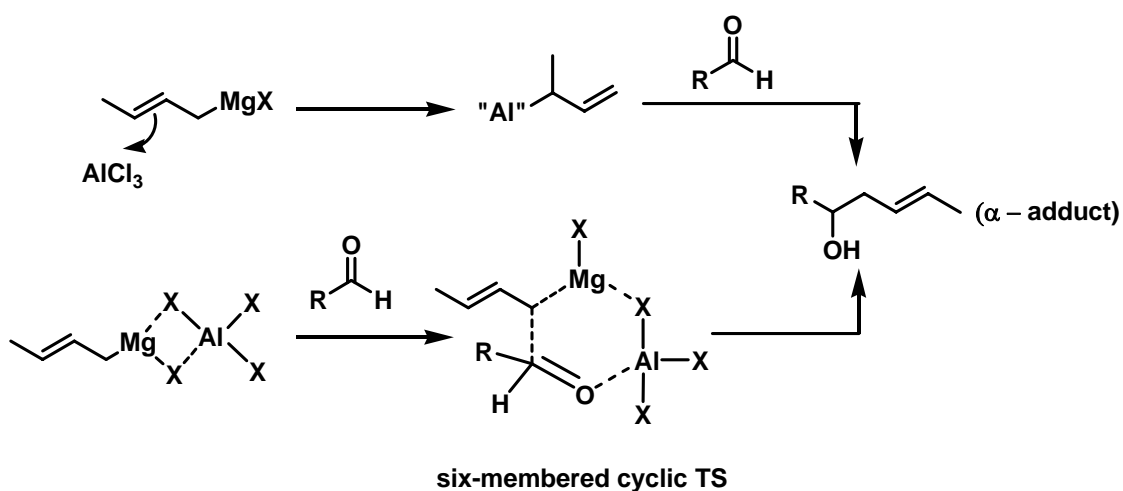
Scheme 3.13. Attempted synthesis of **66**.

Unfortunately in all the cases the homo-coupled product from the halide was found as the main product with the recovery of the starting material **53**. But when the reaction was carried out in diethyl ether as solvent and in the presence of the additive aluminium chloride as a Lewis acid the expected product **66** was formed in 40% yield as 1:1 mixture of the two isomers, together with the homo coupled product from the bromide.⁴² The isomeric ratio was determined by ¹H NMR spectroscopy.

Table 3.3. Conditions to synthesize **66**.

Entry	Conditions	Additive	Solvent	Product
1	0 °C to rt, 2h	-	THF	Homo-coupled diene
2	-78 °C to rt, 4h	-	THF	Homo-coupled diene
3	-78 °C, 4h	AlCl ₃ (3 equiv)	Et ₂ O	Homo-coupled diene
4	-78 °C to rt, 2h	AlCl ₃ (3 equiv)	Et ₂ O	66 (40%) + homo-coupled diene

There are two plausible mechanisms for the regioreversed addition of crotylmagnesium halide to **53** in presence of AlCl₃ (Scheme 3.14).

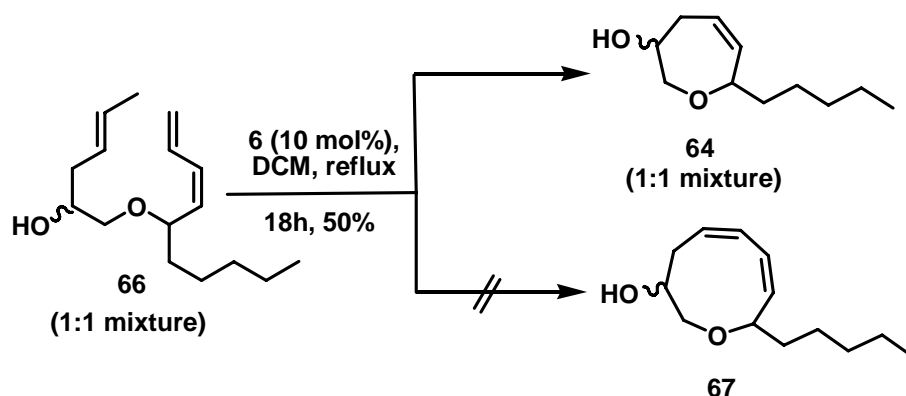


Scheme 3.14. Mechanism of the regioreversed addition of crotylmagnesium halide.

In the first case, the transmetalation of crotyl magnesium reagent to aluminium reagent via S_E2' process followed by rapid S_E2' reaction of the resulting α -metallylaluminium reagent with carbonyl compounds. According to the second mechanism Mg-Al bridged species forms followed by the coordination of carbonyl group to Al-atom to produce α -adduct through a six-membered cyclic transition state. The intermediates are stable only at low temperature and must undergo facile rearrangement at higher temperature.⁴²

3.8.2 Attempted ring-closing metathesis of 66:

When the 1:1 isomeric mixture of the advanced intermediate **66** was treated with 10 mol% of 2nd generation Grubbs catalyst **6** in refluxing DCM for 18h, the mono unsaturated seven-membered ring **64** was formed as 1:1 inseparable mixture of two isomers in 50% yield devoid of any sign of the expected doubly unsaturated nine-membered ring ether **67** (Scheme 3.15). The isomeric ratio was determined by ¹H NMR spectroscopy.

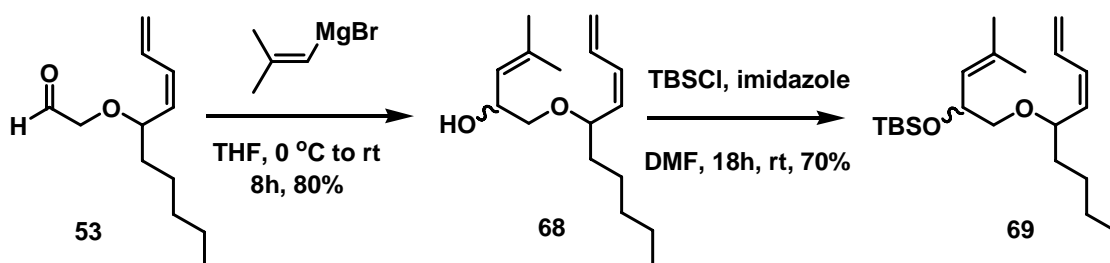


Scheme 3.15. Competition between seven- and nine-membered ring ethers on advanced intermediate **66**.

Therefore it was evident that only one methyl group on the isolated olefin moiety was not sufficiently bulky to drive the initial formation of the ruthenium carbene in the isolated olefin and termination in the conjugated diene moiety. Hence the synthesis of the advanced intermediate with two methyl groups in the isolated olefin moiety was intended.

3.8.3 Dimethylvinylation of aldehyde **53**:

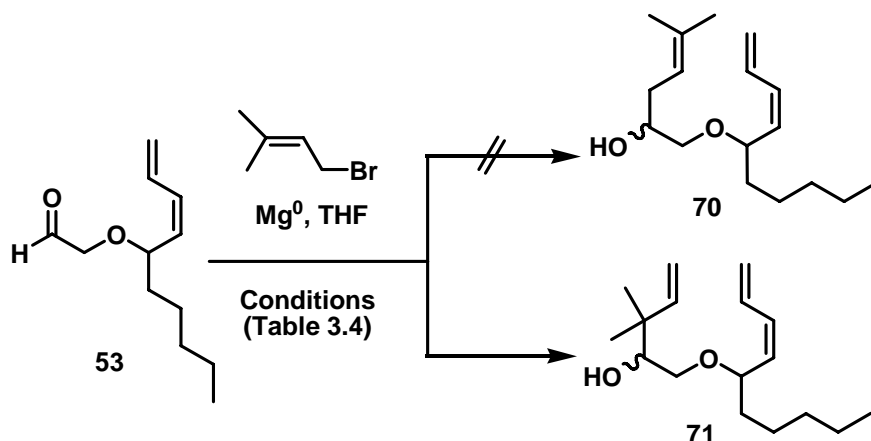
To synthesize the dimethyl substituted advanced intermediate for the regioselective competition between the six- and eight-membered ring ethers, aldehyde **53** was treated with 2-methyl-1-propenyl-magnesiumbromide at 0 °C to room temperature in THF for 8h.⁴³ Alcohol **68** was formed in 80% yield as 1:1 inseparable mixture of two isomers. Alcohol **68** was protected to the TBS ether **69** with the treatment of *t*-butyl dimethyl silyl chloride (TBSCl) and imidazole as base in DMF at room temperature in 70% yield (Scheme 3.16).



Scheme 3.16. Synthesis of the advanced intermediate **69**.

3.8.4 Attempted dimethylallylation of aldehyde **53**:

After achieving **69** successfully the attention was focused on the synthesis of the dimethyl substituted advanced intermediate for the regioselective competition between the seven- and nine-membered cyclic ethers. The aldehyde **53** was treated with dimethylallyl bromide and magnesium metal activated by iodine in THF under different conditions, but the desired product **70** was not formed. Only the undesired product **71** was formed in 60% yield (Scheme 3.17 and Table 3.4).



Scheme 3.17. Attempted synthesis of 70.

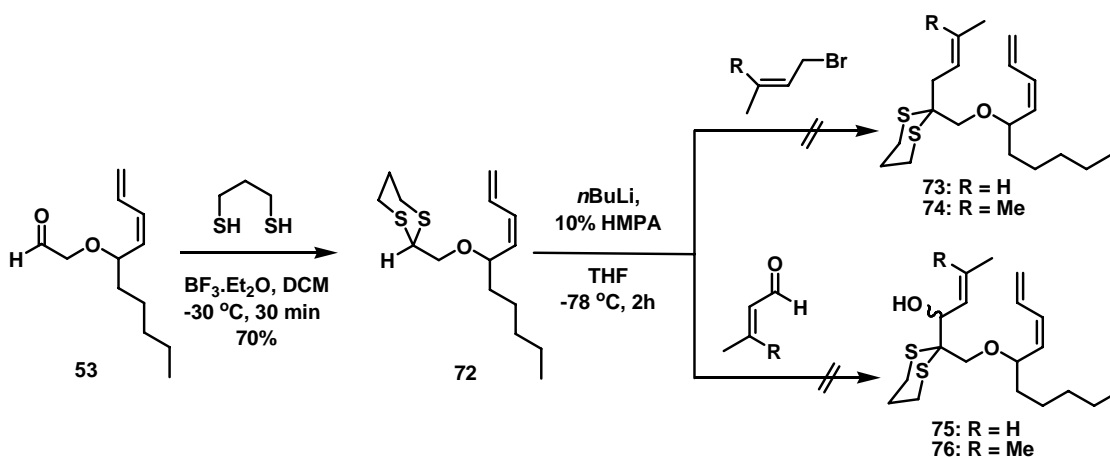
Table 3.4. Conditions for the attempted synthesis of 70.

Entry	Conditions	Time	70 (yield)	71 (yield)
1	-78 °C	3h	-	50%
2	-78 °C to room temperature	3h	-	60%
3	0 °C	3h	-	60%
4	0 °C to room temperature	3h	-	65%

The reason for the above result was that, as soon as the Grignard reagent formed from the dimethylallyl bromide, it rearranged to the most stable tertiary magnesium bromide reagent even at low temperature. To overcome this problem umpolung strategy was adopted to change the polarity of both the reagent and substrate.

3.8.5 Umpolung of aldehyde 53:

The aldehyde **53** was treated with 1,3-propane dithiol in the presence of boron trifluoride diethyl ether complex (BF₃.Et₂O) as a Lewis acid at -30 °C in DCM in 30 minutes to afford the dithiane product **72** in 70% yield (Scheme 3.18).⁴⁴



Scheme 3.18. Attempted deprotonation of dithian **72** and alkylation.

When the dithiane **72** was treated with *n*-butyl lithium in 10% hexamethylphosphoramide (HMPA) as protic solvent in THF at $-78\text{ }^\circ\text{C}$ with either crotyl bromide or dimethylallyl bromide for 2h, neither expected product **73** nor **74** were found. Only the starting material was recovered. The dithiane **72** was also treated with either crotonaldehyde or dimethyl crotonaldehyde separately in the same reaction conditions, but again the expected products **75** or **76** were not found. Here again the starting material was recovered.⁴⁵

The failure of the alkylation was reasoned due to the lack of the acidity of the dithiane **72**. The dithiane **72** forms two interconverting six-membered chair conformations where the acidic proton contains either axial or equatorial position (Figure 3). In the axial conformation the deprotonation is very slow due to the insufficient overlap of the C-H axial bond with the C-S σ^* orbital which is the main reason of the acidity of the dithiane proton. Moreover the diene part in the dithiane **72** also forms a six membered chair type transition state by which the π orbital of the diene donate its electron density to the C-S σ^* orbital which is reason of the lack of acidity in the equatorial conformation.⁴⁶

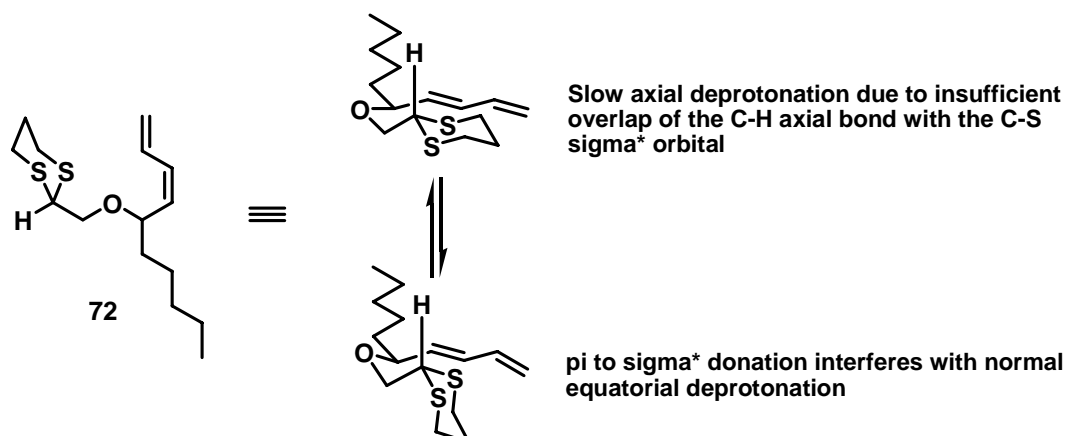
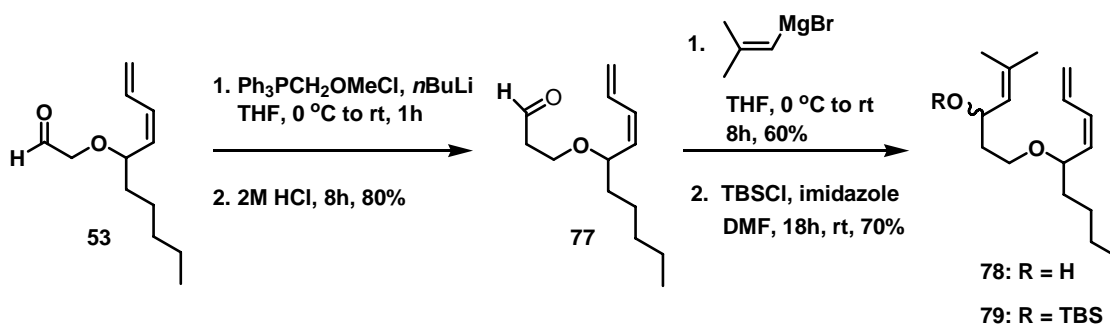


Figure 3. Conformations of the dithiane 72.

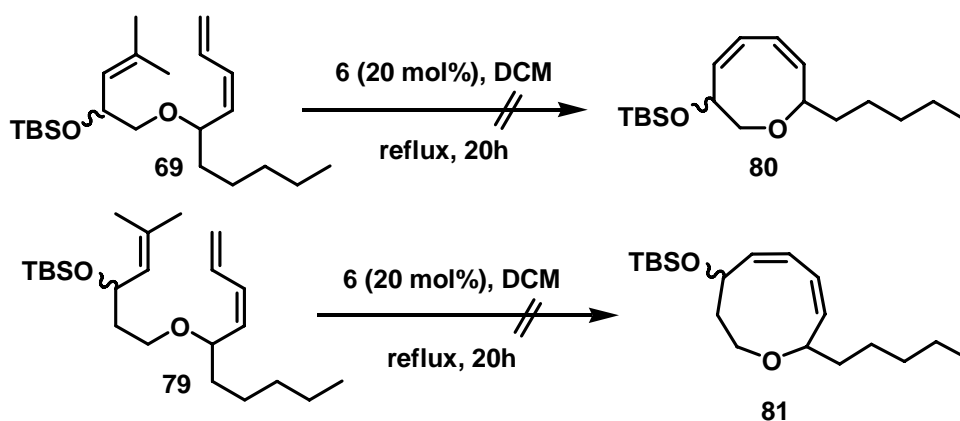
3.8.6 Synthesis of advanced intermediate 79:

Facing this dead end, a bypass synthetic strategy was adopted. The aldehyde **53** was first homologated to aldehyde **77** by Wittig olefination followed by the hydrolysis of the vinyl ether. The aldehyde **53** was added dropwise into the ylide prepared in situ by the treatment of triphenyl methoxymethylphosphonium chloride and *n*-butyl lithium solution at 0 °C and stirred the reaction at room temperature for 30 minutes, then the formed product was hydrolyzed by 1M hydrochloric acid for 8h to afford the homologous aldehyde **77** in 80% yield along with some decomposed product (Scheme 3. 19).⁴⁰ The aldehyde **77** was then treated with 2-methyl-1-propenyl-magnesiumbromide in THF at 0 °C to room temperature for 8h to afford the dimethylallyl alcohol **78** as 1:1 inseparable mixture of two isomers in 60% yield,⁴³ which was then protected with *t*-butyl dimethylsilane using *t*-butyl dimethylsilyl chloride (TBSCl) and imidazole as base in DMF in 18h to afford the TBS protected alcohol **79** in 70% yield.



Scheme 3.19. Synthesis of the advanced intermediate 79.

When both **69** and **79** were treated separately with 20 mol% of the 2nd generation Grubbs catalyst **6** in refluxing DCM and also in refluxing toluene, neither the doubly unsaturated eight-membered cyclic ether **80** nor doubly unsaturated nine-membered cyclic ether **81** were formed (Scheme 3.20).

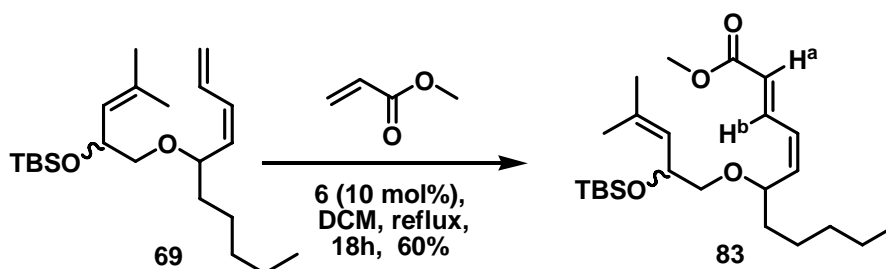


Scheme 3.20. Attempted synthesis of **80** and **81**.

Only the starting material was recovered in both cases, which suggested that dimethyl substituents were enough bulky not to initiate the metathesis in the isolated olefin moiety.

3.8.7 Cross metathesis on advanced intermediate 69:

At this point it was considered whether the initial ruthenium carbene formed in the conjugated olefin moiety or not. To ensure this point precursor **69** (1:1 inseparable mixture of two isomers) was treated with methyl acrylate in the presence of 10 mol% of 2nd generation Grubbs catalyst **6** in refluxing DCM for 18h and the cross metathesis product **83** was isolated as the Z-isomer in the newly formed olefin in 60% yield (Scheme 3.21). The Z-geometry of the newly formed olefin was determined by the high coupling constant ($J_{\text{H}^{\text{a}}-\text{H}^{\text{b}}} = 15.8 \text{ Hz}$) between H^a and H^b protons by ¹H NMR spectroscopy.



Scheme 3.21. Cross metathesis reaction on **69** to synthesize **83**.

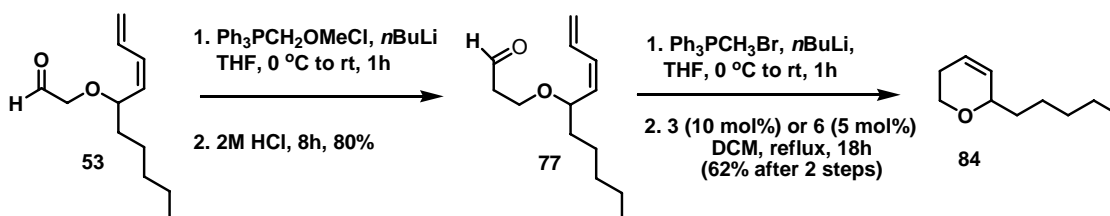
This experiment unambiguously showed that the ruthenium carbene was formed at the conjugated olefin moiety because the highly unstable β - carbonyl-carbene species $[\text{Ru}]=\text{CH}(\text{CO})\text{OMe}$ was not involved in the cross metathesis. It was shown by the Grubbs group that ester-carbene complexes decompose within a few hours at room temperature in contrast to the long life time of catalyst **6** in cross metathesis. The typically low degree of conversion to an ester carbene with its instability and the formation of no homo-coupled product suggested that a β - carbonyl-carbene species $[\text{Ru}]=\text{CH}(\text{CO})\text{OMe}$ was not responsible for the formation of the bulk product (Scheme 3.21).⁴⁷

3.8.8 Synthesis of the deoxy analogue of 58:

To investigate whether the hydroxyl group in the substrates **58** and **61** has a determinant role directing ring-closing metathesis reaction toward the formation of an alkene rather

than a diene, the deoxygenated analogue of **58** was synthesized from the aldehyde intermediate **53** (Scheme 3.22).

Aldehyde **53** was homologated by the Wittig homologation reaction mentioned before to synthesize **77** in 80% yield. The aldehyde **77** was then again subjected to Wittig olefination using triphenylmethylbromide salt and *n*-butyl lithium as base to afford the tri-olefin, which was immediately subjected to the ring-closing metathesis using both Grubbs catalyst **3** (10 mol%) or **6** (5 mol%) in refluxing DCM to afford the six-membered cyclic mono olefin **84** as the sole product in 62% overall yield after 2 steps. This result indicates that the hydroxyl group does not direct the ring-closing metathesis reaction in this case.



Scheme 3.22. Synthesis of deoxygenated analogue **84**.

4. Summary and conclusion:

In this project different diene-ene precursors **30** were synthesized from the commercially available substituted propargyl alcohol by means of iodination, ether formation, diimide reduction of the alkyne to *Z*-olefin, Pd-catalyzed Stille cross coupling reaction, DIBAL reduction, Wittig olefination and allylation or vinylation reactions with corresponding Grignard reagents. Those diene-ene precursors were then treated with commercially available 1st and 2nd generation Grubbs ruthenium carbene catalysts to explore the regioselectivity and reactivity of the diene-ene ring closure under the metathesis conditions to synthesize small and medium size ring ethers. In the formation of medium sized ethers by diene-ene ring-closing metathesis the formation of cyclic allyl ethers with smaller ring size and of pentadienyl ethers with larger ring size compete with each other. From the ring-closing metathesis study it was clear that the initial ruthenium complex was formed in the isolated olefin part and terminated in the conjugated diene part to form

mainly the small sized ring ether except in the case of the competition between five- and seven-membered ring ethers. When the bulk was increased in the isolated olefin part by dimethyl group the ring-closing metathesis reaction did not initiate in the isolated olefin but formed in the conjugated olefin part but it did not terminate in the isolated olefin to form the eight- and nine-membered ring ethers because eight- and nine-membered ring ethers are kinetically and thermodynamically difficult to form.

In conclusion the behavior of conjugated diene with isolated olefin under ring-closing metathesis conditions in presence of 1st and 2nd generation Grubbs catalysts in the synthesis of small to medium size ring ethers has been studied. The formation of the small and medium size ring ethers in the metathesis conditions is totally thermodynamically controlled. In each case it was demonstrated that the thermodynamically controlled more stable rings were formed. In the competition between six- and eight-membered ring formation the more stable six-membered ring ether formed and in the competition between seven- and nine-membered rings the more stable seven-membered ring formed. Moreover it was also confirmed that increasing the bulk in the isolated olefin moiety the metathesis reaction did not form the higher membered ring ethers. So in the attempted formation of medium sized cyclic ethers by means of the diene-ene ring-closing metathesis with exception of the competition between five- and seven-membered rings the smaller ring sizes are formed. It was also shown that the alcohol group in the metathesis precursors did not direct the ring-closing metathesis reaction toward the smaller ring ethers.

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6. Experimental part:

6.1 General experimental procedure:

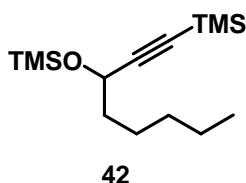
¹H and ¹³C-NMR spectra were recorded on a Varian Mercury 400 spectrometer at room temperature. Chemical shifts are expressed in part per million (ppm) and the spectra are calibrated to the solvent signals of CDCl₃ (7.26 ppm and 77.16 ppm). Coupling constants are given in Hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), dd (doublets of doublet), m (multiplet), br (broad signal), dt (doublet of triplet). Gas chromatography-mass spectrometry (GC-MS) was measured on a Hewlett Packard 6890 GC system coupled to a Hewlett Packard 5973 Mass Selective Detector. A HP 5TA capillary column (0.33 μm x 25 m x 0.2 mm) and helium flow rate of 2 mL/min were used. High resolution mass spectra (HR-MS, 70 eV) were measured on a Jeol SX 102A spectrometer by using electron impact (EI), fast atom bombardment (FAB) techniques. The matrix used for FAB was 3-nitrobenzylalcohol (3-NBA). Thin layer chromatography (TLC) was carried out on Merck precoated silica gel plate (60F-254) using ultra violet light irradiation 254 nm or the KMnO₄ solution (1 g KMnO₄, 6.6 g K₂CO₃, 1.67 mL of 5% NaOH solution, 100 mL water) as staining reagent. Purifications were performed using silica gel from J.T. Baker or Merck (particle size 40-60 μm) under approximately 0.5 bar pressure. All reactions were performed under argon atmosphere with freshly distilled and dried solvents. All solvents were distilled using standard procedures. Unless otherwise stated all the reagents were obtained from Aldrich, Acros Chimica, Fluka, Advanced Chemtech, Avocado, J.T. Baker, Novabiochem, Riedel de Haen, Roth, Sigma or Lancaster and used without further purification.

6.2 General procedure for the ring-closing metathesis:

The triene was dissolved in dry degassed DCM (0.002M) in a two neck round bottom flask under argon. The Grubbs catalyst was added and the solution was stirred at reflux until the starting material was totally consumed (monitored by TLC). The solvent was evaporated and the crude product was subjected to column chromatography.

6.3 Experimental procedure and analytical data:

6.3.1 Synthesis of compound 42:



Ethyl magnesium bromide (1.7 mL, 3.5 mmol, 2M solution in THF) was added dropwise into the solution of oct-1-yn-3-ol **41** (0.2 g, 1.58 mmol) at 0 °C and the solution was stirred for 30 minutes at 0 °C. Trimethylsilyl chloride (0.45 mL, 3.5 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 5h. The reaction was quenched with saturated ammonium chloride solution (10 mL) and the aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layer was washed with brine (2 x 10 mL), dried over Na₂SO₄, concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 19:1) to furnish 0.34 g of the product in 80% yield.

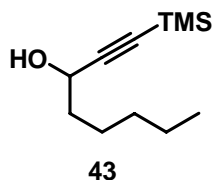
¹H NMR (400 MHz, CDCl₃): δ = 4.27-4.24 (t, *J* = 6.5 Hz, 1H), 1.70-1.60 (m, 2H), 1.47-1.39 (m, 2H), 1.32-1.29 (m, 4H), 0.91-0.87 (t, *J* = 7.3 Hz, 3H), 0.17 (s, 9H), 0.15 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ = 107.2, 88.6, 64.4, 38.1, 31.7, 25.0, 22.9, 14.3, 0.4, 0.0.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₄H₃₀OSi₂ = 270.1835, found = 270.1800 [M]⁺.

R_f = 0.4 (cyclohexane/ ethyl acetate 19:1).

6.3.2 Synthesis of compound 43:



1M HCl solution was added into **42** (0.05 g, 0.18 mmol) in THF at 0 °C and stirred for 1h at this temperature. The reaction was quenched with the saturated NaHCO₃ solution (5 mL) and the aqueous layer was extracted with ethyl acetate (2 x 5 mL) and the combined organic layer was washed with brine (2 x 5 mL), dried over Na₂SO₄, concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 0.03 g of the product in 81% yield.

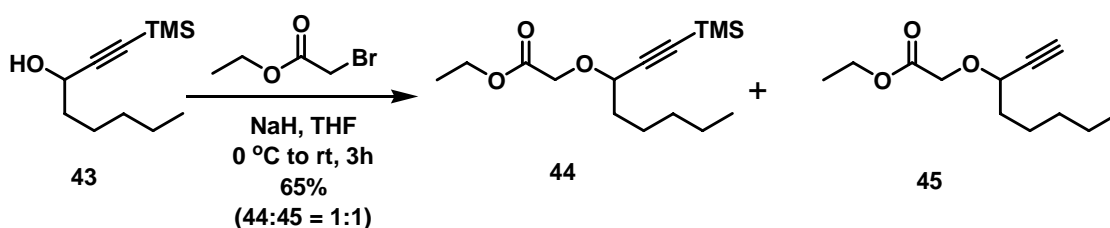
¹H NMR (400 MHz, CDCl₃): δ = 4.30-4.28 (t, *J* = 6.5 Hz, 1H), 2.00 (bs, 1H), 1.72-1.67 (m, 2H), 1.45-1.38 (m, 2H), 1.30-1.29 (m, 4H), 1.01-0.97 (t, *J* = 7.3 Hz, 3H), 0.16 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ = 106.5, 89.3, 64.0, 38.1, 31.7, 25.0, 22.9, 14.3, 0.0.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₁H₂₂OSi = 198.144, found = 198.1408 [M]⁺.

R_f = 0.4 (cyclohexane/ ethyl acetate 9:1).

6.3.3 Synthesis of compound 44 and 45:



A 50 mL two necked flask was charged with sodium hydride (95%) (0.05 g, 2.0 mmol, 2 equiv), 20 mL of THF was added and the suspension was stirred and cooled to 0 °C. To the suspension was added dropwise over 20 minutes a solution of **43** (0.2 g, 1.0 mmol) in THF (10 mL). The reaction was warmed to 25 °C and stirred for 15 minutes. The reaction

was cooled to 0 °C and a solution of ethyl bromoacetate (0.13 mL, 1.2 mmol, 1.2 equiv) in THF (5 mL) was added dropwise over 30 minutes. The reaction was warmed to 25 °C, stirred for 3h and quenched with water (20 mL). The mixture was diluted with water (50 mL) and diethyl ether (50mL) and separated. The aqueous layer was washed with diethyl ether (2 x 50 mL). The combined ether layers were washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 93 mg of the product **44** and 70 mg of the product **45** (total 65% yield).

6.3.3.1 Analytical data of compound **44**:

¹H NMR (400 MHz, CDCl₃): δ = 4.22-4.16 (m, 4H), 1.83-1.68 (m, 2H), 1.50-1.41 (m, 2H), 1.30-1.21 (m, 4H), 1.29-1.26 (t, *J* = 7.1 Hz, 3H), 1.03-0.99 (t, *J* = 7.5 Hz, 3H), 0.16 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ = 170.4, 103.6, 91.8, 71.9, 65.7, 61.1, 35.9, 29.1, 14.6, 14.3, 0.3.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₅H₂₈O₃Si = 284.1808, found = 284. 1800 [M]⁺.

R_f = 0.6 (cyclohexane/ ethyl acetate 9:1).

6.3.3.2 Analytical data of compound **45**:

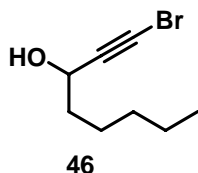
¹H NMR (400 MHz, CDCl₃): δ = 4.23-4.22 (m, 1H), 4.21-4.20 (m, 2H), 4.18-4.17 (m, 1H), 2.45-2.44 (d, *J* = 2.2 Hz, 1H), 1.84-1.75 (m, 2H), 1.52-1.40 (m, 2H), 1.32-1.20 (m, 4H), 1.29-1.26 (t, *J* = 7.1 Hz, 3H), 1.04-1.01(t, *J* = 7.5 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 169.9, 81.6, 74.6, 70.9, 65.5, 60.8, 35.9, 31.7, 28.6, 25.5 14.3, 14.0.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₂H₂₀O₃ = 212.1412, found = 212.1400 [M]⁺.

R_f = 0.4 (cyclohexane/ ethyl acetate 9:1).

6.3.4 Synthesis of compound 46:



Compound **43** (0.3 g, 1.5 mmol) was dissolved in DMF, *N*-bromosuccinimide (0.4 g, 2.27 mmol, 1.5 equiv.) and silver nitrate (0.051 g, 0.3 mmol, 0.2 equiv) were added and the reaction mixture was stirred at room temperature for 45 minutes. The reaction was quenched with saturated ammonium chloride solution (10 mL) and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed thoroughly with water (3 x 10 mL) and brine (2 x 5 mL) and dried over Na₂SO₄, concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 4:1) to furnish 300 mg of the product in nearly quantitative yield.

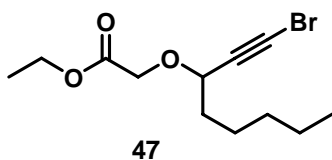
¹H NMR (400 MHz, CDCl₃): δ = 4.50-4.46 (t, *J* = 6.5 Hz, 1H), 1.92 (bs, 1H), 1.72-1.66 (m, 2H), 1.47-1.39 (m, 2H), 1.32-1.29 (m, 4H), 0.91-0.87 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 96.1, 64.4, 38.1, 31.7, 25.0, 22.9, 14.3.

HR-MS (FAB, 70eV): *m/z* calculated for C₈H₁₃BrO = 204.015, found = 204. 0104 [M]⁺.

R_f = 0.4 (cyclohexane/ ethyl acetate 4:1).

6.3.5 Synthesis of compound 47:



A 100 mL two necked flask was charged with sodium hydride (95%) (0.055 g, 2.2 mmol, 1.5 equiv), 30 mL of THF was added and the suspension was stirred and cooled to 0 °C. To the suspension was added dropwise over 20 minutes a solution of compound **46** (0.3

g, 1.47 mmol) in THF (10 mL). The reaction was warmed to 25 °C and stirred for 15 minutes. The reaction was cooled to 0 °C and a solution of ethyl bromoacetate (0.24 mL, 2.2 mmol, 1.5 equiv) in THF (5 mL) was added dropwise over 30 minutes. The reaction was warmed to 25 °C, stirred for 6h and quenched with water (10 mL). The mixture was diluted with water (50 mL) and diethyl ether (50 mL) and separated. The aqueous layer was washed with diethyl ether (2 x 50 mL). The combined ether layers were washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 0.3 g of the product (70% yield).

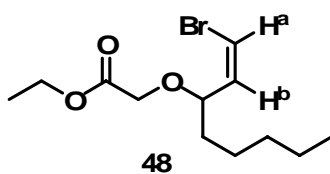
¹H NMR (400 MHz, CDCl₃): δ = 4.39-4.36 (t, *J* = 6.6 Hz, 1H), 4.25-4.14 (m, 4H), 1.80-1.67 (m, 2H), 1.49-1.42 (m, 2H), 1.31-1.24 (m, 4H), 1.30-1.26 (t, *J* = 7.1 Hz, 3H), 0.89-0.86 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 170.5, 93.4, 71.8, 66.0, 61.2, 35.9, 31.7, 25.1, 22.8, 14.5, 14.3.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₂H₁₉BrO₃ = 290.0518, found = 290.0508 [M]⁺.

R_f = 0.4 (cyclohexane/ ethyl acetate 9:1).

6.3.6 Synthesis of compound 48:



To a solution of ethyl compound **47** (1.5 g, 5.17 mmol) and potassium azodicarboxylate (1.5 g, 7.7 mmol, 1.5 equiv), in dioxane (25 mL)/*i*-PrOH (25 mL) under N₂ at room temperature, was added acetic acid (0.91 mL, 15.51 mmol, 3.0 equiv) by syringe pump over 1h. After addition was complete, the mixture was stirred for 1h at room temperature and additional potassium azodicarboxylate (1.5 g, 7.7 mmol, 1.5 equiv) was added. Again acetic acid (0.91 mL, 15.51 mmol, 3.0 equiv) was added slowly by syringe pump over 1h. After complete addition of acetic acid, the mixture was stirred for 1h and additional

potassium azodicarboxylate (0.5 g, 2.56 mmol, 0.5 equiv) and acetic acid (0.30 mL, 5.17 mmol, 1.5 equiv) were added sequentially by the procedure describe above. The mixture was then stirred for 3h, quenched with 1M HCl solution (30 mL) and diluted with diethyl ether (100 mL). The aqueous layer was extracted with diethyl ether (2 x 50 mL), the combined organic layers were washed with water (3 x 20 mL) and brine (2 x 10 mL) and dried over Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) furnished 1.35 g of the product (90% yield).

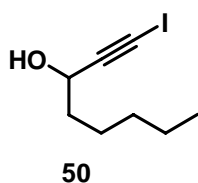
¹H NMR (400 MHz, CDCl₃): δ = 6.42-6.41 (dd, $J_{\text{Ha-Hb}} = 0.9 \text{ Hz}, 7.2 \text{ Hz}$, 1H), 6.05-6.01 (dd, $J_{\text{Ha-Hb}} = 7.2 \text{ Hz}, 8.6 \text{ Hz}$, 1H), 4.36-4.30 (m, 1H), 4.26-4.15 (m, 2H), 4.10-4.00 (m, 2H), 1.82-1.72 (m, 1H), 1.62-1.55 (m, 1H), 1.48-1.41 (m, 6H), 1.30-1.27 (t, $J = 7.2 \text{ Hz}$, 3H), 0.99-0.95 (t, $J = 7.4 \text{ Hz}$, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 170.5, 134.9, 111.4, 79.3, 66.3, 61.1, 35.0, 31.2, 25.1, 22.0, 14.3, 14.1.

HR-MS (FAB, 70eV): m/z calculated for C₁₂H₂₁BrO₃ = 292.0674, found = 292.0650 [M]⁺.

R_f = 0.5 (cyclohexane/ ethyl acetate 9:1).

6.3.7 Synthesis of compound 50:



Compound **41** (3 g, 23.8 mmol) was dissolved in DMF, *N*-iodosuccinimide (6.7 g, 29.76 mmol, 1.25 equiv.) and silver nitrate (0.809 g, 4.76 mmol, 0.2 equiv) were added and the reaction mixture was stirred at room temperature for 45 minutes. The reaction was quenched with saturated ammonium chloride solution (20 mL) and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed thoroughly with water (3 x 50 mL) and brine (2 x 10 mL) and dried over Na₂SO₄,

concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 4:1) to furnish 6 g of the product in quantitative yield.

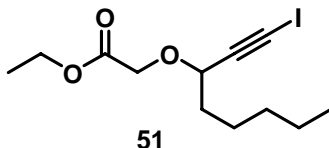
¹H NMR (400 MHz, CDCl₃): δ = 4.50-4.46 (t, *J* = 6.5 Hz, 1H), 1.92 (bs, 1H), 1.72-1.66 (m, 2H), 1.47-1.39 (m, 2H), 1.32-1.29 (m, 4H), 0.91-0.87 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 96.1, 64.4, 38.1, 31.7, 25.0, 22.9, 14.3.

HR-MS (FAB, 70eV): *m/z* calculated for C₈H₁₂OI = 250.9933, found = 250.9938 [M-H]⁺.

R_f = 0.4 (cyclohexane/ ethyl acetate 4:1).

6.3.8 Synthesis of compound 51:



A 250 mL two necked flask was charged with sodium hydride (95%) (1.2 g, 47.62 mmol, 2 equiv), 50 mL of THF was added and the suspension was stirred and cooled to 0 °C. To the suspension was added dropwise over 20 minutes a solution of the compound **50** (6 g, 23.81 mmol) in THF (20 mL). The reaction was warmed to 25 °C and stirred for 15 minutes. The reaction was cooled to 0 °C and a solution of ethyl bromoacetate (3.16 mL, 28.57 mmol, 1.2 equiv) in THF (10 mL) was added dropwise over 30 minutes. The reaction was warmed to 25 °C, stirred for 6h and quenched with water (20 mL). The mixture was diluted with water (100 mL) and diethyl ether (100 mL) and separated. The aqueous layer was washed with diethyl ether (2 x 200 mL). The combined ether layers were washed with brine (2 x 20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 6 g of the product (75% yield).

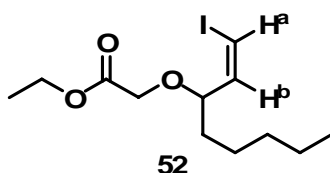
¹H NMR (400 MHz, CDCl₃): δ = 4.39-4.36 (t, *J* = 6.6 Hz, 1H), 4.25-4.14 (m, 4H), 1.80-1.67 (m, 2H), 1.49-1.42 (m, 2H), 1.31-1.24 (m, 4H), 1.30-1.26 (t, *J* = 7.1 Hz, 3H), 0.89-0.86 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.5, 93.4, 71.8, 66.0, 61.2, 35.9, 31.7, 25.1, 22.8, 14.5, 14.3$.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{12}\text{H}_{20}\text{O}_3\text{I} = 339.0457$, found = 339.0466 $[\text{M}+\text{H}]^+$.

$R_f = 0.4$ (cyclohexane/ ethyl acetate 9:1).

6.3.9 Synthesis of compound 52:



To a solution of compound **51** (6 g, 17.75 mmol) and potassium azodicarboxylate (5.16 g, 26.62 mmol, 1.5 equiv), in dioxane (15 mL)/*i*-PrOH (15 mL) under N_2 at room temperature, was added acetic acid (3.07 mL, 53.25 mmol, 3.0 equiv) by syringe pump over 1h. After addition was complete, the mixture was stirred for 1h at room temperature and additional potassium azodicarboxylate (5.16 g, 26.62 mmol, 1.5 equiv) was added. Again acetic acid (3.07 mL, 53.25 mmol, 3.0 equiv) was added slowly by syringe pump over 1h. After complete addition of acetic acid, the mixture was stirred for 1h and additional potassium azodicarboxylate (1.72 g, 8.87 mmol, 0.5 equiv) and acetic acid (1.02 mL, 17.75 mmol, 1.5 equiv) were added sequentially by the procedure describe above. The mixture was then stirred for 3h, quenched with 1M HCl solution (50 mL) and diluted with diethyl ether (100 mL). The aqueous layer was extracted with diethyl ether (2 x 50 mL), the combined organic layers were washed with water (3 x 20 mL) and brine (2 x 10 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) furnished 4.82 g of the product (80% yield).

^1H NMR (400 MHz, CDCl_3): $\delta = 6.50\text{-}6.48$ (dd, $J = 0.8$ Hz, 7.6 Hz, 1H), 6.12-6.08 (dd, $J = 7.6$ Hz, 8.4 Hz, 1H), 4.24-4.18 (m, 3H), 4.09-4.03 (m, 2H), 1.75-1.68 (m, 1H), 1.67-

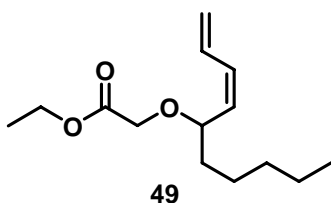
1.49 (m, 1H), 1.32-1.26 (m, 6H), 1.30-1.26 (t, $J = 7.1$ Hz, 3H), 0.90-0.86 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.7, 141.2, 85.4, 82.3, 66.1, 61.0, 34.5, 32.0, 24.8, 22.7, 14.5, 14.2$.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{12}\text{H}_{22}\text{O}_3\text{I} = 341.0614$, found = 341.0628 $[\text{M}+\text{H}]^+$.

$R_f = 0.5$ (cyclohexane/ ethyl acetate 9:1).

6.3.10 Synthesis of compound 49:



To a solution of compound **52** (6 g, 17.64 mmol) in DMF (20 mL) was added $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (0.045 g, 0.17 mmol, 0.01 equiv) and tributyl vinyl tin (7.77 mL, 26.47 mmol, 1.5 equiv). The mixture quickly became black. The solution was stirred at room temperature for 30 minutes, quenched with saturated NH_4Cl solution and diluted with diethyl ether (50 mL). The aqueous layer was washed with water (2 x 20 mL) and brine (2 x 10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 19:1) to furnish 3 g of the product (70% yield).

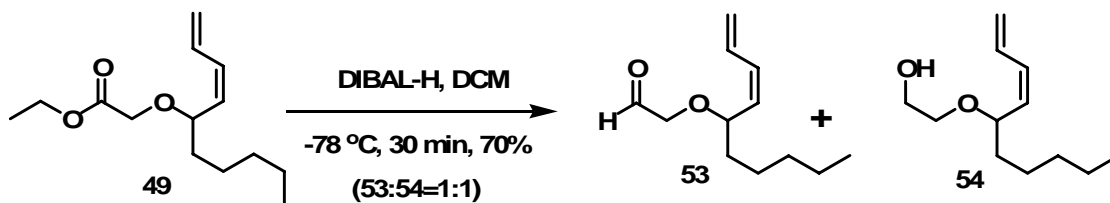
^1H NMR (400 MHz, CDCl_3): $\delta = 6.62\text{-}6.52$ (m, 1H), 6.23-6.17 (dt, $J = 0.6$ Hz, 11.4 Hz, 1H), 5.30-5.28 (m, 1H), 5.27-5.24 (m, 1H), 5.18-5.16 (m, 1H), 4.21-4.20 (m, 1H), 4.21-4.16 (m, 3H), 4.06-3.93 (q, $J = 16.4$ Hz, 2H), 1.76-1.70 (m, 1H), 1.55-1.43 (m, 1H), 1.36-1.28 (m, 6H), 1.28-1.24 (t, $J = 7.1$ Hz, 3H), 0.93-0.89 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.0, 133.3, 131.8, 119.9, 75.7, 65.6, 60.9, 35.7, 31.9, 25.1, 22.8, 14.4, 13.8$.

HR-MS (EI, 70eV): m/z calculated for $\text{C}_{14}\text{H}_{24}\text{O}_3 = 240.1725$, found = 240.1741 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane/ ethyl acetate 19:1).

6.3.11 Synthesis of compound 53 and 54:



To a solution of compound **49** (3.5 g, 14.75 mmol) in DCM (500 mL) at -78 °C, diisobutyl aluminum hydride (1M solution in hexane, 22.12 mL, 22.12 mmol, 1.5 equiv) was added slowly by a syringe pump over 30 minutes. The solution was stirred at -78 °C for 20 minutes, quenched with 1M HCl solution and stirred for 1h. The solution was diluted with diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic layers were washed with water (2 x 10 mL) and brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 1 g of each of the product **53** and **54** (70% yield).

6.3.11.1 Analytical data of compound **53**:

¹H NMR (400 MHz, CDCl₃): δ = 9.70-9.69 (t, *J* = 0.9 Hz, 1H), 6.60-6.51 (m, 1H), 6.23-6.18 (dt, *J* = 0.8 Hz, 11.5 Hz, 1H), 5.30-5.29 (m, 1H), 5.29-5.24 (m, 1H), 5.21-5.18 (m, 1H), 4.30-4.24 (m, 1H), 4.07-3.93 (dq, *J* = 0.9 Hz, 17.9 Hz, 2H), 1.76-1.69 (m, 1H), 1.51-1.45 (m, 1H), 1.32-1.26 (m, 6H), 0.89-0.86 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 201.4, 133.4, 131.4, 131.4, 120.35, 76.4, 74.0, 35.6, 31.9, 25.1, 22.8, 14.2.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₂H₁₉O₂ = 195.1385, found = 195.1396 [M-H]⁺.

R_f = 0.5 (cyclohexane/ ethyl acetate 9:1).

6.3.11.2 Analytical data of compound **54**:

¹H NMR (400 MHz, CDCl₃): δ = 6.66-6.56 (m, 1H), 6.20-6.15 (dt, *J* = 0.8 Hz, 11.4 Hz, 1H), 5.31-4.14 (m, 3H), 4.16-4.10 (m, 1H), 3.84-3.73 (m, 1H), 3.70-3.68 (m, 1H), 3.41-

3.36 (m, 1H), 2.19 (bs, 1H), 1.78-1.59 (m, 2H), 1.30-1.21 (m, 6H), 0.90-0.87 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 133.0, 131.1, 131.4, 120.4, 76.4, 71.0, 62.5, 35.2, 31.6, 25.5, 22.7, 14.2$.

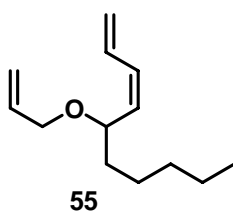
HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{12}\text{H}_{22}\text{O}_2 = 198.162$, found = 198.1600 $[\text{M}]^+$.

$R_f = 0.3$ (cyclohexane/ ethyl acetate 9:1).

6.3.12 Synthesis of compound 53:

To a solution of compound **49** (3.5 g, 14.75 mmol) in diethyl ether (500 mL) at $-78\text{ }^\circ\text{C}$, diisobutylaluminumhydride (1M solution in hexane, 22.12 mL, 22.12 mmol, 1.5 equiv) was added slowly by a syringe pump over 30 minutes. The solution was stirred at $-78\text{ }^\circ\text{C}$ for 20 minutes, quenched with 1M HCl solution and stirred for 1h. The solution was diluted with diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic layers were washed with water (2 x 10 mL) and brine (2 x 10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 2.14 g of the product (75% yield).

6.3.13 Synthesis of compound 55:



To a suspension of triphenylmethylphosphoniumbromide (0.728 g, 2.04 mmol, 2 equiv) in THF (10 mL) at $0\text{ }^\circ\text{C}$, n-butyl lithium solution (2.5 M in hexane solution, 0.82 mL, 2.04 mmol, 2 equiv) was added dropwise (the color of the solution turned red). After stirring at $0\text{ }^\circ\text{C}$ for 30 minutes compound **53** (0.2 g, 1.02 mmol, dissolved in THF) was added dropwise and stirring was continued at $0\text{ }^\circ\text{C}$ for 30 minutes. The reaction was quenched with 10 mL of 1M HCl solution and diluted with 30 mL of diethyl ether. The

aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic layers were washed with water (2 x 10 mL) and brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 19:1) to furnish 148 mg of the product (75% yield).

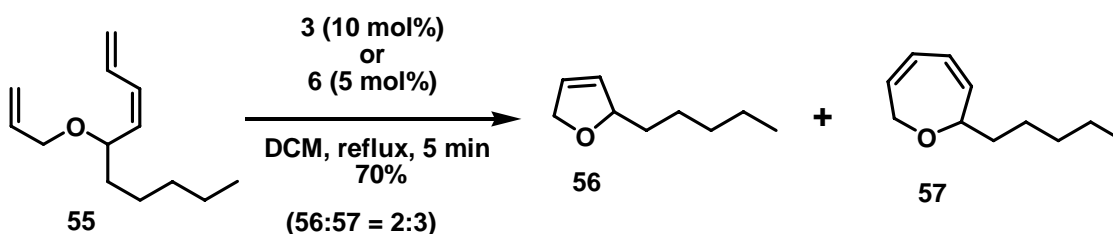
¹H NMR (400 MHz, CDCl₃): δ = 6.59-6.48 (m, 1H), 6.12-6.05 (m, 1H), 5.86-5.78 (m, 1H), 5.26-5.19 (m, 2H), 5.15-5.07 (m, 3H), 4.16-4.13 (m, 1H), 3.96-3.93 (m, 1H), 3.75-3.71 (m, 1H), 1.58-1.57 (m, 1H), 1.38-1.34 (m, 1H), 1.28-1.21 (m, 6H), 0.81-0.79 (t, *J* = 3.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 135.4, 133.3, 132.1, 132.0, 119.0, 116.9, 74.4, 69.2, 35.8, 31.99, 25.1, 22.8, 14.2.

HR-MS (EI, 70eV): *m/z* calculated for C₁₃H₂₂O = 194.1671, found = 194.1700 [M]⁺.

R_f = 0.5 (cyclohexane/ ethyl acetate 19:1).

6.3.14 Synthesis of compound 56 and 57:



6.3.14.1 Analytical data of compound 56:

¹H NMR (400 MHz, CDCl₃): δ = 5.87-5.85 (m, 1H), 5.79-5.77 (m, 1H), 4.83-4.79 (m, 1H), 4.68-4.63 (m, 1H), 4.62-4.56 (m, 1H), 1.55-1.51 (m, 2H), 1.37-1.25 (m, 6H), 0.90-0.86 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 130.1, 126.5, 86.4, 75.1, 36.2, 32.2, 25.2, 22.9, 14.2.

HR-MS (EI, 70eV): *m/z* calculated for C₉H₁₇O = 141.1279, found = 141.1200 [M+H]⁺.

R_f = 0.5 (cyclohexane/ ethyl acetate 10:1).

Yield: 28%.

6.3.14.2 Analytical data of compound 57:

^1H NMR (400 MHz, CDCl_3): δ = 5.94-5.92 (m, 2H), 5.92-5.89 (m, 1H), 5.84-5.80 (m, 1H), 4.43-4.38 (m, 1H), 4.34-4.30 (m, 1H), 4.18-4.16 (m, 1H), 1.60-1.56 (m, 2H), 1.33-1.28 (m, 6H), 0.91-0.85 (t, J = 6.8 Hz, 3H).

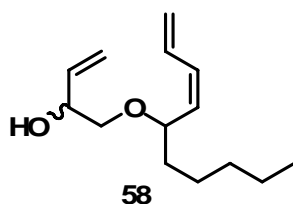
^{13}C NMR (100 MHz, CDCl_3): δ = 138.6, 135.85, 125.8, 125.8, 80.0, 70.3, 35.5, 32.00, 29.9, 25.6, 22.8, 14.3.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{11}\text{H}_{17}\text{O}$ = 165.1279, found = 165.1286 [$\text{M}-\text{H}$] $^+$.

R_f = 0.7 (cyclohexane/ ethyl acetate 10:1).

Yield: 42%.

6.3.15 Synthesis of compound 58:



(1:1 mixture of two isomers)*

* = isomeric ratio determined by ^1H NMR spectroscopy

To a solution of aldehyde **53** (0.2 g, 1.02 mmol) in THF under argon and at 0 °C, vinyl magnesium bromide (1.53 mL, 1.53 mmol, 1.5 equiv, 1M solution in THF) was added dropwise. The reaction was stirred at room temperature for 2h, quenched with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 160 mg of the product (70% yield) as 1:1 inseparable mixture of two isomers.

^1H NMR (400 MHz, CDCl_3): δ = 6.66-6.55 (m, 1H), 6.20-6.13 (m, 1H), 5.85-5.76 (m, 1H), 5.36-5.24 (m, 3H), 5.18-5.16 (m, 2H), 4.29-4.18 (m, 1H), 3.36-3.34 (d, J = 6.04 Hz,

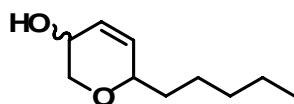
1H), 3.15-3.11 (dt, $J = 0.8$ Hz, 9.2 Hz, 1H), 2.42 (bs, 1H), 1.68-1.63 (m, 1H), 1.47-1.40 (m, 1H), 1.34-1.28 (m, 6H), 0.89-0.86 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 136.9, 136.8, 132.7, 132.7, 132.3, 132.1, 132.8, 119.5, 116.5, 76.2, 75.6, 72.6, 72.1, 72.0, 71.6, 35.7, 35.7, 31.9, 31.9, 25.1, 25.1, 22.7, 14.2$.

HR-MS (EI, 70eV): m/z calculated for $\text{C}_{14}\text{H}_{24}\text{O}_2 = 224.1776$, found = 224.1700 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane/ ethyl acetate 9:1).

6.3.16 Synthesis of compound 59:



59

(1:1 mixture of two isomers)*

* = isomeric ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): $\delta = 5.99$ -5.95 (m, 1H), 5.85-5.76 (m, 1H), 4.21-4.13 (m, 1H), 4.06-4.03 (m, 1H), 3.98-3.95 (m, 1H), 3.86-3.85 (m, 1H), 3.89-3.85 (m, 1H), 3.69-3.65 (dd, $J = 6.8$ Hz, 13 Hz, 1H), 3.44-3.39 (dd, $J = 6.8$ Hz, 11.2 Hz, 1H), 1.96 (bs, 1H), 1.56-1.48 (m, 2H), 1.47-1.40 (m, 2H), 1.38-1.29 (m, 4H), 0.89-0.86 (t, $J = 6.8$ Hz, 3H).

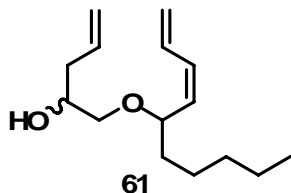
^{13}C NMR (100 MHz, CDCl_3): $\delta = 134.6, 132.9, 128.1, 126.5, 74.6, 73.9, 71.0, 68.6, 63.2, 62.8, 35.2, 34.3, 32.0, 31.9, 25.2, 24.9, 22.8, 14.2, 14.2$.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{10}\text{H}_{17}\text{O}_2 = 169.1229$, found = 169.1247 $[\text{M}-\text{H}]^+$.

$R_f = 0.5$ (cyclohexane/ ethyl acetate 5:1).

Yield: 60%.

6.3.17 Synthesis of compound 61:



(1:1 mixture of two isomers)*

* = isomeric ratio determined by ^1H NMR spectroscopy

To a solution of aldehyde **53** (0.2 g, 1.02 mmol) in THF under argon at 0 °C, allyl magnesium bromide (1.53 mL, 1.53 mmol, 1.5 equiv, 1M solution in diethyl ether) was added dropwise. The reaction was stirred at room temperature for 2h, quenched with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 170 mg of the product (70% yield) as 1:1 inseparable mixture of two isomers.

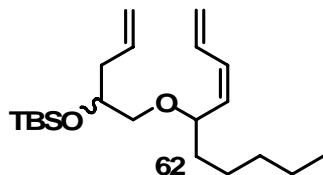
^1H NMR (400 MHz, CDCl_3): δ = 6.66-6.55 (m, 1H), 6.19-6.12 (m, 1H), 5.87-5.77 (m, 1H), 5.31-5.06 (m, 5H), 4.23-4.15 (m, 1H), 3.84-3.76 (m, 1H), 3.51-3.48 (dd, J = 3.8 Hz, 9.1 Hz, 1H), 3.37-3.29 (m, 1H), 3.16-3.12 (dd, J = 7.4 Hz, 9.5 Hz, 1H), 2.25-2.21 (m, 2H), 1.69-1.60 (m, 1H), 1.47-1.39 (m, 1H), 1.30-1.27 (m, 6H), 0.89-0.85 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ = 134.6, 134.6, 132.9, 132.2, 132.1, 131.9, 119.4, 117.7, 76.2, 75.7, 72.3, 71.9, 70.2, 69.9, 38.2, 38.1, 35.8, 35.8, 32.0, 31.9, 25.2, 25.2, 22.8, 14.2.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{15}\text{H}_{25}\text{O}_2$ = 237.1855, found = 237.1847 [$\text{M}-\text{H}$] $^+$.

R_f = 0.5 (cyclohexane/ ethyl acetate 9:1).

6.3.18 Synthesis of compound 62:



(1:1 mixture of two isomers)*

* = isomeric ratio determined by ^1H NMR spectroscopy

To a solution of compound **61** (0.1 g, 0.42 mmol) in 10 mL DMF imidazole (0.057 g, 0.84 mmol, 2 equiv) was added and stirred at room temperature for 15 minutes. Then TBSCl (0.126 g, 0.84 mmol, 2 equiv) was added and stirred at room temperature for 18h, quenched with water and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (3 x 20 mL), brine (2 x 20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9.8:0.2) to furnish 110 mg of the product (75% yield) as 1:1 inseparable mixture of two isomers.

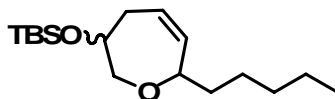
^1H NMR (400 MHz, CDCl_3): δ = 6.66-6.57 (m, 1H), 6.17-6.06 (m, 1H), 5.89-5.76 (m, 2H), 5.08-4.99 (m, 4H), 4.18-4.11 (m, 1H), 3.82-3.77 (m, 1H), 3.39-3.11 (m, 2H), 2.35-2.27 (m, 1H), 2.23-2.13 (m, 1H), 1.74-1.56 (m, 2H), 1.31-1.28 (m, 6H), 0.89-0.87 (m, 12H), 0.07-0.04 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ = 135.4, 135.3, 133.7, 133.7, 132.2, 131.8, 131.6, 119.0, 118.9, 117.1, 117.1, 75.9, 75.6, 72.5, 72.4, 71.6, 71.5, 39.7, 39.7, 35.9, 35.8, 32.1, 32.0, 31.8, 31.7, 26.1, 25.2, 25.1, 22.8, 18.4, 18.4, 14.3, -4.2, -4.4.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{21}\text{H}_{39}\text{O}_2\text{Si}$ = 351.2719, found = 351.2749 [$\text{M}-\text{H}$] $^+$.

R_f = 0.5 (cyclohexane/ ethyl acetate 9.8: 0.2).

6.3.19 Synthesis of compound 63:



63

(1:1 mixture of two isomers)*

* = isomeric ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): δ = 5.69-5.66 (m, 1H), 5.61-5.41 (m, 1H), 4.09-4.03 (m, 1H), 3.98-3.87 (m, 1H), 3.82-3.73 (m, 1H), 3.71-3.66 (dd, J = 6.0 Hz, 11.7 Hz, 1H), 3.44-3.39 (dd, J = 9.2 Hz, 11.5 Hz, 1H), 2.72-2.46 (m, 1H), 2.35-2.08 (m, 1H), 1.60-1.38 (m, 2H), 1.33-1.25 (m, 6H), 0.88-0.87 (m, 12H), 0.05-0.03 (m, 6H).

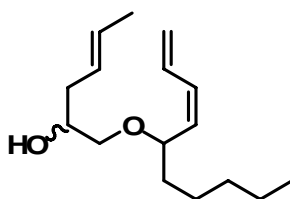
^{13}C NMR (100 MHz, CDCl_3): δ = 136.7, 134.6, 126.9, 125.2, 80.2, 79.1, 78.1, 75.3, 71.9, 69.1, 36.9, 36.4, 35.9, 34.4, 32.1, 32.0, 26.0, 25.4, 25.4, 18.4, 18.3, 14.3, 14.3, -4.5, -4.6.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{17}\text{H}_{33}\text{O}_2\text{Si}$ = 297.225, found = 297.2276 [$\text{M}-\text{H}$] $^+$.

R_f = 0.5 (cyclohexane/ ethyl acetate 9: 1)

Yield: 65%.

6.3.20 Synthesis of compound 66:



66

(1:1 mixture of two isomers)*

* = isomeric ratio determined by ^1H NMR spectroscopy

Magnesium turnings (18.4 mg, 0.765 mmol, 1.5 equiv) were taken under argon in a two neck round bottom flask and activated with a pinch of iodine. 2 mL diethyl ether was

added into the flask and cooled to $-78\text{ }^{\circ}\text{C}$. Crotyl bromide (0.07 mL, 0.765 mmol, 1.5 equiv) was added dropwise and the reaction mixture was stirred for 30 minutes at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was allowed to warm at room temperature and stirred until all the magnesium metal was dissolved to give a turbid solution. The reaction mixture was cooled again at $-78\text{ }^{\circ}\text{C}$ and the aldehyde **53** (0.1 gm, 0.51 mmol, dissolved in diethyl ether) was added into the flask. The reaction mixture was stirred at room temperature for 2h. The reaction was quenched with 10 mL saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 51 mg of the product (40% yield).

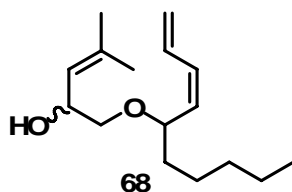
^1H NMR (400 MHz, CDCl_3): δ = 6.63-6.51 (m, 1H), 6.20-6.15 (m, 1H), 5.90-5.87 (m, 1H), 5.51-5.17 (m, 4H), 4.25-4.10 (m, 1H), 3.86-3.70 (m, 1H), 3.49-3.46 (dd, J = 3.7 Hz, 7.1 Hz, 1H), 3.39-3.27 (m, 1H), 3.18-3.14 (dd, J = 3.7 Hz, 7.2 Hz, 1H), 2.22-2.20 (m, 2H), 1.93-1.89 (m, 3H), 1.70-1.65 (m, 1H), 1.48-1.38 (m, 1H), 1.31-1.29 (m, 6H), 0.86-0.82 (t, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ = 133.7, 132.6, 131.9, 131.2, 131.1, 130.9, 125.4, 116.7, 77.2, 76.7, 71.3, 70.9, 70.2, 68.9, 39.2, 38.5, 36.8, 35.8, 32.8, 31.3, 27.2, 26.2, 23.8, 20.5, 14.5.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{16}\text{H}_{27}\text{O}_2$ = 251.2089, found = 251.2012 [$\text{M}-\text{H}$] $^+$.

R_f = 0.5 (cyclohexane/ ethyl acetate 9:1).

6.3.21 Synthesis of compound 68:



(1:1 mixture of two isomers)*

* = isomeric ratio determined by ^1H NMR spectroscopy

To a solution of compound **53** (0.1 gm, 0.51 mmol) in THF at 0 °C 2-methyl-1-propenylmagnesium bromide (2.04 mL, 1.02 mmol, 2 equiv, 0.5 M solution in THF) was added dropwise. The reaction was stirred at room temperature for 8h, quenched with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 103 mg of the product (80% yield) as 1:1 inseparable mixture of two isomers.

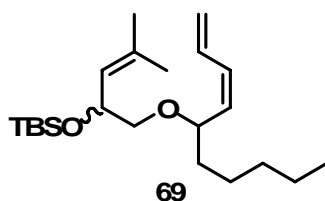
¹H NMR (400 MHz, CDCl₃): δ = 6.67-6.55 (m, 1H), 6.19-6.12 (m, 1H), 6.19-6.12 (m, 1H), 5.28-5.27 (m, 1H), 5.24-5.23 (m, 1H), 5.18-5.15 (m, 1H), 5.13-5.08 (m, 1H), 4.53-4.45 (m, 1H), 4.27-4.19 (m, 1H), 3.44-3.41 (dd, *J* = 3.1 Hz, 9.6 Hz, 1H), 3.32-3.25 (m, 1H), 3.12-3.07 (dd, *J* = 8.9 Hz, 9.6 Hz, 1H), 2.40 (bs, 1H), 1.72-1.71 (d, *J* = 1.0 Hz, 3H), 1.69-1.67 (dd, *J* = 1.4 Hz, 5.4 Hz, 3H), 1.32-1.24 (m, 8H), 0.89-0.86 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 137.5, 137.4, 132.9, 132.9, 132.3, 132.0, 131.9, 131.9, 123.5, 123.4, 119.4, 76.3, 75.4, 72.7, 72.0, 68.3, 67.6, 35.8, 35.8, 32.0, 31.9, 26.0, 25.2, 25.1, 22.79, 18.6, 14.2.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₆H₂₇O₂ = 251.2011, found = 251.2023 [M-H]⁺.

R_f = 0.5 (cyclohexane/ ethyl acetate 9: 1).

6.3.22 Synthesis of compound **69**:



(1:1 mixture of two isomers)*

* = isomeric ratio determined by ¹H NMR spectroscopy

To a solution of compound **68** (0.05 g, 0.35 mmol) in 5 mL DMF, imidazole (0.047 g, 0.714 mmol, 2 equiv) was added and the solution was stirred at room temperature for 15

minutes. Then TBSCl (0.107 g, 0.714 mmol, 2 equiv) was added and after stirring for 18h at room temperature, the reaction was quenched with water and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with water (3 x 10 mL), brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9.8:0.2) to furnish 50 mg of the product (70% yield) as 1:1 inseparable mixture of two isomers.

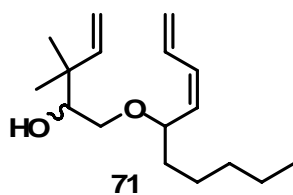
¹H NMR (400 MHz, CDCl₃): δ = 6.69-6.56 (m, 1H), 6.15-6.09 (m, 1H), 5.33-5.26 (m, 1H), 5.25-5.20 (m, 1H), 5.15-5.12 (m, 1H), 5.10-5.03 (m, 1H), 4.49-4.42 (m, 1H), 4.25-4.17 (m, 1H), 3.42-3.37 (dd, *J* = 10.1 Hz, 10.1 Hz, 1H), 3.28-3.25 (dd, *J* = 10.3 Hz, 10.3 Hz, 1H), 3.22-3.18 (dd, *J* = 10.3 Hz, 10.3 Hz, 1H), 3.14-3.10 (dd, *J* = 10.1 Hz, 9.9 Hz, 1H), 1.70-1.68 (dd, *J* = 1.3 Hz, 6.5 Hz, 3H), 1.64-1.62 (dd, *J* = 1.2 Hz, 7.6 Hz, 3H), 1.31-1.26 (m, 8H), 0.88-0.86 (m, 12H), 0.06-0.01 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 133.9, 133.8, 133.4, 133.3, 132.3, 132.2, 131.54, 131.4, 126.7, 126.4, 118.7, 118.7, 75.8, 75.5, 73.2, 73.1, 70.1, 69.4, 35.9, 35.8, 32.0, 31.9, 26.0, 25.9, 25.8, 25.0, 25.0, 22.7, 22.7, 18.6, 18.4, 14.2, -4.3, -4.5.

HR-MS (FAB, 70eV): *m/z* calculated for C₂₂H₄₁O₂Si = 365.2876, found = 365.2864 [M-H]⁺.

R_f = 0.5 (cyclohexane/ ethyl acetate 9.8: 0.2).

6.3.23 Synthesis of compound 71:



(1:1 mixture of two isomers)*

* = isomeric ratio determined by ¹H NMR spectroscopy

Magnesium turning (0.024 g, 1.02 mmol, 2 equiv) was activated with a pinch of iodine crystal under argon atmosphere and was treated with 2-methyl-1-propenyl bromide (0.15 mL, 1.27 mmol, 2.5 equiv) dissolved in 1 mL THF at 0 °C. The reaction mixture was

stirred at room temperature until all the magnesium metal was dissolved. The mixture was treated with a solution of aldehyde **53** (0.1 g, 0.51 mmol) in THF at 0 °C and the reaction mixture was stirred at room temperature for 3h, quenched with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9:1) to furnish 88 mg of the product (65% yield) as 1:1 inseparable mixture of two isomers.

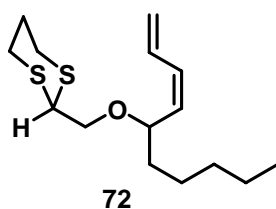
¹H NMR (400 MHz, CDCl₃): δ = 6.61-6.55 (m, 1H), 6.25-6.19 (m, 1H), 5.95-5.88 (m, 1H), 5.45-5.11 (m, 5H), 4.35-4.19 (m, 1H), 3.87-3.70 (m, 1H), 3.56-3.46 (m, 2H), 3.40-3.33 (m, 1H), 3.25-3.15 (m, 1H), , 1.70-1.65 (m, 1H), 1.49-1.40 (m, 1H), 1.35-1.29 (m, 6H), 1.25 (s, 3H), 1.22 (s, 3H), 0.88-0.86 (t, *J* = 6.7 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 135.6, 134.0, 133.0, 132.8, 132.1, 131.9, 120.4, 108.7, 78.2, 76.7, 73.4, 72.9, 71.2, 68.9, 37.2, 36.1, 35.9, 34.8, 32.9, 31.5, 25.6, 25.1, 23.9, 23.2, 22.8, 14.5.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₇H₂₉O₂ = 265.2246, found = 265.2290 [M-H]⁺.

R_f = 0.4 (cyclohexane/ ethyl acetate 9:1).

6.3.24 Synthesis of compound 72:



Compound **53** (0.1 gm, 0.51 mmol) was dissolved in DCM (10 mL), 1,3-propanedithiol (0.1 mL, 1.02 mmol, 2 equiv) was added and the reaction mixture was cooled to -30 °C. To this solution boron trifluoride dimethyl ether complex (0.06 mL, 0.51 mmol, 1 equiv) was added drop wise and the reaction mixture was stirred for 30 min at -30 °C. The reaction mixture was quenched with saturated aqueous NaHCO₃ (10 mL). The aqueous

layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ethyl acetate 9.5: 0.5) to furnish 102 mg of the product in 70% yield.

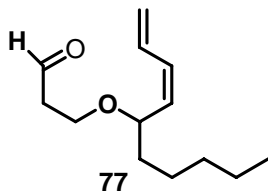
¹H NMR (400 MHz, CDCl₃): δ = 6.66-6.56 (m, 1H), 6.19-6.13 (dt, *J* = 0.9 Hz, 11.6 Hz, 1H), 5.34-5.31 (m, 1H), 5.29-5.23 (m, 1H), 5.19-5.15 (m, 1H), 4.24-4.18 (m, 2H), 3.73-3.65 (m, 1H), 3.54-3.50 (dd, *J* = 5.86 Hz, 10.7 Hz, 1H), 2.86-2.70 (m, 4H), 2.67-2.60 (m, 2H), 1.95-1.85 (m, 2H), 1.31-1.26 (m, 6H), 0.90-0.85 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ=132.9, 132.3, 131.9, 119.5, 76.2, 70.7, 46.7, 35.74, 31.9, 29.5, 26.2, 25.2, 22.8, 14.3.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₅H₂₇OS₂ = 287.1503, found = 287.1544 [M+H]⁺.

R_f = 0.5 (cyclohexane/ ethyl acetate 9.5: 0.5).

6.3.25 Synthesis of compound 77:



To a suspension of methoxymethyltriphenyl phosphonium chloride (0.297 g, 0.867 mmol, 1.7 equiv) in THF at 0 °C, n-butyllithium (0.35 mL, 0.87 mmol, 1.7 equiv, 2.5 M in hexane solution) was added dropwise (the color of the solution turned red). After stirring at 0 °C for 30 minutes aldehyde **53** (0.1 g, 0.51 mmol, dissolved in THF) was added dropwise at 0 °C and stirring was continued at room temperature for 30 minutes. After the aldehyde was consumed (monitored by TLC) 1M HCl solution (10 mL) was added and the mixture was stirred for 8h at room temperature, followed by addition of saturated aqueous NaHCO₃ solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by

silica gel chromatography (cyclohexane/ethyl acetate 9:1) to furnish 85 mg of the product (80% yield).

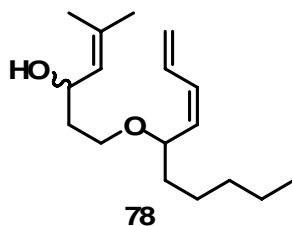
¹H NMR (400 MHz, CDCl₃): δ = 9.77-9.76 (t, *J* = 1.9 Hz, 1H), 6.68-6.58 (m, 1H), 6.20-6.14 (dt, *J* = 0.9 Hz, 11.6 Hz, 1H), 5.31-5.28 (m, 1H), 5.26-5.23 (m, 1H), 5.19-5.16 (m, 1H), 4.20-4.15 (m, 1H), 3.83-3.77 (m, 1H), 3.63-3.59 (m, 1H), 2.63-2.59 (dt, *J* = 1.9 Hz, 7.0 Hz, 2H), 1.63-1.57 (m, 1H), 1.31-1.25 (m, 7H), 0.89-0.85 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 201.7, 132.9, 132.2, 131.9, 119.5, 75.9, 62.3, 44.22, 35.8, 31.9, 25.1, 22.8, 14.2.

HR-MS (FAB, 70eV): *m/z* calculated for C₁₃H₂₁O₂ = 209.1542, found = 209.1530 [M-H]⁺.

R_f = 0.5 (cyclohexane/ethyl acetate 9:1).

6.3.26 Synthesis of compound 78:



(1:1 mixture of two isomers)*

* = isomeric ratio determined by ¹H NMR spectroscopy

To a solution of compound **77** (0.1 g, 0.47 mmol) in THF at 0 °C, 2-methyl-1-propenylmagnesium bromide (1.9 mL, 0.95 mmol, 2 equiv, 0.5 M solution in THF) was added dropwise at 0 °C. The reaction was stirred at room temperature for 8h, quenched with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ethyl acetate 5:1) to furnish 76 mg of the product (60% yield) as 1:1 inseparable mixture of two isomers.

¹H NMR (400 MHz, CDCl₃): δ = 6.66-6.57 (m, 1H), 6.19-6.02 (td, *J* = 11.1 Hz, 1H), 5.29-5.27 (m, 1H), 5.22-5.15 (m, 3H), 4.58-4.51 (m, 1H), 4.18-4.13 (m, 1H), 3.71-3.58

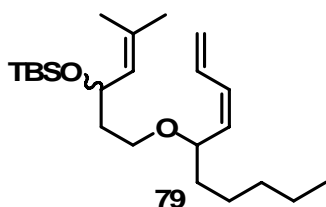
(m, 1H), 3.54-3.35 (m, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 1.29-1.25 (m, 8H), 0.89-0.85 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 134.7, 134.6, 133.1, 133.0, 132.2, 132.1, 132.0, 132.9, 130.7, 127.9, 127.9, 119.3, 75.9, 75.8, 68.4, 68.3, 68.2, 67.1, 66.9, 37.6, 37.2, 32.0, 31.9, 25.9, 25.2, 22.8, 18.4, 14.2$.

HR-MS (EI, 70eV): m/z calculated for $\text{C}_{17}\text{H}_{30}\text{O}_2 = 266.2246$, found = 266.2257 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane/ ethyl acetate 5: 1).

6.3.27 Synthesis of compound 79:



(1:1 mixture of two isomers)*

* = isomeric ratio determined by ^1H NMR spectroscopy

To a solution of compound **78** (0.07 g, 0.263 mmol) in 5 mL DMF, imidazole (0.035 g, 0.526 mmol, 2 equiv) was added and stirred at room temperature for 15 minutes. Then TBSCl (0.08 g, 0.526 mmol, 2 equiv) was added and the reaction was stirred for 18h at room temperature, quenched with water and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with water (3 x 10 mL), brine (2 x 10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure and purified by silica gel chromatography (cyclohexane/ ethyl acetate 9.8:0.2) to furnish 70 mg of the product (70% yield) as 1:1 inseparable mixture of two isomers.

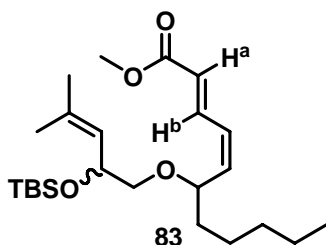
^1H NMR (400 MHz, CDCl_3): $\delta = 6.68-6.57$ (m, 1H), 6.16-6.10 (dt, $J = 0.8$ Hz, 11.5 Hz, 1H), 5.32-5.27 (m, 1H), 5.25-5.20 (m, 1H), 5.15-5.06 (m, 2H), 4.50 (m, 1H), 4.16-4.08 (m, 1H), 3.53-3.41 (m, 1H), 3.33-3.19 (m, 1H), 1.68-1.67 (dd, $J = 1.4$ Hz, 4.2 Hz, 3H), 1.62-1.61 (t, $J = 1.6$ Hz, 3H), 1.43-1.36 (m, 2H), 1.28-1.25 (m, 8H), 0.89-0.85 (m, 12H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 133.9, 132.3, 132.2, 131.6, 131.5, 129.5, 129.5, 118.8, 75.3, 75.2, 67.3, 67.2, 65.2, 39.0, 38.9, 36.0, 35.9, 32.1, 26.2, 25.9, 25.3, 22.8, 18.5, 14.3, -3.9, -4.6$.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{23}\text{H}_{43}\text{O}_2\text{Si} = 379.3032$, found = 379.3045 $[\text{M}-\text{H}]^+$.

$R_f = 0.5$ (cyclohexane/ethyl acetate 9.8:0.2).

6.3.28 Synthesis of compound 83:



To a solution of compound **69** (0.02 g, 0.05 mmol) and methyl acrylate (0.007 mL, 0.08 mmol, 1.5 equiv) in 20 mL degassed DCM (0.002 M) the 2nd generation Grubbs catalyst (0.002 g, 0.005 mmol, 10 mol %) was added and the mixture was refluxed until the starting material was totally consumed (monitored by TLC). The solvent was evaporated under reduced pressure and the crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate 9.8:0.2) to furnish 14 mg of the product (60% yield).

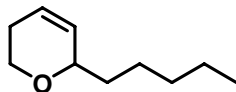
^1H NMR (400 MHz, CDCl_3): $\delta = 7.60-7.51$ (m, 1H), 6.25-6.20 (t, $J = 11.0$ Hz, 1H), 5.92-5.88 (d, $J_{\text{Ha-Hb}} = 15.8$ Hz, 1H), 5.08-5.03 (m, 1H), 4.47-4.42 (m, 1H), 4.31-4.27 (m, 1H), 3.75-3.72 (m, 3H), 3.37-3.11 (m, 2H), 1.70-1.67 (dd, $J = 1.2$ Hz, 7.9 Hz, 3H), 1.64-1.62 (dd, $J = 1.2$ Hz, 9.7 Hz, 3H), 1.30-1.25 (m, 8H), 0.88-0.86 (m, 12H), 0.07-0.02 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 167.9, 142.4, 142.1, 139.3, 133.7, 128.3, 126.3, 122.8, 119.9, 76.0, 75.6, 69.9, 69.5, 51.8, 35.8, 32.1, 26.1, 26.1, 25.9, 25.9, 25.0, 22.8, 18.6, 18.5, 14.2, -4.2, -4.4$.

HR-MS (FAB, 70eV): m/z calculated for $\text{C}_{24}\text{H}_{43}\text{O}_4\text{Si} = 423.2931$, found 423.2945 $[\text{M}-\text{H}]^+$.

$R_f = 0.5$ (cyclohexane/ ethyl acetate 9.8: 0.2).

6.3.29 Synthesis of compound 84:



84

To a suspension of triphenylmethyl phosphonium bromide (0.178 g, 0.5 mmol, 1.5 equiv) in THF (10 mL) at 0 °C, *n*-butyl lithium solution (1.6 M in toluene solution, 0.33 mL, 0.528 mmol, 1.6 equiv) was added dropwise (the color of the solution turned red). After stirring at 0°C for 30 minutes compound **77** (0.07 g, 0.33 mmol, dissolved in THF) was added dropwise and stirring was continued at 0 °C for 30 minutes. The reaction was quenched with 10 mL of 1M HCl solution and diluted with 30 mL of diethyl ether. The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic layers were washed with water (2 x 10 mL) and brine (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure and the crude product was treated with Grubbs catalysts in ring-closing metathesis reaction conditions. The product was purified by silica gel chromatography (cyclohexane/ ethyl acetate 9.8:0.2) to furnish 32 mg of the product (62% yield).

¹H NMR (400 MHz, CDCl₃): $\delta = 5.29-5.30$ (m, 1H), 1.93-1.99 (m, 3H), 1.51-1.60 (m, 2H), 1.29-1.43 (m, 8H), 0.90-0.86 (t, $J = 6.8$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): $\delta = 130.1, 126.5, 86.4, 76.9, 75.1, 36.2, 32.2, 25.2, 22.8, 14.2$

HR-MS (FAB, 70eV): m/z calculated for C₁₀H₁₈O = 154. 1358, found 155. 1391 [M+H]⁺.

$R_f = 0.5$ (cyclohexane/ ethyl acetate 9.8: 0.2).

Chapter B

Solution Phase Synthesis of an Oxepane Library using Solid-Supported Reagents

1. Introduction:

As Douglas Adams famously said “Space is big. You just won’t believe how vastly, hugely, mind-bogglingly big it is”.¹ The same statement is true for the “Chemical Space” also. The total number of possible small organic molecules that populates “Chemical Space” has been estimated to exceed 10^{60} , which is so vast that so far only a very little part has been explored.² The investigations have been greatly influenced by our understanding of biology and directed to the development of many life saving drugs nowadays. Not surprisingly the number of chemical compounds used by biological systems is smaller than the total possible number of small organic molecules. So in terms of numbers of compounds in “biologically relevant chemical space” is a small fraction of the complete “chemical space”.³ The mapping of biologically active space using small molecules is akin to map the stars in the real space. To search effectively new chemical tools to understand biology we need to navigate the “biologically relevant chemical space”. Exploring the “biologically relevant chemical space” using small organic molecules is an ever-growing strategy nowadays.

To understand a biological system, we need to perturb it, which is being persuaded in “Chemical Genetics” studies and is used to illuminate the molecular mechanisms underlying biological processes. Small molecules can alter the functions of proteins by binding to them and inhibiting or activating their normal functions. The use of small molecules is complementary to gene-based methods to disrupt the protein function. For example in the case of deletion mutation all the functions of a protein are lost. Similarly it is also possible to find small molecules which can modify the functions of the protein.⁴ Small molecules are extensively used both in the “Forward Chemical Genetics” and “Reverse Chemical Genetics” which are in direct analogy to “Classical Genetics”. In forward chemical genetics, large collections of structurally unbiased compounds are screened in whole organisms or cells for those that induce specific phenotypic outcomes. However the target identification is an ultimate goal of the forward chemical genetics approach. But the reverse chemical genetics approach requires a known protein target, which is subjected to binding or functional assays to identify a small molecule partner (Fig.1).⁵ The completion of the Human Genome Project has outlined the map for further

exploration towards providing a complete understanding of cellular processes at the molecular level and reveal the gene function, i.e., the examination of proteins that are encoded within. As an increasing demand of combinatorial chemistry, the chemical library approach can be extended to investigate the whole genome/proteome with small molecules. Combinatorial chemistry has become the method of choice to undertake this herculean task.

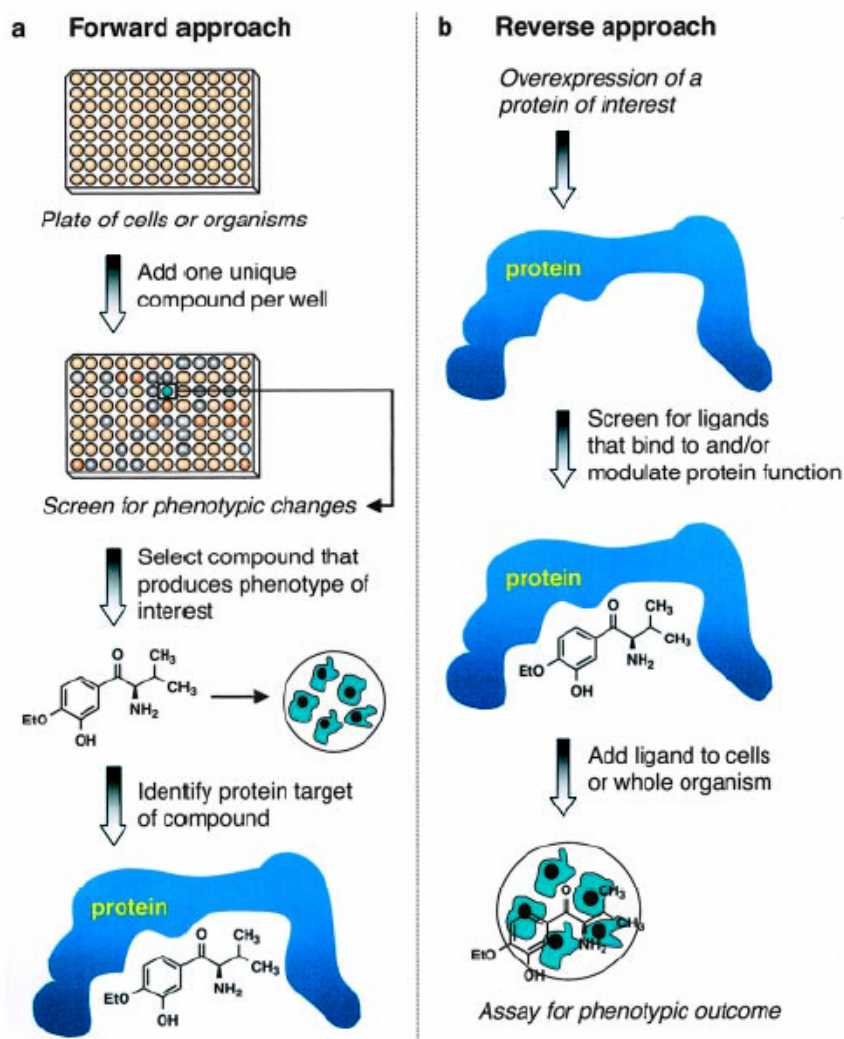


Figure 1. Forward and reverse chemical genetics approach.

Natural products have inspired chemists for the last 100 years by their rich structural diversity and complexity as well as their therapeutic applications. Natural products are viable, biologically validated starting points for combinatorial library design. Such natural product inspired libraries should permit hit or lead compounds to be found with enhanced probability and quantity which would be determined by their “diversity” and “drug likeness” if these libraries are included in high-throughput screening.⁶

The emergent enhancement in the number of new drug targets arising from genomics and proteomics has steered the synthetic chemist into the need for new methods to rapidly assemble pure small molecules ($M_r \sim 250-800$) that possess an increasing level of structural complexity. Such demands have compelled the development of new techniques such as solid-supported reagents. The use of solid-supported reagents and scavengers in multistep chemical synthesis has become an important tool for synthesizing complex target molecules rapidly. Recently the use of solid-supported reagents and scavengers in solution phase chemistry has been developed to meet the demand for diverse compound libraries to be tested in biological assays.⁷

2. Background:

2.1 Polymer-supported solution phase organic synthesis:

2.1.1 Introduction:

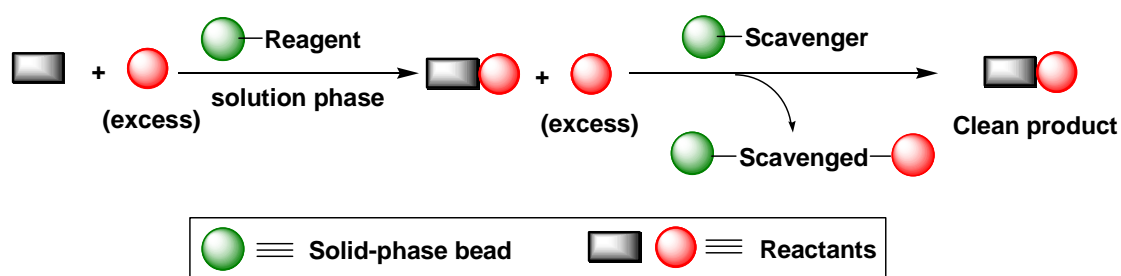
In solution phase organic synthesis, purification and isolation of individual compounds from unwanted byproducts are important determinants of the overall effectiveness and efficiency of a synthesis. After all no reaction is useful if it proceeds quantitatively in the flask, but affords the desired product in mediocre yield following chromatographic isolation. To meet the mounting demand of synthesizing highly pure small molecules with greater level of structural complexity for genomics and proteomics studies, the development of novel techniques is needed. One such technology is the use of polymer-supported reagents used in solution phase organic synthesis. The use of polymer-supported reagents has been demonstrated to be viable to improve efficiency in production of compound collections. This new development is not only important in

target oriented synthesis but also very much applied in the field of combinatorial chemistry and parallel synthesis.

2.1.2 Solid-supported reagents:

Immobilization means tethering the reagents to an insoluble polymeric resin, usually functionalized divinylbenzene cross-linked polystyrene, although many other polymer cores and support materials such as glass beads, silica, cellulose, zeolites and graphite have also been used. In all the cases the reagent is completely insoluble, but the bound reactive species remains freely accessible within the support matrix to both the solvent and to the dissolved reactants. So the reagent can be used in excess to force reaction to completion, leading to clean reaction with the isolation of the desired product only by simple filtration of the resin and solvent evaporation.

Supported scavengers can selectively quench or sequester the byproducts of the reaction or remove excess or unreacted starting material and can be removed by filtration. The use of insoluble polymers and other solid-supported agents to scavenge the byproducts and excess starting materials from complex reaction mixtures without the need of liquid-liquid extractions or the non specific column chromatography is a significant strategy. The working principle of the solid-supported reagents and scavengers is shown in Scheme 2.1.⁷

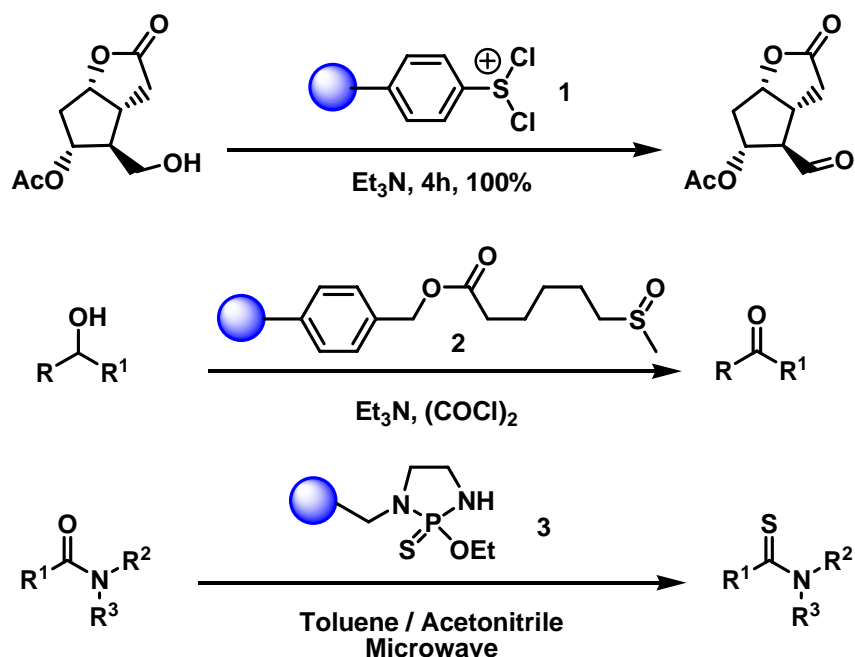


Scheme 2.1. Basic concept of solid-supported reagents and scavengers.

Using solid-supported reagents and scavengers has advantages over both conventional solution phase reactions and substrate-immobilized solid-phase synthesis. The advantages over conventional solution phase synthesis are (i) excess reagents can be used to drive the

reaction to completion without causing the problem with laborious work up process, (ii) toxic, noxious and hazardous reagents and their byproducts can be immobilized and thereby removed from the reaction mixture, (iii) automated synthesis can be adopted and (iv) allows the simultaneous use of multiple reagents that would otherwise be incompatible, for example, oxidizing and reducing reagents. On the other hand, the convenience over the substrate-immobilized solid-phase synthesis are (i) as the chemistry is carried out in solution, standard analytical techniques for example thin-layer chromatography (TLC), gas chromatography-mass spectrometry (GC-MS) can be applied to monitor the reactions, allowing rapid optimization, (ii) convergent syntheses are possible. Equally problematic, in the conventional solid-phase strategy, is the absence of a selective method to cleave the final product from the resin at the end of the sequence; any partially or improperly reacted intermediate will be released into the solution at the same time as the desired compound.

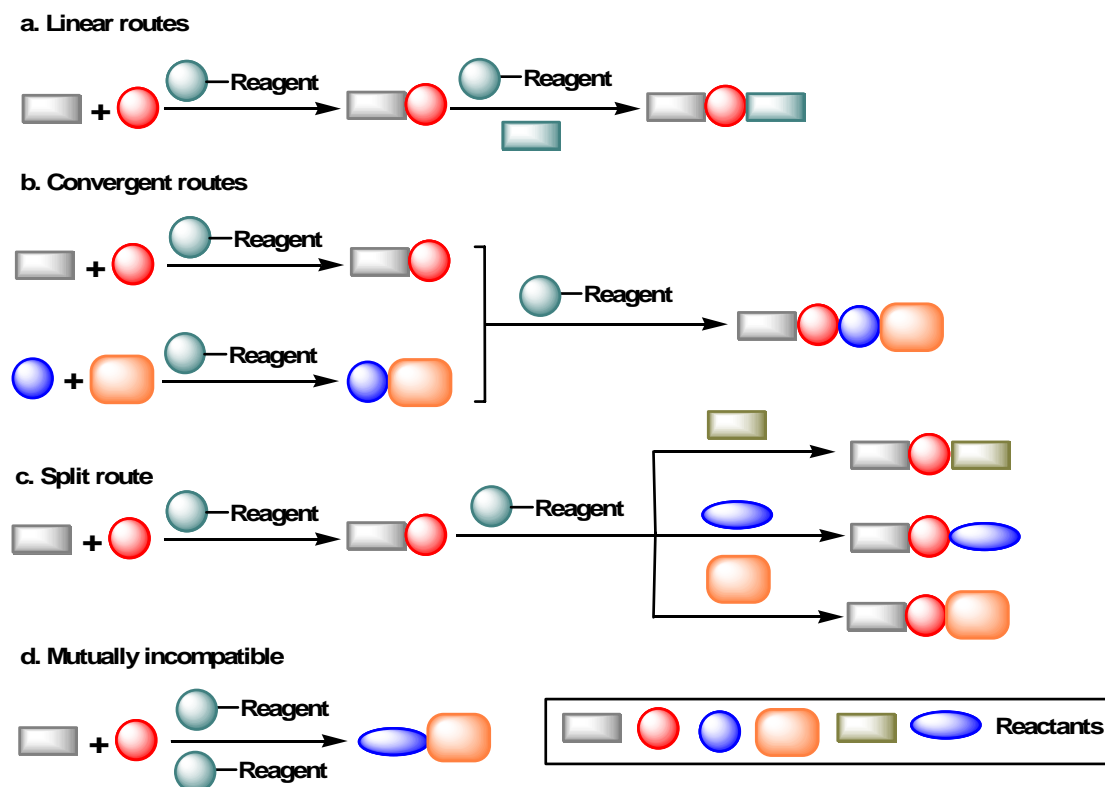
Using solid-supported reagents and scavengers has improved the safety profile of the hazardous reactions. This approach is advantageous for the elimination of the volatile obnoxious sulfur components from Swern oxidation reaction (**1** and **2**)⁸ and for the preparation of the solid supported version of Lawesson's reagent **3** (Scheme 2.2).⁹



Scheme 2.2. Solid supported reagents to remove obnoxious byproducts.

One of the most important achievements of the solid supported reagent approach over the conventional solid phase synthesis is the ease with which the intermediates and reactions can be monitored. The optimization in traditional solid phase synthesis is lengthy and can be minimized by the chemistry carried out in solution, thereby allowing standard analytical techniques to be applied e.g. NMR, GC-MS, LC-MS, TLC and HPLC.

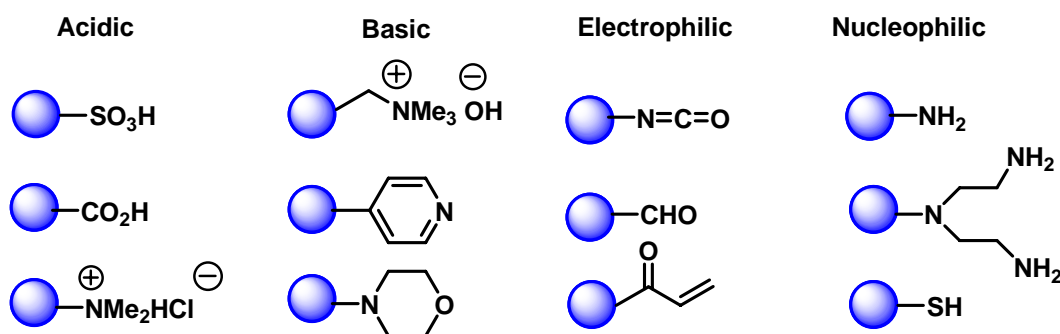
This solid-supported reagents and scavengers can be used not only in single step transformations but also iterative multistep synthesis, convergent or various split and recombination strategy (Scheme 2.3),⁷ which is also another breakthrough over traditional solid phase chemistry. Furthermore, as these reagent systems are anchored on a solid support; they also allow the simultaneous use of multiple reagents to achieve one pot transformations where, because of incompatibility of the reagents, no solution phase equivalent exists.



Scheme 2.3. Applicability of solid supported reagents in synthesis.

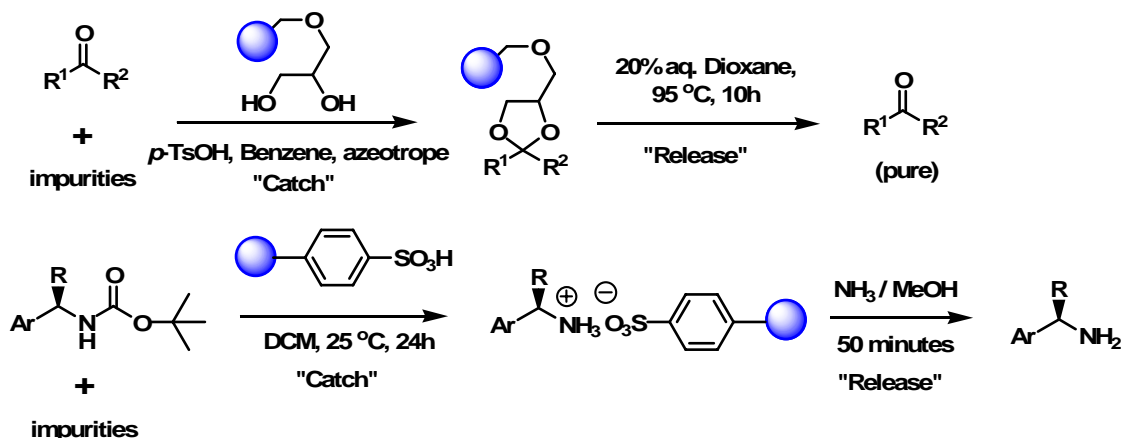
2.1.3 Solid-supported scavengers:

Supported scavengers are also known as ‘sequestering agents’ or ‘quenching agents’. Two different types of scavengers are commonly used: (i) Those that form ionic interactions like acidic or basic resins, termed as ion exchange resins and (ii) those that form covalent bonds like electrophilic and nucleophilic species (Scheme 2.4).¹⁰



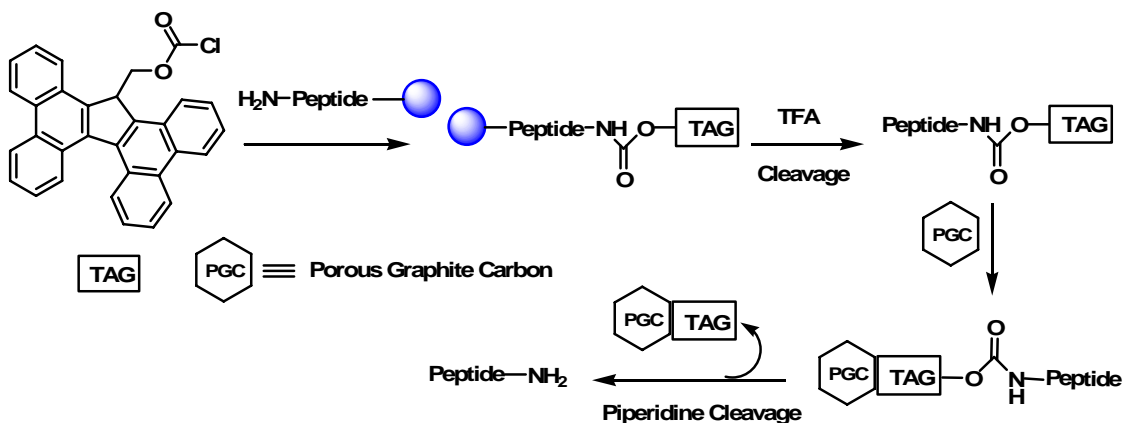
Scheme 2.4. Some examples of polymeric scavenger systems.

One complementary approach in scavenging techniques is the “catch-and-release” technique. The idea behind the “catch-and-release” approach is to use a suitably functionalized solid-support to selectively capture the required product away from any contaminating impurities, filter and then release it (catch-and-release) in a pure form (scheme 2.5).¹⁰



Scheme 2.5. Catch and release technique using solid supported reagents.

Another attractive variant of this approach is to use a hydrophobic adsorption technique for the purification of the intermediates and products. An example of this system is shown in Scheme 2.6.¹¹ Attachment of the ‘tag’ to the amino terminus of the resin bound peptide, followed by cleavage from the solid phase gives the species with several impurities. Treatment with porous graphitized carbon (PGC), which absorbs large aromatic moieties with high affinity, allows the washing of the immobilized material and thus removes the impurities. Base catalyzed cleavage of the ‘tag’ followed by elution provides purified peptide.

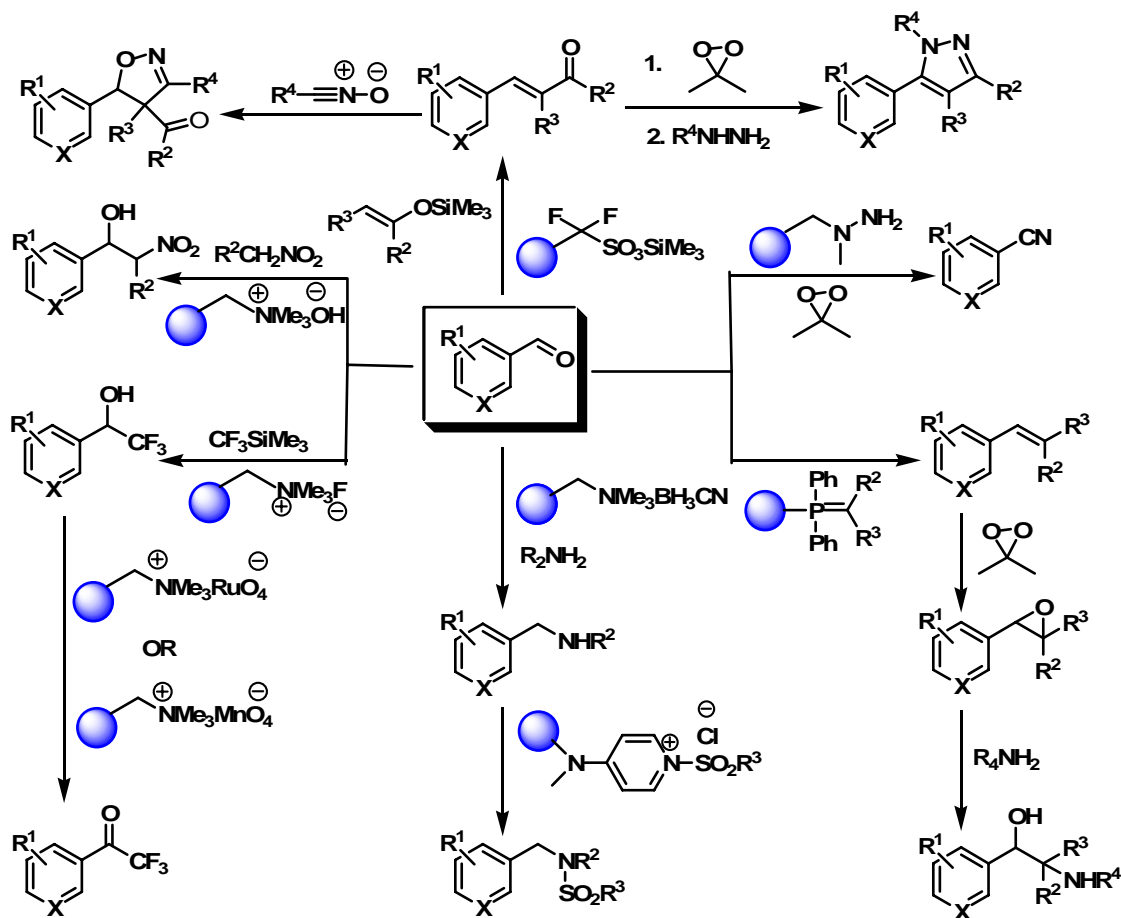


Scheme 2.6. Affinity binding purification of polypeptides and proteins.

2.1.4 Synthesis of small molecules using solid-supported reagents and scavengers:

As the need of biologically relevant small molecules is increasing for chemical genetics and genomics studies, we need to generate small molecule libraries efficiently and rapidly for the high throughput screening.

Using solid-supported reagents and scavengers it is possible by simple chemical manipulations to generate cleanly a wide array of structurally complex molecules from readily available starting materials (scheme 2.7).¹² Using this technique not only diversity oriented synthesis can be done. But this approach can be used successfully in the solution phase combinatorial library synthesis of the natural product inspired small molecules.



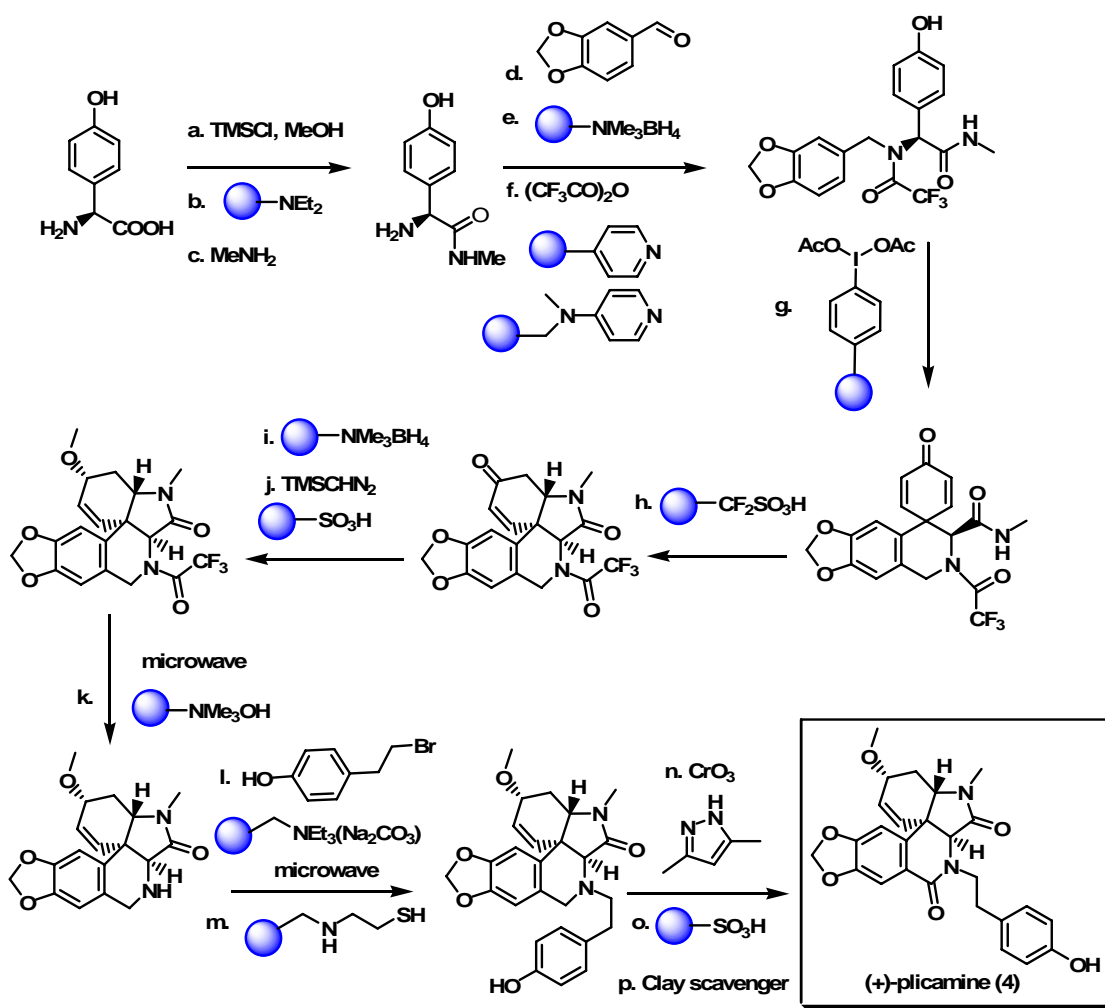
Scheme 2.7. Diversity generation from a common intermediate.

2.1.5 Solid-supported reagents and scavengers in total synthesis:

Not only in the synthesis of small molecule libraries, the solid supported reagents and scavengers have also been used for the total synthesis of natural products. One of the main advantages of using solid-supported reagents and scavengers over traditional solid phase synthesis is that both linear and convergent syntheses strategies can be used. Ley and co-workers have demonstrated this usefulness brilliantly in the total synthesis of the amaryllidaceae alkaloid (+)-plicamine (**4**) and the anti tumor natural products epothilone A and C (**5**) using solid-supported reagents and scavengers.

2.1.5.1 Total synthesis of (+)-plicamine:

Total synthesis of highly complex alkaloid (+)-plicamine (**4**) using solid supported reagents and scavengers is the elegant example where Ley and co-workers demonstrated the strength of this unique technique (Scheme 2.8).¹³

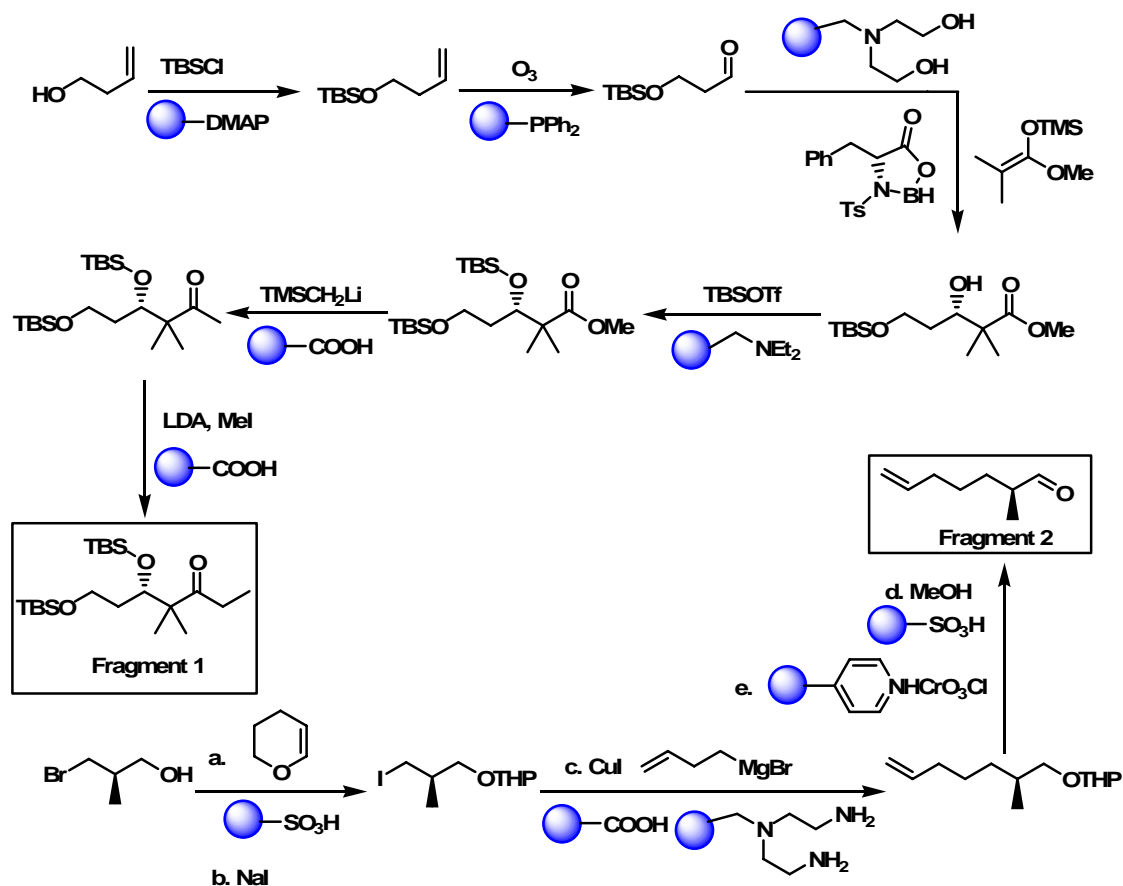


Scheme 2.8. Total synthesis of (+)-plicamine using solid supported reagents and scavengers.

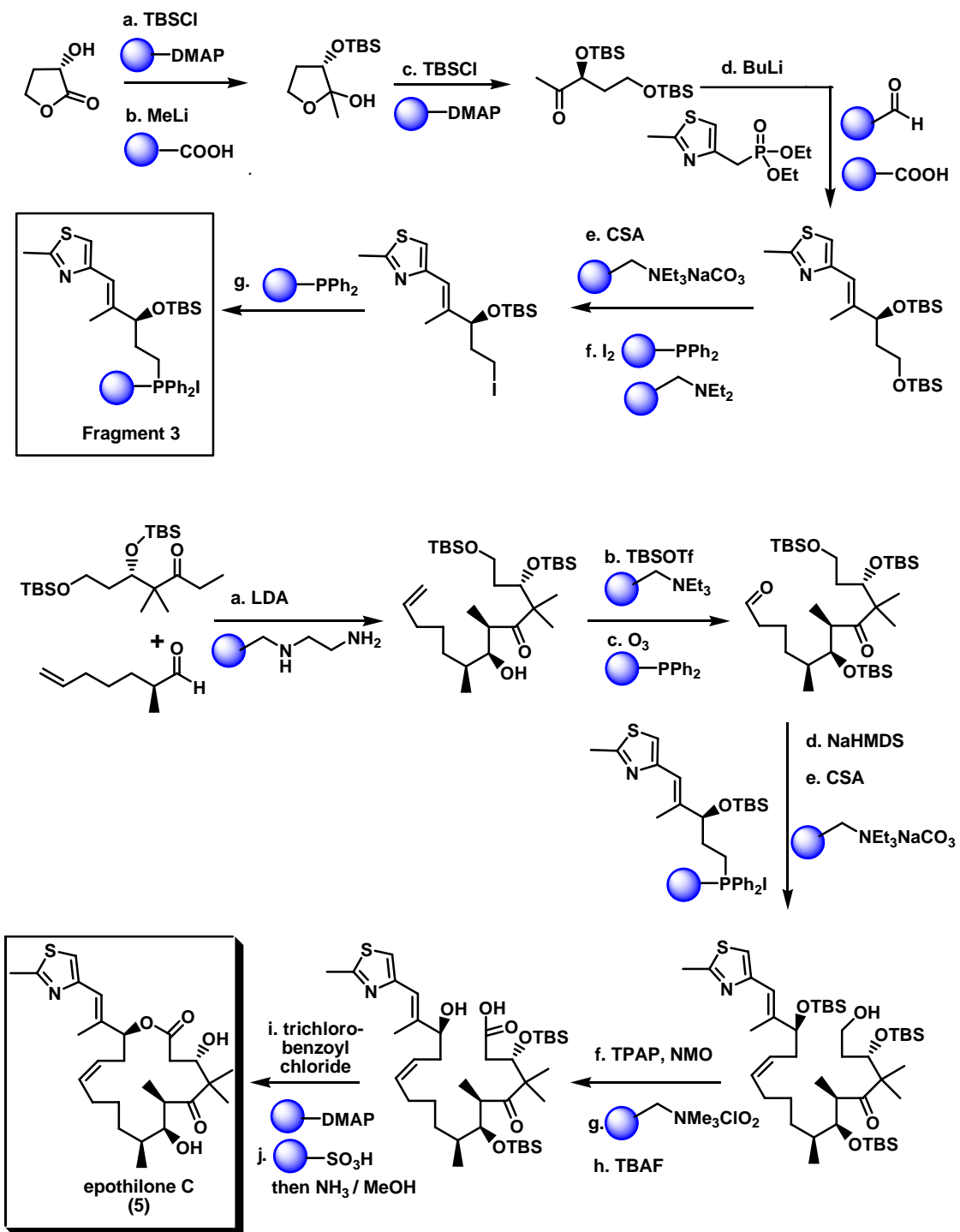
2.1.5.2 Convergent total synthesis of epothilone C:

The epothilone natural products exhibit extraordinary cytotoxicity by promoting GTP-independent tubulin polymerization. Mechanistic investigation revealed that the epothilones mode of action inhibits the growth of tumors by inducing mitotic arrest

followed by cell apoptosis. The Ley group employed immobilized reagents and scavengers to synthesize epothilone C (**5**), in a convergent synthesis, avoiding frequent use of conventional work up and purification procedures.¹⁴ The synthesis of the fragments and the tethering of the fragments in the total synthesis are shown below (Schemes 2.9 and 2.10).



Scheme 2.9. Fragment synthesis in total synthesis of epothilone C.



Scheme 2.10. Total synthesis of epothilone C using solid supported reagents and scavengers.

3. Aim of the project:

Nature is very much efficient in synthesizing different natural products containing seven membered cyclic ethers, so called oxepane scaffold (Figure 3). This oxepane containing natural products are isolated from different components of nature e.g. from plant leaves, from deep sea sponges, corals and marine natural sources. Those oxepane containing natural products have vast array of biological activity e.g. allelopathic and phytotoxic activity which are significant for the plant biology and plant physiology, antifertility activity which can be used as a contraceptive, cytotoxic activity which can be used for the treatment against human cancer cells as an anti tumor agent as well as protein synthesis inhibitors.

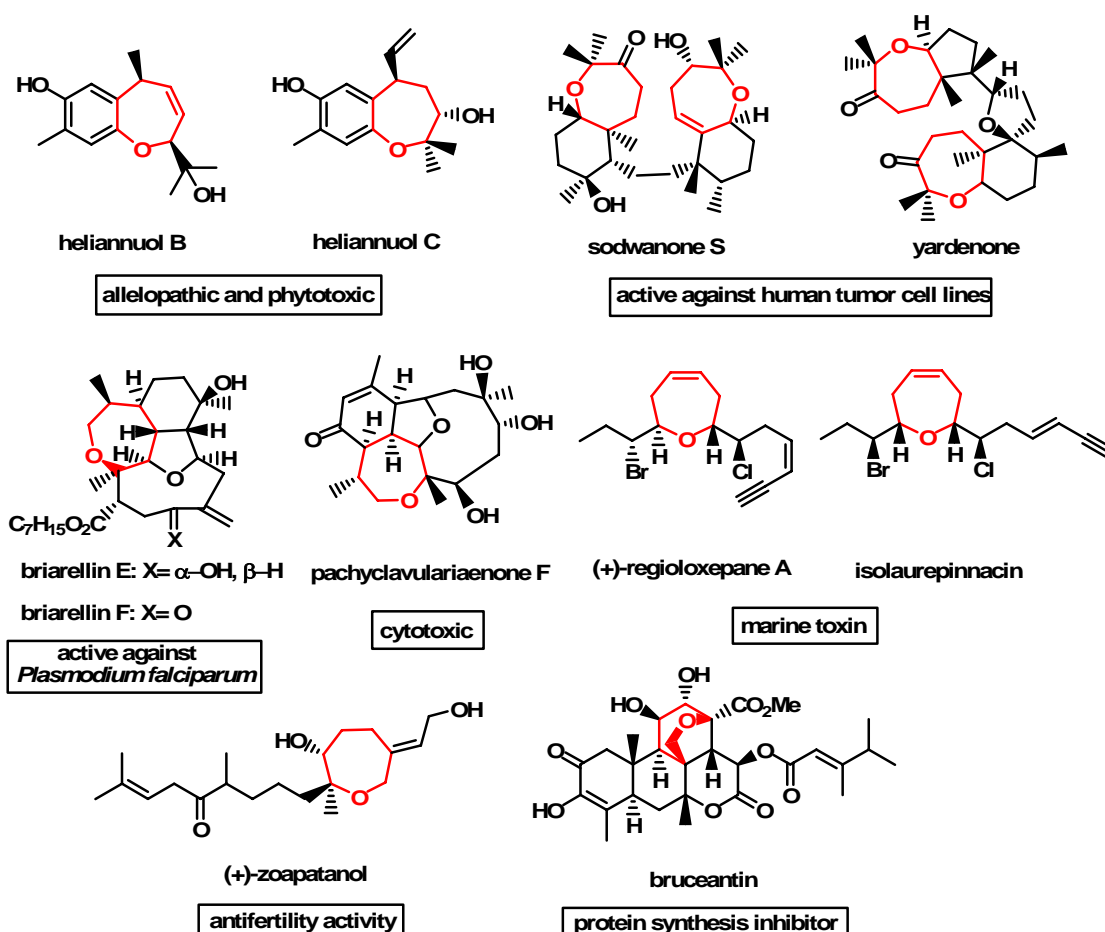


Figure 3. Natural products containing oxepane scaffold having broad range of bioactivity.

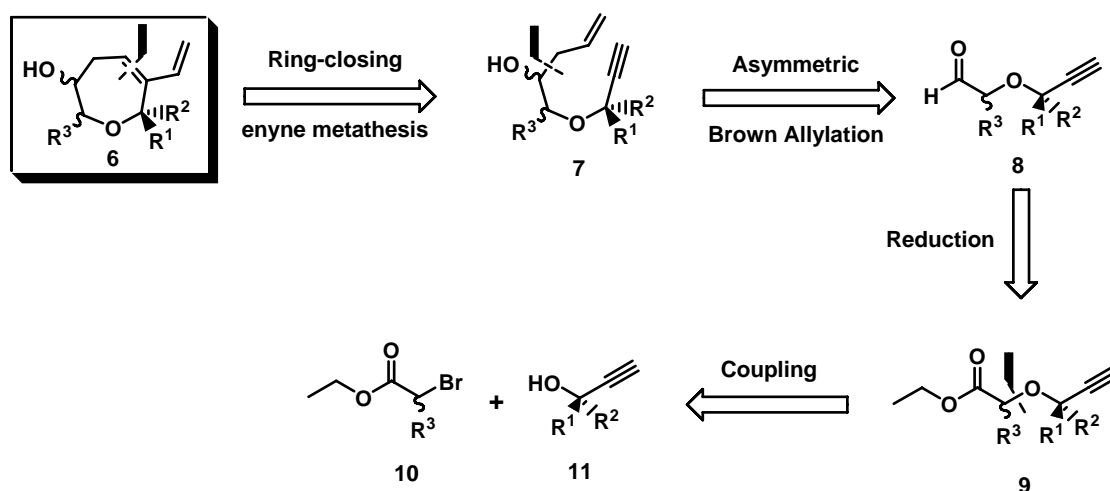
Hence those biologically active oxepane containing natural products can be regarded as chemical entities that were evolutionary selected and validated for binding to particular protein domain. As they are already biologically validated, the underlying structural architecture of such natural products may provide powerful guiding principles for oxepane based library development.

In one hand the main aim of this project is to develop a competent synthetic strategy to produce oxepane library. As the library generation needs to be efficient and realistic, a solution phase combinatorial strategy was intended to develop where different building blocks can be used in parallel to generate a large number of compounds. After developing a solution phase parallel synthetic approach, it is particularly important to mould this synthetic plan in useful and rapid technique. For this reason, on the other hand, the aim of this project is the extensive and convenient use of solid-supported reagents and scavengers in the solution phase parallel synthetic strategy. At the end a one pot synthetic strategy has been endeavored to develop using solid-supported reagents and scavengers without any purification steps in between to generate an oxepane library in a convenient and practical way. Finally the synthesized oxepane library is destined to the high-throughput screening in both forward and reverse chemical genomics studies for their biological validations.

4. Results and discussions:

The focused oxepane scaffold was synthesized by ring closing enyne metathesis as one of the key steps. The starting point of the oxepane library synthesis was different commercially available substituted propargyl alcohol building blocks.

4.1 Retrosynthetic analysis:

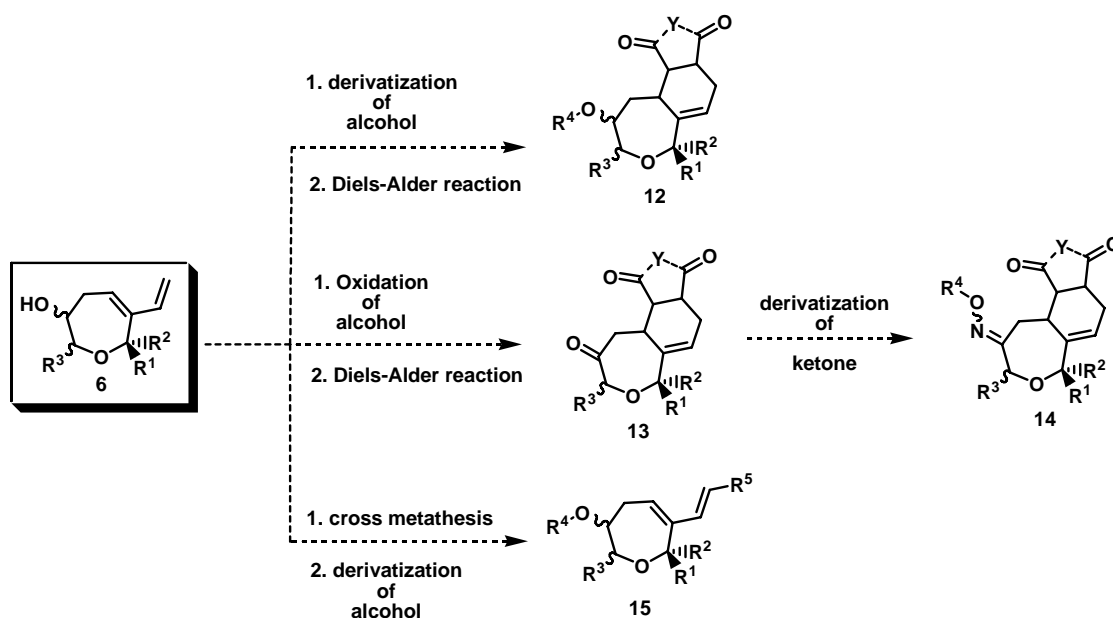


Scheme 4.1. Retrosynthetic analysis of focused oxepane scaffold **6**.

The oxepane diene core **6** can be retrosynthetically disconnected by the ring-closing enyne metathesis reaction which is the key transformation to generate the oxepane moiety from the open chain ene-yne precursor **7** (Scheme 4.1). The ene-yne precursor **7** contains a homoallyl alcohol moiety. The precursor **7** can be prepared in diastereomerically pure form by the asymmetric Brown allylation from the aldehyde precursor **8** which can be prepared from the corresponding ethyl ester **9** by controlled reduction. The ethyl ester **9** can be easily envisioned to be prepared by the coupling of two building blocks: substituted α -bromo ethyl acetate **10** and substituted propargyl alcohol **11**. This is the starting point of the forward synthetic strategy.

4.2 Diversification of the oxepane core:

After synthesizing the oxepane core, further diversification can be achieved on the oxepane core **6** (Scheme 4.2). The alcohol group in **6** can be derivatized and the diene moiety can be diversified using the Diels-Alder reaction to generate library **12**. The alcohol in **6** can be oxidized to the ketone and after Diels-Alder reaction the library **13** can be obtained. The functionalization of ketone in **13** can give rise to the library **14**. The diene moiety in **6** can be derivatized using cross metathesis and the free alcohol can be derivatized to synthesize the library **15**.

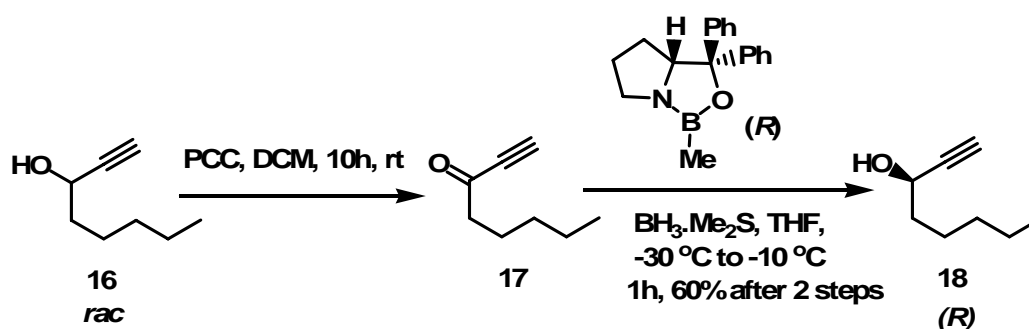


Scheme 4.2. Diversification of oxepane core **6**.

4.3 Synthesis of the substituted propargyl alcohol **18**:

The substituted propargyl alcohol **18** was prepared in enantiomerically pure form from the commercially available racemic alcohol **16** by means of a oxidation-reduction protocol. First the racemic alcohol **16** was oxidized with pyridinium chlorochromate (PCC) in DCM to obtain the ketone **17**. The black residue resulted from the chromium metal from PCC was filtered through a Celite pad and washed thoroughly with DCM to afford the ketone **17** in 98% GC purity. This low molecular weight ketone **17** is volatile.

So the care was taken while evaporating the solvent. The ketone **17** was then treated further without any chromatographic purification. Then the ketone **17** was reduced enantioselectively by using borane-dimethyl sulphide (BMS) complex in the presence of (+)-(*R*)-methyl oxazaborolidine catalyst (CBS catalyst) in THF at -30 °C to -10 °C to afford the alcohol **18** in 60% overall yield after 2 steps in 99% enantiomeric excess (ee) (Scheme 4.2).¹⁵ The determined optical rotation value of **18** showed perfect matching with the commercially available (+)-(*R*)-oct-1-yne-3-ol.¹⁶



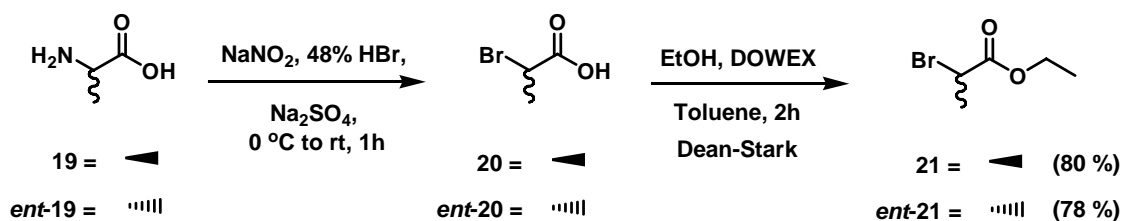
Scheme 4.3. Synthesis of enantiopure propargylic alcohol **18**.

In this reduction procedure 6.0 mol% of the CBS catalyst (Corey-Bakshi-Shibata catalyst) and 0.6 equiv of the BMS complex were used. It was noted that using more than 1.0 equiv of the BMS complex lead to the reduction of the alkyne to alkene and a 1:1 mixture (determined by GC-MS spectroscopy) of unwanted over reduced allyl alcohol formed along with compound **18**. All possible attempts to purify compound **18** from the unwanted over reduced product were in vain. So it is prudent to use 0.6 equiv of BMS complex for this reduction.

4.4 Synthesis of the substituted α -chloro ethyl acetate:

After preparing the substituted propargyl alcohol building block **18** in enantiomerically pure form, the synthesis of the second building block α -halo ethyl acetate in enantiomerically pure form was endeavored from both antipode of alanine. The amino acids **19** and *ent*-**19** were diazotized with sodium nitrite and 48% hydrobromic acid to obtain the corresponding bromopropionic acid **20** and *ent*-**20** respectively in quantitative

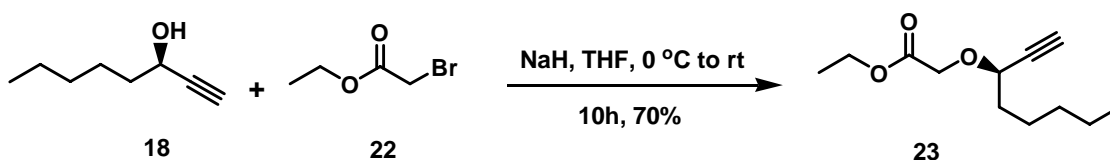
yield and 98% GC purity. The next step was carried out without any chromatographic purification. Both **20** and *ent*-**20** were esterified with ethanol in presence of catalytic amount of DOWEX[®] 50X8-200 acid resin to furnish the desired ethyl ester of α -bromo propionic acid **21** and *ent*-**21** in 80% and 78% yield respectively (Scheme 4.4).¹⁷



Scheme 4.4. Synthesis of enantiomerically pure **21** and *ent*-**21**.

4.5 Coupling of building blocks:

The coupling of the two building blocks was achieved using sodium hydride in THF. When the substituted propargyl alcohol **18** was treated with 95% sodium hydride at 0 °C and coupled with α -bromoethyl acetate **22**, the coupled product **23** was formed in 70% isolated yield (Scheme 4.5).¹⁸

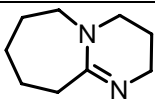
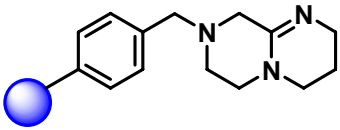
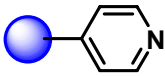


Scheme 4.5. Synthesis of coupling product **23**.

Keeping in mind that this coupling reaction needs to be done to generate a library of oxepanes, many other bases (Table 4.1) were employed which has solid supported analogues. None of them was successful. In all the cases only the starting material **18** was recovered without any trace of product **23** detected. It appeared that triethyl amine (Entry 1), pyridine (Entry 3), imidazole (Entry 4) and polymer supported pyridine (Entry 6) are not enough basic to deprotonate the alcohol **18**. When stronger base DBU (Entry 2) and its polymer supported analogue TBD-methyl polystyrene (Entry 6) were used as base, no

trace of product was detected. In these last two cases, the bases are stronger but they are sterically hindered, hence can not deprotonate the secondary alcohol **18**. It materialized that sodium hydride is the best choice for this reaction because it is enough basic and sterically least hindered to deprotonate the secondary alcohol **18**. Hence it was used further for the library generation.

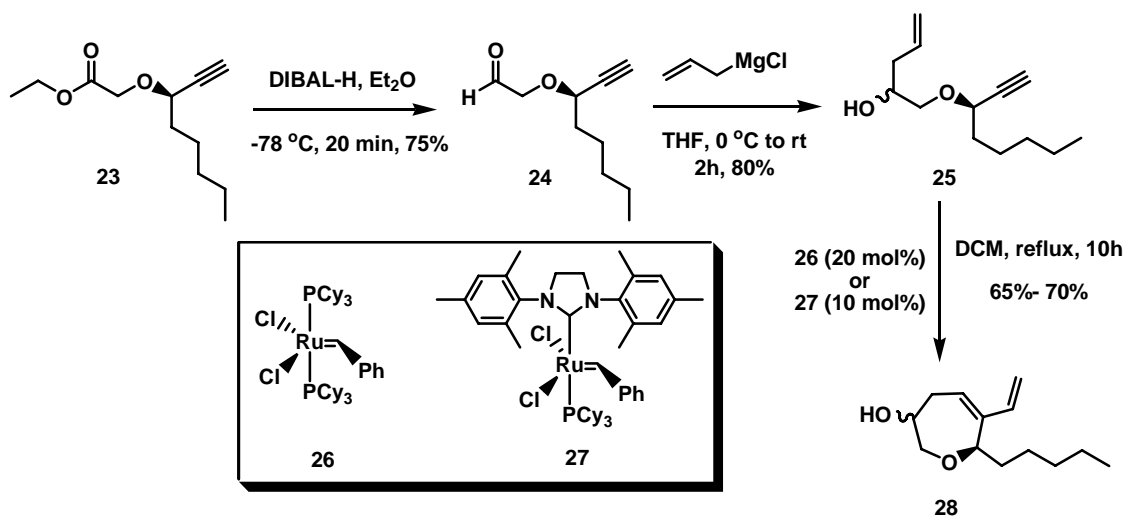
Table 4.1. Base used for the coupling reaction.

Entry	Base	Product
1	Et ₃ N (2 equiv)	Starting material recovered
2	 1,8-Diazabicyclo[5.4.0]undec-7-en (DBU, 2 equiv)	Starting material recovered
3	Pyridine (2 equiv)	Starting material recovered
4	Imidazole (2 equiv)	Starting material recovered
5	 TBD-methyl polystyrene (3 equiv)	Starting material recovered
6	 (3 equiv)	Starting material recovered

4.6 Construction of the oxepane core by ring-closing enyne metathesis:

Having the coupled product in hand the ester functionality in **23** was reduced to the aldehyde **24** directly using diisobutylaluminiumhydride (DIBAL-H) in diethyl ether in 75% yield. The reaction was carried out by slow addition of DIBAL-H (1M solution in hexane or toluene) in diethyl ether solution of **23** at -78 °C temperature. It was interesting

to observe that, if the reaction was carried out using DIBAL-H (1M solution in DCM or THF) in any other solvent system like DCM or THF even at $-78\text{ }^{\circ}\text{C}$, a mixture of the aldehyde **24** and unexpected over reduced alcohol was formed. So the perfect system for the controlled reduction of ester to aldehyde was optimized using DIBAL-H in hexane or toluene and the reaction must be carried out in diethyl ether solution. The aldehyde **24** was allylated using allylmagnesiumchloride in THF to obtain homoallyl alcohol **25** as the 1:1 inseparable mixture of two diastereomers in 80% yield. The diastereomeric ratio was determined by ^1H NMR spectroscopy. When the ring-closing metathesis precursor **25** was treated with commercially available Grubbs 1st generation ruthenium carbene complex **26** (20 mol%) or 2nd generation *N*-heterocyclic carbene complex **27** (10 mol%) in refluxing DCM, the expected seven-membered oxepane diene **28** was formed as the 1:1 inseparable mixture of two diastereomers in 65% and 70% yield respectively (Scheme 4.6).¹⁹ In this case also the diastereomeric ratio was determined by ^1H NMR spectroscopy.



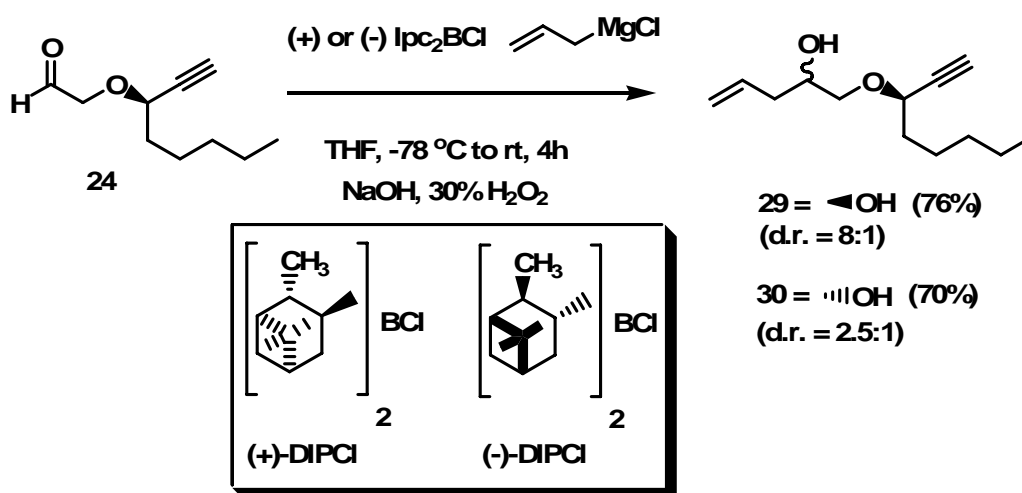
Scheme 4.6. Synthesis of the oxepane **28** by ring-closing enyne metathesis.

It was noteworthy that slightly better yield was obtained using the 2nd generation Grubbs catalyst **27** than the 1st generation Grubbs catalyst **26** (70% vs 65%). Also a less catalyst loading was needed for **27** than **26** (10 mol% vs 20 mol%). Despite the lower yield and higher catalyst loading, the 1st generation Grubbs catalyst **26** was chosen as the viable

catalyst for library generation because of its lower cost than the 2nd generation Grubbs catalyst **27**.

4.7 Asymmetric Brown allylation:

As the decisive enyne ring-closing metathesis reaction smoothly offered the oxepane scaffold, the focus was then turned toward the diastereoselective synthesis of the oxepane system. The diastereo-pure oxepane can be obtained by the asymmetric allylation of the aldehyde **24** to get diastereomerically enriched homoallyl alcohol **29** or **30**. To synthesize diastereomerically pure enyne precursor for the metathesis reaction, Brown's asymmetric allylation reaction was chosen. Aldehyde **24** was treated with either (+) or (-)-diisopinocampheylallylborane prepared in situ by (+) or (-)-diisopinocampheylboron chloride (DIPCl) and allylmagnesiumchloride, in THF to afford homoallyl alcohol **29** and **30** in 76% and 70% yield respectively after hydrolysis of the intermediate alkoxy borane using sodium hydroxide and 30% hydrogen peroxide (Scheme 4.7).²⁰



Scheme 4.7. Asymmetric Brown allylation of aldehyde **24**.

In case of the (+)-DIPCl the diastereomeric ratio was found to be 8:1 in favor of the desired isomer. But in case of the (-)-DIPCl the diastereomeric ratio was 2.5:1 in favor of the desired isomer. The diastereomeric ratio was determined by ¹H NMR spectroscopy.

From the diastereomeric ratio it is clear that the chiral allyl borane formed from (+)-DIPCl is “matched” case for the aldehyde **24**. On the other hand the chiral allyl borane reagent formed from (-)-DIPCl is “mismatched” case. This asymmetric allylation reaction of aldehyde proceeds through a chair like transition state where the larger group on aldehyde occupies an equatorial position and the aldehyde facial selectivity is determined by minimization of steric interaction between the axial “Ipc” ligand and the allyl group.

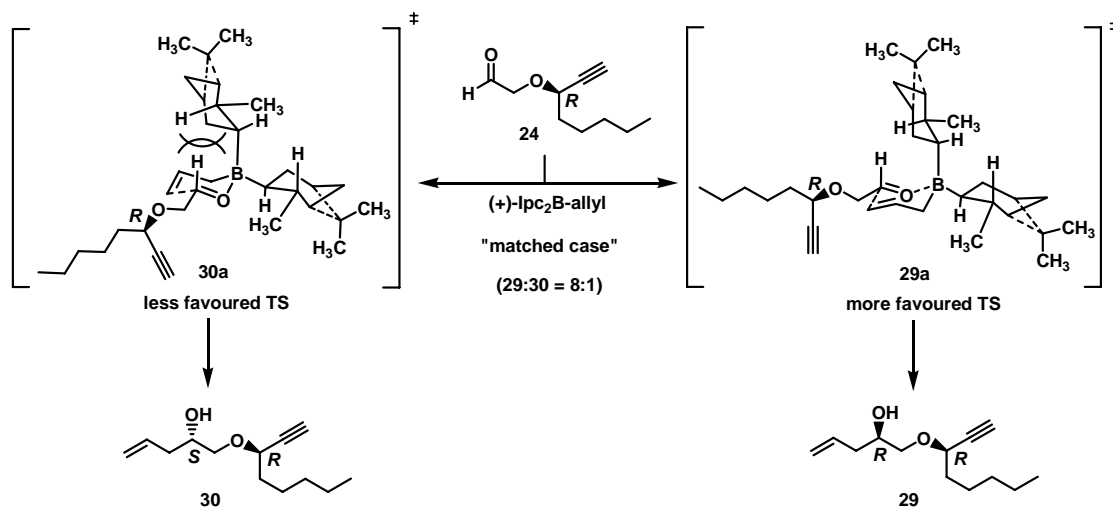


Figure 4.1a. Chair like transition state of the (+)-Ipc₂B-allyl addition to the aldehyde **24**.

When aldehyde **24** was treated with (+)-DIPCl and allylmagnesiumchloride the reaction could proceed through two possible chair like transition states (TS) **29a** and **30a** (Figure 4.1a). In TS **30a**, the axial bulky “Ipc” group is experiencing a steric interaction with the allyl group on “B” atom which makes this TS less favoured. On the other hand in the more favourable TS **29a**, the axial bulky “Ipc” ligand is totally on the other side of the allyl group on “B” atom and not experiencing any steric hindrance with any other bulky group. So the reaction proceeded through the more favourable transition state **29a**. This transition state model explains the stereoselectivity of the major product **29**.

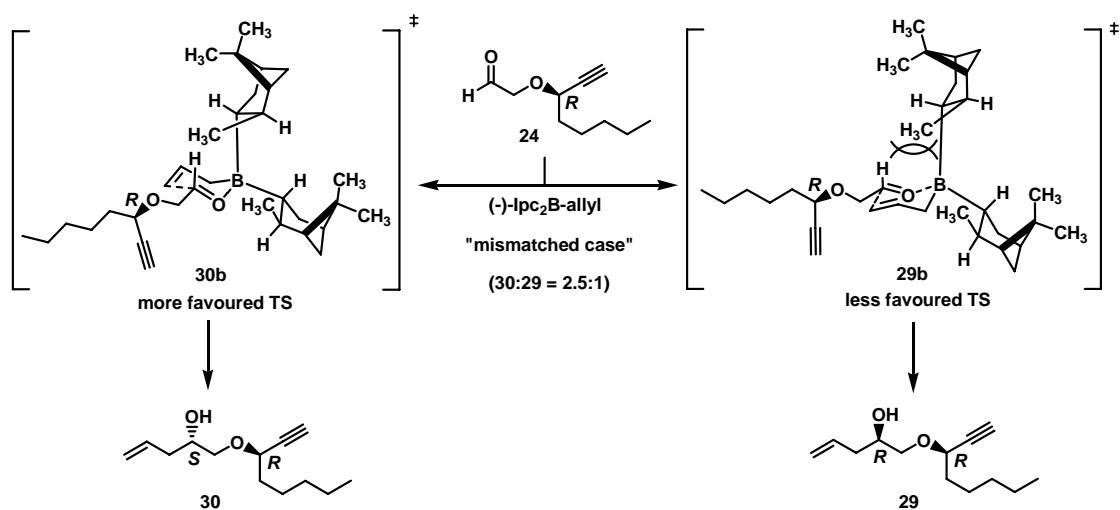
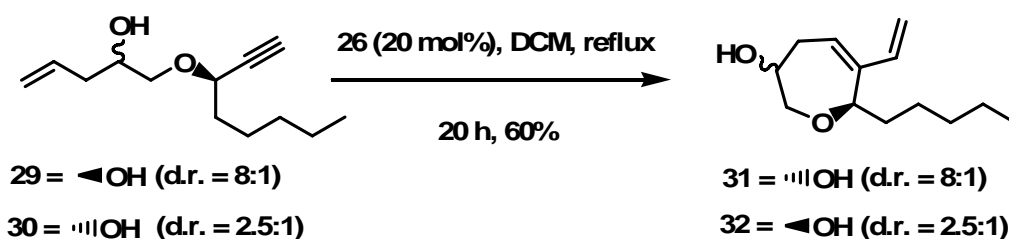


Figure 4.1b. Chair like transition state of the (-)-Ipc₂B-allyl addition to the aldehyde **24**.

Similarly when aldehyde **24** was treated with (-)-DIPCl and allylmagnesiumchloride the reaction could proceed through the chair like transition states (TS) **29b** and **30b** (Figure 4.1b). In the less favoured TS **29b** the methyl group of the axial "Ipc" ligand on "B" is experiencing a steric interference with the allyl group because both of them are in the same side of the chair TS. But in the more favourable TS **30b**, the methyl group on the axial "Ipc" ligand is projected in the opposite direction of the allyl group, hence there is no steric hindrance between them. So obviously the reaction proceeds through the more favourable TS **30b**. The chair like transition state model explains the stereoselectivity of the major product **30**.

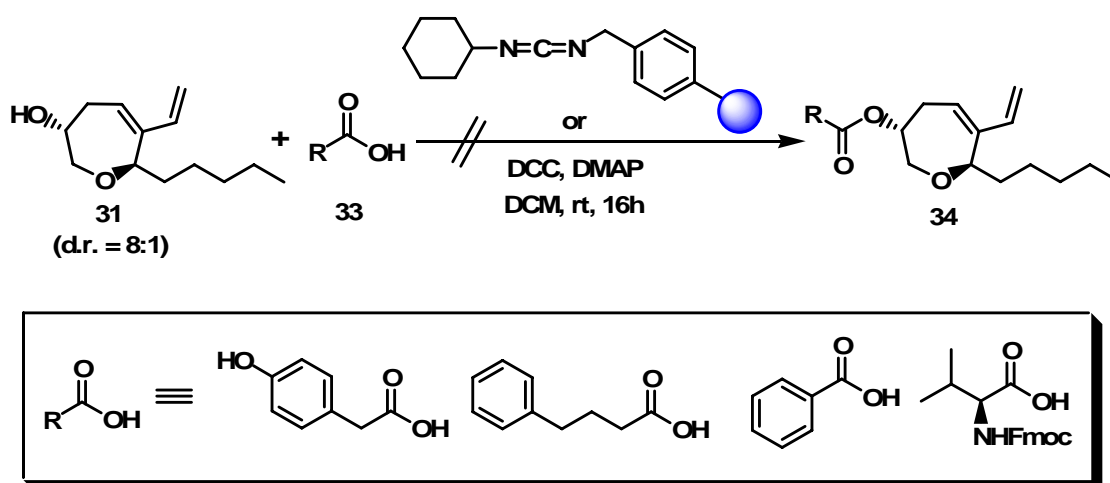
After the Brown's asymmetric allylation of aldehyde **24**, further reactions were carried out without any separation of the diastereomers. When both enyne **29** (8:1 diastereomeric mixture) and **30** (2.5:1 diastereomeric mixture) were treated separately with 20 mol% of the 1st generation Grubbs catalyst **26** in refluxing DCM, the oxepane **31** and **32** were obtained as 8:1 and 2.5:1 inseparable diastereomeric mixture respectively (determined by ¹H NMR spectroscopy) in 60% yield (Scheme 4.8). As the main aim of this project is to develop a synthetic strategy which can be moulded into a one pot protocol, the next steps were carried out without any separation of the diastereomers.



Scheme 4.8. Enyne metathesis of **29** and **30** to afford **31** and **32**.

4.8 Attempted coupling of alcohol and carboxylic acids:²¹

At this point the oxepane scaffold is ready for diversification. First the alcohol **31** (8:1 inseparable mixture of two diastereomers) was attempted to functionalize into ester **34** using different acids **33** (Scheme 4.9).

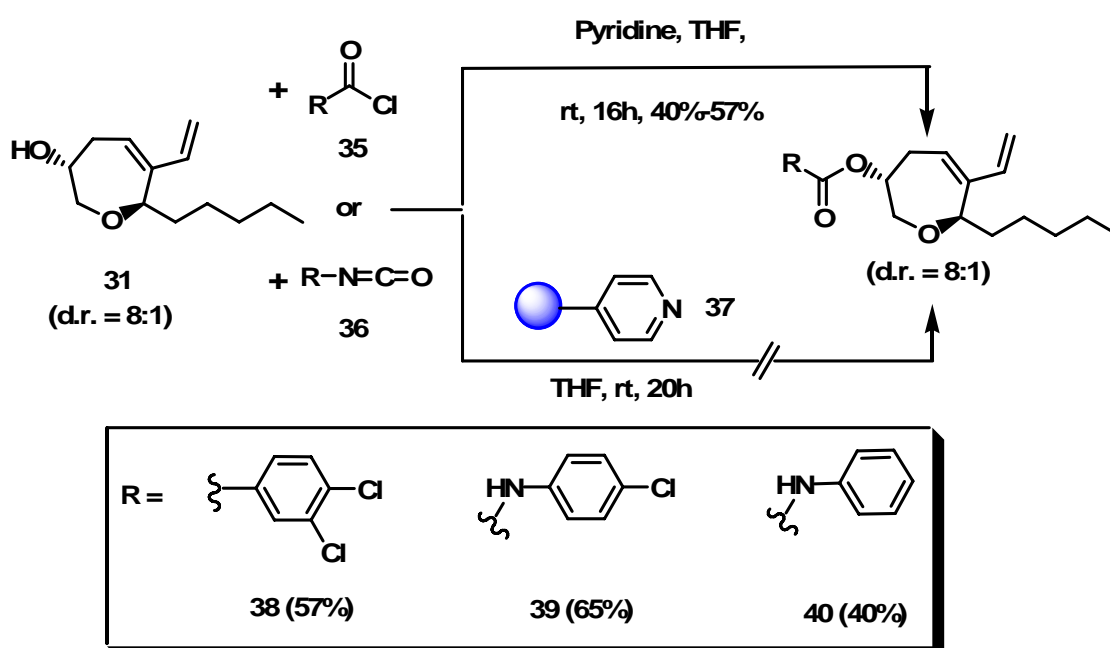


Scheme 4.9. Attempted synthesis of esters **34** by coupling of alcohol and carboxylic acids.

Alcohol **31** was treated with the carboxylic acid **33** in presence of dicyclohexylcarbodiimide (DCC) or its solid supported analogue, *N*-cyclohexylcarbodiimide, *N*-methyl polystyrene, dimethyl amino pyridine (DMAP) as catalyst, in DCM at room temperature. But in none of the cases ester **34** was observed and the unreacted starting material was recovered in all the cases (Scheme 4.9).

4.9 Synthesis of ester and carbamate:²²

From the above coupling attempts it was evident that the carboxylic acids were not the best coupling partner with the alcohol **31**. Also the alcohol **31** is a secondary alcohol which is hence less reactive. So a more reactive coupling partner was necessary to esterify the alcohol in **31**. Acid chlorides were chosen for this purpose. The alcohol in **31** was also derivatized to carbamates using isocyanates as the other coupling partner (Scheme 4.10).



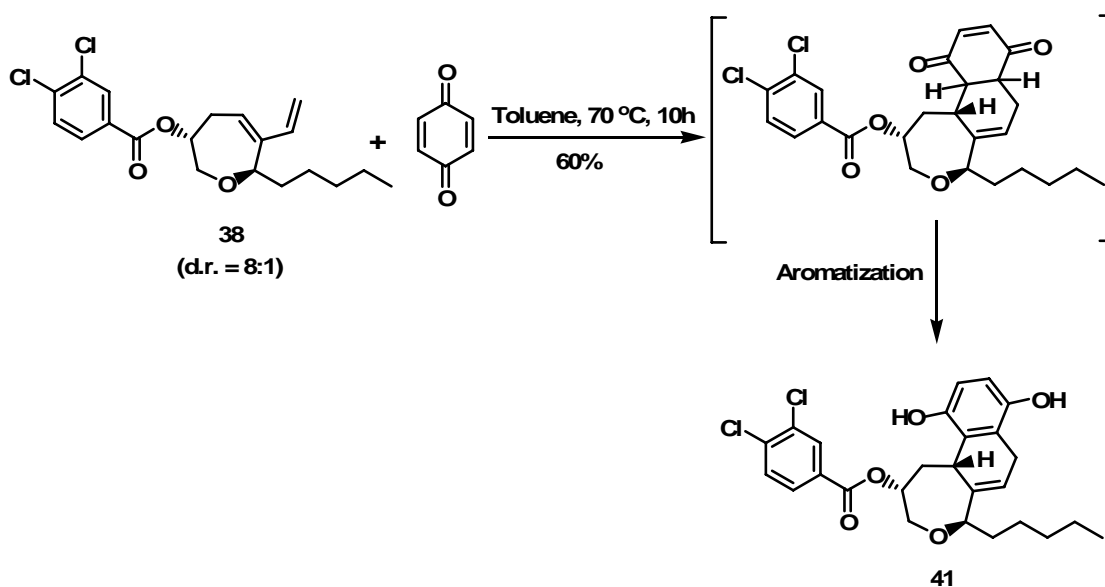
Scheme 4.10. Synthesis of ester **37** and carbamates **38** and **39**.

When alcohol **31** (8:1 inseparable mixture of two diastereomers) was treated with 3,4-dichloro benzoyl chloride **35** or isocyanate **36** (either 4-chlorophenyl isocyanate or phenyl isocyanate) in the presence of pyridine as base, ester **38**, carbamate **39** and **40** were formed in 57%, 65% and 40% yield respectively. The ester **38** and carbamates **39** and **40** were formed as 8:1 inseparable mixture of two diastereomers (diastereomeric ratio was determined by ¹H NMR spectroscopy), which showed that the diastereomeric ratio of the starting material was relayed to the products. Further reaction was carried out without any separation of the diastereomers. To avoid the workup procedure, this coupling

reactions were carried out in presence of poly(4-vinylpyridine) **37** (25% cross-linked) in THF at room temperature for 20h. But all the attempts were unsuccessful and in all the cases starting alcohol **31** was recovered. It was materialized that the polymer supported pyridine is not suitable for this coupling reactions.

4.10 Diels-Alder reaction:

The conjugated diene of the oxepane scaffold was then diversified by Diels-Alder reaction. Ester **38** (8:1 inseparable mixture of two diastereomers) was treated with the electron-poor dienophile *p*-benzoquinone in toluene at 70 °C to obtain the Diels-Alder adduct which was aromatized under the reaction condition to afford **41** as the single diastereoisomer isolated by silica gel flash chromatography in 60% yield (Scheme 4.11).^{23, 19a-c}

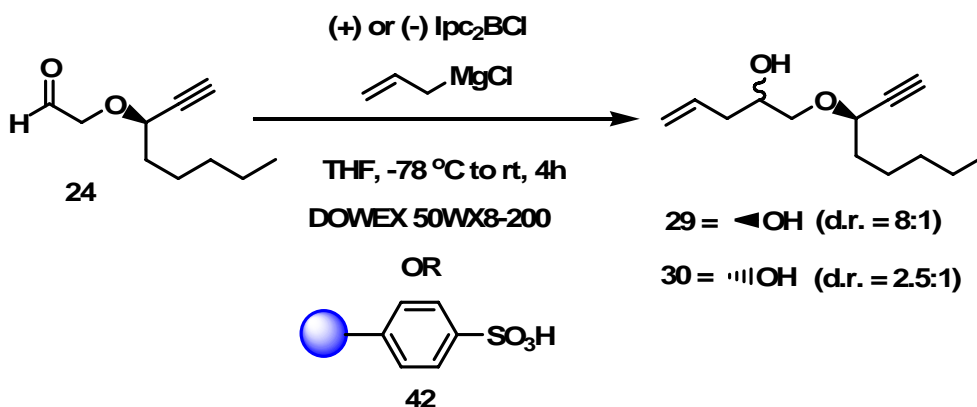


Scheme 4.11. Diels-Alder reaction with **41**.

4.11 Use of polymer-sulfonic acid scavengers in the Brown allylation:

After achieving the fully functionalized oxepane in solution phase, the next task ahead was to reduce the extensive workup and purifications to produce the oxepane library in a fast and efficient way. In this context the effectiveness of the solid supported reagents and scavengers was taken into account. In the whole strategy, the first reaction where the solid supported scavenger was used was the Brown allylation.

The aldehyde **24** was treated with both (+) - and (-) -DIPCl and allylmagnesiumchloride separately in THF. After 4h, when the reactions were complete (determined by TLC), DOWEX[®] 50WX8-200-ion exchange resin^{14b} (8% cross linking, 200-400 mesh) was used to scavenge the excess allylmagnesium chloride. Then the resin was filtered to obtain the homoallyl alcohol **29** and **30** respectively in the same diastereomeric ratio obtained before (Scheme 4.12). The diastereomeric ratio was determined by ¹H NMR spectroscopy of the crude products. The excess allylmagnesiumchloride can also be scavenged by polymer supported sulfonic acid resin **42** (macroporous copoly[styrene-DBV], 70-90 mesh, loading = 3.20 mmol/g) using same method.



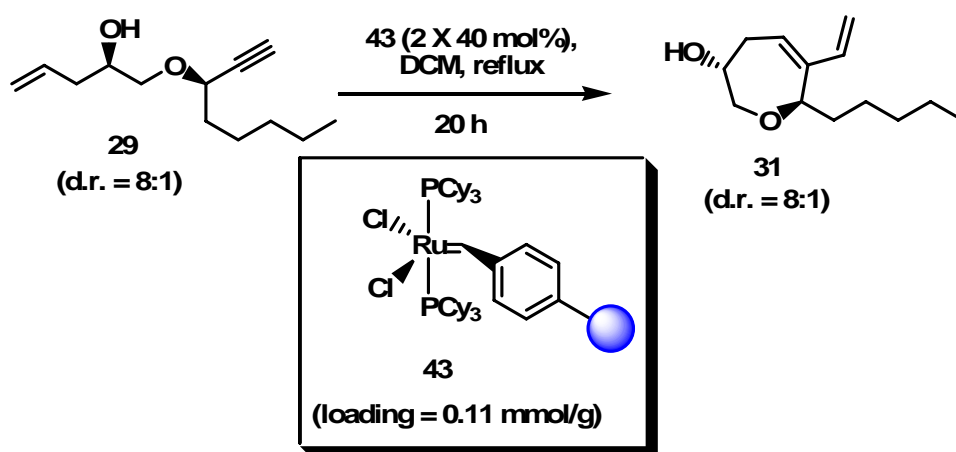
Scheme 4.12. Use of polymer-supported scavengers in the Brown allylation.

Both DOWEX[®] 50WX8-200 and **42** were effectively well to scavenge the excess Grignard reagent, but the commercially available DOWEX[®] 50WX8-200 resin contains some unwanted impurities which could come to the reaction mixture. So using DOWEX[®]

50WX8-200 as the scavenger the product obtained after evaporation of the solvent contains impurities from the resin which can not be removed without chromatography. But on the other hand commercially available sulfonic acid resin **42** does not contain impurities which can create problem in the later stage of the synthesis and the product obtained after filtration of the resin and evaporation of the solvent devoid of any impurities from the scavenging resin. The scavenging resin **42** was chosen for the further library generation.

4.12 Scavenging Ru-metal from the RCM reaction:

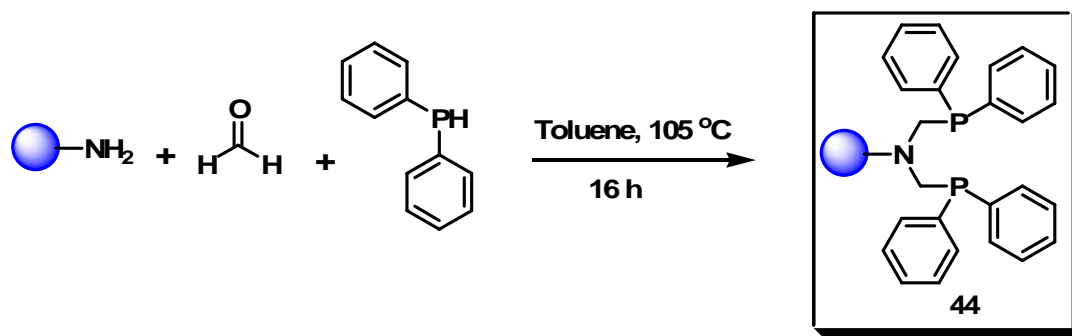
One of the serious experimental drawbacks of using Grubbs Ru-carbene complex in ring-closing metathesis reactions is the removal of the dark-colored, metal containing by-products upon completion of the reaction, since it might effect unwanted synthetic reactions and result in misleading biological screening results. Several research groups have developed different techniques to solve this problem.²⁴ One of those strategies is to use polymer bound olefin metathesis catalysts which can be removed very easily from the reaction mixture by filtration. Hence, when enyne **29** (used from the previous reaction without any further purification) was treated with the commercially available solid supported 1st generation Grubbs catalyst **43** (2 x 40 mol%) developed by Barrett,²⁵ the ring-closed product **31** was obtained (Scheme 4.13).



Scheme 4.13. Solid supported 1st generation Grubbs catalyst **43** used for enyne metathesis.

After filtration of the resin from the reaction mixture, a clear, colorless, crude reaction mixture was obtained. The identity of the product **31** was confirmed by GC-MS and ^1H NMR spectra of the crude sample. The oxepane **31** was formed in the same 8:1 inseparable mixture of two diastereomers as the open chain starting alcohol **29**. The diastereomeric ratio was also determined by ^1H NMR spectroscopy.

The main problem faced in this strategy was twofold. First, the polymer supported 1st generation Grubbs catalyst **43** is very costly and second, it has only low loading (0.11 mmol/g). Hence a large catalyst loading (2 x 40 mol %) of the polymer supported 1st generation Grubbs catalyst **43** was needed for each set of reactions. Based on those points this strategy was not compatible with the synthesis of a large library. So to scavenge the ruthenium metal after the reaction, Breinbauer's²⁶ method was adopted.

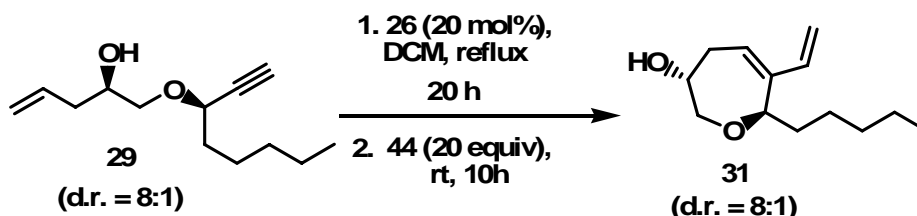


Scheme 4.14. Synthesis of the polymer bound phosphine ligand **49**.

This strategy is inexpensive and efficient. In this technique, the resin bound phosphine **44** was used as a readily accessible P-ligand to chelate the ruthenium metal from the reaction mixture. The resin bound phosphine **44** was synthesized by heating the commercially available amino methylated polystyrene (loading = 1.1 mmol/g), with paraformaldehyde and diphenyl phosphine in toluene at $105\text{ }^\circ\text{C}$ (Scheme 4.14).²⁷

After the ring-closing enyne metathesis reaction was completed (monitored by TLC) with **29** (8:1 mixture of two diastereomers) using the 1st generation Grubbs catalyst **26** (20 mol%), the polymer bound phosphine ligand **44** (20 equiv relative to the catalyst used) was added and the reaction mixture was stirred for 10h at room temperature. The resin

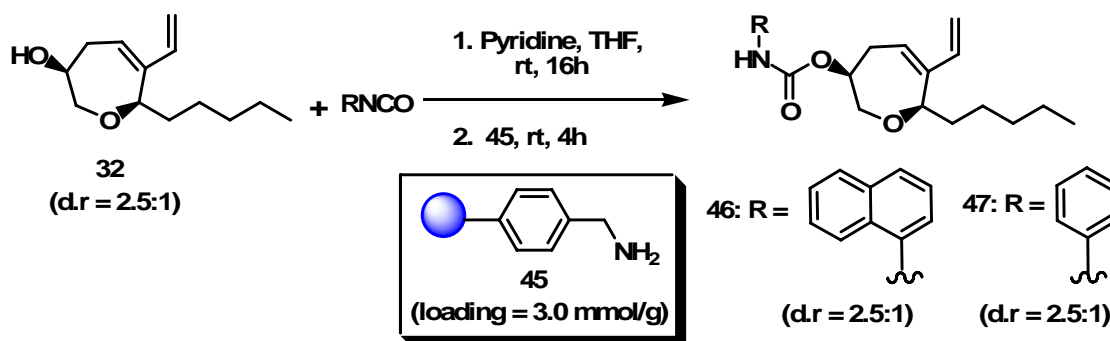
was filtered through a silica gel plug. After removing the solvent, colorless product **31** (8:1 mixture of two diastereomers) was obtained (Scheme 4.15).



Scheme 4.15. Use of the polymer bound scavenger **44** in enyne metathesis of **29**.

4.13 Use of scavengers in carbamate formation:

The next aim was to use polymer bound scavenger for the carbamate formation reaction from the alcohol and isocyanate. In this step the commercially available aminomethylated polystyrene **45** was used as the scavenger for the excess isocyanate. Compound **32** (2.5:1 mixture of two diastereomers) was treated with either 1-naphthyl isocyanate or phenyl isocyanate to obtain the carbamate **46** and **47** respectively in the presence of pyridine as base in THF (Scheme 4.16).



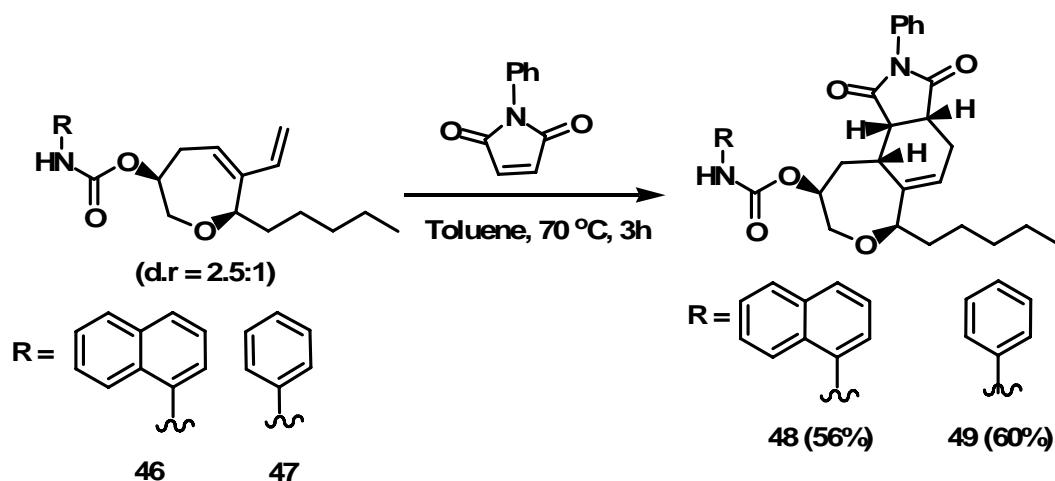
Scheme 4.16. Use of aminomethyl polystyrene **45** as scavenger of isocyanate.

When the reaction was complete after 16h (monitored by TLC), 3 equiv (relative to the excess isocyanate used) of aminomethylated polystyrene **45** (loading = 3.0 mmol/g) was added and the reaction mixture was stirred for 4 h at room temperature. After filtration

and evaporation of solvent, carbamate **46** and **47** were obtained as 2.5:1 inseparable mixture of two diastereomers. The identity and the diastereomeric ratio of the products formed were determined by GC-MS and the ^1H NMR spectra. These crude products were used for the next Diels-Alder reaction without further purification.

4.14 Diels-Alder reaction with *N*-phenylmaleimide:

The crude carbamates **46** and **47** (2.5:1 mixture of two diastereomers) were then heated with *N*-phenyl maleimide as the dienophile in the Diels-Alder reaction in toluene at 70 °C to obtain the tricyclic Diels-Alder adduct **48** and **49** in 56% and 60% overall yield respectively after 2 steps (Scheme 4.17). The pure products were obtained by silica gel flash chromatography as single diastereomer (determined by ^1H NMR spectroscopy).



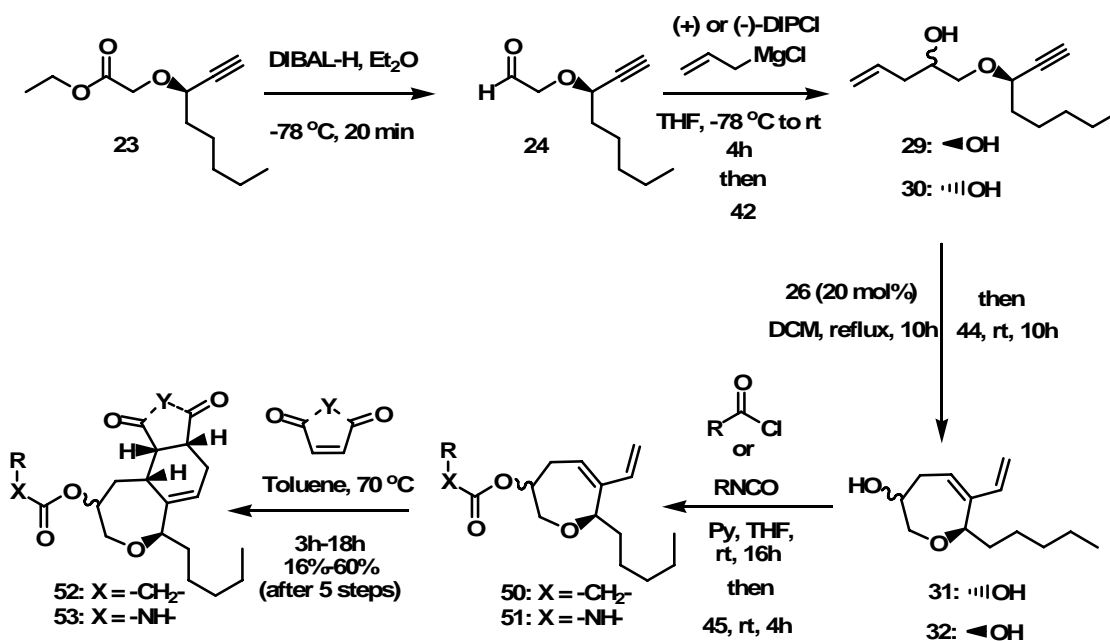
Scheme 4.17. Diels-Alder reaction to synthesize **48** and **49**.

4.15 Development of a one pot synthetic strategy:

At this stage the path was laid down to generate an oxepane library in solution using solid supported reagents and scavengers. The library generation will be practical and quick only if it is performed without any purification of the intermediates. In other words the synthetic strategy must dwell on the use of solid supported reagents and scavengers and all the reactions must be accomplished in one pot.

Keeping those two points in mind, one pot synthesis was commenced from the DIBAL-H reduction of ester **23** to aldehyde **24** (Scheme 4.18). After workup and evaporation of the solvent the crude aldehyde **24** (without any further purification) was treated separately with either (+) - or (-) - DIPC1 and allylmagnesium chloride in THF to obtain both homoallyl alcohol **29** and **30**.

After the completion of the reaction after 4h (TLC monitoring), polymer supported sulfonic acid resin **42** (5 equiv relative to the excess allylmagnesium chloride) was added to scavenge the excess allylmagnesium chloride. The resin was filtered and after removal of the solvent both crude **29** and **30** was treated separately by 20 mol% 1st generation Grubbs catalyst **26** in refluxing DCM to obtain both oxepane **31** and **32** respectively. As soon as the reaction was over after 10h (TLC monitoring), the polymer supported chelating phosphine ligand **44** (20 equiv relative to the catalyst added) was added to scavenge the ruthenium metal. After filtration, the solvent was evaporated to afford colorless crude **31** and **32**.



Scheme 4.18. Synthesis of oxepane **52** and **53** using solid-supported scavengers.

Both oxepane **31** and **32** were treated separately with different commercially available acid chlorides and isocyanates in the presence of pyridine as base in THF to obtain esters and carbamates **50** and **51** respectively. When all the starting material was consumed after 16h (monitored by TLC), aminomethylated polystyrene **45** (3 equiv relative to the excess isocyanate/ 6 equiv relative to the excess acid chlorides added) was added to scavenge the excess isocyanates and acid chlorides. After filtering and removal of solvent, crude **50** and **51** were separately treated with the electron poor dienophiles in toluene at 70 °C for 3h to 18h (depending on the dienophiles used). After the Diels-Alder reaction the crude products were purified by flash chromatography to yield pure **52** and **53** in 16% to 60% overall yields after 5 steps.

The fully functionalized oxepane **52** and **53** were found to be varying inseparable mixtures of two diastereomers (see experimental part for the diastereomeric ratio of the individual compounds). The diastereomeric ratio was determined by ¹H NMR spectroscopy. Using the above one pot synthetic strategy using solid-supported scavengers 17 diverse fully functionalized oxepanes were synthesized in 16% to 60% overall yield after 5 steps. Three different electron poor dienophiles: *p*-benzoquinone, *N*-phenylmaleimide and dimethyl acetylenedicarboxylate were used in the Diels-Alder reaction. The *p*-benzoquinone gave the hydroquinone moiety after aromatization under the reaction conditions. The electron donating groups (eg. 4-methyl and 4-methoxy groups) on the aromatic acid chlorides and isocyanates gave poor overall yield (~ 20% after 5 steps). On the other hand the electron withdrawing groups (eg. 4-chloro and 3,4-dichloro groups) on the aromatic acid chlorides and isocyanates gave better overall yield (~ 60% after 5 steps). It was observed that the tertiary butyl isocyanate and tertiary butyl isothiocyanate were totally unreactive in the carbamate formation condition. This result can be realized because of their bulky nature and the other reacting partner is secondary alcohol on oxepane moiety. Among the 17 oxepane compounds 12 were found to be single diastereomers, 2 were found to be the 4:1 inseparable mixture of two diastereomers and the rest 3 were 8:1 inseparable mixture of two diastereomers. In all the cases the diastereomeric ratio was determined by ¹H NMR spectroscopy. At this point it was assumed that the Diels-Alder reaction with the electron poor dienophiles proceeded exclusively through an *endo*-selective transition state where the dienophile is approaching

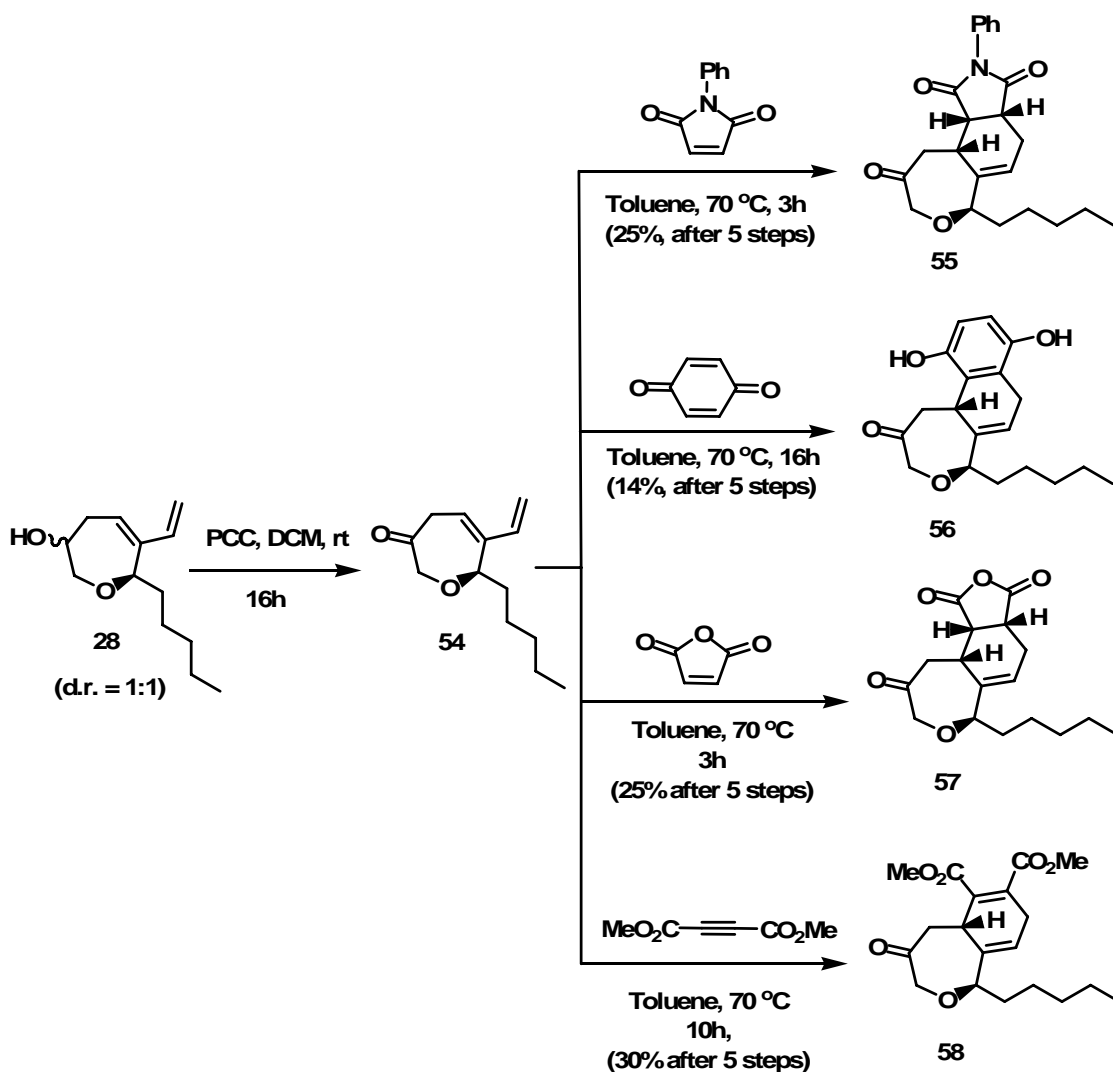
from the opposite phase of the bulky pentyl group near the diene moiety (Scheme 4.26). This assumption will be proved correct later by nOe study of a particular library member (Figure 4.2).

Hence a solution phase one pot synthetic scheme was developed using extractive work up and polymer bound scavenging reagents excluding the purification steps in between. This synthetic strategy was used to generate the combinatorial oxepane library in a practical and efficient way in solution phase where the reactions can be monitored by thin-layer chromatography (TLC) and GC-MS technique.

4.16 Diversification of the oxepane library:

4.16.1 Keto-oxepane library synthesis:

As the one pot strategy was successfully accomplished, the oxepane scaffold was further diversified to produce diverse molecules. When compound **28**, a 1:1 mixture of two diastereomers was oxidized by PCC, ketone **54** was formed. The chromium metal containing residue was filtered from the reaction mixture by a Celite pad and after evaporation of the solvent, crude **54** was obtained which was further treated without any purification. Crude ketone **54** was treated with different dienophiles like *N*-phenyl maleimide, *p*-benzoquinone, maleic anhydride and dimethyl acetylenedicarboxylate separately in toluene at 70 °C to yield the Diels-Alder adducts **55** (25% overall yield after 5 steps), **56** (14% overall yield after 5 steps), **57** (25% overall yield after 5 steps) and **58** (30% overall yield after 5 steps) respectively as single diastereomers (determined by ¹H NMR spectroscopy) after 5 steps (Scheme 4.19). *N*-phenylmaleimide and maleic anhydride reacted quickly (3h), but *p*-benzoquinone and dimethyl acetylenedicarboxylate took longer time (16h and 10h respectively). As before the Diels-Alder adduct with *p*-benzoquinone aromatized under the reaction condition to give rise to catechol moiety. It was also assumed that the Diels-Alder reaction proceeded exclusively through an *endo*-selective transition state where the electron poor dienophiles approached from the opposite phase of the bulky pentyl group near the diene moiety.

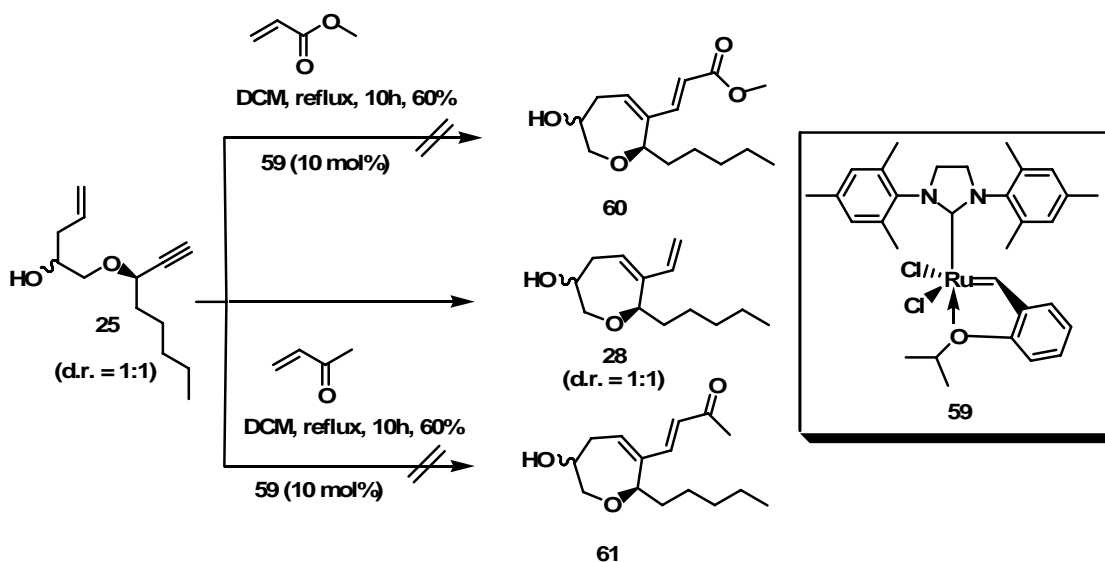


Scheme 4.19. Synthesis of keto-oxepane library.

4.16.2 Tandem ring-closing metathesis/cross-metathesis:

To create a new scaffold based on the oxepane core structure, the tandem ring-closing metathesis/cross-metathesis (RCM/CM) reaction was chosen. When the enyne **25** (1:1 mixture of two diastereomers) was treated with the 2nd generation Hoveyda-Grubbs catalyst **59** and either methyl acrylate or methyl vinyl ketone separately in refluxing DCM, instead of the expected products **60** and **61** respectively, the only product isolated in both the cases was **28** as 1:1 inseparable mixture of two diastereomers in 60% yield

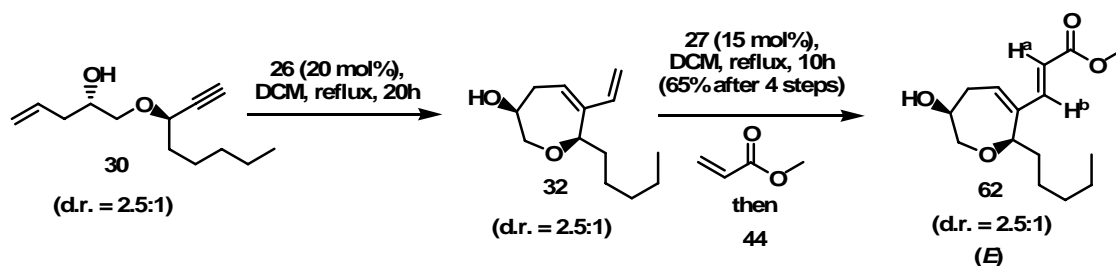
(Scheme 4.20).²⁸ The diastereomeric ratio was determined by GC-MS and ¹H NMR spectroscopy.



Scheme 4.20. Attempted tandem ring-closing metathesis/ cross-metathesis (RCM/CM) reaction.

4.16.3 Stepwise ring-closing metathesis/ cross metathesis:

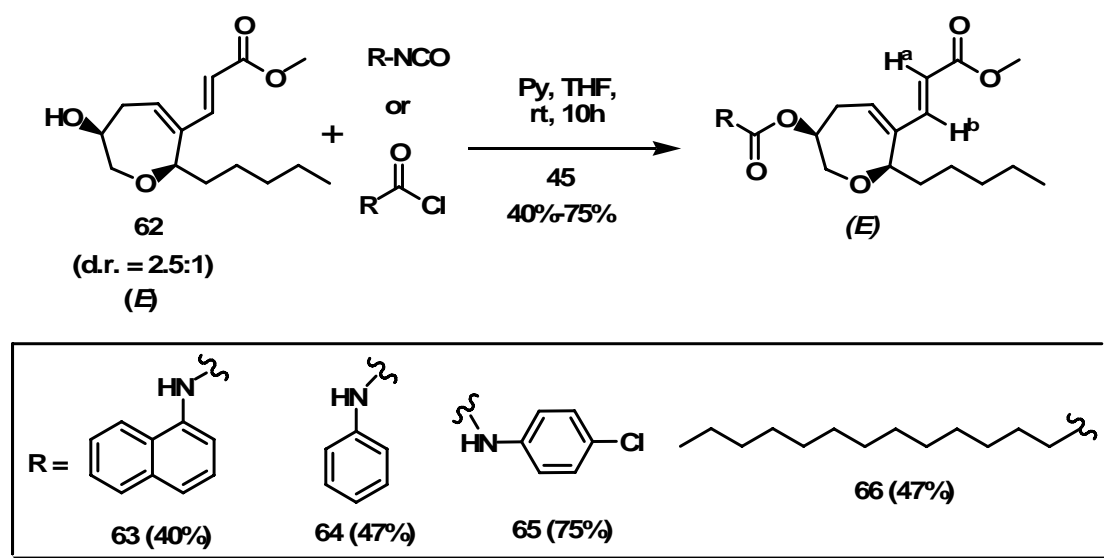
When the attempts of tandem RCM/CM were failed, stepwise RCM/CM reaction was endeavored as the bypass remedy. Compound **30** (2.5:1 mixture of two diastereomers) was treated with 1st generation Grubbs catalyst **26** (20 mol%) in refluxing DCM to obtain the oxepane **32** as 2.5:1 inseparable mixture of two diastereomers. As soon as all the starting material was consumed after 20h (monitored by TLC), the 2nd generation Grubbs catalyst **27** (15 mol%) and methyl acrylate were added to the reaction mixture and the refluxing was continued for 10h to obtain the *E*- cross metathesis product **62** as 2.5:1 inseparable mixture of two diastereomers (determined by ¹H NMR spectroscopy) in 65% overall yield²⁹ after scavenging the ruthenium metal by the scavenging resin **44** (Scheme 4.21).



Scheme 4.21. Stepwise ring-closing metathesis/ cross-metathesis to synthesize **62**.

The *E*-geometry of the newly formed olefin was determined by the higher coupling constant value ($J_{\text{Ha-Hb}} = 16.0$ Hz) between H^{a} and H^{b} in product **65** by the ^1H NMR spectroscopy.

The RCM/CM product **62** (2.5:1 mixture of two diastereomers) was functionalized using isocyanates and acid chlorides in presence of pyridine as base to obtain carbamates and ester **63**, **64**, **65** and **66** respectively in 40% to 75% yield after scavenging the excess isocyanates and acid chloride by the commercially available aminomethylated polystyrene resin **45** (Scheme 4.22).

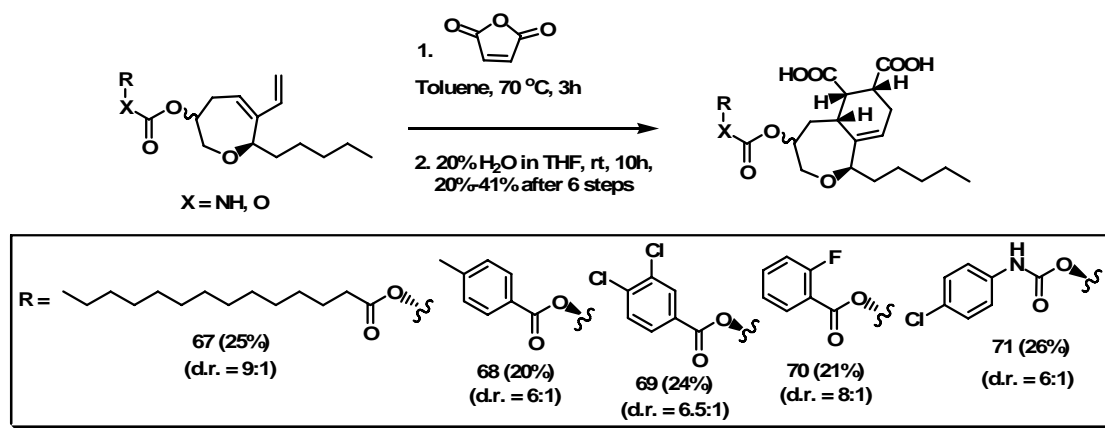


Scheme 4.22. Formation of carbamate **63**, **64**, **65** and ester **66**.

The carbamates and ester were obtained exclusively as single diastereomers (determined by ^1H NMR spectroscopy) after purification by the silica gel flash chromatography. The carbamate **65** from 4-chlorophenyl isocyanate gave a good yield (75% after 5 steps), which again showed that the isocyanate having electron withdrawing group (4-Cl group) on the aromatic ring gives better result than the other products **63** (40% after 5 steps), **64** (47% after 5 steps) and **66** (47% after 5 steps). The *E*-geometry of the starting alcohol remained intact in the product ($J_{\text{Ha-Hb}} \sim 16.0$ Hz).

4.16.4 Diacid synthesis:

Further diversification on the oxepane scaffold was accomplished after the Diels-Alder reaction with maleic anhydride. The diene was heated with maleic anhydride at $70\text{ }^\circ\text{C}$ in toluene for 3h. The anhydride formed after the Diels-Alder reaction was hydrolyzed *in situ* using 20% water in THF at room temperature for 10h. After the reaction was over, the solvent was evaporated and the crude product was purified by silica gel chromatography as mixtures of two diastereomers (determined by ^1H NMR spectroscopy) in 20% to 41% yield after 6 steps (Scheme 4.23).³⁰



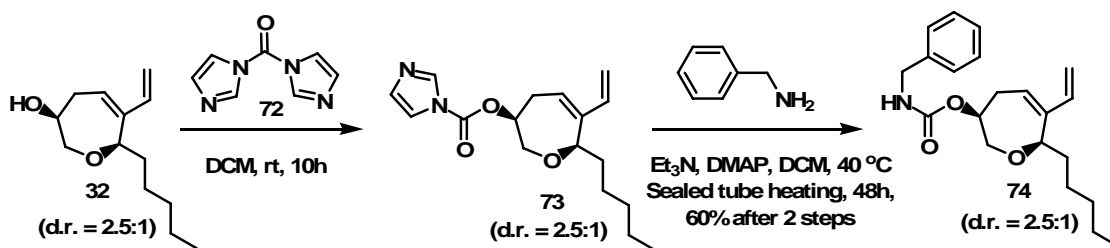
Scheme 4.23. Synthesis of diacids.

Irrespective of the carbamates and esters, the overall yield of the diacids obtained was moderate. The diastereomeric ratio of the products reflected the isomeric ratio of the starting material. It was also assumed that the Diels-Alder reaction with maleic anhydride

was proceeded through an *endo*-selective transition state where the dienophile approached the diene from the opposite phase of the bulky pentyl moiety near diene.

4.16.5 Two step synthesis of carbamate:

To introduce more diversity in the oxepane library, a different two step procedure was adopted to synthesize the carbamates from the secondary alcohol. In this strategy the alcohol **32** (2.5:1 mixture of two diastereomers) was treated with 1,1'-carbonyl diimidazole **72** in DCM to obtain the crude product **73** in 2.5:1 diastereomeric mixture (Scheme 4.24). The diastereomeric ratio was determined by GC-MS of the crude product **73**.

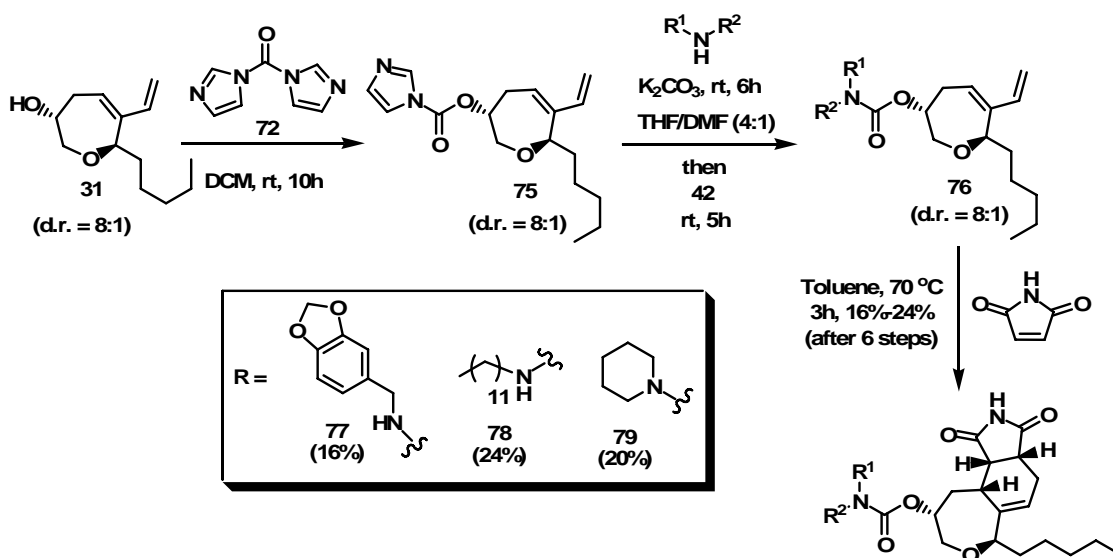


Scheme 4.24. Two Step synthesis of carbamate **74**.

In the next step crude **73** was heated in a sealed tube at 40 °C with triethylamine as base, a catalytic amount of *N,N*-dimethyl amino pyridine (DMAP) and benzyl amine to obtain the carbamate **74** as the same diastereomeric ratio of the starting material in 60% yield after 2 steps.³¹

From the above scheme it was evident that triethylamine was not enough basic to deprotonate the benzyl amine and the reaction required a long time (48h). Hence to synthesize the carbamate in two steps the stronger base potassium carbonate (K₂CO₃) was employed (Scheme 4.25).

When compound **31** (8:1 mixture of two diastereomers) was treated with **72** in DCM, crude **75** was obtained as 8:1 diastereomeric mixture (ratio determined by GC-MS). Then compound **75** was treated with K₂CO₃ in THF: DMF (4:1) solvent mixture with different primary or secondary amines at room temperature.



Scheme 4.25. Two step synthesis of carbamate and diacid **77**, **78** and **79** synthesis.

When the reaction was complete after 6h (determined by TLC), polymer supported sulfonic acid resin **42** (6 equiv relative to the total amount of K_2CO_3 and excess amine) was added to scavenge the excess K_2CO_3 and excess amine at room temperature for 5h. After filtering the resin and evaporating the solvent carbamates **76** (8:1 diastereomeric mixture) were obtained. The ratio was determined by GC-MS. The carbamates **76** were then treated without any purification with maleimide in toluene at 70 °C for 3h to obtain the Diels-Alder adducts in 16% to 24% yield after 6 steps. Two primary amines (piperonylamine and dodecyl amine) and one secondary amine (piperidine) were used for the carbamate synthesis. From the overall yield it was evident that there was no big difference between the reactivity and yield between them. Diels-Alder adducts were purified by silica gel flash chromatography as exclusively single diastereomers, which was determined by 1H NMR spectroscopy and nOe study. The final products **77**, **78** and **79** were obtained in 16%, 24% and 20% overall yield respectively after 6 steps.

The *endo*-transition state in Diels-Alder reaction could give rise to two possible diastereoisomers for the product **77**. The two possible *endo*-isomers are **77a** and **77b** (Figure 4.2).

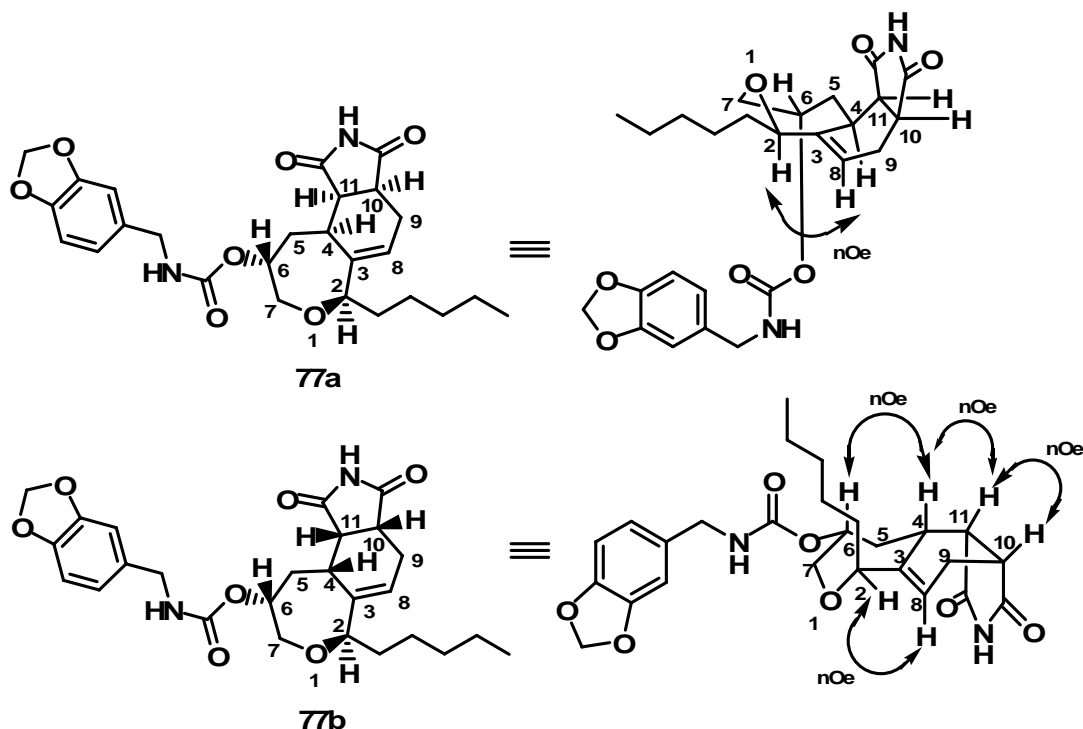


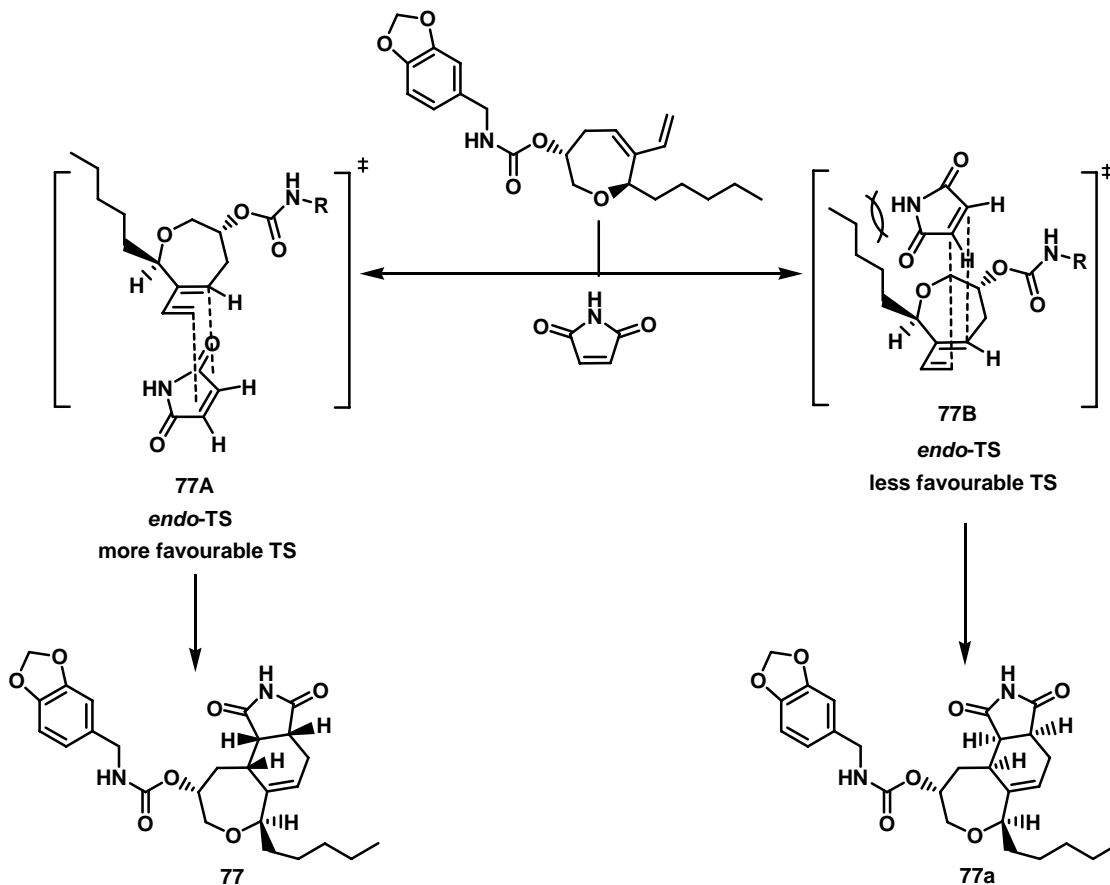
Figure 4.2. nOe study of compound 77.

The Nuclear Overhauser Effect (nOe) study of compound 77 (Table 4.2) showed that when H^2 was irradiated in its resonance frequency the intensity of H^8 was increased which could be possible in both **77a** and **77b** isomers. But when H^6 was irradiated then only the intensity of the H^4 was increased, which suggested that H^6 and H^4 are close in space which could be possible in the **77b** isomer, not in the **77a** isomer. Moreover when H^4 was irradiated in its resonance frequency the intensity of both H^6 and H^{11} were increased suggested that H^4 is closer in space with both H^6 and H^{11} . This results show that the compound **77** and **77b** are identical, rules out the possibility of the **77a** isomer.

Table 4.2. nOe irradiation and intensity of the protons.

Irradiation	Intensity
H^6	H^4 (5.0%), H^5 (3.0 %)
H^4	H^6 (6.0%), H^{11} (3.0%), H^5 (3.0%)
H^2	H^8 (4.0%), H^7 (2.0%)

From the above nOe experiment it was evident that the Brown asymmetric allylation proceeded with the exactly expected stereochemistry. The Diels-Alder reaction was also proceeded through *endo*-selective manner. Based on this experiment the configuration of the other library members have assigned by analogy. The transition state for the Diels-Alder reaction to obtain compound **77** is predicted in the Scheme 4.26.



Scheme 4.26. *Endo*-transition state for the Diels-Alder reaction to synthesize **77**.

The Diels-Alder reaction with maleimide to synthesize compound **77** could proceed through two possible *endo*-transition states. When the maleimide dienophile approaches to the diene from the same phase of the bulky pentyl group in transition state **77B**, it experiences a steric hindrance which destabilizes the transition state and makes it less favoured. So the reaction does not proceed through this transition state leading to the *endo*-product **77a**. But on the other hand, when the dienophile approaches from the

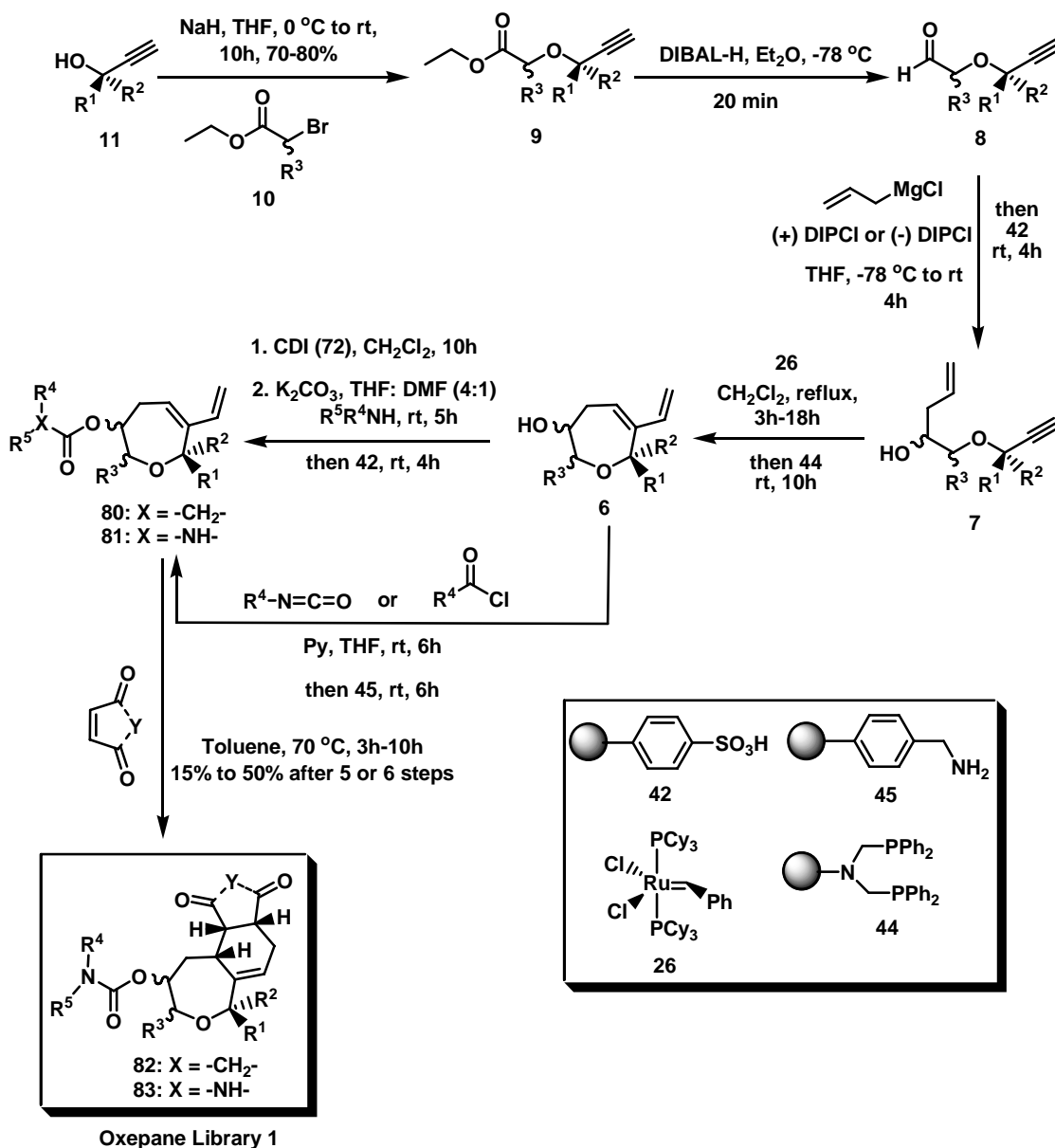
opposite or anti-phase of the bulky pentayl group, it does not experience any steric hindrance which makes the transition state **77A** stable to lead to the product **77**. On the basis of this assumption we envisaged the absolute stereochemistry of all the members of the oxepane library.

4.17 Solution phase parallel synthesis of oxepane library using solid-supported reagents:

As described above a synthetic strategy to produce an oxepane library in very fast and efficient way in one pot using polymer bound scavenging resins has been developed successfully. In this strategy different building blocks were used to produce the diverse library members. The generalized synthetic strategy is shown in Scheme 4.27

The synthesis was initiated with coupling of the substituted propargyl alcohol **11** and the substituted α -bromo ethyl acetate **10** to synthesize the ether **9**. Then the ethyl ester group in **9** was reduced in a controlled way using diisobutylaluminiumhydride in diethyl ether at $-78\text{ }^{\circ}\text{C}$ to afford the aldehyde **8**. After the extractive work up and evaporation of the solvent the crude aldehyde **8** was obtained. The crude aldehyde **8** was then allylated using Brown's asymmetric allylation protocol using both (+)- and (-)-DIPCl as chiral auxiliary to synthesize enantio- or diastereo-pure enyne metathesis precursor **7** after scavenging the excess allyl Grignard reagent by polymer bound sulfonic acid resin **42**. After filtering the resin and evaporation of the solvent crude product **7** was obtained, this was used further for the next reaction without any purification. The enyne ring-closing metathesis reaction was carried out with 1st generation Grubbs catalyst **26** (20 mol%) to afford the oxepane scaffold **6** after scavenging the ruthenium metal using the polymer supported resin **44**. After filtering the resin and evaporation of the solvent, crude oxepane **6** was obtained. The free alcohol in crude product **6** was then diversified to afford carbamate **81** by a two step protocol. First a half carbamate was formed using 1,1'-carbonyl diimidazole (CDI, **72**), then in the presence of K_2CO_3 as base, using primary or secondary amines in parallel carbamate **81** was synthesized. The polymer bound sulfonic acid resin **42** was used to scavenge excess amines and potassium carbonate. The crude carbamate **81** was obtained after filtering the resin and evaporation of the solvent. Finally the diene in crude **81** was

diversified using different dienophiles in parallel to afford the fully functionalized oxepane library **83** in 15% to 50% yield after 6 steps.



Scheme 4.27. General strategy to synthesize oxepane library using solid-supported scavengers.

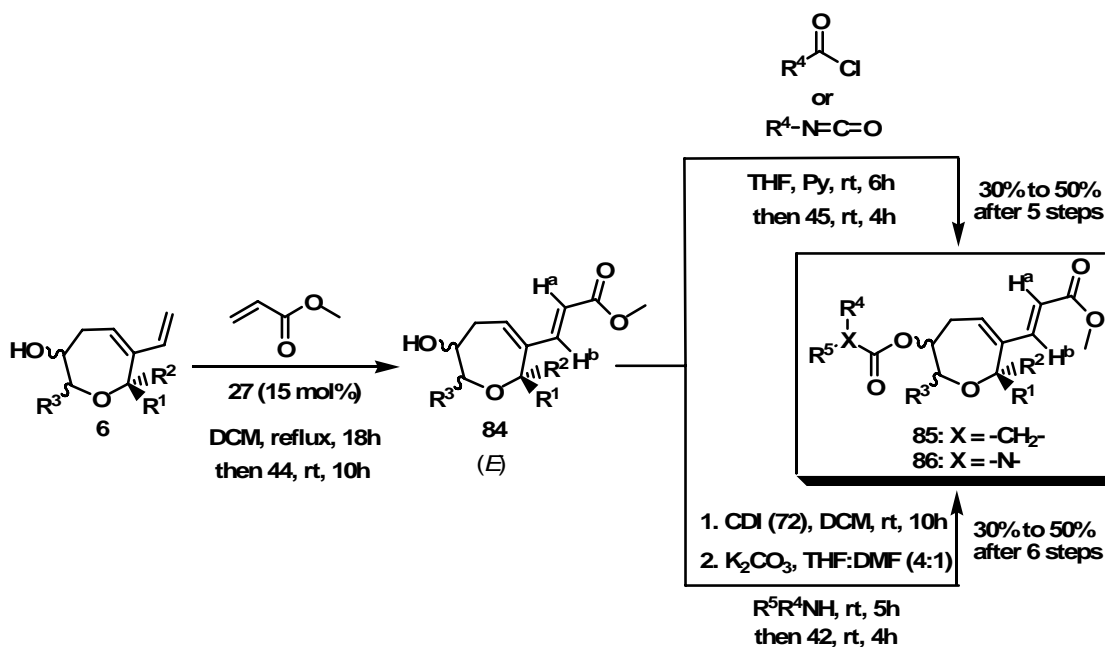
In this strategy 53 oxepanes were synthesized. The final products were purified by silica gel column chromatography and also by preparative thin layer chromatography (PTLC). Some of the oxepane molecules synthesized in this one pot synthetic strategy was formed

as single diastereomers and some were formed as mixtures of the two diastereomers. The diastereomeric ratios of the individual products are shown in the experimental part. The diastereomeric ratios of the individual products are determined by ^1H NMR spectroscopy. It was assumed that the products obtained by the *endo*-selective Diels-Alder reactions, which was determined by the nOe experiment and the transition state model shown before. The building blocks used in this strategy is shown in Figure 4.3. When *p*-benzoquinone was used as the dienophile, the products were formed as hydroquinone after aromatization after the Diels-Alder reaction under the reaction conditions. When maleic anhydride was used as the dienophile, the anhydride formed after the Diels-Alder reaction was hydrolyzed by 20% water in THF to synthesize diacids. The isolated overall yields and the structures of the oxepane molecules synthesized in this strategy are shown in Table 6.1.

The oxepane scaffold **6** was treated in parallel either with isocyanates or acid chlorides to generate esters **80** or carbamates **81** in one step. The excess isocyanates or acid chlorides were scavenged by the aminomethylated polystyrene **45**. The crude ester **80** and crude carbamate **81** were used for the next reactions. After the Diels-Alder reaction with dienophiles the fully functionalized oxepanes **82** and **83** were formed in 15% to 50% overall yield after 5 steps. In this strategy 22 more oxepanes were synthesized. The overall yields and the structures are shown in Table 6.1. The diastereomeric ratios of individual compounds are determined by ^1H NMR spectroscopy and are shown in the experimental part. It was also assumed that the final oxepane molecules are formed as *endo*-selective way. The acid chlorides and the isocyanates building blocks used in this strategy are shown in Figure 4.3.

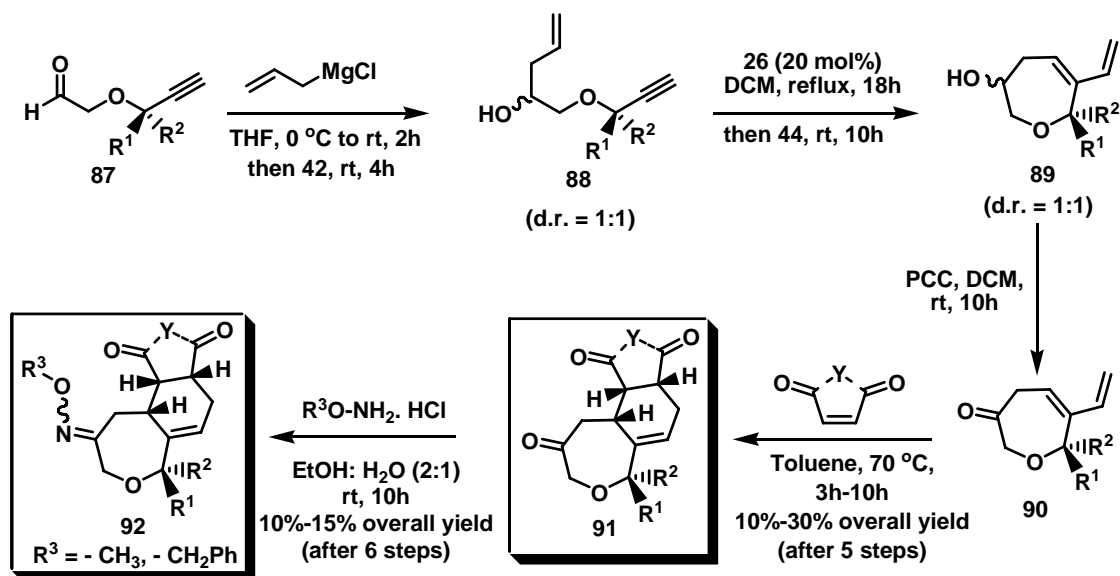
Further diversification was introduced in the oxepane moiety by cross-metathesis reaction. Cross-metathesis reaction was carried out on oxepane **6** using 2nd generation Grubbs catalyst **27** (15 mol%) to generate **84**. The ruthenium metal was scavenged by polymer bound chelating ligand **44**. The resin was filtered and the solvent was evaporated to obtain crude cross-metathesis product **84**. The free alcohol in crude **84** was then diversified to carbamates and esters by the same protocol used before to afford the oxepanes **85** and **86** (Scheme 4.28). The free alcohol in compound **84** was also derivatized to carbamate **86** using the previously mentioned two step protocol using CDI

(72) in the first step and then treating the half carbamate with K_2CO_3 as a base and primary and secondary amines as the coupling partners. The overall yield in this two step protocol was the same as the single step carbamate formation. The products were isolated by silica gel column chromatography. Using this strategies 12 more oxepanes were synthesized. All the products were formed in moderate to good yields (30% to 50%) after 5 steps. All the compounds formed with *E*-selectivity after cross-metathesis and the same geometry was found in the final products. The *E*-geometry in the final products was confirmed by the higher coupling constant value ($J_{H^a-H^b} \sim 16.0$ Hz) between H^a and H^b protons by 1H NMR spectroscopy. The final oxepanes **85** and **86** were formed as single isomers as well as mixture of two diastereomers. The diastereomeric ratios are determined by 1H NMR spectroscopy and are showed in the experimental part for individual compounds. The oxepanes were purified by silica gel column chromatography. The overall isolated yields and the structures of the individual compounds are shown in Table 6.3. The acid chlorides and isocyanates building blocks used in this strategy are shown in Figure 4.3.



Scheme 4.28. Synthesis of oxepanes **85** and **86** from **6**.

A keto oxepane library **91** was synthesized in a one pot synthetic strategy and from library **91** a small collection of *O*-substituted oximes **92** was synthesized by *O*-substituted hydroxyl amine hydrochloride addition reaction (Scheme 4.29). The aldehyde **87** was treated with allylmagnesiumchloride in THF to obtain the enyne metathesis precursor **88** in 1:1 mixture of two isomers. The excess allylmagnesiumchloride was scavenged by polymer supported sulfonic acid resin **42**. The resin was filtered and the solvent was evaporated to obtain crude product **88**. Crude **88** (1:1 mixture of two isomers) was treated with the 1st generation Grubbs catalyst **26** (20 mol%) in refluxing DCM to obtain oxepane **89** in 1:1 mixture of two isomers. After treatment of the reaction mixture with the ruthenium scavenging resin **44**, colorless product **89** was afforded. Without any further purification **89** was treated with pyridinium chlorochromate (PCC) in CH₂Cl₂ to obtain the keto oxepane **90**. After the reaction was over (after 10h), chromium residue was filtered through a Celite pad and solvent was evaporated to obtain colorless crude ketone **90**. Crude ketone **90** was heated at 70 °C in toluene with dienophiles to afford the Diels-Alder adduct **91**.



Scheme 4.29. General procedure to synthesize keto oxepanes **91** and oximes **92**.

Half of the crude product was purified by silica gel column chromatography to obtain pure **91** in 10% to 25% overall yield after 5 steps. The other half of the crude **91** was further treated with either *O*-methylhydroxylamine hydrochloride salt or *O*-benzylhydroxylamine hydrochloride salt in ethanol:water (2:1) mixture at room temperature for 10h to obtain the addition product **92**. Crude **92** was purified by preparative thin layer chromatography (PTLC) to obtain pure **92** in 10% to 15% overall yield (after 6 steps).³²

Using this synthetic strategy 9 more keto oxepane molecules and 6 more oxime molecules were synthesized. It was assumed that the Diels-Alder adducts formed in an *endo*-selective fashion. The Diels-Alder adduct with *p*-benzoquinone gave the hydroquinone moiety after aromatization under the reaction conditions. It was noted in the addition reaction of the keto moiety with the *O*-substituted hydroxyl amine, the *O*-benzylhydroxyl amine gave a better yield and reactivity than the *O*-methylhydroxyl amine. The oxepanes **91** and **92** formed as the diastereomeric mixture of two isomers and the ratios were determined by ¹H NMR spectroscopy. The isomeric ratios of the individual compounds are shown in the experimental part. The isolated overall yields and structure of the compounds are shown in the Table 6.2. The best yield (overall yield 30% after 5 steps) in the keto oxepane library **91** was obtained using dimethylacetylene diacrylate as dienophile and pentyl group as R¹. The lowest overall yield (10% after 5 steps) was obtained using *N*-phenyl maleimide as dienophile and R¹ = R² = -(CH₂)₅- (Table 6.2). In the hydroxyl amine addition reaction the best overall yield (15% after 6 steps) was obtained using *O*-benzylhydroxyl amine and maleimide as dienophile with R¹ = R² = -CH₃ (Table 6.2).

4.18 Building blocks used in the library synthesis:

Six different types of building blocks were used to synthesize the oxepane library. They are (1) substituted propargyl alcohols, (2) substituted α -bromo ethyl acetates, (3) isocyanates, (4) acid chlorides, (5) dienophiles and (6) primary and secondary amines (Figure 4.3).

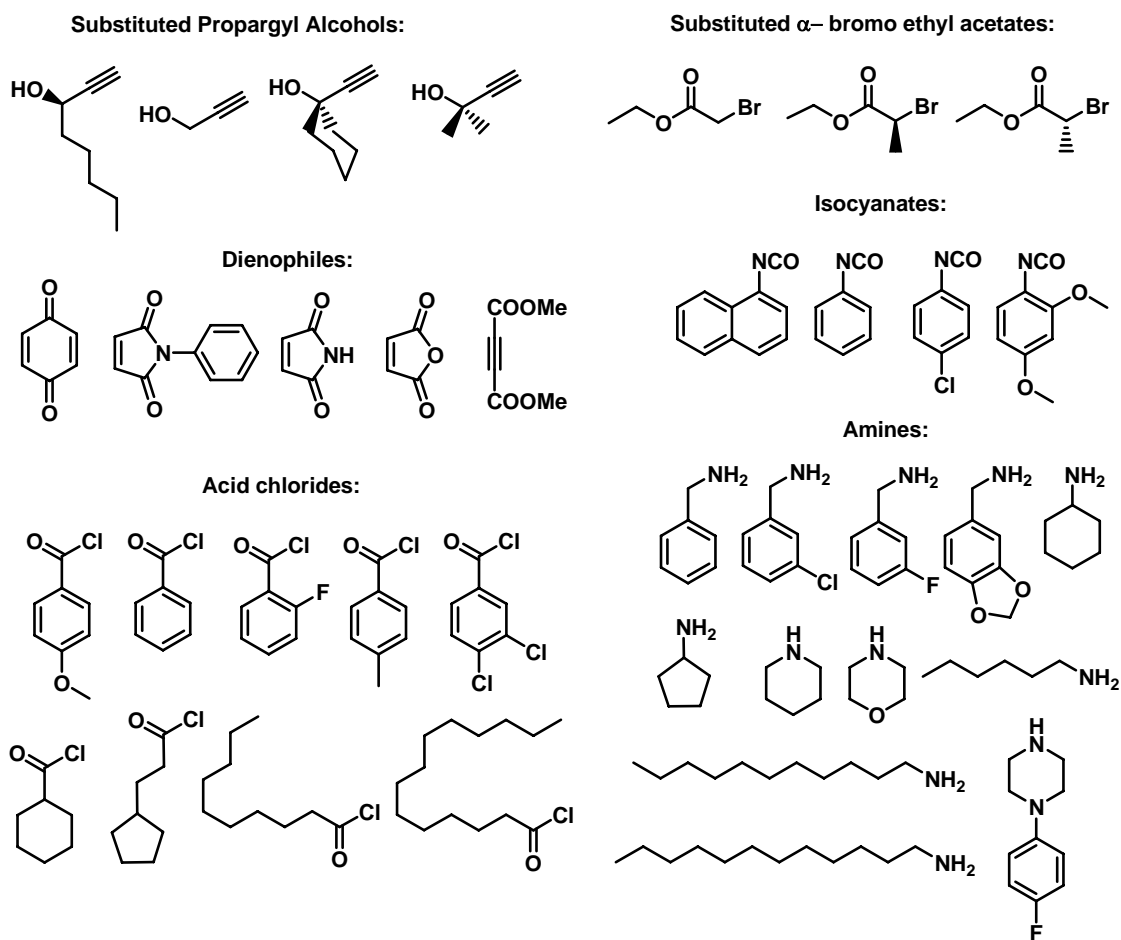


Figure 4.3. Building blocks used in the library synthesis

Among the substituted propargyl alcohol building blocks, all the propargyl alcohols gave moderate to good yields except propargyl alcohol itself. It was noted that the propargyl alcohol is difficult to handle due to its volatility and that reflected in the low yields of the oxepane molecules using this building block. Bromo ethyl acetate showed the best reactivity and yields than the other two building blocks among the substituted α -bromo ethyl acetates. Among the isocyanate building blocks, the 2,4-dimethoxy phenyl isocyanate showed the least reactivity and yield due to its electron donating property as well as the bulkiness *ortho*-substituent. The naphthyl and phenyl isocyanate showed moderate reactivity. The best reactivity was observed with *p*-chloro phenylisocyanate due to its electron withdrawing property. It was noted that the aliphatic acid chlorides are more reactive than the aromatic acid chlorides. Among the aromatic acid chlorides 2-fluoro benzoylchloride and 3,4-dichloro benzoylchloride are most reactive due to their

electron withdrawing character. On the other hand *p*-methoxy and *p*-methyl benzoylchlorides are least reactive due to their electron donating property. It was observed that all the primary and secondary amines reacted equally well with similar reactivity. It was experienced that among the dienophiles *N*-phenyl maleimide, maleimide and maleic anhydride showed the best reactivity. *p*-benzoquinone and diethyl acetylene diacrylate are sluggish reactors among the dienophiles.

5. Summary and outlook:

A solution phase parallel synthetic strategy has been developed to synthesize a fully functionalized oxepane library. In this synthetic strategy the ring-closing enyne metathesis reaction was used as the key reaction to synthesize the oxepane scaffold. The oxepane scaffold was then functionalized to generate an oxepane library. This solution phase synthetic strategy was extended to the use of the solid-supported scavenging technique which leads to the development of a one pot synthetic strategy to produce the oxepane library in a rapid and practical way excluding the extensive separation and purification e.g. chromatography, distillation, extraction and crystallization protocol after each reaction.

At the end a small oxepane library containing 110 molecules (Table 6.1, Table 6.2 and Table 6.3), was synthesized using the advantages of the polymer supported scavenging procedure. The synthesized oxepane molecules will be used in chemical genomics studies to identify the target of interest and also in cell based assays to detect inhibitors or activators in signaling pathways.

6. The compound library:

All the oxepane molecules in the library are shown below in Table 6.1, Table 6.2 and Table 6.3. All the compounds are purified by either silica gel column chromatography or preparative thin layer chromatography. The yields shown in the tables are isolated yields. The amounts of individual compounds (in mg) are shown in the experimental part.

6.1 Oxepane library 1:

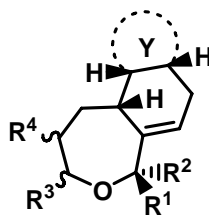
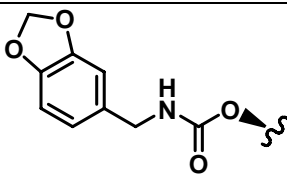
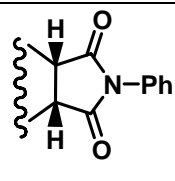
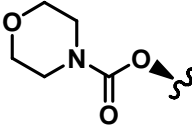
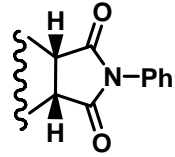
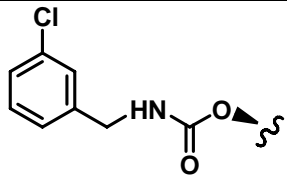
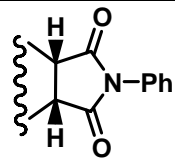
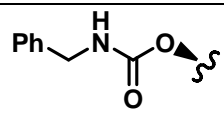
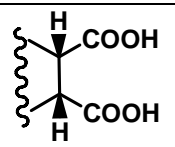
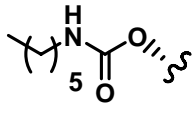
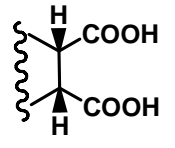
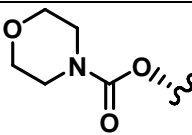
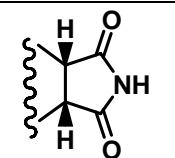
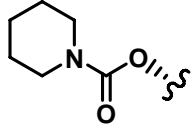
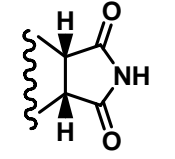
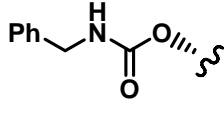
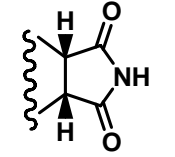
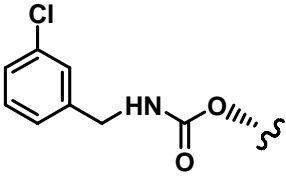
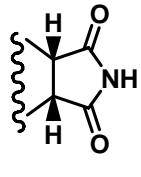
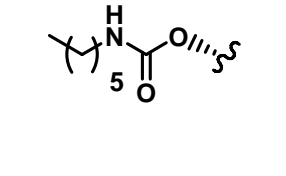
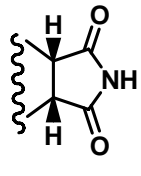
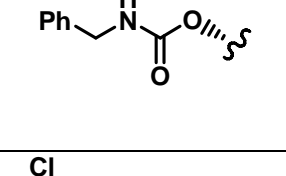
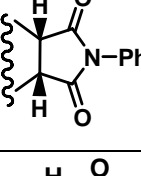
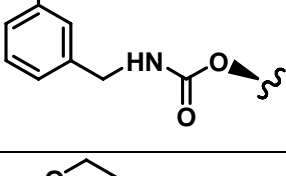
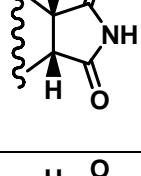
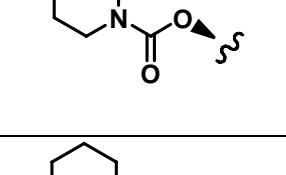
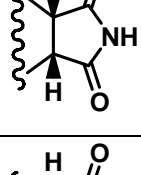
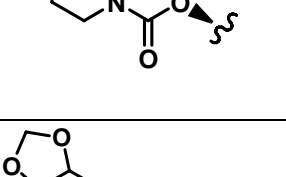
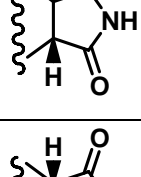
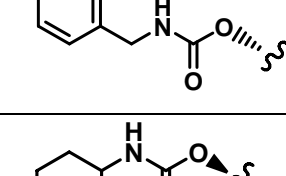
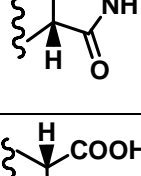
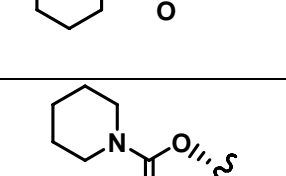
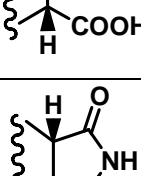
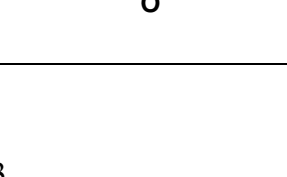
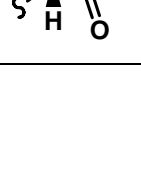


Table 6.1. Oxepane library 1.

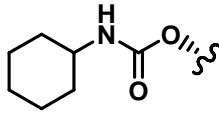
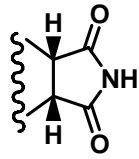
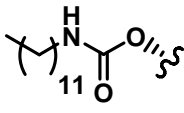
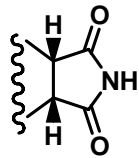
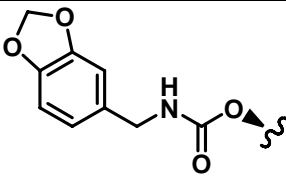
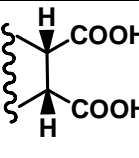
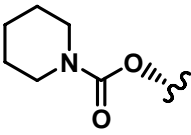
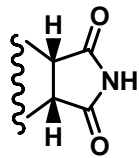
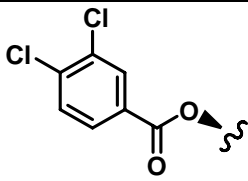
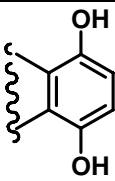
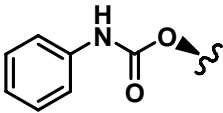
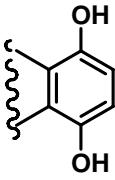
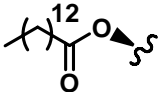
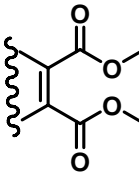
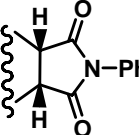
Compound No.	R ¹	R ²	R ³	R ⁴	Y	Isolated Yield
94	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			34 % (after 7 steps)
95	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			32% (after 6 steps)
96	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			40% (after 6 steps)
97	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			15% (after 7 steps)
98	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			32% (after 6 steps)

99	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			32% (after 6 steps)
100	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			34% (after 6 steps)
101	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			32% (after 7 steps)
102	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			20% (after 7 steps)
103	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			15% (after 7 steps)
104	-CH ₃	-CH ₃	-H			30% (after 6 steps)
105	-CH ₃	-CH ₃	-H			22% (after 6 steps)
106	-CH ₃	-CH ₃	-H			20% (after 6 steps)

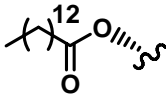
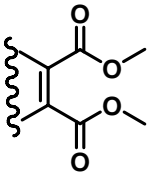
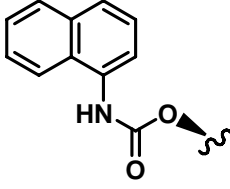
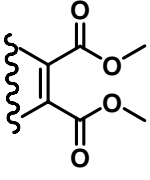
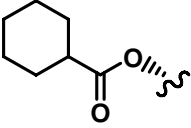
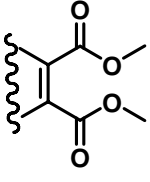
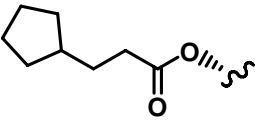
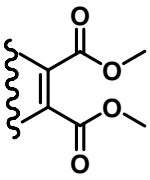
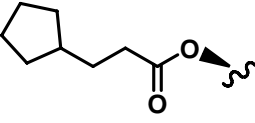
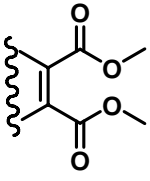
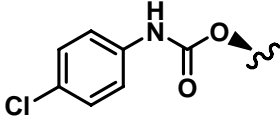
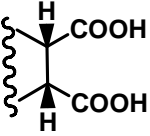
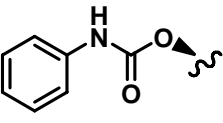
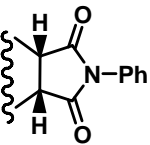
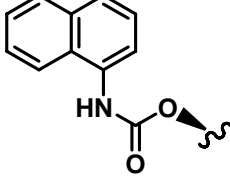
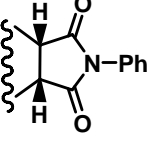
107	-CH ₃	-CH ₃	-H			16% (after 6 steps)
108	-CH ₃	-CH ₃	-H			31% (after 6 steps)
109	-(CH ₂) ₅ -	-(CH ₂) ₅ -	-H			29% (after 6 steps)
110	-CH ₃	-CH ₃	-H			22% (after 6 steps)
111	-CH ₃	-CH ₃	-H			15% (after 6 steps)
112	-CH ₃	-CH ₃	-H			15% (after 6 steps)
113	-CH ₃	-CH ₃	-H			30% (after 6 steps)
114	-CH ₃	-CH ₃	-H			16% (after 7 steps)
115	-H	-H	-H			20% (after 6 steps)

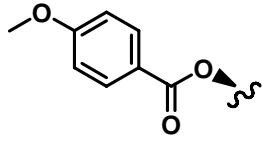
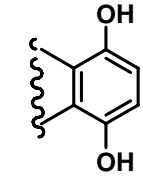
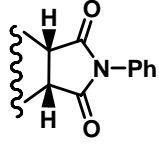
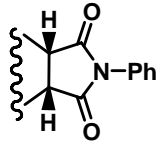
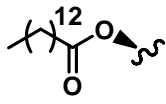
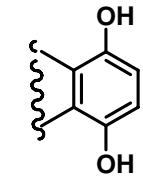
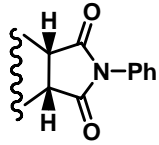
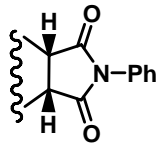
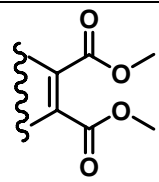
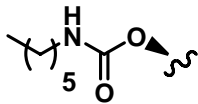
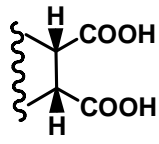
116	-H	-H	-H			26% (after 6 steps)
117	-H	-H	-H			30% (after 6 steps)
118	-H	-H	-H			20% (after 6 steps)
119	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H	-H			16% (after 6 steps)
120	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H	-H			15% (after 6 steps)
77	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H	-H			16% (after 6 steps)
122	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H	-H			15% (after 6 steps)
123	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H	-H			15% (after 6 steps)

124	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			16% (after 6 steps)
125	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			20% (after 6 steps)
130	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			15% (after 6 steps)
121	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			20% (after 6 steps)
126	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			23% (after 6 steps)
93	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			41% (after 7 steps)
127	-CH ₃	-CH ₃	-H			25% (after 7 steps)
128	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			29% (after 6 steps)

129	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			31% (after 6 steps)
78	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			24% (after 6 steps)
131	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			15% (after 7 steps)
79	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			20% (after 6 steps)
132	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			30% (after 5 steps)
133	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			20% (after 5 steps)
134	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			44% (after 5 steps)
135	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	$\xi\equiv\text{CH}_3$	$\xi\equiv\text{OH}$		52% (after 4 steps)

136	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	$\xi\equiv\text{CH}_3$			32% (after 5 steps)
137	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	$\xi\equiv\text{CH}_3$			50% (after 5 steps)
138	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	$\xi\equiv\text{CH}_3$			60% (after 5 steps)
139	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	$\xi\blacktriangleleft\text{CH}_3$			26% (after 5 steps)
41	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			60% (after 5 steps)
70	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			21% (after 6 steps)
67	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			25% (after 6 steps)
69	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			24% (after 6 steps)
68	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			20% (after 6 steps)

140	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			28% (after 5 steps)
141	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			16% (after 5 steps)
142	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			32% (after 5 steps)
143	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			25% (after 5 steps)
144	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			25% (after 5 steps)
71	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			26% (after 6 steps)
49	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			32% (after 5 steps)
48	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			30% (after 5 steps)

145	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			17% (after 5 steps)
146	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	$\xi\blacktriangleleft\text{CH}_3$	$\xi\text{ OH}$		60% (after 4 steps)
147	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	$\xi\blacktriangleleft\text{CH}_3$	$\xi\blacktriangleleft\text{OH}$		70% (after 4 steps)
148	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			23% (after 5 steps)
149	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H	$\xi\text{ OH}$		65% (after 4 steps)
150	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	$\xi\text{ CH}_3$	$\xi\blacktriangleleft\text{OH}$		50% (after 4 steps)
151	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	$\xi\blacktriangleleft\text{CH}_3$	$\xi\blacktriangleleft\text{OH}$		55% (after 4 steps)
152	$\xi\blacktriangleleft(\text{CH}_2)_4\text{CH}_3$	-H	-H			27% (after 7 steps)

6.2 Oxepane library 2:

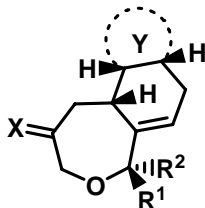
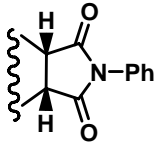
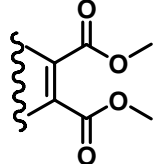
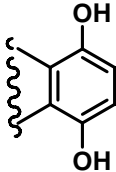
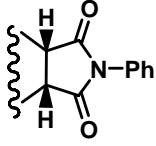
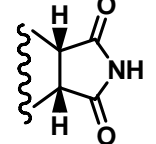




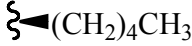
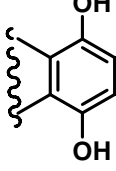


Table 6.2. Oxepane library 2.

Compound No.	R ¹	R ²	X	Y	Yield
58	ζ -(CH ₂) ₄ CH ₃	-H	O		30% (after 5 steps)
57	ζ -(CH ₂) ₄ CH ₃	-H	O		25% (after 5 steps)
55	ζ -(CH ₂) ₄ CH ₃	-H	O		25% (after 5 steps)
153	-(CH ₂) ₅ -	-(CH ₂) ₅ -			10% (after 6 steps)
154	-(CH ₂) ₅ -	-(CH ₂) ₅ -			12% (after 6 steps)
155	-(CH ₂) ₅ -	-(CH ₂) ₅ -	O		15% (after 5 steps)

156	$-(\text{CH}_2)_5-$	$-(\text{CH}_2)_5-$	O		10% (after 5 steps)
157	$-(\text{CH}_2)_5-$	$-(\text{CH}_2)_5-$	O		15% (after 5 steps)
158	$-(\text{CH}_2)_5-$	$-(\text{CH}_2)_5-$		10% (after 6 steps)	
159	$-\text{CH}_3$	$-\text{CH}_3$	O		12% (after 5 steps)
160	$-\text{CH}_3$	$-\text{CH}_3$	O		15% (after 5 steps)
161	$-\text{CH}_3$	$-\text{CH}_3$		15% (after 6 steps)	
162	$-\text{CH}_3$	$-\text{CH}_3$		13% (after 6 steps)	
163		$-\text{H}$		10% (after 6 steps)	
56		$-\text{H}$	O		14% (after 5 steps)

6.3 Oxepane library 3:

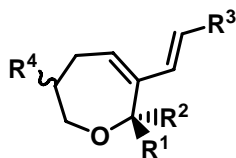
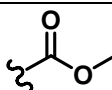
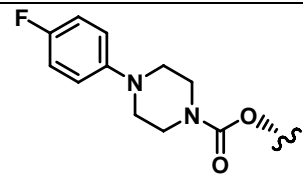
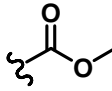
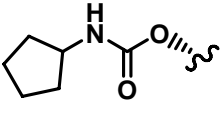
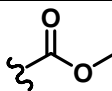
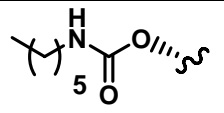
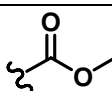
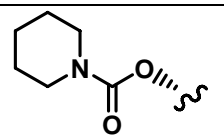
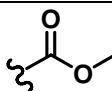
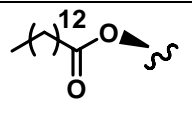
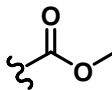

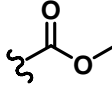
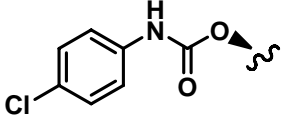
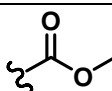
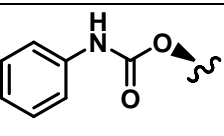
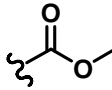
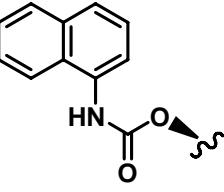
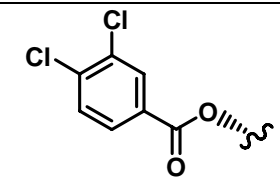
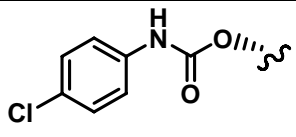
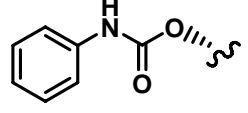
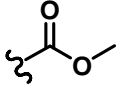


Table 6.3. Oxepane library 3.

Compound No.	R ¹	R ²	R ³	R ⁴	Yield
164	-CH ₃	-CH ₃	-H		40% (after 5 steps)
165	-CH ₃	-CH ₃	-H		25% (after 5 steps)
166	-CH ₃	-CH ₃	-H		29% (after 5 steps)
167	-CH ₃	-CH ₃	-H		40% (after 5 steps)
168	-CH ₃	-CH ₃	-H		45% (after 5 steps)
169	-CH ₃	-CH ₃			35% (after 6 steps)
170	-CH ₃	-CH ₃			36% (after 6 steps)

171	-CH ₃	-CH ₃			38% (after 6 steps)
172	-CH ₃	-CH ₃			35% (after 6 steps)
173	-CH ₃	-CH ₃			35% (after 6 steps)
174	-CH ₃	-CH ₃			30% (after 6 steps)
66	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H			47% (after 5 steps)
175	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H			30% (after 5 steps)
65	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H			75% (after 5 steps)
64	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H			47% (after 5 steps)
63	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H			40% (after 5 steps)
31	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H	-H	ξOH	60% (after 3 steps)
32	$\xi \blacktriangleleft (\text{CH}_2)_4 \text{CH}_3$	-H	-H	$\xi \blacktriangleleft \text{OH}$	60% (after 3 steps)

38	$\xi\text{-(CH}_2\text{)}_4\text{CH}_3$	-H	-H		57% (after 4 steps)
39	$\xi\text{-(CH}_2\text{)}_4\text{CH}_3$	-H	-H		65% (after 4 steps)
40	$\xi\text{-(CH}_2\text{)}_4\text{CH}_3$	-H	-H		40% (after 4 steps)
62	$\xi\text{-(CH}_2\text{)}_4\text{CH}_3$	-H		$\xi\text{-OH}$	65% (after 4 steps)

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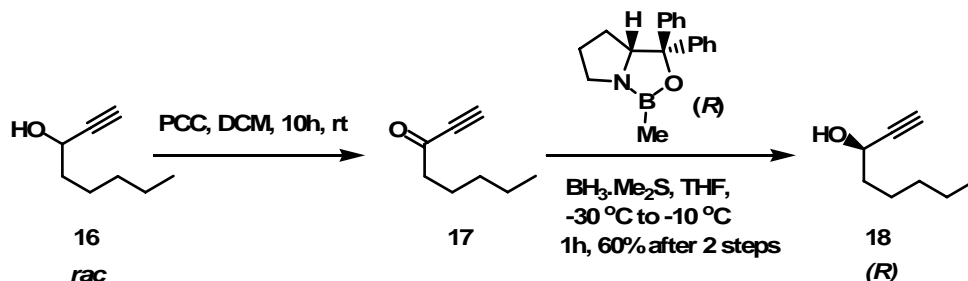
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8. Experimental part:

8.1 General experimental procedures:

^1H and ^{13}C -NMR spectra were recorded on a Varian Mercury 400 spectrometer at room temperature. Chemical shifts are expressed in part per million (ppm) and the spectra's are afterwards calibrated to the solvent signals of CDCl_3 (7.26 ppm and 77.16 ppm). Coupling constants are given in Hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), dd (double of doublet), m (multiplet), dt (doublet of triplet), td (triplet of doublet, br (broad signal). Gas chromatography-mass spectrometry (GC-MS) were measured from a Hewlett Packard 6890 GC system coupled to a Hewlett Packard 5973 Mass Selective Detector. A HP 5TA capillary column (0.33 μm x 25 m x 0.2 mm) and helium flow rate of 2 mL/ min were used. High resolution mass spectra (HR-MS, 70 eV) were measured on a Jeol SX 102A spectrometer by using electron impact (EI), fast atom bombardment (FAB) techniques. The matrix used for FAB was 3-nitrobenzylalcohol (3-NBA). Thin layer chromatography (TLC) was carried out on Merck precoated silica gel plate (60F-254) using ultra violet light irradiation 254 nm or the KMnO_4 solution (1 gm KMnO_4 , 6.6 gm K_2CO_3 , 1.67 mL of 5% NaOH solution, 100 mL water) as staining reagent. Purifications were performed using silica gel from J.T. Baker or Merck (particle size 40-60 μm) under approximately 0.5 bar pressure. All reactions were performed under argon atmosphere with freshly distilled and dried solvents. All solvents were distilled using standard procedures. Unless otherwise stated all the reagents were obtained from Aldrich, Acros Chimica, Fluka, Advance Chemtech, Avocado, J.T. Baker, Novabiochem, Riedel de Haen, Roth, Sigma or Lancaster and used without further purification.

8.1.1 Synthesis of compound 18:



Pyridinium chlorochromate (PCC) (25 g, 3 equiv, 119 mmol) was suspended in DCM and stirred at room temperature for 30 min. Racemic oct-1-yn-3-ol **16** (5 g, 39.7 mmol, dissolved in DCM) was added dropwise into the PCC suspension and the mixture was stirred for 10h at room temperature. The solution was filtered through a silica gel pad, which was washed thoroughly with DCM. The solvent was evaporated to afford the crude oct-1-yn-3-one **17**.

Crude oct-1-yn-3-one **17** and (*R*)-Me oxazaborolidine (CBS) (1M solution in toluene) (0.06 equiv., 2.5 mmol, 2.5 mL) were dissolved in THF in a two neck round bottom flask and cooled to -30 °C. 94% Borane-dimethyl sulfide (BMS) complex (0.6 equiv., 24.19 mmol, 2.3 mL) was added dropwise with a syringe pump into the reaction mixture. The reaction temperature was raised to -10 °C for 1h. The mixture was quenched by dropwise addition of methanol at room temperature and 50 mL NaOH and Na₂CO₃ (2:1) solution was added. The aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed thoroughly with water (3 x 50 mL) and brine (2 x 10 mL) and dried over Na₂SO₄, concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 4:1) to furnish 3 g of the product **18**.

¹H NMR (400 MHz, CDCl₃): δ = 4.37-4.33 (dt, *J* = 2.1 Hz, 8.0 Hz, 1H), 2.45-2.44 (d, *J* = 2.2 Hz, 1H), 2.00 (bs, 1H), 1.73-1.67 (m, 2H), 1.49-1.41 (m, 2H), 1.32-1.25 (m, 4H), 0.90-0.87 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 85.3, 72.9, 62.5, 37.83, 31.6, 24.9, 22.7, 14.2

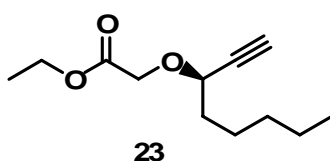
HR-MS (FAB, 70 eV): m/z calculated for C₈H₁₃O = 125.1045, found = 125.1029 [M-H]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 4:1).

[α]_D²⁰: + 6.0° (c = 2, CH₂Cl₂).¹⁶

Yield: 3 gm (60% after 2 steps).

8.1.2 Synthesis of compound 23:



A 250 mL two necked flask was charged with sodium hydride (95%) (1.5 g, 59.5 mmol, 1.5 equiv), 50 mL of THF was added and the suspension was stirred and cooled to 0 °C. To the suspension was added dropwise over 20 minutes a solution of the (*R*)- oct-1-yn-3-ol **18** (5 g, 39.68 mmol) in THF (20 mL). The mixture was warmed to 25 °C and stirred for 15 minutes. The mixture was cooled to 0 °C and a solution of ethyl bromoacetate (6.58 mL, 59.52 mmol, 1.5 equiv) in THF (10 mL) was added dropwise over 30 minutes. The mixture was warmed to 25 °C, stirred for 6h and quenched with water (20 mL). The mixture was diluted with water (100 mL) and diethyl ether (100 mL) and separated. The aqueous layer was washed with diethyl ether (2 x 200 mL). The combined ether layers were washed with brine (2 x 20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 9:1) to furnish 6.7 g of the product **23**.

¹H NMR (400 MHz, CDCl₃): δ = 4.28-4.18 (m, 5H), 2.45-2.44 (d, *J* = 2.2 Hz, 1H), 1.85-1.69 (m, 2H), 1.52-1.44 (m, 2H), 1.32-1.30 (m, 4H), 1.30-1.26 (t, *J* = 7.2 Hz, 3H), 0.90-0.87 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 170.4, 82.1, 74.7, 70.0, 65.7, 61.0, 35.6, 31.6, 24.9, 22.7, 14.4, 14.2.

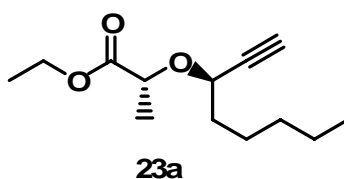
HR-MS (FAB, 70 eV): m/z calculated for C₁₂H₂₀O₃ = 212.1412, found = 212.1400 [M]⁺.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 9:1).

$[\alpha]_D^{20} : + 77.0^\circ$ (c = 2, CHCl_3).

Yield: 5.8 g (70%).

8.1.3 Analytical data of compound 23a:



$^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 4.39\text{-}4.34$ (q, $J = 6.8$ Hz, 1H), 4.23-4.14 (m, 3H), 2.41-2.40 (d, $J = 2.1$ Hz, 1H), 1.82-1.66 (m, 2H), 1.50-1.45 (m, 2H), 1.42-1.41 (d, $J = 7.0$ Hz, 3H), 1.31-1.26 (m, 7H), 0.90-0.87 (t, $J = 7.0$ Hz, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 173.4, 82.8, 74.1, 72.3, 68.9, 60.9, 35.9, 31.7, 24.9, 22.7, 19.2, 14.4, 14.2$.

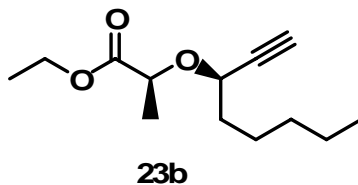
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{13}\text{H}_{22}\text{O}_3 = 226.1569$, found = 226.1566 $[\text{M}]^+$.

$R_f = 0.6$ (cyclohexane: ethyl acetate = 9:1).

$[\alpha]_D^{20} : + 55.25^\circ$ (c = 2, CHCl_3).

Yield: 1.4 g (35%).

8.1.4 Analytical data of compound 23b:



$^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 4.22\text{-}4.13$ (m, 4H), 2.41-2.40 (d, $J = 1.9$ Hz, 1H), 1.80-1.66 (m, 2H), 1.46-1.43 (m, 2H), 1.39-1.38 (d, $J = 6.8$ Hz, 3H), 1.30-1.26 (m, 7H), 0.89-0.86 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 173.3, 82.6, 74.3, 73.7, 69.4, 61.0, 35.7, 31.6, 25.0, 22.7, 18.4, 14.3, 14.2$.

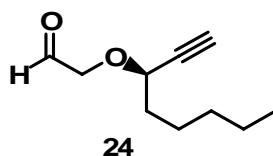
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{13}\text{H}_{22}\text{O}_3 = 226.1569$, found = 226.1566 $[\text{M}]^+$.

$R_f = 0.4$ (cyclohexane: ethyl acetate = 9:1).

$[\alpha]_D^{20} : + 6.75^\circ$ ($c = 2, \text{CHCl}_3$).

Yield: 1.4 g (35%).

8.1.5 Synthesis of compound 24:



To a solution of compound **23** (1.7 g, 8.02 mmol) in diethyl ether (200 mL) at -78°C , diisobutylaluminumhydride (1M solution in hexane, 12.02 mL, 12.02 mmol, 1.5 equiv) was added slowly by a syringe pump over 30 minutes. The solution was stirred at -78°C for 20 minutes, quenched with 1M HCl solution and stirred for 1h. The solution was diluted with diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic layers were washed with water (2 x 10 mL) and brine (2 x 10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 9:1) to furnish 1 g of the product **24**.

^1H NMR (400 MHz, CDCl_3): $\delta = 9.75\text{-}9.74$ (t, $J = 0.98$ Hz, 1H), 4.29-4.24 (dd, $J = 0.96$ Hz, 17.7 Hz, 1H), 4.19-4.15 (dt, $J = 2.2$ Hz, 7.6 Hz, 1H), 4.14- 4.09 (dd, $J = 0.96$ Hz, 17.7 Hz, 1H), 2.48-2.47 (d, $J = 2.2$ Hz, 1H), 1.79-1.70 (m, 2H), 1.52-1.41 (m, 2H), 1.33-1.29 (m, 4H), 0.91-0.87 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 200.9, 81.9, 75.2, 74.1, 70.7, 35.6, 31.6, 24.9, 22.7, 14.2$.

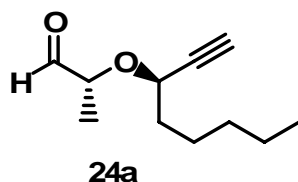
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{10}\text{H}_{16}\text{O}_2 = 168.115$, found = 168.1133 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 4:1).

$[\alpha]_D^{20}$: + 33.5° (c = 2, CHCl₃).

Yield: 1.0 g (75%).

8.1.6 Analytical data of compound 24a:



¹H NMR (400 MHz, CDCl₃): δ = 9.64-9.63 (d, *J* = 1.6 Hz, 1H), 4.22-4.20 (m, 1H), 4.19-4.18 (m, 1H), 2.43-2.42 (d, *J* = 2.2 Hz, 1H), 1.85-1.67 (m, 2H), 1.53-1.46 (m, 2H), 1.34-1.23 (m, 7H), 0.91-0.87 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 203.4, 82.6, 78.1, 74.5, 69.3, 35.9, 31.6, 25.0, 22.7, 16.0, 14.2.

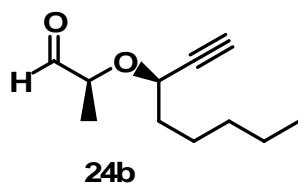
HR-MS (FAB, 70 eV): *m/z* calculated for C₁₁H₁₈O₂ = 182.1307, found = 182.1311 [M]⁺.

R_f = 0.6 (cyclohexane: ethyl acetate = 4:1).

$[\alpha]_D^{20}$: + 58.5° (c = 2, CHCl₃).

Yield: 64%.

8.1.7 Analytical data of compound 24b:



¹H NMR (400 MHz, CDCl₃): δ = 9.75-9.74 (d, *J* = 1.8 Hz, 1H), 4.20-4.16 (dt, *J* = 2.2 Hz, 7.6 Hz, 1H), 4.07-4.01 (dq, *J* = 1.8 Hz, 6.8 Hz, 1H), 2.45-2.44 (d, *J* = 2.2 Hz, 1H), 1.82-1.71 (m, 2H), 1.51-1.44 (m, 2H), 1.33-1.28 (m, 4H), 1.26-1.25 (d, *J* = 7.0 Hz, 3H), 0.91-0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 204.2, 82.8, 79.1, 75.0, 69.3, 35.9, 31.6, 25.0, 22.7, 15.4, 14.2$.

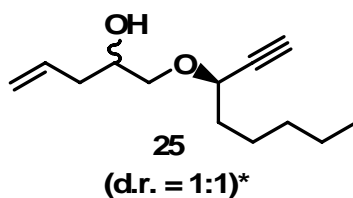
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{11}\text{H}_{18}\text{O}_2 = 182.1307$, found = 182.1311 $[\text{M}]^+$.

$R_f = 0.4$ (cyclohexane: ethyl acetate = 4:1).

$[\alpha]_D^{20} : +12.5^\circ$ ($c = 2, \text{CHCl}_3$).

Yield: 64%.

8.1.8 Synthesis of compound 25:



* = isomeric ratio was determined by ^1H NMR spectroscopy

To a solution of aldehyde **24** (0.1 g, 0.59 mmol) in THF under argon at 0 °C, allyl magnesium chloride (0.45 mL, 0.89 mmol, 1.5 equiv, 2M solution in THF) was added dropwise. The mixture was stirred at room temperature for 2h, quenched with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 9:1) to furnish 100 mg of the product as 1:1 inseparable mixture of two diastereomers.

^1H NMR (400 MHz, CDCl_3): $\delta = 5.89\text{-}5.79$ (m, 1H), 5.15-5.08 (m, 2H), 4.08-4.02 (dq, $J = 1.9$ Hz, 6.6 Hz, 1H), 3.90-3.85 (m, 1H), 3.78-3.74 (dd, $J = 3.3$ Hz, 9.36 Hz, 1H), 3.64-3.60 (dd, $J = 7.2$ Hz, 8.5 Hz, 1H), 3.46-3.43 (dd, $J = 3.5$ Hz, 9.5 Hz, 1H), 3.28-3.24 (dd, $J = 7.6$ Hz, 9.4 Hz, 1H), 2.43-2.42 (dd, $J = 1.6$ Hz, 2.0 Hz, 1H), 2.29-2.25 (m, 2H), 1.77-1.65 (m, 2H), 1.48-1.41 (m, 2H), 1.34-1.24 (m, 4H), 0.90-0.87 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 134.5, 117.9, 83.1, 83.0, 74.1, 74.0, 72.8, 72.4, 70.4, 70.1, 69.9, 69.8, 38.1, 38.0, 35.7, 35.6, 31.6, 25.1, 22.7, 14.2$.

HR-MS (FAB, 70 eV): m/z calculated for C₁₃H₂₃O₂ = 211.162, found = 211.1653 [M+H]⁺.

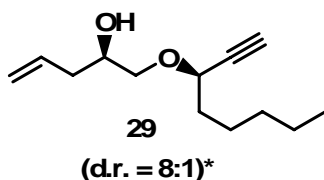
R_f = 0.5 (cyclohexane: ethyl acetate = 4:1).

Yield: 100 mg (80%).

8.2 General procedure for the asymmetric Brown allylation:

(+) or (-)-Diisopinocampyl boron chloride (DIPCl) (1.4 equiv) was dissolved in THF in a two neck round bottom flask and cooled to -78 °C. Allylmagnesiumchloride (2M solution in THF, 1.5 equiv.) was added dropwise into the flask and the solution was stirred at -78 °C for 1h. Then the reaction mixture was brought to room temperature and stirred another 1h at room temperature to allow forming the diisopinocampyl allyl borane complex. Then the mixture was cooled again to -78 °C and the aldehyde (dissolved in THF) was added dropwise into the reaction mixture and the reaction was stirred at -78 °C for 1h. Then the reaction mixture was allowed to warm to room temperature and stirred for another 1h. The reaction was quenched with 50 mL mixture of sodium hydroxide and saturated sodium hydrogen carbonate solution (2:1). The combined organic layers were washed with brine (2 x 20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 9:1) to furnish the product as 8:1 and 2.5:1 inseparable mixture of two diastereomers respectively. Further reaction was carried out without the separation of the diastereomers.

8.2.1 Analytical data of compound 29:



* = isomeric ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 5.89-5.79 (m, 1H), 5.15-5.08 (m, 2H), 4.08-4.02 (m, 1H), 3.90-3.83 (m, 1H), 3.78-3.74 (dd, *J* = 3.4 Hz, 9.5 Hz, 1H, major diastereomer), 3.64-3.60 (dd, *J* = 7.2 Hz, 9.6 Hz, 1H, minor diastereomer), 3.46-3.42 (dd, *J* = 3.5 Hz, 9.4 Hz, 1H, minor diastereomer), 3.28-3.24 (dd, *J* = 7.4 Hz, 9.5 Hz, 1H, major diastereomer), 2.43-2.42 (d, *J* = 1.9 Hz, 1H), 2.28-2.24 (m, 2H), 2.03 (bs, 1H), 1.77-1.66 (m, 2H), 1.48-1.41 (m, 2H), 1.32-1.27 (m, 4H), 0.90-0.87 (t, *J* = 6.9 Hz, 3H).

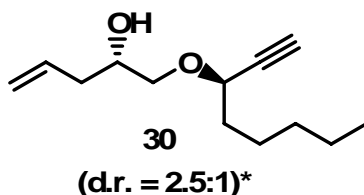
¹³C NMR (100 MHz, CDCl₃): δ = 134.4, 117.9, 83.1, 74.0, 72.8, 72.4, 70.4, 70.0, 38.1, 35.7, 31.6, 25.1, 22.7, 14.2.

HR-MS (FAB, 70 eV): *m/z* calculated for C₁₃H₂₃O₂ = 211.162, found = 211.1653 [M+H]⁺.

R_f = 0.5 (cyclohexane: ethyl acetate = 4:1).

Yield: 70 %.

8.2.2 Analytical data of compound 30:



* = isomeric ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 5.89-5.79 (m, 1H), 5.15-5.08 (m, 2H), 4.07-4.03 (m, 1H), 3.87-3.83 (m, 1H), 3.78-3.74 (dd, *J* = 3.3 Hz, 9.4 Hz, 1H, minor diastereomer), 3.64-3.60 (dd, *J* = 7.0 Hz, 9.6 Hz, 1H, major diastereomer), 3.46-3.43 (dd, *J* = 3.5 Hz, 9.5 Hz, 1H, major diastereomer), 3.28-3.24 (dd, *J* = 7.4 Hz, 9.4 Hz, 1H, minor diastereomer), 2.43-2.42 (d, *J* = 1.9 Hz, 1H), 2.29-2.24 (m, 2H), 1.77-1.65 (m, 2H), 1.48-1.41 (m, 2H), 1.31-1.28 (m, 4H), 0.91-0.87 (t, *J* = 7 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 134.5, 117.9, 83.0, 74.1, 72.8, 72.4, 70.1, 69.8, 38.1, 35.7, 31.7, 25.1, 22.7, 14.2.

HR-MS (FAB, 70 eV): *m/z* calculated for C₁₃H₂₃O₂ = 211.162, found = 211.1653 [M+H]⁺.

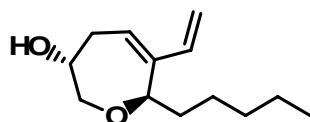
$R_f = 0.5$ (cyclohexane: ethyl acetate = 4:1).

Yield: 70 %.

8.3 General procedure for the enyne metathesis:

The enyne was dissolved in DCM (0.002 M) in a two neck round bottom flask containing a refluxing condenser attached. Argon gas was bubbled through the solution by a needle for 30 minutes. The Grubbs catalyst was added and the reaction mixture was refluxed for 18h. The solvent was evaporated and the residue was purified by silica gel chromatography.

8.3.1 Analytical data of compound 31:



31

(d.r. = 8:1)*

* = isomeric ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): $\delta = 6.23$ - 6.17 (dd, $J = 11.1$ Hz, 17.7 Hz, 1H), 5.71 - 5.68 (dd, $J = 4.9$ Hz, 8.4 Hz, 1H), 5.04 - 4.92 (m, 2H), 4.57 - 4.54 (m, 1H), 4.16 - 4.12 (m, 1H), 4.07 - 4.03 (dd, $J = 5.5$ Hz, 11.4 Hz, 1H), 3.41 - 3.37 (dd, $J = 6.9$ Hz, 12.4 Hz, 1H), 2.85 - 2.81 (m, 1H), 2.36 - 2.29 (m, 1H), 1.74 -, 1.67 (m, 1H), 1.65 - 1.58 (m, 1H), 1.49 - 1.39 (m, 2H), 1.32 - 1.25 (m, 4H), 0.91 - 0.87 (t, $J = 6.9$ Hz, 3H).

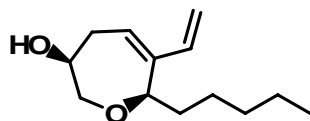
¹³C NMR (100 MHz, CDCl₃): $\delta = 142.9$, 138.7 , 126.2 , 111.9 , 80.6 , 70.5 , 69.9 , 33.2 , 31.9 , 25.5 , 22.9 , 14.3 .

HR-MS (FAB, 70 eV): m/z calculated for C₁₃H₂₂O₂ = 210.162, found = 210.1600 [M]⁺.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 3:2).

Yield: 60%.

8.3.2 Analytical data of compound 32:



32
(d.r. = 2.5:1)*

* = isomeric ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 6.14-6.09 (dd, J = 11.0 Hz, 17.5 Hz, 1H), 5.70-5.66 (dd, J = 5.0 Hz, 8.3 Hz, 1H), 5.02-4.90 (m, 2H), 4.44-4.41 (m, 1H), 4.17-4.11 (m, 1H), 4.12-3.98 (m, 1H), 3.88-3.75 (m, 1H), 2.83-2.75 (m, 1H), 2.30-2.25 (m, 1H), 1.70-, 1.65 (m, 1H), 1.60-1.55 (m, 1H), 1.45-1.35 (m, 2H), 1.30-1.22 (m, 4H), 0.87-0.84 (t, J = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 142.9, 138.7, 126.2, 111.9, 80.6, 70.5, 69.9, 33.2, 32.1, 25.4, 22.9, 14.3.

HR-MS (FAB, 70 eV): m/z calculated for C₁₃H₂₂O₂ = 210.162, found = 210.1600 [M]⁺.

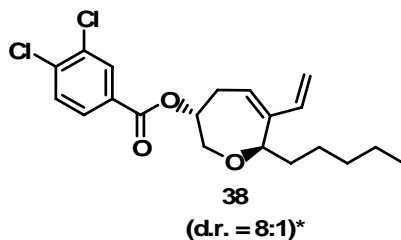
R_f = 0.5 (cyclohexane: ethyl acetate = 3:2).

Yield: 60%.

8.4 General procedure to synthesize ester and carbamates:

To a solution of alcohol **31** (8:1 mixture of two diastereomers) in THF, pyridine (1.5 equiv) and either acid chloride or isocyanate (1.5 equiv) were added and the mixture was stirred at room temperature for 16h. The solvent was evaporated and the residue was purified by silica gel chromatography. The products were formed in the same diastereomeric ration of the starting alcohol **31**.

8.4.1 Analytical data of compound 38:



* = isomeric ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): δ = 7.86-7.48 (m, 3H), 6.26-6.12 (m, 1H), 5.78-5.69 (m, 1H), 5.46-5.29 (m, 1H), 5.07-4.98 (m, 2H), 4.58-4.45 (m, 1H), 4.29-4.25 (dd, J = 7.2 Hz, 12.5 Hz, 1H), 3.51-3.46 (dd, J = 8.0 Hz, 12.4 Hz, 1H), 3.10-3.06 (m, 1H), 2.41-2.34 (m, 1H), 1.78-1.67 (m, 2H), 1.58-1.43 (m, 2H), 1.34-1.28 (m, 4H), 0.91-0.87 (t, J = 6.3 Hz, 3H).

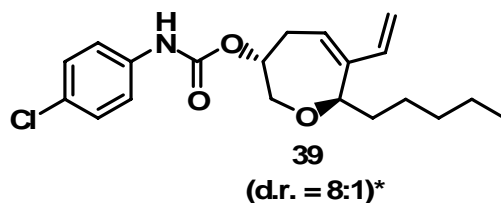
^{13}C NMR (100 MHz, CDCl_3): δ = 164.5, 142.6, 138.0, 137.8, 133.1, 131.8, 130.7, 130.2, 129.0, 125.6, 112.8, 82.5, 75.6, 70.7, 67.5, 34.7, 32.1, 28.6, 25.3, 22.9, 14.3.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{20}\text{H}_{24}\text{Cl}_2\text{O}_3$ = 382.1103, found = 384.1073 $[\text{M}+2\text{H}]^+$.

R_f = 0.5 (cyclohexane: ethyl acetate = 9:1).

Yield: 57% (after 4 steps).

8.4.2 Analytical data of compound 39:



* = isomeric ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): δ = 7.31-7.23 (m, 4H), 6.68 (bs, 1H), 6.23-6.11 (m, 1H), 5.73-5.67 (m, 1H), 5.23-5.21 (m, 1H), 5.08-4.97 (m, 2H), 4.56-4.44 (m, 1H), 4.23-4.18

(dd, $J = 7.2$ Hz, 12.5 Hz, 1H), 3.43-3.38 (dd, $J = 8.0$ Hz, 12.5 Hz, 1H), 3.02-2.97 (m, 1H), 2.41-2.27 (m, 1H), 1.76-1.66 (m, 2H), 1.56-1.45 (m, 2H), 1.33-1.25 (m, 4H), 0.91-0.87 (t, $J = 6.9$ Hz, 3H).

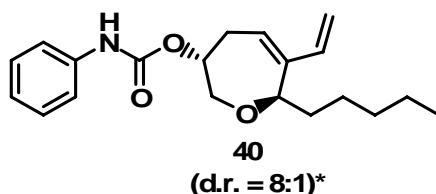
^{13}C NMR (100 MHz, CDCl_3): $\delta = 153.0, 142.5, 138.3, 129.3, 125.9, 120.0, 112.8, 82.4, 70.7, 67.7, 34.7, 32.1, 28.9, 27.8, 25.4, 22.8, 14.3$.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{20}\text{H}_{26}\text{ClNO}_3 = 363.1601$, found = 365.1572 $[\text{M}+2\text{H}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 9:1).

Yield: 65 % (after 4 steps).

8.4.3 Analytical data of compound 40:



* = isomeric ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): $\delta = 7.36$ - 7.27 (m, 5H), 5.68 (bs, 1H), 6.24-6.11 (m, 1H), 5.75-5.68 (m, 1H), 5.25-5.23 (m, 1H), 5.08-5.04 (m, 1H), 5.01-4.97 (m, 1H), 4.56-4.45 (m, 1H), 4.25-4.20 (dd, $J = 7.0$ Hz, 11.8 Hz, 1H), 3.44-3.39 (dd, $J = 8.0$ Hz, 12.3 Hz, 1H), 3.01-2.97 (m, 1H), 2.41-2.32 (m, 1H), 1.77-1.67 (m, 2H), 1.60-1.40 (m, 2H), 1.34-1.26 (m, 4H), 0.91-0.87 (t, $J = 6.6$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 153.1, 142.4, 141.8, 138.3, 138.1, 135.2, 129.3, 126.1, 125.3, 123.6, 118.8, 112.7, 82.3, 70.8, 67.8, 34.6, 32.1, 28.9, 27.8, 25.4, 22.8, 14.3$.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{20}\text{H}_{27}\text{NO}_3 = 329.1991$, found = 330.2011 $[\text{M}+\text{H}]^+$.

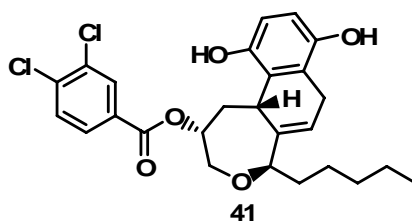
$R_f = 0.5$ (cyclohexane: ethyl acetate = 9:1).

Yield: 40 % (after 4 steps).

8.5 General procedure for the Diels-Alder reaction:

The diene and the dienophile (1.5 equiv) were dissolved in a minimum volume of toluene and the mixture was heated to 70 °C until all the starting material was totally consumed (monitored by TLC). The solvent was removed in vacuo and the crude product was purified by silica gel chromatography.

8.5.1 Analytical data of compound 41:



¹H NMR (400 MHz, CDCl₃): δ = 8.07-7.92 (m, 1H), 7.79-7.71 (m, 1H), 7.53-7.45 (m, 1H), 6.90-6.83 (dd, J = 10.2 Hz, 18.4 Hz, 1H), 6.75-6.75 (d, J = 1.9 Hz, 1H), 6.53-6.52 (d, J = 1.2 Hz, 1H), 5.74-5.73 (dd, J = 1.6 Hz, 5.8 Hz, 1H), 5.30-5.20 (m, 1H), 4.92-4.88 (dd, J = 4.4 Hz, 8.5 Hz, 1H), 4.33-4.28 (dd, J = 6.4 Hz, 12.1 Hz, 1H), 4.24-4.13 (m, 1H), 4.03-3.95 (m, 2H), 3.77-3.73 (m, 1H), 3.63-3.55 (m, 1H), 3.52-3.46 (m, 1H), 2.38-2.19 (m, 1H), 2.03-1.86 (m, 1H), 1.65-1.59 (m, 2H), 1.35-1.24 (m, 6H), 0.88-0.84 (t, J = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 186.8, 185.9, 164.1, 163.6, 149.7, 143.5, 141.3, 140.8, 136.4, 131.7, 130.7, 128.9, 120.8, 113.3, 84.61, 72.5, 69.1, 54.0, 39.9, 35.8, 31.9, 31.8, 29.5, 28.6, 25.9, 25.6, 22.8, 14.2.

HR-MS (FAB, 70 eV): m/z calculated for C₂₆H₃₀Cl₂O₅ = 492.1314, found = 492.1300 [M+2H]⁺.

$[\alpha]_D^{20}$: + 5.6° (c = 2, CHCl₃).

R_f = 0.5 (cyclohexane: ethyl acetate = 4:1).

Yield: 60 % (after 5 steps).

8.6 General procedure for the one pot synthesis of the oxepane library starting from DIBAL-H reduction:

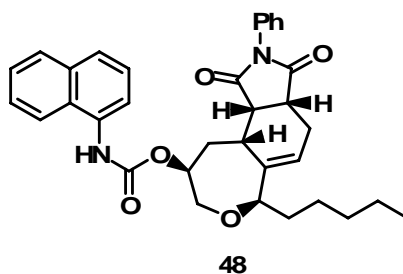
To a solution of the ethyl ester in diethyl ether at $-78\text{ }^{\circ}\text{C}$, diisobutylaluminumhydride (1M solution in hexane, 1.5 equiv) was added slowly by a syringe pumpe over 30 minutes. The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 20 minutes, quenched with 1M HCl solution and stirred for 1h. The solution was diluted with diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL) and the combined organic layers were washed with water (2 x 10 mL) and brine (2 x 10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure.

(+) or (-)-Diisopinocampyl boron chloride (DIPCl) was dissolved in THF in a two neck round bottom flask and cooled to $-78\text{ }^{\circ}\text{C}$. Allylmagnesiumchloride (2M solution in THF, 1.5 equiv.) was added dropwise into the flask and the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1h. Then the reaction mixture was brought to room temperature and stirred another 1h at room temperature to allow for formation of the diisopinocampyl allyl borane complex. Then the mixture was cooled again to $-78\text{ }^{\circ}\text{C}$ and the solution of the crude aldehyde in 5 mL THF was added dropwise into the reaction mixture and the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1h. Then the reaction mixture was allowed to warm to room temperature and stirred another hour. The mixture was diluted with methanol (10 mL) and DOWEX[®] 50WX-200 or sulfonic acid resin **42** was added. The reaction mixture was shaken at room temperature for 6h and then filtered. The resin was washed with methanol and DCM, and the solvent was evaporated to afford the crude homoallyl alcohol.

The crude homoallyl alcohol was dissolved in DCM (0.002 M) in a two neck round bottom flask containing a refluxing condenser attached. Argon gas was bubbled through the solution by a needle for 30 minutes. The Grubbs catalyst was added and the reaction mixture was refluxed for 18h. The polymer bound ruthenium metal scavenger resin **44** (20 equiv relative to the catalyst added) was added and the mixture was shaken at room temperature for 10h and then filtered. The resin was washed with DCM, the solvent was evaporated and the crude pale yellow diene product was dissolved in THF in a two neck round bottom flask and pyridine (1.5 equiv). Either acid chloride or isocyanate (1.5 equiv) was added and the mixture was stirred at room temperature for 16h. The

aminomethylated polystyrene resin **45** (3 equiv. relative to the excess isocyanate or acid chloride) was added and the mixture was shaken for 5h and filtered. The resin was washed with DCM, the solvent was evaporated and the crude product was again dissolved in a minimum amount of toluene. The dienophile (1.5 equiv.) was added and the mixture was heated to 70 °C for 6-10h. The solvent was removed in vacuo and the crude product was purified as their major isomers by silica gel chromatography.

8.6.1 Analytical data of compound **48**:



¹H NMR (400 MHz, CDCl₃): δ = 7.92-7.82 (m, 3H), 7.67-7.65 (d, J = 8.2 Hz, 1H), 7.52-7.43 (m, 6H), 7.39-7.36 (m, 1H), 7.25-7.21 (m, 2H), 5.83-5.80 (t, J = 4.8 Hz, 1H), 5.08-5.07 (m, 1H), 4.23-4.19 (m, 1H), 3.92-3.91 (m, 1H), 3.29-3.26 (m, 1H), 3.22-3.18 (m, 1H), 2.73-2.69 (m, 1H), 2.54-2.49 (m, 1H), 2.30-2.29 (m, 2H), 1.67-1.59 (m, 1H), 1.56-1.45 (m, 1H), 1.32-1.26 (m, 8H), 0.92-0.88 (t, J = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 179.1, 177.7, 154.4, 144.3, 134.3, 132.7, 131.9, 129.4, 128.9, 126.6, 126.5, 125.9, 125.3, 123.1, 82.4, 73.4, 72.8, 45.0, 39.9, 33.0, 32.0, 29.5, 27.1, 25.9, 22.8, 14.3.

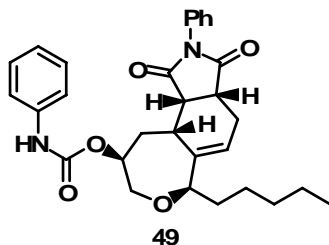
HR-MS (FAB, 70 eV): m/z calculated for C₃₄H₃₆N₂O₅ = 552.2624 found = 552.2600 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4:1).

[α]_D²⁰ : - 26.5° (c = 2, CHCl₃).

Yield: 40 mg (30 % after 5 steps).

8.6.2 Analytical data of compound 49:



¹H NMR (400 MHz, CDCl₃): δ = 7.47-7.43 (m, 2H), 7.39-7.35 (m, 3H), 7.30-7.27 (m, 3H), 7.23-7.19 (m, 2H), 7.07-7.03 (m, 1H), 5.83-5.80 (t, J = 4.9 Hz, 1H), 4.17-4.09 (m, 1H), 3.91-3.88 (t, J = 6.4 Hz, 1H), 3.31-3.27 (m, 1H), 3.21-3.17 (m, 1H), 2.73-2.68 (m, 1H), 2.56-2.53 (m, 1H), 2.24-2.23 (m, 1H), 1.67-1.65 (m, 1H), 1.57-1.52 (m, 1H), 1.30-1.23 (m, 8H), 0.90-0.87 (t, J = 6.6 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 179.1, 177.7, 152.9, 144.3, 143.8, 138.0, 131.9, 129.4, 128.9, 126.5, 123.7, 122.3, 120.7, 82.15, 72.4, 71.1, 45.0, 39.8, 33.3, 33.0, 32.0, 31.9, 29.5, 27.1, 25.9, 23.7, 22.7, 14.3.

HR-MS (FAB, 70 eV): m/z calculated for C₃₀H₃₅N₂O₅ = 503.2468, found = 503.2401 [M+H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

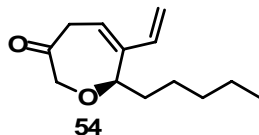
[α]_D²⁰: - 19.8° (c = 1, CHCl₃).

Yield: 34 mg (32% after 5 steps).

8.7 General procedure for PCC oxidation:

To the suspension of pyridinium chlorochromate (3 equiv) in DCM, a solution of the secondary alcohol (1 equiv) in DCM was added. The reaction mixture was stirred for 10h at room temperature and filtered through a Celite pad. The Celite pad was washed thoroughly with DCM. The solvent was evaporated and the residue was purified by silica gel chromatography to afford the pure ketone.

8.7.1 Analytical data of compound 54:



¹H NMR (400 MHz, CDCl₃): δ = 6.20-6.13 (dd, J = 11.6 Hz, 17.8 Hz, 9.2 Hz, 1H), 5.62-5.58 (dd, J = 4.7 Hz, 1H), 5.09-5.01 (m, 2H), 4.49-4.46 (m, 1H), 4.21-4.16 (d, J = 18.2 Hz, 1H), 4.14-4.09 (m, 1H), 4.05-4.00 (d, J = 18.2 Hz, 1H), 2.78-2.72 (dd, J = 9.2 Hz, 13.1 Hz, 1H), 1.87-1.80 (m, 1H), 1.77-1.67 (m, 1H), 1.54-1.45 (m, 2H), 1.34-1.24 (m, 4H), 0.91-0.87 (t, J = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 209.3, 141.3, 137.6, 120.7, 113.6, 82.7, 74.1, 41.1, 34.9, 31.9, 25.1, 22.8, 14.3.

HR-MS (FAB, 70 eV): m/z calculated for C₁₃H₂₀O₂ = 208.1463, found = 208.1458 [M]⁺.

R_f = 0.5 (cyclohexane: ethyl acetate = 9:1).

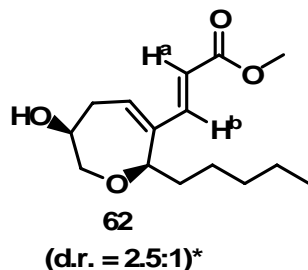
[α]_D²⁰: + 9.0° (c = 1, CHCl₃).

Yield: 20 mg (30% after 5 steps).

8.8 General procedure for the cross metathesis:

The diene (1 equiv) and methyl acrylate (1.5 equiv) were dissolved in DCM in a two neck round bottom flask under argon. The solution was degassed by bubbling argon for 30 minutes. The 2nd generation Grubbs catalyst (20 mol %) was added and the reaction mixture was refluxed for 10h. The solvent was evaporated and the crude product was purified by silica gel chromatography.

8.8.1 Analytical data of compound 62:



* = isomeric ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): δ = 7.13-7.09 (d, $J_{\text{Ha-Hb}}$ = 16.2 Hz, 1H), 6.08-6.05 (dd, J = 5.9 Hz, 8.9 Hz, 1H), 5.07-5.66 (d, $J_{\text{Ha-Hb}}$ = 16.4 Hz, 1H), 4.41-4.37 (m, 1H), 3.88-3.85 (m, 1H), 3.73 (s, 3H), 2.88-2.81 (m, 1H), 2.44-2.37 (m, 1H), 2.04 (bs, 1H), 1.71-1.63 (m, 2H), 1.51-1.43 (m, 2H), 1.31-1.24 (m, 4H), 0.89-0.86 (t, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ = 167.7, 146.4, 140.9, 135.3, 116.2, 81.4, 73.4, 71.4, 51.8, 34.3, 32.7, 32.0, 25.3, 22.8, 14.3

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{15}\text{H}_{24}\text{O}_4$ = 268.1675, found = 269.1648 $[\text{M}+\text{H}]^+$.

R_f = 0.3 (cyclohexane: ethyl acetate = 3:2).

Yield: 65 % (after 4 steps).

8.9 General procedure for the synthesis of diacids:

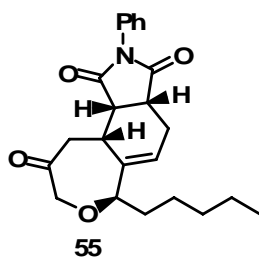
The functionalized diene (1 equiv) and maleic anhydride (1.5 equiv) were dissolved in the minimum volume of toluene and heated at 70 °C for 3h. Then into the reaction mixture 20 % water in THF (5 mL) was added and the mixture was stirred at room temperature for 6h. Water was removed by azeotropic distillation with ethanol and the crude product was purified by silica gel chromatography.

8.10 General procedure for the two step synthesis of carbamate:

The secondary alcohol **31** was dissolved in DCM and 1, 1'-carbonyldiimidazole (1.5 equiv) was added. The mixture was stirred for 10h until the starting material was totally consumed. The solvent was evaporated to afford the imidazole carbamate **75** which was dissolved in THF/DMF (4:1). Anhydrous potassium carbonate (2 equiv) and the primary or the secondary amines were added and the mixture was stirred at room temperature for 6h. The mixture was quenched with the polymer supported sulfonic acid resin **42** (3 equiv relative to the excess amine and K_2CO_3 used) or the DOWEX[®]-50WX-200 resin and stirred at room temperature for 4h. The resin was filtered and washed with DCM and the solvent was evaporated to afford the crude carbamate **76** which was used without any further purification.

8.11 Analytical data of the members of the oxepane library:

8.11.1 Analytical data of compound 55:



¹H NMR (400 MHz, CDCl₃): δ = 7.47-7.38 (m, 3H), 7.26-7.24 (m, 2H), 5.90-5.87 (t, J = 6.0 Hz, 1H), 4.31-4.09 (m, 1H), 4.13-4.09 (d, J = 17.7 Hz, 1H), 3.93-3.88 (d, J = 17.9 Hz, 1H), 3.71-3.64 (t, J = 13.2 Hz, 1H), 3.29-3.27 (m, 1H), 2.96-2.93 (m, 1H), 2.80-2.74 (m, 1H), 2.67-2.62 (dd, J = 4.7 Hz, 13.5 Hz, 1H), 2.38-2.31 (m, 1H), 1.75-1.67 (m, 1H), 1.75-1.67 (m, 1H), 1.56-1.54 (m, 1H), 1.47-1.42 (m, 2H), 1.33-1.20 (m, 6H), 0.87-0.84 (t, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 212.4, 178.4, 176.7, 143.4, 131.8, 129.3, 128.9, 126.4, 124.7, 110.8, 82.8, 73.1, 44.9, 41.9, 39.9, 36.8, 35.8, 31.8, 25.8, 24.5, 22.7, 14.2$

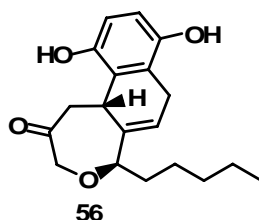
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{23}\text{H}_{28}\text{NO}_4 = 382.1940$, found = 382.1974
[$\text{M}+\text{H}$] $^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 9: 1).

$[\alpha]_D^{20} : + 23.2^\circ$ (c = 1, CHCl_3).

Yield: 14 mg (25% after 5 steps).

8.11.2 Analytical data of compound 56:



^1H NMR (400 MHz, CDCl_3): $\delta = 6.99\text{-}6.76$ (m, 2H), 5.90-5.88 (dd, $J = 2.5$ Hz, 4.3 Hz, 1H), 4.16-4.11 (m, 2H), 4.07-4.00 (m, 1H), 3.81-3.76 (d, $J = 17.7$ Hz, 1H), 3.60-3.54 (dd, $J = 10.9$ Hz, 14.3 Hz, 1H), 3.22-3.14 (m, 1H), 3.0-2.9 (m, 1H), 2.09-2.04 (m, 1H), 1.86-1.79 (m, 1H), 1.60-1.51 (m, 2H), 1.33-1.22 (m, 6H), 0.89-0.86 (t, $J = 6.7$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 203.9, 186.9, 186.6, 147.6, 142.7, 141.5, 138.8, 136.8, 133.4, 132.9, 123.9, 86.6, 75.4, 48.2, 39.5, 34.1, 31.9, 30.0, 25.8, 22.8, 14.3$.

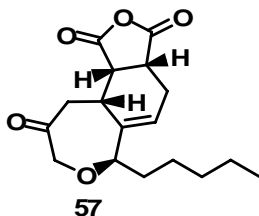
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{19}\text{H}_{24}\text{O}_4 = 316.1675$, found 317.1669
[$\text{M}+\text{H}$] $^+$.

$R_f = 0.4$ (cyclohexane: ethyl acetate = 4:1).

$[\alpha]_D^{20} : + 10.2^\circ$ (c = 1, CHCl_3).

Yield: 8 mg (14 % after 5 steps).

8.11.3 Analytical data of compound 57:



¹H NMR (400 MHz, CDCl₃): δ = 5.89-5.86 (t, J = 5.3 Hz, 1H), 4.16-4.11 (d, J = 18.2 Hz, 1H), 3.91-3.86 (d, J = 18.0 Hz, 1H), 3.69-3.62 (t, J = 13.1 Hz, 1H), 3.43-3.41 (dd, J = 3.0 Hz, 7.3 Hz, 1H), 3.38-3.34 (dd, J = 5.8 Hz, 9.9 Hz, 1H), 2.82-2.76 (m, 1H), 2.75-2.72 (dd, J = 3.0 Hz, 6.4 Hz, 1H), 2.56-2.52 (dd, J = 4.5 Hz, 13.1 Hz, 1H), 2.33-2.26 (m, 1H), 1.73-1.69 (m, 1H), 1.47-1.42 (m, 1H), 1.32-1.25 (m, 6H), 0.91-0.87 (t, J = 6.6 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 211.7, 173.5, 171.6, 143.2, 136.7, 124.9, 82.9, 73.3, 45.9, 41.7, 40.5, 36.5, 35.5, 31.7, 25.6, 24.3, 22.8, 14.2.

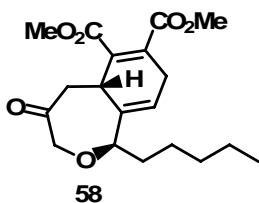
HR-MS (FAB, 70 eV): m/z calculated for C₁₇H₂₂O₅ = 306.1467, found = 306.1411 [M]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 1: 1).

[α]_D²⁰: + 30.8° (c = 2, CHCl₃).

Yield: 13.4 mg (25 % after 5 steps).

8.11.4 Analytical data of compound 58:



¹H NMR (400 MHz, CDCl₃): δ = 5.84-5.77 (t, J = 3.1 Hz, 1H), 4.17-4.10 (d, J = 17.9 Hz, 1H), 4.01-3.98 (m, 1H), 3.91-3.87 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.48-3.39 (m, 1H), 3.07-3.05 (m, 2H), 2.91-2.86 (dd, J = 4.5 Hz, 13.5 Hz, 1H), 2.66-2.60 (dd, J = 9.5

Hz, 13.6 Hz, 1H), 1.78-1.66 (m, 1H), 1.56-1.55 (m, 1H), 1.34-1.25 (m, 6H), 0.92-0.88 (t, $J = 6.6$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 212.4, 168.1, 167.6, 137.9, 135.7, 133.7, 123.2, 119.4, 86.1, 83.3, 75.1, 52.7, 47.7, 36.8, 34.2, 31.9, 31.8, 30.9, 28.4, 25.7, 22.8, 14.2$

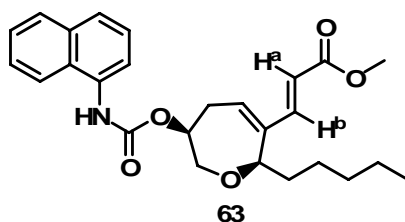
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{19}\text{H}_{26}\text{O}_6 = 350.1729$, found = 351.1700 $[\text{M}+\text{H}]^+$.

$R_f = 0.3$ (cyclohexane: ethyl acetate = 4:1).

$[\alpha]_D^{20}$: -27.2° ($c = 2$, CHCl_3).

Yield: 10.3 mg (30 % after 5 steps).

8.11.5 Analytical data of compound 63:



^1H NMR (400 MHz, CDCl_3): $\delta = 7.87\text{-}7.84$ (m, 3H), 7.66-7.65 (m, 1H), 7.53-7.44 (m, 3H), 7.17-7.13 (d, $J_{\text{Ha-Hb}} = 16.4$ Hz, 1H), 7.03 (bs, 1H), 6.12-6.08 (dd, $J = 5.8$ Hz, 8.9 Hz, 1H), 5.75-5.71 (d, $J_{\text{Ha-Hb}} = 16.2$ Hz, 1H), 5.17-5.13 (m, 1H), 4.45-4.44 (m, 1H), 4.09-4.06 (d, $J = 14.1$ Hz, 1H), 3.88-3.83 (dd, $J = 4.7$ Hz, 14.3 Hz, 1H), 3.76 (s, 3H), 3.12-3.06 (m, 1H), 2.57-2.51 (m, 1H), 1.75-1.70 (m, 2H), 1.54-1.52 (m, 2H), 1.34-1.26 (m, 4H), 0.92-0.89 (t, $J = 7.0$ Hz, 3H),

^{13}C NMR (100 MHz, CDCl_3): $\delta = 167.6, 145.9, 141.2, 134.3, 134.1, 132.6, 129.0, 126.5, 126.2, 126.0, 116.7, 82.2, 74.7, 70.9, 51.9, 34.6, 32.0, 28.5, 27.1, 25.3, 22.9, 14.3$.

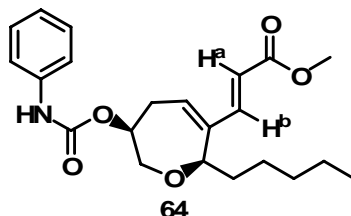
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{26}\text{H}_{31}\text{NO}_5 = 437.2202$, found = 437.2259 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 9:1).

$[\alpha]_D^{20}$: -22.2° ($c = 1$, CHCl_3).

Yield: 30 mg (40 % after 5 steps).

8.11.6 Analytical data of compound 64:



$^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.36$ - 7.25 (m, 4H), 7.15 - 7.11 (d, $J_{\text{Ha-Hb}} = 16.2$ Hz, 1H), 7.07 - 7.03 (m, 1H), 6.70 (bs, 1H), 6.11 - 6.07 (dd, $J = 5.8$ Hz, 8.9 Hz, 1H), 5.73 - 5.69 (d, $J_{\text{Ha-Hb}} = 16.2$ Hz, 1H), 5.10 - 5.04 (m, 1H), 4.44 - 4.41 (m, 1H), 4.02 - 3.98 (d, $J = 14.2$ Hz, 1H), 3.84 - 3.79 (dd, $J = 4.7$ Hz, 14.2 Hz, 1H), 3.75 (s, 3H), 3.07 - 2.99 (m, 1H), 2.51 - 2.44 (m, 1H), 1.74 - 1.65 (m, 2H), 1.54 - 1.46 (m, 2H), 1.33 - 1.25 (m, 4H), 0.91 - 0.87 (t, $J = 6.9$ Hz, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 167.6$, 152.9 , 145.9 , 141.1 , 137.9 , 134.0 , 129.3 , 123.9 , 118.86 , 116.7 , 82.1 , 74.4 , 70.8 , 51.9 , 34.6 , 32.0 , 28.4 , 25.3 , 22.9 , 14.3 .

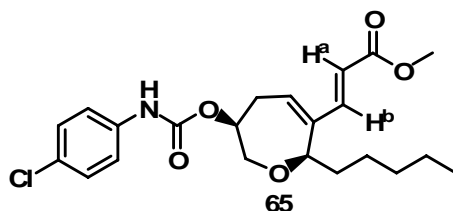
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{22}\text{H}_{29}\text{NO}_5 = 387.2046$, found = 387.2046 $[\text{M}+\text{H}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 9: 1).

$[\alpha]_D^{20}$: -7.2° ($c = 1$, CHCl_3).

Yield: 35.5 mg (47% after 5 steps).

8.11.7 Analytical data of compound 65:



$^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.31$ - 7.23 (m, 4H), 7.14 - 7.11 (d, $J_{\text{Ha-Hb}} = 16.2$ Hz, 1H), 6.74 (bs, 1H), 6.09 - 6.05 (dd, $J = 5.8$ Hz, 8.9 Hz, 1H), 5.73 - 5.69 (d, $J_{\text{Ha-Hb}} = 16.2$ Hz, 1H),

5.08-5.03 (m, 1H), 4.41-4.37 (m, 1H), 4.00-3.97 (d, $J = 14.1$ Hz, 1H), 3.83-3.78 (dd, $J = 4.7$ Hz, 14.3 Hz, 1H), 3.75 (s, 3H), 3.06-2.99 (m, 1H), 2.50-2.43 (m, 1H), 1.71-1.65 (m, 2H), 1.52-1.47 (m, 2H), 1.32-1.25 (m, 4H), 0.90-0.87 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 167.5, 152.9, 145.9, 141.2, 136.6, 133.8, 129.3, 120.0, 116.8, 82.1, 74.6, 70.7, 51.9, 34.6, 32.0, 28.4, 27.1, 25.3, 22.8, 14.3$.

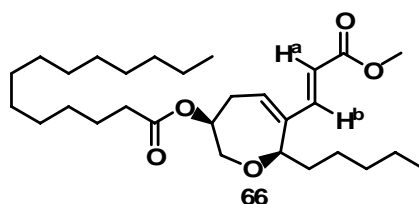
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{22}\text{H}_{28}\text{ClNO}_5 = 421.1656$, found = 423.1666 $[\text{M}+2\text{H}]^+$.

$R_f = 0.4$ (cyclohexane: ethyl acetate = 9:1).

$[\alpha]_D^{20} : -30.5^\circ$ ($c = 1, \text{CHCl}_3$).

Yield: 50 mg (75 % after 5 steps).

8.11.8 Analytical data of compound 66:



^1H NMR (400 MHz, CDCl_3): $\delta = 7.14-7.09$ (d, $J_{\text{Ha-Hb}} = 16.2$ Hz, 1H), 6.08-6.04 (dd, $J = 5.8$ Hz, 9.2 Hz, 1H), 5.72-5.68 (d, $J_{\text{Ha-Hb}} = 16.4$ Hz, 1H), 5.05-5.01 (m, 1H), 4.41-4.38 (m, 1H), 3.90-3.86 (d, $J = 14$ Hz, 1H), 3.74 (s, 3H), 3.00-2.97 (m, 1H), 2.40-2.33 (m, 1H), 2.30-2.26 (t, $J = 7.5$ Hz, 2H), 1.70-1.67 (m, 2H), 1.61-1.57 (m, 2H), 1.52-1.46 (m, 2H), 1.28-1.24 (m, 24H), 0.89-0.85 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 173.6, 167.5, 145.9, 141.1, 134.1, 116.6, 82.1, 73.2, 70.9, 51.8, 34.6, 34.5, 32.1, 32.0, 29.9, 29.8, 29.7, 29.5, 29.4, 29.3, 28.1, 25.2, 25.1, 22.9, 22.8, 14.3, 14.2$.

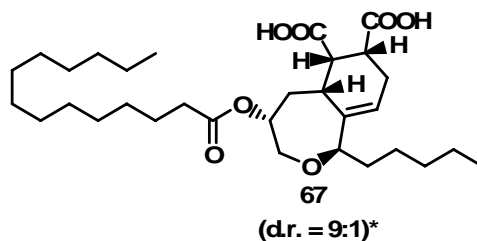
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{29}\text{H}_{51}\text{O}_5 = 479.3658$, found = 479.3692 $[\text{M}+\text{H}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 9: 1).

$[\alpha]_D^{20} : -16.3^\circ$ ($c = 1, \text{CHCl}_3$).

Yield: 25 mg (47% after 5 steps).

8.11.9 Analytical data of compound 67:



* = isomeric ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, $\text{DMSO-}d^6$): δ = 5.42-5.40 (t, J = 3.0 Hz, 1H), 4.59-4.56 (m, 1H), 4.00-3.98 (m, 1H), 3.67-3.64 (m, 1H), 3.13-3.07 (t, J = 10.5 Hz, 1H), 2.83-2.75 (m, 1H), 2.72-2.62 (m, 2H), 2.28-2.24 (t, J = 7.3 Hz, 2H), 2.04-1.94 (m, 1H), 1.83-1.80 (m, 1H), 1.52-1.43 (m, 2H), 1.33-1.27 (m, 30H), 0.90-0.86 (m, 6H).

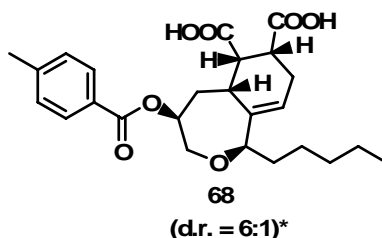
^{13}C NMR (100 MHz, $\text{DMSO-}d^6$): δ = 179.0, 178.5, 170.9, 140.4, 119.3, 79.6, 75.2, 72.9, 54.9, 45.2, 33.5, 32.5, 32.2, 31.7, 30.6, 30.2, 30.1, 29.5, 29.1, 28.5, 27.9, 26.1, 23.7, 23.3, 14.9, 14.2.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{31}\text{H}_{52}\text{O}_7$ = 536.3713, found = 536.3766 $[\text{M}]^+$.

R_f = 0.5 (ethyl acetate: methanol = 9:1).

Yield: 12 mg (25 % after 6 steps).

8.11.10 Analytical data of compound 68:



* = isomeric ratio determined by ^1H NMR spectroscopy

¹H NMR (400 MHz, DMSO-*d*⁶): δ = 7.92-7.90 (d, *J* = 8.2 Hz, 1H), 7.83-7.81 (m, 1H), 7.38-7.34 (t, *J* = 7.3 Hz, 2H), 5.45-5.43 (t, *J* = 3.5 Hz, 1H), 4.05-4.00 (m, 1H), 3.85-3.14 (m, 2H), 2.42 (s, 3H), 2.06-2.00 (m, 2H), 1.78-1.72 (m, 1H), 1.53-1.48 (m, 2H), 1.33-1.22 (m, 8H), 0.90-0.87 (t, *J* = 6.7 Hz, 3H).

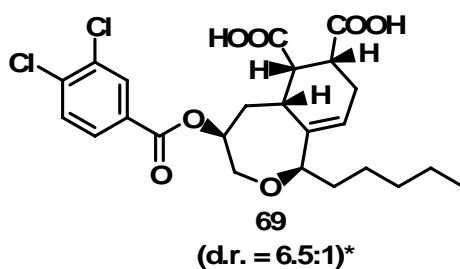
¹³C NMR (100 MHz, DMSO-*d*⁶): δ = 179.3, 178.8, 170.4, 145.3, 140.9, 130.4, 129.5, 126.9, 121.3, 78.3, 75.9, 73.1, 53.0, 45.2, 36.6, 34.2, 30.4, 28.5, 27.2, 26.0, 21.0, 14.1.

HR-MS (FAB, 70 eV): *m/z* calculated for C₂₅H₃₁O₇ = 443.2148, found = 443.2156 [M-H]⁺.

R_f = 0.5 (ethyl acetate: methanol = 9:1).

Yield: 27 mg (30 % after 6 steps).

8.11.11 Analytical data of compound 69:



* = isomeric ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, DMSO-*d*⁶): δ = 8.12-8.04 (m, 1H), 7.96-7.93 (m, 1H), 7.88-7.83 (m, 1H), 5.41-5.39 (t, *J* = 4.0 Hz, 1H), 4.05-4.02 (m, 1H), 3.45-3.29 (m, 3H), 2.84-2.70 (m, 3H), 2.02-1.89 (m, 2H), 1.57-1.45 (m, 2H), 1.34-1.26 (m, 8H), 0.90-0.85 (t, *J* = 6.8 Hz, 3H).

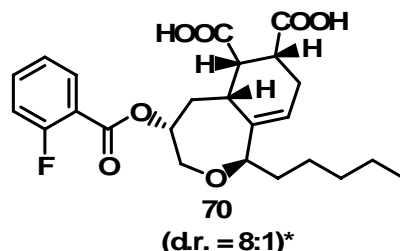
¹³C NMR (100 MHz, DMSO-*d*⁶): δ = 180.5, 178.2, 165.4, 140.7, 138.9, 133.9, 130.4, 129.5, 129.2, 120.9, 80.9, 75.3, 73.1, 53.8, 45.9, 33.5, 32.2, 31.7, 30.6, 29.5, 28.5, 26.1, 23.7, 14.2.

HR-MS (FAB, 70 eV): *m/z* calculated for C₂₄H₂₇Cl₂O₇ = 497.1212, found = 497.1296 [M-H]⁺.

R_f = 0.4 (ethyl acetate: methanol = 9:1).

Yield: 25 mg (24 % after 6 steps).

8.11.12 Analytical data of compound 70:



* = isomeric ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, $\text{DMSO-}d^6$): δ = 7.86-7.82 (dt, J = 1.7 Hz, 8.5 Hz, 1H), 7.73-7.67 (m, 1H), 7.37-7.33 (m, 2H), 5.45-5.44 (t, J = 3.5 Hz, 1H), 4.85-4.79 (m, 1H), 4.06-4.02 (m, 1H), 3.86-3.83 (m, 1H), 3.36-3.25 (m, 2H), 2.85-2.77 (m, 1H), 2.72-2.71 (m, 1H), 2.02-1.99 (m, 2H), 1.59-1.50 (m, 2H), 1.39-1.24 (m, 8H), 0.91-0.87 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $\text{DMSO-}d^6$): δ = 179.3, 178.8, 169.7, 159.4, 135.3, 130.9, 126.6, 120.4, 115.9, 80.5, 75.9, 73.1, 54.9, 41.5, 34.9, 31.9, 31.2, 30.0, 29.1, 28.9, 27.1, 24.7, 14.2.

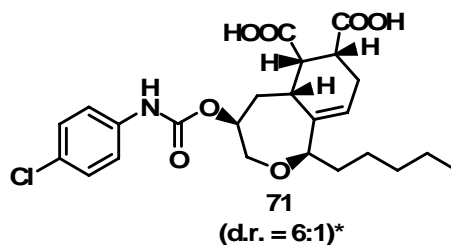
^{19}F NMR (338.6 MHz, $\text{DMSO-}d^6$): -121.1.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{24}\text{H}_{29}\text{FO}_7$ = 448.1897, found = 448.1811 $[\text{M}]^+$.

R_f = 0.3 (ethyl acetate: methanol = 9:1).

Yield: 20 mg (21 % after 6 steps).

8.11.13 Analytical data of compound 71:



* = isomeric ratio determined by ^1H NMR spectroscopy

¹H NMR (400 MHz, DMSO-*d*⁶): δ = 9.88 (bs, 1H), 7.58-7.56 (d, J = 8.6 Hz, 1H), 7.50-7.47 (d, J = 9.0 Hz, 1H), 7.35-7.32 (m, 2H), 5.43-5.41 (t, J = 4.0 Hz, 1H), 4.02-3.91 (m, 1H), 3.40-3.33 (m, 3H), 2.83-2.67 (m, 2H), 2.01-1.87 (m, 2H), 1.71-1.70 (m, 1H), 1.56-1.49 (m, 1H), 1.33-1.28 (m, 9H), 0.91-0.87 (t, J = 6.6 Hz, 3H).

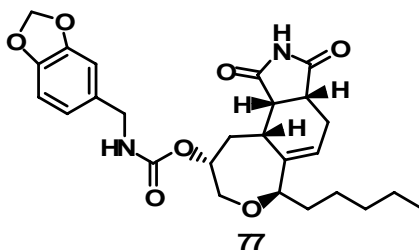
¹³C NMR (100 MHz, DMSO-*d*⁶): δ = 180.3, 179.8, 154.9, 140.9, 133.3, 130.9, 129.5, 124.5, 123.9, 120.6, 80.9, 75.7, 73.1, 54.3, 45.2, 35.2, 33.4, 25.3, 22.0, 14.9.

HR-MS (FAB, 70 eV): m/z calculated for C₂₄H₃₀ClNO₇ = 479.1711, found = 479.1795 [M]⁺.

R_f = 0.4 (ethyl acetate: methanol = 9:1).

Yield: 14.2 mg (26 % after 6 steps).

8.11.14 Analytical data of compound 77:



¹H NMR (400 MHz, CDCl₃): δ = 8.54 (bs, 1H), 6.74-6.70 (m, 3H), 5.92 (s, 2H), 5.74-5.72 (t, J = 4.7 Hz, 1H), 4.74-4.67 (m, 1H), 4.25-4.20 (m, 2H), 3.92-3.88 (m, 1H), 3.86-3.82 (t, J = 6.2 Hz, 1H), 3.32-3.27 (t, J = 11.0 Hz, 1H), 3.16-3.10 (m, 1H), 3.06-3.02 (dd, J = 6.1 Hz, 9.6 Hz, 1H), 2.57-2.52 (m, 1H), 2.10-2.07 (m, 1H), 1.57-1.53 (m, 1H), 1.48-1.45 (m, 2H), 1.28-1.24 (m, 6H), 0.88-0.85 (t, J = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 180.3, 178.5, 155.5, 148.1, 143.9, 132.5, 122.8, 121.1, 108.5, 101.3, 82.5, 72.8, 69.8, 54.1, 46.1, 45.1, 34.1, 33.2, 31.9, 29.5, 27.1, 25.7, 22.8, 14.3.

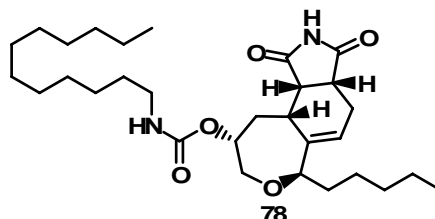
HR-MS (FAB, 70 eV): m/z calculated for C₂₆H₃₁N₂O₇ = 483.221, found = 483.2279 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 19.3° (c = 1, CHCl₃).

Yield: 26 mg (16 % after 6 steps).

8.11.15 Analytical data of compound 78:



¹H NMR (400 MHz, CDCl₃): δ = 8.5 (bs, 1H), 5.76-5.73 (t, J = 5.0 Hz, 1H), 4.71-4.65 (m, 1H), 3.92-3.82 (m, 2H), 3.15-3.04 (m, 4H), 2.83-2.79 (m, 1H), 2.61-2.54 (m, 1H), 2.45-2.37 (m, 1H), 2.10-2.08 (m, 1H), 1.85-1.73 (m, 1H), 1.61-1.40 (m, 3H), 1.28-1.24 (m, 26H), 0.88-0.85 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 180.5, 178.8, 158.9, 155.8, 144.3, 123.0, 82.7, 72.8, 71.6, 53.2, 46.5, 41.6, 41.3, 40.9, 34.5, 33.5, 32.5, 30.7, 30.4, 30.2, 30.1, 29.9, 29.8, 27.5, 27.3, 26.1, 23.2, 23.1, 14.7, 14.6.

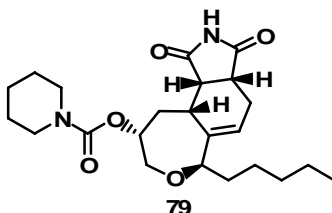
HR-MS (FAB, 70 eV): m/z calculated for C₃₀H₄₉N₂O₅ = 517.372, found = 517.3759 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

$[\alpha]_D^{20}$: + 6.1° (c = 1, CHCl₃).

Yield: 55 mg (24 % after 6 steps).

8.11.16 Analytical data of compound 79:



¹H NMR (400 MHz, CDCl₃): δ = 8.44 (bs, 1H), 5.74-5.72 (t, *J* = 3.5 Hz, 1H), 3.93-3.91 (m, 1H), 3.85-3.83 (m, 1H), 3.40-3.33 (m, 4H), 3.20-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.85-2.79 (m, 1H), 2.62-2.56 (m, 1H), 2.45-2.40 (m, 1H), 2.12-2.09 (m, 1H), 1.90-1.87 (m, 1H), 1.54-1.49 (m, 10H), 1.26-1.24 (m, 6H), 0.88-0.84 (t, *J* = 6.5 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 180.4, 178.7, 162.4, 160.3, 157.1, 154.5, 144.1, 135.3, 122.5, 117.2, 82.5, 73.0, 64.3, 45.0, 33.0, 31.9, 29.5, 25.7, 24.5, 23.0, 22.8, 14.2.

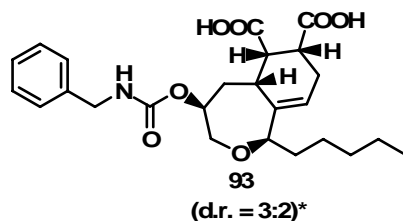
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₃H₃₃N₂O₅ = 418.2468, found = 418.2491 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 26.9° (c = 1, CHCl₃).

Yield: 22 mg (16 % after 6 steps).

8.11.17 Analytical data of compound 93:



* = isomeric ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, DMSO-*d*⁶): δ = 7.76-7.68 (m, 1H), 7.36-7.24 (m, 5H), 5.41-5.39 (t, *J* = 3.5 Hz, 1H), 4.20-4.18 (m, 2H), 4.00-3.98 (m, 1H), 3.35-3.30 (m, 5H), 2.83-2.69 (m, 3H), 2.23-1.92 (m, 1H), 1.87-1.82 (m, 1H), 1.40-1.25 (m, 9H), 0.90-0.87 (t, *J* = 7.0 Hz, 3H).

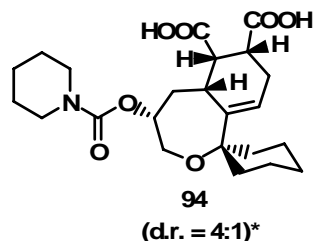
¹³C NMR (100 MHz, DMSO-*d*⁶): δ = 180.6, 178.9, 160.3, 142.6, 140.0, 129.4, 128.3, 127.5, 126.8, 125.4, 120.3, 79.3, 75.2, 71.9, 54.2, 46.9, 42.1, 35.6, 33.2, 32.4, 29.5, 28.2, 27.0, 20.0, 14.5.

HR-MS (FAB, 70 eV): *m/z* calculated for C₂₅H₃₃NO₇ = 459.2257, found = 459.2278 [M-H]⁺.

R_f = 0.5 (ethyl acetate: methanol = 9:1).

Yield: 11 mg (41 % after 7 steps).

8.11.18 Analytical data of compound 94:



* = isomeric ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, $\text{DMSO-}d^6$): δ = 5.48-5.46 (t, J = 3.5 Hz, 1H), 4.48-4.45 (m, 1H), 3.71-3.63 (m, 2H), 3.51-3.30 (m, 4H), 3.08-3.03 (m, 1H), 2.81-2.77 (m, 2H), 2.65-2.63 (m, 1H), 2.65-2.63 (t, J = 4.0 Hz, 1H), 1.90-1.77 (m, 5H), 1.73-1.69 (m, 5H), 1.58-1.43 (m, 6H), 1.22-1.17 (m, 2H).

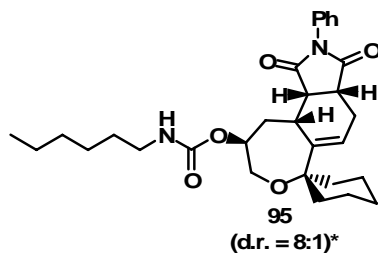
^{13}C NMR (100 MHz, $\text{DMSO-}d^6$): δ = 184.1, 177.4, 168.3, 154.7, 148.3, 137.0, 121.6, 79.8, 73.2, 66.8, 65.6, 60.7, 51.2, 50.3, 45.2, 37.6, 36.6, 35.1, 32.5, 30.5, 28.6, 27.3, 27.2, 26.7, 26.2, 24.9, 24.7, 22.3, 21.7.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{23}\text{H}_{32}\text{NO}_7$ = 434.2257, found = 434.2296 $[\text{M}-\text{H}]^+$.

R_f = 0.5 (ethyl acetate: methanol = 9:1).

Yield: 70 mg (34 % after 7 steps).

8.11.19 Analytical data of compound 95:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 7.50-7.45 (m, 2H), 7.41-7.39 (m, 1H), 7.31-7.27 (m, 2H), 5.82-5.78 (m, 1H), 4.77-4.73 (m, 1H), 3.61-3.58 (m, 1H), 3.26-3.19 (m, 2H), 3.16-3.09 (m, 2H), 2.80-2.74 (m, 1H), 2.53-2.44 (m, 1H), 2.07-1.82 (m, 2H), 1.71-1.57 (m, 6H), 1.48-1.43 (m, 4H), 1.30-1.25 (m, 8H), 0.89-0.86 (t, *J* = 6.0 Hz, 3H).

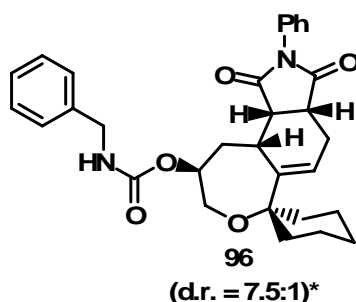
¹³C NMR (100 MHz, CDCl₃): δ = 179.4, 177.4, 156.2, 155.5, 149.4, 148.7, 132.0, 129.4, 129.3, 128.7, 126.6, 126.5, 121.5, 120.6, 78.5, 72.1, 69.7, 64.4, 54.1, 53.7, 44.9, 44.7, 41.2, 38.7, 31.9, 31.6, 31.4, 26.6, 26.0, 22.7, 21.9, 21.6, 14.2.

HR-MS (FAB, 70 eV): *m/z* calculated for C₃₀H₄₁N₂O₅ = 509.2937, found = 509.2971 [M+H]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 4: 1).

Yield: 78 mg (32% after 6 steps).

8.11.20 Analytical data of compound 96:



* = inseparable mixture, ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 7.48-7.45 (m, 3H), 7.41-7.39 (m, 1H), 7.31-7.27 (m, 3H), 7.23-7.17 (m, 3H), 7.13 (bs, 1H), 5.84-5.81 (dd, *J* = 2.7 Hz, 6.8 Hz, 1H), 4.81-4.76 (m, 1H), 4.31-4.28 (m, 2H), 3.83-3.63 (m, 1H), 3.26-3.16 (m, 1H), 3.14-3.09 (dd, *J* = 6.6 Hz, 9.9 Hz, 1H), 2.79-2.72 (m, 1H), 2.52-2.45 (m, 1H), 2.07-2.00 (m, 1H), 1.93-1.86 (m, 2H), 1.71-1.58 (m, 6H), 1.28-1.14 (m, 6H).

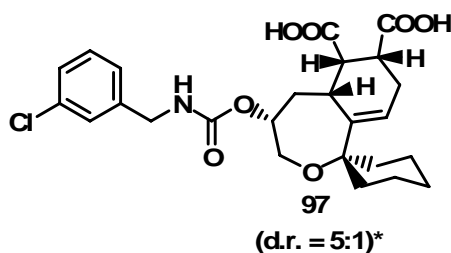
¹³C NMR (100 MHz, CDCl₃): δ = 179.4, 177.4, 155.6, 148.6, 140.8, 134.6, 131.9, 130.2, 129.4, 128.8, 127.7, 126.5, 125.7, 121.6, 79.5, 71.4, 69.7, 54.1, 47.6, 44.9, 43.8, 41.2, 38.7, 35.7, 31.9, 29.5, 27.1, 25.9, 21.9, 21.6.

HR-MS (FAB, 70 eV): m/z calculated for $C_{31}H_{34}N_2O_5 = 514.2468$, found = 514.2445
[M]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 4: 1).

Yield: 99 mg (40% after 6 steps).

8.11.21 Analytical data of compound 97:



* = inseparable mixture, ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, DMSO-*d*⁶): $\delta = 7.37-7.23$ (m, 5H), 5.48-5.50 (t, $J = 4.8$ Hz, 1H), 4.52-4.49 (m, 3H), 4.38-4.19 (m, 2H), 2.99-2.93 (m, 3H), 2.81-2.78 (m, 2H), 1.89-1.09 (m, 14H).

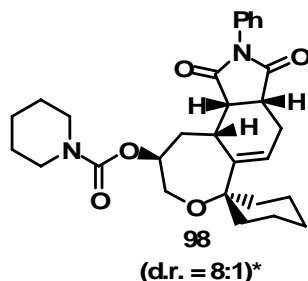
¹³C NMR (100 MHz, DMSO-*d*⁶): $\delta = 178.2, 177.1, 156.8, 145.5, 143.2, 133.9, 131.1, 127.8, 127.6, 127.5, 126.7, 79.8, 69.4, 56.7, 35.1, 34.5, 33.0, 30.5, 28.6, 27.3, 26.7$.

HR-MS (FAB, 70 eV): m/z calculated for $C_{25}H_{29}ClNO_7 = 490.1711$, found = 490.1759
[M-H]⁺.

R_f = 0.4 (ethyl acetate: methanol = 9:1).

Yield: 32 mg (15 % after 7 steps).

8.11.22 Analytical data of compound 98:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): δ = 7.46-7.43 (m, 2H), 7.40-7.35 (m, 1H), 7.29-7.26 (m, 2H), 5.81-5.78 (dd, J = 2.6 Hz, 6.9 Hz, 1H, major isomer), 5.77-5.75 (dd, J = 2.4 Hz, 7.2 Hz, 1H, minor isomer), 4.79-4.72 (m, 1H), 3.78-3.71 (m, 1H), 3.59-3.56 (m, 1H), 3.41-3.31 (m, 4H), 3.24-3.07 (m 2H), 2.79-2.72 (m, 1H), 2.53-2.43 (m, 1H), 2.05-2.01 (m, 1H), 1.91-1.87 (m, 1H), 1.71-1.42 (m, 16H).

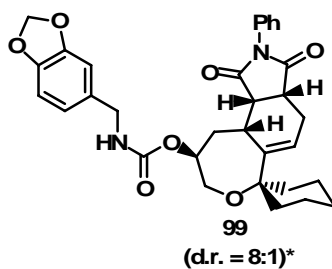
^{13}C NMR (100 MHz, CDCl_3): δ = 179.5, 177.6, 177.4, 155.0, 154.5, 149.4, 148.8, 132.0, 129.4, 129.3, 128.8, 128.7, 126.6, 126.5, 121.4, 120.6, 71.1, 69.7, 64.5, 63.5, 54.1, 53.6, 45.0, 44.8, 38.7, 36.6, 33.4, 31.9, 29.5, 27.1, 26.0, 24.5, 21.9, 21.6.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_5$ = 491.2624, found = 491.2600 $[\text{M}-\text{H}]^+$.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

Yield: 75 mg (32% after 6 steps).

8.11.23 Analytical data of compound 99:



* = inseparable isomers, determined by ^1H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 7.49-7.45 (m, 2H), 7.42-7.38 (m, 1H), 7.30-7.28 (m, 2H), 6.78-6.71 (m, 3H), 5.92 (s, 2H), 5.83-5.81 (dd, *J* = 2.6 Hz, 6.8 Hz, 1H), 4.80-4.75 (m, 1H), 4.24-4.21 (m, 2H), 3.63-3.59 (m, 1H), 3.26-3.16 (m, 2H), 3.14-3.09 (m, 1H), 2.78-2.74 (m, 1H), 2.52-2.44 (m, 1H), 2.09-2.06 (m, 1H), 1.92-1.86 (m, 2H), 1.71-1.57 (m, 5H), 1.28-1.16 (m, 5H).

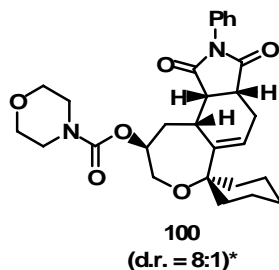
¹³C NMR (100 MHz, CDCl₃): δ = 179.4, 177.4, 148.7, 148.1, 147.1, 132.6, 131.9, 129.4, 129.3, 128.8, 128.6, 126.6, 126.5, 121.6, 121.0, 120.6, 108.4, 101.2, 78.5, 72.5, 71.2, 69.7, 64.4, 54.1, 53.7, 45.1, 44.7, 38.7, 31.9, 31.1, 29.5, 27.1, 26.0, 22.1, 21.9, 21.6.

HR-MS (FAB, 70 eV): *m/z* calculated for C₃₂H₃₄N₂O₇ = 558.2366, found = 558.2300 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

Yield: 87 mg (32 % after 6 steps).

8.11.24 Analytical data of compound 100:



*= inseparable mixture, determined by ¹H NMR

¹H NMR (400 MHz, CDCl₃): δ = 7.50-7.46 (m, 2H), 7.41-7.39 (m, 1H), 7.32-7.29 (m, 2H), 5.84-5.82 (dd, *J* = 2.6 Hz, 6.9 Hz, 1H), 4.84-4.77 (m, 1H), 3.68-3.66 (m, 1H), 3.62-3.59 (m, 4H), 3.48-3.36 (m, 4H), 3.27-3.20 (m, 1H), 3.16-3.10 (m, 1H), 2.84-2.76 (m, 1H), 2.53-2.39 (m, 1H), 2.09-2.05 (m, 1H), 1.92-1.89 (m, 1H), 1.75-1.58 (m, 6H), 1.30-1.25 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 179.3, 179.2, 177.5, 177.3, 154.9, 154.4, 149.2, 148.7, 131.9, 129.4, 128.7, 126.6, 126.4, 121.5, 120.7, 78.5, 71.7, 69.6, 66.7, 64.3, 63.3, 54.0,

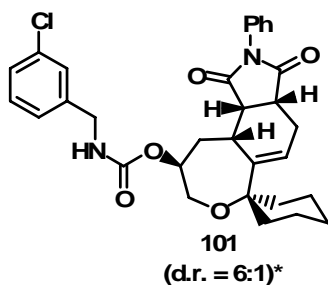
53.6, 44.9, 44.2, 38.7, 38.6, 36.6, 35.9, 33.3, 31.9, 29.4, 27.1, 25.9, 22.2, 22.0, 21.9, 21.6, 21.5.

HR-MS (FAB, 70 eV): m/z calculated for C₂₈H₃₄N₂O₆ = 494.2417, found = 494.2477 [M]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 4: 1).

Yield: 80 mg (34 % after 6 steps).

8.11.25 Analytical data of compound 101:



*= inseparable mixture, determined by ¹H NMR

¹H NMR (400 MHz, CDCl₃): δ = 7.48-7.45 (m, 2H), 7.41-7.39 (m, 1H), 7.31-7.28 (m, 3H), 7.23-7.18 (m, 3H), 7.13 (bs, 1H), 5.84-5.81 (dd, *J* = 2.7 Hz, 6.8 Hz, 1H), 4.81-4.76 (m, 1H), 4.31-4.29 (m, 2H), 3.83-3.60 (m, 1H), 3.26-3.16 (m, 1H), 3.14-3.09 (dd, *J* = 6.6 Hz, 9.9 Hz, 1H), 2.79-2.72 (m, 1H), 2.52-2.45 (m, 1H), 2.07-2.06 (m, 1H), 1.93-1.86 (m, 1H), 1.71-1.58 (m, 6H), 1.28-1.14 (m, 6H).

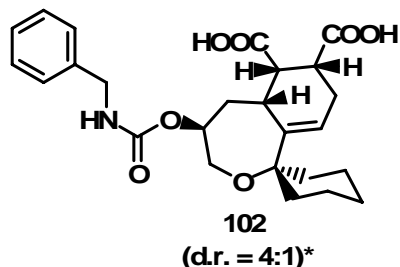
¹³C NMR (100 MHz, CDCl₃): δ = 179.4, 177.4, 156.3, 155.6, 148.6, 140.8, 134.6, 131.9, 130.2, 129.4, 128.8, 127.8, 126.6, 125.8, 121.7, 120.7, 79.5, 71.4, 69.7, 54.1, 47.6, 44.9, 43.9, 38.7, 36.5, 35.7, 31.9, 29.5, 27.1, 25.9, 21.9, 21.6.

HR-MS (FAB, 70 eV): m/z calculated for C₃₁H₃₃ClN₂O₅ = 548.2078, found = 548.2094 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

Yield: 83 mg (32 % after 7 steps).

8.11.26 Analytical data of compound 102:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, $\text{DMSO-}d^6$): δ = 7.75-7.72 (t, J = 6.1 Hz, 1H), 7.36-7.24 (m, 5H), 5.48-5.47 (t, J = 3.5 Hz, 1H), 4.48-4.46 (m, 1H), 4.20-4.17 (t, J = 5.3 Hz, 2H), 3.74-3.70 (m, 1H), 3.55-3.50 (m, 1H), 3.39-3.30 (m, 5H), 2.78-2.76 (m, 2H), 1.67-1.35 (m, 10H).

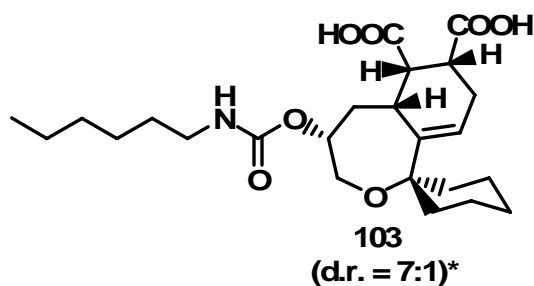
^{13}C NMR (100 MHz, $\text{DMSO-}d^6$): δ = 177.2, 156.6, 148.2, 140.6, 129.2, 129.1, 127.8, 121.6, 79.8, 72.5, 65.7, 51.5, 44.6, 43.2, 37.7, 36.8, 33.0, 32.6, 30.5, 27.3, 27.1, 26.7, 26.6, 22.3, 22.2.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{25}\text{H}_{31}\text{NO}_7$ = 457.2101, found = 457.2155 $[\text{M}]^+$.

R_f = 0.4 (ethyl acetate: methanol = 9: 1).

Yield: 45 mg (20% after 7 steps).

8.11.27 Analytical data of compound 103:



* = inseparable mixture ratio determined by ^1H NMR spectroscopy

¹H NMR (400 MHz, DMSO-*d*⁶): δ = 5.48-5.47 (t, *J* = 4.3 Hz, 1H), 4.48-4.42 (m, 1H), 3.73-3.62 (m, 5H), 3.55-3.47 (m, 5H), 3.01-2.92 (m, 3H), 2.82-2.76 (m, 3H), 1.85-1.37 (m, 14H), 0.90-0.87 (t, *J* = 6.9 Hz, 3H).

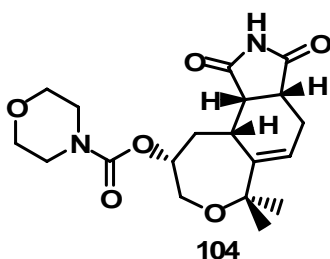
¹³C NMR (100 MHz, DMSO-*d*⁶): δ = 176.8, 159.3, 156.0, 136.8, 123.5, 121.3, 120.3, 79.6, 74.3, 69.5, 51.9, 41.3, 32.3, 31.6, 30.3, 29.9, 26.6, 25.9, 22.7, 22.1.

HR-MS (FAB, 70 eV): *m/z* calculated for C₂₄H₃₇NO₇ = 451.257, found = 451.2592 [M]⁺.

R_f = 0.4 (dichloromethane: methanol = 9: 1).

Yield: 25 mg (15 % after 7 steps).

8.11.28 Analytical data of compound 104:



¹H NMR (400 MHz, CDCl₃): δ = 8.91 (bs, 1H), 5.81-5.78 (dd, *J* = 2.8 Hz, 6.8 Hz, 1H), 4.77-4.69 (m, 1H), 3.54-3.65 (m, 6H), 3.42-3.30 (m, 5H), 3.11-3.00 (m, 3H), 2.67-2.58 (m, 1H), 2.43-2.33 (m, 1H), 2.05-1.98 (m, 1H), 1.31 (s, 3H), 1.22 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 180.7, 178.8, 154.5, 147.9, 124.4, 121.6, 78.4, 73.0, 66.7, 65.2, 46.1, 44.4, 39.8, 32.7, 31.8, 29.5, 27.4, 27.1, 22.0, 20.8.

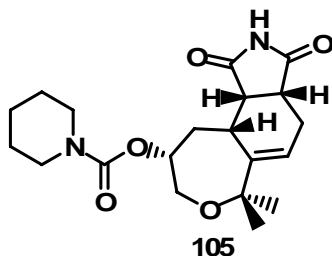
HR-MS (FAB, 70 eV): *m/z* calculated for C₁₉H₂₅N₂O₆ = 377.1791, found = 377.1723 [M-H]⁺.

R_f = 0.5 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 5.6° (c = 1, CHCl₃).

Yield: 45 mg (23 % after 6 steps).

8.11.29 Analytical data of compound 105:



¹H NMR (400 MHz, CDCl₃): δ = 5.79-5.77 (dd, J = 2.8 Hz, 6.9 Hz, 1H), 4.75-4.68 (m, 1H), 3.55-3.51 (m, 1H), 3.29-3.23 (m, 4H), 3.11-3.04 (dd, J = 9.6 Hz, 17.7 Hz, 2H), 3.00-2.97 (dd, J = 6.6 Hz, 9.8 Hz, 1H), 2.66-2.56 (m, 1H), 2.42-2.35 (m, 1H), 2.02-1.98 (m, 1H), 1.52-1.50 (m, 4H), 1.47-1.44 (m, 4H), 1.30 (s, 3H), 1.20 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 180.7, 178.7, 154.5, 148.1, 121.4, 78.2, 72.5, 65.4, 54.1, 46.1, 44.9, 39.8, 32.7, 31.9, 31.1, 29.5, 27.5, 27.1, 24.5, 22.0, 22.2.

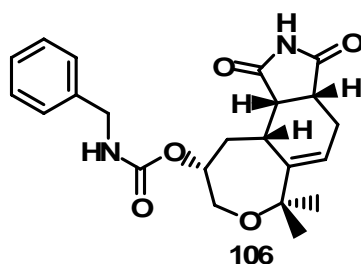
HR-MS (FAB, 70 eV): m/z calculated for C₂₀H₂₇N₂O₅ = 375.1998 found = 375.1920 [M-H]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 3.5: 0.5).

[α]_D²⁰: + 10.1° (c = 1, CHCl₃).

Yield: 53 mg (22% after 6 steps).

8.11.30 Analytical data of compound 106:



¹H NMR (400 MHz, CDCl₃): δ = 8.95 (bs, 1H), 7.29-7.19 (m, 5H), 5.78-5.75 (dd, J = 2.8 Hz, 6.7 Hz, 1H), 4.75-4.69 (m, 1H), 4.35-4.23 (m, 2H), 3.56-3.53 (m, 1H), 3.24-3.19

(m, 1H), 3.07-3.01 (m, 2H), 2.99-2.95 (m, 1H), 2.65-2.55 (m, 1H), 2.36-2.32 (m, 1H), 2.02-1.98 (m, 2H), 1.29 (s, 3H), 1.22 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 180.7, 178.8, 156.3, 155.6, 147.8, 138.6, 128.8, 127.7, 121.7, 78.5, 72.6, 69.8, 65.2, 54.1, 46.1, 45.2, 39.7, 32.6, 31.9, 31.1, 29.5, 27.4.

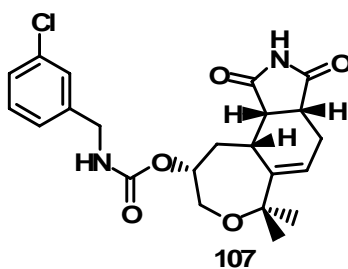
HR-MS (FAB, 70 eV): m/z calculated for C₂₂H₂₇N₂O₅ = 399.1842, found = 399.1893 [M+H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 30.6° (c = 1, CHCl₃).

Yield: 49mg (20% after 7 steps).

8.11.31 Analytical data of compound 107:



¹H NMR (400 MHz, CDCl₃): δ = 8.94 (bs, 1H), 7.31-7.15 (m, 4H), 5.85-5.83 (dd, J = 2.8 Hz, 6.7 Hz, 1H), 4.83-4.75 (m, 1H), 4.35-4.32 (m, 2H), 3.62-3.59 (m, 1H), 3.32-3.27 (m, 1H), 3.13-3.03 (m, 3H), 2.63-2.56 (m, 1H), 2.43-2.41 (m, 1H), 2.07-2.02 (m, 2H), 1.36 (s, 3H), 1.28 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 180.7, 178.8, 155.7, 147.7, 140.7, 134.6, 130.1, 127.8, 125.8, 121.7, 72.8, 69.8, 65.1, 54.1, 46.1, 44.6, 39.7, 31.9, 29.5, 27.4, 27.1.

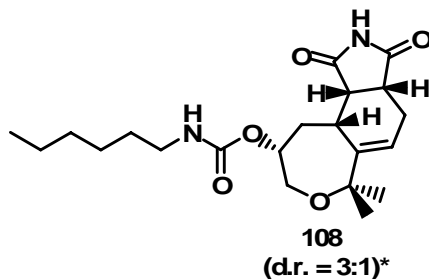
HR-MS (FAB, 70 eV): m/z calculated for C₂₂H₂₄ClN₂O₅ = 431.1452, found = 431.1400 [M-H]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 2.5° (c = 1, CHCl₃).

Yield: 44 mg (16% after 6 steps).

8.11.32 Analytical data of compound 108:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): δ = 9.09 (bs, 1H), 5.78-5.76 (dd, J = 2.5 Hz, 6.7 Hz, 1H), 4.67-4.65 (m, 1H), 3.55-3.37 (m, 1H), 3.24-3.18 (m, 1H), 3.10-2.96 (m, 4H), 2.65-2.55 (m, 1H), 2.40-2.29 (m, 1H), 1.99-1.95 (m, 1H), 1.45-1.42 (m, 2H), 1.29-1.20 (m, 14H), 0.84-0.82 (t, J = 5.9 Hz, 3H).

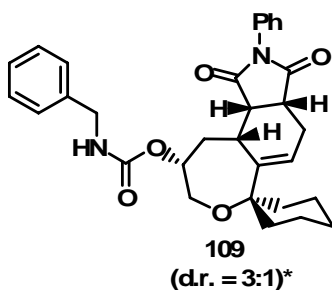
^{13}C NMR (100 MHz, CDCl_3): δ = 180.9, 178.9, 171.4, 156.2, 155.5, 147.9, 135.3, 121.6, 120.6, 72.2, 70.7, 69.8, 65.2, 60.6, 54.1, 46.1, 41.2, 39.7, 33.2, 31.9, 31.6, 30.9, 30.0, 29.4, 27.8, 27.1, 26.6, 22.7, 14.2.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{21}\text{H}_{31}\text{N}_2\text{O}_5$ = 391.2311, found = 391.2397 $[\text{M}-\text{H}]^+$.

R_f = 0.3 (cyclohexane: ethyl acetate = 3: 2).

Yield: 78 mg (31 % after 6 steps).

8.11.33 Analytical data of compound 109:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 7.49-7.45 (m, 2H), 7.41-7.39 (m, 1H), 7.34-7.26 (m, 7H), 5.83-5.81 (dd, *J* = 2.4 Hz, 6.9 Hz, 1H), 4.81-4.77 (m, 1H), 4.37-4.32 (m, 2H), 4.15-4.04 (m, 1H), 3.80-3.70 (m, 1H), 3.67-3.60 (m, 1H), 3.24-3.19 (m, 1H), 3.13-3.11 (m, 1H), 2.80-2.72 (m, 1H), 2.53-2.47 (m, 1H), 2.40-2.34 (m, 1H), 1.96-1.87 (m, 2H), 1.77-1.55 (m, 6H), 1.30-1.11 (m, 5H).

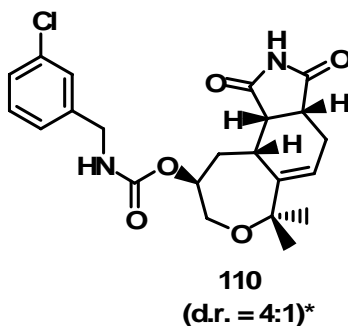
¹³C NMR (100 MHz, CDCl₃): δ = 179.4, 177.4, 171.4, 155.6, 148.7, 138.7, 131.9, 129.5, 129.3, 128.8, 128.7, 127.7, 126.5, 126.3, 121.6, 120.7, 79.5, 71.8, 69.7, 64.4, 60.6, 54.1, 53.7, 48.1, 47.9, 45.2, 44.7, 43.9, 42.2, 39.2, 38.4, 34.6, 31.9, 29.5, 27.9, 27.1, 23.9, 21.9, 21.6, 20.9, 14.4.

HR-MS (FAB, 70 eV): *m/z* calculated for C₃₁H₃₄N₂O₅ = 514.2468, found = 514.2445 [M]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 4: 1).

Yield: 31 mg (15 % after 6 steps).

8.11.34 Analytical data of compound 110:



* = inseparable mixture, ratio determined by ¹H NMR

¹H NMR (400 MHz, CDCl₃): δ = 8.68 (bs, 1H), 7.30-7.16 (m, 4H), 5.76-5.75 (dd, *J* = 2.6 Hz, 6.5 Hz, 1H), 4.71-4.77 (m, 1H), 4.34-4.25 (m, 2H), 3.78-3.74 (m, 1H), 3.46-3.40 (m, 1H), 3.10-2.98 (m, 3H), 2.67-2.56 (m, 2H), 2.38-2.26 (m, 1H), 1.86-1.82 (m, 1H), 1.32 (s, 3H), 1.24 (s, 3H).

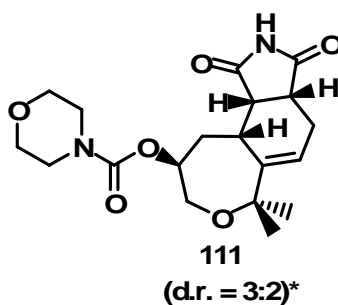
¹³C NMR (100 MHz, CDCl₃): δ = 180.6, 178.8, 148.3, 147.8, 141.5, 140.8, 134.6, 130.3, 130.1, 128.0, 127.8, 127.7, 126.1, 120.7, 69.8, 54.0, 45.7, 44.7, 39.5, 33.3, 31.9, 30.9, 29.5, 27.8, 27.1.

HR-MS (FAB, 70 eV): m/z calculated for C₂₂H₂₄ClN₂O₅ = 431.1452, found = 431.1400 [M-H]⁺.

R_f = 0.2 (cyclohexane: ethyl acetate = 3: 2).

Yield: 25mg (10% after 6 steps).

8.11.35 Analytical data of compound 111:



* = inseparable mixture, ratio determined by ¹H NMR

¹H NMR (400 MHz, CDCl₃): δ = 8.70 (bs, 1H), 5.82-5.79 (dd, *J* = 2.7 Hz, 6.8 Hz, 1H), 4.76-4.74 (m, 1H), 3.68-3.53 (m, 5H), 3.43-3.37 (m, 5H), 3.12-3.00 (m, 3H), 2.71-2.62 (m, 1H), 2.42-2.29 (m, 1H), 2.05-1.78 (m, 1H), 1.35 (s, 3H), 1.26 (s, 3H).

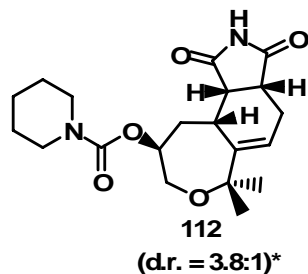
¹³C NMR (100 MHz, CDCl₃): δ = 180.5, 178.7, 178.5, 154.9, 148.5, 147.9, 120.6, 78.4, 71.7, 66.8, 65.2, 64.4, 54.0, 46.1, 45.8, 39.5, 36.7, 33.4, 30.9, 29.5, 27.9, 27.4, 27.1, 21.7.

HR-MS (FAB, 70 eV): m/z calculated for C₁₉H₂₅N₂O₆ = 377.1791, found = 377.1723 [M-H]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 3: 2).

Yield: 30 mg (15 % after 6 steps).

8.11.36 Analytical data of compound 112:



* = inseparable mixture, ratio determined by ^1H NMR

^1H NMR (400 MHz, CDCl_3): δ = 5.76-5.73 (dd, J = 2.3 Hz, 7.0 Hz, 1H), 4.75-4.72 (m, 1H), 3.78-3.73 (m, 1H), 3.57-3.32 (m, 4H), 3.12-3.07 (m, 1H), 3.05-3.00 (m, 2H), 2.67-2.61 (m, 1H), 2.36-2.29 (m, 1H), 1.80-1.76 (m, 1H), 1.60-1.53 (m, 8H), 1.34 (s, 3H), 1.27 (s, 3H).

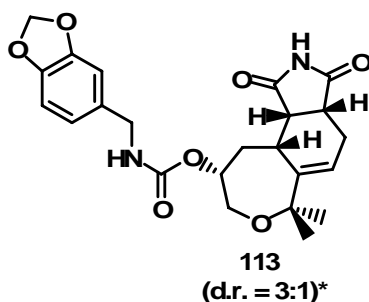
^{13}C NMR (100 MHz, CDCl_3): δ = 180.6, 178.6, 154.9, 148.6, 148.1, 120.4, 71.1, 69.8, 54.1, 45.9, 39.5, 33.4, 31.9, 31.1, 29.5, 27.9, 27.1, 24.6, 24.5, 21.7.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_5$ = 375.1998, found = 375.1900 $[\text{M}-\text{H}]^+$.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

Yield: 28 mg (15 % after 6 steps).

8.11.37 Analytical data of compound 113:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 9.12 (bs, 1H), 6.76-6.63 (m, 3H), 5.89 (s, 2H), 5.78-5.76 (dd, *J* = 2.6 Hz, 6.5 Hz, 1H), 4.73-4.67 (m, 1H), 4.21-4.09 (m, 2H), 3.55-3.37 (m, 1H), 3.23-3.18 (m, 1H), 3.08-2.95 (m, 2H), 2.55-2.61 (m, 1H), 2.36-2.27 (m, 1H), 2.00-1.80 (m, 1H), 1.31-1.29 (m, 2H), 1.22 (s, 3H), 1.21 (s, 3H).

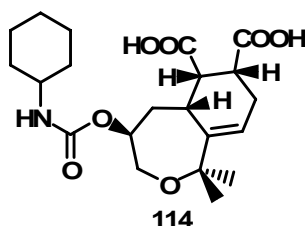
¹³C NMR (100 MHz, CDCl₃): δ = 181.0, 179.0, 171.5, 156.3, 155.6, 148.1, 148.0, 147.8, 147.0, 132.6, 121.7, 121.1, 120.8, 120.7, 108.5, 101.3, 78.5, 72.6, 69.9, 54.1, 46.1, 45.8, 45.1, 39.7, 33.3, 32.7, 31.9, 30.9, 29.5, 27.8, 27.1, 24.1, 21.7, 21.3.

HR-MS (FAB, 70 eV): *m/z* calculated for C₂₃H₂₅N₂O₇ = 441.174, found = 441.1782 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

Yield: 82 mg (30 % after 6 steps).

8.11.38 Analytical data of compound 114:



¹H NMR (400 MHz, DMSO-*d*⁶): δ = 8.01 (bs, 1H), 5.49-5.47 (t, *J* = 3.7 Hz, 1H), 5.08-5.03 (m, 1H), 3.46-3.36 (m, 4H), 3.26-3.09 (m, 1H), 2.82-2.64 (m, 1H), 1.99-1.55 (m, 3H), 1.33-0.97 (m, 16H).

¹³C NMR (100 MHz, DMSO-*d*⁶): δ = 179.1, 178.9, 167.3, 166.1, 131.5, 130.3, 79.3, 74.9, 69.4, 56.7, 47.8, 43.7, 41.4, 41.1, 40.8, 40.2, 40.0, 38.7, 35.7, 33.7, 30.5, 28.1, 24.4, 21.2.

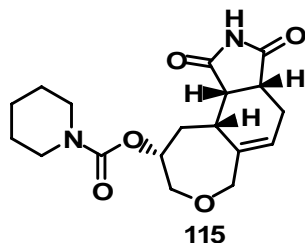
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₁H₃₀NO₇ = 408.2101, found = 408.2196 [M-H]⁺.

R_f = 0.5 (ethyl acetate: methanol = 9:1).

[α]_D²⁰: - 24.8° (c = 1, CHCl₃).

Yield: 21 mg (16 % after 7 steps).

8.11.39 Analytical data of compound 115:



¹H NMR (400 MHz, CDCl₃): δ = 5.83-5.80 (t, J = 5.0 Hz, 1H), 4.26-4.16 (m, 1H), 4.08-3.95 (m, 2H), 3.93-3.89 (m, 2H), 3.39-3.34 (m, 4H), 3.19-3.15 (m, 2H), 3.08-3.05 (m, 1H), 2.68-2.56 (m, 2H), 2.38-2.32 (m, 1H), 2.23-2.19 (m, 2H), 1.57-1.41 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 178.6, 177.4, 153.3, 141.3, 140.8, 124.0, 123.1, 74.2, 73.7, 72.6, 71.6, 68.5, 60.7, 52.8, 45.4, 43.8, 40.8, 33.9, 30.7, 28.3, 23.3.

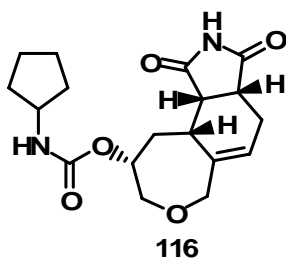
HR-MS (FAB, 70 eV): m/z calculated for C₁₈H₂₅N₂O₅ = 349.1685, found = 349.1629 [M+H]⁺.

R_f = 0.2 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 15.8° (c = 2, CHCl₃).

Yield: 32 mg (20 % after 6 steps).

8.11.40 Analytical data of compound 116:



¹H NMR (400 MHz, CDCl₃): δ = 5.75-5.73 (t, J = 3.7 Hz, 1H), 4.09-4.03 (m, 1H), 3.99-3.95 (m, 1H), 3.91-3.87 (m, 4H), 3.79-3.77 (d, J = 6.8 Hz, 4H), 3.27-3.21 (dd, J = 8.2 Hz, 15.3 Hz, 1H), 3.03-3.02 (t, J = 4.0 Hz, 1H), 2.23-2.17 (m, 1H), 2.08-2.02 (m, 2H), 1.75-1.62 (m, 6H), 1.27-1.20 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ = 168.4, 167.5, 149.1, 143.2, 136.7, 134.8, 129.5, 128.9, 126.7, 120.9, 79.2, 78.0, 70.2, 68.5, 52.9, 52.6, 47.2, 37.4, 35.6, 31.3, 29.4, 28.9, 27.1, 25.9, 21.9, 21.4.

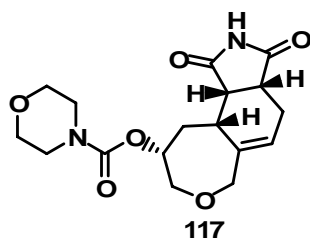
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_5$ = 349.1685, found = 349.1622 $[\text{M}+\text{H}]^+$.

R_f = 0.3 (cyclohexane: ethyl acetate = 3: 2).

$[\alpha]_D^{20}$: + 2.5° (c = 2, CHCl_3).

Yield: 20 mg (26 % after 7 steps).

8.11.41 Analytical data of compound 117:



^1H NMR (400 MHz, CDCl_3): δ = 8.15 (bs, 1H), 4.35-4.25 (m, 1H), 4.15-4.05 (m, 2H), 3.98-3.90 (m, 1H), 3.70-3.60 (m, 4H), 3.52-3.37 (m, 4H), 3.22-3.18 (m, 1H), 3.17-3.09 (m, 1H), 2.87-2.62 (m, 3H), 2.47-2.23 (m, 4H), 1.83-1.66 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ = 179.5, 177.5, 158.4, 140.2, 120.6, 80.9, 75.2, 71.9, 67.9, 66.3, 52.9, 48.9, 48.5, 42.1, 32.7, 29.1, 26.9.

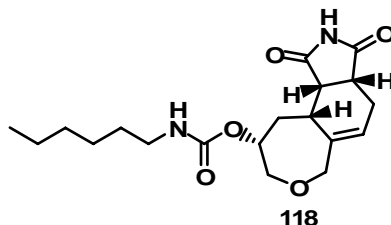
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_6$ = 351.1478, found = 351.1424 $[\text{M}+\text{H}]^+$.

R_f = 0.3 (cyclohexane: ethyl acetate = 3: 2).

$[\alpha]_D^{20}$: + 6.5° (c = 1, CHCl_3).

Yield: 10 mg (20 % after 5 steps).

8.11.42 Analytical data of compound 118:



¹H NMR (400 MHz, CDCl₃): δ = 5.83-5.82 (t, J = 3.5 Hz, 1H), 4.23-4.25 (dd, J = 13.3 Hz, 19.5 Hz, 1H), 4.11-4.09 (m, 2H), 3.95-3.89 (t, J = 11.8 Hz, 2H), 3.30-3.25 (dd, J = 6.8 Hz, 13.5 Hz, 1H), 3.19-3.04 (m, 6H), 2.73-2.57 (m, 2H), 2.36-2.34 (m, 1H), 2.21-2.19 (m, 1H), 1.50-1.31 (m, 5H), 1.28-1.22 (m, 5H), 0.88-0.85 (t, J = 6.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 179.9, 178.6, 161.4, 141.9, 125.3, 97.4, 74.9, 74.5, 54.0, 46.5, 42.1, 41.3, 38.4, 35.2, 31.5, 31.3, 30.1, 29.9, 29.4, 27.1, 26.2, 22.7, 14.2.

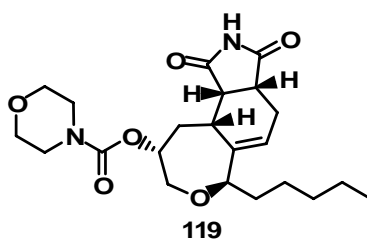
HR-MS (FAB, 70 eV): m/z calculated for C₁₉H₂₇O₅ = 363.1998, found = 363.1924 [M-H]⁺.

R_f = 0.5 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: - 10.8° (c = 1, CHCl₃).

Yield: 30 mg (20 % after 6 steps).

8.11.43 Analytical data of compound 119:



¹H NMR (400 MHz, CDCl₃): δ = 8.44 (bs, 1H), 5.76-5.74 (t, J = 4.8 Hz, 1H), 4.75-4.68 (m, 1H), 3.93-3.90 (m, 1H), 3.86-3.83 (t, J = 6.4 Hz, 1H), 3.66-3.62 (m, 4H), 3.47-3.40 (m, 4H), 3.36-3.31 (t, J = 11.0 Hz, 1H), 3.18-3.12 (m, 1H), 3.08-3.04 (dd, J = 5.9 Hz, 9.5

Hz, 1H), 2.62-2.54 (m, 1H), 2.45-2.41 (m, 1H), 2.13-2.09 (m, 1H), 1.90-1.81 (m, 1H), 1.58-1.48 (m, 1H), 1.46-1.37 (m, 2H), 1.28-1.24 (m, 6H), 0.88-0.85 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 180.1, 178.5, 154.4, 143.9, 135.3, 122.7, 82.4, 73.4, 71.3, 66.8, 53.5, 46.2, 40.7, 34.2, 33.1, 32.4, 31.9, 25.7, 22.9, 22.7, 14.2$.

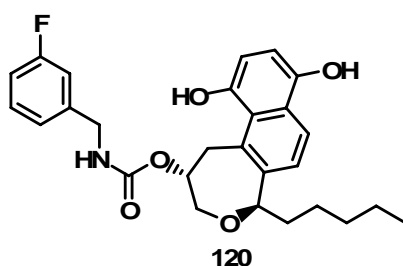
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_6 = 420.226$, found = 420.2295 $[\text{M}]^+$.

$R_f = 0.3$ (cyclohexane: ethyl acetate = 3: 2).

$[\alpha]_D^{20} : +12.0^\circ$ ($c = 1, \text{CHCl}_3$).

Yield: 22 mg (16 % after 7 steps).

8.11.44 Analytical data of compound 120:



^1H NMR (400 MHz, CDCl_3): $\delta = 8.03-8.01$ (d, $J = 8.0$ Hz, 1H), 7.53-7.46 (m, 2H), 7.05-6.92 (m, 4H), 6.90-6.89 (m, 2H), 5.19-5.16 (m, 1H), 4.85-4.82 (m, 2H), 4.45-4.43 (m, 1H), 4.35-4.34 (m, 1H), 4.21-4.14 (m, 1H), 3.92-3.91 (m, 1H), 3.50-3.42 (m, 1H), 1.95-1.89 (m, 1H), 1.80-1.73 (m, 1H), 1.56-1.54 (m, 2H), 1.34-1.25 (m, 4H), 0.91-0.88 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 163.9, 160.3, 152.0, 147.4, 142.5, 140.7, 137.2, 132.4, 129.4, 127.2, 126.3, 123.9, 120.9, 118.2, 114.0, 110.2, 109.5, 85.9, 78.2, 75.6, 45.3, 40.0, 33.6, 32.9, 30.4, 23.6, 22.7, 14.2$.

^{19}F NMR (338.6 MHz, CDCl_3): -120.1.

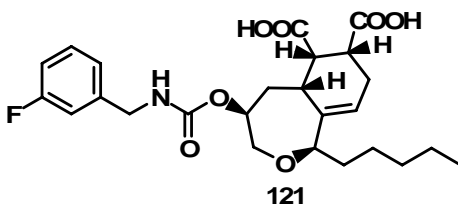
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{27}\text{H}_{30}\text{FNO}_5 = 467.2108$, found = 467.2198 $[\text{M}]^+$.

$R_f = 0.3$ (cyclohexane: ethyl acetate = 3: 2).

$[\alpha]_D^{20}$: + 36.1° (c = 1, CHCl₃).

Yield: 12 mg (15 % after 6 steps).

8.11.45 Analytical data of compound 121:



¹H NMR (400 MHz, DMSO-*d*⁶): δ = 7.79-7.78 (m, 1H), 7.40-7.38 (m, 1H), 7.09-7.07 (m, 3H), 5.36-5.34 (t, *J* = 5.3 Hz, 1H), 4.27-4.19 (m, 2H), 4.01-3.94 (m, 1H), 3.87-3.85 (m, 1H), 3.64-3.37 (m, 3H), 2.76-2.64 (m, 2H), 1.80-1.75 (m, 2H), 1.53-1.44 (m, 2H), 1.29-1.27 (m, 6H), 0.90-0.88 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, DMSO-*d*⁶): δ = 178.5, 178.2, 160.5, 156.2, 147.3, 145.9, 141.8, 136.5, 121.6, 120.5, 115.5, 110.9, 78.0, 76.2, 69.1, 51.8, 45.9, 42.1, 39.9, 32.0, 30.5, 29.1, 27.2, 26.9, 25.6, 22.9, 14.6.

¹⁹F NMR (338.6 MHz, DMSO-*d*⁶): -122.2.

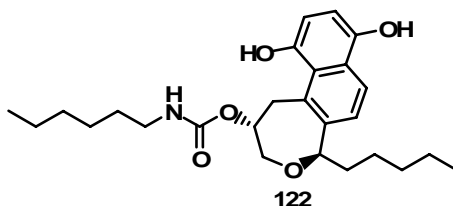
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₅H₃₁FNO₇ = 476.2163, found = 476.2122 [M-H]⁺.

R_f = 0.4 (ethyl acetate: methanol = 9:1).

$[\alpha]_D^{20}$: - 2.9° (c = 1, CHCl₃).

Yield: 16 mg (20 % after 7 steps).

8.11.46 Analytical data of compound 122:



¹H NMR (400 MHz, CDCl₃): δ = 8.03-8.01 (d, *J* = 8.0 Hz, 1H), 7.49-7.48 (d, *J* = 8.0 Hz, 1H), 6.92-6.86 (dd, *J* = 10.0 Hz, 12.8 Hz, 2H), 5.09-5.06 (m, 1H), 4.83-4.79 (dd, *J* = 4.4 Hz, 8.8 Hz, 1H), 4.50-4.48 (m, 1H), 4.21-4.18 (m, 1H), 4.02-3.98 (m, 1H), 3.49-3.44 (dd, *J* = 9.2 Hz, 12.0 Hz, 1H), 3.16-3.13 (m, 2H), 1.94-1.89 (m, 1H), 1.81-1.75 (m, 1H), 1.59-1.42 (m, 4H), 1.36-1.25 (m, 11H), 0.91-0.85 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 160.8, 152.0, 146.9, 138.3, 129.0, 126.3, 122.9, 119.2, 110.7, 108.2, 80.3, 76.5, 72.0, 42.9, 36.2, 33.6, 32.7, 30.3, 26.9, 25.6, 22.7, 22.2, 14.6, 14.2.

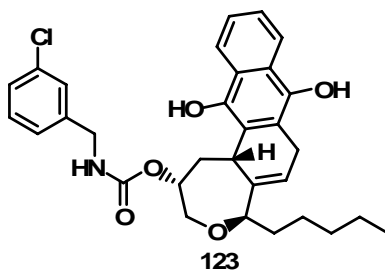
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₆H₃₇NO₅ = 443.2672, found = 443.2691 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 5.0° (c = 2, CHCl₃).

Yield: 8 mg (15 % after 6 steps).

8.11.47 Analytical data of compound 123:



¹ NMR (400 MHz, CDCl₃): δ = 8.23 (bs, 1H), 8.14-8.06 (m, 2H), 7.76-7.69 (m, 2H), 7.21-7.20 (m, 3H), 7.06-7.05 (m, 1H), 5.73-5.71 (t, *J* = 3.7 Hz, 1H), 5.29-5.25 (m, 1H), 5.01-4.94 (m, 1H), 4.88-4.85 (m, 2H), 4.29-4.28 (m, 2H), 4.13-4.10 (m, 1H), 3.95-3.88 (m, 2H), 2.02-1.98 (m, 1H), 1.91-1.86 (m, 1H), 1.34-1.32 (m, 2H), 1.24-1.18 (m, 6H), 0.85-0.81 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 183.5, 183.4, 142.9, 140.7, 134.7, 133.9, 132.5, 130.7, 130.1, 126.7, 126.4, 120.7, 117.4, 84.5, 79.5, 74.0, 47.6, 43.9, 41.3, 38.4, 35.8, 33.6, 31.8, 27.5, 25.6, 25.2, 24.1, 22.7, 20.7, 14.2.

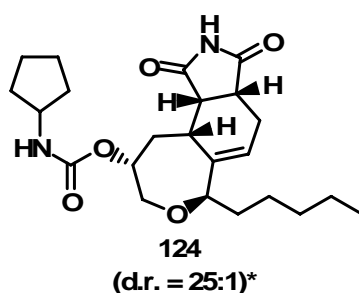
HR-MS (FAB, 70 eV): m/z calculated for C₃₁H₃₄ClNO₅ = 535.2126, found = 535.2169 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

[α]_D²⁰: + 20.1° (c = 2, CHCl₃).

Yield: 23 mg (15 % after 6 steps).

8.11.48 Analytical data of compound 124:



* = inseparable mixture, ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 8.51 (bs, 1H), 5.77-5.74 (t, *J* = 4.8 Hz, 1H), 4.76-4.69 (m, 1H), 3.95-3.91 (m, 1H), 3.87-3.84 (t, *J* = 6.4 Hz, 1H), 3.56-3.54 (m, 1H), 3.38-3.33 (dd, *J* = 10.6 Hz, 11.5 Hz, 1H), 3.17-3.12 (m, 1H), 3.08-3.04 (m, 1H), 2.84-2.80 (m, 1H), 2.57-2.55 (t, *J* = 4.7 Hz, 1H), 2.46-2.39 (m, 1H), 2.14-2.11 (m, 1H), 1.92-1.83 (m, 1H), 1.58-1.54 (m, 1H), 1.48-1.45 (m, 1H), 1.28-1.26 (m, 13H), 0.88-0.85 (t, *J* = 6.8 Hz, 3H).

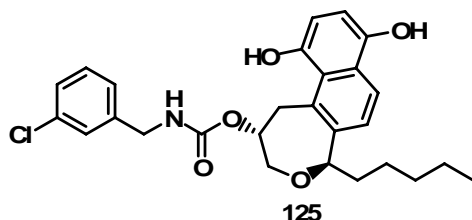
¹³C NMR (100 MHz, CDCl₃): δ = 180.2, 178.5, 154.3, 143.9, 122.7, 118.9, 115.9, 115.7, 82.4, 73.4, 69.8, 54.0, 50.6, 46.2, 40.7, 34.2, 33.1, 31.9, 29.5, 25.7, 22.9, 14.2.

HR-MS (FAB, 70 eV): m/z calculated for C₂₃H₃₃N₂O₅ = 417.2468, found = 417.2457 [M-H]⁺.

R_f = 0.5 (cyclohexane: ethyl acetate = 3: 2).

Yield: 30 mg (16 % after 6 steps).

8.11.49 Analytical data of compound 125:



$^1\text{H NMR}$ (400 MHz, CDCl_3): δ = 8.02-8.00 (d, J = 8.0 Hz, 1H), 7.48-7.45 (d, J = 8.0 Hz, 1H), 7.31-7.28 (m, 1H), 7.26-7.24 (m, 2H), 7.17-7.16 (m, 1H), 6.91-6.83 (m, 2H), 5.21-5.15 (m, 1H), 4.87-4.82 (m, 2H), 4.42-4.38 (m, 1H), 4.33-4.31 (m, 1H), 3.90-3.86 (m, 1H), 3.49-3.43 (t, J = 10.4 Hz, 1H), 1.92-1.90 (m, 1H), 1.80-1.74 (m, 1H), 1.60-1.52 (m, 2H), 1.33-1.29 (m, 4H), 0.91-0.87 (t, J = 6.8 Hz, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ = 162.5, 162.5, 151.9, 146.9, 143.9, 141.7, 135.0, 131.2, 130.4, 128.9, 127.1, 124.9, 118.9, 118.0, 112.1, 110.2, 108.5, 83.9, 76.2, 75.5, 46.3, 41.0, 34.5, 33.2, 31.4, 24.6, 21.7, 14.0.

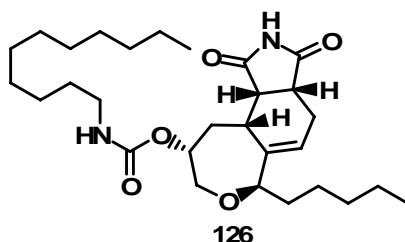
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{27}\text{H}_{30}\text{ClNO}_5$ = 483.1813, found = 483.1839 $[\text{M}]^+$.

R_f = 0.3 (cyclohexane: ethyl acetate = 3: 2).

$[\alpha]_D^{20}$: + 2.9° (c = 1, CHCl_3).

Yield: 12 mg (20 % after 6 steps)

8.11.50 Analytical data of compound 126:



¹H NMR (400 MHz, CDCl₃): δ = 8.51 (bs, 1H), 5.77-5.74 (t, *J* = 5.0 Hz, 1H), 4.87-4.40 (m, 1H), 3.91-3.83 (m, 2H), 3.13-3.04 (m, 5H), 2.83-2.80 (m, 1H), 2.59-2.55 (m, 1H), 2.45-2.39 (m, 1H), 1.84-1.78 (m, 1H), 1.61-1.53 (m, 3H), 1.47-1.24 (m, 26H), 0.88-0.85 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 180.2, 178.5, 158.7, 144.0, 122.7, 82.4, 72.5, 71.3, 53.6, 46.2, 41.3, 41.0, 40.6, 34.2, 33.2, 31.9, 30.4, 30.1, 29.8, 29.7, 29.7, 29.5, 27.1, 27.0, 25.7, 22.9, 22.8, 14.3, 14.2.

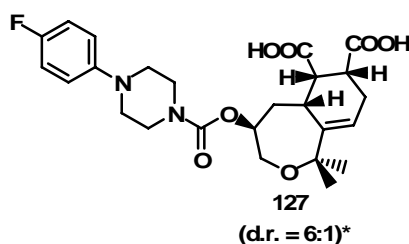
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₉H₄₇N₂O₅ = 503.3563, found = 503.3581 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 25.8° (*c* = 2, CHCl₃).

Yield: 50 mg (23 % after 6 steps).

8.11.51 Analytical data of compound 127:



* = inseparable mixture, ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, DMSO-*d*⁶): δ = 7.11-7.06 (m, 4H), 5.51-5.48 (t, *J* = 5.0 Hz, 1H), 5.08-5.03 (m, 10H), 3.54-3.37 (m, 2H), 2.72-2.64 (m, 1H), 1.94-1.69 (m, 3H), 1.35-0.97 (m, 8H).

¹³C NMR (100 MHz, DMSO-*d*⁶): δ = 180.1, 178.5, 167.3, 163.2, 154.6, 148.7, 118.8, 116.1, 79.4, 74.9, 69.4, 56.7, 49.9, 47.7, 43.7, 41.4, 40.6, 40.0, 38.7, 36.7, 35.6, 33.7, 32.9, 31.7, 27.3, 26.7, 24.5, 21.2.

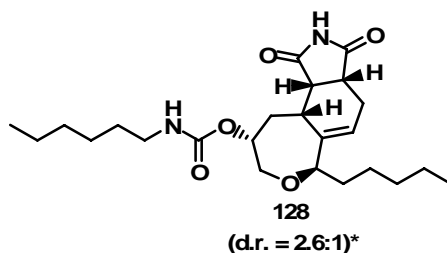
¹⁹F NMR (338.6 MHz, DMSO-*d*⁶): -123.8.

HR-MS (FAB, 70 eV): *m/z* calculated for C₂₅H₃₁FN₂O₇ = 490.2115, found = 490.2199 [M]⁺.

$R_f = 0.3$ (ethyl acetate: methanol = 9:1).

Yield: 42 mg (20 % after 7 steps).

8.11.52 Analytical data of compound 128:



* = inseparable mixture, ratio determined by ^1H NMR

^1H NMR (400 MHz, CDCl_3): $\delta = 9.09$ (bs, 1H), 5.79-5.77 (dd, $J = 2.5$ Hz, 6.4 Hz, 1H), 4.72-4.65 (m, 2H), 3.55-3.37 (m, 1H), 3.24-3.19 (m, 1H), 3.10-2.96 (m, 4H), 2.65-2.55 (m, 1H), 2.40-2.28 (m, 1H), 2.00-1.95 (m, 1H), 1.48-1.39 (m, 2H), 1.27-1.20 (m, 14H), 0.85-0.81 (m, 6H).

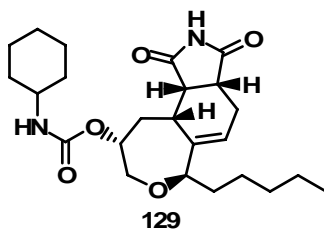
^{13}C NMR (100 MHz, CDCl_3): $\delta = 180.9, 178.9, 171.4, 156.2, 155.5, 147.9, 135.3, 121.6, 120.6, 70.7, 69.8, 65.2, 60.6, 54.1, 46.1, 45.8, 41.2, 39.6, 33.2, 31.9, 31.6, 31.1, 30.9, 29.9, 29.4, 27.4, 27.1, 26.6, 22.7, 14.2, 14.1$.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{24}\text{H}_{39}\text{N}_2\text{O}_5 = 435.2781$, found = 435.2719 $[\text{M}+\text{H}]^+$.

$R_f = 0.4$ (cyclohexane: ethyl acetate = 3: 2).

Yield: 56 mg (29 % after 7 steps).

8.11.53 Analytical data of compound 129:



¹H NMR (400 MHz, CDCl₃): δ = 8.41 (bs, 1H), 5.73-5.71 (t, *J* = 3.0 Hz, 1H), 4.86-4.39 (m, 1H), 3.88-3.83 (m, 1H), 3.42-3.39 (m, 1H), 3.28-3.05 (m, 2H), 2.57-2.54 (m, 1H), 2.40-2.07 (m, 2H), 1.89-1.80 (m, 2H), 1.68-1.65 (m, 4H), 1.30-1.08 (m, 15H), 0.87-0.84 (t, *J* = 6.5 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 180.7, 178.9, 171.4, 169.6, 158.4, 157.5, 143.9, 135.3, 122.8, 85.2, 82.4, 69.9, 63.4, 54.1, 50.0, 49.4, 46.2, 40.6, 34.1, 33.5, 31.9, 29.4, 27.1, 25.8, 25.1, 24.9, 22.7, 14.2.

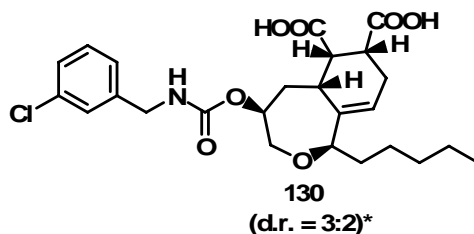
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₄H₃₅N₂O₅ = 431.2624, found = 431.2656 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 11.9° (c = 1, CHCl₃).

Yield: 60 mg (31 % after 6 steps).

8.11.54 Analytical data of compound 130:



* = inseparable mixture, ratio determined by ¹H NMR

¹H NMR (400 MHz, DMSO-*d*⁶): δ = 7.82-7.77 (m, 1H), 7.41-7.37 (m, 1H), 7.32-7.29 (m, 1H), 7.26-7.23 (m, 2H), 5.40-5.37 (t, *J* = 5.0 Hz, 1H), 4.44-4.37 (m, 1H), 4.22-4.15 (m, 2H), 4.00-3.99 (m, 1H), 3.94-3.93 (m, 1H), 3.87-3.85 (d, *J* = 10.4 Hz, 1H), 3.17-3.65 (m, 1H), 3.05-3.01 (m, 2H), 2.98-2.92 (m, 1H), 2.91-2.77 (m, 2H), 2.02-1.94 (m, 1H), 1.87-1.77 (m, 1H), 1.53-1.35 (m, 2H), 1.30-1.26 (m, 6H), 0.89-0.87 (t, *J* = 6.8 Hz, 3H).

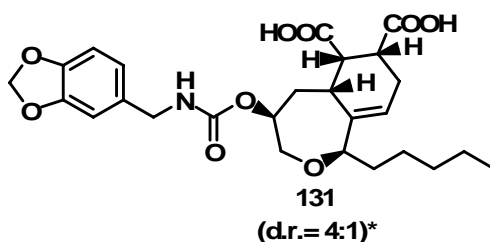
¹³C NMR (100 MHz, DMSO-*d*⁶): δ = 177.2, 178.1, 155.8, 148.5, 146.0, 142.8, 135.0, 134.0, 121.2, 119.6, 112.7, 111.0, 71.5, 75.2, 70.1, 52.8, 44.2, 42.1, 40.9, 33.0, 31.5, 30.1, 28.2, 27.0, 25.6, 22.8, 14.3.

HR-MS (FAB, 70 eV): m/z calculated for $C_{25}H_{31}ClNO_7 = 492.1867$, found = 492.1882
[M-H]⁺.

R_f = 0.4 (ethyl acetate: methanol = 9:1).

Yield: 15 mg (15 % after 7 steps).

8.11.55 Analytical data of compound 131:



* = inseparable mixture, ratio determined by ¹H NMR

¹H NMR (400 MHz, DMSO-*d*⁶): $\delta = 7.69$ -7.64 (m, 1H), 6.87-6.83 (m, 2H), 6.75-6.71 (m, 1H), 5.36-5.33 (t, $J = 4.4$ Hz, 1H), 4.11-3.99 (m, 3H), 3.93-3.82 (m, 2H), 3.09-2.92 (m, 1H), 2.82-2.71 (m, 4H), 2.02-1.94 (m, 1H), 1.83-1.77 (m, 1H), 1.50-1.47 (m, 2H), 1.33-1.27 (m, 6H), 0.90-0.87 (t, $J = 6.8$ Hz, 3H).

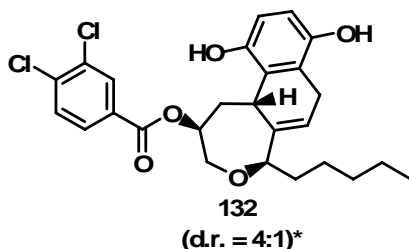
¹³C NMR (100 MHz, DMSO-*d*⁶): $\delta = 179.5, 178.2, 154.3, 147.3, 146.9, 140.8, 135.5, 122.6, 120.8, 114.6, 112.9, 101.3, 80.5, 73.2, 70.1, 50.8, 46.9, 40.2, 38.5, 35.2, 30.9, 28.5, 27.6, 26.9, 25.6, 22.8, 14.2$.

HR-MS (FAB, 70 eV): m/z calculated for $C_{26}H_{34}NO_9 = 502.2155$, found = 502.2198 [M-H]⁺.

R_f = 0.4 (ethyl acetate: methanol = 9:1).

Yield: 20 mg (15 % after 7 steps).

8.11.56 Analytical data of compound 132:



* = inseparable mixture, ratio determined by ^1H NMR

^1H NMR (400 MHz, CDCl_3): δ = 8.06-7.97 (m, 2H), 7.80-7.77 (m, 1H), 7.48-7.41 (m, 2H), 5.45-5.42 (m, 1H), 4.90-4.88 (m, 1H), 4.21-4.17 (m, 1H), 4.12-4.08 (m, 1H), 4.00-3.96 (m, 1H), 2.08-2.02 (m, 1H), 1.88-1.82 (m, 1H), 1.63-1.48 (m, 2H), 1.36-1.25 (m, 8H), 0.93-0.86 (t, J = 6.8 Hz, 3H).

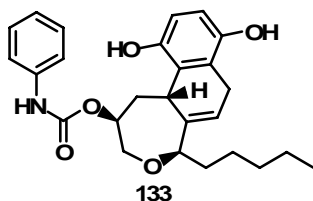
^{13}C NMR (100 MHz, CDCl_3): δ = 186.8, 185.9, 164.1, 163.6, 149.7, 143.5, 141.3, 140.8, 136.4, 131.7, 130.7, 128.9, 120.8, 113.3, 84.61, 72.5, 69.1, 54.0, 39.9, 35.8, 31.9, 31.8, 29.5, 28.6, 25.9, 25.6, 22.8, 14.2.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{26}\text{H}_{30}\text{Cl}_2\text{O}_5$ = 492.1314, found = 492.1300 $[\text{M}+2\text{H}]^+$.

R_f = 0.3 (cyclohexane: ethyl acetate = 4:1).

Yield: 20 mg (30 % after 5 steps).

8.11.57 Analytical data of compound 133:



^1H NMR (400 MHz, CDCl_3): δ = 8.03-8.02 (d, J = 8.0 Hz, 1H), 7.49-7.47 (d, J = 8.0 Hz, 1H), 7.34-7.27 (m, 2H), 7.05-7.02 (t, J = 7.2 Hz, 1H), 6.91-6.85 (q, J = 10.2 Hz, 2H), 6.60 (bs, 1H), 5.20-5.17 (t, J = 5.2 Hz, 1H), 4.86-4.83 (dd, J = 4.4 Hz, 8.5 Hz, 1H), 4.19-

4.16 (d, $J = 13.8$ Hz, 1H), 4.00-3.98 (m, 1H), 3.94-3.89 (dd, $J = 3.0$ Hz, 13.9 Hz, 1H), 2.05-2.00 (m, 1H), 1.86-1.83 (m, 1H), 1.62-1.58 (m, 2H), 1.37-1.33 (m, 6H), 1.28-1.24 (m, 2H), 0.93-0.89 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 165.1, 162.6, 148.3, 142.4, 141.2, 140.1, 137.4, 132.7, 131.7, 127.9, 121.8, 112.3, 83.6, 73.8, 69.1, 53.0, 40.9, 35.8, 31.9, 31.8, 29.0, 28.2, 25.0, 24.6, 22.8, 14.2$.

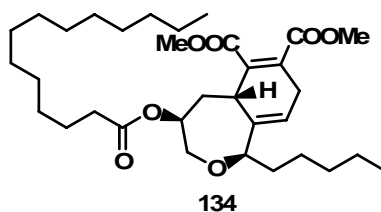
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{26}\text{H}_{32}\text{NO}_5 = 438.2202$, found = 438.2298 $[\text{M}+\text{H}]^+$.

$R_f = 0.4$ (cyclohexane: ethyl acetate = 4: 1).

$[\alpha]_D^{20}$: -15.0° ($c = 2, \text{CHCl}_3$).

Yield: 20 mg (20 % after 5 steps).

8.11.58 Analytical data of compound 134:



^1H NMR (400 MHz, CDCl_3): $\delta = 5.71$ - 5.70 (t, $J = 1.7$ Hz, 1H), 4.95-4.92 (m, 1H), 4.01-3.94 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.61-3.57 (m, 1H), 3.42-3.37 (dd, $J = 9.2$ Hz, 12.1 Hz, 1H), 3.35-3.32 (m, 1H), 3.05-3.03 (m, 2H), 2.30-2.25 (m, 1H), 2.22-2.18 (t, $J = 7.5$ Hz, 1H), 1.72-1.69 (m, 1H), 1.62-1.53 (m, 4H), 1.33-1.22 (m, 16H), 0.90-0.85 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 172.8, 168.3, 167.8, 141.7, 138.1, 134.1, 119.8, 79.7, 71.5, 65.5, 52.7, 52.5, 38.5, 36.4, 34.6, 32.1, 31.9, 30.6, 9.8, 29.6, 29.5, 29.4, 29.3, 28.5, 25.6, 25.1, 22.9, 22.8, 14.3, 14.2$.

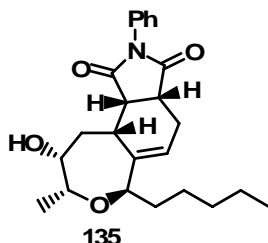
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{33}\text{H}_{54}\text{O}_7 = 562.3870$, found = 562.3800 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 9: 1).

$[\alpha]_D^{20}$: -10.9° ($c = 1, \text{CHCl}_3$).

Yield: 32.5 mg (44% after 5 steps).

8.11.59 Analytical data of compound 135:



¹H NMR (400 MHz, CDCl₃): δ = 7.46-7.42 (m, 2H), 7.39-7.37 (m, 1H), 7.19-7.17 (m, 2H), 5.81-5.78 (t, J = 5.1 Hz, 1H), 4.19-4.17 (t, J = 6.4 Hz, 1H), 4.01-3.98 (m, 1H), 3.79-3.75 (m, 1H), 3.30-3.24 (dt, J = 4.1 Hz, 8.9 Hz, 1H), 3.20-3.16 (dd, 5.6 Hz, 9.2 Hz, 1H), 2.76-2.71 (m, 2H), 2.47-2.39 (m, 1H), 2.25-2.19 (m, 1H), 2.05-1.99 (m, 1H), 1.85 (bs, 1H), 1.58-1.51 (m, 2H), 1.29-1.25 (m, 6H), 1.24-1.22 (d, J = 6.8 Hz, 3H), 0.89-0.85 (t, J = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 178.9, 177.4, 144.2, 131.9, 129.4, 128.9, 126.6, 126.3, 122.5, 73.8, 73.6, 45.1, 39.9, 34.7, 33.4, 33.2, 32.1, 27.1, 25.9, 24.0, 22.8, 14.2.

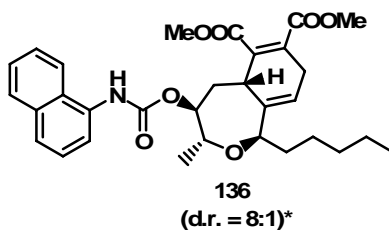
HR-MS (FAB, 70 eV): m/z calculated for C₂₄H₃₀NO₄ = 396.2253, found = 396.2298 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

[α]_D²⁰: + 39.3° (c = 1, CHCl₃).

Yield: 42 mg (52% after 4 steps).

8.11.60 Analytical data of compound 136:



* = inseparable mixture, ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 7.87-7.84 (m, 3H), 7.68-7.66 (m, 1H), 7.57-7.44 (m, 3H), 6.80 (bs, 1H), 5.79-5.73 (t, *J* = 4.0 Hz, 1H), 4.72-4.66 (m, 1H), 4.31-4.30 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.66-3.62 (m, 1H), 3.47-3.44 (m, 1H), 3.05-3.03 (m, 2H), 2.47-2.42 (m, 1H), 1.74-1.67 (m, 1H), 1.59-1.57 (m, 2H), 1.36-1.22 (m, 9H), 0.92-0.88 (t, *J* = 6.8 Hz, 3H).

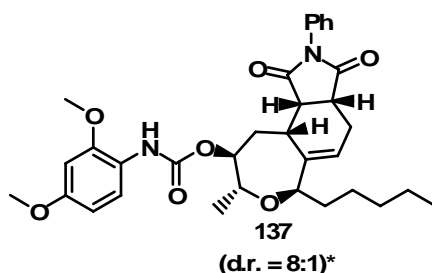
¹³C NMR (100 MHz, CDCl₃): δ = 168.3, 167.8, 150.8, 148.0, 146.4, 143.6, 142.3, 138.6, 134.3, 134.0, 132.5, 128.9, 126.5, 126.0, 119.2, 116.5, 78.5, 78.1, 69.7, 52.7, 36.8, 32.0, 30.2, 28.7, 26.0, 22.8, 19.5, 14.3.

HR-MS (FAB, 70 eV): *m/z* calculated for C₃₁H₃₇NO₇ = 535.257, found = 535.2500 [M]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 4: 1).

Yield: 13 mg (32 % after 5 steps).

8.11.61 Analytical data of compound 137:



* = inseparable mixture, ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 7.97-7.95 (m, 1H), 7.46-7.37 (m, 3H), 7.16-7.14 (m, 3H), 6.47-6.45 (m, 2H), 5.85-5.84 (t, *J* = 2 Hz, 1H), 4.91-4.90 (m, 1H), 4.20-4.09 (m, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 3.31-3.29 (m, 1H), 3.19-3.15 (dd, *J* = 4.6 Hz, 8.9 Hz, 1H), 2.37-2.25 (m, 2H), 1.60-1.58 (m, 1H), 1.33-1.31 (d, *J* = 6.8 Hz, 3H), 1.28-1.25 (m, 8H), 0.89-0.86 (t, *J* = 6.7 Hz, 3H).

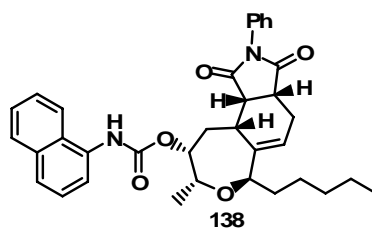
¹³C NMR (100 MHz, CDCl₃): δ = 179.0, 177.7, 164.9, 149.2, 145.0, 142.6, 132.0, 129.4, 126.6, 121.0, 104.1, 98.9, 76.2, 74.9, 71.1, 55.8, 45.6, 40.8, 32.1, 29.5, 27.1, 26.1, 22.8, 14.3.

HR-MS (FAB, 70 eV): m/z calculated for $C_{33}H_{41}N_2O_7 = 577.2836$, found = 577.2869
[M+H]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 4: 1).

Yield: 14.4 mg (50% after 5 steps).

8.11.62 Analytical data of compound 138:



¹H NMR (400 MHz, CDCl₃): $\delta = 7.87$ -7.85 (m, 3H), 7.70-7.66 (m, 1H), 7.54-7.41 (m, 5H), 7.39-7.37 (m, 1H), 7.17-7.14 (m, 2H), 7.02 (bs, 1H), 5.90-5.85 (t, $J = 4.5$ Hz, 1H), 4.99-4.94 (m, 1H), 4.27-4.25 (m, 1H), 4.18-4.11 (m, 1H), 3.32-3.30 (m, 1H), 3.27-3.24 (m, 1H), 2.89-2.84 (m, 1H), 2.74-2.71 (m, 1H), 2.36-2.31 (m, 1H), 2.17-2.16 (m, 2H), 1.61-1.57 (m, 2H), 1.45-1.43 (m, 2H), 1.33-1.24 (m, 7H), 0.89-0.86 (t, $J = 6.7$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): $\delta = 178.8, 177.2, 164.6, 137.5, 134.3, 132.6, 131.9, 129.4, 128.9, 128.9, 126.5, 126.2, 125.9, 122.4, 76.6, 71.6, 69.7, 54.0, 51.8, 45.5, 40.6, 36.2, 33.1, 32.2, 29.5, 27.1, 26.0, 25.1, 22.8, 14.3$.

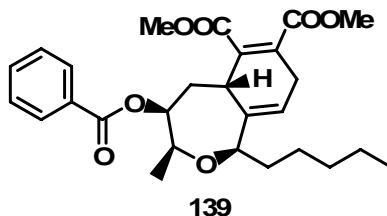
HR-MS (FAB, 70 eV): m/z calculated for $C_{35}H_{38}N_2O_5 = 566.2781$, found = 566.2751
[M]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 9: 1).

[α]_D²⁰: + 3.6° (c = 1, CHCl₃).

Yield: 12 mg (60 % after 5 steps).

8.11.63 Analytical data of compound 139:



¹H NMR (400 MHz, CDCl₃): δ = 7.63-7.58 (m, 3H), 7.56-7.46 (m, 2H), 5.67-5.66 (t, J = 3.4 Hz, 1H), 5.20-5.16 (m, 1H), 3.94-3.88 (m, 1H), 3.79-3.78 (m, 1H), 3.75 (s, 3H), 3.61-3.55 (m, 1H), 3.49 (s, 3H), 3.15-3.07 (m, 1H), 3.02-2.95 (m, 1H); 2.24-2.19 (dd, J = 4.0 Hz, 14.2 Hz, 1H), 2.01-1.94 (m, 1H), 1.72-1.69 (m, 2H), 1.57-1.55 (m, 1H), 1.37-1.32 (m, 9H), 0.92-0.88 (t, J = 6.6 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 172.3, 168.5, 168.3, 165.9, 139.2, 137.5, 134.0, 133.4, 132.3, 130.5, 130.4, 129.8, 129.6, 128.7, 128.6, 115.6, 83.1, 79.9, 78.8, 52.5, 52.3, 36.3, 35.8, 31.9, 28.0, 26.1, 22.8, 20.9, 14.3.

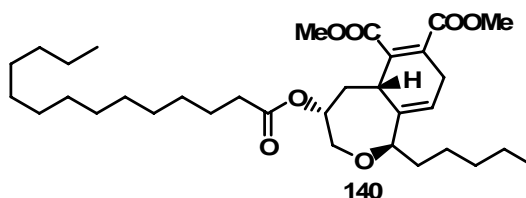
HR-MS (FAB, 70 eV): m/z calculated for C₂₇H₃₅O₇ = 471.2305, found = 471.2338 [M+H]⁺.

R_f = 0.5 (cyclohexane: ethyl acetate = 4: 1).

Yield: 10 mg (26% after 5 steps).

[α]_D²⁰: + 13.0° (c = 1, CHCl₃).

8.11.64 Analytical data of compound 140:



¹H NMR (400 MHz, CDCl₃): δ = 5.54-5.53 (t, J = 3.3 Hz, 1H), 4.93-4.89 (m, 1H), 4.05-4.01 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.71-3.63 (m, 1H), 3.60-3.56 (m, 1H), 3.47-3.43

(dd, $J = 0.76$ Hz, 13.5 Hz, 1H), 3.04-3.01 (m, 2H), 2.38-2.35 (m, 2H), 2.21-2.14 (m, 1H), 1.65-1.57 (m, 4H), 1.42-1.35 (m, 1H), 1.32-1.25 (m, 26H), 0.89-0.85 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 173.5, 168.4, 168.2, 168.0, 167.9, 142.9, 138.7, 134.6, 119.2, 84.1, 70.8, 69.3, 64.3, 52.5, 40.1, 36.5, 34.8, 32.8, 31.9, 29.9, 29.8, 29.7, 29.4, 29.3, 28.4, 25.6, 25.2, 22.9, 22.8, 14.3, 14.2$.

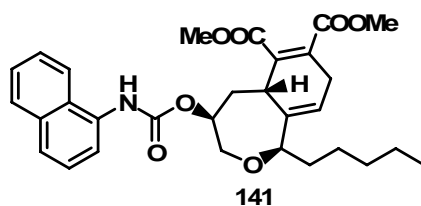
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{33}\text{H}_{54}\text{O}_7 = 562.387$, found = 562.3899 $[\text{M}]^+$.

$R_f = 0.4$ (cyclohexane: ethyl acetate = 4: 1).

$[\alpha]_D^{20} : +29.0^\circ$ ($c = 2, \text{CHCl}_3$).

Yield: 21 mg (28 % after 5 steps).

8.11.65 Analytical data of compound 141:



^1H NMR (400 MHz, CDCl_3): $\delta = 7.86$ -7.80 (m, 3H), 7.67-7.65 (d, $J = 8.2$ Hz, 1H), 7.54-7.44 (m, 3H), 6.84 (bs, 1H), 5.75-5.70 (t, $J = 4.3$ Hz, 1H), 5.04-4.97 (m, 1H), 4.02-3.99 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.63-3.55 (m, 1H), 3.40-3.37 (m, 1H), 3.10-3.06 (m, 2H), 2.46-2.42 (dd, $J = 5.9$ Hz, 12.6 Hz, 1H), 1.75-1.71 (m, 1H), 1.63-1.54 (m, 3H), 1.35-1.25 (m, 6H), 0.92-0.88 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 168.3, 167.8, 153.5, 151.4, 141.7, 137.9, 134.3, 134.1, 132.5, 128.9, 126.5, 126.2, 126.0, 119.6, 80.1, 73.0, 52.7, 52.5, 38.7, 36.3, 31.9, 30.7, 28.5, 27.1, 25.7, 22.8, 14.3$.

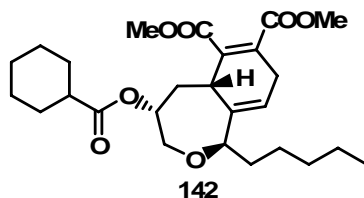
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{30}\text{H}_{35}\text{NO}_7 = 521.2414$, found = 521.2485 $[\text{M}]^+$.

$R_f = 0.3$ (cyclohexane: ethyl acetate = 4: 1).

$[\alpha]_D^{20} : -5.1^\circ$ ($c = 1, \text{CHCl}_3$).

Yield: 16 mg (16 % after 5 steps).

8.11.66 Analytical data of compound 142:



¹H NMR (400 MHz, CDCl₃): δ = 5.67-5.66 (t, J = 2.3 Hz, 1H), 4.93-4.92 (m, 1H), 4.12-4.09 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.72-3.69 (m, 1H), 3.68-3.62 (m, 1H), 3.59-3.54 (dd, J = 1.6 Hz, 13.5 Hz, 1H), 3.06-3.01 (m, 2H), 2.42-2.36 (m, 1H), 2.42-2.36 (m, 1H), 2.16-2.12 (m, 1H), 1.97-1.88 (m, 2H), 1.76-1.72 (m, 3H), 1.68-1.53 (m, 2H), 1.45-1.40 (m, 3H), 1.38-1.23 (m, 9H), 0.91-0.87 (t, J = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 175.7, 168.1, 142.2, 139.1, 133.4, 118.9, 78.9, 70.7, 64.6, 52.5, 52.4, 43.3, 38.8, 35.9, 32.0, 30.3, 29.6, 28.9, 28.4, 25.9, 25.7, 25.5, 22.8, 14.2.

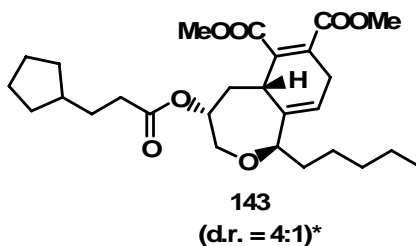
HR-MS (FAB, 70 eV): m/z calculated for C₂₆H₃₈O₇ = 462.2618, found = 462.2699 [M]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 4: 1).

[α]_D²⁰: + 1.9° (c = 1, CHCl₃).

Yield: 18 mg (32 % after 5 steps).

8.11.67 Analytical data of compound 143:



* = inseparable mixture, ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 5.62-5.60 (dd, J = 2.5 Hz, 4.8 Hz, 1H), 4.87-4.86 (m, 1H), 4.09-4.04 (m, 1H), 3.70 (s, 6H), 3.63-3.58 (m, 1H), 3.50-3.46 (dd, J = 1.5 Hz, 13.6

Hz, 1H), 2.99-2.95 (m, 2H), 2.34-2.31 (t, $J = 7.8$ Hz, 2H), 2.12-2.07 (m, 1H), 1.73-1.68 (m, 4H), 1.58-1.44 (m, 10H), 1.27-1.18 (m, 5H), 0.84-0.81 (t, $J = 7.0$ Hz, 3H).

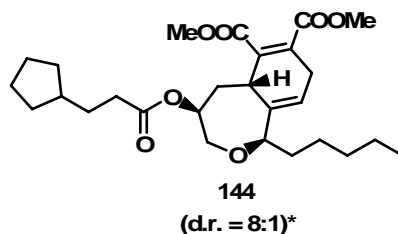
^{13}C NMR (100 MHz, CDCl_3): $\delta = 173.6, 168.2, 167.9, 142.2, 138.8, 133.7, 119.0, 78.9, 71.0, 64.3, 52.5, 39.9, 38.9, 35.9, 34.1, 32.7, 32.6, 32.0, 31.4, 30.3, 28.5, 25.7, 25.3, 22.8, 14.2$.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{27}\text{H}_{40}\text{O}_7 = 476.2774$, found = 476.2700 $[\text{M}]^+$.

$R_f = 0.3$ (cyclohexane: ethyl acetate = 4: 1).

Yield: 14 mg (25 % after 5 steps).

8.11.68 Analytical data of compound 144:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): $\delta = 5.60$ - 5.58 (dd, $J = 1.7$ Hz, 5.1 Hz, 1H), 4.94-4.86 (m, 1H), 4.15-4.11 (dd, $J = 6.4$ Hz, 12.3 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.70-3.67 (t, $J = 4.6$ Hz, 1H), 3.47-3.42 (dd, $J = 8.9$ Hz, 12.3 Hz, 1H), 3.38-3.33 (m, 1H), 3.06-3.04 (m, 1H), 3.03-2.99 (m, 1H), 2.29-2.21 (m, 3H), 1.86-1.83 (m, 2H), 1.75-1.69 (m, 3H), 1.60-1.56 (m, 8H), 1.32-1.22 (m, 5H), 0.90-0.87 (t, $J = 7.1$ Hz, 3H).

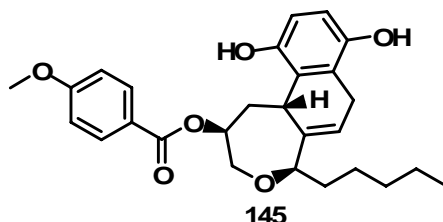
^{13}C NMR (100 MHz, CDCl_3): $\delta = 173.6, 168.2, 167.9, 142.2, 138.8, 133.7, 119.0, 78.9, 71.0, 64.3, 52.5, 39.9, 38.9, 35.9, 34.1, 32.7, 32.6, 32.0, 31.4, 30.3, 28.5, 25.7, 25.3, 22.8, 14.2$.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{27}\text{H}_{40}\text{O}_7 = 476.2774$, found = 476.2700 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 4: 1).

Yield: 14 mg (25 % after 5 steps).

8.11.69 Analytical data of compound 145:



$^1\text{H NMR}$ (400 MHz, CDCl_3): δ = 8.04-8.00 (m, 1H), 7.92-7.87 (m, 2H), 7.48-7.46 (m, 1H), 6.89-6.84 (m, 2H), 5.36-5.32 (t, J = 8.0 Hz, 1H), 4.89-4.86 (dd, J = 4.4 Hz, 8.5 Hz, 1H), 4.19-4.16 (m, 1H), 4.09-4.08 (m, 1H), 3.97-3.92 (dd, J = 3.3 Hz, 14.0 Hz, 1H), 3.84 (s, 3H), 3.80-3.76 (m, 1H), 2.06-2.03 (m, 1H), 1.87-1.81 (m, 1H), 1.60-1.57 (m, 2H), 1.51-1.28 (m, 6H), 0.92-0.88 (t, J = 6.9 Hz, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ = 187.7, 184.9, 165.8, 163.6, 149.8, 141.3, 136.6, 132.7, 131.9, 131.7, 131.4, 126.2, 122.9, 113.7, 83.7, 72.1, 55.6, 36.5, 31.9, 28.8, 25.8, 22.8, 14.3.

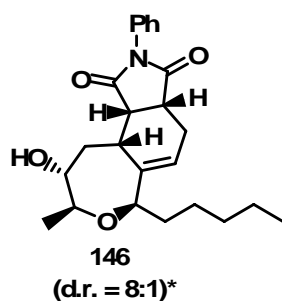
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{27}\text{H}_{33}\text{O}_6$ = 453.2199, found = 453.2232 $[\text{M}+\text{H}]^+$.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

Yield: 15 mg (17% after 5 steps).

$[\alpha]_D^{20}$: - 62.5° (c = 2, CHCl_3).

8.11.70 Analytical data of compound 146:



* = inseparable mixture, ratio determined by $^1\text{H NMR}$ spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 7.48-7.44 (m, 2H), 7.40-7.38 (m, 1H), 7.30-7.26 (m, 2H), 5.81-5.78 (m, 1H), 4.07-4.06 (m, 1H), 3.64-3.59 (q, *J* = 6.4 Hz, 1H), 3.57-3.56 (t, *J* = 3.12 Hz, 1H), 3.26-3.16 (m, 3H), 2.72-2.66 (m, 1H), 2.54-2.48 (m, 1H), 1.91-1.86 (m, 1H), 1.63-1.56 (m, 2H), 1.34-1.25 (m, 6H), 1.20-1.19 (d, *J* = 6.6 Hz, 3H), 0.91-0.88 (t, *J* = 6.6 Hz, 3H).

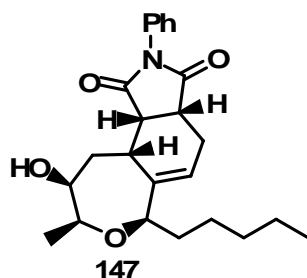
¹³C NMR (100 MHz, CDCl₃): δ = 178.1, 176.2, 142.6, 130.7, 128.1, 127.5, 125.2, 120.9, 77.9, 70.3, 67.8, 43.5, 37.8, 34.7, 32.2, 31.1, 29.7, 25.2, 21.9, 21.4, 19.1, 13.4.

HR-MS (FAB, 70 eV): *m/z* calculated for C₂₄H₃₀NO₄ = 396.2253, found = 396.2298 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

Yield: 30 mg (50 % after 5 steps).

8.11.71 Analytical data of compound 147:



¹H NMR (400 MHz, CDCl₃): δ = 7.46-7.43 (m, 2H), 7.42-7.37 (m, 1H), 7.22-7.20 (m, 2H), 5.77-5.74 (t, *J* = 5.0 Hz, 1H), 3.93-3.89 (m, 1H), 3.33-3.29 (m, 2H), 3.28-3.25 (dd, *J* = 4.5 Hz, 9.0 Hz, 1H), 3.20-3.17 (dd, *J* = 5.9 Hz, 9.5 Hz, 1H), 2.89-2.86 (m, 1H), 2.72-2.67 (td, *J* = 4.6 Hz, 15.1 Hz, 1H), 2.51-2.44 (m, 1H), 2.12-2.04 (m, 2H), 1.64-1.57 (m, 2H), 1.49-1.39 (m, 2H), 1.30-1.21 (m, 7H), 0.90-0.86 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 179.2, 177.7, 144.6, 132.1, 129.5, 129.4, 128.9, 126.7, 121.4, 80.9, 79.9, 76.4, 45.3, 39.8, 37.9, 33.8, 33.2, 32.1, 27.2, 25.9, 22.9, 19.7, 14.3.

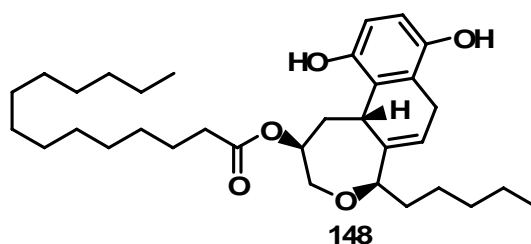
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₄H₃₀NO₄ = 396.2253, found = 396.2298 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

Yield: 73 mg (70% after 4 steps).

$[\alpha]_D^{20}$: + 21.0° (c = 2, CHCl₃).

8.11.72 Analytical data of compound 148:



¹H NMR (400 MHz, CDCl₃): δ = 6.72 (s, 2H), 5.63-5.62 (d, J = 3.9 Hz, 1H), 4.90-4.89 (m, 1H), 4.09-4.04 (m, 2H), 3.97-3.93 (m, 1H), 3.51-3.48 (d, J = 13.5 Hz, 1H), 3.31-3.24 (m, 1H), 2.99-2.92 (dd, J = 2.8 Hz, 24.1 Hz, 1H), 2.51-2.46 (q, J = 7.1 Hz, 2H), 1.98-1.93 (m, 1H), 1.75-1.65 (m, 1H), 1.39-1.25 (m, 30H), 0.89-0.83 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 186.9, 185.9, 173.9, 143.9, 143.1, 140.6, 136.8, 136.3, 119.4, 84.3, 70.8, 69.4, 40.5, 36.5, 34.9, 32.1, 31.9, 29.9, 29.5, 29.4, 28.8, 25.6, 25.2, 24.7, 22.9, 22.8, 14.3, 14.2.

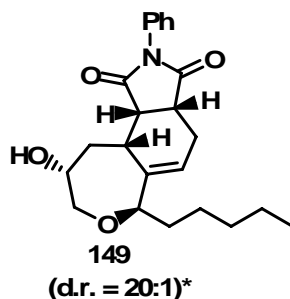
HR-MS (FAB, 70 eV): m/z calculated for C₃₃H₅₃O₅ = 529.3815, found = 529.3895 [M+H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

$[\alpha]_D^{20}$: - 2.2° (c = 2, CHCl₃).

Yield: 16 mg (23 % after 5 steps).

8.11.73 Analytical data of compound 149:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): δ = 7.49-7.45 (m, 2H), 7.41-7.37 (m, 1H), 7.27-7.26 (m, 2H), 5.79-5.77 (t, J = 4.7 Hz, 1H), 3.97-3.93 (t, J = 6.6 Hz, 1H), 3.83-3.82 (m, 1H), 3.80-3.76 (m, 1H), 3.32-3.28 (m, 1H), 3.26-3.24 (m, 1H), 3.18-3.14 (dd, J = 6.4 Hz, 9.7 Hz, 1H), 2.65-2.62 (dd, J = 4.6 Hz, 7.7 Hz, 2H), 2.17-2.16 (m, 1H), 2.09-2.05 (m, 1H), 1.62-1.51 (m, 2H), 1.29-1.25 (m, 8H), 0.90-0.86 (t, J = 6.7 Hz, 3H).

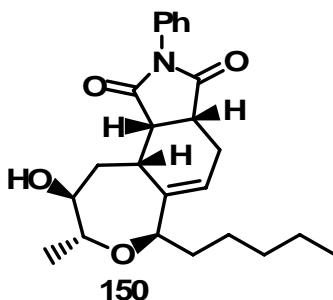
^{13}C NMR (100 MHz, CDCl_3): δ = 179.0, 177.6, 144.0, 136.1, 131.9, 129.4, 129.3, 128.9, 126.6, 126.5, 123.4, 83.2, 72.8, 71.0, 44.6, 39.0, 37.0, 33.7, 31.9, 31.6, 25.7, 22.7, 22.6, 14.2.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{23}\text{H}_{28}\text{NO}_4$ = 382.2097, found = 382.2011 [$\text{M}-\text{H}$] $^+$.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

Yield: 10 mg (65% after 4 steps).

8.11.74 Analytical data of compound 150:



¹H NMR (400 MHz, CDCl₃): δ = 7.46-7.42 (m, 2H), 7.39-7.34 (m, 1H), 7.19-7.17 (m, 2H), 5.76-5.73 (t, *J* = 4.7 Hz, 1H), 4.09-4.06 (t, *J* = 6.4 Hz, 1H), 4.00-3.94 (m, 1H), 3.72-3.70 (m, 1H), 3.32-3.27 (dt, *J* = 3.72 Hz, 8.8 Hz, 1H), 3.18-3.14 (dd, *J* = 5.7 Hz, 9.2 Hz, 1H), 3.04-3.00 (m, 1H), 2.78-2.71 (ddd, *J* = 3.52 Hz, 5.6 Hz, 16.0 Hz, 1H), 2.47-2.43 (m, 1H), 2.41-2.37 (m, 1H), 1.96-1.91 (m, 1H), 1.58-1.50 (m, 2H), 1.29-1.27 (m, 6H), 1.26-1.24 (d, *J* = 6.8 Hz, 3H), 0.89-0.85 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 179.2, 177.8, 145.0, 132.1, 129.45, 128.9, 126.7, 121.6, 76.7, 73.6, 72.8, 45.3, 40.4, 33.5, 32.1, 31.3, 31.2, 26.1, 24.3, 22.9, 16.4, 14.3.

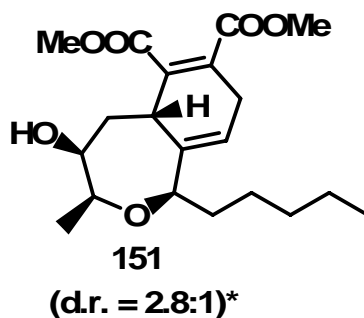
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₄H₃₀NO₄ = 396.2253, found = 396.2298 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

[α]_D²⁰: + 6.0° (c = 1, CHCl₃).

Yield: 53 mg (50% after 5 steps).

8.11.75 Analytical data of compound 151:



* = inseparable mixture, ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 5.59-5.58 (t, *J* = 3.2 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.72-3.69 (m, 1H), 3.61-3.54-3.54 (m, 1H), 3.46-3.42 (m, 1H), 3.34-3.25 (m, 1H), 3.05-3.03 (m, 1H), 3.02-2.98 (m, 1H), 1.99 (bs, 1H), 1.96-1.93 (dd, *J* = 3.4 Hz, 7.1 Hz, 2H), 1.70-1.60 (m, 2H), 1.57-1.53 (m, 2H), 1.34-1.30 (m, 4H), 1.28-1.27 (d, *J* = 6.4 Hz, 3H), 0.91-0.87 (t, *J* = 6.6 Hz, 3H).

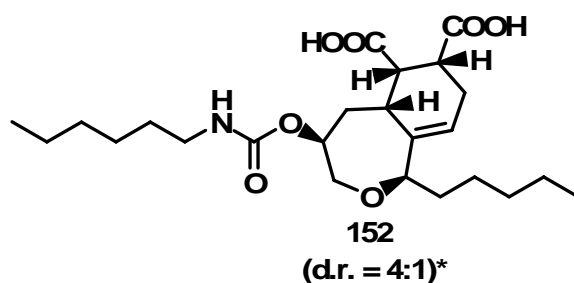
^{13}C NMR (100 MHz, CDCl_3): $\delta = 168.5, 168.4, 143.3, 140.3, 137.8, 136.8, 134.4, 133.1, 118.4, 115.0, 83.7, 82.9, 82.2, 76.0, 74.6, 52.6, 52.5, 43.9, 41.0, 36.3, 34.8, 33.2, 31.9, 31.8, 28.4, 28.2, 26.0, 25.7, 22.8, 20.8, 19.3, 14.3$.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{20}\text{H}_{31}\text{O}_6 = 367.2042$, found = 367.2072 $[\text{M}+\text{H}]^+$.

$R_f = 0.4$ (cyclohexane: ethyl acetate = 3: 2).

Yield: 68 %.

8.11.76 Analytical data of compound 152:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 8.01$ (bs, 1H), 5.67-5.65 (t, $J = 4.0$ Hz, 1H), 4.60-4.56 (m, 1H), 3.89-3.47 (m, 3H), 3.10-3.05 (m, 2H), 2.85-2.70 (m, 2H), 2.56-2.19 (m, 3H), 1.96-1.70 (m, 2H), 1.33-1.27 (m, 16H), 0.90-0.86 (m, 6H).

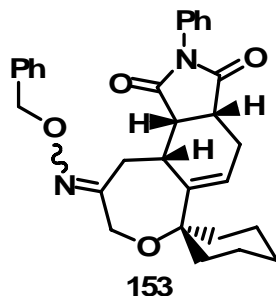
^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta = 182.0, 179.9, 158.3, 140.5, 121.3, 80.9, 75.3, 69.2, 54.0, 45.9, 42.9, 35.2, 33.6, 31.7, 30.3, 27.9, 26.6, 22.9, 22.3, 14.9, 14.2$.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{24}\text{H}_{38}\text{NO}_7 = 452.2727$, found = 452.2795 $[\text{M}-\text{H}]^+$.

$R_f = 0.5$ (ethyl acetate: methanol = 9:1).

Yield: 8.0 mg (30 % after 7 steps).

8.11.77 Analytical data of compound 153:



¹H NMR (400 MHz, CDCl₃): δ = 7.34-7.28 (m, 8H), 7.15-7.13 (m, 2H), 5.83-5.81 (dd, J = 2.0 Hz, 6.9 Hz, 1H), 5.03 (s, 2H), 4.08-4.05 (d, J = 14.4 Hz, 1H), 3.95-3.91 (d, J = 14.3 Hz, 1H), 3.54-3.48 (m, 1H), 3.26-3.21 (m, 1H), 3.18-3.11 (m, 1H), 2.81-2.73 (m, 1H), 2.51-2.44 (m, 1H), 1.97-1.89 (m, 2H), 1.64-1.60 (m, 4H), 1.25-1.19 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): 179.4, 177.5, 165.6, 156.3, 147.2, 137.5, 131.9, 129.5, 128.8, 128.5, 128.0, 126.7, 121.7, 91.7, 78.6, 76.2, 44.6, 38.2, 36.1, 31.4, 29.9, 26.0, 25.8, 21.9, 21.6.

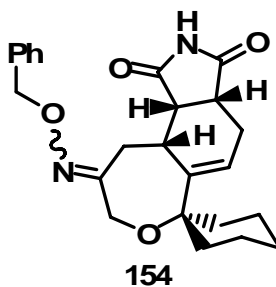
HR-MS (FAB, 70 eV): m/z calculated for C₃₀H₃₂N₂O₄ = 484.2362, found = 484.2301 [M]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 4: 1).

[α]_D²⁰: + 16.2° (c = 1, CHCl₃).

Yield: 6 mg (10 % after 6 steps).

8.11.78 Analytical data of compound 154:



¹H NMR (400 MHz, CDCl₃): δ = 7.35-7.28 (m, 5H), 5.79-5.77 (dd, *J* = 2.4 Hz, 7.3 Hz, 1H), 5.02 (s, 2H), 4.05-4.02 (d, *J* = 14.4 Hz, 1H), 3.92-3.88 (d, *J* = 14.2 Hz, 1H), 3.44-4.38 (m, 1H), 3.11-3.02 (m, 3H), 2.66-2.62 (m, 1H), 2.34-2.28 (m, 1H), 1.96-1.86 (m, 2H), 1.62-1.55 (m, 4H), 1.28-1.25 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 179.6, 177.6, 156.1, 147.8, 138.0, 128.5, 128.3, 127.9, 121.5, 78.5, 76.0, 64.4, 45.6, 39.6, 36.2, 30.7, 29.9, 25.9, 25.5, 21.8, 21.6.

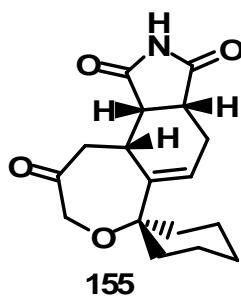
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₄H₂₈N₂O₄ = 408.2049, found = 408.2011 [M]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 3.9° (c = 2, CHCl₃).

Yield: 8 mg (12 % after 6 steps).

8.11.79 Analytical data of compound 155:



¹H NMR (400 MHz, CDCl₃): δ = 8.44 (bs, 1H), 5.86-5.83 (dd, *J* = 2.9 Hz, 6.8 Hz, 1H), 4.02-3.98 (d, *J* = 17.9 Hz, 1H), 3.91-3.87 (d, *J* = 17.9 Hz, 1H), 3.78-3.72 (m, 1H), 3.10-3.07 (m, 2H), 2.79-2.73 (dd, *J* = 7.0 Hz, 16.4 Hz, 1H), 2.67-2.60 (m, 1H), 2.38-2.28 (m, 1H), 2.25-2.21 (m, 1H), 1.99-1.95 (m, 1H), 1.87-1.84 (m, 1H), 1.72-1.65 (m, 2H), 1.58-1.48 (m, 4H), 1.29-1.17 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 210.9, 179.8, 177.9, 147.5, 122.7, 79.2, 70.5, 54.0, 45.2, 41.4, 39.6, 35.6, 29.5, 25.8, 22.4, 21.6, 21.5.

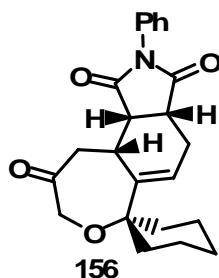
HR-MS (FAB, 70 eV): *m/z* calculated for C₁₇H₂₂NO₄ = 304.1471, found = 304.1456 [M+H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

Yield: 22 mg (15% after 5 steps).

$[\alpha]_D^{20}$: + 2.0° (c = 2, CHCl₃).

8.11.80 Analytical data of compound 156:



¹H NMR (400 MHz, CDCl₃): δ = 7.49-7.45 (m, 2H), 7.41-7.40 (m, 1H), 7.29-7.25 (m, 2H), 5.90-5.88 (dd, J = 2.8 Hz, 6.9 Hz, 1H), 4.04-3.99 (d, J = 17.9 Hz, 1H), 3.93-3.89 (d, J = 18.0 Hz, 1H), 3.23-3.19 (m, 2H), 2.83-2.77 (dd, J = 7.0 Hz, 16.4 Hz, 1H), 2.75-2.71 (m, 1H), 2.40-2.31 (m, 1H), 2.03-2.00 (m, 1H), 1.89-1.86 (m, 1H), 1.71-1.51 (m, 6H), 1.32-1.20 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 210.6, 178.7, 176.9, 147.6, 131.8, 129.5, 129.0, 126.6, 122.9, 79.3, 70.6, 44.0, 41.4, 38.4, 35.7, 29.9, 25.9, 22.8, 21.6.

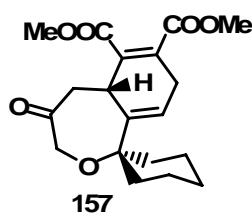
HR-MS (FAB, 70 eV): m/z calculated for C₂₃H₂₅NO₄ = 379.1784, found = 379.1700 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 9: 1).

Yield: 19 mg (10% after 5 steps).

$[\alpha]_D^{20}$: + 4.0° (c = 2, CHCl₃).

8.11.81 Analytical data of compound 157:



¹H NMR (400 MHz, CDCl₃): δ = 5.75-5.73 (t, *J* = 3.7 Hz, 1H), 4.09-4.03 (m, 1H), 3.99-3.95 (m, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 2.23-2.16 (m, 1H), 2.08-2.02 (m, 2H), 1.75-1.61 (m, 6H), 1.27-1.20 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ = 211.9, 168.4, 167.5, 149.1, 143.2, 136.7, 134.8, 129.5, 128.9, 120.8, 79.2, 70.2, 52.9, 52.8, 47.2, 37.4, 35.6, 29.9, 28.9, 27.1, 25.9, 21.9, 21.4.

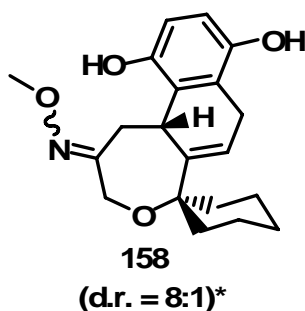
HR-MS (FAB, 70 eV): *m/z* calculated for C₁₉H₂₄O₆ = 348.1573, found = 348.1526 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

Yield: 26 mg (15% after 5 steps).

[α]_D²⁰: + 6.0° (c = 1, CHCl₃).

8.11.82 Analytical data of compound 158:



* = inseparable mixture, ratio determined by ¹H NMR spectroscopy

¹H NMR (400 MHz, CDCl₃): δ = 6.54-6.51 (dd, *J* = 1.7 Hz, 12.1 Hz, 1H), 6.22-6.18 (dd, *J* = 1.0 Hz, 12.0 Hz, 1H), 5.74-5.63 (m, 1H), 4.11 (s, 3H), 3.97-3.88 (m, 5H), 1.60-1.70 (m, 2H), 1.20-1.32 (m, 6H), 0.92-0.83 (m, 4H).

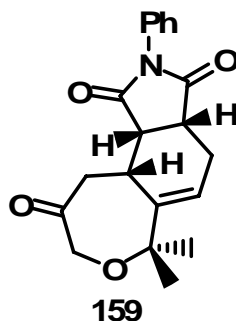
¹³C NMR (100 MHz, CDCl₃): δ = 165.2, 148.4, 147.5, 147.0, 134.5, 129.2, 119.9, 114.2, 112.4, 90.7, 69.9, 61.1, 36.8, 35.2, 31.4, 28.3, 23.6, 21.9, 20.6.

HR-MS (FAB, 70 eV): *m/z* calculated for C₂₀H₂₅NO₄ = 343.1784, found = 343.1723 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1)..

Yield: 10 mg (10 % after 6 steps).

8.11.83 Analytical data of compound 159:



$^1\text{H NMR}$ (400 MHz, CDCl_3): δ = 7.48-7.45 (m, 2H), 7.41-7.39 (m, 1H), 7.28-7.26 (m, 2H), 5.92-5.89 (dd, J = 2.8 Hz, 6.7 Hz, 1H), 3.99-3.98 (d, J = 2.3 Hz, 2H), 3.86-3.79 (m, 1H), 3.23-3.20 (dd, J = 4.4 Hz, 2H), 2.82-2.77 (dd, J = 6.8 Hz, 16.4 Hz, 1H), 2.75-2.69 (m, 1H), 2.44-2.33 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ = 210.3, 178.7, 176.9, 147.0, 131.8, 129.5, 129.5, 129.0, 126.6, 126.3, 122.9, 78.8, 71.4, 54.0, 43.9, 41.3, 38.3, 29.6, 29.5, 27.4, 22.9, 22.7.

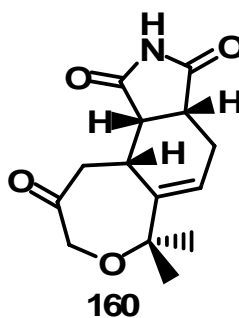
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_4$ = 340.1471, found = 340.1400 $[\text{M}+\text{H}]^+$.

R_f = 0.5 (cyclohexane: ethyl acetate = 8:1).

Yield: 38 mg (10% after 5 steps).

$[\alpha]_D^{20}$: + 14.0° (c = 1, CHCl_3).

8.11.84 Analytical data of compound 160:



¹H NMR (400 MHz, CDCl₃): δ = 8.78 (bs, 1H), 5.88-5.85 (dd, *J* = 2.9 Hz, 6.8 Hz, 1H), 3.98-3.97 (d, *J* = 3.9 Hz, 2H), 3.79-3.69 (m, 1H), 3.14-3.05 (m, 2H), 2.79-2.74 (dd, *J* = 6.9 Hz, 16.5 Hz, 1H), 2.63-2.59 (m, 1H), 2.38-2.23 (m, 2H), 1.39 (s, 3H), 1.35 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 210.7, 180.0, 178.2, 146.9, 135.3, 122.8, 78.8, 71.3, 69.8, 54.0, 45.1, 41.3, 39.5, 31.9, 29.5, 29.0, 27.3, 22.7, 22.4.

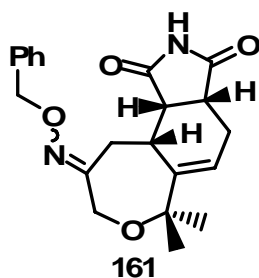
HR-MS (FAB, 70 eV): *m/z* calculated for C₁₄H₁₆NO₄ = 262.1158, found = 262.1190 [M-H]⁺.

R_f = 0.3 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 22.0° (c = 1, CHCl₃).

Yield: 31 mg (10 % after 5 steps).

8.11.85 Analytical data of compound 161:



¹H NMR (400 MHz, CDCl₃): δ = 7.33-7.28 (m, 5H), 5.83-5.81 (dd, *J* = 2.5 Hz, 7.4 Hz, 1H), 5.05 (s, 2H), 4.05-3.93 (m, 3H), 3.19-3.05 (m, 3H), 2.36-2.23 (m, 3H), 1.29-1.25 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 178.5, 176.2, 160.7, 143.9, 141.2, 129.9, 129.4, 127.6, 126.2, 116.9, 78.3, 75.2, 68.9, 53.6, 43.2, 28.0, 27.5, 26.9, 25.1, 11.5.

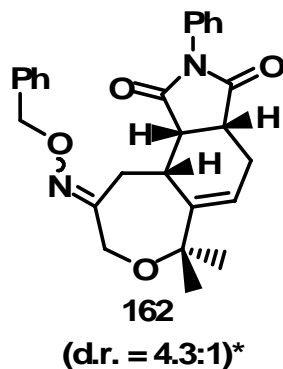
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₁H₂₃N₂O₄ = 367.1736, found = 367.1704 [M-H]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

[α]_D²⁰: + 5.0° (c = 2, CHCl₃).

Yield: 8 mg (15 % after 6 steps).

8.11.86 Analytical data of compound 162:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): δ = 7.36-7.30 (m, 8H), 7.15-7.13 (m, 2H), 5.87-5.85 (dd, J = 2.4 Hz, 7.0 Hz, 1H), 5.03 (s, 2H), 3.51-3.45 (m, 1H), 3.27-3.22 (m, 2H), 3.18-3.14 (dd, J = 6.4 Hz, 9.9 Hz, 1H), 2.81-2.72 (m, 1H), 1.93-1.91 (m, 2H), 1.75-1.74 (m, 2H), 1.32-1.30 (m, 6H).

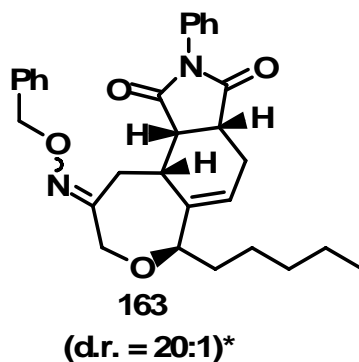
^{13}C NMR (100 MHz, CDCl_3): δ = 179.3, 177.5, 156.0, 146.5, 137.4, 136.3, 131.8, 129.5, 128.6, 128.5, 126.7, 121.7, 78.3, 76.3, 64.9, 44.6, 38.0, 31.7, 29.9, 27.5, 25.7, 22.9, 21.8.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_4$ = 444.2049, found = 444.2087 $[\text{M}]^+$.

R_f = 0.5 (cyclohexane: ethyl acetate = 4: 1).

Yield: 7.3 mg (13 % after 6 steps).

8.11.87 Analytical data of compound 163:



* = inseparable mixture, ratio determined by ^1H NMR spectroscopy

^1H NMR (400 MHz, CDCl_3): δ = 7.37-7.31 (m, 8H), 7.15-7.14 (m, 1H), 7.13-7.12 (m, 1H), 5.85-5.82 (t, J = 4.5 Hz, 1H), 5.05 (s, 2H), 4.02-3.98 (m, 2H), 3.38-3.27 (m, 2H), 3.21-3.15 (m, 2H), 2.65-2.62 (m, 2H), 1.70-1.64 (m, 2H), 1.31-1.23 (m, 8H), 0.91-0.87 (t, J = 7.0 Hz, 3H).

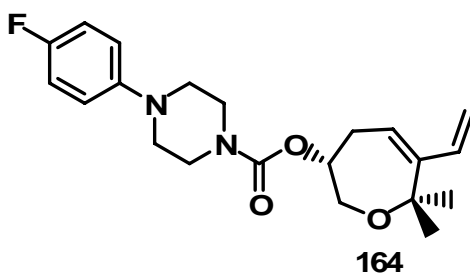
^{13}C NMR (100 MHz, CDCl_3): δ = 179.2, 177.4, 156.0, 142.6, 137.5, 131.8, 129.5, 128.9, 128.6, 128.4, 126.7, 124.0, 83.6, 76.3, 70.0, 44.3, 38.6, 33.6, 31.9, 27.0, 25.7, 22.8, 22.2, 14.2.

HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_4$ = 486.2519, found = 486.2573 $[\text{M}]^+$.

R_f = 0.4 (cyclohexane: ethyl acetate = 3: 2).

Yield: 7.6 mg (10 % after 6 steps).

8.11.88 Analytical data of compound 164:



¹H NMR (400 MHz, CDCl₃): δ = 6.96-6.90 (m, 2H), 6.88-6.85 (m, 2H), 6.25-6.12 (m, 1H), 5.88-5.70 (m, 1H), 5.30-5.25 (m, 1H), 5.06-5.01 (m, 1H), 4.21-4.17 (dd, *J* = 5.3 Hz, 13.0 Hz, 1H), 3.70-3.65 (m, 2H), 3.62-3.58 (m, 4H), 3.10-2.88 (m, 4H), 2.79-2.74 (m, 1H), 2.60-2.20 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 158.5, 154.9, 148.1, 145.9, 140.7, 120.5, 118.9, 118.2, 116.6, 116.0, 80.2, 74.1, 65.8, 50.9, 49.9, 48.6, 48.3, 28.9, 27.5, 26.1.

¹⁹F NMR (338.6 MHz, CDCl₃): -123.8.

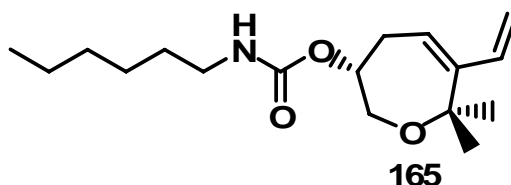
HR-MS (FAB, 70 eV): *m/z* calculated for C₂₁H₂₇N₂O₃ = 374.2006, found = 374.2099 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 4: 1).

[α]_D²⁰: - 19.2° (c = 1, CHCl₃).

Yield: 30 mg (40 % after 4 steps).

8.11.89 Analytical data of compound 165:



¹H NMR (400 MHz, CDCl₃): δ = 6.22-6.15 (m, 1H), 5.89-5.78 (m, 1H), 5.33-5.21 (m, 1H), 5.09-5.03 (m, 1H), 4.25-4.17 (dd, *J* = 5.4 Hz, 13.2 Hz, 1H), 3.75-3.69 (m, 2H), 3.16-3.09 (m, 2H), 2.77-2.73 (m, 1H), 2.63-2.25 (m, 1H), 1.67-1.55 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.36-1.33 (m, 6H), 0.89-0.86 (t, *J* = 6.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 158.8, 148.9, 140.5, 121.1, 116.2, 80.1, 74.2, 65.9, 42.2, 32.9, 29.6, 27.8, 27.0, 26.6, 22.9, 14.2.

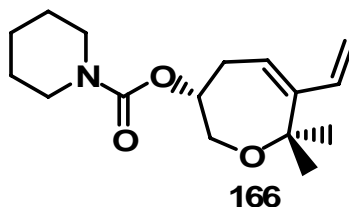
HR-MS (FAB, 70 eV): *m/z* calculated for C₁₇H₂₉NO₃ = 295.2147, found = 295.2199 [M]⁺.

R_f = 0.6 (cyclohexane: ethyl acetate = 4: 1).

[α]_D²⁰: - 7.1° (c = 1, CHCl₃).

Yield: 20 mg (35 % after 4 steps).

8.11.90 Analytical data of compound 166:



¹H NMR (400 MHz, CDCl₃): δ = 6.25-6.15 (m, 1H), 5.86-5.77 (m, 1H), 5.35-5.25 (m, 1H), 5.07-5.02 (m, 1H), 4.29-4.19 (dd, *J* = 5.0 Hz, 13.0 Hz, 1H), 3.79-3.65 (m, 2H), 3.62-3.58 (m, 4H), 2.76-2.70 (m, 1H), 2.65-2.30 (m, 1H), 1.71-1.52 (m, 6H), 1.38 (s, 3H), 1.32 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 158.9, 148.3, 140.3, 121.4, 117.0, 80.5, 74.8, 65.3, 47.7, 46.8, 30.2, 27.8, 27.2, 26.9, 25.8, 25.3.

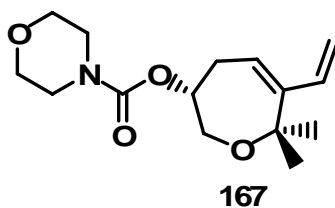
HR-MS (FAB, 70 eV): *m/z* calculated for C₁₆H₂₅NO₃ = 279.1834, found = 279.1898 [M]⁺.

R_f = 0.6 (cyclohexane: ethyl acetate = 4: 1).

[α]_D²⁰: + 20.2° (c = 1, CHCl₃).

Yield: 25 mg (30 % after 4 steps).

8.11.91 Analytical data of compound 167:



¹H NMR (400 MHz, CDCl₃): δ = 6.29-6.10 (m, 1H), 5.96-5.87 (m, 1H), 5.43-5.35 (m, 1H), 5.11-5.05 (m, 1H), 4.30-4.25 (dd, *J* = 4.9 Hz, 12.5 Hz, 1H), 3.96-3.87 (m, 4H), 3.72-3.40 (m, 6H), 2.87-2.79 (m, 1H), 2.75-2.40 (m, 1H), 1.38 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 156.3, 149.3, 141.3, 120.4, 116.0, 80.7, 74.4, 67.9, 67.3, 65.3, 47.9, 47.6, 30.6, 26.9, 26.4$.

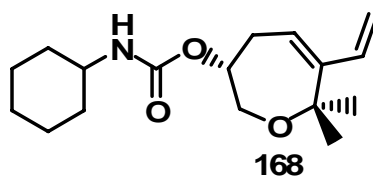
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{15}\text{H}_{23}\text{NO}_4 = 281.1627$, found = 281.1623 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 3: 2).

$[\alpha]_D^{20}$: -19.3° ($c = 2, \text{CHCl}_3$).

Yield: 15 mg (20 % after 4 steps).

8.11.92 Analytical data of compound 168:



^1H NMR (400 MHz, CDCl_3): $\delta = 8.1$ (bs, 1H), 6.20-6.15 (m, 1H), 5.90-5.81 (m, 1H), 5.40-5.30 (m, 1H), 5.17-5.04 (m, 1H), 4.28-4.22 (dd, $J = 4.8$ Hz, 12.0 Hz, 1H), 3.74-3.54 (m, 3H), 2.85-2.75 (m, 1H), 2.79-2.48 (m, 1H), 1.79-1.43 (m, 10H), 1.38 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 156.9, 147.3, 140.9, 121.0, 116.9, 80.4, 75.0, 68.8, 49.0, 34.5, 33.9, 30.1, 29.2, 27.8, 27.0, 22.9, 220.2$.

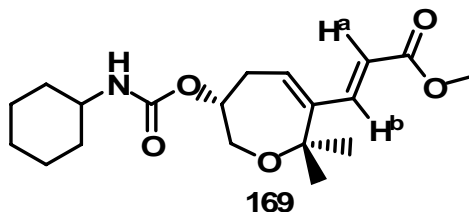
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{17}\text{H}_{27}\text{NO}_3 = 293.1991$, found = 293.1999 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 4: 1).

$[\alpha]_D^{20}$: $+4.1^\circ$ ($c = 2, \text{CHCl}_3$).

Yield: 14 mg (22 % after 4 steps).

8.11.93 Analytical data of compound 169:



¹H NMR (400 MHz, CDCl₃): δ = 7.13-7.09 (d, $J_{\text{Ha-Hb}}$ = 15.4 Hz, 1H), 6.00-5.96 (d, $J_{\text{Ha-Hb}}$ = 15.6 Hz, 1H), 5.93-5.89 (m, 1H), 4.96-4.95 (m, 1H), 4.60-4.58 (m, 1H), 4.00-3.95 (dd, J = 5.3 Hz, 13.7 Hz, 1H), 3.72 (s, 3H), 3.66-3.61 (m, 1H), 3.44-3.42 (m, 1H), 2.73-2.68 (m, 1H), 2.54-2.49 (m, 1H), 1.90-1.86 (m, 2H), 1.70-1.64 (m, 2H), 1.59-1.54 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.16-1.08 (m, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.3, 155.2, 145.4, 125.9, 119.2, 80.9, 73.3, 69.7, 65.8, 54.0, 51.8, 49.9, 33.6, 31.9, 29.5, 28.8, 25.7, 24.9.

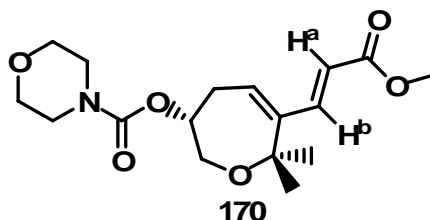
HR-MS (FAB, 70 eV): m/z calculated for C₁₉H₂₉NO₅ = 351.2046, found = 351.2018 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 9: 1).

[α]_D²⁰: - 14.1° (c = 2, CHCl₃).

Yield: 30 mg (35 % after 7 steps).

8.11.94 Analytical data of compound 170:



¹H NMR (400 MHz, CDCl₃): δ = 7.13-7.09 (d, $J_{\text{Ha-Hb}}$ = 16.0 Hz, 1H), 5.99-5.96 (d, $J_{\text{Ha-Hb}}$ = 15.6 Hz, 1H), 5.91-5.89 (m, 1H), 5.02-4.97 (m, 1H), 4.03-3.99 (dd, J = 5.7 Hz, 13.7

Hz, 1H), 3.73 (s, 3H), 3.67-3.66 (m, 1H), 3.63-3.61 (m, 4H), 3.44-3.42 (m, 4H), 2.77-2.70 (m, 1H), 2.56-2.49 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 167.3, 155.1, 145.3, 145.2, 125.7, 119.3, 80.9, 74.4, 69.7, 66.8, 65.7, 54.1, 51.8, 31.9, 29.5, 28.7, 27.6, 26.1$.

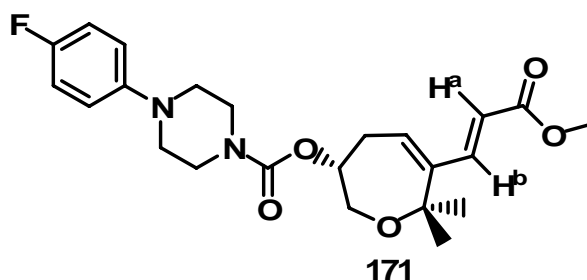
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{17}\text{H}_{25}\text{NO}_6 = 339.1682$, found = 339.1651 $[\text{M}]^+$.

$R_f = 0.4$ (cyclohexane: ethyl acetate = 3: 2).

$[\alpha]_D^{20}$: -29.5° ($c = 1, \text{CHCl}_3$).

Yield: 30 mg (36 % after 7 steps).

8.11.95 Analytical data of compound 171:



^1H NMR (400 MHz, CDCl_3): $\delta = 7.15\text{-}7.11$ (d, $J_{\text{Ha-Hb}} = 15.6$ Hz, 1H), 6.98-6.93 (m, 2H), 6.87-6.84 (m, 2H), 6.01-5.97 (d, $J_{\text{Ha-Hb}} = 15.6$ Hz, 1H), 5.95-5.91 (m, 1H), 5.04-4.99 (m, 1H), 4.06-4.01 (dd, $J = 5.7$ Hz, 13.8 Hz, 1H), 3.73 (s, 3H), 3.70-3.66 (m, 1H), 3.61-3.58 (m, 4H), 3.10-2.98 (m, 4H), 2.78-2.73 (m, 1H), 2.56-2.15 (m, 1H), 1.40 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 167.3, 158.9, 156.6, 154.9, 148.1, 145.3, 125.7, 119.3, 118.9, 118.8, 115.9, 115.7, 80.9, 74.4, 65.8, 54.1, 51.8, 50.6, 31.9, 29.5, 28.7, 27.6, 26.1$.

^{19}F NMR (338.6 MHz, CDCl_3): -123.8 .

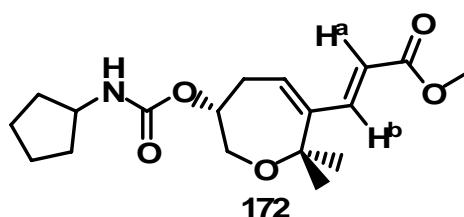
HR-MS (FAB, 70 eV): m/z calculated for $\text{C}_{23}\text{H}_{29}\text{FN}_2\text{O}_5 = 432.2061$, found = 432.2011 $[\text{M}]^+$.

$R_f = 0.5$ (cyclohexane: ethyl acetate = 2: 1).

Yield: 40 mg (38% after 5 steps).

$[\alpha]_D^{20}$: - 1.5° (c = 1, CHCl₃).

8.11.96 Analytical data of compound 172:



¹H NMR (400 MHz, CDCl₃): δ = 7.13-7.09 (d, $J_{\text{Ha-Hb}}$ = 15.6 Hz, 1H), 5.99-5.96 (d, $J_{\text{Ha-Hb}}$ = 15.6 Hz, 1H), 5.93-5.90 (t, J = 7.2 Hz, 1H), 4.97-4.96 (m, 1H), 4.65-4.63 (m, 1H), 4.00-3.91 (m, 2H), 3.72 (s, 3H), 3.67-3.61 (m, 1H), 2.73-2.65 (m, 1H), 2.55-2.48 (m, 1H), 1.93-1.90 (m, 2H), 1.65-1.54 (m, 4H), 1.39 (s, 3H), 1.34 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.3, 155.6, 145.4, 145.1, 125.9, 119.2, 80.9, 73.4, 69.7, 65.7, 54.1, 52.9, 51.8, 33.4, 31.9, 29.5, 28.8, 27.6, 26.0, 23.7.

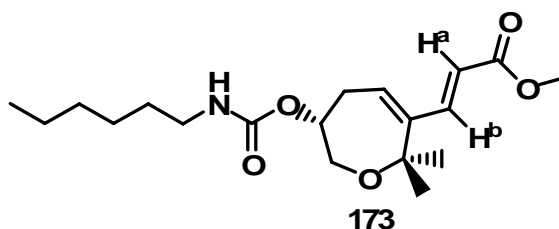
HR-MS (FAB, 70 eV): m/z calculated for C₁₈H₂₇NO₅ = 337.1889, found = 337.1859 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 9: 1).

$[\alpha]_D^{20}$: - 3.0° (c = 1, CHCl₃).

Yield: 28 mg (35 % after 7 steps).

8.11.97 Analytical data of compound 173:



¹H NMR (400 MHz, CDCl₃): δ = 7.14-7.09 (d, $J_{\text{Ha-Hb}} = 15.6$ Hz, 1H), 6.00-5.96 (d, $J_{\text{Ha-Hb}} = 15.6$ Hz, 1H), 5.93-5.89 (m, 1H), 4.99-4.96 (m, 1H), 4.70-4.67 (m, 1H), 4.01-3.96 (dd, $J = 5.3$ Hz, 13.7 Hz, 1H), 3.73 (s, 3H), 3.68-3.61 (m, 1H), 3.15-3.10 (q, $J = 6.6$ Hz, 2H), 2.71-2.66 (m, 1H), 2.55-2.50 (m, 1H), 1.47-1.43 (m, 2H), 1.39 (s, 3H), 1.34 (s, 3H), 1.27-1.24 (m, 6H), 0.89-0.85 (t, $J = 6.8$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.3, 156.1, 145.4, 125.9, 119.2, 80.9, 73.5, 65.7, 51.8, 41.2, 31.6, 30.1, 28.8, 27.6, 26.6, 26.0, 22.7, 14.2.

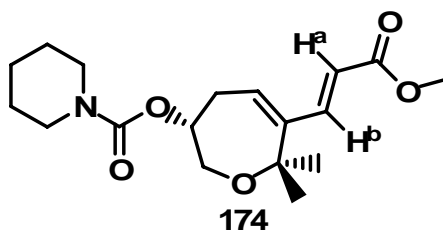
HR-MS (FAB, 70 eV): m/z calculated for C₁₉H₃₁NO₅ = 353.2202, found = 353.2269 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 9: 1).

[α]_D²⁰: - 12.8° (c = 1, CHCl₃).

Yield: 30 mg (35 % after 7 steps).

8.11.98 Analytical data of compound 174:



¹H NMR (400 MHz, CDCl₃): δ = 7.15-7.11 (d, $J_{\text{Ha-Hb}} = 15.6$ Hz, 1H), 6.00-5.96 (d, $J_{\text{Ha-Hb}} = 15.6$ Hz, 1H), 5.94-5.91 (m, 1H), 5.01-4.95 (m, 1H), 4.04-3.99 (dd, $J = 5.8$ Hz, 13.8 Hz, 1H), 3.73 (s, 3H), 3.67-3.63 (dd, $J = 3.3$ Hz, 13.6 Hz, 1H), 3.39-3.36 (m, 4H), 2.73-2.69 (m, 1H), 2.56-2.49 (m, 1H), 1.58-1.54 (m, 2H), 1.50-1.49 (m, 4H), 1.39 (s, 3H), 1.34 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 167.4, 155.1, 145.5, 145.2, 126.1, 119.1, 80.8, 73.9, 69.7, 65.9, 54.0, 51.8, 45.9, 31.9, 29.5, 28.8, 27.5, 26.2, 25.9, 24.6.

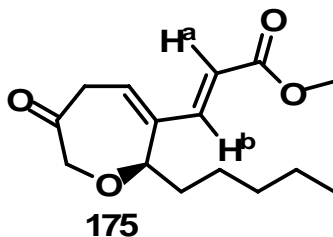
HR-MS (FAB, 70 eV): m/z calculated for C₁₈H₂₇NO₅ = 337.1889, found = 337.1859 [M]⁺.

R_f = 0.4 (cyclohexane: ethyl acetate = 9: 1).

$[\alpha]_D^{20}$: - 25.0° (c = 1, CHCl₃).

Yield: 24 mg (30 % after 7 steps).

8.11.99 Analytical data of compound 175:



¹H NMR (400 MHz, CDCl₃): δ = 7.19-7.15 (d, $J_{\text{Ha-Hb}}$ = 16.8 Hz, 1H), 6.01-5.97 (dd, J = 4.7 Hz, 9.2 Hz, 1H), 5.78-5.73 (d, $J_{\text{Ha-Hb}}$ = 16.2 Hz, 1H), 4.48-4.46 (m, 1H), 4.26-4.21 (d, J = 18.2 Hz, 1H), 4.05-4.00 (d, J = 18.2 Hz, 1H), 3.76 (s, 3H), 3.73-3.71 (m, 1H), 2.92-2.86 (dd, J = 9.3 Hz, 13.2 Hz, 1H), 1.84-1.67 (m, 4H), 1.33-1.28 (m, 4H), 0.91-0.88 (t, J = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 210.1, 165.5, 146.9, 142.2, 135.5, 115.9, 77.9, 72.3, 40.1, 33.4, 32.1, 27.1, 25.9, 22.8, 14.2.

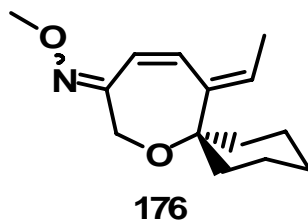
HR-MS (FAB, 70 eV): m/z calculated for C₁₅H₂₂O₄ = 266.1518, found = 266.1529 [M]⁺.

R_f = 0.5 (cyclohexane: ethyl acetate = 9: 1).

$[\alpha]_D^{20}$: + 6.1° (c = 2, CHCl₃).

Yield: 20 mg (30% after 6 steps).

8.11.100 Analytical data of compound 176:



¹H NMR (400 MHz, CDCl₃): δ = 6.63-6.51 (m, 1H), 5.74-5.63 (m, 1H), 4.44-4.43 (m, 1H), 4.11-4.09 (m, 3H), 3.88-3.87 (m, 2H), 1.29-1.20 (m, 8H), 0.89-0.83 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.4, 145.1, 143.7, 125.5, 120.6, 99.1, 72.1, 63.1, 35.8, 28.6, 22.4, 22.0, 21.8, 21.3, 14.1.

HR-MS (FAB, 70 eV): m/z calculated for C₁₄H₂₁NO₂ = 235.1572, found = 235.1511 [M]⁺.

R_f = 0.5 (cyclohexane: ethyl acetate = 4: 1).

Yield: 17 mg (30 % after 5 steps).

Thesis in a nutshell:

Small and medium ring oxygen heterocycles are essential and significant structural frameworks in many natural products having a wide range of biological activities. Total synthesis of those natural products guided a path to synthesize small and medium ring ethers embedded in their structure as well. Recently ring-closing metathesis reaction has been used widely in the synthesis of natural products containing small and medium ring ethers. In this context this thesis was aimed to synthesize small and medium ring ether scaffolds by ring-closing metathesis reaction.

One major half of this thesis is dedicated to the ring-closing metathesis in diene-ene moiety in synthesizing small and medium ring systems. Diene-ene ring-closing metathesis has been applied in synthesizing macrocycles in natural product synthesis. The same diene-ene ring-closing metathesis reaction behaves in an interesting and hitherto unknown way to synthesize small and medium ring ether systems. In this perspective competition between the formation of larger and smaller rings was observed. In the light of diene-ene ring-closing metathesis reaction, competitions between five- versus seven-membered ring formation, six- versus eight-membered ring formation and seven- versus nine-membered ring formation were studied.

To acquire the knowledge about the competition reactions, the open chain precursors of the competition were synthesized from commercially available substituted propargyl alcohol. A common aldehyde intermediate was synthesized from the propargyl alcohol by means five steps synthetic procedure. The diene-ene open chain precursor for the competition of five- versus seven-membered ring ethers was synthesized from the aldehyde intermediate by well known Wittig olefination reaction. When this diene-ene precursor was exposed to metathesis reaction using either 1st or 2nd generation Grubbs ruthenium carbene complex, five-membered ring ether with mono unsaturation and seven-membered ring ether with double unsaturation were obtained. It was also demonstrated that the formation of the five- and seven-membered rings was not kinetically controlled but it was thermodynamically controlled.

The open chain precursor to explore the competition between the six- versus eight-membered rings was synthesized by vinylation of the aldehyde. When the diene-ene

precursor was exposed in the metathesis condition, only more thermodynamically stable six-membered mono-unsaturated cyclic ether was formed devoid of any trace of eight-membered ring ether.

The precursor to investigate the competition between seven-versus nine-membered ring ethers was obtained by allylation of the aldehyde intermediate. When this diene-ene precursor was treated under the metathesis condition, only the more thermodynamically stable seven-membered ring ether was obtained without any trace of nine-membered ring ether.

It was evident that in the metathesis condition, the initiation of the reaction occurred by the formation of ruthenium carbene at the isolated olefin moiety and terminated at the diene moiety, hence forming the small sized ring ethers. Synthesizing the larger ring ethers containing double unsaturation was envisioned by this diene-ene metathesis condition by introducing the bulky group on the isolated olefin moiety. Hence the initial ruthenium carbene must form in the diene moiety first and terminate in the isolated olefin to afford the larger ring ethers. The advanced intermediates containing bulky groups in the isolated olefin moiety were synthesized from the same aldehyde intermediate. When those advanced intermediates were treated with the 2nd generation Grubbs ruthenium carbene complex, surprisingly the rings did not close to offer either eight-membered or nine-membered ring ethers though the initial ruthenium carbene formed in the conjugated diene moiety. So it was concluded from the above study that the formation of the small and medium size ring ethers in the metathesis condition is totally thermodynamic.

The other half of this thesis dealt with the solid-supported solution phase synthesis of oxepane library. Oxepane, seven-membered cyclic ether is abundant in various natural products having broad range of biological activities. Hence those biologically active pre validated oxepane containing natural products may provide powerful guiding principles for oxepane based library development. While developing small molecule combinatorial library in solution phase, the synthetic strategy must be practical, sensible and rapid. In this context the solution phase combinatorial synthesis of an oxepane library was developed using solid-supported reagents and scavengers. In this synthetic strategy, the oxepane scaffold was synthesized by the key ring-closing enyne metathesis reaction. After achieving the oxepane scaffold, it was diversified to generate the fully

functionalized oxepane library. The library generation was commenced from the combinatorial coupling of different commercially available substituted propargyl alcohols with the substituted α -bromo ethyl acetates. After functional group modifications of this coupling product, the ring-closing enyne metathesis precursor was synthesized. Upon exposure of this precursor to either 1st or 2nd generation Grubbs ruthenium carbene complex, an oxepane scaffold containing a free alcohol group and a diene moiety was formed. On one hand, the free alcohol group in the oxepane scaffold was derivatized to esters and carbamates. On the other hand, the diene moiety was derivatized by well known Diels-Alder reaction to generate the library.

To reduce the extensive workup and purification procedure in each of the steps in the synthetic strategy and thus speed up the library generation, the use of solid supported reagents and scavengers emerged. The sulfonic acid resin was used to scavenge the Grignard reagent used in the allylation reaction *en route* to the oxepane scaffold. A solid-supported chelating ligand was used to scavenge the ruthenium metal from the enyne metathesis reaction mixture. A solid-supported resin bound primary amine was used to scavenge the excess acid chlorides and isocyanates from the esterification and carbamate formation reaction. The same polymer bound sulfonic acid resin was used to remove the excess primary and secondary amines as well as the base used in the carbamate formation reaction. In most of the steps in this synthetic strategy a polymer bound scavenging reagent was used to eliminate the extensive workup procedure and labourious purification steps. The diene moiety in the oxepane scaffold was also functionalized using cross metathesis reaction by Grubbs ruthenium carbene. The free alcohol group in the oxepane moiety was oxidized to ketone and further functionalized to the oximes.

At the end combining all the experience using solid-supported reagents and scavengers in this strategy a one pot synthetic strategy was developed to generate the fully functionalized oxepane library. In this one pot strategy, all the reactions were carried out devoid of any workup and purification steps. The only purification step was carried out at the end of the route to provide the pure oxepane molecule for the further studies. Finally, a small library (containing 110 molecules) of fully functionalized oxepane was synthesized. This one pot synthetic strategy was proved to be competent, practical and viable for the rapid generation of the oxepane molecules. It was envisioned that the

synthesized oxepane molecules would be used in future for both forward and reverse chemical genomics and chemical genetics studies to indentify the target of interest and as well as in cell based assays to detect the inhibitors or activators in the signaling pathways.

Abbreviations:

Ac	Acetyl (CH ₃ CO)
aq.	Aqueous
Ar	Aromatic
Bn	Benzyl (PhCH ₂)
Bu	Butyl
CDI	Carbonyl diimidazole
Cp	Cyclopentyl
CSA	Camphor sulfonic acid
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-en
DCC	<i>N,N</i> -Dicyclohexyl carbodiimide
DCM	Dichloromethane (CH ₂ Cl ₂)
DIBAL-H	Diisobutylaluminiumhydride
DIPCl	Diisopinocampheylboron chloride
DMAP	<i>N,N</i> -Dimethylamino pyridine
DMF	<i>N,N</i> -Dimethyl formamide
DMSO	<i>N,N</i> -Dimethyl sulfoxide
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
EI	Electron Impact
<i>ent</i>	Enantiomer
equiv.	Equivalent
Et	Ethyl (CH ₃ CH ₂)
eV	Electron volt
FAB	Fast atom bombardment
Fmoc	9-Fluorenylmethoxycarbonyl
GC-MS	Gas chromatography-mass spectroscopy
h	Hour
HMPA	Hexamethylphosphoramide

HPLC	High performance liquid chromatography
HR-MS	High resolution mass spectroscopy
Hz	Hertz
IBX	2-iodoxybenzoic acid
Ipc	Isopinocampheyl
<i>i</i> -Pr	<i>iso</i> propyl
LC-MS	Liquid chromatography-mass spectroscopy
LDA	Lithium diisopropylamide
Me	Methyl (CH ₃)
Min	Minute
mmol	Milimol
MOM	Methoxy methyl (CH ₃ OCH ₂)
NaHMDS	Sodium hexamethyldisilazide
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
<i>n</i> -Bu	normal butyl (CH ₃ CH ₂ CH ₂ CH ₂)
NMR	Nuclear magnetic resonance
nOe	Nuclear overhauser effect
<i>p</i>	<i>para</i>
PCC	Pyridinium chlorochromate
Ph	Phenyl (C ₆ H ₅)
Piv	Pivaloyl [(CH ₃) ₃ CCO]
Ppm	Parts per million
PTLC	Preparative thin layer chromatography
Py	Pyridine
R _f	Retention factor
rt	Room temperature
TBAF	Tetrabutylammonium fluoride
<i>t</i> -Bu	<i>tertiary</i> butyl [(CH ₃) ₃ C]
TBS	tertiary butyl dimethyl silyl [(CH ₃) ₃ CSi(CH ₃) ₂]
TBDPS	tertiary butyl diphenyl silyl [(CH ₃) ₃ CSi(C ₆ H ₅) ₂]

Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl [(Me ₂ CH) ₃ Si]
TLC	Thin layer chromatography
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TMS	Trimethyl silyl [(CH ₃) ₃ Si]
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl (<i>p</i> -toluenesulfonyl)
TS	Transition state
$[\alpha]_D^{20}$	Specific optical rotation

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Erklärung:

“Ich versichere, dass ich die von mir vorgelegte Dissertation selbständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit – einschließlich Tabellen, Karten und Abbildungen-, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie noch nicht veröffentlicht worden ist, sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen dieser Promotionsordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Herrn Professor Dr. Herbert Waldmann betreut worden.”

Sudipta Basu
Dortmund

Bisher sind folgende Teilpublikationen veröffentlicht worden:

1. “*Regioselectivity in the Formation of Small- and Medium- Sized Cyclic Ethers by Diene- Ene Ring-Closing Metathesis*” S. Basu and H.Waldmann, *J. Org. Chem.*, **2006**, *71*, 3977-3979.
2. “*Compound library development guided by protein structure similarity clustering and natural product structure*” M. A. Koch, L. –O. Wittenberg, S. Basu, D. A. Jeyaraj, E. Gourzoulidou, K. Reinecke, A. Odermatt and H. Waldmann, *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 16721-16726.

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