Stereoselective Construction of C-C Double Bonds via Olefin Metathesis: From Tethered Reactions to Water-Soluble Catalysts for Stereoretentive Metathesis

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“Success is not final, failure is not fatal; it is the courage to continue that counts.”

Winston Churchill

Declaration

I declare that this thesis has been composed solely by myself, and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where it is stated otherwise, by reference or acknowledgement, the work presented is entirely my own.

Berlin, 26th October 2021

Kajsa Lood

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Publications

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Conferences

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Abstract

Natural products have proved to be a major resource in the discovery and development of many pharmaceuticals that are in use today. There is a wide variety of biologically active natural products that contain conjugated polyenes or benzofuran structures. Therefore, new synthetic methods for the construction of such building blocks are of great interest to synthetic chemists. The recently developed one-pot tethered ring-closing metathesis approach allows for the formation of *Z,E*-dienoates in high stereoselectivity. The extension of this method with a Julia-Kocienski olefination protocol would allow for the formation of conjugated trienes in a stereoselective manner. This strategy was applied in the total synthesis of conjugated triene containing (+)-bretonin B. Additionally, investigations of cross metathesis using methyl substituted olefins were pursued. This methodology was applied, as a one-pot cross metathesis/ring-closing metathesis sequence, in the total synthesis of benzofuran containing 7-methoxywutaifuranal. Finally, the design and synthesis of a catalyst for stereoretentive metathesis in aqueous media was investigated.

Abbreviations

Bn	Benzyl
CM	Cross metathesis
DCM	Dichloromethane
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCVC	Dry column vacuum chromatography
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMF	Dimethylformamide
DMAP	4-Dimethylaminopyridine
DMP	Dess-Martin periodinane
GC	Gas chromatography
KHMDS	Potassium bis(trimethylsilyl)amide
m-CPBA	*meta*-Chloroperoxybenzoic acid
MeOH	Methanol
NaHMDS	Sodium bis(trimethylsilyl)amide
NHC	N-Heterocyclic carbene
NMR	Nuclear magnetic resonance
PEG	Polyethylene glycol
p-TSA	*para*-Toluenesulfonic acid
PMB	*para*-Methoxybenzyl
RCM	Ring-closing metathesis
ROM	Ring-opening metathesis
ROMP	Ring-opening metathesis polymerisation

t-AmOK	Potassium *tert*-amylate
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TEOF	Triethyl orthoformate
THF	Tetrahydrofuran
TLC	Thin layer chromatography

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1 Introduction

The advent of organic synthesis was marked by Wöhler's synthesis of urea in 1828.[1] This discovery had a profound impact on science and society. It has countless applications, ranging from synthesis of natural products and pharmaceuticals to discovering and developing new synthetic methods and strategies.[2] Ever since its invention, the synthesis of naturally occurring substances has been of the utmost importance in synthetic organic chemistry.[3]

Progress in the field of total synthesis has largely been dependent on the ability to create carbon frameworks.[4] Traditionally, Grignard, Diels-Alder, and Wittig reactions have served as the most important methods used to construct carbon-carbon bonds. However, over the last quarter of the 20th century palladium-catalysed cross-coupling reactions and olefin metathesis have emerged as rivals to the aforementioned methodologies.[4]

The success of olefin metathesis is largely due to the design and development of catalysts that promote these transformations in a highly efficient and stereoselective fashion.[5] For biological applications, and as a greener alternative, catalysts have also been developed in order to conduct olefin metathesis in aqueous media.[6] Thus, olefin metathesis has been extensively utilised in the field of organic synthesis, and has had a particular impact in the total synthesis of natural products.[4-5]

There is a wide variety of biologically active natural products that contain conjugated polyenes or benzofuran structures, for example, polyene-containing compounds manumycin A (anti-fungal) and rapamycin (anti-bacterial), and benzofuran-based compounds angelicin (anti-proliferative) and bergapten (anti-tumour), as shown in Figure 1.[7-8] Therefore, new synthetic methods towards such derivatives are of great importance.

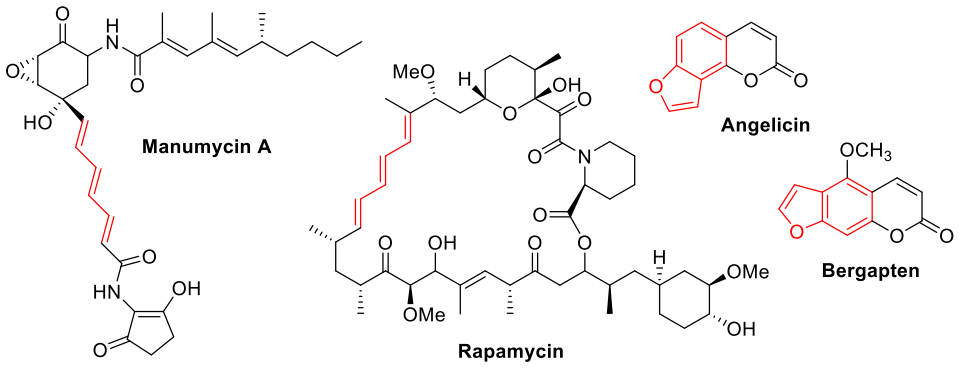
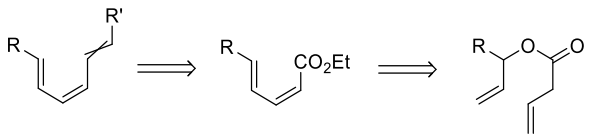


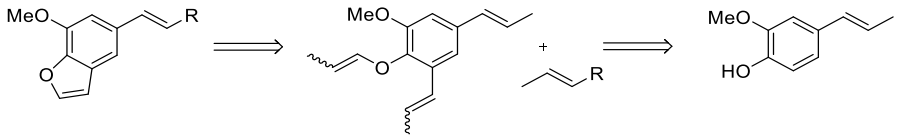
Figure 1. Representative examples of bio-active natural products.

There are many ways to obtain conjugated trienes. One approach would be to utilise the recently developed one-pot tethered ring-closing metathesis (RCM) sequence.[9] The extension of this method with a carbonyl olefination protocol, would allow for the synthesis of a target molecule containing a conjugated triene in a highly stereoselective fashion (Scheme 1).



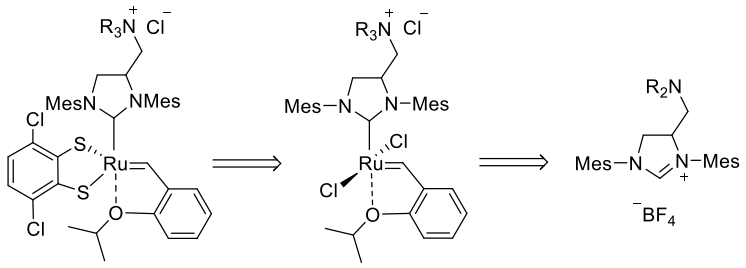
Scheme 1. Retro-synthetic route for the synthesis of polyenes via tethered RCM combined with a carbonyl olefination protocol.

Cross metathesis (CM) using methyl substituted olefins would circumvent the problems which are often associated with catalyst decomposition. Applying this strategy as a one-pot CM/RCM protocol in the synthesis of a benzofuran target molecule is expected to be an efficient approach, which may find additional applications in the future (Scheme 2).



Scheme 2. Retro-synthetic route for the synthesis of benzofurans using a one-pot CM/RCM sequence.

The development of new catalysts is essential in olefin metathesis. The design and synthesis of a stereoretentive metathesis catalyst that contains a quaternary ammonium group for homogeneous reactions in polar solvents, such as alcohols or water, would be a positive step towards more environmentally friendly reaction conditions (Scheme 3).



Scheme 3. Retro-synthetic route to obtain a quaternary ammonium catalyst for stereoretentive metathesis in polar solvents, such as alcohols and water.

2 Aim

In this thesis, four objectives were pursued:

(1) To apply a highly stereoselective tethered ring-closing metathesis (RCM) protocol in the total synthesis of a conjugated triene containing natural product.

(2) To investigate cross metathesis (CM) between methyl-substituted olefins, via the following steps:
   - Optimisation of the reaction conditions.
   - Evaluation of the scope of the reaction.

(3) To apply the CM methodology as a one-pot CM/RCM sequence in the total synthesis of a benzofuran target compound.

(4) To investigate stereoretentive metathesis in polar solvents such as alcohols and water, via the following steps:
   - Design and synthesis of quaternary ammonium tagged ruthenium-based catalysts.
   - Evaluation of the developed catalyst in stereoretentive metathesis model reactions.

3 Theoretical Background

3.1 Natural Products

Bioactive natural products obtained from plants, animals, and microorganisms, have been used for the treatment of many diseases since ancient times.[10] They have served as a major source in the discovery and development of many pharmaceuticals that are in use today, and about half of the drugs on the market are derived from natural products.[11] Penicillin G, morphine and quinine are representative examples of natural substances that are the foundation of modern pharmaceutical care (Figure 2).[11]

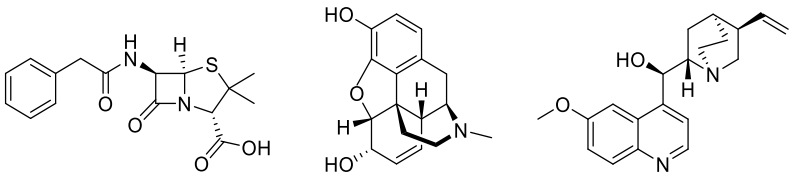


Figure 2. Examples of historically important natural products.

Natural products have also contributed with an exceptional set of research opportunity deriving from their unique structures and biological properties.[12] For example, the total synthesis of the antimalarial agent quinine led to a broad knowledge about the construction of heteroaromatic systems and the distinctive properties of quinoline and piperidine rings.[12]

Total synthesis plays a key role in the development of new reactions and reagents, which further demonstrates the importance of this field.[3] Advances in stereoselective methodology and asymmetric catalysis have allowed for the construction of more complex natural products in an enantioselective manner.[13] Moreover, synthesis of natural products may also contribute to the discovery of unsolved synthetic problems. Thus, total synthesis often serves as a measure of the power of a given reaction.[12]

The overall course of total synthesis has changed dramatically over time. Initially the focus was on the synthesis of scarcely occurring natural products and thereby rendering them readily available for structural confirmation, elucidation and biological investigation.[2] Whereas now, the focus lies on the development of more sustainable and environmentally friendly methods. In other words, simplifying existing synthetic strategies in order to obtain certain compounds.[14]

3.1.1 Polyene Natural Products

Natural and/or bioactive products that contain conjugated polyene moieties represent a large and structurally diverse group of compounds.[15] Representative examples are chivosazole F, myxalamide A and lipoxin A, which exhibit anti-tumour, antibacterial and anti-inflammatory properties respectively (Figure 3).[16-17]

Over the years much effort has been devoted towards improving previously discovered synthetic methods in order to obtain conjugated polyenes.[16] However, the construction of conjugated polyenes is a considerable challenge. The synthesis is often accompanied by problems with stereoselectivity, reactivity, and product stability.[18] Polyene moieties can be sensitive to heat, light, and strongly acidic or basic conditions, which often results in the need for mild conditions.[18]

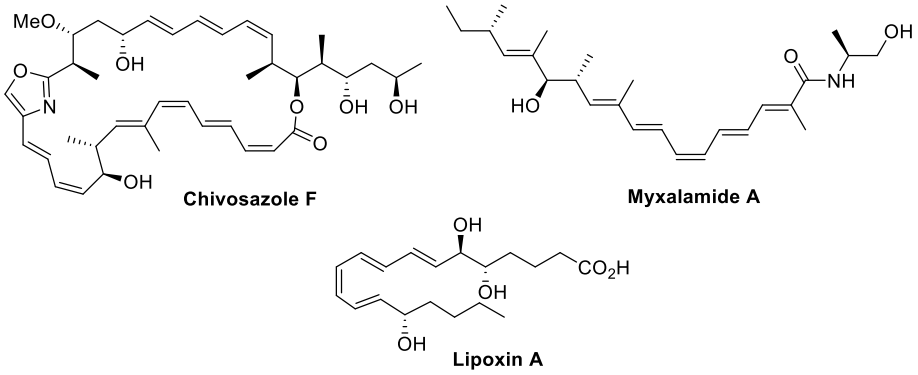


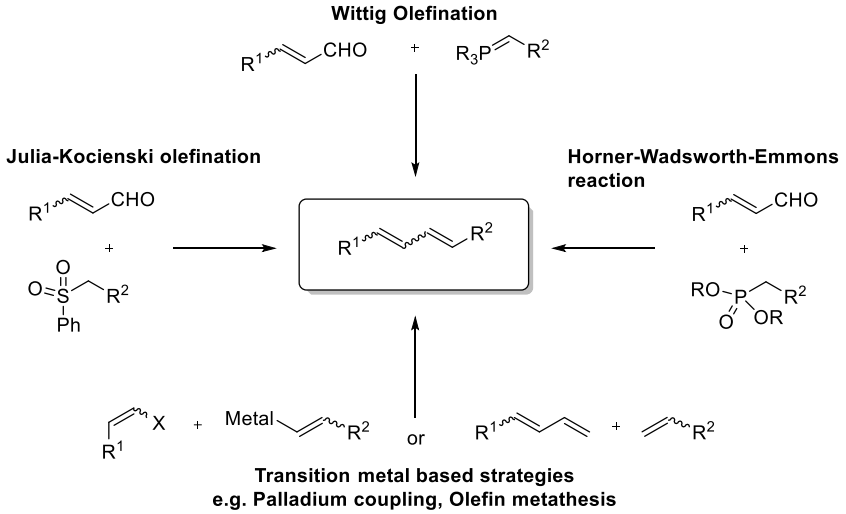
Figure 3. Selected examples of natural products containing polyenes.

Natural products containing all *E*-configured conjugated polyenes tend to be more stable than those containing a *Z*-configured double bond. Thus, polyenes with at least one *Z*-configured double bond are, both, more difficult to construct and especially prone to isomerisation to the *E*-configured isomer, due to certain thermodynamic principles.[16]

Additional problems arise when an olefination method leads to a mixture of *cis* and *trans* isomers. Since, in this instance, separating the mixture to obtain the desired isomer (if this is possible at all) would lead to a reduced yield. Thus, there are two principal requirements for polyene synthesis: 1) a reliable olefination method that produces alkenes in high stereoselectivity, and 2) a methodology that is mild and functional-group tolerant.[17]

There are several ways to create conjugated polyenes as outlined in Scheme 4. Traditionally, C-C double bond condensation methods such as, Wittig, Horner-Wadsworth-Emmons (HWE), and Julia-Kocienski olefinations, have been used.[17] However, transition metal-based strategies,

e.g. palladium-catalysed cross coupling and olefin metathesis, have emerged as a complement to the above-mentioned procedures in the synthesis of conjugated double bonds (Scheme 4).[15, 17]



Scheme 4. Common general strategies to access conjugated polyenes.

Natural product (+)-bretonin B (**1**) was isolated from an unidentified sea-water sponge belonging to the class *Demospongiae*, found in the North Brittany Sea.[19] It consists of a glycerol moiety esterified at the secondary alcohol by a *para*-hydroxybenzoyl group and etherified at the primary alcohol position by a (4*E*,6*Z*,8*E*)-trienic C12 carbon chain (Figure 4).

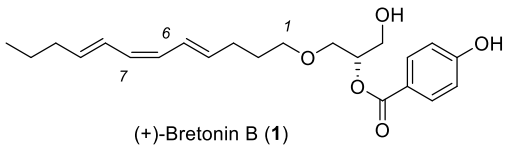
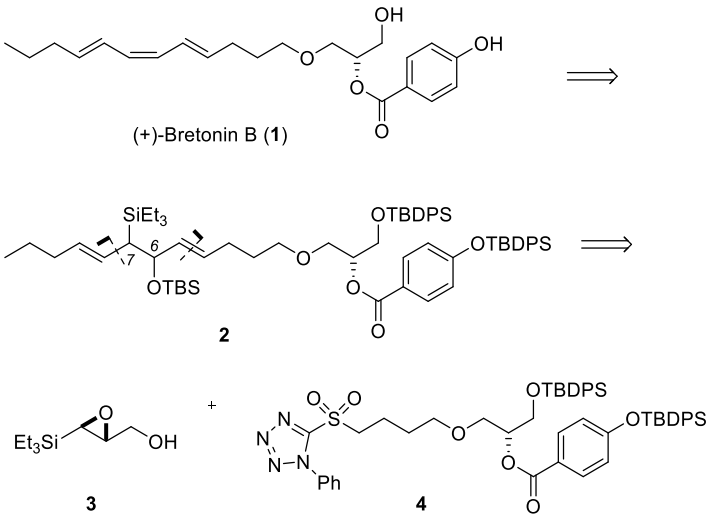


Figure 4. Natural product (+)-bretonin B (**1**).

Two syntheses of this natural product have been reported, both rely on the construction of the C6=C7 bond by olefination methods. In the first synthesis, an unselective Wittig olefination was applied to obtain both the (4*E*,6*E*,8*E*)- and (4*E*,6*Z*,8*E*)-isomers of bretonin B in a ca 1:1 ratio.[20] More recently, Bach et al. reported the second total synthesis of (+)-bretonin B (**1**).[21]

They demonstrated that the (*E*,*Z*,*E*)-triene core can be stereoselectively accessible by employing an α-silyl epoxide opening, a Julia-Kocienski olefination, and a late-stage Peterson elimination as key steps, as shown in Scheme 5. This total synthesis includes a 9-step linear sequence and (+)-bretonin B (**1**) could be isolated with an overall yield of 31%.[21]



Scheme 5. Retro-synthetic route to (+)-bretonin B (**1**) as reported by Bach et al.[21]

3.1.2 Benzofuran Natural Products

Benzofuran derivatives are a class of compounds that are ubiquitous in nature.[22] Numerous reports have shown that benzofuran compounds exhibit a variety of biological activities.[8] Thus, natural products containing benzofuran moieties have attracted much attention for their potential application as pharmaceuticals.[8] For example, wutaiensal, xanthotoxin, and usnic acid show anti-tubercular, anti-tumour, and anti-bacterial properties respectively (Figure 5).[8, 23]

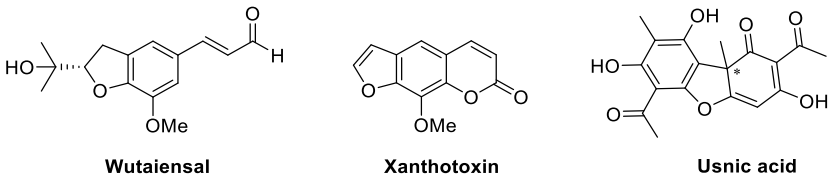
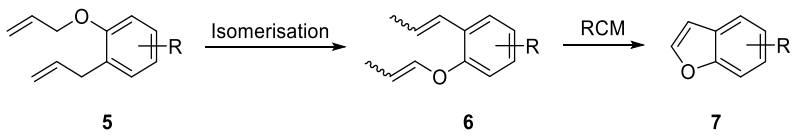


Figure 5. Examples of benzofuran natural products.

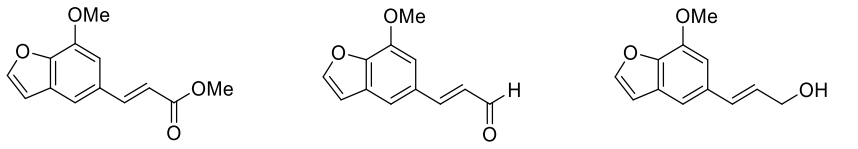
Owing to the immense interest in this class of compounds, many different approaches have been applied in the construction of benzofuran rings. Common methods to obtain benzofuran moieties include, the Heck reaction, palladium cross-couplings, heterocyclisation, and photochemical reactions.[8] One of the most popular of these methods involves palladium-catalysed cyclisation protocols.[24] In recent years, ring-closing metathesis (RCM) has emerged as an important method for the construction of benzofuran moieties, often in combination with a ruthenium-mediated isomerisation sequence (Scheme 6).[24]



Scheme 6. Construction of benzofurans via RCM.

The construction of benzofuran rings is well established in organic synthesis, which means there is an exceptional foundation for further development of new synthetic methods in the future.[24]

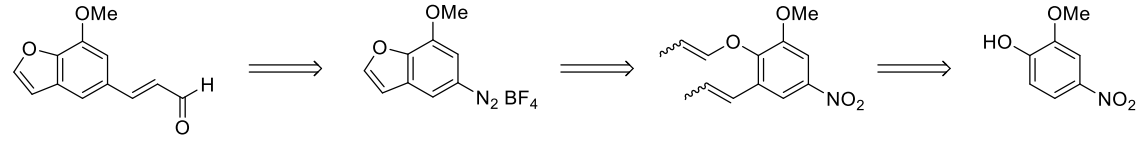
Secondary plant metabolites containing a benzofuran propanoid structure, were isolated from the shrub *Zanthoxylum wutaiense*.[23] Among these were 7-methoxy-methylwutaifuranate (**8**), 7-methoxywutaifuranal (**9**), and 7-methoxywutaifuranol (**10**) (Figure 6). Anti-tubercular activity was observed at a level of 35 μg/mL of 7-methoxywutaifuranal (**9**) against *Myobacterium tuberculosis*.[23]



7-Methoxymethylwutaifuranate (**8**) 7-Methoxywutaifuranal (**9**) 7-Methoxywutaifuranol (**10**)

Figure 6. Secondary plant metabolites isolated from *Zanthoxylum wutaiense*.

Natural product 7-methoxywutaifuranal (**9**) has previously been synthesised by Schmidt and Wolf.[25] The retro-synthetic route is outlined in Scheme 7. The total synthesis proceeded via an RCM sequence to transform **12** into benzofuran **11**. This was followed by a Pd-catalysed Heck-type coupling (Matsuda-Heck reaction) of the electron-rich arene diazonium salt to furnish natural product 7-methoxywutaifuranal (**9**). The total synthesis proceeded over 10 linear steps with an overall yield of 26%.[25]



7-Methoxywutaifuranal (**9**) **11** **12** **13**

Scheme 7. Retro-synthetic route to 7-methoxywutaifuranal (**9**) as reported by Schmidt and Wolf.[25]

3.2 Olefin Metathesis

Metathesis is derived from the Greek words *meta* (change) and *thesis* (position), which in chemistry can be translated into the exchange of parts of two substances. Thus, olefin metathesis involves a rearrangement of unsaturated carbon-carbon bonds between the reactants, in the presence of a well-defined metal carbene catalyst.[26]

The most well-known metathesis catalysts were prepared in the 1990s and are based on molybdenum and ruthenium as early transition metals.[26] One of the most important molybdenum based carbene systems **Mo-1**, was reported by Schrock et al. (Figure 7).[27] The major advantage of alkoxy imido molybdenum catalyst **Mo-1** is its high reactivity to a broad range of substrates and the fact that the alkoxides in the system can easily be exchanged to adjust the activity. However, some critical drawbacks of Mo-based complexes include poor functional group tolerance as well as high sensitivity to air and moisture.[28]

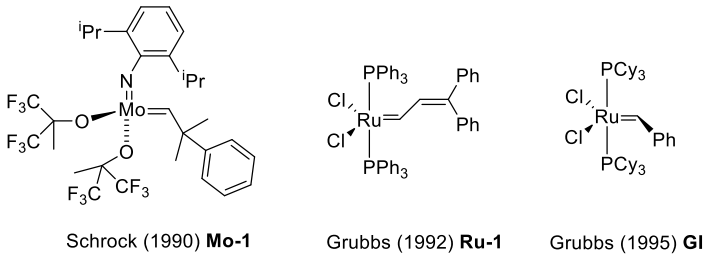
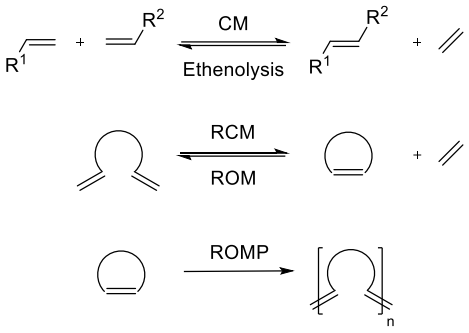


Figure 7. The first well-defined metal carbene complexes Schrock's **Mo-1** and Grubbs' **Ru-1** and **GI**.

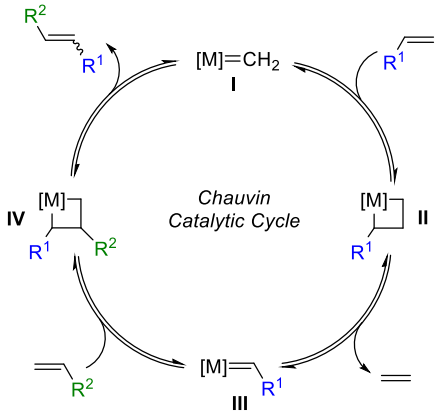
The first well-defined ruthenium-based alkylidene catalyst **Ru-1** was reported by Grubbs et al.[29] This complex was further modified into what is now known as Grubbs' 1st generation catalyst **GI**, containing PCy_3 (Cy = cyclohexyl) ligands and a benzylidene moiety (Figure 7).[30] These Ru(II)-carbenes were shown to exhibit a higher functional group tolerance and a higher tolerance to air and moisture compared to the previously mentioned molybdenum complex **Mo-1**.[26]

There are different types of olefin metathesis reactions e.g., cross metathesis (CM), ring-opening metathesis (ROM), ring-closing metathesis (RCM), and ring-closing metathesis polymerisation (ROMP), as outlined in Scheme 8. CM allows for the connection of two alkenes, RCM is an intramolecular reaction forming medium to large sized rings from acyclic diene precursors, whereas ROMP is thermodynamically favoured for strained ring systems. These reactions all proceed according to the same mechanism.[28]



Scheme 8. Overview of different types of olefin metathesis reactions.

The generally accepted mechanism for olefin metathesis was first described by Hérisson and Chauvin in 1971 (Scheme 9).[31] The catalytic cycle consists of 4 steps: 1) [2+2] cycloaddition between a metal alkylidene complex with an olefin to form metallacyclobutane **II**, 2) elimination of ethylene which results in alkylidene complex **III**, 3) [2+2] cycloaddition with another olefin to form metallacyclobutane **IV**, and 4) cycloreversion to give the product as well as regenerate the catalyst. Olefin metathesis is a reversible reaction, but in this case the elimination of ethylene drives the reaction to completion.



Scheme 9. The Chauvin mechanism proposed in 1971.

The mechanism showed that the metal carbene was initiating the reaction, and this discovery has further triggered the investigations into more versatile and active catalysts.[32] Ruthenium alkylidenes emerged as the most used catalysts due to their exceptional functional group tolerance and the fact that they can be handled without a glove box and Schlenk techniques.[28]

The driving force in the development of Grubbs' 2nd generation catalyst **GII** (Figure 8), was the need for more active catalysts that could be used for transformations that the 1st generation catalysts could not accomplish, for example metathesis of sterically demanding and electron-poor olefins.[33]

This complex contains a mesityl substituted *N*-heterocyclic carbene (NHC) ligand, which is significantly larger and more electron-donating than the phosphine (PCy_3) used in the parent catalyst **GI**. Thus, this leads to a dramatically increase in reactivity.[34] Furthermore, the reduced ability of NHC ligand to accept π-back bonding from the metal further enhances the selectivity for olefin binding and contributes to the remarkable performance of these systems in metathesis reactions.[35]

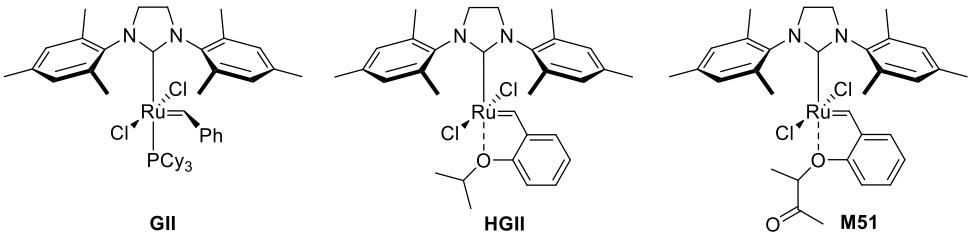


Figure 8. Examples of 2nd generation catalysts containing NHC-ligands.

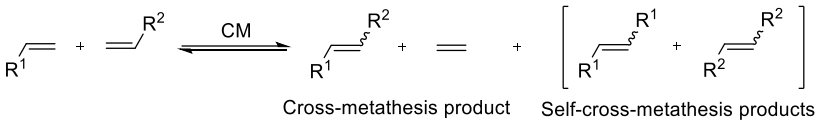
A totally phosphine-free catalyst, Hoveyda-Grubbs' 2nd generation complex **HGII**, containing a isopropoxystyrene moiety was reported by Hoveyda et al. (Figure 8).[36] This catalyst proved to be even more stable in the presence of water and oxygen, due to the chelating oxygen in the isopropoxystyrene ligand, and therefore, also further increased metathesis activity.[36]

Catalyst **M51** contains another modification where a carbonyl group is present on the chelating benzylidene moiety (Figure 8). The additional coordination of the carbonyl oxygen to the metal center enhances the stability of this complex, which leads to higher activity towards more difficult substrates.[37-38] However, the 1st generation catalysts continue to provide excellent results in certain metathesis reactions, and it should be noted that there is no robust, universal metathesis catalyst.

It shall be noted that, Yves Chauvin, Robert H. Grubbs and Richard R. Shrock were awarded the Nobel Prize in Chemistry 2005, for the discovery of a variety of highly active catalysts and for the elucidation of the reaction mechanism.[39] This pioneering work requires no additional reagents beyond the metal carbene and, in most cases, the only other product formed is easy to remove, such as ethylene. Hence, olefin metathesis has become one of the fastest and most robust synthetic techniques for creating carbon frameworks.[4, 39]

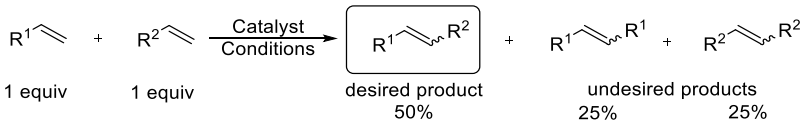
3.2.1 Cross Metathesis

Olefin cross metathesis (CM) has emerged as one of the most utilised techniques over the last decades for the formation of C-C double bonds.[40] In this reaction, double bonds from two olefins are broken and rearranged to form a cross-metathesis product. The reaction is reversible; however, the release of ethylene drives to reaction to completion, as shown in Scheme 10.[41]



Scheme 10. General principle of CM.[41]

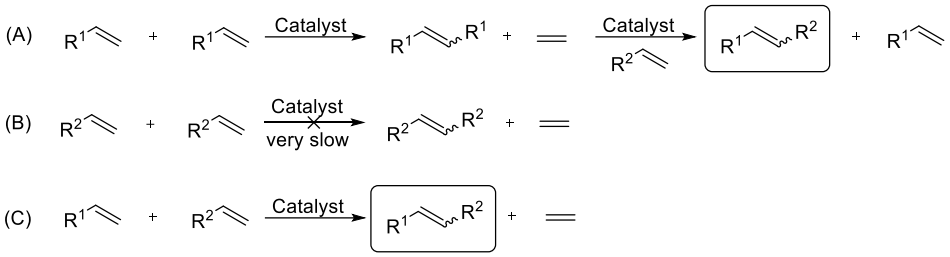
The product selectivity problems associated with CM depend not only on the catalyst, but also on the substrate.[40] For example, if two olefins exhibit similar reactivity and the catalyst cannot differentiate between them, then there will be a mixture of products, as a result. Thus, if the reaction goes to completion, the desired product will, statistically, be obtained with a maximum yield of 50%, and two additional undesired products will be formed via a self-metathesis process, as shown in Scheme 11.[41]



Scheme 11. Statistical distribution of CM products.

This statistical distribution of CM products can be avoided, either by modifying the electronic or steric properties, and thereby the reactivity of one of the olefins, or, alternatively, by adding one of the cross-partners in large excess.[41]

To predict the selectivity of a CM, the olefins can be divided into different types with respect to their reactivity, as shown in Scheme 12: (A) Type I: Rapid homodimerisation, homodimers consumable; (B) Type II: Slow homodimerisation, homodimers only partially consumable; (B) Type III: No homodimerisation, homodimers not consumable; Type IV: Olefins inert to CM, but do not deactivate the catalyst (spectator olefins); (C) Selective CM: Reaction between Type I and Type II/III (Scheme 12). [40]

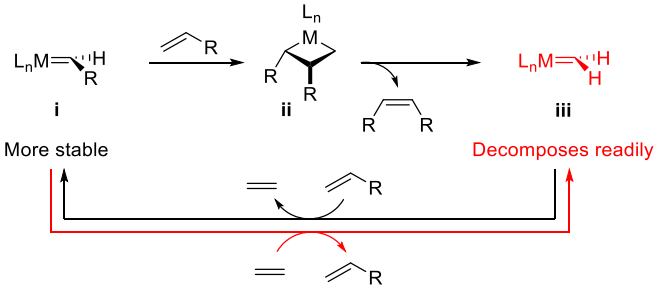


Scheme 12. CM between Type I and Type II/III olefins.

Broadly, this is a reactivity gradient where Type I is the most reactive, i.e. sterically unhindered and electron-rich olefins, and Type IV is the least reactive, i.e. sterically hindered and/or electron-deficient olefins.[40] Additionally, there are a few rules for selective CM: 1) Reaction between two of Type I olefins lead to statistical distribution of products, 2) Reaction between two olefins of the same type (II/III) will give nonselective CM, and 3) reaction between olefins of two different types gives selective CM.[40]

Another issue of CM that must be noted is the poor stereoselectivity of the newly formed olefin.[42] Usually a mixture of *E*- and *Z*-olefins is obtained after the reaction, although the formation of *E*-configured double bonds is thermodynamically favoured. This is due to the small energy difference between the two isomers, which is typically reflected in the ratio 9:1 (*E*:*Z*).[42] Obtaining *Z*-configured products is a difficult task that requires specially designed *Z*-selective catalysts or other methodologies such as tethered RCM.

Unstable catalyst intermediates, e.g., a methylidene complex, can also cause problems in cross metathesis. These are formed when terminal alkenes are used as cross-partners. Mono-substituted alkenes are inexpensive and widely accessible compounds that can be converted to valuable derivatives by cross metathesis. As outlined in Scheme 13, a carbene or alkylidene (i) undergoes a reaction with a monosubstituted alkene, which, via metallacyclobutane (ii), gives the homocoupling product as well as methylidene complex (iii).[43]



Scheme 13. A general problem of methylidene complex intermediacy.[43]

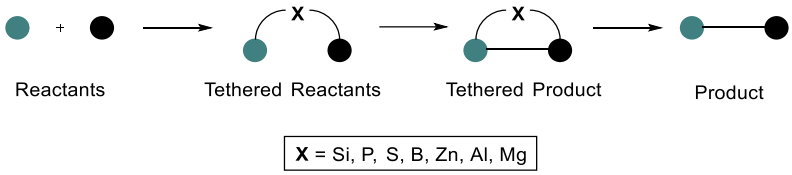
However, a general problem arises with the fact that methylidene species (iii) can decompose readily and at such a rate that the transformation can be brought to a halt.[43] This intermediate can also cause post-metathesis isomerisation, which becomes an additional challenge especially when *Z*-selectivity is desired.[43]

Furthermore, the by-product (ethylene) that is produced in the process can convert the relatively stable complex (i) to methylidene (iii). This can be avoided by removing ethylene from the reaction, however, as long as terminal alkenes are used, methylidene formation will occur (Scheme 13).[44] In order to circumvent this problem addition of a methylene capping agent to reactions of monosubstituted alkenes, allowed the reaction to proceed via a more stable ethylidene species. Thus, this resulted in higher stereoselectivities and yields.[43]

3.2.2 Tethered Olefin Metathesis

Intramolecular reactions have many advantages compared to intermolecular reactions. These include higher reaction rates and higher regio- and stereoselectivity.[45] The concept of tethering two reactants to create an intramolecular reaction was introduced to circumvent the problems associated with intermolecular reactions, such as cross metathesis, previously described in Section 3.2.1. Thus, the use of temporary tethers has emerged as a well-established strategy in the field of olefin metathesis.[46]

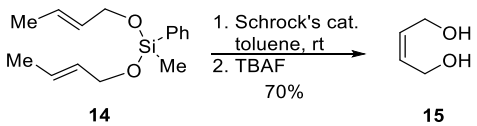
Optimal tethers display good stability towards the reaction conditions and are readily removed, or functionalised to provide the products often not available from an intermolecular reaction with the same reactants.[45] As shown in Scheme 14, two reactants are connected through a labile bond to a temporary tether (X), transforming an intermolecular reaction into an intramolecular reaction. Thus, it decreases the entropic demands of the reaction, which enables the use of mild conditions, and leads to higher reaction rates.[46]



Scheme 14. Principal of temporary tethers in organic synthesis.[46]

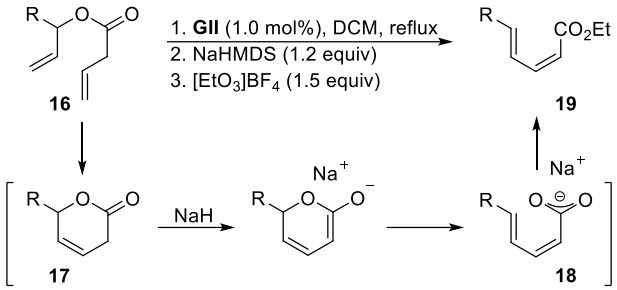
After the reaction has taken place, the tether is readily removed or functionalised to provide the products.[46] In olefin metathesis, it was first used to transform a cross metathesis (CM) into a ring-closing metathesis (RCM), in order to increase efficiency, selectivity, and stereoselectivity of the reaction.[47]

One of the most commonly used tethers is silicon, since it is readily accessible, stable to a large number of reaction conditions, and it is easily cleaved at the end of the reaction.[46] The first temporary silicon-tethered RCM was reported by Grubbs et al.,[48] as a methodology to construct achiral 1,4-diols. First, the RCM of the tethered reactants **14** takes place by using Schrock's catalyst, followed by a traceless removal of the silicon tether which furnishes the acyclic 1,4-diol **15** (Scheme 15).



Scheme 15. Temporary silicon-tethered RCM sequence as reported by Grubbs et al.[48]

Often the tether used is temporary and is cleaved after the reaction. However, a more atom-economical way of using this strategy would be to have a permanent tether that can be further used after the reaction in the form as a functional group. One example is the one-pot ring-closing metathesis base-induced elimination-alkylation reaction that was recently developed by Schmidt et al. (Scheme 16).[9] Here, a carboxylate group is used as the tether, and remains as a valuable functional group after the cleavage.



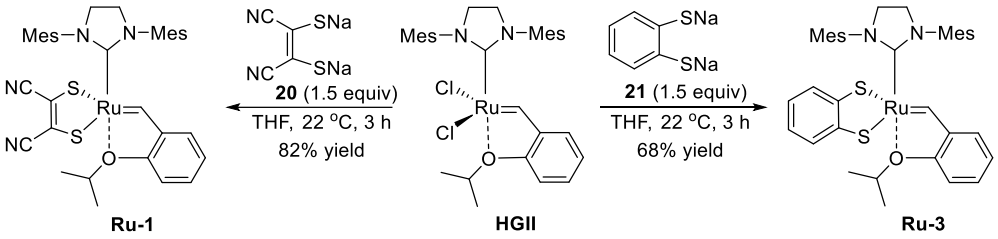
Scheme 16. RCM-eliminative ring opening sequence.[9]

In the first step of the reaction sequence, ester **16** undergoes a RCM to give cyclised compound **17**. This is followed by a base-induced elimination to corresponding carboxylate **18**, which after alkylation using Meerwein's salt ($[Et_3O]BF_4$) furnishes (2*Z*,4*E*)-dienoate **19** exclusively (Scheme 16).

3.2.3 Stereoretentive Metathesis

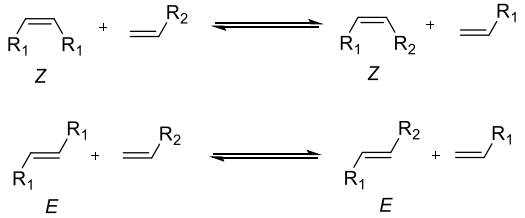
Since the advent of olefin metathesis, there has been a high demand for the development of catalysts that would provide olefins with high stereochemical purity.[49] Stereoretentive metathesis based on ruthenium dithiolate complexes has gained a lot of attention over the past few years. This is due to the great functional group tolerance combined with the ability to produce both *Z*- and *E*-alkenes with high stereoretention.[50]

The first stereoretentive catalysts **Ru-2** and **Ru-3** were reported by Hoveyda et al. in 2013 (Scheme 17).[51] These complexes were conveniently synthesised in a one-step procedure, by substituting the chloride ligands with dithiolate ligands **20** and **21** of commercially available Hoveyda-Grubbs 2nd generation catalyst **HGII**, as shown in Scheme 17.



Scheme 17. Synthesis of the first Ru-dithiolate catalysts **Ru-2** and **Ru-3**.[51]

These complexes were initially described as being highly *Z*-stereoselective olefin metathesis catalysts.[51] However, after subsequent investigations by Grubbs et al.,[42] it was concluded that they are in fact stereoretentive catalysts able to transform both *E*- and *Z*-configured olefins into the *E*- and *Z*-configured products respectively.[52] Thus, in stereoretentive metathesis, the stereochemistry is retained throughout the reaction: *Z*-olefin starting materials lead to *Z*-olefin products and *E*-olefin starting materials lead to *E*-olefin products, as shown in Scheme 18.



Scheme 18. General principle of stereoretentive metathesis.

Since the geometry of *E*- and *Z*-configured olefins differs significantly, each type of olefin may require a different catalyst. Through steric and electronic variations, the catalysts can be tuned to be more active towards either one diastereomer. For instance, in the reaction with *Z*-alkenes, the substituent at the β-position must point down in order to create a new *Z*-alkene product. If

this space is blocked by a complex containing a very bulky NHC-ligand, the substituent at the β-position of a *Z*-alkene will be forced to point down, thus creating a new *Z*-configured alkene (Figure 9).[50]

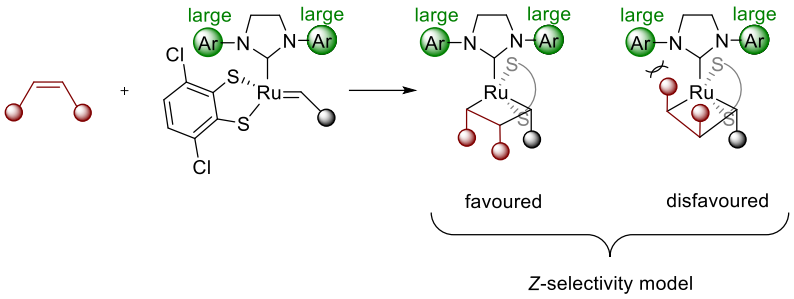
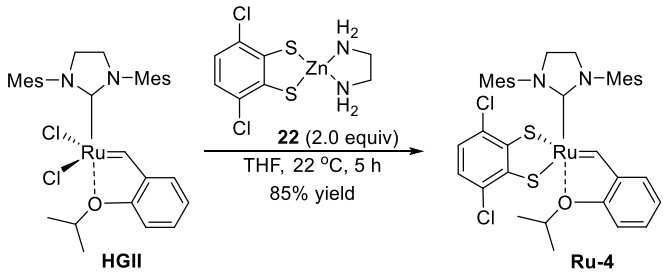


Figure 9. Model for *Z*-selectivity in stereoretentive metathesis.[52]

Dithiolate complex **Ru-4** was shown to have moderate to good catalytic activity in both the *E*- and *Z*-stereoretentive processes. Thus, this complex is commonly used as a catalyst for these transformations.[50] It was introduced by Hoveyda et al. in 2015,[53] and is synthesised in a similar manner as the previously described dithiolate complexes (Scheme 19).



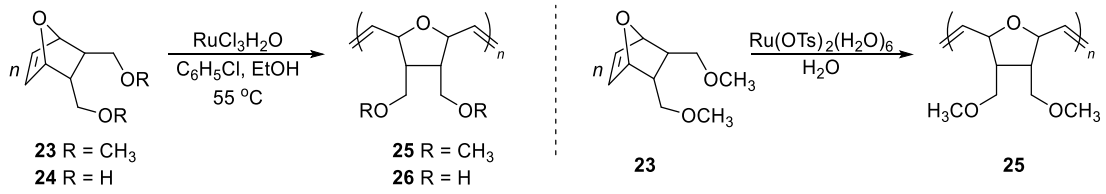
Scheme 19. Synthesis of general stereoretentive catalyst **Ru-4**.[53]

It shall be noted that replacing the chloride ligands on ruthenium with more electron-donating ligands generally leads to lower catalyst activity. Therefore, higher catalyst loadings (5-10 mol%) are typically necessary.[54] Moreover, the stereoretentive process for *E*-alkenes is not as efficient or practical as the *Z*-stereoretentive process, which is another major limitation that needs to be addressed.[50]

3.2.4 Olefin Metathesis in Aqueous Media

Water is a universal solvent in nature, and it is obviously considered the greenest solvent for organic chemistry. It is not only environmentally friendly, but it is also non-flammable and non-toxic, and is, therefore, risk-free. Thus, this is why water has been widely investigated recently as a replacement for more conventional solvents.[6] In this respect, olefin metathesis in aqueous media appears to be an interesting alternative for the synthesis or modification of biologically relevant molecules, which are often polar, and have good solubility in water.[55]

The first examples of olefin metathesis performed in aqueous media were reported in the late 1980s.[56-57] So called "ill-defined" catalysts, specifically $RuCl_3 \cdot H_2O$ and $Ru(OTs)_2(H_2O)_6$, were used in a ROMP with 7-oxanorbornene derivatives **23** and **24** (Scheme 20). However, these complexes proved to have limited usefulness, not only due to slow initiation rates, but also because of the detrimental effect of water on the reaction mixture.[55]



Scheme 20. The first aqueous metatheses catalysed by Ru(III)-salts.[56]

Since then, several strategies have been applied to facilitate aqueous olefin metathesis. There are two main approaches: the first one involves the use of standard water-insoluble catalysts (metathesis "on water"), where the reaction is performed with the use of surfactants or ultrasound; the second approach is to employ specially designed catalysts that are water-soluble (metathesis "in water").[58]

Ruthenium-based catalysts are among the most tolerable and robust metathesis catalysts and are widely utilised for metatheses in aqueous media.[55] In order to synthesise water-soluble catalysts, a highly polar ligand is required. Ionic tags (e.g. ammonium salts, carboxylic salts or sulfonic salts) or hydrophilic polymers such as polyethylene glycols (PEGs) are generally used as a tether group on the ligand to increase water-solubility.[59]

The first ammonium-tagged ruthenium catalysts **Ru-5** and **Ru-6** were discovered by Grubbs et al. in 1996, with the aim of mediating olefin metathesis in protic solvents, such as water and alcohols (Figure 10).[60] However, these complexes appeared to have low stability, especially in

water and, therefore, showed limited activity in olefin metathesis reactions (other than ROMP).[55]

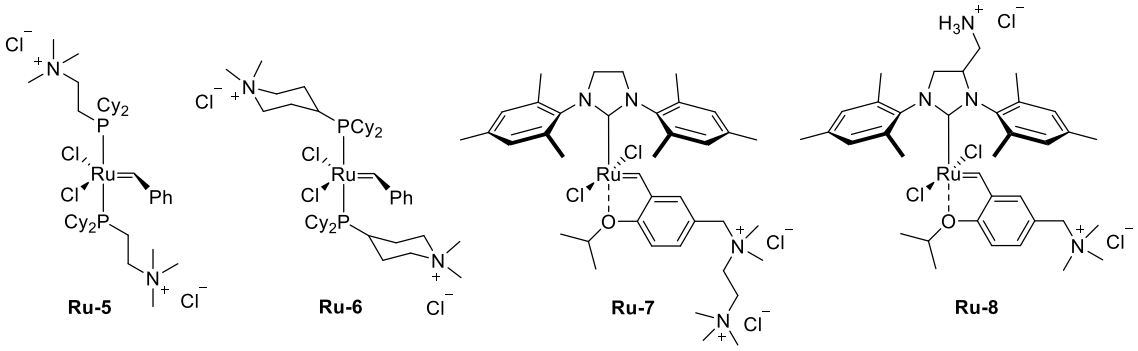


Figure 10. Examples of historic ammonium tagged water soluble catalysts.

Later on, Grubbs et al. reported NHC-catalysts **Ru-7** and **Ru-8** which bear quaternary ammonium tags (Figure 10).[61] These proved to be more stable and exhibited higher activity in a wide range of olefin metathesis transformations performed in water.[62]

The use of quaternary ammonium ($NR_3^+Cl^-$) groups instead of hydrochloride ($NH_3^+Cl^-$) in the catalyst would allow for its potential application in biological processes under neutral pH.[58] Quaternary ammonium chloride tagged complexes AquaMet **Ru-9** and StickyCat **Ru-10** were reported in 2012 by Grela et al. (Figure 11).[58, 63]

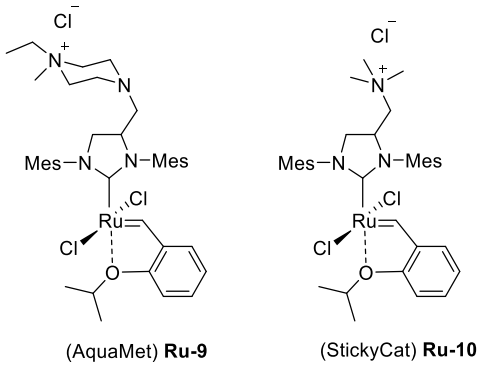


Figure 11. Examples of quaternary ammonium tagged catalysts.

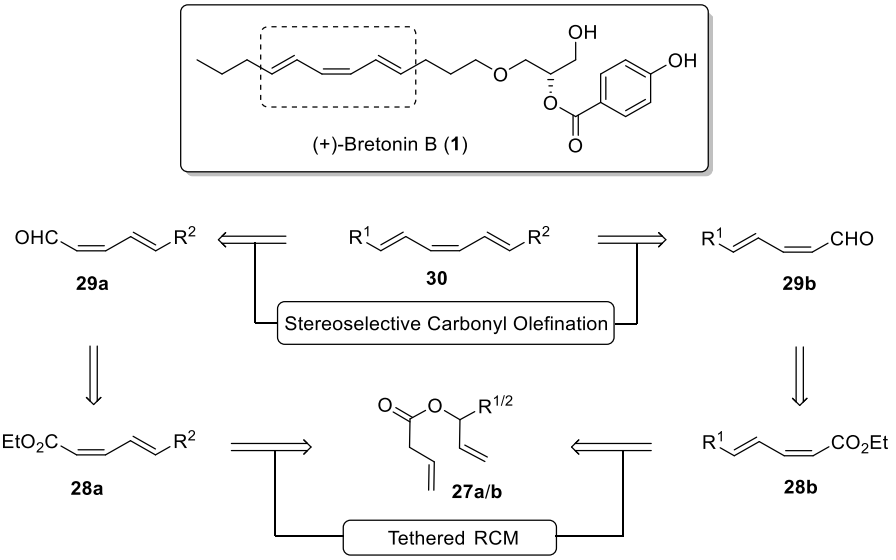
These complexes showed to be stable in water, even in the presence of air, and promoted various olefin metathesis reactions. Additionally, the quaternary ammonium groups in **Ru-9** and **Ru-10** increase the affinity to silica gel (or basic aluminium). Thus, they facilitate easy removal of ruthenium residues after the reaction, which is especially important in the pharmaceutical industry.[62-63]

4 Results and Discussion

4.1 Total Synthesis of (+)-Bretonin B via Tethered Ring-Closing Metathesis

Natural product (+)-bretonin B (**1**), described in Section 3.1.1, possesses a relatively rare, and synthetically challenging, (*E*,*Z*,*E*)-triene moiety. Thus, this compound was chosen as a demonstrative example for the application of the tethered ring-closing metathesis sequence developed by Schmidt et al.,[9] described in Section 3.2.2.

An overview of the key steps of the two synthetic strategies to be investigated is outlined in Scheme 21. With a focus on the intriguing *E*,*Z*,*E*-conjugated triene pattern **30**, the construction would start with the aforementioned method, namely the tethered RCM approach, which would transform allyl esters **27a/b** into the corresponding *Z*,*E*-dienoates **28a/b** in a highly stereoselective fashion.

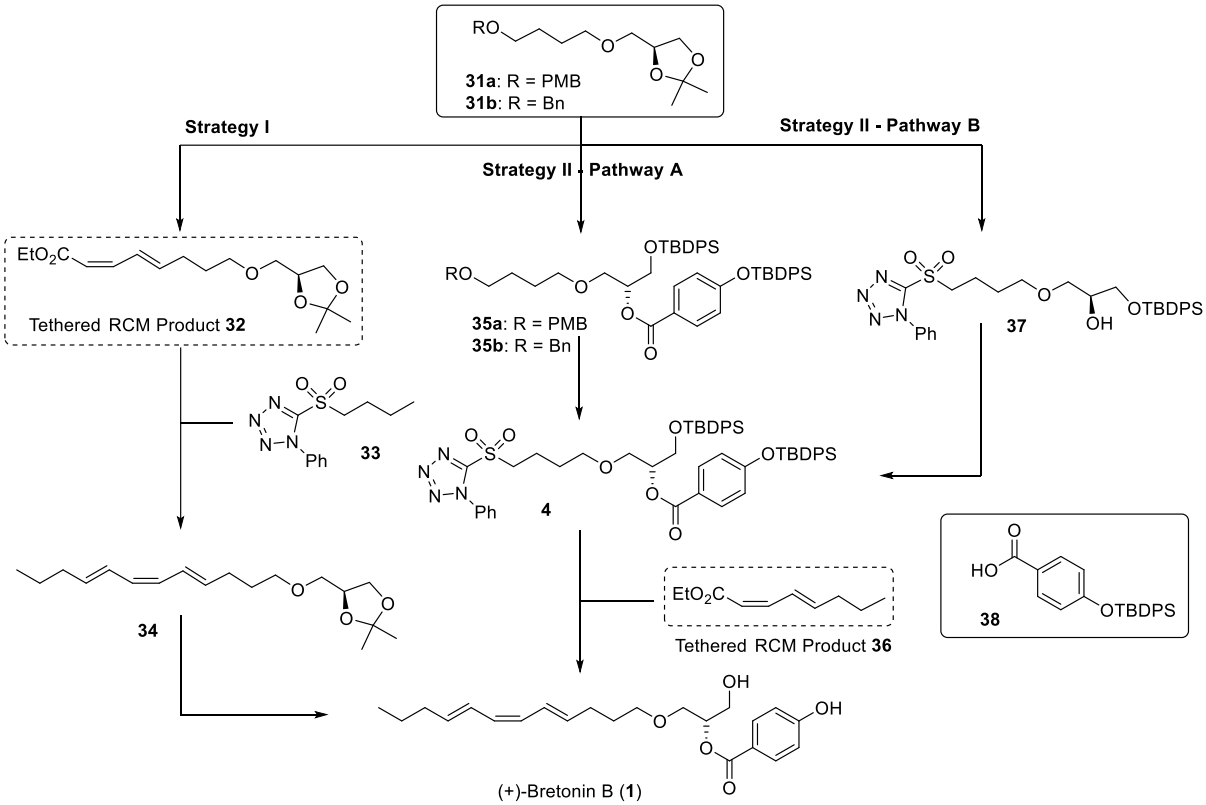


Scheme 21. Overview of the two strategies for the total synthesis of (+)-bretonin B (**1**).

A reduction of **28a/b** into the corresponding *Z*,*E*-dienals **29a/b**, followed by an *E*-stereoselective carbonyl olefination protocol, would allow the formation of the desired *E*,*Z*,*E*-conjugated triene **30** in high stereoselectivity. The advantage of this approach is that it would make it possible to introduce the last *E*-configured double bond from both directions, which increases the number of available synthetic routes. Thus, these two different strategies, constructing compound **30** from either direction, were to be investigated in parallel.

A more detailed overview of the two strategies to be investigated is outlined in Scheme 22. Building block **31a/b**, the common precursor for both synthetic strategies, carries the stereocenter and allows for the construction of the conjugated triene from both directions. The

key steps of Strategy I, involve an early assembly of the *E*,*Z*,*E*-triene moiety. Tethered RCM product **32** would be converted to the corresponding aldehyde, which would then be subjected to an *E*-stereoselective Julia-Kocienski olefination in order to construct conjugated triene **34**. It should be noted that there are only a few examples where fully conjugated trienes have been constructed via an *E*-selective Julia-Kocienski olefination of dienals. However, all of these reactions involve *E*,*E*-configured dienals.[64-65] In the next step, a late-stage Mitsunobu reaction would introduce building block **38** as well as invert the stereocenter. These key steps of Strategy I would allow access to (+)-bretonin B (**1**) (Scheme 22).



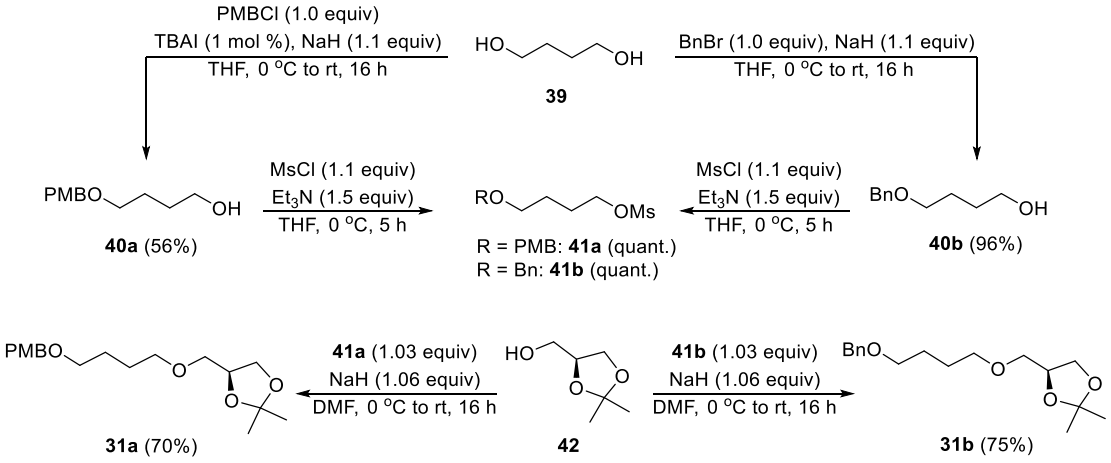
Scheme 22. Overview of the synthetic strategies towards (+)-bretonin B (**1**).

In Strategy II, however, the conjugated triene would be furnished in a later stage of the synthesis, via an *E*-stereoselective Julia-kocienski olefination, as shown in Scheme 22. Additionally, two pathways (A and B) towards the required Julia-Kocienski reagent **4** were to be investigated. Pathway A would follow a similar route as already reported by Bach et al.,[21] but with an evaluation of the protecting group strategy, using *para*-methoxybenzyl (PMB) and benzyl (Bn) at the primary alcohol of **31a/b** and **35a/b**. Whereas pathway B would approach Julia-Kocienski reagent **4** via a different route, introducing building block **38** in the last step (Scheme 22).

4.1.1 Synthesis of Building Blocks 31a/b and 38

The first step in the total synthesis of (+)-bretonin B (**1**) was to synthesise building blocks **31a/b** and **38**, common precursors for both strategies. An orthogonal protection group strategy was required for the several hydroxyl groups in the molecule. The more robust and sterically demanding *tert*-butyldiphenylsilyl (TBDPS) protecting group was chosen, along with two different protecting group protocols which were to be investigated, i.e. PMB and Bn. The more expensive PMB-group is usually cleaved by oxidation and was employed previously in the total synthesis of (+)-bretonin B (**1**) by Bach et al.[21] Meanwhile, Bn-group is cleaved via reductive conditions.

The synthesis started with a mono-protection of commercially available butadiol **39**. First, the PMB-protecting group was introduced, following procedures in the literature,[21] using PMBCl, NaH as a base, and tetrabutylammonium iodide (TBAI) in a catalytic amount, as shown in Scheme 23. This resulted in mono-PMB protected **40a** in a moderate yield of 56%, which can be explained by the double protection of the diol that occurred. In the next attempt at the mono-protection, a large excess of butadiol **39** and BnBr were used. This resulted in the desired Bn-protected alcohol **40b** which was obtained in 96% yield.

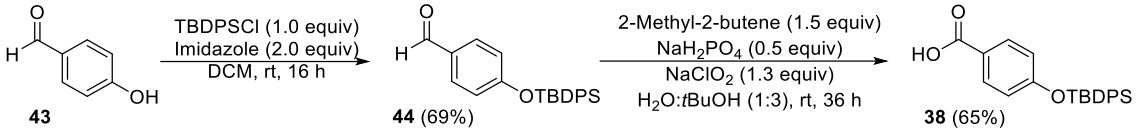


Scheme 23. Synthesis of protected compound **31a/b**.

Following procedures in the literature,[21] mesylate chloride (MsCl) and triethylamine (Et_3N) were used to transform the hydroxyl group of **40a/b** into good leaving groups. Crude products **41a/b** were obtained, without further purification, in quantitative yields. The next step involved a substitution reaction in order to introduce the protected glycerol moiety equipped with the stereocenter. Here, commercially available enantiopure acetonide **42** was reacted with mesylate

41a and **41b** respectively using NaH as a base. This gave precursors **31a** and **31b** in 70% and 75% yields, respectively (Scheme 23).

The synthesis of building block **38** started with a TBDPS-protection of commercially available *p*-hydroxybenzaldehyde **43** to give compound **44** in a moderate yield of 69% (Scheme 24). This was followed by a Pinnick reaction protocol,[21] using 2-methyl-2-butene as a scavenger and $NaClO_2$ as an oxidising agent. This resulted in desired benzoic acid **38** which was isolated in a moderate yield as shown in Scheme 24.

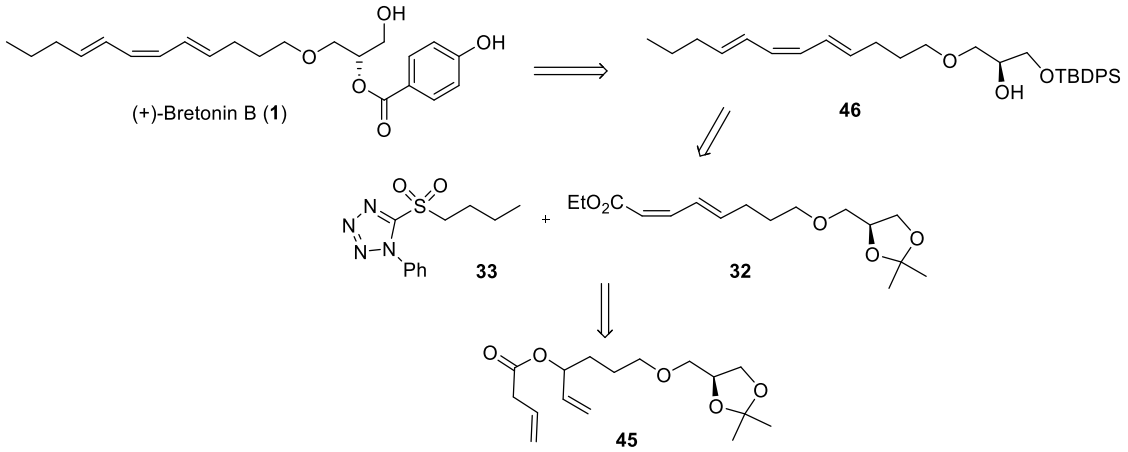


Scheme 24. Synthesis of TBDPS-protected benzoic acid **38**.

These building blocks were used in both of the synthetic strategies that were investigated towards the total synthesis of (+)-bretonin B (**1**).

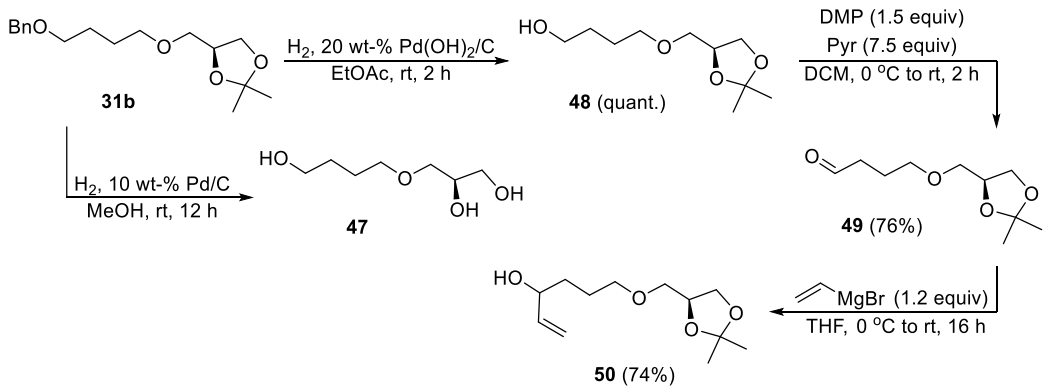
4.1.2 Strategy I: Early Construction of the Conjugated Triene Moiety

The retro-synthetic route of the first strategy to be investigated is outlined in Scheme 25. The tethered RCM approach would convert allyl ester **45** into the corresponding *Z*,*E*-dienoate **32** in high stereoselectivity. The *E*,*Z*,*E*-configured triene would then be constructed relatively early in the synthesis via an *E*-selective Julia-Kocienski olefination protocol. A late-stage Mitsunobu reaction would then invert the configuration of the stereocenter, as well as introduce the *para*-hydroxybenzoyl group (building block **38**), and allow access to (+)-bretonin B (**1**).



Scheme 25. Retro-synthetic route of the total synthesis of (+)-bretonin B (**1**).

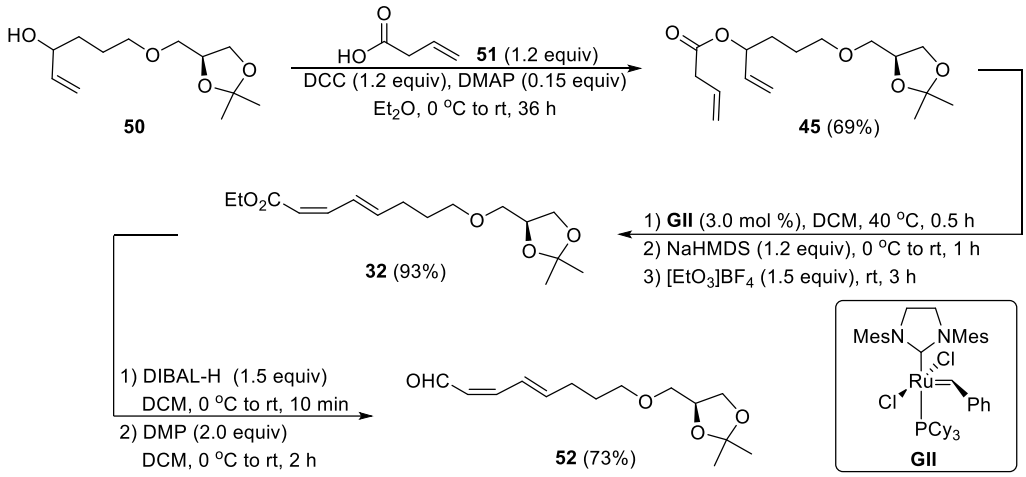
The synthesis started with a deprotection of the benzyl group of the previously synthesised Bn-protected **31b**, as outlined in Scheme 26. Following procedures in the literature,[66] the benzyl was cleaved via hydrogenolysis using H_2 and 10 wt-% Pd/C as a catalyst in MeOH. However, this resulted in subsequent cleavage of the acetonide and gave compound **47** with no trace of the desired product. A new experiment was performed using 20 wt-% $Pd(OH)_2/C$ in EtOAc under 1 atm H_2 for 2 h, and, with these conditions, the desired product **48** was obtained in a quantitative yield (Scheme 26).



Scheme 26. Synthesis of acetonide **50**.

In the next step of the synthesis, a Dess-Martin oxidation protocol was applied in order to convert alcohol **48** into aldehyde **49**. Using Dess-Martin periodinane (DMP) as an oxidising agent together with pyridine as a base, furnished aldehyde **49**, which was isolated in a moderate yield of 76%. This was followed by a Grignard reaction, where aldehyde **49** was further transformed using vinylmagnesium bromide in THF, to give alcohol **50** in 74% yield (Scheme 26).

As outlined in Scheme 27, the synthesis continued with a Steglich-esterification. Here, vinylacetic acid **51**, a catalytic amount of 4-dimethylaminopyridine (DMAP), and *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a coupling reagent, were used to convert **50** into allyl ester **45**. This proceeded smoothly and gave the desired product in 69% yield.

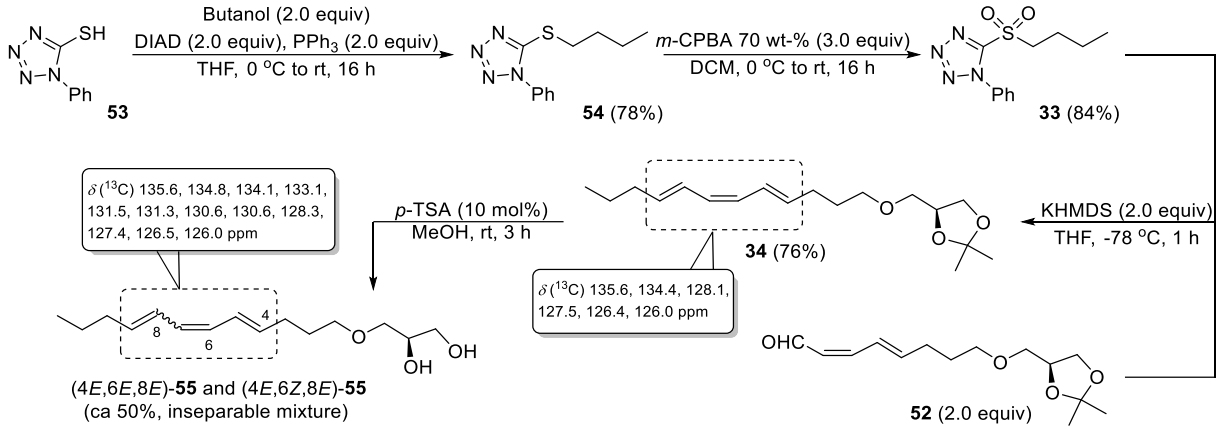


Scheme 27. Synthesis of *Z*,*E*-dienal **52**.

The one-pot tethered RCM approach was employed to transform allyl ester **45** into *Z*,*E*-butenoate **32**.[9] In the first step Grubbs' 2nd generation catalyst **GII** was used in 3 mol% under reflux. The reaction was monitored by TLC and, after completion, the mixture was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (NaHMDS) was used as a base, in order to induce an elimination, to form the corresponding carboxylate. Subsequent trapping of the carboxylate intermediate was performed using Meerwein's salt (Et_3OBF_4), which gave desired *Z*,*E*-dienoate **32** in 93% yield (Scheme 27).

According to procedures in the literature,[9] the transformation of *Z*,*E*-butenoate **32** into aldehyde **52** was performed by reduction, using diisobutylaluminium hydride (DIBAL-H), followed by subsequent oxidation with DMP. In this way the problem of over-reduction of the ester to the corresponding alcohol is circumvented. This gave the desired product **52** in a moderate yield of 73%, as shown in Scheme 27.

Julia-Kocienski reagent **33** was synthesised in two steps starting from commercially available 1-phenyl-1*H*-tetrazole-5-thiol **53** in accordance with literature procedures.[21] The first step involved a Mitsunobu reaction using commercially available butanol, diisopropyl azodicarboxylate (DIAD), and triphenyl phosphine (PPh_3). This resulted in sulfide **54** in 78% yield. Oxidation of the sulfide was executed by employing *meta*-chloroperoxybenzoic acid (*m*-CPBA) as the oxidising agent. This gave Julia-Kocienski reagent **33** in 84% yield, as shown in Scheme 28.



Scheme 28. Synthesis of (*E*,*Z*,*E*)-acetonide **34** via Julia-Kocienski olefination, followed by deprotection to isomerised **55**.

Freshly prepared aldehyde **52** was subjected to an *E*-selective Julia-Kocienski olefination protocol,[21] in order to obtain the *E*,*Z*,*E*-configured acetonide **34**. Julia-Kocienski reagent **33** was used in 2 equivalents, and was metalated using potassium bis(trimethylsilyl)amide (KHMDS) in THF at -78 °C. Aldehyde **52** was added to the reaction and resulted in *E*,*Z*,*E*-triene **34**, which was obtained as a single diastereomer in a 76% yield (Scheme 28).

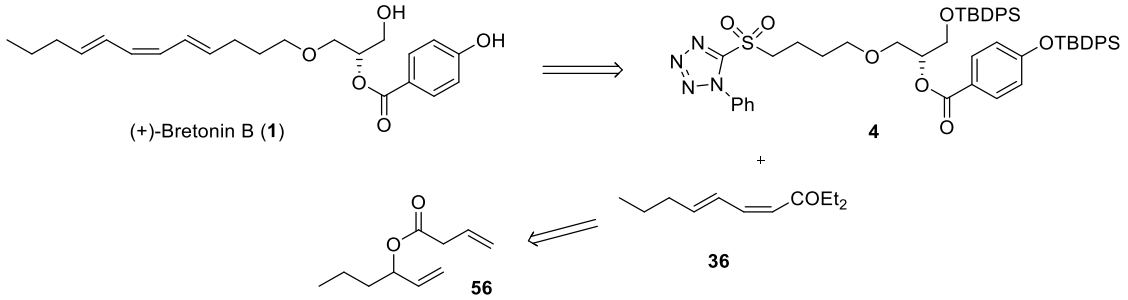
The assignment of the (4*E*,6*Z*,8*E*)-configured triene pattern via ^{1}H NMR measurements is not straightforward due to overlapping peaks in the olefinic region. However, a more reliable assignment for the configuration is possible through the comparison of the ^{13}C NMR data for triene **34** with those previously reported for all *E*-configured (4*E*,6*E*,8*E*)-dodecatriene-1-ol (^{13}C δ 134.6, 133.3, 131.3, 131.1, 130.6, 130.6) and (4*E*,6*Z*,8*E*)-dodecatriene-1-ol (^{13}C δ 135.8, 134.3, 128.3, 127.4, 126.6, 126.0).[67-68]

In order to introduce the last building block, namely TBDPS-protected benzoic acid **38**, a deprotection of the acid-labile acetonide, followed by TBDPS-protection of the primary alcohol was to be performed. A Mitsunobu esterification incorporating **38** would then give TBDPS-protected bretonin B. As outlined in Scheme 28, the attempted cleavage of the acetonide to

obtain diol **55** was performed using a catalytic amount of *para*-toluenesulfonic acid (*p*-TSA) in MeOH. However, this resulted in subsequent isomerisation of the *E*,*Z*,*E*-triene pattern of diol **55** into the corresponding *E*,*E*,*E*-configured product **55**. Furthermore, the reaction did not go to completion but resulted in only 50% yield of a mixture of the two isomers. This is very likely due to the acid sensitivity of the *Z*-configured double bond and thereby, further demonstrates the challenge in the synthesis of this *E*,*Z*,*E*-configured conjugated triene.

4.1.3 Strategy II: Late-Stage Julia-Kocienski Olefination

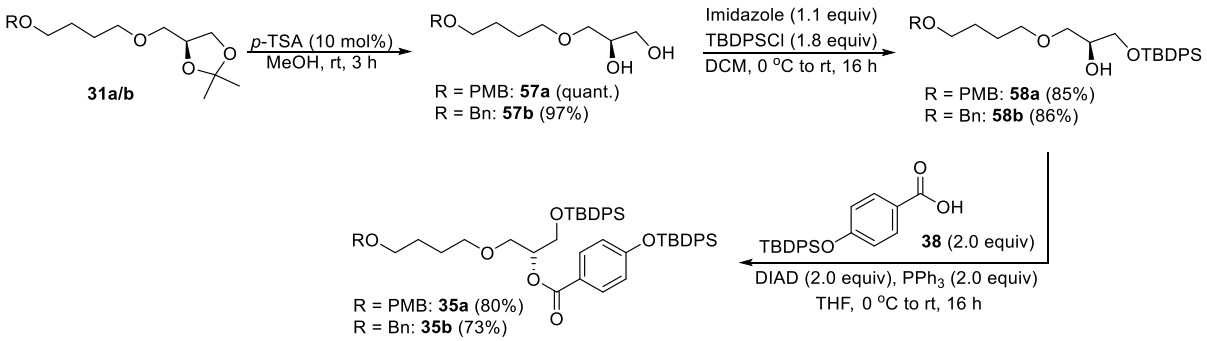
The retro-synthetic route for the second strategy is outlined in Scheme 29. The approach here would be to construct the challenging conjugated triene moiety from the opposite direction. The one-pot tethered RCM protocol would transform allyl ester **56** into the *Z,E*-dienoate **36**. A late-stage introduction of the *E*-configured double bond via a Julia-Kocienski protocol would minimise the risk of isomerisation of the sensitive *E,Z,E*-triene pattern previously observed. After deprotection of the TBDPS-groups, this would give desired natural product (+)-bretonin B (**1**).



Scheme 29. Retro-synthetic route of the total synthesis of (+)-bretonin B (**1**).

The Julia-Kocienski reagent **4** that would be required to do this, has already been synthesised by Bach et al.[21] As mentioned earlier in Section 4.1, two different synthetic pathways (A and B) were to be investigated in parallel in order to obtain this building block. This would also include an evaluation of the two protecting group strategies using PMB and Bn at the primary alcohol.

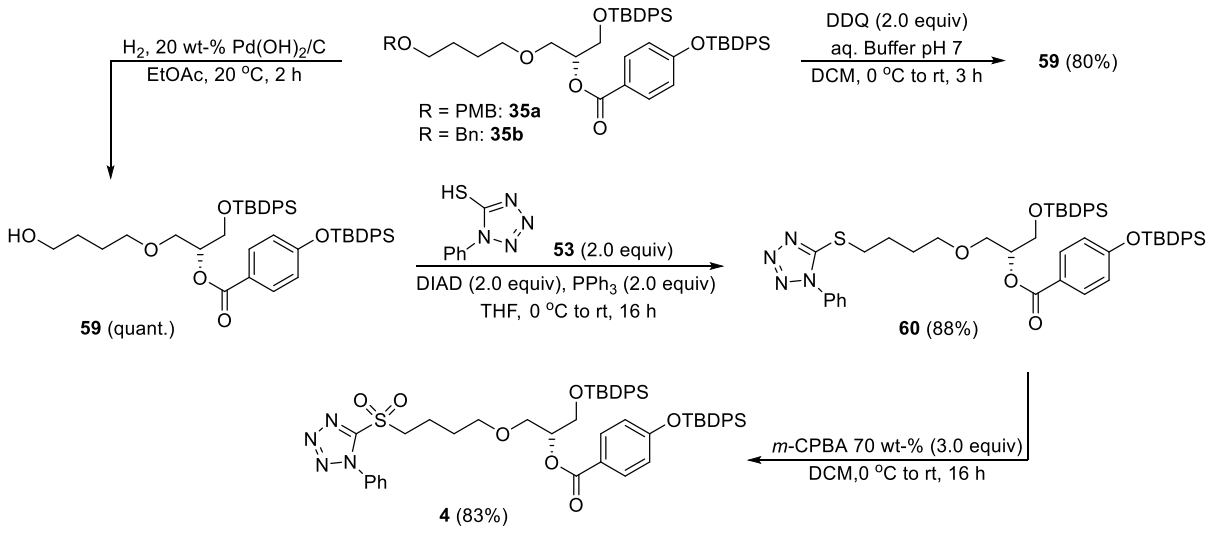
Following synthetic pathway A, previously synthesised acetonides **31a/b** were subjected to a catalytic amount of *p*-TSA in MeOH to remove the acid labile acetonide moiety, as shown in Scheme 30. This resulted in diols **57a** and **57b** in very high yields.



Scheme 30. Synthesis of compounds **35a** and **35b**.

Before building block **38** could be introduced, a mono-protection of the primary alcohol was performed. Diols **57a** and **57b** were transformed to TBDPS-protected **58a** and **58b** using the imidazole as a base in DCM which was continuously stirred overnight. This resulted in desired products **58a** and **58b** in comparable yields (Scheme 30). However, it shall be noted that, even with the bulky TBDPS-group, silyl migration occurred onto the secondary alcohol upon leaving the reaction for more than a day. A Mitsunobu protocol, using DIAD as a coupling reagent and triphenyl phosphine (PPh_3), allowed for the introduction of building block **38** to alcohols **58a** and **58b**. This resulted in a slightly higher yield of PMB-protected **35a** in comparison to Bn-protected **35b** (Scheme 30).

As outlined in Scheme 31, the cleavage of the PMB-protecting group of **35a** was performed under oxidative conditions using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidising agent. This resulted in desired product **59** in 80% yield. However, deprotection of the Bn-protecting group, which was done under reductive conditions using 20 wt-% $Pd(OH)_2/C$ under 1 atm H_2, proved to be even more efficient, and gave alcohol **59** in quantitative yield.



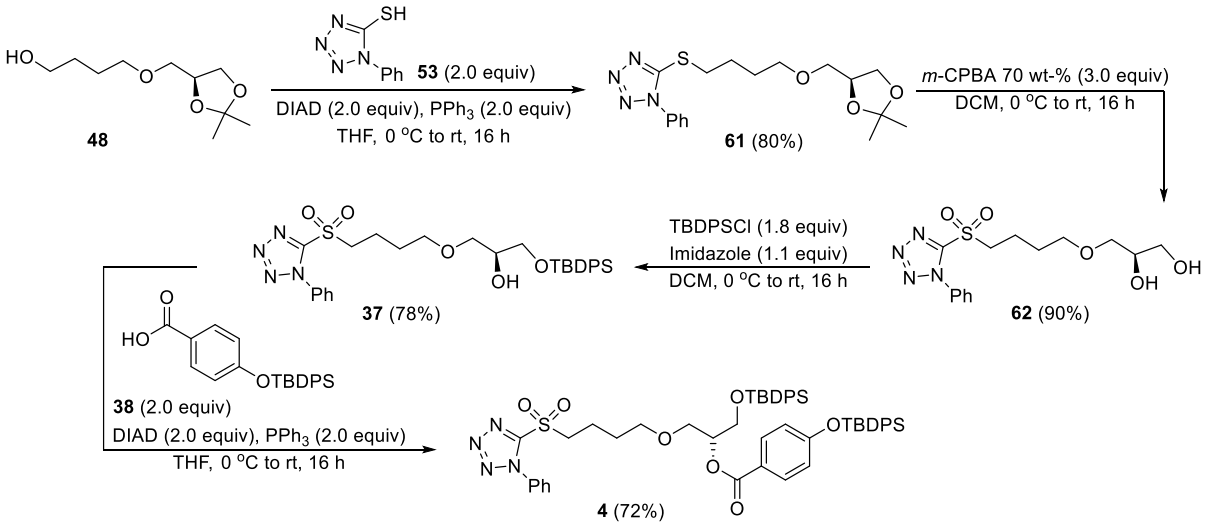
Scheme 31. Synthesis of Julia-Kocienski reagent **4** via pathway A.

The next step proceeded with an introduction of commercially available thiol **53**, via a Mitsunobu reaction. This was done using DIAD as a coupling reagent and PPh_3 as an oxygen scavenger. Sulfide **60** was isolated in 88% yield, and subsequent oxidation using *m*-CPBA as an oxidising agent resulted in Julia-Kocienski reagent **4** in 83% yield (Scheme 31).

Comparing the protecting group strategies that were applied, the use of the cheaper protecting group benzyl proved to be a slightly better choice compared to the PMB-group. However, both

strategies were successful, and Julia-Kocienski reagent **4** was obtained via this pathway (A) in an overall yield of 32% and 16% over 9 steps, using protecting group Bn and PMB respectively.

The other synthetic pathway (B) towards Julia-Kocienski reagent **4**, started with alcohol **48** which was reacted with commercially available thiol **53** under Mitsunobu conditions (Scheme 32). DIAD was used as a coupling reagent along with triphenyl phosphine (PPh_3). Sulfide **61** was isolated in 80% yield, and was then transformed further into the corresponding the sulfone, using 70 wt-% *m*-CPBA as an oxidising agent. Unexpectedly, this led to the subsequent cleavage of the acetonide group and gave diol **62** in 90% yield. The fact that there is at least 10% of *m*-chlorobenzoic acid present in the reagent bottle, and that it is also formed as a by-product of the actual reaction, explains why the acid-labile acetonide group was removed. Delightfully, this also led to a significant shortening of the synthetic route, as only two steps remained in order to obtain Julia-Kocienski reagent **4**.

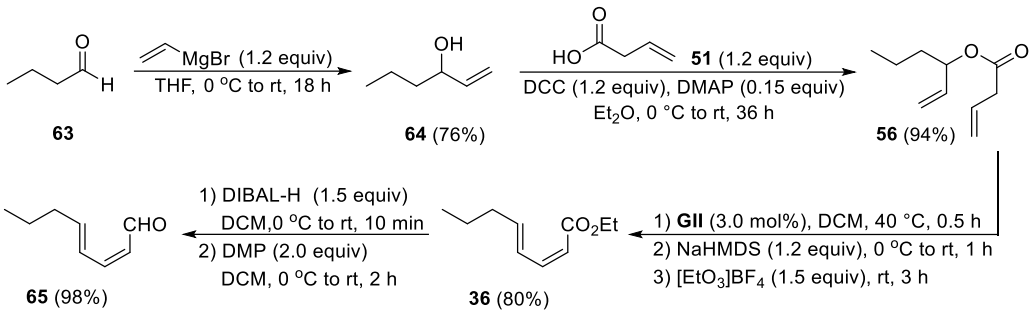


Scheme 32. Synthesis of Julia-Kocienski reagent **4** via pathway B.

The synthesis continued with a selective TBDPS-protection of the primary alcohol of diol **62**, using imidazole as a base. This gave TBDPS-protected compound **37** in a high yield of 78%. The last step in the synthesis was a Mitsunobu inversion. Building block **38** was introduced to alcohol **37**, using DIAD as a coupling reagent, and the desired product **4** was obtained in a 72% yield (Scheme 32).

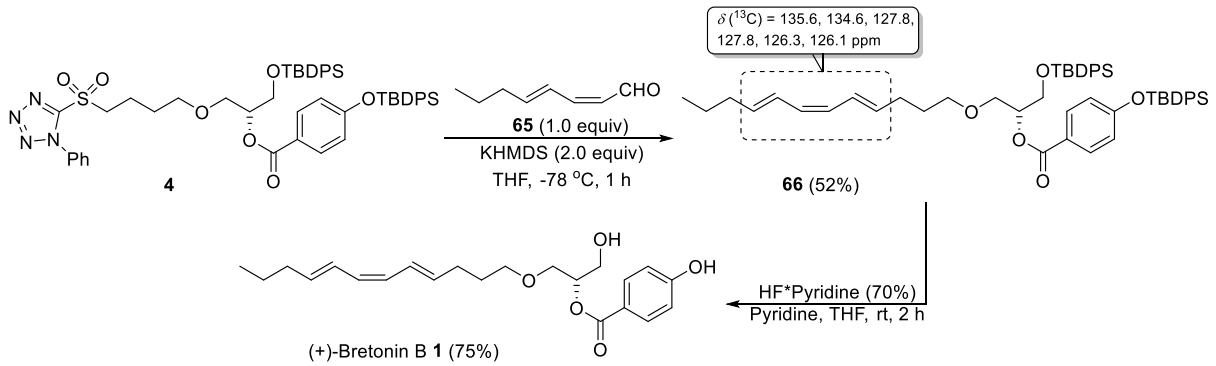
A comparison of the two synthetic approaches (pathway A and B) to obtain Julia-Kocienski reagent **4**, showed that the strategies gave very similar results. In this instance, pathway B gave the desired product in an overall yield of 29% over 8 steps, whereas pathway A gave the desired product in an overall yield of 32% over 9 steps.

The required *Z*,*E*-configured dienal **65** was synthesised starting from commercially available butanal **63**. A Grignard reaction with vinylmagnesium bromide was performed to give alcohol **64** as shown in Scheme 33. This was followed by a Steglich esterification with vinylacetic acid **51**, which resulted in diallyl ester **56** in 94% yield. The tethered RCM sequence further transformed ester **56** into the corresponding *Z*,*E*-dienoate **36** in high stereoselectivity and in an 80% yield.



Scheme 33. Synthesis of *Z*,*E*-dienal **65**.

The synthesis continued with a transformation of dienoate **36** into the corresponding aldehyde. This was done in two steps: first, a reduction using DIBAL-H as the reducing agent, followed by a subsequent oxidisation employing DMP. *Z*,*E*-Dienal **65** was successfully isolated as a citrus-smelling yellow liquid in 98% yield. It shall be noted that this aldehyde is prone to decomposition (Scheme 33). Therefore, freshly prepared dienal **65** was directly subjected to the Julia-Kocienski olefination, which was carried out using KHMDS as a base in THF at -78 °C. This furnished TBDPS-protected bretonin B **66** in high stereoselectivity in a moderate yield of 52%, as shown in Scheme 34. Full NMR spectroscopic structure elucidation and signal assignment revealed the ^{13}C NMR chemical shift pattern for the *E*,*Z*,*E*-configured conjugated triene.



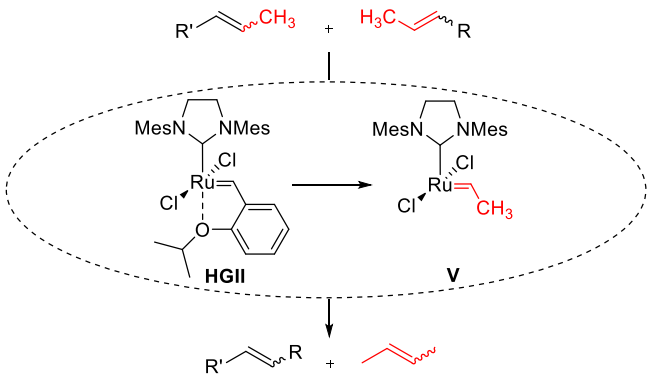
Scheme 34. Completion of the total synthesis of (+)-bretonin B (**1**) via Julia-Kocienski olefination followed by deprotection of the TBPDS-protecting groups.

The final step involved cleavage of the TBDPS-protecting groups of compound **66**, using Olah's reagent (HF•Pyr) as the fluoride source. This resulted in the desired natural product (+)-bretonin B (**1**), which was isolated in 75% yield. However, substantial isomerisation of the *E*,*Z*,*E*-conjugated triene into the *E*,*E*,*E*-configured triene was observed upon it standing in room temperature for a few hours, which was also reported by Bach et al.[21] Remarkably, TBDPS-protected bretonin B **66**, which was not an intermediate in Bach's total synthesis, was shown to be configurationally stable at room temperature for several days. Thus, this indicates that the *E*,*Z*,*E*-conjugated triene moiety of (+)-bretonin B (**1**) most likely isomerised due to exposure to acidic conditions.

Pathway A and B proved to give very similar results using Bn as a protecting group. Pathway A gave (+)-bretonin B (**1**) in an overall yield of 12% over 11 steps; Pathway B gave (+)-bretonin B (**1**) in an overall yield of 11% over 10 steps.

4.2 Cross Metathesis using Methyl Substituted Olefins

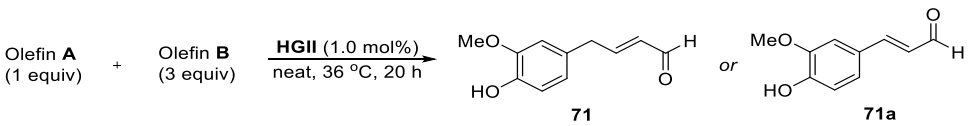
Cross metathesis using substrates that are methyl substituted, would bypass the problems associated with the unstable methylidene intermediate formed during CM reactions with terminal olefins, as described in Section 3.2.1. This would instead lead to the formation of a more stable ethylidene complex (V), and an easy-to-remove by-product, 2-butene, as outlined in Scheme 35.

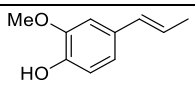
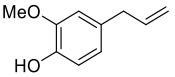
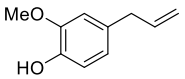
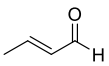
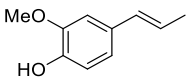
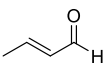


Scheme 35. Cross metathesis using methyl-substituted olefins.

In order to investigate this theory, initial experiments using both terminal and methyl substituted alkenes were performed. The reactions were done on a 1.00 mmol scale and conversions were calculated via ^{1}H NMR, as depicted in Table 1.

Table 1. Comparison of CM between terminal and methyl substituted olefins.



Entry	Olefin A		Olefin B		Conversion (%)[a]
1		**67**		**68**	0
2		**69**		**68**	67
3		**69**		**70**	0
4		**67**		**70**	94

[a] Conversion was calculated via ^{1}H NMR.

The first reaction was performed using commercially available isoeugenol **67** and acrolein **68**, and this resulted in no conversion (Table 1, Entry 1). In the second attempt, eugenol **69** and acrolein **68** were reacted under the same conditions and gave aldehyde **71** in 67% conversion (Table 1, Entry 2). However, when using eugenol **69** and crotonaldehyde **70,** the reaction yet again gave a 0% conversion (Table 1, Entry 3).

Interestingly, a very high conversion to the desired product **71a** was obtained using isoeugenol **67** and crotonaldehyde **70** (Table 1, Entry 4). This illustrates the importance of proceeding the reaction via a more stable ruthenium intermediate, such as the ethylidene complex (described in Section 3.2.1). It shall be noted that there are no examples known in the literature for the cross metathesis of isoeugenol **67** and α,β-unsaturated aldehydes. Indeed, more sterically hindered substrates are usually more demanding in cross metathesis, and terminal alkenes are normally expected to give higher conversions.

The conversions were calculated using ^{1}H NMR, as shown in Figure 12. The newly formed product **71a**, O=C**H** signal (in red) is integrated and compared with the starting material isoeugenol **67**, -C**H**$_3$ signal (in blue) which is also integrated.

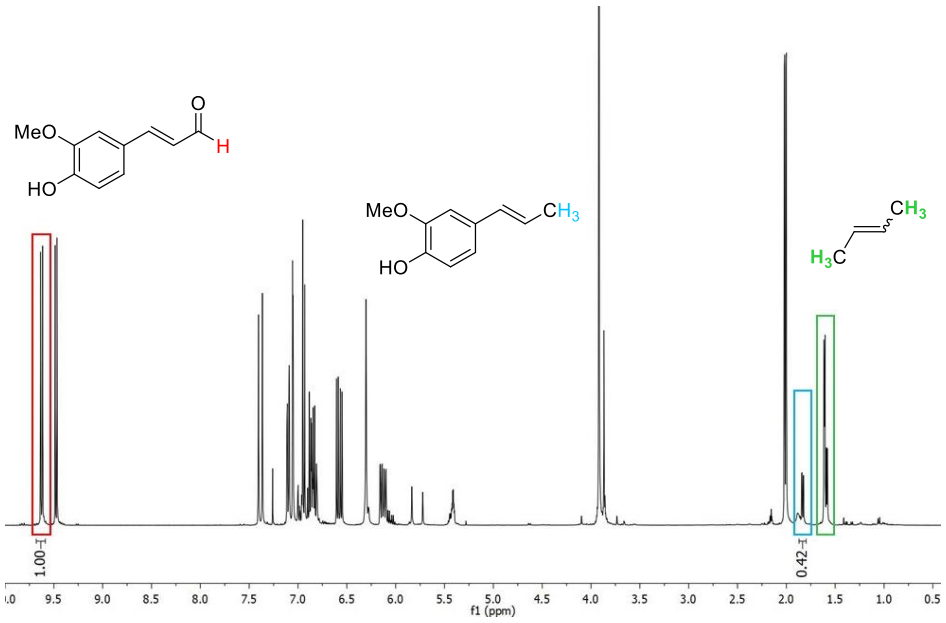


Figure 12. ^{1}H NMR spectrum of the reaction mixture using isoeugenol **67** and crotonaldehyde **70**. The conversion was determined through comparison of the integrals of the signals from starting material **67** (blue) and the newly formed product **71a** (red). The by-product (2-butene) signal is indicated in green.

The formation of 2-butene (in green) was also observed in the ^{1}H NMR spectrum (Figure 12). This, additionally, demonstrates that the reaction proceeds via the more stable ethylidene species and, where this by-product is formed as a consequence.

Further evaluations of the cross metathesis between methyl-substituted olefins were to be performed, including optimisation of the cross-metathesis reaction between isoeugenol **67** and crotonaldehyde **70** (Table 1, Entry 4), followed by a scope and then application in the total synthesis of 7-methoxywutaifuranal (**9**).

4.2.1 Optimisation of the Cross Metathesis Sequence

The first step of the optimisation process was to find a suitable catalyst for the cross metathesis of isoeugenol **67** and crotonaldehyde **70**. Three catalysts were considered i.e.: Grubbs' 2nd generation **GII**, Hoveyda-Grubbs' 2nd generation **HGII**, and Umicore's **M51**, as shown in Figure 13. All of these are commercially available and have shown good activity in various olefin metathesis reactions, including cross metathesis (Section 3.2).

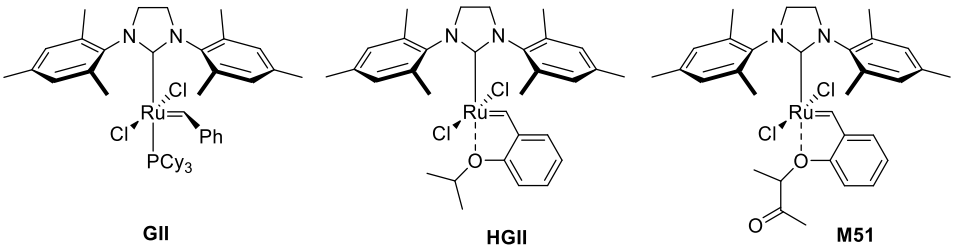
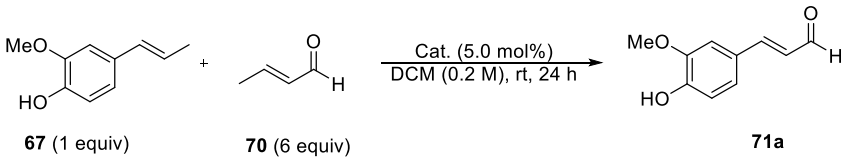


Figure 13. Catalysts to be evaluated for the CM reaction.

Isoeugenol **67** and crotonaldehyde **70** were used in a 1:6 ratio, and the reactions were carried out with a catalyst loading of 5 mol% in dry DCM (0.2 M) at ambient temperature, as shown in Table 2. The results proved to be very similar, with conversions ranging between 86-91%. Hoveyda-Grubbs' 2nd generation catalyst **HGII** gave a slightly higher conversion (Table 2, Entry 2) and, therefore, the optimisation of the reaction was to be continued using **HGII** as a catalyst.

Table 2. Comparison of catalysts in the CM between isoeugenol **67** and crotonaldehyde **70**.



Entry	Catalyst	Conversion (%)[a]
1	**GII**	86
2	**HGII**	91
3	**M51**	88

[a] Conversion was calculated via ^{1}H NMR.

The next step in the optimisation process was to investigate the ratio between the cross partners, as well as, variations in catalyst loading, time, temperature, and concentration, as shown in Table 3. The reactions were performed on a 1.00 mmol scale and the conversions were calculated using ^{1}H NMR.

Table 3. Optimisation of the conditions for CM between isoeugenol **67** and crotonaldehyde **70**.

Entry	Crotonaldehyde 70 (equiv.)	HGII (mol%)	Solvent	Conc. (M)	Temp. (°C)	Conversion[a] (%)
1	6	3.0	DCM	0.2	35	95
2	6	2.0	DCM	0.2	35	96
3	6	1.0	DCM	0.2	35	94
4	6	0.50	DCM	0.2	35	71
5	6	0.50	DCM	1.5	35	91
6	6	0.10	DCM	1.5	35	traces
7	2	0.10	DCM	1.5	35	40
8	2	0.50	DCM	1.5	35	78
9	3	1.0	neat	-	35	94
10	3	0.50	neat	-	35	92
11	3	0.25	neat	-	35	90
12	3	0.10	neat	-	35	49
13	3	0.25	neat	-	80	91
14	3	0.10	neat	-	80	71
15	2	0.25	neat	-	80	93
16	2	0.10	neat	-	80	89
17	1.5	0.25	neat	-	80	96
18	1.5	0.10	neat	-	80	91
19	1.5	0.05	neat	-	80	66
20[b]	1.5	0.25	neat	-	80	90
21[b]	1.5	0.25	neat	-	25	80
22[c]	1.5	0.25	neat	-	25	90
23	1	0.25	neat	-	80	90[d]
24	1	0.10	neat	-	80	86[d]
25	1	0.05	neat	-	80	79[d]
26	1	0.01	neat	-	80	traces

All the reactions were performed on a 1.00 mmol scale. [a] Conversion was calculated via ^{1}H NMR. [b]Reaction time 1 h. [c]Reaction time 2 h. [d]Traces of self-metathesis product **72**.

The first experiments showed that the catalyst loading could be lowered from 3 to 1 mol% without any loss in the conversion (Table 3, Entries 1-3). An attempt to go as low as 0.5 mol% with the same conditions, showed a significant decrease in the conversion (Table 3, Entry 4). However, by increasing the concentration from 0.2 to 1.5 M, the conversion improved considerably (Table 3, Entry 5). An attempt at lowering the catalyst loading even more using these conditions only lead to traces of the desired product (Table 3, Entry 6).

The optimisation process was continued by lowering the ratio between the cross partners from 6 to 2 equivalents of crotonaldehyde **70**, but otherwise with the same conditions (Table 3, Entries 7-8). An interesting trend was observed, where a higher the concentration correlated with a higher conversion. Thus, this led to the use of neat conditions.

In Table 3 (Entries 9-12), crotonaldehyde **70** was used in 3 equivalents with a lowering of the catalyst loading from 1 to 0.1 mol%. Higher conversions of >90% are immediately obtained (Table 3, Entries 9-11). However, when using a catalyst loading as low as 0.1 mol%, there is a substantial reduction of the conversion to 49% (Table 3, Entry 12).

Following these results, there were further attempts to optimise the reaction by changing other parameters. The temperature was increased to 80 °C which led to a substantial improvement in the conversion (Table 3, Entries 13-14). Decreasing the equivalents of crotonaldehyde **70** further, and thereby increasing the concentration, again gave better conversions (Table 3, Entries 15-18). However, when a catalyst loading of 0.05 mol% was used, the conversion decreased significantly to 66% (Table 3, Entry 19).

An evaluation of the time of the reaction was then carried out (Table 3, Entries 20-22). These experiments showed that with a higher temperature (80 °C) the reaction reached a conversion of 90% in 1 hour. Meanwhile, at 25 °C the reaction reached the same conversion in 2 hours.

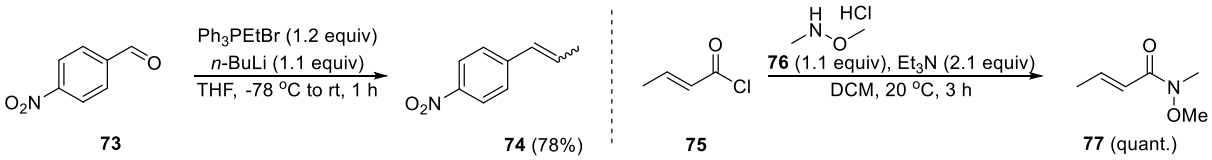
Attempts at further lowering the ratio to 1:1 between the two reacting olefins, and decreasing the catalyst loading resulted in high conversions. However, the formation of self-metathesis product **72** was observed (Table 3, Entries 23-25), and when using a very low catalyst loading of only 0.01 mol% barely any product was formed (Table 3, Entry 26).

This optimisation process showed that a very high concentration allowed for the use of very low catalyst loadings, without any loss in the conversion. Thus, the optimised conditions (Table 3, Entry 22) were used in further investigations into the scope of the reaction.

4.2.2 Scope of the Cross Metathesis Sequence

The investigations of the cross metathesis of methyl substituted olefins, continued with an evaluation of the scope of the reaction using the previously optimised conditions in the CM of isoeugenol **67** and crotonaldehyde **70**. Special attention was given to functional group tolerance, and the electronic properties, through varying the substituents of the aryl-olefin. The effect of the degree of substitution of the unsaturated bond on the coupling with aryl-olefins was also to be investigated.

Commercially available methyl substituted olefins, containing various functional groups as well as, *cis*-diacetoxy butene **78** and dimethyl itaconate **84** were used in Scope I with isoeugenol **67**. The precursors, propenyl nitrobenzene **74** and Weinreb amide **77** were to be synthesised, as shown in Scheme 36. Commercially available nitro-benzaldehyde **73** was converted to propenyl nitro-benzene **74** via a Wittig olefination protocol as described in the literature.[69] The triphenyl phosphonium ylide was obtained using *n*-BuLi as a base at -78 °C. This was followed by addition of aldehyde **73**, which furnished the desired product in 78% yield (Scheme 36).



Scheme 36. Synthesis of propenyl nitrobenzene **74** and Weinreb amide **77**.

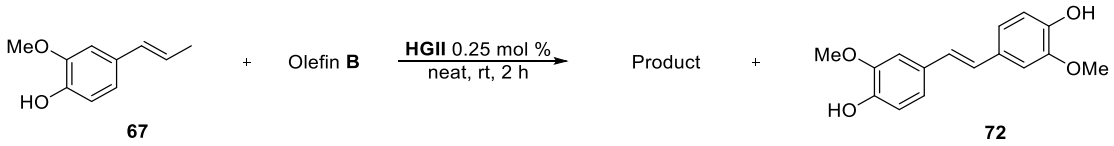
Following procedures in the literature,[70] commercially available crotonoyl chloride **75** was transformed to the corresponding Weinreb amide **77** using *N*-methoxy methylamine hydrochloride salt **76** and Et_3N as a base. This resulted in the desired product in quantitative yield (Scheme 36).

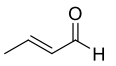
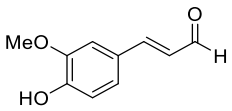
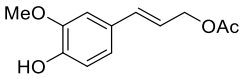
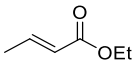
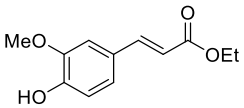
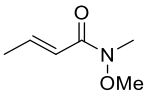
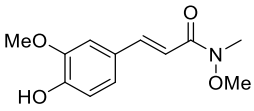
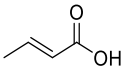
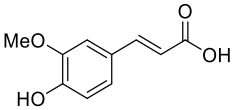
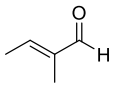
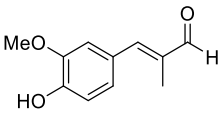
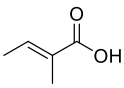
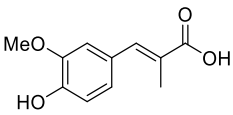
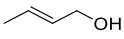
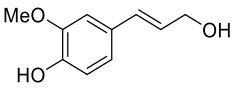
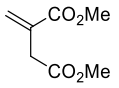
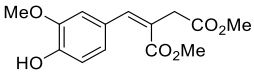
In Scope I, the cross metathesis between isoeugenol **67** and olefins **B** bearing varied functionalities was explored (Table 4). The standard reaction that had been previously optimised, using crotonaldehyde **70**, resulted in 82% conversion. The desired product **71a** was isolated with a yield of 78%, which confirms the calculated conversion (Table 4, Entry 1).

Attempts at using *Z*-diacetoxy butene **78** and ethyl butenoate **79** under more forceful conditions, with a temperature at 80 °C, resulted in high conversions but also in the formation of self-metathesis product **72** (Table 4, Entries 2-3). In these cases, the ester functionality proved to be more troublesome when conjugated to the double bond. Very similar results were obtained in the experiments using previously synthesised Weinreb amide **77**, and crotonic acid **80** (Table

4, Entries 4-5). A high conversion was observed, however, only in a 1:1 ratio of products **71d/e** and dimer **72**.

Table 4. Scope I: CM between isoeugenol **67** and olefins **B**.



Entry	Olefin B	(equiv)	Product		Conversion (%)[a]	Ratio 71 : 72
1		**70** (1.5)		**71a**	82	1[b] : 0
2[c]		**78** (1.0)		**71b**	86	9 : 1
3[c]		**79** (1.5)		**71c**	95	6 : 4
4[d]		**77** (1.5) (3.0)		**71d**	84 78	1 : 1 9 : 1
5[e]		**80** (1.5)		**71e**	87	1 : 1
6[c]		**81** (1.5)		**71f**	69	0 : 1
7[e]		**82** (1.5)		**71g**	78	0 : 1
8[e]		**83** (1.5)		**71h**	38	9 : 1
9[e]		**84** (1.5)		**71i**	80	0 : 1

All the reactions were performed on a 1.00 mmol scale. [a] Conversion was calculated via ^{1}H NMR. [b] Isolated yield 78%. [c] Temperature: 80 °C. [d] 2.5 mol% **HGII**; Solvent: DCM (4 M). [e] Solvent: DCM (2 M).

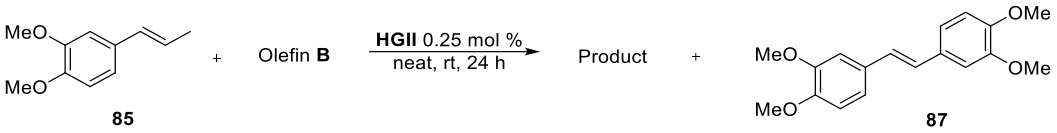
Following this, a new experiment was performed, using 3 equivalents of Weinreb amide **77** with 2.5 mol% of catalyst, which proved to be successful and gave a 78% conversion and a 9:1 ratio of Weinreb product **71d** (Table 4, Entry 4).

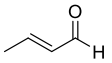
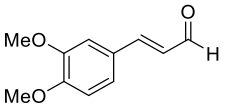
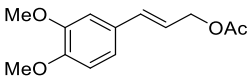
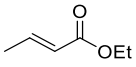
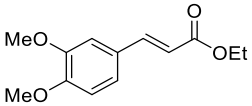
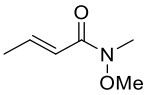
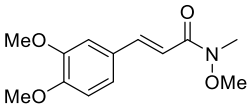
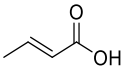
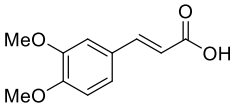
Unfortunately, more sterically demanding substrates, such as tiglic aldehyde **81** and tiglic acid **82**, showed to be very troublesome, and with these reactions only self-metathesis product **72** was observed (Table 4, Entries 6-7). Also, the use of dimethyl itaconate **84** gave the same results (Table 4, Entry 9). Coupling isoeugenol **67** with crotyl alcohol **83** gave a very low conversion yet there were traces of product **71h** (Table 4, Entry 8).

The results, depicted in Table 4, indicate that the success of the reaction is highly dependent on the substrate, which is often the case in Ruthenium-catalysed cross-metathesis reactions. Indeed, in order to introduce more sterically hindered or functionalities conjugated to the double bond required more harsh conditions, such as higher temperatures and higher catalyst loadings. These results, also, show that the self-metathesis of isoeugenol **67** is faster than the cross metathesis with a more challenging CM-partner.

In Scope II methyl isoeugenol **85** was used (Table 5), which contains two methoxy substituents that alters the electronic properties so that the double bond gets more electron-deficient compared to that of isoeugenol **67**. In the first attempt, using crotonaldehyde **70**, gave a high conversion of 81% and the desired product **86a** was isolated in a 79% yield (Table 5, Entry 1).

Table 5. Scope II: Methyl isoeugenol **85** and olefins **B**.



Entry	Olefin B	(equiv)	Product		Conversion (%)[a]	Ratio 86 : 87
1		**70** (1.5)		**86a**	81	9[b] : 1
2		**78** (1.5)		**86b**	68	9 : 1
3		**79** (1.5)		**86c**	81	7 : 3
4[d]		**77** (1.5)		**86d**	68	1 : 1
5[c]		**80** (1.5)		**86e**	58	7 : 3

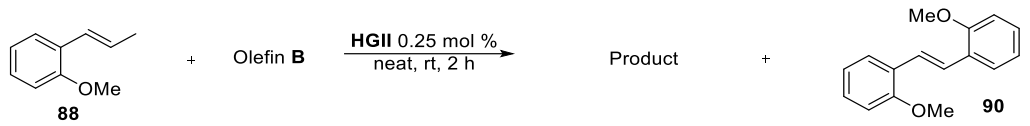
All the reactions were performed on a 1.00 mmol scale. [a] Conversion was calculated via ^{1}H NMR. [b]Isolated yield 79%. [c]Solvent: DCM (4 M). [d]2.5 mol% **HGII**; Solvent: DCM (4 M).

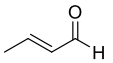
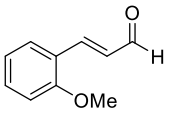
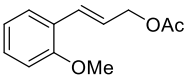
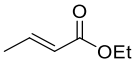
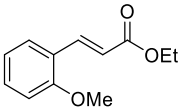
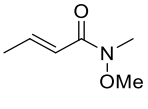
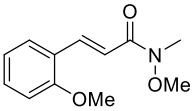
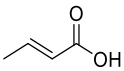
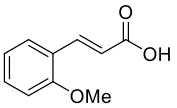
The reaction, using *Z*-diacetoxy butene **78** as a CM-partner gave a slightly lower conversion, however, a 9:1 ratio to the desired product 86b and self-metathesis product **87** (Table 5, Entry 2). Crotonic acid **80** and ester **79** were more troublesome substrates, and attempts to perform cross metathesis using these as CM-partners resulted in a 7:3 ratio of product **86e/c** and self-metathesis product **87** (Table 5, Entries 3 and 5).

Cross metathesis, using ester **79**, gave a higher conversion, which was to be expected since crotonic acid **80** is a more demanding substrate. Using Weinreb amide **77** as a CM-partner proved to be difficult as well, and only a 68% conversion to a 1:1 ratio of the desired product **86d** and dimer **87** was observed (Table 5, Entry 4).

In Scope III, *trans*-anethol **88** was to be evaluated. The first reaction was performed under standard conditions using crotonaldehyde **70** (Table 6, Entry 1). This resulted in a conversion of 79% with a 9:1 of ratio to product **89a** and self-metathesis product **90**. The desired product was isolated in a moderate yield of 51%. The next attempt, using *Z*-diacetoxy butene **78** and ester **79** as CM-partners, gave high conversions (Table 6, Entries 2-3). However, ester **79** proved to be more challenging, as only a 6:4 ratio of product **89c** and dimer **90** was observed.

Table 6. Scope III: *trans*-Anethol **88** and olefins **B**.



Entry	Olefin B	(equiv)	Product		Conversion (%)[a]	Ratio 89 : 90
1		**70** (1.5)		**89a**	79	9[b] : 1
2[d]		**78** (1.5)		**89b**	86	8 : 2
3[d]		**79** (1.5)		**89c**	80	6 : 4
4[e]		**77** (1.5)		**89d**	86	2 : 8
5[c]		**80** (1.5)		**89e**	45	7 : 3

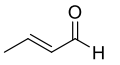
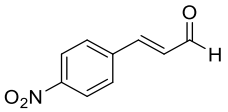
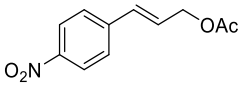
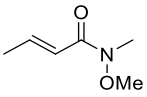
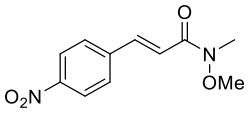
All the reactions were performed on a 1.00 mmol scale. [a] Conversion was calculated via ^{1}H NMR. [b]Isolated yield 51%. [c]Solvent: DCM (4 M). [d]Temperature: 80 °C [e]2.5 mol% **HGII**; Solvent: DCM (4 M).

More forceful conditions were applied in order to introduce Weinreb amide **77**, using 2.5 mol% catalyst (Table 6, Entry 4). A high conversion was obtained, yet there was a 2:8 ratio of the desired product **89d** and dimer **90**. This is probably due to an already high rate at which the self-metathesis reaction occurs, and thus a higher catalyst loading enhances this effect. The attempt at using crotonic acid **80** gave a relatively low conversion, yet a 7:3 ratio of product **89e** and dimer **90**.

In Scope III, *trans*-Anethol **88** proved to be a quite difficult substrate, since this compound very quickly undergoes self-metathesis. This is probably due to the electron-donating effect of the methoxy-group placed in the *ortho*-position, which makes the double-bond more electron-rich.

In Scope IV, the investigations continued using the previously synthesised nitrobenzene **74**, as outlined in Table 7. This is expected to be a very demanding substrate due to the strong electron-withdrawing nitro-group placed in *para*-position. Indeed, this proved to be a very difficult task, and the catalyst activity was completely inhibited by the strong electron-withdrawing effect of this type of cross-metathesis partner. In these cases no conversion was observed.

Table 7. Scope IV: CM between propenyl nitro benzene **74** and olefins **B**.

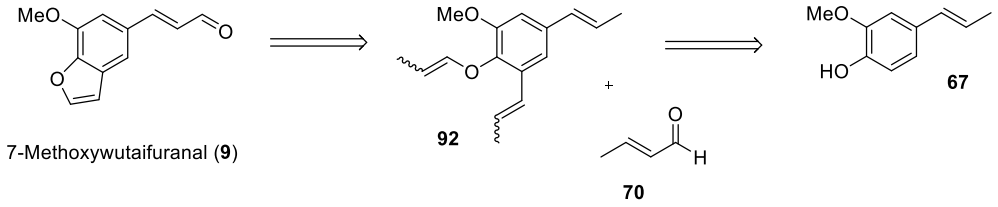
Entry	Olefin B (equiv)		Product		Conversion (%)
1		**70** (1.5)		**91a**	no conv.
2		**78** (1.5)		**91b**	no conv.
3		**77** (1.5)		**91d**	no conv.

In summary, compounds containing carboxylic acid, ester, or Weinreb amide as functional groups were found to be more demanding CM-partners. In these cases, only moderate conversions were obtained, despite higher temperatures and catalyst loadings. However, these results still demonstrate the importance of ensuring that the reaction proceeds via the more stable ethylidene species, as this route enables higher conversions at a lower catalyst loading.

4.2.3 Synthesis of 7-Methoxywutaifuranal via One-Pot CM/RCM

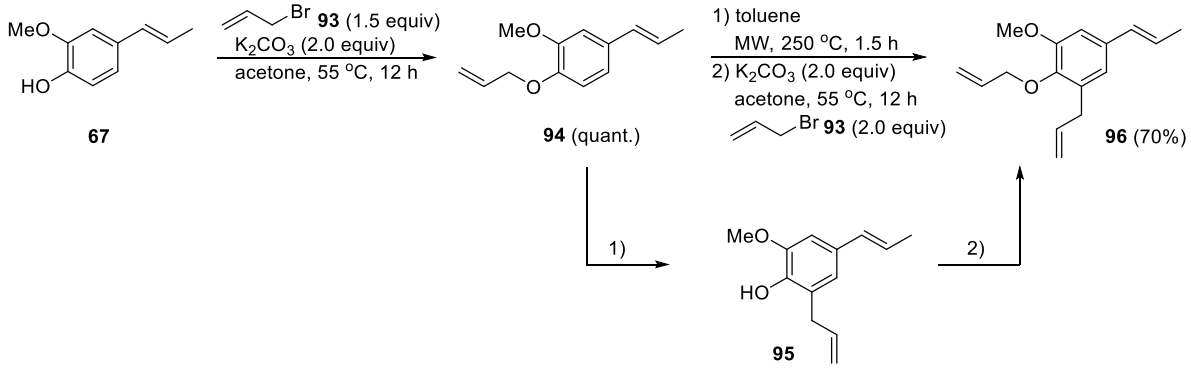
The application of the previously investigated cross-metathesis approach in the synthesis of a target compound, would further demonstrate the power of the reaction between methyl substituted alkenes. As a showcase example, natural product 7-methoxywutaifuranal (**9**) (described in Section 3.1.2) was chosen.

The retro-synthetic route to 7-methoxywutaifuranal (**9**) is outlined in Scheme 37. Commercially available isoeugenol **67** would be subjected to repeated *O*-allylation protocols and a microwave promoted Claisen rearrangement. A Ru-hydride catalysed isomerisation sequence would give propenyl ether **92**, which, via the key step in the synthesis, a one-pot CM/RCM sequence with crotonaldehyde **70**, would undergo a transformation to natural product **9**.



Scheme 37. Retro-synthetic route to 7-methoxywutaifuranal (**9**).

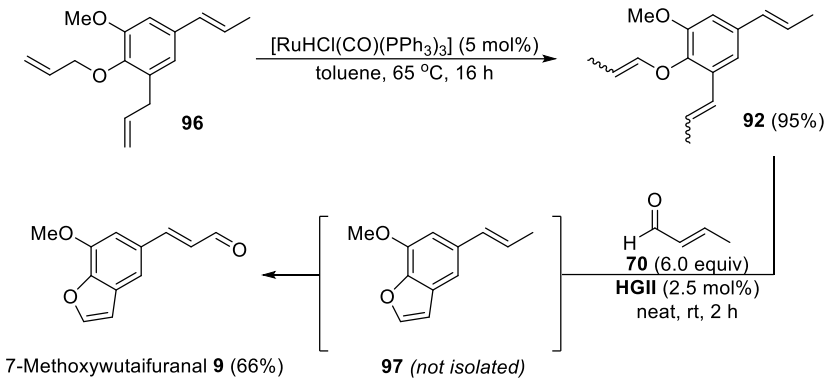
The synthesis of 7-methoxywutaifuranal (**9**) started with commercially available isoeugenol **67**, which was allylated under standard conditions using allyl bromide **93** and potassium carbonate as a base (Scheme 38). This resulted in *O*-allylated product **94** in quantitative yield. A Claisen rearrangement under microwave irradiation at a temperature of 250 °C for 1.5 h furnished desired rearrangement product **95**, which was used in the next step without further purification (Scheme 38).



Scheme 38. Synthesis of compound **96**.

Subsequent *O*-allylation of **95**, under the same conditions as used earlier, worked well and resulted in compound **96**, which was obtained in 70% yield (Scheme 38). The resulting allyl

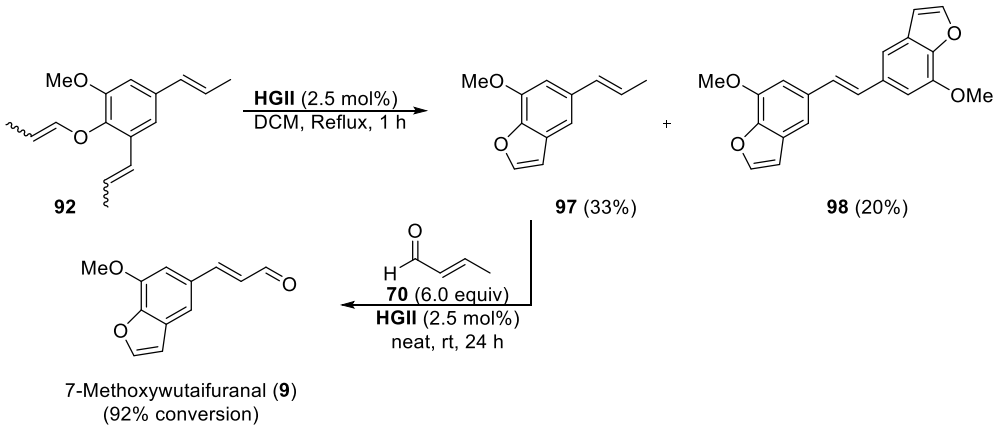
ether **96** was further converted to corresponding compound **92** via Ru-hydride complex catalysed isomerisation using [RuHCl(CO)(PPh_3)$_3$] as the hydride source. Propenyl ether **92** was obtained in nearly quantitative yield, but as a mixture of all possible geometrical isomers, as shown in Scheme 39.



Scheme 39. Synthesis of 7-methoxywutaifuranal (**9**) via one-pot CM/RCM.

The final step involved a one-pot CM/RCM sequence of propenyl ether **92**, using 2.5 mol% of Hoveyda-Grubbs' 2nd generation catalyst **HGII** and crotonaldehyde **70** in excess under neat conditions. The reaction was monitored by TLC and was stirred at room temperature for 2 h. This resulted in 7-methoxywutaifuranal (**9**) in 66% yield over the two steps (Scheme 39).

In order to evaluate the cross-metathesis reaction, RCM-product **97** was to be isolated and then applied to the cross-metathesis protocol. As outlined in Scheme 40, compound **92** was subjected to the RCM reaction using a catalyst loading of 2.5 mol% under reflux. This resulted in the formation of self-metathesis product **98** (20% yield) and the desired compound **97** in a very low yield of 33%.



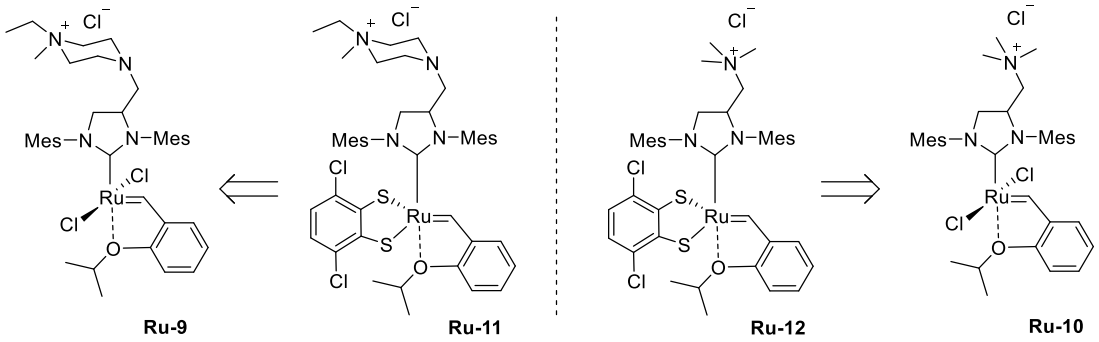
Scheme 40. Synthesis of RCM product **97** followed by CM to obtain natural product **9**.

The further transformation of RCM product **97** via the CM sequence with crotonaldehyde **70** (6 equivalents) under neat conditions, resulted in a 92% conversion to the desired natural product (Scheme 40). This demonstrates that the one-pot CM/RCM sequence was more convenient and gave a higher yield of the desired product than the two-step reaction sequence. Natural product 7-methoxywutaifuranal (**9**) was obtained in an overall yield of 44% over 5 steps.

4.3 Stereoretentive Metathesis in Polar Solvents

Since the birth of stereoretentive metathesis, tremendous efforts have been made to improve and develop new dithiolate based ruthenium catalysts,[49] as described in Section 3.2.3. A wide range of ruthenium catalysts have been developed that conduct different types of olefin metathesis in water (Section 3.2.4). However, there are no such examples, of a stereoretentive dithiolate complex designed for use in polar solvents, such as alcohols and water, reported in the literature. Thus, the preparation of a stereoretentive catalyst, which would be stable and efficient for reactions in neat water and/or alcohols, was to be investigated.

The retro-synthetic route towards polar stereoretentive catalysts **Ru-11** and **Ru-12** is outlined in Scheme 41. These complexes would be designed to bear a quaternary ammonium tag ($NR_3^+Cl^-$) instead of a hydrochloride ($NH_3^+Cl^-$) in the NHC-ligand, as this would allow for possible applications in biological systems under neutral pH. Therefore, commercially available (StickyCat) **Ru-10** and (AquaMet) **Ru-9** were chosen as the parent complexes to be converted into the corresponding stereoretentive complexes **Ru-11** and **Ru-12** (Scheme 41).

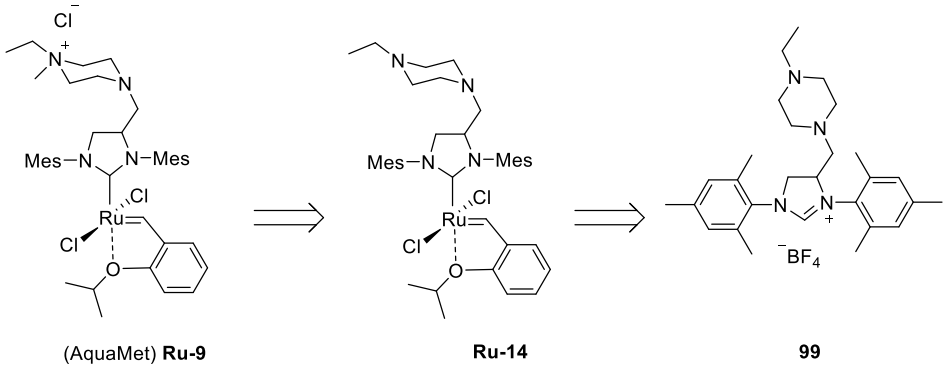


Scheme 41. Retro-synthetic route to polar stereoretentive catalysts **Ru-11** and **Ru-12** (Mes = 2,4,6-tri-methylphenyl).

AquaMet **Ru-9** would be synthesised according to procedures in the literature.[58] This would be followed by a transformation to stereoretentive catalyst **Ru-11** via a ligand exchange of the chloride ligands to the dithiolate moiety. Meanwhile, StickyCat **Ru-10** would be purchased, and then directly converted to dithiolate complex **Ru-12** in one step via the ligand exchange reaction. Both synthetic routes to the two quarternary ammonium chloride tagged stereoretentive catalysts **Ru-11** and **Ru-12** were investigated in parallel.

4.3.1 Synthesis of Quaternary Ammonium Complex AquaMet

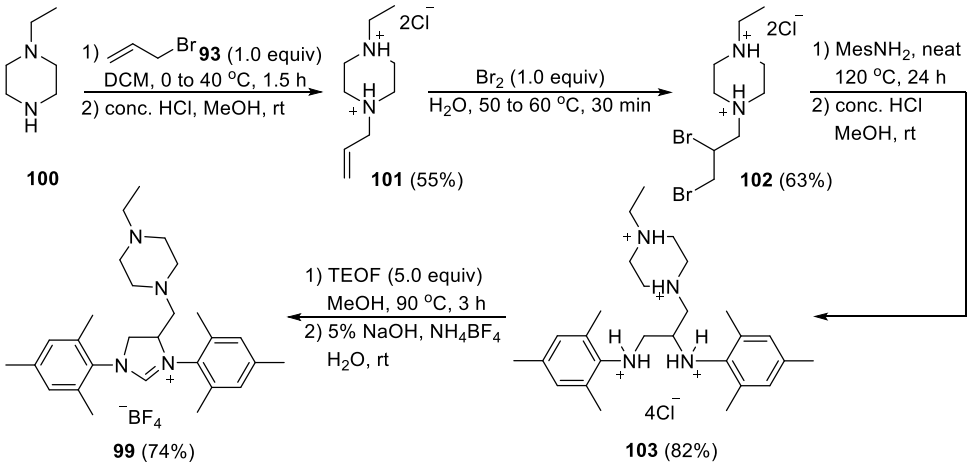
The first step in the synthesis of quaternary ammonium tagged stereoretentive catalyst **Ru-11**, was to prepare ruthenium complex AquaMet **Ru-9**, as it contains the ammonium tagged NHC ligand. In order to do this, the synthesis started with the construction of a trialkylamino-group containing NHC-salt **99**, as outlined in Scheme 42.



Scheme 42. Retro-synthetic route to obtain AquaMet **Ru-9** (Mes = 2,4,6-tri-methylphenyl).

Complex **Ru-14** would then be available via two ligand exchange reactions, using indenylidene complex **Ind-I** or Grubbs' first-generation catalyst **GI** as the ruthenium source: (1) Introduction of NHC-salt **99** via exchange of PCy_3 (2) Exchange of the second ligand (PCy_3) with styrene **104**. The synthesised complex **Ru-14** bearing the trialkylamino group would then be treated with methyl chloride to yield quaternary ammonium tagged complex AquaMet **Ru-9** (Scheme 42).

Following procedures in the literature,[58] commercially available ethylpiperazine **100** was subjected to a *N*-allylation protocol using allyl bromide **93**, as outlined in Scheme 43.

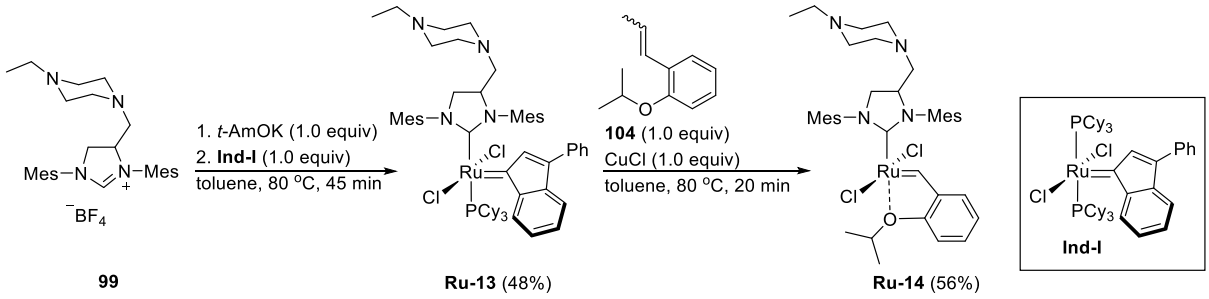


Scheme 43. Synthesis of NHC ligand **99** starting from ethylpiperazine **100**.

The product was converted into the corresponding hydrogen chloride salt **101**, which was isolated via crystallisation in 55% yield. The bromination of the double bond of **101** proceeded in water and gave **102** in 63% yield. The introduction of the mesitylene moieties were performed under neat conditions using 2,4,6-trimethylanilline in large excess. The reaction was heated for 24 hours and, after, reactive crystallisation using conc. HCl, salt **103** was obtained in a very good yield.

The last step of the synthesis of NHC ligand **99**, was a cyclisation using triethyl orthoformate (TEOF) in MeOH at 90 °C. After treatment with ammonium tetrafluoroborate (NH_4BF_4) in the presence of a 5% NaOH solution, the desired salt **99** was obtained in 74% yield (Scheme 43). This four-step procedure resulted in an overall yield of 21% of NHC-ligand **99** over 4 steps.

The synthesis of complex **Ru-14** and the introduction of the synthesised NHC-ligand **99** was investigated using two different ruthenium sources: indenylidene complex **Ind-I** and Grubbs' 1st generation catalyst **GI**. The first attempt was executed in a two-step reaction sequence using **Ind-I** as the ruthenium source for the ligand exchange reactions, as outlined in Scheme 44.

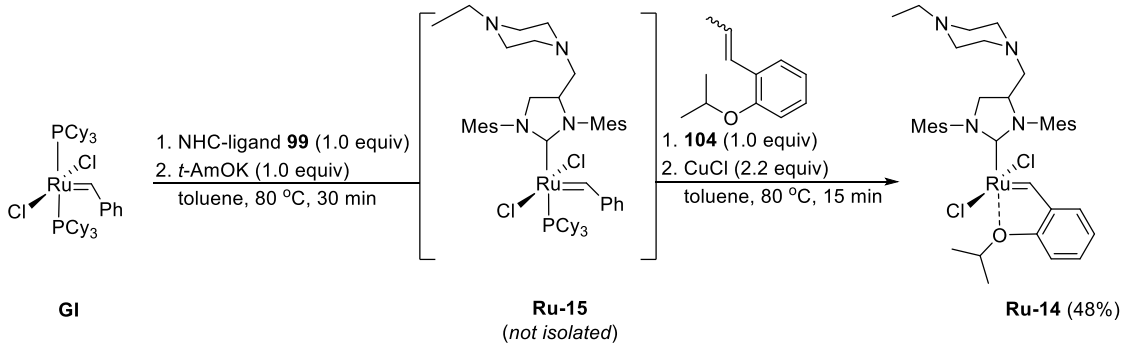


Scheme 44. Synthesis of trialkylammonium complex **Ru-14** from **Ind-I**.

In the first step, deprotonation of NHC salt **99** was accomplished using potassium *tert*-amylate (*t*-AmOK) as a base in dry toluene. The free NHC generated, was reacted *in situ* with **Ind-I**, and after column chromatography complex **Ru-13** was isolated in 48% yield as a red solid.

The synthesis continued with the introduction of oxygen chelating benzylidene ligand **104**, which underwent a second ligand exchange with **Ru-13**. Copper chloride (CuCl) was used as a scavenger of the dissociating phosphine ligand (PCy_3). The desired complex **Ru-14** was isolated in 56% yield as a green solid (Scheme 44). This two-step procedure resulted **Ru-14** in an overall yield of 27%.

The second strategy to obtain complex **Ru-14** was to be investigated. This would be done via a one-pot procedure using Grubbs' first-generation catalyst **GI** as the ruthenium source, as shown in Scheme 45.

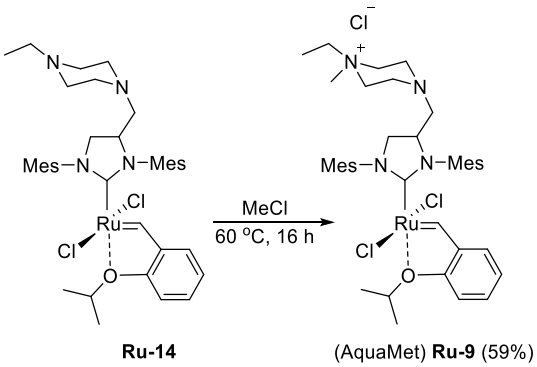


Scheme 45. One-pot synthesis of **Ru-14** from **GI**.

Deprotonation of NHC-ligand **99** was achieved using *t*-AmOK as a base. This resulted in the free carbene, which was reacted *in situ* with complex **GI**. The reaction was monitored by TLC and, after, completion of the ligand exchange, styrene **104** was added to the precursor **Ru-15**, which was followed by addition of CuCl as a scavenger. This resulted in the desired complex **Ru-14** in 48% yield.

A comparison of the two procedures using two different ruthenium sources (**Ind-I** and **GI**), showed that the one-pot procedure (using **GI**) proved to be both more convenient and resulted in a higher overall yield (48%). The two-step reaction sequence using **Ind-I** only gave an overall yield of 27%. This is perhaps due to the fact that Grubbs' 1st generation catalyst is more reactive than indenylidene complex **Ind-I**, and possibly because there was one purification step less in the one-pot procedure.

The last step in the synthesis of AquaMet **Ru-9**, involved a methylation of the nitrogen on the NHC ligand to get the quaternary nitrogen center "tagged". Following procedures in the literature,[58] quaternarisation of the neutral complex **Ru-14** was executed using methyl chloride (MeCl). The reaction was heated to 60 °C in a pressurised ampulla overnight and, after excess MeCl was evaporated, (AquaMet) **Ru-9** was obtained in 59% yield, as shown in Scheme 46.

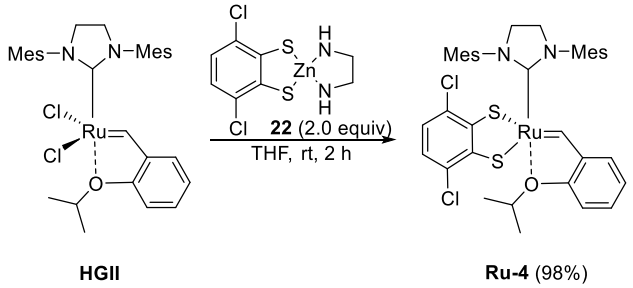


Scheme 46. Completion of the synthesis of (AquaMet) **Ru-9**.

4.3.2 Synthesis of Stereoretentive Catalysts

The previously synthesised quaternary ammonium tagged complex (AquaMet) **Ru-9** and the purchased (StickyCat) **Ru-10** were to be converted into the corresponding dithiolate complexes **Ru-11** and **Ru-12**. One of the resulting complexes would then be applied in stereoretentive metathesis model reactions. The dithiolate complexes would be formed in a one-step procedure using zinc dithiolate **22** in a ligand exchange with the chloride ligands, as described in Section 4.3.

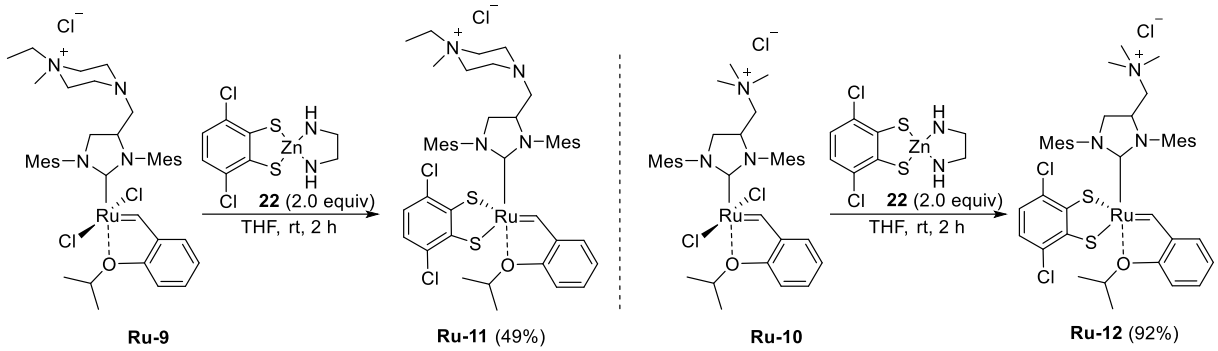
The first step was to synthesise standard dithiolate complex **Ru-4**, which would be used to compare the activity of the newly designed complexes in model reactions. Following procedures in the literature,[53] Hoveyda-Grubbs' 2nd generation catalyst **HGII** was subjected to a ligand exchange reaction using zinc dithiolate **22** in a glovebox (Scheme 47). The desired complex **Ru-4** was obtained in a high yield of 98%.



HGII **Ru-4** (98%)

Scheme 47. Synthesis of stereoretentive catalyst **Ru-4**.

As shown in Scheme 48, previously synthesised catalyst AquaMet **Ru-9** was subjected to the same procedure as described above. After the completion of the reaction, the purification of the crude product proceeded as follows: the solvent (THF) was evaporated, the crude product was redissolved in DCM, and the solution was filtered of zinc chloride. However, the newly formed dithiolate complex **Ru-11** was hardly soluble in DCM which made the purification process very tedious. This is reflected in the lower yield of 49% that was obtained after recrystallisation from pentane.



Scheme 48. Synthesis of ammonium tagged stereoretentive catalysts **Ru-11** and **Ru-12**.

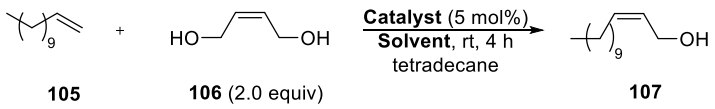
Commercially available StickyCat **Ru-10** was transformed into the corresponding dithiolate complex **Ru-12** in a yield of 92%, as shown in Scheme 48. The higher yield obtained is partly due to the increased solubility in DCM of **Ru-12** compared to the previously synthesised dithiolate complex **Ru-11**. The solubility problems are most likely due to the quaternary ammonium group in the NHC ligand. However, it turned out that **Ru-12** had much better solubility in MeOH but was only partially soluble in THF and water. Therefore, the activity of tagged stereoretentive complex **Ru-12** in stereoretentive metathesis model reactions was to be evaluated.

4.3.3 Stereoretentive Metathesis in Polar Solvents

The activity of the synthesised dithiolate complex **Ru-12** was to be investigated through its application as a catalyst in model reactions performed in THF, and polar solvents, such as alcohols and water. The first model reaction, using benchmark substrates, investigated is outlined in Table 8. This is a well-established reaction for stereoretentive metathesis, and it would therefore be possible to compare the results to those in the literature.[49]

These reactions were carried out with 5 mol% of catalyst, using dodecene **105** and *cis*-butendiol **106** as coupling partners, and with THF as a solvent. The reaction was analysed using gas chromatography (GC), with tetradecane as an internal standard. To evaluate the newly synthesised catalyst **Ru-12**, an experiment using the standard dithiolate complex **Ru-4** was performed for comparison (Table 8, Entry 1).

Table 8. Stereoretentive metathesis of dodecene **105** and *cis*-butendiol **106**.



105 **106** (2.0 equiv) **107**

Entry	Catalyst	Solvent	Conversion[a]
1	**Ru-4**	THF	77%
2	**Ru-12**	THF	33%
3	**Ru-12**	THF:MeOH (1:1)	70%

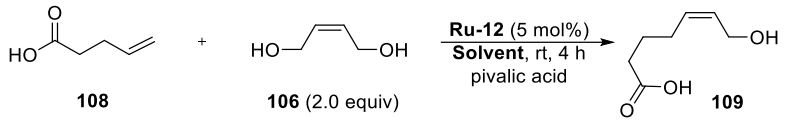
[a]Determined by GC.

Standard stereoretentive catalyst **Ru-4** gave a conversion of 77% which was mainly the desired *Z*-configured product **107**. These results match the ones reported in the literature,[49] and show that the starting materials and the solvent are of good purity. However, under the same conditions, using **Ru-12** as a catalyst, there was a low conversion of 33% (Table 8, Entry 2).

This is probably due to the poor solubility of this complex in THF. However, the fact that dithiolate complex **Ru-12** is soluble in MeOH led to a new experiment which was performed in THF:MeOH (1:1) mixture (Table 8, Entry 3). Delightfully, this gave a conversion of 70% to the desired *Z*-olefin **107** with high stereoretention, and showed that complex **Ru-12** has a comparable activity to standard complex **Ru-4**.

Then a model reaction for stereoretentive metathesis in water was designed. This was inspired by procedures in the literature,[71] where pentenoic acid **108** was chosen as the cross partner with *Z*-butendiol **106**. Pivalic acid was used as an internal standard for the GC analysis, since it resembles the compounds that were to be analysed and should be inert to the reaction conditions. As mentioned earlier, complex **Ru-12** is minimally soluble in water but dissolves well in MeOH. Therefore, the initial experiments were performed in MeOH and water mixtures, as outlined in Table 9.

Table 9. Stereoretentive metathesis in methanol and water mixtures.



Entry	Solvent	Conversion[a]
1	MeOH	34%
2	MeOH:H_2O (3:1)	12%
3	MeOH:H_2O (1:1)	8%
4	MeOH:H_2O (1:3)	2%

[a]Determined by GC.

These preliminary results proved to be very promising. Since, even though the conversions were relatively low, there was still catalyst activity, and this shows that the dithiolate complex is relatively stable in the presence of water. It shall be noted also, that in these experiments, the Z-configured product **109** was obtained in high stereoretention. However, the poor conversions could be due to the fact that **Ru-12** is minimally soluble in water. This is also reflected by the increased conversions observed when more MeOH was used. Pentenoic acid **108** is arguably quite a demanding substrate, due to its potential to coordinate to the metal-center of the catalyst.

5 Conclusion and Outlook

One of the objectives of this work was to apply a highly stereoselective tethered RCM sequence in the total synthesis of a conjugated triene containing natural product, (+)-bretonin B (**1**). In order to accomplish this, an extension of this method, using an *E*-selective Julia-Kocienski olefination protocol to obtain the *E,Z,E*-conjugated triene moiety, was investigated via two strategies.

The first strategy involved an early assembly of the intriguing triene moiety. The required *Z,E*-dienoate **32** was obtained via the tethered RCM approach in high stereoselectivity in a 93% yield. This was followed by an oxidation/reduction sequence to the corresponding *Z,E*-dienal **52**, which was then subjected to an *E*-selective Julia-Kocienski protocol. The desired conjugated *E,Z,E*-triene acetonide **34** was obtained in high stereoselectivity in 76% yield. However, isomerisation to the *E,E,E*-isomer was observed after the attempted cleavage of the acetonide protecting group. Thus, this strategy proved to be unsuccessful.

The second strategy was to construct the sensitive conjugated triene at a late stage in the synthesis. This was done via two synthetic pathways (A and B), which were both successful. Pathway B contained a step less than pathway A and was therefore superior and, in a 10-step sequence, gave (+)-bretonin B (**1**) in an overall yield of 11%.

As the first objective was achieved, a possible extension of this work would be to create the enantiomer of (+)-bretonin B (**1**), via synthetic route B. This could be achieved by using a Steglich esterification protocol (to introduce building block **38**), which would retain the stereocenter of building blocks **37** or **58a/b** and thereby, allow the formation of the corresponding enantiomer.

The second and third objectives were to evaluate a cross metathesis sequence using methyl substituted olefins, and then to apply this methodology in the synthesis of a target compound respectively. First, the cross-metathesis reaction between isoeugenol **67** and crotonaldehyde **70** was optimised. A 90% conversion to the desired product **71a** was observed when performing the reaction using 1.5 equivalents of crotonaldehyde **70** and Hoveyda-Grubbs' 2nd generation **HGII** (0.25 mol%) as a catalyst under neat conditions at ambient temperature.

The scope of the reaction showed that when using substrates with a more electron-deficient double bond, there was a lower conversion to the CM product. In the case of nitro-substituted styrene **74**, the activity of the catalyst was completely inhibited. The most successful substrates

for this transformation proved to be isoeugenol **67** and crotonaldehyde **70**, as compounds containing ester, carboxylic acid, or Weinreb amide as functional groups demanded much more forceful conditions.

The third objective was to apply the reaction as a one-pot CM/RCM sequence in the synthesis of 7-methoxywutaifuranal (**9**), and this proved to be successful. The one-pot CM/RCM sequence worked well and 7-methoxywutaifuranal (**9**) was obtained in 66% yield. The total synthesis included 5 steps and gave the target compound in an overall yield of 44%. The logical next step would be to apply the one-pot CM/RCM approach in the synthesis of 7-methoxywutaifuranate (**8**) and 7-methoxywutaifuranol (**10**).

The fourth objective was to design and synthesise a quaternary ammonium tagged dithiolate catalyst for stereoretentive metathesis in polar solvents, such as alcohols and water. Accordingly, two quaternary ammonium tagged dithiolate complexes were successfully synthesised, whereof one, dithiolate complex **Ru-12,** was used in initial experiments in model reactions in THF, and methanol/water mixtures. The preliminary results proved to be very promising. Tagged complex **Ru-12** gave a conversion of 70% to the *Z*-configured olefin **107** in a THF:MeOH (1:1) mixture. This is comparable to the conversions observed when using the common dithiolate complex **Ru-4**.

The experiments performed in MeOH and water mixtures gave very low conversions, which is probably due to the low solubility of complex **Ru-12** in water. Further research can be done in this area, and the first step would be to increase the solubility of complex **Ru-12** by incorporating a second quaternary ammonium tag, as this would be necessary in order to perform the reaction in neat water.

6 Experimental Section

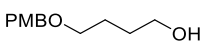
6.1 General Remarks

All experiments involving air and moisture sensitive chemicals were conducted using standard Schlenk technique or by using a glovebox under an atmosphere of dry nitrogen or argon. Dichloromethane (DCM), diethyl ether, methanol and toluene were purified with a solvent purification system. All other chemicals were either purchased from Sigma-Aldrich, Alfa Aesar, J&K, TCI, Roth and MERCK or prepared according to cited literature. Microwave reactions were carried out in an Anton-Paar-monowave 300 or Anton-Paar-monowave 400 reactor (monowave, maximum power 850 W, temperature control by IRsensor, vial volume 20 mL). All microwave reactions were conducted in sealed vessels; reaction mixture temperatures are reported within the respective procedures. Dry column vacuum chromatography[72] or standard flash column chromatography were performed on silica gel 60. Analytical thin layer chromatography (TLC) was carried out on Merck "TLC Silica Gel 60 F254" pre-coated plates. Typical solvent systems for development of the plates were PE/EtOAc or PE/MTBE mixtures. UV active spots were detected with UV light at 254 nm. TLC plates were stained with $KMnO_4$ water solution or ceric ammonium molybdate. ^{1}H NMR experiments were obtained at 300, 400, 500 or 600 MHz and ^{13}C NMR experiments were recorded at 75, 125 or 151 MHz. NMR chemical shifts are reported in ppm and referred to residual solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 5.32 and 53.84 ppm for ^{1}H and ^{13}C in CD_2Cl_2, 4.79 ppm for ^{1}H in D_2O respectively. Multiplicities are denoted as: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet) and m (multiplet), br (broad). Coupling constants (*J*) are given in Hz. GC analyses were performed using Clarus 580 chromatograph. IR measurements were carried out as ATR-FTIR spectra using a Perkin-Elmer UARTTWO instrument. Wavenumbers (ν) are given in cm^{-1} and the peak intensities are denoted as: strong (s), medium (m), weak (w). High-resolution mass spectra were obtained by ESI-TOF or EI-TOF on Micromass Manchester Waters Inc. instruments. Specific rotations were measured using JASCO DIP-1000 and P-2000 polarimeters in a 10 cm cuvette at 589 nm. Concentrations are given in $g*100mL^{-1}$.

6.2 Total Synthesis of (+)-Bretonin B via Tethered Ring Closing Metathesis

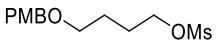
6.2.1 Synthesis of Building Block 31a/b and 38

4-((4-Methoxybenzyl)oxy)butan-1-ol (40a)[21]



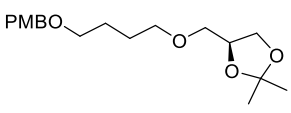
To a solution of 1,4-butadiol **39** (3.05 g, 2.99 mL, 40.0 mmol) in THF (150 mL) at 0 °C was NaH (60 wt-% dispersion in mineral oil, 1.76 g, 44.0 mmol) added portion wise. After 30 min TBAI (148 mg, 1.0 mol%) and PMBCl (5.30 mL, 38.5 mmol) in THF (15 mL) were added. The reaction mixture was stirred at ambient temperature for 16 h. H_2O (80 mL) was added carefully, and the aqueous layer was separated and extracted with EtOAc (2x 100 mL). The combined organic layers were washed with H_2O (2x 100 mL) and brine (2x 100 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give 4-((4-methoxybenzyl)oxy)butan-1-ol **40a** (4.57 g, 21.7 mmol, 56% yield) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.62 (t, J = 5.7 Hz, 2H), 3.49 (t, J = 5.8 Hz, 2H), 2.42 (s, OH), 1.72 – 1.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 130.4, 129.4, 114.0, 72.8, 70.2, 62.8, 55.4, 30.3, 26.9. Analytical data match those previously reported in the literature.[21]

4-((4-Methoxybenzyl)oxy)butyl methanesulfonate (41a)[21]



To a solution of alcohol **40a** (4.54 g, 21.6 mmol) in THF (95 mL) at 0 °C were Et_3N (3.28 g, 4.35 mL, 32.4 mmol) and MsCl (2.73 g, 1.84 mL, 23.8 mmol) added. The reaction mixture was stirred at 0 °C for 5 h before sat. aq. NH_4Cl (50 mL) was added. The aqueous layer was separated and extracted with Et_2O (3x 50 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product **41a** was used in the next step without further purification.

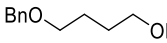
(*S*)-4-((4-((4-methoxybenzyl)oxy)butoxy)methyl)-2,2-dimethyl-1,3-dioxolane (31a)[21]



To a solution of (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol **42** (873 mg, 0.82 mL, 6.61 mmol) in DMF (12 mL) at 0 °C was NaH (60 wt-% dispersion in mineral oil, 219 mg, 7.24 mmol) added portion wise. After 1.5 h crude product **40a** (6.80 mmol) in DMF (75 mL) was added dropwise and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (70 mL) and the aqueous layer was separated and extracted with Et_2O (5x 15 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$, filtered, and evaporated under

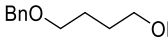
reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*S*)-4-((4-((4-methoxybenzyl)oxy)butoxy)methyl)-2,2-dimethyl-1,3-dioxolane **31a** (1.50 g, 4.63 mmol, 70% yield) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 7.2 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.45 (s, 2H), 4.27 (p, J = 6.0 Hz, 1H), 4.07 (dd, J = 8.3, 6.4 Hz, 1H), 3.82 (s, 3H), 3.74 (dd, J = 8.2, 6.4 Hz, 1H), 3.69 – 3.38 (m, 6H), 1.75 – 1.49 (m, 4H), 1.44 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 130.9, 129.3, 113.9, 109.5, 74.9, 72.7, 72.0, 71.7, 70.0, 67.1, 55.4, 26.9, 26.6, 26.5, 25.6. Analytical data match those previously reported in the literature.[21]

4-(Benzyloxy)butan-1-ol (40b)[73]



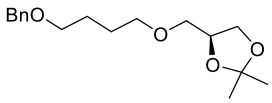
To a suspension of NaH (8.10 g, 60 wt-% dispersion in mineral oil, 202 mmol) in THF (130 mL) at 0 °C was 1,4-butadiol **39** (75.7 g, 74.0 mL, 840 mmol) added dropwise. The solution was stirred at 20 °C for 2 h. Benzyl bromide (BnBr) (28.7 g, 20.0 mL, 168 mmol) in THF (40 mL) was added dropwise and the reaction was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (150 mL) and the aqueous layer was separated and extracted with EtOAc (3x 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give 4-(benzyloxy)butan-1-ol **40b** (29.1 g, 161 mmol, 96% yield) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 4.52 (s, 2H), 3.63 (t, J = 5.8 Hz, 2H), 3.52 (t, J = 5.8 Hz, 2H), 2.28 (s, 1H), 1.77 – 1.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.5, 127.8, 127.8, 73.2, 70.5, 62.8, 30.2, 26.8. Analytical data match those previously reported in the literature.[73]

4-(Benzyloxy)butyl methanesulfonate (41b)



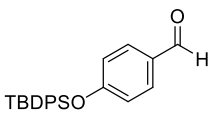
The title compound was synthesized in analogy to a previously published procedure:[21] To a solution of **40b** (6.11 g, 34.7 mmol) in THF (150 mL) at 0 °C were Et_3N (5.27 g, 6.99 mL, 52.1 mmol) and methanesulfonyl chloride (MsCl) (4.38 g, 2.95 mL, 38.2 mmol) added. The reaction mixture was stirred at 0 °C for 5 h before sat. aq. NH_4Cl (40 mL) was added. The aqueous layer was separated and extracted with Et_2O (3x 40 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Crude product **41b** was used in the next step without further purification.

(*S*)-4-((4-(Benzyloxy)butoxy)methyl)-2,2-dimethyl-1,3-dioxolane (31b)



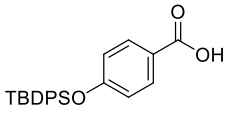
The title compound was synthesized in analogy to a previously published procedure:[21] To a solution of (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol **42** (3.78 g, 3.53 mL, 28.6 mmol) in DMF (325 mL) at 0 °C was NaH (1.26 g, 60 wt-% dispersion in mineral oil, 31.3 mmol) added portion wise. After 1.5 h mesylate **41b** (8.52 g, 29.5 mmol) in DMF (55 mL) was added dropwise and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (250 mL) and the aqueous layer was separated and extracted with Et_2O (5x 30 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*S*)-4-((4-(benzyloxy)butoxy)methyl)-2,2-dimethyl-1,3-dioxolane **31b** (6.29 g, 21.4 mmol, 75% yield) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 4.50 (s, 2H), 4.25 (p, J = 6.0 Hz, 1H), 4.04 (dd, J = 8.2, 6.4 Hz, 1H), 3.72 (dd, J = 8.2, 6.4 Hz, 1H), 3.57 – 3.42 (m, 5H), 3.41 (dd, J = 9.9, 5.6 Hz, 1H), 1.74 – 1.60 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 128.5, 127.7, 127.6, 109.5, 74.9, 73.0, 72.0, 71.6, 70.3, 67.1, 26.9, 26.6, 26.5, 25.6; IR (ATR) ν 2961 (m), 1736 (s), 1249 (m), 1170 (s), 918 (s); HRMS (ESI) calcd for $C_{17}H_{26}NaO_4$ $[M+Na]^+$ 191.1048, found 191.1044; $[\alpha]_D^{23}$ = +9.4 (c 1.0, $CHCl_3$).

4-((*tert*-Butyldiphenylsilyl)oxy)benzaldehyde (44)[21]



4-Hydroxybenzaldehyde **43** (1.52 g, 12.5 mmol) and imidazole (2.16 g, 32.5 mmol) were dissolved in DCM (20 mL). *tert*-Butyl(chloro)diphenylsilane (TBDPSCl) (2.46 g, 4.23 mL, 16.3 mmol) was added and the reaction was stirred at 20 °C for 16 h. Another portion of 4-hydroxybenzaldhyde **7** (458 mg, 3.75 mmol) was added and the reaction was stirred at 20 °C for another 5 h. Sat. aq. NH_4Cl (15 mL) was added, and the aqueous phase was separated and extracted with Et_2O (3x 40 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give 4-((*tert*-butyldiphenylsilyl)oxy)-benzaldehyde **44** (4.03 g, 11.2 mmol, 69% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.71 (d, J = 7.5 Hz, 4H), 7.65 (d, J = 8.5 Hz, 2H), 7.49 – 7.35 (m, 6H), 6.87 (d, J = 8.4 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 161.4, 135.5, 132.1, 131.8, 130.4, 130.4, 128.1, 120.5, 26.6, 19.6. Analytical data match those previously reported in the literature.[21]

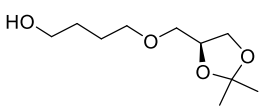
4-((*tert*-Butyldiphenylsilyl)oxy)benzoic acid (38)[21]



Benzaldehyde **44** (7.95 g, 22.1 mmol) was dissolved in H_2O (45 mL) and *t*BuOH (120 mL). 2-Methyl-2-butene (2.33 g, 3.35 mL, 33.2 mmol), NaH_2PO_4 (1.33 g, 11.1 mmol) and $NaClO_2$ (2.60 g, 28.7 mmol) were added. The reaction mixture was stirred at ambient temperature for 4 days. The aqueous phase was separated and extracted with EtOAc (5x 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give 4-((*tert*-butyldiphenylsilyl)oxy)benzoic acid **38** (5.74 g, 15.2 mmol, 69% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.8 Hz, 2H), 7.75 – 7.66 (m, 4H), 7.49 – 7.33 (m, 6H), 6.80 (d, J = 8.8 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 160.7, 135.6, 132.3, 132.2, 130.3, 128.1, 122.4, 119.9, 26.6, 19.6. Analytical data match those previously reported in the literature.[21]

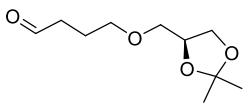
6.2.2 Strategy I: Synthesis of Isomerised Diol 55

(*S*)-4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)butan-1-ol (48)[66]



Benzyl ether **31b** (5.00 g, 17.0 mmol) was dissolved in EtOAc (85 mL) and 20 wt-% $Pd(OH)_2$/C (2.04 g) was added. The system was flushed with H_2 and the reaction mixture was then exposed to 1 atm of H_2 at ambient temperature for 2 h. The heterogeneous mixture was filtered through celite and washed with EtOAc. Crude product **48** (3.48 g, 17.0 mmol, quantitative yield) a colourless liquid was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (p, J = 5.9 Hz, 1H), 4.03 (dd, J = 8.2, 6.5 Hz, 1H), 3.70 (dd, J = 8.2, 6.4 Hz, 1H), 3.67 – 3.57 (m, 2H), 3.57 – 3.38 (m, 4H), 2.37 (s, 1H), 1.72 – 1.58 (m, 4H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.6, 74.8, 72.0, 71.8, 66.9, 62.7, 30.0, 26.9, 26.5, 25.5; IR (ATR) ν 3420 (s, broad), 2936 (m), 2868 (m), 1455 (w), 1371 (m), 1052 (s); HRMS (ESI) calcd for $C_{10}H_{21}O_4$ $[M+H]^+$ 205.1440, found 205.1425; $[\alpha]_D^{22}$ = +8.6 (c 1.0, $CHCl_3$).

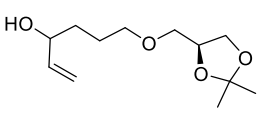
(*S*)-4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)butanal (49)[66]



To a solution of alcohol **48** (1.33 g, 6.53 mmol) and pyridine (3.99 mL, 49.0 mmol) in DCM (65 mL) at 0 °C was DMP (4.16 g, 9.80 mmol) added portion wise. The reaction mixture was stirred at 20 °C for 2 h. The reaction was quenched with sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1:1). The aqueous layer was separated and extracted with DCM (3x 30 mL). The combined organic layers were dried /with $MgSO_4$,

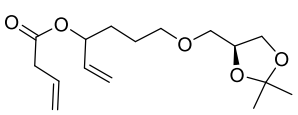
filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*S*)-4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)butanal **49** (1.01 g, 4.99 mmol, 76% yield) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 4.17 (m, 1H), 3.99 (dd, *J* = 8.3, 6,4 Hz, 1H), 3.65 (dd, *J* = 8.3, 6.4 Hz, 1H), 3.39 (m, 3H), 3.37 (dd, *J* = 10.0, 5.4 Hz, 1H), 2.47 (td, *J* = 7.1, 1.6 Hz, 2H), 1.87 (p, *J* = 6.7 Hz, 2H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 109.4, 74.7, 71.9, 70.5, 66.8, 40.8, 26.8, 25.4, 22.5; IR (ATR) *v* 2934 (m), 2869 (m), 1723 (s), 1370 (m), 1118 (s), 1078 (s), 843 (m); HRMS (ESI) calcd for $C_{10}H_{19}O_4$ $[M+H]^+$ 203.1283, found 203.1271; $[\alpha]_D^{22}$ = +3.3 (c 1.0, $CHCl_3$).

6-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)hex-1-en-3-ol (50)



A solution of aldehyde **49** (959 mg, 4.74 mmol) in THF (25 mL) was cooled to 0 °C. Vinylmagnesium bromide (5.69 mL, 1 M in THF, 5.69 mmol) was added dropwise and the reaction was stirred at ambient temperature for 18 h. The reaction was quenched with sat. aq. NH_4Cl (25 mL) and the aqueous layer was separated and extracted with Et_2O (3x 25 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give 6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)hex-1-en-3-ol **50** (807 mg, 3.50 mmol, 74% yield) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.3, 10.4, 6.0 Hz, 1H), 5.20 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.07 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.24 (p, *J* = 6.0 Hz, 1H), 4.16 – 4.06 (m, 1H), 4.03 (dd, *J* = 8.3, 6.4 Hz, 1H), 3.70 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.56 – 3.38 (m, 4H), 2.30 (br s, 1H), 1.76 – 1.50 (m, 4H), 1.39 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 114.6, 109.5, 74.8, 72.8, 72.0, 71.8, 66.9, 34.1, 26.9, 25.7, 25.5; IR (ATR) *v* 3448 (s, broad), 2935 (w), 2866 (w), 1371 (m), 1212 (s), 1052 (s); HRMS (ESI) calcd for $C_{12}H_{23}O_4$ $[M+H]^+$ 231.1596, found 231.1610; $[\alpha]_D^{22}$ = +7.8 (c 1.0, $CHCl_3$).

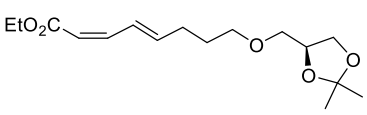
6-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)hex-1-en-3-yl but-3-enoate (45)



Allyl alcohol **50** (639 mg, 2.77 mmol), DMAP (51.3 mg, 0.42 mmol) and 3-butenoic acid **51** (286 mg, 0.28 mL, 3.32 mmol) were dissolved in Et_2O (28 mL). The solution was cooled to 0 °C and DCC (684 mg, 3.32 mmol) was added. The reaction was stirred at 20 °C for 36 h. The reaction mixture was cooled to 0 °C, filtered and washed with Et_2O. The filtrate was washed with aq. HCl (1 M) and

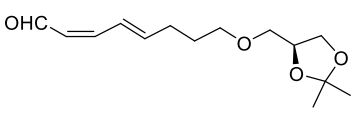
sat. aq. $NaHCO_3$. The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give 6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)hex-1-en-3-yl but-3-enoate **45** (570 mg, 1.91 mmol, 69% yield) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 16.8, 9.8, 7.0 Hz, 1H), 5.76 (ddd, *J* = 17.0, 10.5, 6.3 Hz, 1H), 5.30 – 5.10 (m, 5H), 4.24 (p, *J* = 6.0 Hz, 1H), 4.04 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.71 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.54 – 3.35 (m, 4H), 3.09 (dt, *J* = 7.0, 1.5 Hz, 2H), 1.73 – 1.52 (m, 4H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 136.4, 130.4, 118.6, 117.0, 109.5, 74.9, 74.8, 72.0, 71.3, 67.0, 39.5, 30.9, 26.9, 25.6, 25.3; IR (ATR) *v* 2986 (w), 1735 (s), 1370 (w), 1170 (s); HRMS (ESI) calcd for $C_{16}H_{27}O_5$ $[M+H]^+$ 299.1858, found 299.1888; $[\alpha]_D^{22}$ = +6.5 (c 1.0, $CHCl_3$).

Ethyl (2*Z*,4*E*)-8-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)octa-2,4-dienoate (32)



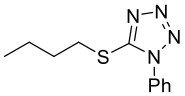
To a solution of **45** (287 mg, 0.96 mmol) in degassed dry DCM (10 mL) at reflux was added second generation Grubbs' 2nd generation catalyst **GII** (24.4 mg, 3.0 mol%). The reaction mixture was stirred under reflux until the starting material was fully consumed, as indicated by TLC (2 h). The solution was cooled to 0 °C and sodium bis(trimethylsilyl)amide (NaHMDS) (1 M in THF, 1.15 mL, 1.15 mmol) was added. The reaction was stirred at 20 °C for 3 h. Meerwein's salt $[Et_3O]BF_4$ (273 mg, 1.44 mmol) was added, and the reaction mixture was stirred for 3 h. The solution was filtered through celite and washed with DCM. The solvent was evaporated under reduced pressure and the crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give ethyl (2*Z*,4*E*)-8-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)octa-2,4-dienoate **32** (267 mg, 0.89 mmol, 93% yield) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 1H), 6.52 (t, *J* = 11.3 Hz, 1H), 6.04 (dt, *J* = 14.6, 7.0 Hz, 1H), 5.56 (d, *J* = 11.3 Hz, 1H), 4.25 (p, *J* = 6.1 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.04 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.71 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.56 – 3.35 (m, 4H), 2.26 (q, *J* = 7.3 Hz, 2H), 1.72 (p, *J* = 6.7 Hz, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 145.2, 144.6, 127.4, 116.0, 109.5, 74.9, 72.0, 71.1, 67.0, 60.0, 29.7, 28.8, 26.9, 25.6, 14.4; IR (ATR) *v* 2935 (w), 1712 (s), 1370 (m), 1175 (s), 1031 (m); HRMS (ESI) calcd for $C_{16}H_{27}O_5$ $[M+H]^+$ 299.1858, found 299.1869; $[\alpha]_D^{24}$ = +10.3 (c 1.0, $CHCl_3$).

(2*Z*,4*E*)-8-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)octa-2,4-dienal (52)



A solution of ester (2*Z*,4*E*)-**32** (188 mg, 0.62 mmol) in DCM (6 mL) was cooled to 0 °C. DIBAL-H (0.92 mL, 1 M in hexane, 0.92 mmol) was added slowly and the reaction was stirred at 20°C. After 10 min brine (5 mL) and a minimum amount of HCl (1 M) were added and the aqueous layer was separated and extracted with DCM (3x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was redissolved in DCM (6 mL) and the solution was cooled to 0 °C before Dess-Martin-periodinane (DMP) (533 mg, 1.24 mmol) was added and the reaction was stirred at 20°C for 2 h. The reaction was quenched with sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1:1). The aqueous layer was separated and extracted with DCM (3x 10 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (2*Z*,4*E*)-8-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)octa-2,4-dienal **52** (114 mg, 0.45 mmol, 73% yield) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.14 (d, J = 7.9 Hz, 1H), 7.14 – 6.98 (m, 1H), 6.95 – 6.83 (m, 1H), 6.16 (dt, J = 14.4, 7.2 Hz, 1H), 5.82 – 5.73 (m, 1H), 4.25 (p, J = 6.0 Hz, 1H), 4.04 (dd, J = 8.2, 6.4 Hz, 1H), 3.71 (dd, J = 8.3, 6.4 Hz, 1H), 3.55 – 3.35 (m, 4H), 2.31 (q, J = 7.5 Hz, 2H), 1.74 (p, J = 6.8 Hz, 2H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 147.9, 146.2, 126.1, 124.8, 109.6, 74.9, 72.1, 70.9, 66.9, 29.8, 28.7, 26.9, 25.5; IR (ATR) ν 2932 (w), 1666 (s), 1370 (m), 1115 (s); HRMS (ESI) calcd for $C_{14}H_{23}O_4$ $[M+H]^+$ 255.1596, found 255.1576; $[\alpha]_D^{24}$ = +8.5 (c 1.0, $CHCl_3$).

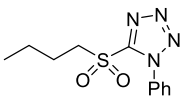
5-(Butylthio)-1-phenyl-1*H*-tetrazole (54)



1-Butanol (222 mg, 0.27 mL, 3.00 mmol), thiol **53** (1.07 g, 6.00 mmol) and PPh_3 (1.18 g, 4.50 mmol) were dissolved in THF (120 mL). DIAD (639 mg, 3.15 mmol) was added dropwise at 0 °C. After 30 min the reaction mixture was allowed to warm to 20 °C and stirred for 16 h. The reaction was quenched with sat. aq. NH_4Cl (90 mL) and the aqueous layer was separated and extracted with Et_2O (3x 60 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified with column chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give 5-(butylthio)-1-phenyl-1*H*-tetrazole **54** (549 mg, 2.34 mmol, 78% yield) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 5H), 3.39 (t, J = 7.4 Hz, 2H), 1.80 (p, J = 7.4 Hz, 2H), 1.47 (dq, J = 14.6, 7.3 Hz, 2H),

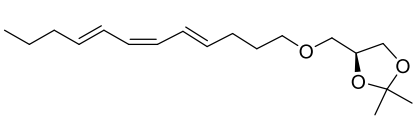
0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 133.9, 130.2, 129.9, 33.2, 31.2, 21.9, 13.6; IR (ATR) ν 2959 (m), 1597 (m), 1499 (s), 1385 (s), 759 (s); HRMS (EI) calcd for $C_{11}H_{14}N_4S_1$ $[M]^+$ 234.0939, found 234.0930.

5-(Butylsulfonyl)-1-phenyl-1*H*-tetrazole (33)



Tetrazole **54** (500 mg, 2.14 mmol) was dissolved in DCM and the solution was cooled to 0 °C. *m*-CPBA (1.48 g, 6.42 mmol) was added, and the reaction mixture was stirred at 20 °C for 16 h. The crude product was purified with column chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give 5-(butylsulfonyl)-1-phenyl-1*H*-tetrazole **33** (476 mg, 1.79 mmol, 84% yield) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.54 (m, 5H), 3.77 – 3.68 (m, 2H), 1.93 (p, J = 7.7 Hz, 2H), 1.53 (h, J = 7.8 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 133.2, 131.6, 129.8, 125.2, 55.9, 24.0, 21.6, 13.5; IR (ATR) ν 2963 (w), 1497 (m), 1335 (s), 1149 (s), 916 (w); HRMS (ESI) calcd for $C_{11}H_{15}N_4O_2S_1$ $[M+H]^+$ 267.0916, found 267.0903.

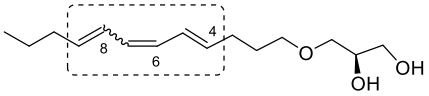
(*S*)-4-((((4*E*,6*Z*,8*E*)-Dodeca-4,6,8-trien-1-yl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane (34)



To a solution of Julia-Kocienski reagent **33** (240 mg, 0.90 mmol) in THF (21 mL) at -78 °C was potassium bis(trimethylsilyl)amide (KHMDS) (1.28 mL, 0.7 M in toluene, 0.90 mmol) added dropwise. The resulting yellow solution was stirred for 3 min before (2*Z*,4*E*)-dienal **52** (114 mg, 0.45 mmol) in THF (14 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h. Sat. aq. NH_4Cl (45 mL) was added dropwise -78 °C and the biphasic mixture was allowed to reach room temperature. The aqueous phase was separated and extracted with Et_2O (3x 30 mL) and the combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-(((4*E*,6*Z*,8*E*)-dodeca-4,6,8-trien-1-yl)oxy)propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate **34** (99.4 mg, 0.34 mmol, 76% yield) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 – 6.41 (m, 2H), 5.94 – 5.78 (m, 2H), 5.68 (dq, J = 14.6, 7.2 Hz, 2H), 4.26 (p, J = 6.1 Hz, 1H), 4.06 (dd, J = 8.2, 6.4 Hz, 1H), 3.73 (dd, J = 8.2, 6.4 Hz, 1H), 3.59 – 3.37 (m, 4H), 2.24 – 2.04 (m, 4H), 1.69 (p, J = 7.0 Hz, 2H), 1.46 – 1.39 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.4, 128.1, 127.5, 126.4, 126.0, 109.5, 74.9, 72.0, 71.2, 67.0, 35.2, 29.5, 29.3, 26.9, 25.6,

22.7, 13.9; IR (ATR) *v* 2929 (m), 1455 (w), 1117 (m), 962 (s); HRMS (ESI) calcd for $C_{18}H_{31}O_3$ $[M+H]^+$ 295.2273, found 295.2244; $[\alpha]_D^{25}$ = +6.6 (c 1.0, $CHCl_3$).

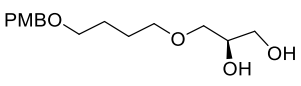
(*R*)-3-(((4*E*,6*Z*,8*E*)-Dodeca-4,6,8-trien-1-yl)oxy)propane-1,2-diol ((4*E*,6*E*,8*E*)-55 and (4*E*, 6*Z*,8*E*)-55)



Acetonide **34** (42.5 mg, 0.14 mmol) was dissolved in MeOH (0.5 mL) and DCM (0.5 mL). *p*-TSA•3H_2O (2.52 mg, 10 mol%) was added, and the reaction mixture was stirred at ambient temperature for 4 h. $NaHCO_3$ (100 mg) and water (2 mL) were added. The aqueous phase was separated and extracted with EtOAc (3x 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure to furnish crude diol **55** (ca. 20 mg, 0.07 mmol, ca. 50%) as a ca. 2:3 mixture of (4*E*,6*E*,8*E*)- and (4*E*,6*Z*,8*E*)-isomers. Selected characteristic NMR data were obtained from the mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58−6.40 (m, 2H, (*E*,*Z*,*E*)-isomer), 6.21−5.98 (m, 4H, (*E*,*E*,*E*)-isomer), 5.91−5.77 (m, 2H, (*E*,*Z*,*E*)-isomer), 5.77−5.66 (m, 2H, (*E*,*Z*,*E*)- and (*E*,*E*,*E*)-isomer)); ^{13}C NMR data of (4*E*,6*Z*,8*E*)-**55**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 134.1, 128.3, 127.4, 126.5, 126.0; ^{13}C NMR data of (4*E*,6*E*,8*E*)-**55**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 133.1, 131.5, 131.3, 130.6, 130.6; HRMS (ESI) m/z calcd for $C_{15}H_{27}O_3$ $[M + H]^+$ 255.1960, found 255.1973.

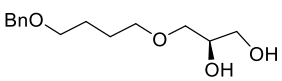
6.2.3 Strategy II: Synthesis of Julia-Kocienski reagent 4

(*R*)-3-(4-((4-Methoxybenzyl)oxy)butoxy)propane-1,2-diol (57a)[21]



Acetonide **31a** (2.64 g, 8.98 mmol) was dissolved in wet MeOH (20 mL). *p*-TSA•3H_2O (161 mg, 10 mol%) was added and the reaction mixture was stirred at ambient temperature for 4 h. Solid $NaHCO_3$ and H_2O were added. The aqueous phase was separated and extracted with EtOAc (8x 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Crude product **57a** was used in the next step without further purification.

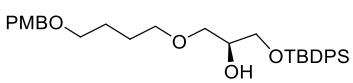
(*R*)-3-(4-(Benzyloxy)butoxy)propane-1,2-diol (57b)



Acetonide **31b** (2.64 g, 8.98 mmol) was dissolved in MeOH (20 mL). *p*-TSA•3H_2O (161 mg, 10 mol%) was added and the reaction mixture was stirred at room temperature for 4 h. Solid $NaHCO_3$ and H_2O were added. The aqueous phase was separated and extracted with EtOAc (8x 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Crude product **57b** (2.27 g, 8.67 mmol, 97% yield) a yellow liquid was used in the next step without further purification.

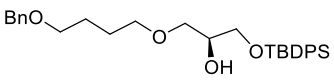
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.17 (m, 5H), 4.50 (s, 2H), 3.89 – 3.76 (m, 1H), 3.73 – 3.53 (m, 2 H), 3.53 – 3.39 (m, 6H), 2.95 (br s, OH), 2.58 (br s, OH), 1.74 – 1.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.5, 127.8, 127.7, 73.0, 72.5, 71.5, 70.7, 70.2, 64.3, 26.6, 26.5; IR (ATR) ν 3392 (s, broad), 2930 (w), 1454 (w), 1093 (s), 697 (m); HRMS (ESI) calcd for $C_{14}H_{23}O_4$ $[M+H]^+$ 255.1596, found 255.1575; $[\alpha]_D^{25}$ = -1.7 (c 1.0, $CHCl_3$).

(*S*)-1-(4-methoxyphenyl)-13,13-dimethyl-12,12-diphenyl-2,7,11-trioxa-12-silatetradecan-9-ol (58a)[21]



Diol **57a** (530 mg, 1.86 mmol) was dissolved in DMF (23 mL). Imidazole (247 mg, 3.63 mmol) and TBDPSCl (545 mg, 0.52 mL, 1.99 mmol) in DMF (10 mL) were added dropwise at 0 °C. The reaction was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (15 mL) and the aqueous layer was separated and extracted with Et_2O (4x 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give (*S*)-1-(4-methoxyphenyl)-13,13-dimethyl-12,12-diphenyl-2,7,11-trioxa-12-silatetradecan -9-ol **58a** (831 mg, 1.59 mmol, 85% yield) as a pale-yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.66 (m, 4H), 7.47 – 7.35 (m, 6H), 7.26 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.43 (s, 2H), 3.93 – 3.86 (m, 1H), 3.80 (s, 3H), 3.72 (d, J = 5.4 Hz, 2H), 3.56 – 3.43 (m, 6H), 2.52 (s, OH), 1.68 – 1.62 (m, 4H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 135.7, 133.7, 131.2, 129.9, 129.3, 127.9, 114.1, 72.7, 71.8, 71.5, 71.1, 70.1, 65.3, 55.5, 27.1, 26.7, 26.7, 19.5. Analytical data match those previously reported in the literature.[21]

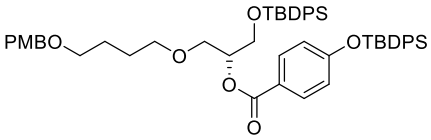
(*S*)-13,13-Dimethyl-1,12,12-triphenyl-2,7,11-trioxa-12-silatetradecan-9-ol (58b)



Diol **57b** (1.61 g, 6.33 mmol) was dissolved in DMF (80 mL). Imidazole (836 mg, 12.3 mmol) and TBDPSCl (1.86 g, 1.75 mL, 6.77 mmol) in DMF (32 mL) were added dropwise at 0 °C. The reaction was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (60 mL) and the aqueous layer was separated and extracted with Et_2O (4x 40 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*S*)-13,13-dimethyl-1,12,12-triphenyl-2,7,11-trioxa-12-silatetradecan-9-ol **58b** (2.69 g, 5.45 mmol, 86% yield) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 3H), 7.49 – 7.21 (m, 11H), 4.50 (s, 2H), 3.88 (p, J = 5.3 Hz,

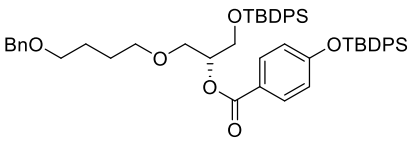
1H), 3.71 (d, *J* = 5.4 Hz, 2H), 3.55 – 3.42 (m, 6H), 2.49 (s, 1H), 1.73 – 1.61 (m, 4H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 135.7, 133.4, 129.9, 128.5, 127.9, 127.8, 127.6, 73.0, 71.6, 71.4, 70.9, 70.2, 65.0, 27.0, 26.6, 26.6, 19.4; IR (ATR) *v* 3457 (s, broad), 3070 (w), 2857 (m), 1428 (m), 1104 (s), 699 (s); HRMS (ESI) calcd for $C_{30}H_{41}O_4Si$ $[M+H]^+$ 493.2774, found 493.2761; $[\alpha]_D^{24}$ = -2.5 (c 1.0, $CHCl_3$).

(*R*)-1-(4-Methoxyphenyl)-13,13-dimethyl-12,12-diphenyl-2,7,11-trioxa-12-silatetradecan-9-yl 4-((tert-butyldiphenylsilyl)oxy)benzoate (35a)[21]



Secondary alcohol **58a** (834 mg, 1.60 mmol), benzoic acid **38** (1.21 g, 3.20 mmol) and PPh_3 (844 mg, 3.20 mmol) were dissolved in THF (42 mL) and cooled to 0 °C. DIAD (647 mg, 0.63 mL, 3.20 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (30 mL) and the aqueous layer was separated and extracted with Et_2O (3x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*R*)-1-(4-methoxyphenyl)-13,13-dimethyl-12,12-diphenyl-2,7,11-trioxa-12-silatetradecan-9-yl 4-((tert-butyldiphenylsilyl)oxy)benzoate **35a** (1.13 g, 1.28 mmol, 80% yield) as a colourless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.83 – 7.77 (m, 2H), 7.73 – 7.71 (m, 4H), 7.63 – 7.61 (m, 4H), 7.49 – 7.41 (m, 2H), 7.41 – 7.29 (m, 8H), 7.26 – 7.23 (m, 4H), 6.97 – 6.83 (m, 2H), 6.82 – 6.72 (m, 2H), 5.27 (p, *J* = 5.0 Hz, 1H), 4.39 (s, 2H), 3.87 (d, *J* = 4.6 Hz, 2H), 3.80 (s, 3H), 3.76 – 3.66 (m, 2H), 3.52 – 3.37 (m, 4H), 1.62 (p, *J* = 3.0 Hz, 4H), 1.12 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.8, 159.9, 159.2, 135.7, 135.5, 133.4, 132.3, 131.7, 130.8, 130.3, 129.8, 129.7, 129.3, 128.0, 127.8, 127.7, 123.3, 119.6, 113.9, 73.3, 72.6, 71.4, 69.9, 69.0, 62.8, 55.4, 26.9, 26.5, 26.5, 19.6, 19.4. Analytical data match those previously reported in the literature.[21]

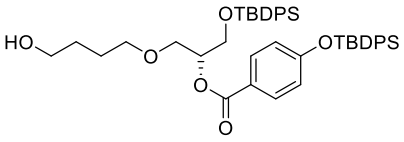
(*R*)-13,13-Dimethyl-1,12,12-triphenyl-2,7,11-trioxa-12-silatetradecan-9-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate (35b)



Secondary alcohol **58b** (1.87 g, 3.80 mmol), benzoic acid **38** (2.86 g, 7.60 mmol) and PPh_3 (2.00 g, 7.60 mmol) were dissolved in THF (100 mL) and cooled to 0 °C. DIAD (1.54 g, 1.50 mL, 7.60 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and the aqueous

layer was separated and extracted with Et_2O (3x 40 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*R*)-13,13-dimethyl-1,12,12-triphenyl-2,7,11-trioxa-12-sila-tetradecan-9-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate **35b** (2.37 g, 2.78 mmol, 73% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.8 Hz, 2H), 7.76 – 7.70 (m, 4H), 7.67 – 7.58 (m, 4H), 7.50 – 7.19 (m, 17H), 6.79 (d, J = 8.8 Hz, 2H), 5.29 (p, J = 5.0 Hz, 1H), 4.47 (s, 2H), 3.89 (d, J = 4.6 Hz, 2H), 3.73 (d, J = 5.7 Hz, 2H), 3.52 – 3.42 (m, 4H), 1.69 – 1.62 (m, 4H), 1.14 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 159.9, 138.8, 135.7, 135.6, 133.4, 132.4, 132.4, 131.7, 130.3, 129.8, 128.5, 128.1, 127.8, 127.8, 127.7, 127.6, 123.3, 119.7, 73.3, 72.9, 71.4, 70.2, 69.1, 62.8, 29.2, 27.1, 26.9, 26.6, 22.8, 19.6, 19.4; IR (ATR) ν 3071 (w), 2931 (m), 1716 (m), 1603 (m), 1508 (m), 1258 (s); HRMS (ESI) calcd for $C_{53}H_{63}O_6Si_2$ $[M+H]^+$ 851.4163, found 851.4081; $[\alpha]_D^{27}$ = -10.5 (c 1.0, $CHCl_3$).

(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(4-hydroxybutoxy)propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate (59)

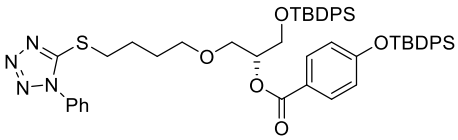


Procedure A:[21] PMB-protected **35a** (1.35 g, 1.53 mmol) was dissolved in a mixture of DCM (80 mL) and a pH 7 buffer (4.0 mL). DDQ (694 mg, 3.06 mmol) was added at 0 °C and the reaction mixture was stirred at ambient temperature for 3 h. The reaction was quenched with aq. sat. $NaHCO_3$ (25 mL) and the aqueous phase was separated and extracted with DCM (4x 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-(4-hydroxybutoxy)propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate **59** (1.05 g, 1.38 mmol, 90% yield) as a pale yellow oil.

Procedure B: Benzyl ether **35b** (200 mg, 0.23 mmol) was dissolved in EtOAc (3 mL) and 20 wt-% $Pd(OH)_2/C$ (55.2 mg) was added. The system was flushed with H_2 and the reaction mixture was then exposed to 1 atm of H_2 at ambient temperature for 2 h. The heterogeneous mixture was filtered through celite and washed with EtOAc. Crude product **59** (175 mg, 0.23 mmol, quantitative yield) a pale-yellow oil was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.7 Hz, 2H), 7.75 – 7.69 (m, 4H), 7.65 – 7.59 (m, 4H), 7.49 – 7.13 (m, 12H), 6.78 (d, J = 8.7 Hz, 2H), 5.29 (p, J = 5.0 Hz, 1H), 3.88 (d, J = 4.8 Hz, 2H), 3.75 (d, J = 5.1 Hz, 2H), 3.58 (t, J = 5.9 Hz, 2H), 3.54 – 3.44 (m, 2H), 1.90

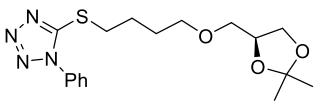
(br s, 1H), 1.70 – 1.54 (m, 4H), 1.12 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 160.0, 135.7, 135.6, 133.4, 133.4, 132.4, 132.4, 131.7, 130.3, 129.8, 129.8, 128.1, 127.8, 127.8, 123.2, 119.7, 73.2, 71.5, 69.3, 62.7, 30.0, 26.9, 26.6, 19.6, 19.4; IR (ATR) *v* 3424 (s, broad), 2931 (m), 1716 (m), 1603 (m), 1428 (m); HRMS (ESI) calcd for $C_{46}H_{57}O_6Si_2$ $[M+H]^+$ 761.3694, found 761.3720; $[\alpha]_D^{27}$ = -10.4 (c 1.0, $CHCl_3$). Analytical data match those previously reported in the literature.[21]

(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(4-((1-phenyl-1*H*-tetrazol-5-yl)thio)butoxy)propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate (60)[21]



Primary alcohol **59** (720 mg, 0.95 mmol), 1-phenyl-1*H*-tetrazole-5-thiol **53** (338 mg, 1.89 mmol) and triphenylphosphine (PPh_3) (372 mg, 1.42 mmol) were dissolved in THF (36 mL) and cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD) (203 mg, 0.19 mL, 0.99 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (30 mL) and the aqueous layer was separated and extracted with Et_2O (3x 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-(4-((1-phenyl-1*H*-tetrazol-5-yl)thio)-butoxy)propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate **60** (770 mg, 0.84 mmol, 88% yield) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 2H), 7.76 – 7.67 (m, 4H), 7.64 – 7.60 (m, 4H), 7.57 – 7.51 (m, 5H), 7.49 – 7.19 (m, 12H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.30 (p, *J* = 5.2 Hz, 2H), 3.88 (d, *J* = 4.6 Hz, 2H), 3.74 (d, *J* = 5.3 Hz, 2H), 3.57 – 3.44 (m, 2H), 3.40 (t, *J* = 7.2 Hz, 2H), 1.95 – 1.79 (m, 2H), 1.76 – 1.62 (m, 2H), 1.13 (s, 9H, 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 160.1, 154.5, 135.7, 135.6, 133.6, 133.6, 132.7, 132.6, 131.7, 130.3, 130.1, 129.9, 129.8, 129.8, 129.4, 128.1, 127.8, 127.8, 124.1, 123.8, 119.8, 73.5, 70.9, 69.5, 63.0, 33.5, 28.8, 27.0, 26.7, 26.3, 19.7, 19.4. Analytical data match those previously reported in the literature.[21]

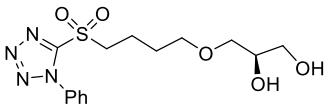
(*S*)-5-((4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)butyl)thio)-1-phenyl-1*H*-tetrazole (61)



Primary alcohol **48** (1.20 g, 5.87 mmol), 1-phenyl-1*H*-tetrazole-5-thiol **53** (2.09 g, 11.7 mmol) and triphenylphosphine (PPh_3) (2.30 g, 8.81 mmol) were dissolved in THF (225 mL) and cooled to 0 °C.

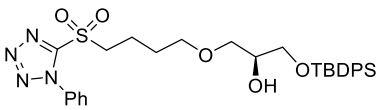
Diisopropyl azodicarboxylate (DIAD) (1.26 g, 1.23 mL, 6.22 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (100 mL) and the aqueous layer was separated and extracted with Et_2O (3x 60 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*S*)-5-((4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)butyl)thio)-1-phenyl-1*H*-tetrazole **61** (1.70 g, 4.67 mmol, 80% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.48 (m, 5H), 4.23 (p, *J* = 6.0 Hz, 1H), 4.03 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.69 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.58 – 3.45 (m, 3H), 3.45 – 3.36 (m, 3H), 1.90 (p, *J* = 7.2, 6.8 Hz, 2H), 1.72 (p, *J* = 6.5 Hz, 2H), 1.39 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 133.8, 130.2, 129.9, 123.9, 109.5, 74.8, 72.1, 70.9, 66.9, 33.2, 28.6, 26.9, 26.1, 25.5; IR (ATR) *v* 2985 (w), 2867 (w), 1597 (w), 1499 (s), 1241 (m); HRMS (EI) calcd for $C_{17}H_{24}N_4O_3S$ $[M]^+$ 364.1569, found 364.1564; $[\alpha]_D^{23}$ = +8.9 (c 1.0, $CHCl_3$).

(*R*)-3-(4-((1-Phenyl-1*H*-tetrazol-5-yl)sulfonyl)butoxy)propane-1,2-diol (62)



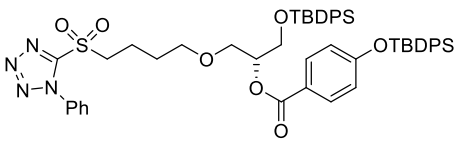
To a solution of **61** (1.91 g, 5.24 mmol) in DCM (120 mL) at 0 °C was *m*-chloroperoxybenzoic acid (*m*-CPBA) (2.69 g, 15.7 mmol, 70%) added portion wise. The reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with aq. sat. $Na_2S_2O_3$ (80 mL) and the aqueous phase was separated and extracted with DCM (3x 60 mL). The combined organic layers were washed with aq. sat. $NaHCO_3$, dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by filtration through a plug of silica gel to give (*R*)-3-(4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butoxy)propane-1,2-diol **62** (1.68 g, 4.71 mmol, 90% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.52 (m, 5H), 3.90 – 3.85 (m, 1H), 3.85 – 3.76 (m, 2H), 3.70 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.60 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.56 – 3.43 (m, 4H), 2.70 (s, 1H), 2.47 (s, 1H), 2.06 (p, *J* = 7.4 Hz, 2H), 1.79 (p, *J* = 6.8, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 133.1, 131.6, 129.9, 125.2, 72.5, 70.8, 70.4, 64.0, 55.8, 27.9, 19.6; IR (ATR) *v* 3401 (s, broad), 2873 (w), 1497 (m), 1338 (s), 1149 (s); HRMS (ESI) calcd for $C_{14}H_{21}N_4O_5S$ $[M+H]^+$ 357.1233, found 357.1208; $[\alpha]_D^{24}$ = -1.5 (c 1.0, $CHCl_3$).

(*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(4-((1-phenyl-1*H*-tetrazol-5 yl)sulfonyl)butoxy)propan-2-ol (37)



Diol **62** (1.64 g, 4.60 mmol) was dissolved in DMF (60 mL). Imidazole (611 mg, 8.97 mmol) and TBDPSCl (1.35 g, 1.27 mL, 4.92 mmol) in DMF (25 mL) were added dropwise at 0 °C. The reaction was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (40 mL) and the aqueous layer was separated and extracted with Et_2O (4x 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give (*S*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-(4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butoxy)propan-2-ol **37** (2.14 g, 3.60 mmol, 78% yield) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 6H), 7.63 – 7.55 (m, 3H), 7.47 – 7.35 (m, 6H), 3.94 – 3.85 (m, 1H), 3.84 – 3.74 (m, 2H), 3.71 (d, *J* = 5.5 Hz, 2H), 3.58 – 3.44 (m, 4H), 2.58 (d, *J* = 4.5 Hz, 1H), 2.04 (p, *J* = 7.5 Hz, 2H), 1.76 (p, *J* = 6.4 Hz, 2H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 135.7, 133.3, 133.2, 131.6, 130.0, 129.9, 127.9, 125.3, 72.0, 70.9, 70.4, 65.0, 55.9, 28.1, 27.0, 19.6, 19.4; IR (ATR) *v* 3562 (s, broad), 2930 (w), 2858(w), 1340 (m), 1111 (s); HRMS (ESI) calcd for $C_{30}H_{39}N_4O_5SSi$ $[M+H]^+$ 595.2410, found 595.2398; $[\alpha]_D^{24}$ = -3.2 (c 1.0, $CHCl_3$).

(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butoxy)propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate (4)

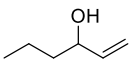


Pathway A:[21] To a solution of **60** (720 mg, 0.78 mmol) in DCM (18 mL) at 0 °C was *m*-chloroperoxybenzoic acid (*m*-CPBA) (413 mg, 2.40 mmol, 70%) added portion wise. The reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with aq. sat. $Na_2S_2O_3$ (20 mL) and the aqueous phase was separated and extracted with DCM (3x 20 mL). The combined organic layers were washed with aq. sat. $NaHCO_3$, dried with $MgSO_4$, filtered ad evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-(4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butoxy)-propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate **4** (620 mg, 0.65 mmol, 83% yield) as a colourless oil.

Pathway B: Secondary alcohol **37** (1.28 g, 2.15 mmol), benzoic acid **38** (1.62 g, 4.30 mmol) and PPh_3 (1.13 g, 4.30 mmol) were dissolved in THF (60 mL) and cooled to 0 °C. DIAD (870 mg, 0.85 mL, 4.30 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and the aqueous layer was separated and extracted with Et_2O (3x 40 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-(4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butoxy) propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate **4** (1.47 g, 1.54 mmol, 72% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.7 Hz, 2H), 7.74 – 7.66 (m, 6H), 7.64 – 7.57 (m, 7H), 7.49 – 7.30 (m, 9H), 7.29 – 7.22 (m, 3H), 6.78 (d, J = 8.7 Hz, 2H), 5.27 (p, J = 4.9 Hz, 1H), 3.86 (d, J = 4.7 Hz, 2H), 3.78 – 3.62 (m, 4H), 3.57 – 3.44 (m, 2H), 2.01 (p, J = 7.4 Hz, 2H), 1.73 (p, J = 6.2 Hz, 2H), 1.12 (s, 5H), 1.02 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 160.0, 153.6, 135.7, 135.6, 133.4, 133.3, 133.2, 132.4, 132.4, 131.7, 131.5, 130.3, 129.8, 129.8, 128.0, 127.8, 127.8, 125.2, 123.1, 119.7, 73.1, 70.5, 69.5, 62.8, 55.9, 28.2, 26.9, 26.6, 19.6, 19.6, 19.4; IR (ATR) ν 2931 (w), 1714 (m), 1603 (m), 1259 (s), 1112 (s), 700 (s); HRMS (ESI) calcd for $C_{53}H_{60}N_4NaO_7SSi_2$ $[M+Na]^+$ 975.3613, found 975.3626; $[\alpha]_D^{25}$ = -7.8 (c 1.0, $CHCl_3$). Analytical data match those previously reported in the literature,[21] except for the specific rotation (reported value:[21] $[\alpha]_D^{20}$ = +7.8 (c 1.0, $CHCl_3$)).

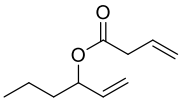
6.2.4 Strategy II: Synthesis of ethyl (2*Z*,4*E*)-octa-2,4-dienal (57) from butanal

Hex-1-en-3-ol (64)[9]



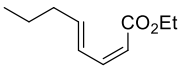
A solution of butanal **63** (2.00 g, 2.46 mL, 27.8 mmol) in THF (140 mL) was cooled to 0 °C. Vinylmagnesium bromide (33.4 mL, 1 M in THF, 33.4 mmol) was added dropwise and the reaction was stirred at 20 °C for 18 h. The reaction was quenched with sat. aq. NH_4Cl (100 mL) and the aqueous layer was separated and extracted with Et_2O (3x 80 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give hex-1-en-3-ol **64** (2.12 g, 21.2 mmol, 76% yield) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddd, J = 16.9, 10.3, 6.2 Hz, 1H), 5.19 (dt, J =17.2, 1.5 Hz, 1H), 5.07 (dt, J = 10.3, 1.4 Hz, 1H), 4.08 (q, J = 6.2 Hz, 1H), 1.82 (s, 1H), 1.61 – 1.24 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 114.5, 73.1, 39.3, 18.7, 14.1. Analytical data match those previously reported in the literature.[9]

Hex-1-en-3-yl but-3-enoate (56)[9]



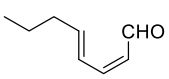
Allyl alcohol **64** (1.56 g, 15.6 mmol), DMAP (281 mg, 2.30 mmol) and 3-butenoic acid **51** (1.61 g, 1.60 mL, 18.7 mmol) were dissolved in Et_2O (160 mL). The solution was cooled to 0 °C and DCC (3.85 g, 18.7 mmol) was added. The reaction was stirred at 20 °C for 36 h. The reaction mixture was cooled to 0 °C, filtered and washed with Et_2O. The filtrate was washed with aq. HCl (1 M) and sat. aq. $NaHCO_3$. The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give hex-1-en-3-yl but-3-enoate **56** (2.46 g, 14.7 mmol, 94% yield) as a pale-yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (ddt, J = 17.0, 9.7, 6.9 Hz, 1H), 5.77 (ddd, J = 17.0, 10.5, 6.4 Hz, 1H), 5.32 – 5.09 (m, 5H), 3.09 (d, J = 7.0 Hz, 2H), 1.73 – 1.46 (m, 2H), 1.40 – 1.25 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 136.6, 130.5, 118.6, 116.7, 75.0, 39.6, 36.4, 18.4, 13.9; IR (ATR) ν 2961 (m), 1736 (s), 1249 (m), 1170 (s), 918 (s); HRMS (ESI) calcd for $C_{10}H_{16}NaO_2$ $[M+Na]^+$ 191.1048, found 191.1044.

Ethyl (2*Z*,4*E*)-octa-2,4-dienoate (36)[9]



To a solution of allyl ester **56** (500 mg, 2.97 mmol) in degassed dry DCM (30 mL) at reflux was added second generation Grubbs' 2nd generation catalyst **GII** (75.6 mg, 3.0 mol%). The reaction mixture was stirred under reflux until the starting material was fully consumed, as indicated by TLC (2 h). The solution was cooled to 0 °C and sodium bis(trimethylsilyl)amide (NaHMDS) (1 M in THF, 3.56 mL, 3.56 mmol) was added. The reaction was stirred at 20 °C for 3 h. Meerwein's salt $[Et_3O]BF_4$ (845 mg, 4.46 mmol) was added, and the reaction mixture was stirred for 3 h. The solution was filtered through celite and washed with DCM. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give ethyl (2*Z*,4*E*)-octa-2,4-dienoate **36** (400 mg, 2.38 mmol, 80% yield) as a pale-yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (ddt, J = 15.2, 11.3, 1.4 Hz, 1H), 6.54 (td, J = 11.3, 0.8 Hz, 1H), 6.06 (dt, J = 14.9, 7.0 Hz, 1H), 5.56 (dd, J = 11.4, 0.9 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 2.18 (q, J = 7.0 Hz, 2H), 1.47 (h, J = 7.3 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 145.6, 145.5, 127.2, 115.7, 60.0, 35.2, 22.1, 14.5, 13.9; IR (ATR) ν 2961 (m), 1713 (m), 1422 (w), 1178 (s); HRMS (EI) calcd for $C_{10}H_{16}O_2$ $[M]^+$ 168.1150, found 168.1156.

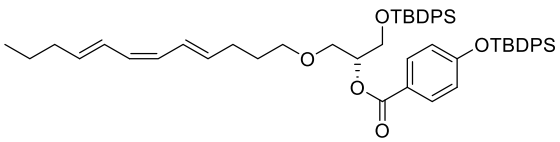
(2*Z*,4*E*)-Octa-2,4-dienal (65)[9]



A solution of (2*Z*,4*E*)-dienoate **36** (421 mg, 2.50 mmol) in DCM (25 mL) was cooled to 0 °C. DIBAL-H (5.0 mL, 1 M in hexane, 5.00 mmol) was added slowly and the reaction was stirred at 20 °C. After 10 min brine (15 mL) and a minimum amount of HCl (1 M) were added and the aqueous layer was separated and extracted with DCM (3x 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was redissolved in DCM (25 mL) and the solution was cooled to 0 °C before Dess- Martin-periodinane (DMP) (2.13 g, 5.00 mmol) was added and the reaction was stirred at 20°C for 2 h. The reaction was quenched with sat. aq. $NaHCO_3$:$Na_2S_2O_3$ (1:1). The aqueous layer was separated and extracted with DCM (3x 30 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (2*Z*,4*E*)-octa-2,4-dienal **65** (305 mg, 2.46 mmol, 98% yield) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.17 (d, J = 7.9 Hz, 1H), 7.12 – 6.82 (m, 2H), 6.17 (dt, J = 14.4, 7.1 Hz, 1H), 5.78 (dd, J = 10.5, 8.0 Hz, 1H), 2.21 (q, J = 7.2 Hz, 2H), 1.50 (h, J = 7.3 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 148.1, 147.1, 125.9, 124.6, 35.2, 22.0, 13.8; IR (ATR) ν 2960 (m), 1664 (s), 1634 (s), 1229 (m), 953 (m); HRMS (ESI) calcd for $C_8H_{13}O$ $[M+H]^+$ 125.0966, found 125.0962.

6.2.5 Strategy II: Completion of the Total Synthesis of (+)-Bretonin B (1)

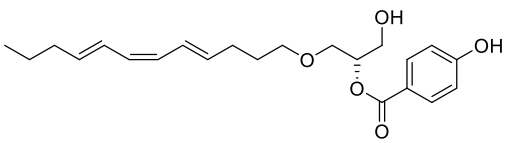
(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(((4*E*,6*Z*,8*E*)-dodeca-4,6,8-trien-1-yl)oxy)propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate (66)



To a solution of **4** (618 mg, 0.65 mmol) in THF (15 mL) at -78 °C was potassium bis(trimethylsilyl)amide (KHMDS) (0.93 mL, 0.7 M in toluene, 0.65 mmol) added dropwise. The resulting yellow solution was stirred for 3 min before (2*Z*,4*E*)-dienal **65** (40.2 mg, 0.32 mmol) in THF (12 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h. Sat. aq. NH_4Cl (30 mL) was added dropwise -78 °C and the biphasic mixture was allowed to reach room temperature. The aqueous phase was separated and extracted with Et_2O (3x 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing

polarity) to give (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-(((4*E*,6*Z*,8*E*)-dodeca-4,6,8-trien-1-yl)oxy)propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate **66** (143 mg, 0.17 mmol, 52% yield) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.8 Hz, 2H, $C_{ar}H$), 7.74 – 7.70 (m, 4H, $C_{ar}H$), 7.65 – 7.61 (m, 4H, $C_{ar}H$), 7.47 – 7.42 (m, 2H, $C_{ar}H$), 7.41 – 7.35 (m, 6H, $C_{ar}H$), 7.35 – 7.24 (m, 5H, $C_{ar}H$), 6.78 (d, J = 8.8 Hz, 2H, $C_{ar}H$), 6.47 (dd, J_{trans} = 14.8, 10.4 Hz, 2H, $CH_3CH_2CH_2CH$=C*H*, C*H*=$CHCH_2CH_2CH_2O$), 5.90 – 5.78 (m, 2H, CH=C*H*=C*H*=CH), 5.67 (ddt, J_{trans} = 22.1, 14.6, 7.1 Hz, 2H, $CH_3CH_2CH_2CH$=CH, CH=C*H*$CH_2CH_2CH_2O$), 5.28 (p, J = 5.0 Hz, 1H, OCH_2CHCH_2OSi), 3.89 (d, J = 4.6 Hz, 2H, OCH_2CHCH_2OSi), 3.72 (dd, J = 5.3, 1.6 Hz, 2H, OCH_2CHCH_2OSi), 3.52 – 3.41 (m, 2H, $CH_2CH_2CH_2O$), 2.15 (q, J = 7.2 Hz, 2H, $CH_2CH_2CH_2O$), 2.10 (q, J = 7.2 Hz, 2H, $CH_3CH_2CH_2$), 1.70 – 1.60 (m, 2H, $CH_2CH_2CH_2O$), 1.49 – 1.38 (m, 2H, CH_3CH_2), 1.12 (s, 9H, $OSiC(CH_3)_3$), 1.02 (s, 9H, $C_{ar}OSiC(CH_3)_3$), 0.92 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8 (*C*OO), 160.0 (C_{ar}OSi), 135.7 (C_{ar}), 135.6 and 134.6 ($CH_3CH_2CH_2C$H=CH, CH=*C*$HCH_2CH_2CH_2O$), 133.5 (C_{ar}), 132.4 (C_{ar}), 131.7 (C_{ar}), 130.3 (C_{ar}), 129.8 (C_{ar}), 129.8 (C_{ar}), 128.1 (C_{ar}), 127.8 and 127.8 (CH=*C*H=CH=CH, CH=CH=*C*H=CH), 127.6 (C_{ar}), 126.3 and 126.1 (*C*H=$CHCH_2CH_2CH_2O$, $CH_3CH_2CH_2CH$=*C*H), 123.3 ($C_{ar}COO$), 119.7 (C_{ar}), 73.3 (OCH_2CHCH_2OSi), 71.1 ($CH_2CH_2CH_2O$), 69.1 (OCH_2CHCH_2OSi), 62.8 (OCH_2CHCH_2OSi), 35.2 ($CH_3CH_2CH_2$), 29.6 ($CH_2CH_2CH_2O$), 29.5 ($CH_2CH_2CH_2O$), 26.9 ($SiC(CH_3)_3$), 26.6 ($SiC(CH_3)_3$), 22.7 (CH_3CH_2), 19.6 ($SiC(CH_3)_3$), 19.4 ($SiC(CH_3)_3$), 13.9 (CH_3); IR (ATR) ν 3072 (w), 2957 (m), 2931 (m), 1716 (m), 1603 (m), 1508 (m), 1428 (m), 125 9 (s), 1164 (m), 1112 (s), 911 (m), 735 (m) 700 (s); HRMS (ESI) calcd for $C_{54}H_{66}NaO_5Si_2$ $[M+Na]^+$ 873.4341, found 873.4348; $[\alpha]_D^{24}$ = -8.1 (c 1.0, $CHCl_3$). Analytical data match those previously reported in the literature.[21]

(*S*)-1-(((4*E*,6*Z*,8*E*)-Dodeca-4,6,8-trien-1-yl)oxy)-3-hydroxypropan-2-yl 4-hydroxybenzoate (1)[21]



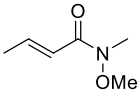
HF•pyridine complex (0.62 mL, ~70% HF and 30% pyridine) was added dropwise to a solution of **66** (138 mg, 0.16 mmol) and dry pyridine (1.27 mL) in THF (8 mL) at 20 °C. After 2 h was the reaction mixture filtered through a pad of silica gel, eluting with Et_2O. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give (*S*)-1-(((4*E*,6*Z*,8*E*)-dodeca-4,6,8-trien-1-yl)oxy)-3-hydroxypropan-2-yl 4-hydroxybenzoate **1** (45.7 mg, 0.12 mmol, 75% yield) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 8.7 Hz, 2H, $C_{ar}H$), 6.79 (d, J = 8.8 Hz, 2H, $C_{ar}H$), 6.51 – 6.43 (m, 2H, $CH_3CH_2CH_2CH$=C*H*, C*H*=$CHCH_2CH_2CH_2O$), 5.88

– 5.79 (m, 2H, CH=C*H*=C*H*=CH), 5.73 – 5.56 (m, 2H, $CH_3CH_2CH_2CH$=CH, CH=C*H*$CH_2CH_2CH_2O$), 5.24 – 5.20 (m, 1H, OCH_2CHCH_2OH), 4.01 – 3.95 (m, 2H, OCH_2CHCH_2OH), 3.84 – 3.71 (m, 2H, OCH_2CHCH_2OH), 3.58 – 3.45 (m, 2H, $CH_2CH_2CH_2O$), 2.21 – 2.11 (m, 2H, $CH_2CH_2CH_2O$), 2.10 – 2.02 (m, 2H, $CH_3CH_2CH_2$), 1.72 – 1.64 (m, 2H, $CH_2CH_2CH_2O$), 1.45 – 1.36 (m, 2H, CH_3CH_2), 0.90 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 166.6 (*C*OO), 161.1 (C_{ar}OH), 135.8 and 134.0 ($CH_3CH_2CH_2CH$=CH, CH=*C*H$CH_2CH_2CH_2O$), 132.2 (C_{ar}), 128.3 and 127.4 (CH=*C*H=*C*H=CH), 126.6 and 126.0 (*C*H=CH$CH_2CH_2CH_2O$, $CH_3CH_2CH_2CH$=*C*H), 121.7 (C_{ar}COO), 115.5 (C_{ar}), 73.2 (OCH_2CHCH_2OH), 71.4 ($CH_2CH_2CH_2O$), 70.5 (OCH_2CHCH_2OH), 63.3 (OCH_2CHCH_2OH), 35.1 ($CH_3CH_2CH_2$), 29.5 ($CH_2CH_2CH_2O$), 29.3 ($CH_2CH_2CH_2O$), 22.6 (CH_3CH_2), 13.9 (CH_3); IR (ATR) *ν* 3329 (s, broad), 2929 (m), 2871 (m), 1711 (m), 1687 (m), 1608 (m), 1593 (m), 1272 (s), 1165 (m), 1114 (m), 851 (w), 700 (w); HRMS (ESI) calcd for $C_{22}H_{31}O_5$ $[M+H]^+$ 375.2171, found 375.2144; $[\alpha]_D^{22}$ = +4.5 (c 1.0, $CHCl_3$). All analytical data match those previously reported by Bach and coworkers.[21] Isomerisation to all-E-configured bretonin A was observed upon standing at ambient temperature (signals emerged in the region of 6.07−5.98 ppm in the ^{1}H NMR spectrum).

6.3 Cross Metathesis using Methyl Substituted Olefins

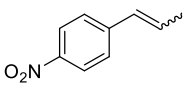
6.3.1 Synthesis of Substrates for CM

(*E*)-*N*-Methoxy-*N*-methylbut-2-enamide (77)[74]



To a stirred suspension of *N*-methoxy methylamine hydrochloride salt **76** (6.42 g, 66.0 mmol) in DCM (300 mL) at 0 °C was triethylamine (13.1 mL, 9.24 g, 126.0 mmol) slowly added and the reaction mixture was stirred at 0 °C for 30 min. Crotonoyl chloride **75** (5.76 mL, 6.30 g, 60.0 mmol) was added dropwise and the reaction was allowed to reach 20 °C and was stirred for 3 h. The reaction was quenched with aq. HCl (1 M) and the aqueous layer was separated and extracted with DCM (3x 40 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product (*E*)-*N*-methoxy-*N*-methylbut-2-enamide **77** (7.75 g, 60.0 mmol, quantitative yield), a pale-yellow liquid, was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dq, J = 15.3, 6.9 Hz, 1H), 6.41 (dd, J = 15.3, 1.8 Hz, 1H), 3.68 (s, 3H), 3.22 (s, 3H), 1.90 (dd, J = 6.9, 1.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 143.1, 120.3, 61.8, 32.5, 18.3. Analytical data match those previously reported in the literature.[70]

(*E*)- and (*Z*)-1-Nitro-4-(prop-1-en-1-yl)benzene (74)[69]



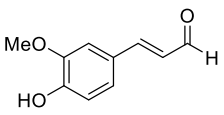
Wittig reagent Ph_3PEtBr (2.42 g, 6.52 mmol) was dissolved in THF (8 mL) and the colourless mixture was cooled to -78 °C. *n*-BuLi (2.39 mL, 2.5 M in hexane, 5.97 mmol) was added dropwise to the solution. The reaction mixture was allowed to warm to ambient temperature and stirred for 10 min. The orange mixture was cooled to -78 °C and 4-nitrobenzaldehyde **73** (820 mg, 5.43 mmol) in THF (5 mL) was added dropwise. The reaction was stirred for 10 min at -78 °C and then at ambient temperature for 30 min. The reaction mixture was quenched with pentane (50 mL), filtered through a pad of celite and washed with pentane. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give a mixture of (*E*)- and (*Z*)-1-nitro-4-(prop-1-en-1-yl)benzene **74** (687 mg, 4.21 mmol, 78% yield) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.2, 1.4 Hz, 0.71H), 7.86 (dd, J = 8.1, 1.3 Hz, 0.33H), 7.60 – 7.55 (m, 1.03H), 7.54 – 7.48 (m, 0.36H), 7.44 – 7.36 (m, 1.46H), 7.33 (ddd, J = 8.6, 7.2, 1.6 Hz, 0.34H), 6.85 (dd, J = 15.6, 1.8 Hz, 0.32H), 6.72 (dd, J = 11.6, 2.0 Hz, 0.72H), 6.25 (dq, J = 15.5, 6.7 Hz, 0.34H), 5.94 (dq, J = 11.5, 7.1 Hz, 0.74H), 1.94 (dd, J = 6.7, 1.8 Hz, 1.00H), 1.73 (dd, J = 7.1, 1.8 Hz, 2.24H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 147.8, 133.4, 132.9,

132.8, 132.7, 132.1, 131.7, 129.1, 128.5, 127.8, 127.5, 126.2, 126.1, 124.6, 124.5, 19.0, 14.5. Analytical data match those previously reported in the literature.[69]

6.3.2 General Procedure for Cross Metathesis

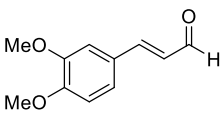
A stock solution of catalyst **HGII** (15.7 mg) in DCM (3 mL) was prepared. Stock solution (0.25 mL) was transferred to a sealed vial. After removing the solvent under reduced pressure, olefin **A** (1.0 equiv) and olefin **B** (1.5 equiv) were added. The reaction mixture was stirred at ambient temperature for 2 h. An aliquot of the reaction mixture was dissolved in $CDCl_3$ and analysed by ^1H NMR to calculate the conversion.

(*E*)-3-(4-Hydroxy-3-methoxyphenyl)acrylaldehyde (71a)



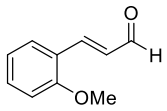
Following the general procedure for CM, isoeugenol **67** (164 mg, 0.15 mL, 1.00 mmol) and crotonaldehyde **70** (105 mg, 0.12 mL, 1.50 mmol) were used. The crude product was purified via dry column vacuum chromatography to give (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylaldehyde **71a** (139 mg, 0.78 mmol, 78% yield) as a red solid, mp 80-82 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 15.8 Hz, 1H), 7.12 (dd, J = 8.2, 2.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.59 (dd, J = 15.8, 7.7 Hz, 1H), 6.02 (s, 1H), 3.95 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 153.3, 149.1, 147.1, 126.8, 126.6, 124.2, 115.1, 109.6, 56.2; IR (ATR) ν 3380 (s), 2850 (m), 1725 (m), 1513 (s), 1227 (s).

(*E*)-3-(3,4-Dimethoxyphenyl)acrylaldehyde (86a)



Following the general procedure for CM, 1,2-dimethoxy-2-propenylbenzol **85** (178 mg, 0.17 mL, 1.00 mmol) and crotonaldehyde **70** (105 mg, 0.12 mL, 1.50 mmol) were used. The crude product was purified via dry column vacuum chromatography to give (*E*)-3-(3,4-dimethoxyphenyl)acrylaldehyde **86a** (151 mg, 0.79 mmol, 79% yield) as a pale yellow solid, mp 78-80 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 15.8 Hz, 1H), 7.14 (dd, J = 8.3, 2.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.59 (dd, J = 15.8, 7.7 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 152.9, 152.1, 149.5, 127.1, 126.8, 123.5, 111.2, 110.0, 56.1, 56.0; IR (ATR) ν 2890 (w), 1667 (s), 1595 (m), 1464 (w), 1267 (s); HRMS (ESI) calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0865, found 193.0857.

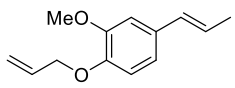
(*E*)-3-(2-Methoxyphenyl)acrylaldehyde (89a)



Following the general procedure for CM, *trans*-Anethol **88** (148 mg, 0.15 mL, 1.00 mmol) and crotonaldehyde **70** (105 mg, 0.12 mL, 1.50 mmol) were used. The crude product was purified via dry column vacuum chromatography to give (*E*)-3-(2-methoxyphenyl)acrylaldehyde **89a** (82.7 mg, 0.51 mmol, 51% yield) as a yellow solid, mp 60 - 63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 15.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.60 (dd, J = 15.8, 7.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 162.4, 152.8, 130.5, 126.9, 126.7, 114.7, 55.6; IR (ATR) v 2805 (m), 1663 (m), 1246 (m), 1125 (m), 960 (w); HRMS (ESI) calcd for $C_{10}H_{11}O_2$ $[M+H]^+$ 163.0759, found 163.0761.

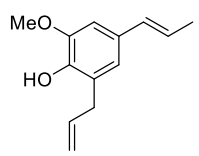
6.3.3 Total Synthesis of 7-Methoxywutaifuranal (9)

(*E*)-1-(Allyloxy)-2-methoxy-4-(prop-1-en-1-yl)benzene (94)



To a suspension of K_2CO_3 (2.77 g, 20.0 mmol) in acetone (30 mL) were added isoeugenol **67** (1.50 mL, 1.64 g, 10.0 mmol) and allyl bromide **93** (1.30 mL, 1.81 g, 15.0 mmol,). The reaction mixture was stirred under reflux for 12 h. The reaction mixture was cooled to ambient temperature, filtered through a pad of celite and washed with acetone. The solvent was evaporated under reduced pressure and crude product (*E*)-1-(allyloxy)-2-methoxy-4-(prop-1-en-1-yl)benzene **94** (2.04 g, 10.0 mmol, quantitative yield) obtained as a colourless liquid. NMR spectra revealed a mixture of *E*- and *Z*-isomers. ^{1}H NMR of the predominant *E*-isomer (400 MHz, $CDCl_3$) 6.90 (d, J = 1.8 Hz, 1H), 6.87 – 6.78 (m, 2H), 6.34 (dd, J = 15.6, 1.8 Hz, 1H), 6.17 – 6.01 (m, 2H), 5.40 (dd, J = 17.3, 1.6 Hz, 1H), 5.28 (dd, J = 10.5, 1.5 Hz, 1H), 4.60 (dt, J = 5.4, 1.6 Hz, 2H), 3.88 (s, 3H), 1.87 (dd, J = 6.6, 1.7 Hz, 3H); ^{13}C NMR of the predominant *E*-isomer (101 MHz, $CDCl_3$) δ 149.5, 147.2, 133.5, 131.6, 130.7, 123.9, 118.6, 117.9, 113.5, 109.0, 70.0, 55.9, 18.4; IR (ATR) v 2850 (w), 1510 (s), 1463 (m), 1263 (s), 1138 (s); HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1229, found; 205.1225.

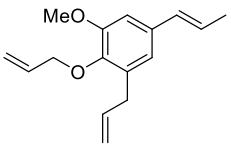
(*E*)-2-Allyl-6-methoxy-4-(prop-1-en-1-yl)phenol (95)



Compound **94** (2.04 g, 10.0 mmol) was dissolved in toluene (15 mL) and was stirred at 250 °C in a microwave for 1.5 h. The solvent was removed under reduced pressure and the crude product was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, J = 13.4, 1.9 Hz, 2H), 6.31 (dd, J = 15.8, 1.9 Hz, 1H), 6.06 – 5.80 (m, 2H), 5.08 – 4.90 (m, 2H), 3.80 (s, 3H), 3.37 – 3.26 (m, 2H), 1.82 – 1.74 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 142.7, 136.7, 131.0, 129.9,

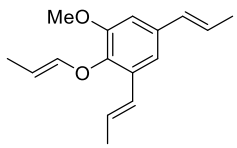
125.7, 123.4, 120.4, 115.6, 106.0, 56.1, 34.0, 18.5; IR (ATR) *v* 2860 (w), 1463 (m) 1291 (m), 1145 (m), 906 (s); HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1229, found 205.1223.

(*E*)-1-Allyl-2-(allyloxy)-3-methoxy-5-(prop-1-en-1-yl)benzene (96)



To a suspension of K_2CO_3 (1.01 g, 7.26 mmol) in acetone (18 mL) were added compound **95** (742 mg, 3.63 mmol) and allyl bromide **93** (0.63 mL, 876 mg, 7.26 mmol). The reaction was stirred under reflux for 12 h. The reaction mixture was cooled to ambient temperature, filtered through a pad of celite and washed with acetone. The solvent was evaporated under reduced pressure and the crude product was purified via dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give (*E*)-1-allyl-2-(allyloxy)-3-methoxy-5-(prop-1-en-1-yl)benzene **96** (619 mg, 2.53 mmol, 70% yield) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 – 6.71 (m, 2H), 6.33 (dd, *J* = 15.7, 1.7 Hz, 1H), 6.21 – 6.03 (m, 2H), 5.96 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.37 (ddq, *J* = 17.1, 5.8, 1.6 Hz, 1H), 5.21 (ddq, *J* = 10.4, 4.2, 1.4 Hz, 1H), 5.12 – 4.97 (m, 2H), 4.47 (dt, *J* = 5.8, 1.4 Hz, 2H), 3.86 (s, 3H), 3.40 (d, *J* = 6.5 Hz, 2H), 1.89 (dd, *J* = 6.6, 1.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 145.1, 137.4, 134.6, 134.0, 134.0, 130.9, 125.0, 120.0, 117.3, 115.7, 107.8, 74.0, 55.8, 34.4, 18.5; IR (ATR) *v* 2825 (w), 1582 (m), 1488 (m), 1332 (w), 1150 (s); HRMS (ESI) calcd for $C_{16}H_{22}O_2$ $[M+H]^+$ 245.1542, found 245.1544.

1-Methoxy-3,5-di((*E*)-prop-1-en-1-yl)-2-(((*E*)-prop-1-en-1-yl)oxy)benzene (92)

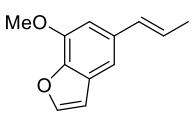


Compound **96** (1.11 g, 4.54 mmol) was dissolved in dry toluene (45 mL). $[RuHCl(CO)(PPh_3)_3]$ (215 mg, 5.0 mol%) was added and the reaction was stirred at 65 °C for 24 h. The reaction mixture was cooled to ambient temperature and the solvent was evaporated under reduced pressure. The crude product was purified via dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give 1-methoxy-3,5-di((*E*)-prop-1-en-1-yl)-2-(((*E*)-prop-1-en-1-yl)oxy)benzene **92** (1.05 g, 4.31 mmol, 95% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 2.1 Hz, 1H), 6.61 (dq, *J* = 16.1, 1.9 Hz, 1H), 6.35 (dd, *J* = 15.8, 1.7 Hz, 1H), 6.31 – 6.11 (m, 2H), 6.07 (dq, *J* = 6.1, 1.7 Hz, 1H), 4.59 (qd, *J* = 6.8, 6.0 Hz, 1H), 3.84 (s, 3H), 1.94 – 1.85 (m, 6H), 1.81 (dd, *J* = 6.9, 1.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 145.7, 142.6, 134.5, 131.7, 130.7, 127.7, 125.4, 125.0, 115.9, 108.1, 102.0, 56.1, 19.0, 18.4, 9.20; IR (ATR) *v* 2840 (m), 1668 (m), 1446 (m), 1215 (s), 961 (s); HRMS (ESI) calcd for $C_{16}H_{22}O_2$ $[M+H]^+$ 245.1542, found 245.1539.

Procedure for Ring-Closing Metathesis

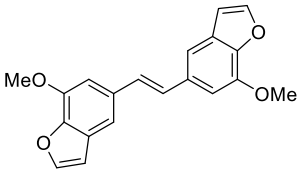
Compound **92** (244 mg, 1.00 mmol) was dissolved in DCM (5 mL) and the solution was stirred under reflux. Catalyst **HGII** (15.7 mg, 2.5 mol%) was added and the reaction was stirred for 24 h. The solvent was evaporated under reduced pressure and the crude product was purified via dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give corresponding RCM-product **97** and S-CM product **98**.

(*E*)-7-Methoxy-5-(prop-1-en-1-yl)benzofuran (97)



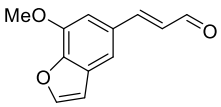
Following the procedure for RCM, (*E*)-7-methoxy-5-(prop-1-en-1-yl)benzofuran **97** (63.0 mg, 0.33 mmol, 33% yield) was isolated as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 2.1 Hz, 1H), 7.12 (d, J = 1.5 Hz, 1H), 6.85 (d, J = 1.5 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 6.48 (dq, J = 15.6, 1.8 Hz, 1H), 6.21 (dq, J = 15.7, 6.6 Hz, 1H), 4.02 (s, 3H), 1.91 (dd, J = 6.6, 1.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 145.4, 143.9, 134.3, 131.5, 129.3, 124.8, 111.3, 107.1, 104.3, 56.1, 18.6; IR (ATR) ν 2825 (m), 1596 (m), 1464 (m), 1145 (s), 1088 (w); HRMS (ESI) calcd for $C_{12}H_{13}O_2$ $[M+H]^+$ 189.0916, found 189.0921.

(*E*)-1,2-Bis(7-methoxybenzofuran-5-yl)ethene (98)



Following the procedure for RCM, (*E*)-1,2-bis(7-methoxy-benzofuran-5-yl)ethene **98** (64.1 mg, 0.20 mmol, 20% yield) was isolated as a white solid, mp 167-169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 2.1 Hz, 2H), 7.33 (d, J = 1.4 Hz, 2H), 7.14 (s, 2H), 7.03 (d, J = 1.6 Hz, 2H), 6.77 (d, J = 2.1 Hz, 2H), 4.09 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6, 145.6, 144.3, 133.8, 129.5, 128.4, 112.2, 107.2, 104.6, 56.2; IR (ATR) ν 2850 (m), 1596 (m), 1341 (m), 1259 (w), 1140 (m), 729 (s); HRMS (ESI) calcd for $C_{20}H_{17}O_4$ $[M+H]^+$ 321.1127, found 321.1132.

7-Methoxywutaifuranal (9)



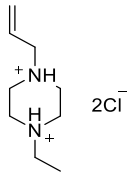
To a mixture of compound **92** (244 mg, 1.00 mmol) and crotonaldehyde **70** (0.48 mL, 421 mg, 6.00 mmol) was catalyst **HGII** (15.7 mg, 2.5 mol%) added. The reaction mixture was stirred at ambient temperature for 2 h. The crude product was purified via dry column vacuum chromatography (SiO_2; eluent: hexanes/MTBE mixtures of increasing polarity) to give 7-methoxywutaifuranal **9** (134 mg, 0.66 mmol, 66% yield) as a colourless solid, mp 103-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d,

J = 7.7 Hz, 1H), 7.66 (d, *J* = 2.2 Hz, 1H), 7.54 (d, *J* = 15.8 Hz, 1H), 7.41 (d, *J* = 1.5 Hz, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 6.70 (dd, *J* = 15.8, 7.7 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 153.7, 146.3, 146.3, 146.0, 130.3, 129.7, 127.9, 116.0, 107.3, 105.5, 56.3; IR (ATR) ν 3150 (w), 2750 (w), 1670 (s), 1465 (m), 1342 (m), 1122 (s); HRMS (ESI) calcd for $C_{12}H_{11}O_3$ $[M+H]^+$ 203.0708, found 203.0714.

6.4 Stereoretentive Metathesis in Polar Solvents

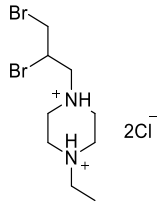
6.4.1 Synthesis of AquaMet (Ru-9)

1-Allyl-4-ethylpiperazine-1,4-diium (101)[58]



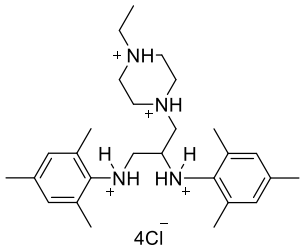
1-Ethylpiperazine **100** (98.3 g, 70.3 mL, 788 mmol) was dissolved in DCM (500 mL) and the solution was cooled to 0 °C. Allyl bromide **93** (91.8 g, 103 mL, 788 mmol) was slowly added. The reaction mixture was heated to reflux for 1.5 h and was then cooled to ambient temperature. The solution was washed with aq. NaOH (10%, 350 mL), dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (100 mL) and conc. HCl (157 mL) was added to the solution. The solvent was removed under vacuum and the crude product was crystallised from EtOH/Et_2O to give 1-allyl-4-ethylpiperazine-1,4-diium **101** (98.3 g, 433 mmol, 55% yield) as a white solid. ^{1}H NMR (400 MHz, D_2O) δ 5.96 – 5.84 (m, 1H), 5.67 – 5.60 (m, 2H), 3.89 (d, J = 7.3 Hz, 2H), 3.82 – 3.40 (br, 8H), 3.33 (q, J = 7.4 Hz, 2H), 1.33 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, D_2O) δ 127.9, 124.4, 58.7, 52.3, 48.0, 47.9, 8.5. Analytical data match those previously reported in the literature.[58]

1-(2,3-Dibromopropyl)-4-ethylpiperazine-1,4-diium (102)[58]



1-Allyl-4-ethylpiperazine-1,4-diium **101** (98.0 g, 431 mmol) was dissolved in H_2O (200 mL) and the solution was heated to 50 °C. Bromine (69.6 g, 22.4 mL, 431 mmol) was added in such a rate that the temperature did not exceed 60 °C. After the addition was completed, the water was evaporated under reduced pressure. The crude product was recrystallised from EtOH to give 1-(2,3-dibromopropyl)-4-ethylpiperazine-1,4-diium **102** (105 g, 431 mmol, 63% yield) as a white solid. ^{1}H NMR (400 MHz, D_2O) δ 4.13 – 3.39 (m, 13H), 3.34 (q, J = 7.3 Hz, 2H), 1.33 (t, J = 7.3 Hz, 3H). Analytical data match those previously reported in the literature.[58]

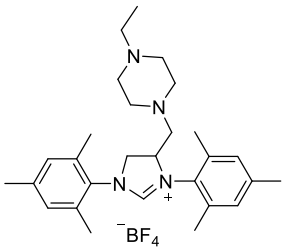
1-(2,3-Bis(mesitylammonio)propyl)-4-ethylpiperazine-1,4-diium (103)[58]



Compound **102** (20 g, 51.7 mmol) was dissolved in freshly distilled 2,4,6-trimethylanilline (111 mL) and the reaction mixture was heated to 120 °C for 24 h. The solution was cooled to ambient temperature and aq. NaOH (15%, 190 mL) was added. The aqueous layer was separated and extracted with DCM (150 mL). The organic layer was washed with H_2O (50 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure.

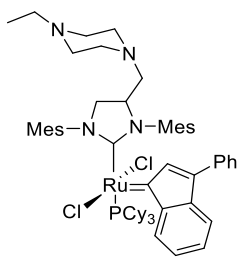
The excess of 2,4,6-trimethylanilline was removed by distillation. The crude product was dissolved in MeOH (100 mL) and conc. HCl (20.6 mL) was added. The solvent was removed under reduced pressure and the crude product was crystallised from acetone to give 1-(2,3-bis(mesitylammonio)propyl)-4-ethylpiperazine-1,4-diium **103** (24.2 g, 42.5 mmol, 82% yield) as a white solid. ^{1}H NMR (400 MHz, D_2O) δ 6.87 (d, J = 5.9 Hz, 4H), 3.90 – 3.82 (m, 1H), 3.74 (dd, J = 13.4, 8.0 Hz, 2H), 3.67 – 3.54 (m, 2H), 3.45 (dd, J = 14.0, 9.4 Hz, 2H), 3.31 – 3.22 (m, 4H), 3.22 – 3.13 (m, 2H), 2.24 - 2.05 (m, 20H), 1.31 (t, J = 7.3 Hz, 3H). Analytical data match those previously reported in the literature.[58]

4-((4-Ethylpiperazin-1-yl)methyl)-1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate (99)[58]



Compound **103** (24.2 g, 42.5 mmol) was dissolved in MeOH (58 mL) and triethyl orthoformate (32.1 g, 36.1 mL, 213 mmol) was added. The reaction mixture was stirred at 90 °C for 3 h. The solvent was removed under reduced pressure and the crude product was dissolved in H_2O (34 mL). A solution of NH_4BH_4 (6.68 g, 63.8 mmol) in H_2O (68 mL) and aq. NaOH (5%, 62 mL) were added. The aqueous phase was separated and extracted with DCM (100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The crude product was purified by recrystallisation from DCM/CCl_3 mixture to give 4-((4-ethylpiperazin-1-yl)methyl)-1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate **99** (16.3 g, 31.5 mmol, 74% yield) as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.08 (s, 1H), 7.04 (d, J = 6.1 Hz, 4H), 5.01 (dq, J = 11.4, 7.5 Hz, 1H), 4.56 (t, J = 11.9 Hz, 1H), 4.10 (dd, J = 12.4, 8.4 Hz, 1H), 2.74 (dd, J = 7.2, 1.5 Hz, 2H), 2.44 – 2.30 (m, 26H), 2.25 (q, J = 7.2 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H). Analytical data match those previously reported in the literature.[58]

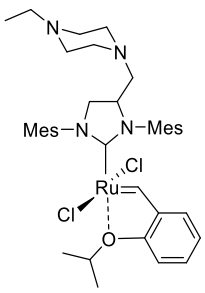
Complex Ru-13[58]



Potassium t-amylate (32.8 mg, 36.5 µL, 65.0 µmol) was added to a suspension of NHC-ligand **99** (39.5 mg, 76.0 µmol) in toluene (5 mL). The mixture was stirred at room temperature for 20 min. **Ind-I** (50.0 mg, 54.2 µmol) was added and the reaction mixture was stirred at 80 °C for 1 h. The mixture was cooled down to ambient temperature and the solvent was removed under reduced pressure. The crude product was filtered through a short pad of SiO_2 (eluent: hexanes/EtOAc mixtures of increasing polarity) and the solvent was removed under

reduced pressure to give complex **Ru-13** (28.0 mg, 26.0 µmol, 48% yield) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 – 8.59 (m, 1H), 7.81 – 7.59 (m, 2H), 7.59 – 7.44 (m, 2H), 7.42 – 7.33 (m, 2H), 7.21 – 7.08 (m, 2H), 7.07 – 6.99 (m, 3H), 6.44 – 6.36 (m, 1H), 6.08 – 5.82 (m, 1H), 4.46 – 4.18 (m, 1H), 4.17 – 4.06 (m, 1H), 3.99 – 3.58 (m, 1H), 2.74 – 2.71 (m, 3H), 2.68 – 2.55 (m, 3H), 2.57 – 2.39 (m, 3H), 2.37 – 2.02 (m, 21H), 1.88 – 1.80 (m, 3H), 1.65 – 1.35 (m, 15H), 1.26 (t, J = 7.1 Hz, 3H), 1.11 – 0.74 (m, 15H). Analytical data match those previously reported in the literature.[58]

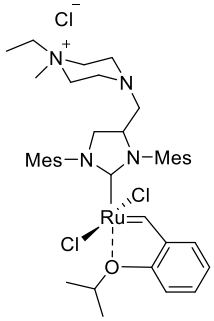
Complex Ru-14



Method A:[58] Styrene **104** (6.33 mg, 6.33 µL, 39.0 µmol) and CuCl (3.9 mg, 39.0 µmol) were dissolved in toluene (2 mL). Complex **Ru-13** (28.0 mg, 26.0 µmol) was added, and the reaction mixture was stirred at 80 °C for 20 min. The mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give complex **Ru-14** (10.9 mg, 15.0 µmol, 56% yield) as a green solid.

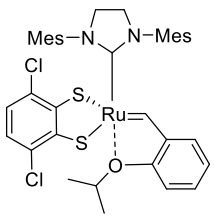
Method B: Potassium t-amylate (30.7 mg, 34.1 µL, 60.8 µmol) was added to a suspension of NHC-ligand **99** (31.6 mg, 60.8 µmol) in toluene (5 mL). The reaction mixture was stirred vigorously at ambient temperature for at least 10 min. Ruthenium complex **GI** (50 mg, 60.8 µmol) was added and the mixture was stirred at 80 °C for 30 min. Styrene **104** (29.6 mg, 29.6 µL, 182 µmol) was added followed by addition of CuCl (13.4 mg, 134 µmol). The reaction mixture was stirred at 80 °C for 15 min. The mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. The resulting residue was dissolved in EtOAc, filtered through cotton wool and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes/EtOAc mixtures of increasing polarity) to give complex **Ru-14** (21.2 mg, 29.2 µmol, 48% yield) as a green solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.53 (s, 1H), 7.47 (ddd, J = 8.3, 7.2, 1.8 Hz, 1H), 7.10 – 7.02 (m, 4H), 6.92 – 6.90 (m, 1H), 6.85 (td, J = 7.4, 0.8 Hz, 0H), 6.78 (d, J = 8.3 Hz, 0H), 4.89 (heptet, J = 6.2 Hz, 1H),4.63 – 4.50 (m, 1H), 4.27 (t, J = 10.5 Hz, 1H), 4.00 (dd, J = 10.5, 8.4 Hz, 1H), 2.76 – 2.68 (m, 2H), 2.55 – 2.24 (m, 28H), 1.25 (d, J = 6.0 Hz, 6H), 1.05 (t, J = 7.2 Hz, 3H). Analytical data match those previously reported in the literature.[58]

Complex (AquaMet) Ru-9[58]



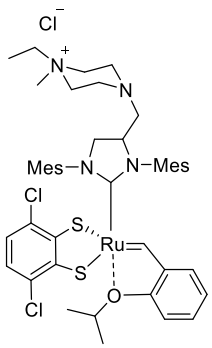
Complex **Ru-14** (10.9 mg, 14.5 µmol) was added to a pressure reactor and MeCl was added. The reactor was sealed and stirred at 60 °C for 24 h. The crude product was purified by filtration through a short pad of Al_2O_3 (eluent: MeOH/DCM mixtures of increasing polarity) to give (AquaMet**) Ru-9** (6.80 mg, 8.50 µmol, 59%) as a green solid. ^{1}H NMR (400 MHz, CD_2C_2) δ 16.41 (s, 1H), 7.56 (ddd, *J* = 8.9, 7.0, 2.1 Hz, 1H), 7.13 – 7.02 (m, 4H), 6.97 – 6.88 (m, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.89 (heptet, *J* = 6.0 Hz, 1H), 4.67 – 4.58 (m, 1H), 4.28 (t, *J* = 10.5 Hz, 1H), 3.90 (t, *J* = 9.6 Hz, 1H), 3.74 – 3.72 (m, 1H), 3.63 (s, 1H), 3.54 (br s, 2H), 3.30 – 3.21 (m, 5H), 2.89 – 2.81 (m, 3H), 2.79 – 2.69 (m, 3H), 2.53 – 2.25 (m, 18H), 1.36 (t, J = 7.4 Hz, 3H), 1.20 (s, 6H). Analytical data match those previously reported in the literature.[58]

Dithiolate complex Ru-4[53]



In a glovebox, catalyst **HGII** (95.3 mg, 0.15 mmol) and zinc dithiolate **22** (76.3 mg, 0.23 mmol) were dissolved in THF (10 mL) in a glovebox. The reaction mixture was stirred at 22 °C for 2 h. The solvent was evaporated, and the crude product was dissolved in DCM (5 mL) and filtered through celite. The filtrate was evaporated to dryness and the residue was washed with pentane (2x 5 mL) to give complex **Ru-4** (115 mg, 0.15 mmol, 98%) as a brown solid. ^{1}H NMR (400 MHz, CD_2C_2) δ 14.30 (s, 1H), 7.32 – 7.28 (m, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.97 (s, 2H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.84 – 6.75 (m, 2H), 6.62 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.17 (br s, 1H), 5.34 – 5.26 (m, 2H), 3.94 (s, 4H), 2.53 (br s, 6H), 2.36 – 2.27 (m, 3H), 2.21 (s, 6H), 1.69 (d, *J* = 6.6 Hz, 3H), 1.63 (br s, 3H), 1.50 (d, *J* = 6.6 Hz, 3H). Analytical data match those previously reported in the literature.[53]

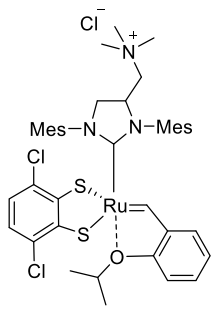
Dithiolate complex Ru-11



In a glovebox, catalyst (AquaMet) **Ru-9** (28.1 mg, 35.0 µmol) and zinc dithiolate **22** (11.7 mg, 35.0 µmol) were dissolved in THF (3 mL) in a glovebox. The reaction mixture was stirred at 22 °C for 2 h. The solvent was evaporated, and the crude product was dissolved in DCM (2 mL) and filtered through celite. The filtrate was evaporated to dryness and the residue was washed with pentane (2x 2 mL) to give complex **Ru-11** (16.0 mg, 17.0 µmol, 49%) as a brown solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 14.19 (s, 1H), 7.30

(m, 1H), 7.19 – 6.99 (m, 3H), 6.96 – 6.73 (m, 4H), 6.71 – 6.47 (m, 2H), 6.34 (s, 1H), 4.90 – 3.49 (m, 9H), 3.44 – 2.85 (m, 9H), 2.76 – 2.05 (m, 18H), 1.45 – 1.04 (m, 9H).

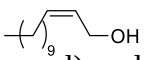
Dithiolate complex Ru-12



In a glovebox, catalyst (StickyCat) **Ru-10** (500 mg, 0.68 mmol) and zinc dithiolate **22** (342 mg, 1.02 mmol) were dissolved in THF (25 mL) in a glovebox. The reaction mixture was stirred at 22 °C for 2 h. The solvent was evaporated, and the crude product was dissolved in DCM (20 mL) and filtered through celite. The filtrate was evaporated to dryness and the residue was washed with pentane (2x 10 mL) to give complex **Ru-12** (544 mg, 0.62 mmol, 92%) as a brown solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 14.36 (s, 1H), 7.44 – 7.14 (m, 2H), 7.03 – 6.95 (m, 2H), 6.89 – 6.76 (m, 4H), 6.71 – 6.38 (m, 1H), 5.21 – 4.36 (m, 2H), 4.14 – 3.83 (m, 2H), 3.04 – 2.49 (m, 18H), 2.33 – 2.10 (m, 9H), 1.88 – 1.76 (m, 3H), 1.53 – 1.27 (m, 6H).

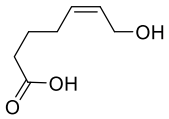
6.4.2 General Procedure for Stereoretentive Metathesis in Polar Solvents

(*Z*)-Tridec-2-en-1-ol (107)



To a solution of 1-dodecene **105** (0.30 mmol), cis-butendiol **106** (55.6 mg, 0.60 mmol) and tetradecane (10 µL) as an internal standard in THF (1.50 mL) was added **Ru-8** (13.1 mg, 5.0 mol%). The reaction mixture was stirred at room temperature for 4 h. Conversion was calculated via GC.

(*Z*)-7-Hydroxyhept-5-enoic acid (109)



To a solution of pent-4-enoic acid **108** (30.3 mg, 0.30 mmol), (*Z*)-but-2-ene-1,4-diol **106** (55.6 mg, 0.60 mmol) and pivalic acid (3.09 mg, 0.03 mmol) as an internal standard in MeOH (1.50 mL) was added **Ru-8** (13.1 mg, 5.0 mol%). The reaction mixture was stirred at room temperature for 4 h. Conversion was calculated via GC.

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