The intramolecular oxa-Michael reaction for tetrahydropyran formation : mechanism and synthesis

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2019

Csokas, D. (2019). The intramolecular oxa-Michael reaction for tetrahydropyran formation : mechanism and synthesis. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/104818>

<https://doi.org/10.32657/10220/48088>

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

SINGAPORE

**The Intramolecular oxa-Michael Reaction for Tetrahydropyran
Formation:
Mechanism and Synthesis**

Csokas Daniel

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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Formation:
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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Doctor of Philosophy

2019

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This thesis contains material from 1 paper published in the following peer-reviewed journal and from papers accepted at conferences in which I am listed as an author. Also, this thesis contains material from 1 manuscript, which is yet to be published in a peer-reviewed journal.

The results of **Chapter 1** provided material for two conference papers:

Csókás, D.; Li, L.; Palani K.; Bates, R. W. New approach for the formation of tetrahydropyran ring in the synthesis of Bistramide D (poster), PACCON, Bangkok (TH), Feb. 9-11., 2016

Csókás, D.; Li, L.; Palani K.; Bates, R. W. New approach for the synthesis of Bistramide D (poster), ICOS 21, Mumbai (IN), Dec. 11-16., 2016

The contributions of the co-authors are as follows:

- Prof R. W. Bates provided the initial project direction.
- The results of preliminar study by Li, L. and Palani K. (former group members) provided guidance in my research.
- I performed all the laboratory work (synthesis, test reactions, compound characterization) at the School of Physical and Mathematical Sciences (Chemistry and Biological Chemistry).

The results of **Chapter 2** provided material for a manuscript: D. Csókás, A. H. X. Ying, R. O. Ramabhadranb*, R. W. Bates* How an Early or Late Transition State Impacts the Stereoselectivity of Tetrahydropyran Formation by Intramolecular oxa-Michael Addition

The contributions of the co-authors are as follows:

- Prof R. W. Bates provided the initial project direction.

- I performed the majority of the laboratory work (synthesis, test reactions, compound characterization) at the School of Physical and Mathematical Sciences (Chemistry and Biological Chemistry). Experiments with the acid-catalyzed cyclisation was performed by Annabel Ho current group member.
- I performed all the DFT calculations under R. O. Ramabhadran's guidance.
- I prepared the computational part and the supporting information of the manuscript. The manuscript was revised by Prof R. W. Bates and Dr. R. O. Ramabhadran.

The results of **Chapter 2** provided material for two conference papers:

Csókás, D.; Ramabhadran, R. O.; Bates, R. W. A combined DFT and experimental study of the oxa-Michael reaction in THP synthesis. Interpretation of the selectivity-determining factors. (poster), PACCON, Hat Yai (TH), Feb. 7-9., 2018

D. Csokas, R. O. Ramabhadran, A. Ho, R. W. Bates* Combined DFT and experimental study of the base and acid catalyzed oxa-Michael reaction in THP synthesis: reinterpretation of the selectivity-determining factors. (poster), 255th ACS National Meeting, New Orleans (USA), March 18-22., 2018

The contributions of the co-authors are as follows: see above

Chapter 3 is published as D. Csókás, R. W. Bates* Synthesis of the proposed structure of cryptoconcatone H. *Synlett* **2019**, *30*, 178–180. DOI: 10.1055/s-0037-160965

The contributions of the co-authors are as follows:

- Prof R. W. Bates provided the initial project direction.

- I performed all the laboratory work (synthesis, test reactions, compound characterization) at the School of Physical and Mathematical Sciences (Chemistry and Biological Chemistry).
- I prepared the figures and the supporting information of the published paper.

19th March 2019
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Date

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Walter Daniel

Acknowledgements

First and foremost, I must express my appreciation to **Professor Roderick Bates** for giving me the opportunity to work in his group. He strengthened my fundamental knowledge of organic chemistry and thanks to him I learned how to look at scientific problems. Under his patient guidance, I believe I have grown as a scientist. More importantly, he provided me the opportunity to experience the wonders of the Indian cuisine in the most authentic way as possible. Here, I must express great thanks to **Raghunath O. Ramabhadran** at IISER Tirupati for teaching me how to apply computational chemistry to study the *oxa*-Michael cyclisation reaction. I am deeply indebted to **Singapore Ministry of Education** and **Nanyang Technological University** for the generous financial support to pursue my doctoral studies. I am very grateful to **Ms. Goh Ee Ling** for her help and the perfectly operating NMR facility at NTU.

I would like to acknowledge the current Ph.D. students in the Bates group; **Ivan, Weiting, Anders, Annabel, Loi** for the friendly atmosphere. Special thanks to Ivan, who gave me tremendous help with the academic administrative tasks and the IT issues.

I would like to thank the ‘Hungarian team’ at NTU, namely, **Barát Viktor, Bati Gábor, Katona Dávid**, and **Balázs László** for the invaluable time spent together.

While doing my Ph.D. in Singapore, I was fortunate to encounter many interesting and kind people. I would like to thank all these people; **Ronny William** and **Asadulla Mallick** for their friendship, **Joanna Loh** for her sincere kindness, **Moss Trestman** for feeding us with incredibly delicious food, **Nabila Syed Azman** for the time we spent together, **Nguyen Doan** for constantly expressing endless enthusiasm for organic synthesis, and lastly **Salbiah** for her understanding and support.

Thanks to the cross-border research in Singapore, we had the opportunity to meet **Professor Kürti László** a few times, who always shared his experiences in research with us, of which we will be always thankful.

I would like to express my most sincere gratitude to **Bea** and **Jim** for their enormous amount of help that I have gotten in the last three years as well as for the exhilarating lessons; all of this has a huge impact on this work.

I would also like to thank all of **my friends** in Hungary for not forgetting about me during my time in Singapore.

I am grateful to my former chemistry teacher and my friend **Schelb Tamás** who taught me the habit of precise work, which is essential for the cultivation of this scientific field.

Finally, and most importantly, I thank my **Mom** for her unconditional love and everlasting support, without that, none of these would have been possible.

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Abstract

Bistramides are a class of complex natural products containing three fragments, namely tetrahydropyran, amino acid and spiroketal. With respect to the biological relevance of Bistramide family, they have attracted much attention by the synthetic community. However, to our knowledge, no total synthesis of *Bistramide D* has been reported. Thus far, our laboratory has completed the synthesis of the THP ring and amino acid units, and has devised a route to the spiroketal. The current work describes a new synthetic approach towards the scale-up synthesis of THP ring.

Our research group has had a longstanding interest in the synthesis of THP-containing natural products. The base- and acid-catalysed intramolecular *oxa*-Michael reaction proved to be a widely applicable method for the stereoselective elaboration of the THP ring. Despite the vast amount of precedents in syntheses, no clear explanation for the origin of stereocontrol has been disclosed. Thus, we provide a tangible explanation for the observed selectivity, which is based on a combined DFT and experimental study.

The structural clarification of misassigned natural products has a long history and continues to be a recurring predicament. In this context, the ambiguous structural elucidation and the insufficient NMR data of *Cryptoconcatone H* prompted us to embark on a synthesis of the reported structure. The *cis*-THP core of the proposed structure was established via a tandem deprotection – intramolecular *oxa*-Michael cyclisation. Our synthetic study provides evidence that the proposed structure of the isolated natural product is incorrect.

Abbreviations

Boc	– <i>t</i> -butyloxycarbonyl
BOM	– benzyloxymethyl acetal
CAN	– ceric ammonium nitrate
(<i>S</i>)-CBS	– Corey-Bakshi-Shibata catalyst (alkyl-oxazaborolidine)
DBU	– 1,8-diazabicycloundec-7-ene
DCM	– dichloromethane
DIBAL-H	– diisobutylaluminium hydride
DIPEA	– <i>N,N</i> -diisopropylethylamine
HPLC	– high pressure liquid chromatography
IBX	– 2-iodoxybenzoic acid
<i>m</i> -CPBA	– <i>m</i> -chloroperoxybenzoic acid
PG	– protecting group
PMB	– <i>p</i> -methoxybenzyl ether
EE	– ethoxyethyl acetal
RT	– room temperature
TBAF	– tetra- <i>N</i> -butylammonium fluoride
THF	– tetrahydrofuran
DMSO	– dimethyl sulfoxide
THP	– tetrahydropyran
TLC	– thin layer chromatography
TS	– transition state
Bn	– benzyl group
TES	– triethylsilyl
TBDPS	– <i>t</i> -butyldiphenylsilyl
TMS	– trimethylsilyl
TBS	– <i>t</i> -butyldimethylsilyl
TIPS	– triisopropylsilyl
Tf	– trifluoromethylsulfonyl (triflate)
DMAP	– 4-dimethylaminopyridine
CSA	– camphorsulfonic acid

PPTS – pyridinium *p*-toluenesulfonate
DMS – borane dimethyl sulfide
CB – catecholborane
Ipc – diisopinocampheylborane
Tol – tosyl
HMDS – hexamethyldisilazane
TsOH – *p*-toluenesulfonic acid
Py – pyridine
DFT – density functional theory
QM – quantum mechanics
MMFF – Merck molecular force field
HF – Hartree–Fock
NMR – nuclear magnetic resonance
COSY – correlation spectroscopy
Ph – phenyl
DABCO – 1,4-diazabicyclo[2.2.2]octane
TMEDA – *N,N,N',N'*-tetramethylethylenediamine
Protonsponge – 1,8-bis(dimethylamino)naphthalene
SMD – solvation model based on density
OPLS – optimized potentials for liquid simulations
H – enthalpy
NBO – natural bond orbital
LUMO – lowest energy unoccupied molecular orbital
HOMO – highest energy occupied molecular orbital
CM – cross metathesis
RCM – ring-closing metathesis
ECD – electronic circular dichroism

Chapter 1

TETRAHYDROPYRAN OF BISTRAMIDE D

1. Introduction

1.1. Biological relevance of *Bistramides*

Recent studies have shown that the *Bistramide* family (A, B C, D, K and 39-oxobistramide K), which were isolated as marine toxin from tunicates *Lissoclinum bistratum*^{1,2} and *Trididemnum cyclops*³ marine organism, has remarkable antiproliferative activities.⁴ These naturally occurring substances exhibited *in vitro* cytotoxicity towards a number of tumor cell lines. *Bistramide A* was the most extensively studied member of the Bistramide family. It displayed activity against several cell lines: central nervous system tumors, renal carcinoma⁵, bronchial carcinoma⁶, human melanoma⁷, human leukemia⁸, bronchopulmonary carcinoma⁹, and human lung carcinoma¹⁰ cell lines with noteworthy IC₅₀ values.

Figure 1. Structure of Bistramide D

It has recently been proved that actin is the primary cellular receptor of Bistramide A.^{11,12} In addition to its essential cellular processes, actin as cytoskeletal protein has a key role in tumor cell growth. The potent antiproliferative effect of the *Bistramides* can be explained by their unique binding features of their architecture. Bistramides are built from three main fragments (Figure 1.). The central amino acid portion and the spiroketal subunit are suspected to be essential for the effective protein-binding through an excellently organized hydrogen bonding network and combinations of van der Waals interactions (*vide infra*). The THP fragment does not participate in the *Bistramide*-actin interplay, although the enone moiety as potential Michael-acceptor displays a crucial role in the enhanced cytotoxicity of the *Bistramide* based substances¹³ (e.g.: *Bistramide A*). In one of the pioneer studies, it was noted that *Bistramide D* and *K* were less toxic than *Bistramide A*, *B*, and *C* in lung carcinoma cell lines¹⁰. Further studies have reported additional effects, for instance, modification in cell morphology^{8,14}, alteration in cytoskeletal organization¹⁴, enhanced protein phosphorylation⁸, apoptosis^{15,16} and ability to block sodium¹⁷ and calcium^{18,19} channels.

The most extensive study with respect to the structural behaviour of *Bistramide A* towards the globular actin protein has been made by *Kozmin et al*^{11,12}. This important study provides the basis for a rational structure-based drug design, thereby enabling the pharmaceutical chemists to tune the properties of potential candidates. Interestingly, *Bistramide A* has no resemblance with the well-known G-acting binding natural products as to their structures. In their paper, the high-resolution crystal structure of *Bistramide A* - actin complex was reported, in which actin adopted a commonly closed tertiary structure. *Bistramide A* itself interacted with the similar binding region as is the case of other actin-binding natural products. However, it had a couple of different distinct features such as the nearly totally elongated conformation between the two subdomains and the highly extended hydrogen-bonding system (Figure 2.). The enone side chain was not notably involved in the protein binding, rather it was

oriented toward the solvent space. As for the spiroketal part, it occupied a large hydrophobic pocket, assisting the process of docking to the protein. In contrast to actin-binding natural products, in Bistramides, the amino-acid bridge connecting the two lipophilic sides bears five heteroatoms which are capable of H-bonding. This allowed for the penetration into the binding pocket of the actin. Furthermore, the authors assumed that Bistramide A has a further stabilizing effect on actin conformation, preventing nucleotide exchange. As a consequence of these particular key units, the Bistramide family is endowed with suitable structural features for creating an effective bonding-interaction with the target actin.

Figure 2. (A) Electron density of Bistramide A (B, C) Interaction of Bistramide A with actin in different representation (adapted from Kozmin, S. A. J Am. Chem. Soc. 2006, 128, 3882-3883.)

More recently, pharmaceutical chemists have started focusing on the structural complexity of potential drug molecules so as to escape from flatland represented in several drugs on the market.²⁰ The determinative interaction with the target protein can be more sophisticated by means of more complex spatial architecture, which also entails the possibility of various conformations. For characterization, two simple descriptors of complexity were proposed that refer to three-dimensionality as well as to the saturation of the candidate. The latter is defined by the number of sp^3 hybridized carbons per total carbon number and the number of chiral carbon in molecule.²¹ It has been demonstrated that both factors can provide a good correlation

with successful hits in clinical testing. All the Bistramides as polyketid-based natural products comprise at least eleven stereogenic centers. Thus, it is justified to opine this natural product family fulfils the requirement of complexity. Built on these facts, we believe, Bistramides deserve more attention in view of their syntheses.

1.2. Selected synthetic approaches towards the THP ring

The goal of this section is to briefly describe the different methods used in stereoselective synthesis of tetrahydropyrans. The literature of THP-containing natural products encompasses numerous successful syntheses, which were encouraged by their interesting biological properties. Not surprisingly, a large number of methods have been elaborated for the synthesis of such ring systems, ensuring the possibility of endless choice for synthetic chemists (Figure 3.).²² Given the retrosynthetic analysis of the THP ring, all disconnections were found to be possible as shown in the following examples. The figures 4-7 are dedicated to providing a brief graphical summary of fundamental synthetic approaches towards the construction of THP ring.

Figure 3. Retrosynthetic approaches towards THP ring

O-C2: Conjugate addition (a comprehensive listing and discussion see Chapter 2), Nucleophilic substitution cyclization²³, Alkene-mediated cyclization²⁴, Epoxide ring-opening²⁵

C2-C3: Prins reaction²⁶, Petasis-Ferrier rearrangement²⁷, Panek annulations²⁸

C3-C4: Ring-closing metathesis²⁹

Others: Hetero-Diels-Alder reaction³⁰, Lactol reduction³¹, Lactone reduction followed by reductive acetylation or allylation³²

One of the simplest strategies to establish the stereochemistry in the THP-ring relies on S_N2 -type nucleophilic substitution. The substitution takes place with inversion at the electrophilic carbon centre. The stereochemical outcome is determined by the existing

stereochemistry of the nucleophilic centre and the leaving group. Thus, this methodology readily gives access to both the 2,6-*trans* and 2,6-*cis* THP rings.

In the case of the alkene-mediated cyclization, which proceeds via either π -allyl or π -complex, the stereochemical outcome can be predicted by the relative steric demands of the formed π -palladium complexes. Hence, 2,6-*cis* stereochemical outcome is often prevalent in comparison with 2,6-*trans* as all the substituents in *cis* arrangement are resided in equatorial positions, avoiding unfavourable 1,3-diaxial interactions (Figure 4.). Similar stereochemical consideration can be done when the electrophile is either mercury, halonium or selenium cation. However, based on the literature examples, stereochemical outcome tends to be dependent on individual cases when the carbon chain is highly substituted, and further conformational analysis of either the onium intermediate or the starting compound is required.

Figure 4. Synthetic strategies based on O-C2 disconnection

The reactions which fall into the C2-C3 disconnection strategy are based on the same reaction mechanism. This involves the formation of the oxonium cation. This type of cyclization proceeds via a chair-like transition state followed by the formation of secondary carbocation stabilized by orbital overlap. In the favoured TS, the 2,6-substituent are *cis*. The stereochemistry of C4 is highly dictated by the nature of the present nucleophilic trapping reagent (Figure 5.).

Figure 5. Synthetic strategies based on C2-C3 disconnection

When the THP ring is assembled by intramolecular metathesis, the stereochemistry is defined according to the initial configuration of the substituents. In best-case scenario, the present stereogenic centres are not affected by the ring-closing metathesis reaction (Figure 6.).

Figure 6. Synthetic strategy based on C3-C4 disconnection

When the aldehyde is the dienophile, stereochemical consequences of hetero-Diels–Alder cyclisation can be predicted by the simple FMO theory and additional steric consideration. In a few cases, this cyclisation method only constructs the pyran scaffold and further transformation is needed to introduce the required stereochemistry. In principle, the stereochemical outcome of transformation based on lactol or lactone reduction is well-predictable. The origin of the stereoselectivity is explained by the axial attack of the nucleophile on the half-chair conformation of oxocarbenium ion, which preferentially gives the 2,6-*trans* THP via chair-like TS. However, care should be taken because base- or acid-mediated epimerisation can occur under the employed conditions, which ultimately leads to the thermodynamically favored 2,6-*cis* product (Figure 7.).

Figure 7. Other commonly used strategies

In most of the depicted reactions, the stereochemical outcome (*cis* or *trans* THP core) is well-predictable based on simple stereochemical models. However, there has been no

proposed stereochemical model or elucidation of the observed stereochemical outcome of *oxa*-Michael cyclisation. Chapter 2, therefore, focuses on stereochemical considerations of *oxa*-Michael cyclisation supported by computational and experimental studies.

1.5 Synthesis of THP ring of *Bistramides*

The primary aim of this section is to provide an insight into the key reactions used to build the THP ring of *Bistramides*.

Thus far, numerous accomplished total³³ and fragment³⁴ synthesis have been reported towards the *Bistramide* family. However, no total synthesis of *Bistramide D* has been achieved, except for a stereoselective hemi-synthesis³⁵ starting from *Bistramide A* by *Solladié* and co-workers. They reported the stereoselective reduction of *Bistramide A* to *D* derivative (Figure 1.). After an extensive optimisation, LiBHEt₃ was found to be the suitable reducing agent for selective keto-reduction, providing an excellent diastereoselectivity (95:5).

Kitching et al. elaborated the synthesis of THP ring of *Bistramide A* in two different ways.^{34f} In the first route, the synthesis began with the modification of enantiopure epoxide **18**, and the requisite intermediate **19** for cyclization was achieved over eight simple functional group transformations (Figure 8). After the cleavage of the protecting group, treatment of diol with mercury acetate prompted the cyclization to afford the THP scaffold **20**.

Figure 8. *Kitching's* first route for THP ring synthesis

In the second method, they used a known aldehyde **21** as the starting precursor to prepare the desired ring system (Figure 9). The cyclization was accomplished upon PdCl₂ mediated carbonylation of compound **22**, the product of which instantaneously underwent an *oxa*-Michael cyclisation yielding THP core **23**.

Figure 9. Kitching's second route for THP ring synthesis

Wipf envisioned preparing THP ring from D-glucose through several functional group manipulations (Figure 10).^{33e} In 17 steps, they managed to synthesize the THP fragment of *Bistramide C*. A few years later, the same group described the total synthesis of *Bistramide C* with a conceptually different approach towards the THP ring. The new synthetic route involved a methylalumination with the chiral Erker's zirconocene catalyst for installing the methyl group, Sharpless asymmetric epoxidation to introduce the hydroxyl group to the carbon chain. First, the aldehyde **27** was converted into the corresponding acetylated hemiacetal **28**. Ultimately, the resultant acetylated hemiacetal **28** was subjected to reductive allylation with allyltrimethylsilane in the presence of BiBr_3 to access the THP **29** of the *Bistramide C*.

Figure 10. Wipf's method for the THP synthesis

Kozmin and co-workers served the first total synthesis of *Bistramide A*.^{33f} In the synthesis of THP ring, Brown crotylboration was used to construct the two stereogenic centers at the early stage of the synthesis (Figure 11.). Then the sequential acetylation and ring-closing

metathesis afforded the precursor **33**. The reduction with DIBAL-H followed by acetylation gave intermediate **34**, which upon ZnCl_2 prompted reductive aldol reaction led to the THP ring with conjugate enone moiety **35**.

Figure 11. Synthesis of THP ring by Kozmin

Crimmins *et al.* developed a new synthetic route for the synthesis of THP fragment of *Bistramide A* (Figure 12.).^{33d} The synthesis started with an asymmetric aldol reaction employing Evans-type chiral auxiliary that resulted in the *syn* isomer **37** in an excellent diastereomic ratio (98:2). After further elongation of the substituted carbon chain with Wittig reaction followed by the reduction of the double bond, the lactonisation was affected by treatment with PPTS. The reductive acylation with *i*-Bu₂AlH then TMSOTf induced aldol reaction provided the tetrahydropyran core **41**.

Figure 12. Crimmins's synthetic route to THP ring

Panek's synthesis was shown to be the most resourceful concept amongst *Bistramide A* syntheses.^{33c} Panek applied a [4+2] annulations strategy for the THP and spiroketal fragment (Figure 13.). Furthermore, the synthesis of the three fragments was based on the highly similar organosilanes as starting materials. In the first step, the tetrahydropyran ring was constructed by a stereocontrolled annulation reaction of compound **42** with the aldehyde **43**. The final structure of the ring system was elaborated in further nine simple steps.

Figure 13. Panek's tactic for the synthesis of THP scaffold

Yadav's synthesis was also based on the exploitation of lactol formation-reduction protocol (Figure 14.).^{34a} The synthesis began with elongation of a known epoxide to furnish compound **46**. The ring opening reaction of epoxide **46** with Me_3Al reagent gave the corresponding unsaturated ester **47**. Similar to Crimmins's protocol, lacton **48** was prepared followed by reductive acylation protocol to furnish the THP fragment **49**.

Figure 14. Yadav's synthesis for THP ring

Piva et al. utilized the *oxa*-Michael conjugate addition to construct the normethyl THP ring of *Bistramide A* (Figure 15).^{34e} After having synthesized the **52** precursor for cyclization over five steps, the cyclisation was carried out under kinetic conditions (NaH, -78 °C) to give rise to the preferential formation of *trans* isomer. Unfortunately, the ring closure proceeded with low diastereoselectivity (1.5:1), resulting in a mixture of *trans* and *cis* product.

Figure 15. Piva's approach towards THP ring

In our group the efficient total synthesis of *Bistramide D* has been intensively studied. Successful preliminary experiments and synthesis attempts were done by previous Ph.D. students *Kalpana Palani*³⁶ and *Li Lu*³⁷. Our laboratory has accomplished the synthesis of the THP ring^{38,39}, the amino acid fragment and have discovered a viable synthetic route for the synthesis of the spiroketal unit.

The synthesis of THP ring started from **50** (*S*)-epichlorohydrin which determined the stereochemistry of the final compound (Figure 16.). The reaction of epoxide **54** with the lithium salt of 1-butyne in the presence of boron trifluoride etherate gave the **55** alcohol in excellent yield. Exposure of alcohol to di-*tert*-butyl dicarbonate in the presence of catalytic amounts of DMAP furnished the desired carbonate in good yield. Hydrogenation of the triple bond was

achieved by using P2 nickel, resulting in intermediate **56**. The cyclization reaction was realized using elemental iodine in acetonitrile, which led to the labile **57** iodo carbonate as a mixture of *cis* / *trans* isomers in 4:1 ratio. To obtain the desired **58** *trans* alkene, they employed the highly *syn*-selective iodoso elimination method, instead of the normal base induced procedure which could have led to a mixture of alkenes. Hydrolysis of lactone was effected under basic conditions followed by protection of hydroxyl group with BOM-Cl to result the **59** epoxide. Elongation of **59** intermediate was carried out by ring-opening reaction using **60** chiral sulfone, and then the cleavage of sulfone group gave **61** product. Cross-metathesis of diene with methyl acrylate using the Grubbs-II catalyst furnished the unsaturated ester **62** in fairly good yield (76%). Ultimately, the *oxa*-Michael type ring closure was effected by treatment with *t*BuOK to yield the desired **63** THP scaffold.

Figure 16. Our group's synthesis scheme of THP fragment

2. Results and Discussion

2.1. Scale-up of current THP synthesis

As it was mentioned above, previous Ph.D. students *Kalpana Palani* elaborated a route to THP intermediate **63**. However, the late-stage of synthesis was only executed on milligram scale. Thus, the first phase of my Ph.D. program was dedicated to the scale-up synthesis of epoxide **59**. Starting point was the Boc-protected alkyne **64**. To establish the *cis* geometry, our first attempt was the Lindlar's catalyst (Figure 17).⁴⁰ This reducing agent is a heterogeneous Pd catalyst attenuated by lead carbonate and quinoline. To our disappointment, the reaction did not provide the desired product, only the starting material was isolated. Next, P2-nickel catalyst was utilized. This catalyst was generated *in situ* by the reduction of Ni(OAc)₂ with NaBH₄. Gratifyingly, the catalyst resulted in the desired *cis* product **56** within 2 hours in a high yield (99%).

Figure 17. Hydrogenation of the Boc-protected alkyne

One of our primary aims was to improve the selectivity of iodocyclisation reaction.³⁹ In this step of the synthesis, the lactonization was effected by using elemental iodine,⁴¹ which led to a mixture of diastereomers (Figure 18) *syn* and *anti* products in different ratios depending on the utilized conditions.⁴²

Figure 18. *syn* and *anti* products of iodocyclisation reaction

The mechanism of iodocyclisation involves a chair-like TS (Figure 19).⁴³ The major *syn* product arises from the TS where all the substituents occupy equatorial position. By contrast, in the TS of the minor *anti* product one of the substituents is located in axial position.

Figure 19 TSs of idosocyclization leading to *syn* and *anti* diastereomers

Previously, *Kalpana* also attempted to improve the diastereoselectivity by testing several different conditions.³⁶ The best selectivity was found to be 4:1 in favor of the *syn* product. Our intention was to further enhance the diastereomeric ratio. The first strategy was to find a highly reactive iodonium cation source that allows us to lower the temperature, thereby giving rise to an improved selectivity (Table 1). Our target reactants were iodine monochloride (ICl), iodine monobromide (IBr) and Ag-salt activated elemental iodine.⁴⁴ Based on the preliminary experimentation, the employed solvent appeared to play an important role with regards to the selectivity. Therefore, a few variations of acetonitrile and toluene with different iodine cation source were tested as well.

Table 1. Optimization of iodocyclisation reaction

Entry	I ⁺ source – solvent combination	t	T	Conversion % (based on NMR)	Diastereoselectivity (based on isolated yield)
1	ICl - toluene	ON	-80°C	32	-
2	ICl – toluene	ON	-40°C	38	-
3	ICl - acetonitrile	ON	-40°C	39	-
4	I ₂ – acetonitrile (control)	ON	-10°C	100	1:4
5	IBr - toluene	ON	-75°C	93	1:10
6	I ₂ - DCM	ON	-40°C	18	-
7	IBr - acetonitrile	ON	-40°C	70	-
8	IBr -toluene	ON	-40°C	decomposed	-
9	I ₂ /AgOTf - DCM	ON	-80°C	no reaction	-

ICl was not efficient as the obtained conversions were significantly low irrespective of the solvents and the temperature (entry 1,2,3). Therefore, the diastereomers were not isolated and the diastereomer ratio was not determined. We performed a control reaction with elemental iodine, and the diastereomer ratio obtained by *Kalpana* appeared to be reproducible (entry 4). Use of IBr in toluene at -75 °C led to a highly improved diastereoselectivity (entry 5). Unfortunately, the yield was significantly lower (37 % with respect to *syn* product) than that in the original procedure (67 % with respect to *syn* product). Iodine in DCM did not proceed well even after an extended reaction time (entry 6). IBr in acetonitril improved the conversion, but it was till far from a synthetically useful level (entry 7). Interestingly, the reaction with IBr in toluene at -40 °C completely decomposed (entry 8). To enhance the electrophilicity of iodine, we attempted to activate it by using silver-triflate at low temperature. However, the reaction did not take place under these conditions (entry 9). Despite several attempts, we resorted to return to the original method.

To install the double bond by eliminating the iodide function, we opted for the iodoso elimination method developed by *Reich*.⁴⁵ This type of elimination affords the *cis* product with a high selectivity owing to the reaction mechanism (Figure 20.).

Figure 20. general representation of the *syn* elimination

After having separated the *syn* and *anti* diastereomers, we subjected the *syn* product **57** to iodo elimination (Figure 26.). We conducted the reaction with 3 eqv. of *meta*-chloroperoxybenzoic acid followed by *Kalpana*'s work-up procedure.³⁶

Figure 21. Iodoso elimination of carbonate

Despite washing the mixture with aq. NaHSO₃ solution multiple times, *m*-CPBA-like impurity (based on aromatic peaks in the NMR spectrum) was seen in the crude product. In order to entirely remove this impurity from the final product, we tested different saturated solutions while varying the duration of the washing, such as Na₂SO₃ solution, freshly made Na₂S₂O₃ solution, NaHCO₃ solution and their combinations. Unfortunately, none of them was found to be suitable for the effective removal of the impurity. We concluded that it was not the peroxide per se, it was likely to be resulted from the decomposition of *m*-CPBA. As an alternative tactic to initiate the elimination of iodine, we performed the reaction with hydrogen peroxide-urea in the presence of trifluoroacetic anhydride in Na₂HPO₄ buffer (Figure 22.). No reaction occurred under these conditions, and the starting material was recovered.⁴⁶

Figure 22. An alternative way for iodoelimination

We intended to avoid the column chromatography since the carbonate **58** proved to be unstable on silica gel. Thus, we decided to carry this impurity further with the hope that it could

interconvert to such substances which remains in aqueous phase upon work-up. In the next step, the methanolysis of carbonate **58** with K_2CO_3 provided the desired epoxide **65** which was devoid of the unknown impurity (Figure 23.).

Figure 23. Hydrolysis of the carbonate followed by ring closure

Employing the conditions reported by *Kaplana*,³⁹ the protection of hydroxide group was carried out using BOM-Cl. In contrast to the reported result, we only isolated the product **66** originated from the ring opening of epoxide (Figure 24.).

Figure 24. Protection of hydroxyl group with BOM-Cl

Given the low diastereoselectivity of the iodocyclisation reaction, we had to devise an alternative approach to the synthesis of *Kalpna*'s epoxide.

2.2. New synthetic approach to Kalpana's epoxide

As shown in the retrosynthetic analysis (Figure 25.), our strategy for the construction of *Kalpana's epoxide* was based on a sequential modification of 3-hydroxy ester. The required chiral starting material can be easily prepared from commercial available β -dioxo ester. Reduction of the ester followed by the introduction of allyl moiety could yield the corresponding ketone. Achieving the migration of the double bond, the second stereogenic centre was planned to be installed by diastereoselective reduction of the ketone group. Upon selective deprotection and based-mediated ring cyclization, the target epoxide was expected to be obtained.

Figure 25. Retrosynthetic analysis of *Kalpana's epoxide*

The group of enantiopure β -hydroxy-alkyl esters seemed to be a good starting material in our synthesis plan. There are numerous ways to efficiently synthesize such building blocks in asymmetric manner. The ruthenium-catalyzed enantioselective hydrogenation of β -ketoesters is widely used for this purpose.⁴⁷ The most notable aspect of the method is that the reaction can be carried out under atmospheric hydrogen pressure by utilizing a suitable catalyst system.⁴⁸ After thoroughly reviewing the relevant literature, we found that there was no published procedure for methyl or ethyl 4-chloroacetoacetate under atmospheric pressure. Most of the reported methods employed high pressure.⁴⁹ Hence, we decided to use the existing

protocols at atmospheric pressure, and then determine the resulting enantioselectivity. The catalyst was generated by treatment of bis(2-methylallyl)(COD)ruthenium complex with (*R*)-BINAP in the presence of HBr (Figure 26.)

Figure 26. Preparation of catalyst for asymmetric hydrogenation

The reaction with ethyl 4-chloroacetoacetate **67** was performed in methanol at 65 °C under atmospheric hydrogen pressure using the prepared catalyst complex (Figure 27.). The conversion of the reaction was complete, but the yield was unexpectedly low (8%). Moreover, the methyl ester **69** was isolated as major product instead of ethyl derivative after column chromatography. Presumably, due to the presence of acid residue the transesterification could occur at an elevated temperature.

Figure 27. Asymmetric hydrogenation of ethyl 4-chloroacetoacetate

In the next attempt, we used degassed absolute methanol to improve the yield given the fact that the catalyst is sensitive towards air and trace amount of water. Similarly, the methyl ester was formed in a large quantity and the yield was approximately the same as before. A control ¹H-NMR of starting material revealed that the ethyl 4-chloroacetoacetate **67** decomposed to chloroacetone **70** upon storage, and only 20% of the mixture was the expected compound (Figure 28.).

Figure 28. Decomposition of 4-chloroacetoacetate to chloroacetone

By repeating the reaction with a new bottle of β -ketoester in methanol at 50 °C, we observed the formation of both esters in 50% overall yield. To eliminate the transesterification process, we carried out the reaction in methanol at RT employing prolonged reaction time (72 h). The formation of the methyl ester was not observed, but the conversion was as little as 35%. We changed the solvent to ethanol; however, the reaction did not proceed with full conversion at 50 °C after 20 h. After column chromatography, the ethyl ester **68** was isolated in yield of 35%. The enantioselectivity of methyl ester derivative was determined by chiral HPLC. Surprisingly, all the applied conditions showed a significantly decreased enantioselectivity (<65 *ee*). In conclusion, our experiments with asymmetric hydrogenation have shown that this approach was not feasible for the synthesis of β -hydroxy-esters.

Alternatively, kinetic resolution of racemic epichlorohydrin **71** followed by carbonylation of the enantiomerically enriched epoxide **72** appeared to be an elegant method for the synthesis of β -hydroxy-esters (Figure 29.).⁵⁰ The kinetic resolution relied on *Jacobsen's* procedure, which was scaled up to multigram scale (37 g). To our delight, the enantioselectivity was equally high on small and large scale (<99% *ee*).

Figure 29. Kinetic resolution of racemic epichlorohydrin

It is necessary to mention that only half of the amount of the epoxide can be isolated in an enantioenriched form at best since we started with a 1:1 racemic mixture.⁵¹ The acid-mediated oxidation of (*R,R*)-Jacobsen's catalyst **74** gave the catalytic active form of the catalyst **75**. The hydrokinetic resolution was conducted in the presence of 0.55 equivalent water in absolute THF. The desired epoxide **72** was isolated by means of vacuum distillation and the obtained yield (43%) was identical to that reported by Jacobsen.⁵⁰

To introduce carbomethoxy or ethoxy functional group, we intended to exploit the carbomethoxylation process as a highly regioselective and stereoretentive reaction.⁵² Building upon literature precedent in which atmospheric CO pressure was utilized in the presence of catalytic amounts of dicobalt octacarbonyl to effect the ring opening reaction,⁵³ we treated the enantiomerically enriched epichlorohydrin **72** this way to attain the corresponding β -hydroxy-ester **69** (Figure 30.).

Figure 30. Carbonylation of epichlorohydrin with dicobalt octacarbonyl

The reaction was performed in absolute methanol at RT using CO balloon in the presence of dicobalt octacarbonyl without prior purification. After 1 day, the carbon monoxide balloon was removed and vented in a fume hood cautiously. In contrast to reported yields, the carbonylation reaction occurred in low yield (28 %). It was thought that the highly air-sensitive cobalt catalyst had decomposed upon storage. The color of dicobalt octacarbonyl was supposed to be orange but our catalyst was purple. Thus, we repeated the reaction with a newly ordered bottle of catalyst. Despite the fact that catalyst was found to be more active towards elemental iodine (intense bubbling was observed in DCM) than the previous batch, the reaction brought no success. Our next intention was to purify the catalyst by sublimation. Prior to subjecting the epoxide to carbonylation reaction, we sublimed the carbonyl complex, which led to markedly cleaner substance. Much to our surprise, the reaction with purified catalyst did not afford the desired product in satisfactory yield. Moreover, formation of a side-product was observed. After column chromatography, we managed to identify the structure of side-product by ^1H - and ^{13}C -NMR spectroscopy (Figure 31.). It was found to be the 1,3-dichloro-2-propanol **76** which arose from the ring opening of the epoxide by the attack of the present chloride ion. The highly symmetrical structure of the by-product was manifested in a simple ^1H -NMR spectrum. The d at 3.7 ppm, which corresponds to the two CH_2 groups, could unarguably confirmed this.

Figure 31. ^1H -NMR and ^{13}C -NMR of 1,3-dichloro-2-propanol

Additional evidence for proposed reaction pathway was provided by a publication from 1964, in which the authors observed the same by-product in the course of the carbomethoxylation of epichlorohydrin in the presence of glycidyltrimethylammonium halide cocatalysts.⁵⁷ In their study the reaction in methanol under high CO pressure (1600-9000 psi) at elevated temperature furnished the methyl 4-chloro-3-hydroxybutyrate in low yield (~ 20%). Besides, they isolated 1-chloro-3-methoxy-2-propanol as a minor by-product which was not observed in our experiments.⁵⁸ Recent publications do not report the formation of such side-products neither in reaction conducted under high pressure nor in reaction conducted under atmospheric pressure. In an attempt to improve the yield and to eliminate the side-product, we increased the pressure to 4 bar. Reaction provided the same impurity profile, and the yield did not rise to synthetically useful level either.

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desired β -hydroxy-ester product **68** in excellent yield (97%) (Figure 33.).⁶⁰ The reaction was conducted in ethanol at RT using freshly sublimed catalyst under 7 bar CO pressure.

Figure 33. Optimized reaction conditions for the carbonylation

To prove the importance of purity of dicobalt octacarbonyl catalyst, we performed a control experiment, in which the non-purified catalyst was used in the presence of DMAP. From this experiment, it turned out that purity of catalyst was shown to be a crucial point of efficiency since the non-purified catalyst led to a large decrease in the yield.

After having established the optimal conditions for carbonylation, the protection of hydroxyl group was attempted. We needed to utilize such a protecting group that is orthogonal towards other benzyl ether-type protecting groups at a later stage of the synthesis. For this purpose, 4-methoxybenzyl-2,2,2-trichloroacetimidate **79** was used. PMB-trichloroacetimidate provided an opportunity to protect base sensitive compounds under mild acidic conditions. The protecting group can be cleaved using oxidizing agent, such as ceric ammonium nitrate (CAN) or under strongly acidic conditions.⁶¹ Trichloroacetimidate was prepared from 4-methoxybenzyl alcohol **77** with trichloroacetonitrile **78** under strongly basic conditions in the presence of phase transfer catalyst (Figure 34.).⁶²

Figure 34. Preparation of the precursor of protecting group

We conducted many preliminary optimization reactions to find the most suitable reaction conditions. The most convenient procedure for introducing the PMB-group involved camphorsulfonic acid as catalyst.⁶³ However, the overnight reaction with 10 mol% CSA in DCM afforded the protected ether **80** in low yield (17%) along with larger amount of by-product. It was possible to separate the by-product from the target compound by column chromatography. The by-product was the symmetric oxybis(methylene)bis(methoxybenzene) **81** which was likely to be the result of the presence of water (Figure 35.).

Figure 35. Protection of the hydroxyl group using PMB-trichloroacetimidate

In the hope of having access to the desired compound without observing the formation of the ether by-product, we used activated molecular sieve (3Å) to eliminate the water from the reaction. In this way, the product was obtained in improved but not satisfactory yield (52%). We also tried using 10 mol% PPTS to promote the reaction, but the reaction failed to proceed to more than 40% conversion even after 72 h. To avoid using column chromatography, we attempted to purify the product **80** from trichloroacetamide by extracting it with hexane multiple times. By this protocol, the ester **80** was achieved in yield of 63%. Attempts to use an excess of PMB-trichloroacetimidate with the aim of improving the yield failed to work. As a result of decomposition of excess reagent upon work-up, the product could not be isolated purely. The protected ester was best achieved by using lesser polar solvents, such as ether (68%) and toluene (74%). The reaction was carried out with 1.05 eqv. of PMB-trichloroacetimidate and 10 mol% CSA in toluene stirring overnight at RT, and subsequently, the product was

isolated by extraction with hexane. However, from a practical point of view, the use of acidic Amberlyst would have been more desirable as to the simplicity of its removal. Unfortunately, the reaction conducted with Amberlyst-15 did not go to completion even after 24 hours. Thus, the camphorsulfonic acid remained the catalyst for promoting the reaction.

In parallel with these experiments, we also intended to elaborate the synthesis using ethoxyethyl acetal protecting group (Figure 36). Protection of the hydroxyl group was succeeded by employing 2 eqv. of ethyl vinyl ether **82** in the presence of catalytic amount of ppts in essentially quantitative yield (99%).

Figure 36. Protection of the hydroxyl group as its ethoxyethyl acetal

We envisioned that the allyl moiety could be installed through a Weinreb-amide-like intermediate (Figure 37.). Reaction of ethoxyethyl acetal protected ester **83** and morpholine with isopropylmagnesium chloride did not give the desired amide **84**.⁶⁴

Figure 37. Attempt at the synthesis of morpholine amide

The PMB-protected ester was exposed to *N,O*-dimethylhydroxylamide hydrochloride in the presence of isopropylmagnesium chloride at -40 °C, but only a little amount of product **85** was isolated after column chromatography (Figure 38.). We assumed that the PMB part interfered with magnesium cation at elevated temperature cleaving the ether bound.

Figure 38. Attempt of the synthesis of Weinreb-amide

We decided to rely on the strategy in which we elaborate the introduction of allyl part via sequential modification of ester, namely reduction of carboethoxy group followed by a Barbier reaction with allyl bromide (Figure 39.). The EE-protected ester **83** was readily converted into the corresponding aldehyde **86** in excellent yield (96 %). Reaction of ester **83** with DIBAL-H was conducted in toluene at -78°C to furnish aldehyde **86** which was used in the next step without further purification.⁶⁵ The aldehyde **86** was subjected to Barbier reaction using activated zinc in the mixture of THF and saturated NH_4Cl solution in a 1:4 ratio.⁶⁶ Under this conditions, compound **87** was obtained in high yield (86%) as an inseparable diastereomeric mixture.

Figure 39. The synthesis scheme of EE-protected enone

The subsequent oxidation of compound **87** with IBX was found to be surprisingly capricious.⁶⁷ At the outset, we could not oxidize the alcohol to ketone completely, only 20% yield was obtained. We thought that the low yield was due to the highly acid-sensitive property of EE-protecting group where the acid residue may be originated from IBX. To circumvent the

low tolerance toward acid, we treated the alcohol **87** with IBX in the presence of NaHCO_3 . Surprisingly, the oxidization reaction did proceed at all. We repeated the reaction with DBU instead of inorganic base, but no reaction was observed. Based on the literature precedents, we attempted to oxidize the alcohol by treatment with Dess-Martin reagent using excess of pyridine.⁶⁸ However, no reaction occurred under these conditions. In the meantime, we detected a highly non-polar substance in the starting material. As it turned out, the by-product **90** was derived from the intramolecular cyclization between the ethoxyethyl acetal and the hydroxyl group (Figure 39.). After a couple of weeks, even at 0 °C in the fridge, virtually the whole amount of the material was transformed into the corresponding cyclised product **90**. After repeating the synthesis of alcohol **87**, we immediately attempted to oxidize it to ketone in DMSO overnight. The desired product **88** was formed in moderate yield (58%). Even though the alcohol **87** was freshly prepared and the reaction time was not longer than 12 h, the cyclization side-reaction could not be avoided under such reaction conditions. In the next step, DBU was successfully applied to bring about the double bond migration providing the enone product **89** in good yield (76%).⁶⁹

Alternatively, we went through the synthesis scheme with the PMB-protected ester as well (Figure 40.). Reduction using DIBAL-H proceeded with full conversion in toluene, but the yield was not as good as that of EE-protected ester. Upon evaporation of the toluene, the aldehyde **91** was engaged in decomposition reaction producing black resinous substances. Using diethyl ether as a solvent and evaporating it at RT, a good yield was obtained (86%). The product was isolated as a pale-yellow oil and used in the next step without further purification. Barbier reaction of aldehyde **91** gave the desired product **92** (87%). Oxidation reaction using IBX proceeded cleanly to furnish compound **93** in good yield (89%). Similarly, migration reaction of double bond was effected by DBU to give the enone **94** (87%).

Figure 40. The synthesis scheme of PMB-protected enone

With both differently protected enones in hand, we embarked on the installation of the second chiral centre. We intended to reduce the ketone group using complex metal hydrides by taking advantage of the ability of 1,3-*oxa* systems to engage in chelation control.⁷⁰ A 1,3-*oxa* compound with Lewis acidic metal hydrides can form of a half-chair complex in which the sterically demanding substituent occupies pseudo-equatorial position. The hydride delivery can be realized under favorable axial attack. As shown in Figure 41., under such a stereocontrol the major isomer is the *syn* via chair-like TS, as opposed to minor *anti* product that arises from the energetically higher twist-boat TS.

Figure 41. Stereocontrolled hydride addition (resulting conformation is depicted for the sake of clarity)

We chose the well-known *Lu*-conditions first as a suitable reducing system to give rise to the preferential formation of *syn* product.⁷¹ We proposed that the cerium cation can willingly coordinate to the oxygen atom. Furthermore, in the case of α,β -unsaturated ketones

Luche reaction is known for exhibiting an exclusive preference for 1,2-addition. The replacement of some of the hydride ligands in borohydride with alkoxy groups leads to a harder character, thus allowing for an increased affinity for the carbonyl group. Reaction of both α,β -unsaturated ketones with an excess of CeCl_3 at low temperature proceeded with ease without showing the formation of the 1,4-product (Figure 42.). In the case of PMB-protected derivative **95**, based on the crude ^1H -NMR spectrum, the reaction exhibited low diastereoselectivity as the benzylic range contained more than one set of *d* and *d*.

Figure 42. Attempt at the diastereoselective reduction under *Luche* conditions

Due to a highly complex NMR spectrum of EE-protected compound, it was virtually impossible to tell which diastereomer had been formed as a major product. To address this problem, we subjected the EE-protected enone **96** to hydrolysis with the hope of that the ^1H -NMR spectrum becomes simpler. The crude ^1H -NMR spectrum indicated that both diastereomers **97** formed in an equal quantity.

We also attempted to use LiAlH_4 for the selective reduction.^{73a} Due to the more ionic Al-H bond we thought that it may be more selective towards 1,2-addition than NaBH_4 . By

subjecting the EE-protected compound **89** to such reducing conditions, we could not isolate any product. Consequently, we did not pursue this approach with the EE-protected derivative towards the synthesis of *syn* product.

The reduction with $\text{LiAlH}(\text{O}-t\text{-Bu})_3$ was reported as a suitable method for diastereoselective reduction.⁷² By treatment of the PMB-protected enone **94** with $\text{LiAlH}(\text{O}-t\text{-Bu})_3$ at low temperature, the saturated product **97** was formed and the 1,4-addition was observed exclusively (Figure 43.).

Figure 43. Additional attempts at the diastereoselective reduction and a conclusive region of ^1H -NMR spectrum of the saturated product **97**

Reduction of such enones with zinc borohydride often provides the *syn* product with good diastereoselectivity and in high yield.⁷³ However, our case was found to be an exception since the reaction did not afford the product with appreciable selectivity. The *in situ* generated $\text{Zn}(\text{BH}_4)_2$ could reduce the PMB-protected enone **94** at $-20\text{ }^\circ\text{C}$ in absolute Et_2O . However, reduction did not go to full completion and both isomers **95** were equally formed (Figure 43.).

We attempted the reduction with LiAlH_4 using a large excess of LiI at $-78\text{ }^\circ\text{C}$ in absolute Et_2O .⁷⁴ This reaction was shown to provide the best result as 6:4 isomer mixture isomers in 60% overall yield. After column chromatography, we had the opportunity to determine the structure of the two isomers. However, relying only on the ^1H -NMR spectra, we could not determine which isomer formed as a major product.

Taken together, we decided to move on to chiral oxazaborolidines as a well-studied catalytic system for asymmetric reduction. CBS (*Corey-Bakshi-Shibata*) catalyst was emerged as a broadly applicable catalyst in various hydrogenation reactions, as a result, noteworthy amount of literature precedents is available.⁷⁵ The purpose of the preliminary experiments was to examine which diastereomer can be obtained in our case. We decided to rely on the literature precedents, thus (*S*)-CBS catalyst was chosen which likely leads us to the required configuration of the stereogenic center (Figure 44.). There are two possible ways to establish the resulting configuration of OH-group. One of them involves the separation of the two diastereomers, and subsequent deprotection. After converting them into cyclic acetals, the coupling constants and NOE experiments can reveal which is the *syn* and *anti* isomer. The other attempt to confirm the stereochemistry is that, after separating the isomers we carry both isomers through the synthesis until the epoxide stage. Ultimately, we compare the NMR spectra of the two diastereomers with NMR spectrum of *Kalpana*'s epoxide. We chose the latter way to determine the stereochemistry.

We started the experimentation with catalytic amount of *n*-Bu-(*S*)-CBS using 2 eqv. borane dimethyl sulfide complex (BMS) **98** as a reducing agent.⁷⁶ The reaction was performed in absolute DCM and BMS was added in one portion at $-40\text{ }^\circ\text{C}$, and then stirred overnight. The reaction did not go to completion; thus, we allowed the reaction to warm to RT and it was stirred overnight again. The excess of borane was quenched by addition of mixture of 1 M HCl and MeOH. The crude NMR showed the formation of the saturated by-product **97** (12%). Based on

the integration in the ^1H -NMR spectrum of saturated by-product **97**, only the double bond saturation occurred, the carbonyl group remained intact. Upon column chromatography, we only isolated one diastereomer in low yield (33%). We repeated the reaction with Me-(*S*)-CBS, which was proved to be more active as the reduction was complete at $-20\text{ }^\circ\text{C}$ within 12 hours. However, the selectivity was not satisfactory as both diastereomers appeared on the TLC with equal intensity. Furthermore, based on the crude ^1H -NMR spectrum, the saturated by-product **97** was detectable again (16%). To enhance the reaction rate in the case of *n*-Bu-(*S*)-CBS, we elevated the reaction temperature to $0\text{ }^\circ\text{C}$. Due to the three accessible hydrides in borane dimethylsulfide, we only utilized 0.65 eqv. of BMS for the reduction of ketone. Under these conditions, the reaction went to completion after 4 hours. After work-up, we isolated both diastereomers in a 7:1 ratio in overall yield of 73%, and by-product in 11% yield.

Figure 44. Diastereoselective reduction employing (*S*)-CBS catalyst

We also tried catechol borane (CB) **99** as a frequently used reducing agent in such reactions.⁷⁷ Reduction of the ketone was conducted with 2 eqv. of CB added in one portion at $-40\text{ }^\circ\text{C}$. After 12 hours, the reaction was quenched with a mixture of HCl-MeOH. In the crude ^1H -NMR spectrum, there was no alkene peaks, rather, peaks which refer to the presence of the saturated alkane side-chain. In an effort to avoid the saturation of the double bond, we repeated

the reaction at $-78\text{ }^{\circ}\text{C}$ using the same number of equivalents. However, there was no reaction at this given temperature. We intended to decrease the amount of CB, hence, we repeated the reaction with only 1.05 eqv. of CB in DCM at $-40\text{ }^{\circ}\text{C}$. Although the formation of the desired compound was seen on the TLC upon acidic work-up, we could not isolate the desired alcohol, only a complex mixture was obtained. We speculated that the intermediate of the reduction was not stable under acidic conditions. Presumably, due to the strong propensity of catechol to engage in oxidation reaction in the presence of acid, further oxidation reactions were induced in the crude mixture. Reactions with catechol borane always resulted in a dark greenish crude mixture upon acidic work-up.

Next, we conducted the reaction with a slow addition of the solution of CB in toluene into a solution of ketone in toluene at $-40\text{ }^{\circ}\text{C}$ so as to avoid uncatalyzed reduction. We discovered that decomposition reaction of the product could be avoided if only methanol was used to quench the reaction. Washing with NaHCO_3 solution, and then upon column chromatography we isolated only one product in yield of 61%, presumably the *syn* isomer, and the side-product was not formed in isolable quantity. Two important conclusions stand out from these experiments. The employed work-up procedure found to be critical in achieving the desired product. Moreover, the formation of the by-product can be suppressed by a slow addition of the reducing agent.

With the intention to verify that the *syn* isomer **100** was achieved in the course of CBS reduction, we continued the synthesis with the isolated main product (Figure 45.). Exposure of this compound to BOM-Cl in the presence of *N,N*-diisopropylethylamine furnished the desired product **102** in moderate yield (44%).

Figure 45. Protection of hydroxyl group with BOM-Cl

The selective deprotection reaction of the PMB group with cerium ammonium nitrate was achieved in a mixture of acetone-water at RT. Unfortunately, the pure product **103** was isolated in 40% yield. We suspected that the resultant HNO_3 interfere with the product. To circumvent the possibly acid formation, we added 4 eqv. of pyridine into the reaction. Interestingly, an instant precipitate formation was observed and the deprotection reaction did not take place.

Figure 46. Selective deprotection of hydroxide using CAN and the ring closure in presence of base

The epoxide was achieved in an analogous manner to *Kalpana's* procedure. Treating the alcohol **103** with powdered NaOH in THF yielded the epoxide **59** in excellent yield (98%). To our delight, the ^1H - and ^{13}C -NMR spectra of the epoxide were in full agreement with previously reported spectra.

4. Conclusion

This work has reported a conceptually different approach towards the synthesis of THP ring. The synthesis was found to be scalable using commercially available reagents. We elaborated the synthesis starting from racemic epichlorohydrin followed by kinetic resolution. We succeed in optimizing the reaction conditions of the epoxide carbonylation. The introduction of the allyl proceeded via allylation of aldehyde. Subsequent oxidation and isomerisation resulted in enone system which was subjected to asymmetric reduction. In this step, we have discovered a competitive reaction - the reduction of the double bond. Upon protection and selective deprotection, both of which showed moderate but reproducible yields, the ring closure resulted in the target compound. The synthesis of *Kalpana's* epoxide was accomplished in 11 steps in 5.3% overall yield.

5. Experimental section

Where it was necessary the reaction was carried out under inert atmosphere using nitrogen in oven-dried glassware which was previously cooled down under vacuum. Syringes and needles were dried under vacuum for one hour prior to use. Methanol was distilled from activated magnesium under nitrogen. DCM was distilled from CaH_2 under nitrogen, THF from the mixture of sodium and benzophenone under nitrogen. All chemicals were purchased from Alfa Aesar or Sigma Aldrich. Column chromatography was performed by using silica 230-400 mesh. NMR spectra were recorded in CDCl_3 using JEOL ECA 400 or JEOL ECA 400 SL spectrometers. Chemical shifts are given in ppm and coupling constants in Hz. The following abbreviations are introduced for the multiplicity of the signals: s (singlet), d (doublet), t (triplet), (quartet), m (multiplet). Full data was only collected for the new compounds. High-resolution mass spectrometry (HRMS) measurements were performed on Micromass® Q-ToF Premier™ (ESI-TOF) employing electrospray ionization technique (ESI) in methanol solutions. Reported accurate mass was only identified using the most abundant isotope (for instance: ^{35}Cl).

(*S*)-ethyl 4-chloro-3-hydroxybutanoate (**66**)

The freshly sublimed dicobalt octacarbonyl (2.2 mmol, 0.025 eqv.) was placed in the sealed tube under nitrogen, and then absolute methanol (90 ml), (*S*)-epichlorohydrin (89.1 mmol) and DMAP (2.2 mmol, 0.025 eqv.) were added. The reaction mixture was stirred under a CO atmosphere (7 bar) at room temperature for 24 h. After opening the sealed tube, carbon

monoxide was vented in a fume hood carefully. The reaction mixture was diluted with diethyl ether (~400 mL) and was stirred for 60 min., and then filtered through a pad of silica washed with diethyl ether. The solvent was removed in vacuum to afford the titled compound as pale-yellow oil (97%) which was used in the next step without purification. NMR spectral data matched that previously reported in the literature⁶⁵.

(S)-ethyl 4-chloro-3-((4-methoxybenzyl)oxy)butanoate (**68**)

(1S)-(+)-10-camphorsulfonic (2.2 mmol, 0.1 eqv.) acid was added in one portion to a solution of ester **68** (22.1 mmol) and **79** PMB trichloroacetimidate (23.22 mmol, 1.05 eqv.) in toluene (30 ml), and the reaction was stirred overnight at ambient temperature. The reaction was quenched by adding saturated NaHCO₃ solution. The phases were separated and the aqueous layer was extracted EtOAc (1X). The combined organic phase was dried over anhydrous Na₂SO₄ and filtered through a pad of silica washed with EtOAc. The solvent was removed *in vacuo* to furnish the crude product with residue of PMB-acetamide. The desired compound **68** was isolated by extraction with hexane, and then the companied hexane phases were concentrated to afford the titled compound (74%).

NMR spectral data matched that previously reported in the literature⁶⁵.

(S)-4-chloro-3-((4-methoxybenzyl)oxy)butanal (**91**)

To a solution of ester **68** (16.5 mmol) in absolute diethyl ether (150 ml) was added DIBAL-H (17.3 mmol, 1.05 eqv.) at - 78 °C over 30 minutes, and the reaction was stirred for 30 min at this temperature. The reaction was quenched by the addition of EtOAc (200 µl) and saturated aqueous solution of Rochelle's salt was added and the mixture was stirred for 90 min at RT. The aqueous phase was separated and extracted with EtOAc (2X). The combined organic phase was washed with water (1X) and brine (1X), dried over anhydrous Na₂SO₄ and then filtered through a pad of silica washed with EtOAc. The solvent was carefully removed *in vacuo* and the product **91** was used directly in the next step without further purification. NMR spectral data matched that previously reported in the literature⁶⁵.

(6*S*)-7-chloro-6-((4-methoxybenzyl)oxy)hept-1-en-4-ol (**92**)

To a solution of aldehyde **91** (15.27 mmol) in mixture of saturated aqueous NH₄Cl (12 ml) and THF (3 ml) allyl bromide (30.5 mmol, 2 eqv.) and the activated zinc (30.5 mmol, 2 eqv.) was portionwise added to the reaction mixture at 0 °C. After being stirred at this temperature, the reaction was allowed to warm to RT and stirred for 1 h. The mixture was then filtered through a pad of Celite washed with EtOAc, and the phases were separated. The aqueous phase was washed with EtOAc (2X), and the combined organic phase was washed with water and brine, then dried over anhydrous Na₂SO₄. The crude mixture was filtered through a pad of silica washed with EtOAc, and the solvent was removed *in vacuo* to provide the product **92** (87 %) as a mixture of the two diastereomers.

¹H NMR (400 MHz, CDCl₃): 7.30-7.20 (m, 2H), 6.88 (dd, *J* = 8.3, 1.6 Hz, 2H), 5.86-5.75 (m, 1H), 5.14-5.08 (m, 2H), 4.66 (dd, *J* = 11.1, 6.9 Hz, 1H), 4.48 (dd, *J* = 13.1, 11.1 Hz, 1H), 3.80-3.96 (m, 5H), 3.80 (s, 3H), 3.66-3.58 (m, 2H), 2.96 (br d, *J* = 1.7 Hz, 1H), 2.28-2.15 (m, 2H), 2.04 (d, *J* = 4.0 Hz, 2H), 1.87-1.64 (m, 2H), 1.58 (s, 1H)

¹³C NMR (100 MHz, CDCl₃): 159.6, 159.6, 134.6, 130.0, 129.8, 129.8, 129.4, 118.3, 118.0, 114.1, 114.0, 100.0, 76.8, 75.7, 72.1, 71.5, 69.8, 67.1, 55.4, 46.0, 45.5, 42.4, 42.1, 39.2, 38.8. (In principal, 30 carbon peaks should be seen as two diastereomers were formed. Due to the great extent of their structural similarity, not all carbon signals are distinguishable in practice. The reported ¹³C NMR data only contains 25 carbon peaks. In addition, some carbon peaks may be obscured beneath the peak of CDCl₃ solvent.)

IR (cm⁻¹): 1643, 1514, 1456, 1302, 1247, 1175, 1080, 1034, 918, 822, 750, 494

HRMS: Calculated for C₁₅H₂₂ClO₃ (M+H)⁺: 285.1258, Found: 285.1256

[α]_D²¹: -57.6 (*c* = 0.35, CHCl₃)

(*S*)-7-chloro-6-((4-methoxybenzyl)oxy)hept-1-en-4-one (**93**)

To a solution of **92** (7.5 mmol) in DMSO (16 ml) was added IBX (11.3 mmol 1.5 eqv.) in one portion and the reaction mixture was stirred overnight at RT. The crude reaction mixture was filtered through a pad of Celite and washed with EtOAc. The mixture was then diluted with EtOAc (80 ml) and water (160 ml). The phases were separated and the aqueous layer was extracted with EtOAc (2X). The combined organic layers were washed with water (1X) and brine (1X), then dried over anhydrous Na₂SO₄. The mixture was filtered through a pad of silica

gel, then concentrated to furnish the titled compound **93** (89%). The isolated product was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃): 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.90 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.19 (m, 1H), 5.12 (m, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.16 (m, 1H), 3.80 (s, 3H), 3.59 (d, *J* = 4.9 Hz, 2H), 3.19 (d, *J* = 6.9 Hz, 2H), 2.87-2.73 (m, 2H)

¹³C NMR (100 MHz, CDCl₃): 206.4, 159.6, 130.2, 130.0, 129.7, 119.4, 114.0, 74.3, 72.24, 55.4, 48.8, 45.7, 45.2 (one carbon peak may be obscured beneath the peak of CDCl₃ solvent)

IR (cm⁻¹): 1714, 1614, 1514, 1302, 1250, 1175, 1078, 1034, 924, 824, 748

HRMS: Calculated for C₁₅H₂₀ClO₃ (M+H)⁺: 283.1101, Found: 283.1105

[α]_D²¹: -37.2 (*c* = 0.40, CHCl₃)

(*S*, *E*)-7-chloro-6-((4-methoxybenzyl)oxy)hept-2-en-4-one (**94**)

DBU (0.34 mmol, 0.1 eqv.) was added to a solution of **93** (3.4 mmol) in DCM (24 ml) and the reaction was stirred at RT overnight. The reaction mixture was then filtered through a pad of silica washed with DCM, the solvent was evaporated. The crude product was purified by silica gel flash chromatography (hexane:ethyl acetate = 95:5) to give the desired compound (**94**) (89%).

¹H NMR (400 MHz, CDCl₃): 7.24 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.86 (dq, *J* = 15.8, 6.8 Hz, 1H), 6.12 (dq, *J* = 15.8, 1.6 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.25-4.13 (m, 1H), 3.78 (s, 3H), 3.63 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.59 (dd, *J* = 11.5,

4.5 Hz, 1H), 2.92 (dd, $J = 16.7, 6.9$ Hz, 1H), 2.85 (dd, $J = 16.7, 5.4$ Hz, 1H), 1.89 (dd, $J = 6.8, 1.6$ Hz, 3H)

^{13}C NMR (100 MHz, CDCl_3): 197.7, 159.5, 143.9, 132.4, 130.0, 129.7, 113.9, 74.5, 72.1, 55.4, 46.1, 42.6, 18.4. (one carbon peak may be obscured beneath the peak of CDCl_3 solvent)

IR (cm^{-1}): 1715, 1667, 1634, 1614, 1514, 1443, 1373, 1301, 1248, 1175, 1085, 1034, 972, 824, 750, 740, 569

HRMS: Calculated for $\text{C}_{15}\text{H}_{20}\text{ClO}_3$ ($\text{M}+\text{H}$) $^+$: 283.1101, Found: 283.1100

$[\alpha]_{\text{D}}^{21}$: -17.6 ($c = 0.5$, CHCl_3)

General procedure for CBS-reduction

A solution of catecholborane (0.37 mmol, 1.05 eqv.) in toluene (2 ml) was added dropwise to a solution of enone **94** (0.36 mmol) and (*S*)-(-)-2-butyl-CBS-oxazaborolidine (0.71 mmol, 0.2 eqv.) in toluene (5 ml) at $-40\text{ }^\circ\text{C}$ over 1 hour using syringe pump. The reaction was stirred at $-40\text{ }^\circ\text{C}$ for additional 3 hours. The reaction was quenched by addition of MeOH (50 μl) and stirred for 30 minutes. The reaction mixture was washed with saturated NaHCO_3 solution (2X), then the organic phase was filtered through a thin pad of silica gel and concentrated. The residue was purified by silica gel flash chromatography (hexane:ethyl acetate = 80:20) to give *syn* (61%) isomer as a colourless oil.

***syn*-diastereomer: (4*R*,6*S*,*E*)-7-chloro-6-((4-methoxybenzyl)oxy)hept-2-en-4-ol (**100**):**

^1H NMR (400 MHz, CDCl_3): 7.27 (d, $J = 8.7$ Hz, 1H), 6.88 (d, $J = 8.7$ Hz, 1H), 5.63 (dq, $J = 15.2, 6.4, 0.9$ Hz, 1H), 5.45 (ddq, $J = 15.2, 7.0, 1.5$ Hz, 1H), 4.64 (d, $J = 11.1$ Hz, 1H), 4.46 (d,

$J = 11.1$ Hz, 1H), 4.22 (dd, $J = 12.6, 7.0$ Hz, 1H), 3.75-3.87 (m, 1H), 3.80 (s, 1H), 3.63 (dd, $J = 10.6, 3.5$ Hz, 1H), 3.59 (dd, $J = 10.6, 4.6$ Hz, 1H), 2.59 (br s, 1H), 1.87 (dd, $J = 14.2, 7.9$ Hz, 1H), 1.81 (dd, $J = 9.4, 5.0$ Hz, 1H), 1.67 (ddd, $J = 6.4, 1.5, 0.6$ Hz, 3H)

^{13}C NMR (100 MHz, CDCl_3): 159.6, 133.5, 129.8, 129.6, 127.1, 114.1, 71.5, 71.2, 55.4, 45.7, 40.0, 17.7. (one carbon peak may be obscured beneath the peak of CDCl_3 solvent)

IR (cm^{-1}): 1717, 1614, 1586, 1514, 1456, 1301, 1248, 1082, 968, 822, 750, 704

HRMS: Calculated for $\text{C}_{15}\text{H}_{22}\text{ClO}_3$ ($\text{M}+\text{H}$) $^+$: 285.1258, Found: 285.1251

$[\alpha]_{\text{D}}^{21}$: -41.7 ($c = 0.23$, CHCl_3)

anti-diastereomer: (4*S*,6*S*,*E*)-7-chloro-6-((4-methoxybenzyl)oxy)hept-2-en-4-ol (**101**):

^1H NMR (400 MHz, CDCl_3): 7.29 (d, $J = 8.5$ Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 1H), 5.63-5.71 (m, 1H), 5.45-5.51 (m, 1H), 4.64 (d, $J = 11.1$ Hz, 1H), 4.50 (d, $J = 11.1$ Hz, 1H), 4.25-4.30 (m, 1H), 3.91 (m, 1H), 3.88-3.93 (m, 1H), 3.59 (d, $J = 5.2$ Hz, 1H), 2.11 (br s, 1H), 1.82 (ddd, $J = 14.4, 8.5, 3.4$ Hz, 1H), 1.74 (ddd, $J = 14.5, 8.9, 3.6$ Hz, 1H), 1.68 (d, $J = 6.5$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): 159.5, 133.8, 123.0, 129.8, 126.4, 114.0, 75.7, 72.0, 69.3, 55.4, 46.1, 39.8, 17.7 (one carbon peak may be obscured beneath the peak of CDCl_3 solvent)

IR (cm^{-1}): 1614, 1514, 1456, 1301, 1246, 1172, 1080, 1034, 966, 822, 748, 698, 569, 511

HRMS: Calculated for $\text{C}_{15}\text{H}_{22}\text{ClO}_3$ ($\text{M}+\text{H}$) $^+$: 285.1258, Found: 285.1254

$[\alpha]_{\text{D}}^{21}$: -50.6 ($c = 0.3$, CHCl_3)

1-((((2*S*,4*R*,*E*)-4-((benzyloxy)methoxy)-1-chlorohept-5-en-2-yl)oxy)methyl)-4-methoxybenzene (**102**)

DIPEA (0.70 mmol, 1.5 eqv.) and 60% technical BOM-Cl (0.70 mmol, 189 μ l, 1.5 eqv.) were added sequentially to a solution of alcohol **100** (0.47 mmol) in DCM (4 ml) at -40 °C. The mixture was allowed to warm to RT and then stirred overnight. The reaction was quenched with saturated NH_4Cl solution and extracted with DCM. The combined organic phases were washed with water and brine, then dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel flash chromatography hexane:ethyl acetate = 95:5) to give the product **102** (44%) as a colourless oil.

^1H NMR (400 MHz, CDCl_3): 7.36-7.25 (m, 8H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.58 (dq, $J = 15.3$, 6.5 Hz, 1H), 5.25 (ddq, $J = 15.3$, 8.5, 1.4 Hz, 1H), 4.78 (d, $J = 6.7$ Hz, 1H), 4.66 (d, $J = 6.7$ Hz, 1H), 4.63 (d, $J = 11.1$ Hz, 1H), 4.57 (d, $J = 11.1$ Hz, 1H), 4.48 (d, $J = 11.5$ Hz, 1H), 4.44 (d, $J = 11.5$ Hz, 1H), 4.20 (dd, $J = 14.9$, 7.3 Hz, 1H), 3.79 (s, 1H), 3.70 (dq, $J = 7.4$, 4.9 Hz, 1H), 3.63 (dd, $J = 9.8$, 3.1 Hz, 1H), 3.60 (dd, $J = 9.8$, 3.3 Hz, 1H), 1.96-2.03 (m, 1H), 1.81 (ddd, $J = 14.0$, 7.4, 5.1 Hz, 1H), 1.69 (dd, $J = 6.5$, 1.5 Hz, 3H)

^{13}C NMR (100 MHz, CDCl_3): 159.4, 138.0, 130.6, 130.5, 130.3, 129.6, 128.5, 128.0, 127.7, 113.9, 100.0, 91.4, 75.3, 74.0, 71.3, 69.6, 55.4, 46.3, 38.6, 17.8. (one carbon peak may be obscured beneath the peak of CDCl_3 solvent)

IR (cm^{-1}): 1614, 1514, 1379, 1302, 1248, 1173, 1096, 1026, 970, 822, 741, 689

HRMS: Calculated for $\text{C}_{23}\text{H}_{29}\text{ClO}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 427.1652, Found: 427.1664

$[\alpha]_{\text{D}}^{21}$: -49.4 ($c = 0.1$, CHCl_3)

(2*S*,4*R*,*E*)-4-((benzyloxy)methoxy)-1-chlorohept-5-en-2-ol (**103**)

To solution of protected alcohol **102** in acetone (2 ml) and water (8 dropps) was added CAN in one portion at 0 °C. The reaction was stirred for 75 minutes at RT. The mixture was filtered through a thin pad of silica, and dried over anhydrous Na₂SO₄, then evaporated. The crude mixture was purified by silica gel flash chromatography (hexane:ethyl acetate = 90:10) to give the **103** product (40%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃): 7.27-7.35 (m, 4H), 5.72 (dq, *J* = 15.3, 6.5 Hz, 1H), 5.29 (ddq, *J* = 15.3, 8.5, 1.5 Hz, 1H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.30 (td, *J* = 8.5, 5.4 Hz, 1H), 3.95-4.01 (m, 1H), 3.56 (dd, *J* = 9.1, 2.9 Hz, 1H), 3.52 (dd, *J* = 9.1, 3.7 Hz, 1H), 3.24 (d, *J* = 2.9 Hz, 1H), 1.87-1.74 (m, 2H), 1.71 (dd, *J* = 6.5, 1.5 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃): 137.7, 130.9, 123.0, 128.6, 128.0, 127.9, 91.2, 76.2, 70.4, 69.9, 49.5, 39.9, 17.8 (one carbon peak may be obscured beneath the peak of CDCl₃ solvent)

IR (cm⁻¹): 1647, 1456, 1404, 1022, 704

HRMS: Calculated for C₁₅H₂₁ClO₃Na (M+Na)⁺: 307.1077, Found: 307.1083

[α]_D²¹: 90.8 (*c* = 0.1, CHCl₃)

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7. NMR Spectra

Chapter 2 A COMBINED EXPERIMENTAL AND DFT STUDY OF *OXA*-MICHAEL CYCLISATION IN THP SYNTHESIS

1. Introduction

Our research group has had a longstanding interest in the synthesis of tetrahydropyran-containing natural products. *Diospongin A*¹, *Curvulone B*², *Cyanolide A*³, *Clavosolide*⁴ and the tetrahydropyran ring of *Bistramide D*^{5,6} have succumbed to synthesis with the aid of *oxa*-Michael reaction in our research group. The base- and acid-catalyzed intramolecular *oxa*-Michael cyclisation proved to be a widely applicable method for the stereoselective construction of the tetrahydropyran moiety with various substitution patterns. This approach continues to be amongst the most realizable reaction in the area of total synthesis of tetrahydropyran-containing natural products, which has been proven in a large number of publications.^{7,8,9,10,11} In the case of the base-catalysed cyclisation, the reaction begins with the deprotonation of the alcohol, thereby enabling the cyclisation to take place by the attack of the generated alkoxide (Figure 47). As for the acid-catalysed cyclisation, the first step is the protonation of the carbonyl group, thus enhancing the electrophilicity of the β -carbon. Due to the increased reactivity, the hydroxyl group can attack the Michael-acceptor to form the tetrahydropyran ring.

Figure 47 A simple representation of the base- and acid-catalysed *oxa*-Michael cyclisation. The outcome of the reaction can be both *cis* and *trans* tetrahydropyran.

The intramolecular cyclisation can afford either the *trans* or the *cis* diastereomer. However, even if it is the simplest *oxa*-Michael cyclization, the stereoselectivity-governing factors still remain dubious and elusive. An important question concerns the stereochemical outcome. If the nucleophile is a secondary alcohol, then either the 2,6-*cis* or the 2,6-*trans* isomer may be formed. The 2,6-*cis* isomer, with diequatorial substituents will, of course, be the thermodynamically favoured product. When the activating group is a ketone, then this isomer is always formed under acid catalysis. In complete contrast, when the electron withdrawing group is an ester and basic catalysis is applied, then the major product is likely to be the 2,6-*trans* isomer. It is important to ask why the formation of the 2,6-*trans* isomer should be kinetically favoured. To our knowledge, no thorough experimental or computational studies to probe the stereochemical outcome of this reaction have been reported. With the intent to address this ambiguity, we dedicated a fraction of my PhD research to a detailed investigation of the base- and acid-catalysed *oxa*-Michael cyclisation. The pursuit of our investigation was further reinforced by the general selectivity patterns found amongst the literature examples after reviewing over 100 publications. The characteristic features of these recognised patterns are described in detail in the following section. It needs mentioning that we only focus on the examples that are devoid of poly-condensed ring systems and, in which the geometry of the double in the Michael-acceptor is (*E*).

1.1. Literature review of base- and acid-catalysed *oxa*-Michael cyclisation and its analysis

This section will review all types of bases used to promote the cyclisation and the very interesting selectivity patterns which proved generalizable to a high degree. Before we embark on a detailed analysis of the literature review, I would like to introduce four arbitrary-categories which formed the basis of the forthcoming literature review (Figure 48). After an exhaustive review of the precedents, we came to realise that the following classification aids us to recognise certain trends in selectivity as well as to systematize the reactions. The way we arranged the conditions applied is as follows: 1.) Various bases with unprotected-OH 2.) TBAF with silylprotected-OH 3.) Acids with unprotected-OH 4.) Acids with silylprotected-OH. The reasoning behind such a categorization will be discussed throughout the review.

Figure 48 The four arbitrary-categories based on the catalyst and the state of the hydroxyl group.

1.1.1. Various bases with unprotected-OH

The category involves the cases in which the cyclisation occurs by deprotonating the hydroxyl group *in situ*. In general, the base triggering the cyclisation can be either strong inorganic base (*t*BuOK, NaH, F⁻(relatively strong)) or mild organic base (DBU). The examples of the first category are shown in Figure 49.

There are several examples for 2,6-*trans* selectivity at -78°C, even if the molecule is highly substituted. All these reactions were effected by using strong bases (*t*BuOK, NaH) and quenched at -78°C so as to avoid any isomerisation reaction. On the basis of this observation, it seems reasonable to assume that the ‘2,6-*trans* phenomenon’ is resistant to substitution pattern on the carbon chain. Secondly, there is a temperature range (-35 – RT), within which the isomerisation reaction resulting in the formation of the more stable 2,6-*cis* isomer is likely to occur. This is also rather astonishing given the fact that the tendency to adopt 2,6-*cis* arrangement at a relatively elevated temperature is exclusive regardless of other substituents. An obvious question arises from this tendency. Why do we witness a ‘2,6-dominance’ over other positions? By virtue of the logic of a synthesis in which *oxa*-Michael cyclisation applied, the substituents in position 6 (not the Michael-acceptor) tend to be larger than the others. Consequently, this is the substituent that locks the conformation in such a way that it must adopt an equatorial position in either the reactive conformer or in the final product. Hence, this substituent acts as a reference point. It is our view that this therefore serves a right to use the notion of 2,6-*trans* or -*cis* selectivity pertaining to cyclisation of multisubstituted precursors, while not mentioning the relative position of the other substituents. Although we are delighted with the widespread 2,6-tendency and intrigued to examine the root-cause of this phenomenon, we also believe such a generalization must be done with care and attention. We selected out the purely 2,6-disubstituted examples in Figure 50, Figure 51, Figure 52 and the multisubstituted precursors are shown as well.

There are there examples in which the reaction time of the cyclisation was only 5-10 mins, and the major isomer turned out to be the *trans*. We believe, in this case it is likely that the diastereomer ratio is governed by the $\Delta\Delta G^\ddagger$ of the transition states at the very beginning of the reaction, but the thermodynamically induced isomerization becomes dominant over time at this given temperature. Thus, the initial isomer ratio is evidently dependent on the reaction time.

The reactions with TBAF and DBU afforded the 2,6-*cis* isomer at reflux in all cases, which can be attributable to either kinetic or thermodynamic control. To our knowledge, no investigation has been done to identify the nature of the present control in these reactions. We believe this question must be addressed in our investigation (section 2.1.2).

It stands out from the review that hexamethyldisilazane-type (HMDS) bases did not give consistent results in terms of selectivity. This puzzling reactivity will also be discussed (section 2.1.1.).

On the basis of ‘The exception proves the rule’, it is worth mentioning that there a few exceptions (highlighted in bright blue). These exceptions are the synthesis of *Bistramide A* by *O. Piva*⁵⁵ and C10-C17 segment of *Pederin* by *M. R.Hoffmann*⁵⁸ and *Madeirolide A* by *I. Paterson*⁵³. The cyclisation reactions were effected at -78 °C and allowed to warm to RT furnishing 2,6-*trans* tetrahydropyran as a major isomer. The *trans* selectivity obtained by gradually increasing the temperature stands in contrast to the experimentally observed thermodynamic isomerisation in other cases.

Despite the reaction conditions indicated in the article, it appeared necessary to inspect the supporting information. In cases such *Rapamycin* by *P. Arya*,²¹ *Herboxidiene* by *T. R. Webb*,³³ *C2–C16 fragment of phorboxazole A* by *J.S. Yadav*,⁴⁶ the exact reaction conditions differed from that in the article. Namely, the reaction was conducted at -78 °C, but it was quenched by adding water then allowed to warm to RT. However, the resultant hydroxide is likely to induce isomerisation reaction at RT as similar cases have shown.

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purely 2,6-disubstituted

2,6-disubstituted tetrahydropyrans
M. G. Banwell(1996)
tBuOK
trans

SCH 351448
K. D. Brabander(2002)
tBuOK
trans

THP of Bistramide D analogue
R. W. Bates(2008)
NaH
trans

polysubstituted

Macrolactin
P. R. Krishna(2014)
tBuOK
trans

Bistramide A
P. G. Goekjian(2012)
tBuOK
trans

Aspergillides A and B
H. Fuwa(2010)
tBuOK
trans

THP of 2,6-substituted THPs
O. Piva(2010)
tBuOK
trans

THP of Bistramide D
G. Sabitha(2011)
tBuOK
trans

Cryptopyranmoscatone A3,
Cryptopyranmoscatone B4
G. Sabitha(2018)
tBuOK
trans

THP of Bistramide D
R. W. Bates(2014)
tBuOK
trans

Stereodivergent Synthesis of
Highly Substituted THPs
C. Schneider (2000)
tBuOK
trans

Figure 50 Substrates that follow the *trans* selectivity rule at -78 °C.

Figure 51 Substrates that follow the *cis* selectivity rule above 0°C.

Figure 52 Continuation of substrates that follow the *cis* selectivity rule above 0°C.

1.1.2. F^- with silylprotected-OH

This category consists of the cyclisation reactions which are not directly effected by deprotonation with the basic fluoride anion. The fluoride anion cleaves the silicon-oxygen bond generating the nucleophilic alkoxide anion. As can be seen in Figure 53, there is no clear tendency as to the preferred stereochemistry in the reactions performed at RT. It needs to be mentioned that the case of C1-C23 subunit of *Spirastrellolide B* by *A. J. Phillips*⁸³ and *Centrolobine* by *S. Chandrasekhar*⁷⁴ might be acid-catalysed reactions since the immediate protonation of the resultant alkoxide and the carbonyl group can take place in the presence of the hydrogen-fluoride. The latter would initiate an acid-catalysed reaction. In order to find substitution-selectivity patterns, we look for purely 2,6-disubstituted cases. We only found two examples which provided purely 2,6-disubstituted tetrahydropyrans (Figure 54). The precursor of *Centrolobine* resulted in *cis* stereochemistry at 60°C in the presence of HFpy but as mentioned it might fall into the acid-catalysed category.⁷⁴ The other example leading to purely 2,6-disubstituted THP is the precursor in the synthesis of *Curvulone B* by *S. Takahashi*.⁷¹ The reaction with TBAF at RT furnish the *trans* tetrahydropyran as a major isomer. Unfortunately, due to the few available examples, selectivity trends, if any, cannot be noticed.

Figure 53 Summary of *oxa*-Michael cyclisation with silylprotected-OH precursors with F- (from (*E*)- α,β -unsaturated substrate, not fused bicyclic ring system)

Figure 54 Precursors with silylprotected-OH of purely 2,6 disubstituted THPs

1.1.3 Acids with unprotected-OH

This group involves the reactions which were brought about by using acid, and the precursors were unprotected alcohols. In sharp contrast to the previous examples, an exclusive 2,6-*cis* selectivity can be observed. As inspection of Figure 55 reveals, the superiority of *cis* selectivity is irrespective of the substituent pattern, the applied acid and the temperature. A thorough experimental study was done by *Fuwa et al.*, in which a comparative study of various α,β -unsaturated ester surrogates was presented accompanied with a broad substrate scope.¹² It was shown that not only thio-groups but also heterocycles with slight electron-withdrawing property, such as 2-oxazolidinone imide, 2,5-dimethylpyrrole amide, can be suitable carbonyl-activating functional group in the cyclisation.

Figure 55 Summary of acid-catalysed *oxa*-Michael cyclisation with unprotected-OH precursors (from (*E*)- α,β -unsaturated substrate, not fused bicyclic ring system)

1.1.4 Acids with protected-OH

The fourth category showcases the reactions between the precursors with protected-OH and various acids (Figure 56). In the course of these reactions, free OH-group is formed *in situ* by deprotection. In principle, the acid protonates the oxygen, thereby enabling the cleavage of Si-O bond with the present methanol in a catalytic manner. For the HF-catalysed reactions, the cleavage is done by the fluoride anion to liberate the oxygen atom followed by its protonation. The second role of the acid is activation of the carbonyl group to initiate the cyclisation. Similar to the latter group of reactions, the *cis* selectivity is exclusive. No example for 2,6-*trans* selectivity was found.

Figure 56 Summary of acid-catalysed oxa-Michael cyclisation with protected-OH precursors (from (*E*)- α,β -unsaturated substrate, not fused bicyclic ring system)

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1.2 Computational studies of oxa-Michael cyclisation and current explanations for selectivity

This section is dedicated to summarizing all the computational studies that have been carried out in the field of *oxa*-Michael cyclisation. This summary contains our critical comments as well. The first study dates back to 1997 and the most recent one was published in 2017 (Figure 57). Yet, there has been no systematic study of a simple model system that is aimed to investigate what sort of factors and what extent they contribute to stereo-determining process.

Figure 57 The level of theory and the utmost revelation of the different computational studies on *oxa*-Michael cyclisation.

Martín et al. attempted to provide an explanation for the *trans* selectivity observed in the base-catalysed cyclisation of 4-chloro-(*E*)-esters.¹³ The *trans* selectivity was accounted for by chelation control. In the chelation, the metal cation is located between the ester and the pendant alkoxide group. Based on their calculation, TS-*trans*, which adopts *s-cis* geometry with respect to the enone moiety, is energetically more favourable than TS-*cis* having *s-trans* geometry (Figure 58). In addition, the authors mentioned that the TSs were reached very early considering the long bond-forming distance.

Figure 58 Simplified explanation of stereoselectivity in the oxa-Michael cyclisation studied by *Martín et al.*

From the theoretical point of view, the HF/6-31G* level of theory does not take into account electron correlation. The error arising due to the lack of correlation should therefore be taken into consideration when it comes to drawing a conclusion based on the energies. Further, their computational approach was based on an exaggerated statement, namely, “*it is well known that alkali metal salts of carbanions exist predominantly as ion pairs ... and the associated cation may also play a crucial role in the stereoselectivity*”.¹³ However, no control experiment, such as the usage of a suitable crown-ether for the sequestration of the cation, was done to confirm the importance of the cation in the selectivity-determining process. We believe this approach is somewhat reprehensible owing to its simplification. This paper has been cited more than forty-five times at present and the explanation provided for *trans* selectivity has been widely accepted and used.

Shortly after, *Yonemitsu et al.* performed PM3 semiempirical calculations¹⁴ in order to better understand the observed selectivity of the intramolecular cyclisation, which was applied in the synthesis of Halichondrin B natural product (Figure 59). They found the Bürgi-Dünitz angle to be a reasonable explanation for the observed *trans* selectivity.¹⁵ The attack of the nucleophile was closer to tetrahedral angle in TS-*trans*, forming the third ring through a boat-like transition state. The earliness of the TSs was stated as well.

Figure 59 TSs leading to fused ring system by Yonemitsu *et al.* at PM3 semiempirical level.

Schneider *et al.* reported a stereodivergent synthesis of highly substituted tetrahydropyrams, which involved a *t*BuOK-catalysed *oxa*-Michael cyclisation at low temperature. The understanding of the selectivity in the cyclisation was attempted through theoretical calculations by PM3 semiempirical method (Figure 60).¹⁶ To simplify the calculation, the K^+ cation was excluded from their model. It was shown that enone moiety preferentially adopts *s-cis* over the *s-trans* conformation, which would suffer a severe allylic-strain (5-6 kcal/mol). This does not conform to the explanation of selectivity provided by Martín *et al.*, in which the *s-trans* conformation of the *cis*-TS accounted for its higher energy and for the global *trans*-THP preference.¹³ The more tetrahedral Bürgi-Dünitz trajectory, which equals to a better overlapping effect, was appeared to be the selectivity-determining factor again. Their TSs were also reactant-like based on the distance between the alkoxide and the β -carbon, but this detail was not highlighted in their discussion.

Figure 60 Bare anion TSs by *Schneider et al.* at PM3 semiempirical level.

The following reaction investigated by *Ohkata et al.* is somewhat different from the previous examples. The alkylation of the thiol group of (*E*)- α,β -unsaturated substrate with MeI in the presence of AgBF followed by desilylation with TBAF furnished 2,5-disubstituted tetrahydropyrans. The results of their AM1 calculations showed that the product ratio is governed by 1,3-diaxial-like repulsion in a chair-like transition state which is only present in the TS-*cis* (Figure 61).¹⁷ However, no discussion of the structural information of the TSs was reported.

Figure 61 Model TSs leading to 2,5-disubstituted THPs by *Ohkata et al.* from AM1 calculations

Rein et al. provided mechanistic insights into the hetero-Michael cyclizations which was employed to build the tetrahydropyran ring of *Pyranicin* and *Pyragonicin* natural products.¹⁸ They postulated that the reactive conformers of precursors correlated with diastereomeric

transition states in energy (Figure 62). Thus, only the conformational space of the anionic reactant was examined with a constrained alkoxide- β -carbon distance (1.5 Å) by molecular mechanics calculations, employing the MMFF force field. It was found that in only one conformer is the allylic strain between the Michael-acceptor and the γ -substituent minimized when the alkoxide nucleophile is to attack the double bond. This conformer leads to the 2,6-*trans* product.

Figure 62 Reactive conformers from molecular mechanics calculations by *Rein et al.*

Clarke et al. described a stereodivergent *oxa*-Michael cyclisation that could lead to the diastereoselective synthesis of either the *cis*- or the *trans*-tetrahydropyran depending on the activation mode (Figure 63).¹⁹ This study has been the most up-to-date work until now which utilizes state-of-the-art computational methods to elucidate the selectivity. The authors consider two possible factors to explain the *trans* selectivity of the TBAF-mediated cyclisation. The lowest-energy TSs are presumed to adopt a boat-like TS that invokes a hydrogen bond between the alkoxide and the δ -OH. The energy difference is partly attributable to a semi-eclipsed interaction (37°) between the β - and γ -hydrogen atoms, whilst this interaction is absent in the *trans* TS. Another contributing factor is the increased steric repulsion arising from a pseudo-1,3-diaxial interaction between the hydrogen atoms in the 2,6-*cis* TS. The distance between the

two hydrogen atoms is 2 Å, which is shorter than their Van der Waals radius together (2.4 Å). The examination of the TFA-catalysed cyclisation revealed that the reaction proceeds preferentially through a chair-like transition state. The origin of the *cis* preference appeared to be more tangible as compared to that in TBAF-mediated cyclisation. The *cis* selectivity is mainly ascribed to the lack of 1,3-diaxial repulsion in the *cis*-TS. Unfortunately, the forming-bond distance was not indicated in the article.

Figure 63 TSs of the TBAF- and TFA-mediated cyclisation at B3LYP/6-31G*+ level of theory by Clarke *et al.*

As the previous examples have shown that there has been no systematic study on a simple *oxa*-Michael reaction but only specific examples. Due to the complexity of the studied model in conjunction with the approximations, it is greatly challenging to pinpoint the subtle differences in each case; all the above-discussed models explain the stereoselectivity differently. This scenario motivated us to venture into a thorough combined theoretical/experimental investigation of the *oxa*-Michael cyclisation

2. Results and Discussion

2.1. Test reactions with 2,6-model substrate

The core of our experimental investigation was the 2,6-case on account of its abundance in natural products. On the other hand, the conspicuous bulkiness of the 2,6-substituents, which tends to prevail over those of others in various positions, also justified an extensive experimentation with 2,6-disubstituted tetrahydropyran. In addition, the lack of a general idea of the possible stereo-determining factors prompted us to launch an investigative study on a simple substrate foremost. Our primary aim was to simplify the variables so that a clearer picture can be obtained. Hence, the compound **3** was chosen as a model substrate (Figure 64).

The treatment of benzaldehyde **1** with Grignard reagent generated from 5-bromo-1-pentene led to alcohol **2** in a moderate yield. The desired precursor **3** was then accessible by cross-metathesis reaction with methyl acrylate in an excellent yield. The exposure to Grubbs-II catalyst did not result in the formation of the (*Z*)-isomer in a detectable quantity by ¹H-NMR spectroscopy.

Figure 64 Synthesis of the precursor of 2,6-THP.

2.1.1. Strong base-catalysed oxa-Michael cyclisation

The purpose of the first set of experiments was to examine the significance of the cation in the stereo-determining step (Table 1). All the reported reactions were repeated in triplicate. As can be seen in the literature review (Figure 49), in a majority of cases, *t*BuOK was used at -78°C to initiate the oxa-Michael reaction. For that reason, we first started experimenting with *t*BuOK.²⁰ THF was the solvent as all the above-mentioned cyclisations were effected in this particular solvent. The reaction at -78°C afforded a mixture of 1:0.17 in favour of the *trans* isomer (determination of stereochemistry can be found in section 4.). There was no significant change in the diastereomer ratio when the suitable [18]-crown-6 was utilized in order for the potassium to be sequestered (entry 1, 2). However, there was a slight decrease in diastereomer ratio when 25 equivalents of [18]-crown-6-ether was used (entry 3). It is noteworthy that 25 equivalents [18]-crown-6 was not entirely soluble in THF, the mixture was opaque at -78°C. To test the solvent effect, the cyclisation reaction was carried out in toluene (less polar and non-coordinating). The same diastereoselectivity, but a much slower reaction rate was observed (entry 4). which is rather the consequence of the low solubility of *t*BuO⁻ alkoxide in toluene. In contrast, the reaction with *t*BuOK in the presence of [18]-crown-6 in toluene went to completion with little erosion of selectivity (entry 5). This was rationalized to be a result of the increased solubility of the alkoxide in the presence of [18]-crown-6. *t*BuONa was proved to be as selective as *t*BuOK (entry 6) in the absence of [15]-crown-5. This observation would suggest that there is no difference between K⁺ and Na⁺ cation considering the selectivity. However, the presence of [15]-crown-5 led to a decrease in selectivity from 1:0.2 to 1:0.5, yet the *trans* isomer remained the dominant isomer (entry 6, 7). Furthermore, *t*BuONa in toluene could not give rise to cyclisation at -78°C (entry 8, 9), which was likely due to low solubility of the base.

Figure 65 Interrogation of 2,6-THP model substrate with strong bases.

Table 1

Entry	Base	Solvent	T	t	Conversion	Selectivity (trans:cis)	Additive
1.	<i>t</i> BuOK	THF	-78°C	2h	100%	1:0.2	-
2.	<i>t</i> BuOK	THF	-78°C	2h	100%	1:0.2	5 eqv. [18]-crown-6
3.	<i>t</i> BuOK	THF	-78°C	2h	100%	1:0.3	25 eqv. [18]-crown-6
4.	<i>t</i> BuOK	toluene	-78°C	15h	27%	1:0.2	-
5.	<i>t</i> BuOK	toluene	-78°C	15h	100%	1:0.3	5 eqv. [18]-crown-6
6.	<i>t</i> BuONa	THF	-78°C	2h	100%	1:0.2	-
7.	<i>t</i> BuONa	THF	-78°C	2h	100%	1:0.5	5 eqv. [15]-crown-5
8.	<i>t</i> BuONa	toluene	-78°C	15h	no reaction	-	-
9.	<i>t</i> BuONa	toluene	-78°C	15h	very little P	-	5 eqv. [15]-crown-5
10.	<i>t</i> BuOLi	THF	-60°C	15h	86%	1:0.7	-
11.	<i>t</i> BuOLi	THF	-78°C to RT	15h	0%	-	5 eqv. [12]-crown-4
12.	MeONa	THF-MeOH (1:1)	-78	15h	0%	-	-
13.	<i>i</i> PrONa	THF-MeOH (1:1)	-78	15h	35%	1:0.2	-
14.	phosphazene	THF	-78	15h	50%	1:0.4	-

After this observation, we first started wondering if the complexation between K^+ and [18]-crown-6 is not complete and, as a result, no change in selectivity was observed in the presence of [18]-crown-6. However, based on the ample synthetic precedents, one equivalent of the crown-ether is sufficient enough for full complexation. Besides, *Schneider et al.* calculated the $\log K$ of the complexation in a range of solvents,²¹ apart from THF. The $\log K$ was already found to be a huge value in the MeOH, hence, the complexation in THF would be even more favourable. The crystal structure of the *t*BuOK⋯[18]-crown-6 complex lends further support to the idea of a highly favorable complexation.²² To ensure that complexation is complete, to a solution of [18]-crown-6 in THF was added *t*BuOK in THF solution at RT and the mixture was stirred for 15 mins. The mixture was then cooled down to -78 °C and stirred for 10 mins. After that, a solution of alcohol in THF was added dropwise.

The decreased selectivity with the combination of *t*BuONa and [15]-crown-5 can be rationalized in the following way. Eliminating the cation from the equation by using crown-ether is a simplified approximation. The cation in the crown-ether forms an intimate ion pair with *t*BuO⁻ anion to a varying degree. Consequently, when *t*BuO⁻ approaches the acidic OH-group, the cation...crown-ether complex must be situated around the bare *t*BuO⁻. By this reasoning, it may be assumed that the Na⁺...[15]-crown-5 complex is closer to the substrate owing to the shorter ionic radius of Na⁺ cation (116 ppm),²³ thereby greatly interfering with the axial-substituent. This effect is less pronounced with K⁺ cation as the ion pair less tight taking into account the longer ionic radius of K⁺ cation (152 ppm).

If the chelation model was relevant, an obvious experiment would involve *t*BuOLi due to its more Lewis acidic character in the series. *t*BuOLi turned out to be an interesting case as the newly opened bottles never worked neither at low, nor at elevated temperature. We set out to prepare its THF solution by reacting *t*BuLi with *t*BuOH in THF. *t*BuOLi appeared to be surprisingly unstable as the freshly prepared solution turned red then brown in one day while being stored at -20 °C. Although we would expect the Li⁺ cation to have the greatest ability amongst Na⁺, K⁺ ions to engage in chelation the Li⁺ cation showed a poor selectivity in the cyclisation (entry 10). No reaction with *t*BuOLi occurred in the presence of [12]-crown-4 (entry 11), which may be accounted for by the fact that this reagent is quite unreliable and renders the cyclisation capricious.

Much to our surprise, we were faced by difficulties with regard to the reactions with MeONa and *i*PrONa. The preparation of their THF solution was not straightforward, as it was virtually impossible to dissolve them in THF using 1 equivalent of the corresponding alcohol. Unfortunately, neither of their THF solutions was commercially available. Therefore, we resorted to the preparation of their THF-MeOH (1:1) solutions. The reaction with MeONa did not proceed (entry 12). *i*PrONa showed a slightly enhanced reactivity with the same selectivity

as *t*BuOM bases at a low temperature, but the conversion was still far lower (entry 13). We suspect that the decreased catalytic activity may be attributed to the presence of MeOH.

The experimental results thus far indicate no chelation effect as there is no difference in selectivity with and without the crown-ether. Also, there is no difference on changing from K^+ to Na^+ .

To exclude the entire presence of the cation, phosphazene super base was utilized (Figure 66). Although this base is not as basic as *t*BuO⁻,²⁴ it was still a reasonable probe for the reaction to test the hypothesis of chelation. The cyclisation proceeded with reduced conversion and somewhat lower selectivity favouring the *trans* isomer (entry 14). The results thus far indicate no chelation effect.

Figure 66 Structure of phosphazene P2-*t*-Bu base and pK_a (DMSO) values of conjugate acids for the sake of comparison

To test if the anion has any effect on the selectivity, we intended to replace the anion in the applied base. For this purpose, the obvious choice was the HMDS-type bases. (Table 2) Surprisingly, no diastereomer ratio was obtained that would show any tendency correlating with either the previous results or one another (for instance entry 16: low T only *cis*!).

Table 2

Entry	Base	Solvent	T	t	Conversion	Selectivity (<i>trans</i> : <i>cis</i>)	Additive
15.	KHMDS	THF	RT	15h	100%	1:0.55	-
16.	KHMDS	THF	-78°C	15h	100%	only <i>cis</i>	-
17.	KHMDS	THF	-78°C	15h	11%	1:0.3	5 eqv. [18]-crown-6
18.	KHMDS	THF	reflux	15h	100%	0.25:1	-
19.	NaHMDS	THF	RT	15h	100%	1:0.5	-
20.	NaHMDS	THF	-78°C	1.5h	32%	1:0.2	-
21.	NaHMDS	THF	-78°C	15h	34%	1:0.6	5 eqv. [15]-crown-5
22.	NaHMDS	THF	reflux	15h	100%	only <i>cis</i>	-
23.	LiHMDS	THF	RT	15h	85%	0.6:1	-
24.	LiHMDS	THF	-50°C	3d	15%	1:0.9	-
25.	LiHMDS	THF	-78°C to RT	2d	100%	0.5:1	-
26.	LiHMDS	THF	reflux	15h	100%	only <i>cis</i>	-
27.	KHMDS	THF	-78°C	15h	no reaction	-	TMEDA
28.	NaHMDS	THF	-78°C	15h	no reaction	-	TMEDA
29.	LiHMDS	THF	-78°C	15h	no reaction	-	TMEDA

Only the reflux conditions gave the same results because the *cis* isomer was the sole product at this given temperature. This is most likely due to the thermodynamic equilibrium which is present at an elevated temperature. The usage of crown-ether decelerated the cyclisation (entry 17, 21). More surprisingly, the cyclisation could not be effected in the presence of TMEDA (entry 27, 28, 29). This observation is quite surprising as TMEDA is supposed to enhance the basicity of the HMDS-bases. After thoroughly reading the literature of HMDS-bases, it turned out that these bases are highly prone to form various oligomers,²⁵ degree of which is dependent on the solvent, the concentration and the cation (Figure 67). The different size of the oligomers may affect the stereo-induction process in the cyclisation as well as the basicity. Because of this, we are facing a more complex situation here.

Figure 67 Formation of various types of HMDS-oligomers. This figure was adopted from *Angew. Chem. Int. Ed.* **2013**, 52, 1470- 1487.

This may also be the reason for those examples in the literature review the selectivity of which seem to be inconsistent, namely *Phorboxazole A* by *G. Pattenden*,¹⁴ *C1–C15 Segment of Spirastrellolide A* by *M. Shibasaki*,¹⁵ *bis(tetrahydropyran)spiroacetal fragment of Lituarines* by *J. Robertson*¹⁸ (Figure 49). Hence, no reliable conclusion can be drawn from HMDS bases.

2.1.2. Mild base-catalysed oxa-Michael cyclisation

It was of interest to determine whether weak bases could trigger the *oxa*-Michael cyclisation (Table 3). In these experiments, 1 equivalents of the base were used. Certain bases were absolutely unable to give rise to cyclisation regardless of temperature (entry 30-46). The reaction with tetramethylguanidine at an elevated temperature was found to be sluggish (entry 49), whereas TBAF²⁶ and DBU²⁷ displayed a better performance at an elevated temperature furnishing the *cis* isomer as a major product (entry 52, 53). Since TBAF and DBU are the two most frequently applied bases in the *oxa*-Michael cyclisation, we only focused on these both bases in the further experiments (Table 4).

Table 3

Entry	Base	Solvent	T	t	Conversion	Selectivity (<i>trans</i> : <i>cis</i>)
30.	NEt ₃	THF	RT	41 d	no reaction	-
31.	pyridine	THF	RT	15 h	no reaction	-
32.	TMEDA	THF	RT	15 h	no reaction	-
33.	DIPEA	THF	RT	15 h	no reaction	-
34.	tetramethylguanidine	THF	RT	41 d	no reaction	-
35.	K ₂ CO ₃	THF	RT	41 d	no reaction	-
36.	Cs ₂ CO ₃	THF	RT	41 d	no reaction	-
37.	NEt ₃	THF	reflux	15 h	no reaction	-
38.	pyridine	THF	reflux	15 h	no reaction	-
39.	TMEDA	THF	reflux	15 h	no reaction	-
40.	DIPEA	THF	reflux	15 h	no reaction	-
41.	DMAP	THF	reflux	15 h	no reaction	-
42.	DABCO	THF	reflux	15 h	no reaction	-
43.	imidazole	THF	reflux	15 h	no reaction	-
44.	proton sponge	THF	reflux	15 h	no reaction	-
45.	pyrrolidine	THF	reflux	15 h	no reaction	-
46.	piperidine	THF	reflux	15 h	no reaction	-
47.	K ₂ CO ₃	THF	reflux	15 h	23%	1:0.37
48.	K ₂ CO ₃	MeOH	reflux	15 h	messy NMR	~0.7:1
49.	tetramethylguanidine	THF	reflux	15 h	20%	1:0.65

The reaction with TBAF resulted in the *cis* isomer as a sole product at reflux. By contrast, the reaction in the presence of TBAF at RT proceeded with a reverse selectivity with full conversion (entry 50). It was obvious that the prevalence of *trans* isomer could not be explained by chelation control in this case. The experiments in toluene revealed that there was a large decrease in catalytic activity in a less polar solvent (entry 54). The *trans* isomer was the major isomer using TBAF in toluene at 60°C (entry 58). However, the diastereomer ratio

changed upon reflux ($\sim 110^{\circ}\text{C}$), and then the *cis* isomer became prevalent (entry 55). This indicates that the reaction with TBAF in toluene is under kinetic control.

Table 4

Entry	Base	Solvent	T	t	Conversion	Selectivity (<i>trans:cis</i>)
50.	TBAF	THF	RT	15h	100%	1:0.5
51.	DBU	THF	RT	15h	14%	0.4:1
52.	TBAF	THF	reflux	2.5h	100%	only <i>cis</i>
53.	DBU	THF	reflux	15h	100%	0.5:1
54.	TBAF	toluene	RT	15h	no reaction	-
55.	TBAF	toluene	reflux	15h	100%	0.15:1
56.	DBU	toluene	RT	15h	10%	0.5:1
57.	DBU	toluene	reflux	15h	100%	0.4:1
58.	TBAF	toluene	60°C	15h	100%	1:0.6
59.	DBU	toluene	60°C	15h	72%	0.4:1
60.	TBAF	toluene	60°C	4d	100%	1:0.7
61.	DBU	toluene	60°C	4d	100%	0.4:1

DBU showed a poor selectivity (entry 53, 57, 59, 61) at an elevated temperature in all cases. The reactions at RT proceeded with low conversion and the dominant isomer was always the *cis* (entry 51, 56). More interestingly, irrespective the temperature or the solvent, the selectivity with DBU was always about 0.4-0.5:1 in favour of *cis* isomer.

Fortunately, the *trans* and the *cis* isomer were separable by column chromatography so that the process of isomerisation could be examined (Table 5). The *cis* isomer, which is the thermodynamically favoured isomer, showed no change in diastereomer ratio upon exposure to bases (entry 62, 63, 64). In contrast to the *cis* isomer, the *trans* isomer could undergo isomerisation to varying degrees. *t*BuOK provoked the isomerisation at RT (entry 67). Reflux temperature was needed to bring about the isomerisation with TBAF (entry 68). The isomerisation with DBU was not detected even at elevated temperature (entry 66, 69). This observation led to a very interesting revelation that the reaction with TBAF or DBU were under kinetic control at RT. Nevertheless, the reaction with TBAF became thermodynamically controlled at an elevated temperature, as opposed to the reaction with DBU. The latter remained kinetically controlled reaction at an elevated temperature. It is worth highlighting the reaction

with TBAF and DBU resulted in an opposite selectivity at a low temperature, which implies that there is a significant difference in stereo-determining process of the two cyclisations.

When the solvent was changed to toluene the formation of the *cis* isomer was nearly negligible at 60°C (entry 70,71). Upon reflux in toluene the degree of isomerisation was greater, but still was not complete (entry 72, 73). Based on this observation, it could be concluded that thermodynamic control played a key role in those reactions which were conducted in THF at an elevated temperature, regardless of the base. As for the reactions in toluene, this was not always the case. The selectivity was governed by kinetic control but there was a little isomerisation in the background, which affected the ratio to a little extent. For instance, (entry 58), the reaction with TBAF in toluene resulted in a 1:0.6 ratio in favour of *trans* at 60°C, after 4 days the ratio changed to 1:0.7 (entry 60). When the temperature was increased to ~110 °C the isomerisation was accelerated, and the influence of thermodynamic control on the diastereomer ratio became greater (entry 55).

In conclusion, the experimental findings clearly show that the thermodynamic and the kinetic control can significantly be dependant not only on the temperature, but also on the solvent and the nature of the base.

Table 5

Entry	Base	Solvent	T	t	Change with respect to initial ratio	d.r. (trans:cis)	Starting material
62.	<i>t</i> BuOK	THF	reflux	15h	no change	-	<i>cis</i> isomer
63.	TBAF	THF	reflux	15h	no change	-	<i>cis</i> isomer
64.	DBU	THF	reflux	15h	no change	-	<i>cis</i> isomer
65.	TBAF	THF	RT	15h	no change	-	<i>trans</i> isomer
66.	DBU	THF	RT	15h	no change	-	<i>trans</i> isomer
67.	<i>t</i> BuOK	THF	RT	2h	change	only <i>cis</i>	<i>trans</i> isomer
68.	TBAF	THF	reflux	15h	change	only <i>cis</i>	<i>trans</i> isomer
69.	DBU	THF	reflux	15h	no change	-	<i>trans</i> isomer
70.	TBAF	toluene	60°C	15h	change	1:0.07	<i>trans</i> isomer
71.	DBU	toluene	60°C	15h	change	1:0.02	<i>trans</i> isomer
72.	TBAF	toluene	reflux	15h	change	1:0.38	<i>trans</i> isomer
73.	DBU	toluene	reflux	15h	change	1:0.12	<i>trans</i> isomer

0.2 equivalent of the *t*BuOK and 1 equivalent of the non-alkoxide (TBAF, DBU) were used

Elevated temperature can give rise to thermodynamic-driven isomerization resulting the *cis* isomer. However, this temperature depends on the *pK*_a of the applied base. In the case of strong alkoxide base, complete isomeration can be obtained at around 0 °C and above. In contrast, DBU and F⁻ requires reflux temperature to prompt such an isomeration.

Solvent greatly affects the rate of the cyclisation regardless of the nature of the control. Toluene as aprotic apolar solvent drastically slows down the cyclisation in the kinetically-controlled case. Likewise, the thermodynamically-driven isomerisation in toluene is rather slow. Tetrahydrofuran was found to be the optimal solvent for this type of cyclisation.

Interestingly, many amine/imine-type bases were found to be insufficient for cyclisation with the exception of DBU. In addition, fluoride anion appeared rather effective as an inorganic base as well.

2.2. *oxa*-Michael cyclisation of substrates with varied substitution pattern

After all this, we went on to synthesize further substrates which gave us access to 2,5-, 2,4-, 2,3-disubstituted THP rings. We wanted to see if the same trend could be observed with *t*BuOK, TBAF and DBU.

The synthesis of the 2,3-THP precursor **10** began with the treatment of 4-phenylcyclohexanone **6** with hydrogen peroxide in the presence of iron(II) sulfate to open the six-membered ring in an oxidative manner. Despite the low yield of the oxidation (33%), the reaction was performed on gram scale, thus resulting the carboxylic acid **7** in sufficient quantity, which upon simple reduction with lithium aluminium hydride furnished alcohol **8**. The conversion of alcohol **6** into the corresponding enoate ester **9** proved straightforward and high-yielding (86%) with methyl acrylate in the presence of Grubbs-II catalyst.

The precursor of 2,5-THP **12** was prepared over two steps. Styrene oxide **10** underwent ring opening reaction with the Grignard reagent prepared from 4-bromo-1-butene, giving access to alcohol **11**. Ultimately, the enoate ester **12** moiety was installed through a cross-metathesis reaction employing Grubbs-II catalyst in a fairly good yield (75%).

The penultimate intermediate **13** was at my disposal thanks to *Annabel Ho* Ph.D. candidate.²⁸ The precursor of 2,4-THP **14** could be accessed from the cross-metathesis reaction of **13** with methyl acrylate in a good yield (80%).

Figure 68 Synthesis of the precursors of 2,5-, 2,4-, 2,3-THP.

In the case of 2,5-disubstituted THP (Figure 69, Table 6), the 2,5-*cis* (ex-aq) product was observed as a major product with a slightly decreased selectivity at -78°C (entry 74). The reaction between the precursor of 2,6-THP and *t*BuOK was almost instantaneous to give the 2,6-*cis* (eq-eq) isomer exclusively. However, in this case, the isomerisation into the most stable *trans* (eq-eq) isomer appeared to be significantly slower than for 2,6-disubstituted THP (entry 75, 76). The reaction with *t*BuOK at RT resulted in a 1:1 mixture of the isomers after 2 hours, which upon an extended reaction time gave a 1:0.35 mixture favouring the *trans* isomer. A similar pattern was observed with TBAF. The *cis* isomer was by a small margin the major product (1:0.8) at RT, but the *trans* isomer was the sole product at an elevated temperature after 15 hours (entry 77, 78, 79). This further supported the idea that the reaction was under kinetic control with TBAF at ambient temperature, but it is under thermodynamic control at reflux. The cyclisation was much slower with DBU at RT, exhibiting a 5% conversion after 15 hours (entry 80). At reflux, this reaction went to 60% conversion (entry 81). Notably, the selectivity was found to be the same at both temperature: 1:0.65 in favour of the *trans* (eq-eq) isomer.

Figure 69 Interrogation of 2,5-THP model substrate with bases.

Table 6

Entry	Base	Solvent	T	t	Conversion	Selectivity (cis:trans)
74.	<i>t</i> BuOK	THF	-78°C	2h	100%	1:0.3
75.	<i>t</i> BuOK	THF	RT	3h	100%	1:1
76.	<i>t</i> BuOK	THF	RT	15h	100%	0.35:1
77.	TBAF	THF	RT	15h	100%	1:08
78.	TBAF	THF	reflux	2h	100%	1:1
79.	TBAF	THF	reflux	15h	100%	only trans
80.	DBU	THF	RT	15h	5%	0.65:1
81.	DBU	THF	reflux	3h	60%	0.65:1

0.2 equivalent of the *t*BuOK and 1 equivalent of the non-alkoxide (TBAF, DBU) were used

For the 2,4-disubstituted THP (Figure 70, Table 7), the use of *t*BuOK at -78°C resulted in the *trans* (eq-ax) isomer as a sole product (entry 82). This was the highest selectivity that was observed in the kinetically controlled series. In addition, *t*BuOK at RT could drive the isomerisation to exclusive formation of the *cis* isomer (entry 83). Only moderate selectivity (0.7:1) was observed with TBAF at RT favouring the *cis* (eq-eq) isomer (entry 84). At reflux, the proportion of the *cis* isomer became higher (entry 85). When the base was changed to DBU, the reactivity and selectivity pattern was very similar to that obtained in the previous cases. Using DBU at RT gave a little conversion (13%), which increased on heating. Ultimately, the cyclisation could be driven to full completion after 15 hours at reflux (entry 86, 85, 87). Again, the selectivity was the same in all the three cases, 0.5:1 in favour of the *cis* (eq-eq) isomer.

Figure 70 Interrogation of 2,4-THP model substrate with bases.

Table 7

Entry	Base	Solvent	T	t	Conversion	Selectivity (trans:cis)
82.	<i>t</i> BuOK	THF	-78°C	2h	100%	only <i>trans</i>
83.	<i>t</i> BuOK	THF	RT	2h	100%	only <i>cis</i>
84.	TBAF	THF	RT	15h	100%	0.7:1
85.	TBAF	THF	reflux	2h	100%	0.15:1
86.	DBU	THF	RT	15h	13%	0.5:1
87.	DBU	THF	reflux	3h	66%	0.5:1
88.	DBU	THF	reflux	15h	100%	0.5:1

0.2 equivalent of the *t*BuOK and 1 equivalent of the non-alkoxide (TBAF, DBU) were used

The reactivity of 2,3-THP appeared to be slightly different (Figure 71, Table 8). The cyclisation with TBAF was very sluggish (entry 91, 92). Reflux, a higher catalyst loading and prolonged reaction time were required to observe a full conversion, giving a mixture modestly favouring the *trans* (eq-eq) isomer (entry 93). We assumed that it is likely to be the steric hindrance of the β -carbon by the Ph-group. DBU was found to be completely inefficient to provoke the cyclisation regardless of the temperature (entry 94,95). A useful level of selectivity in favour of the *cis* (eq-ax) isomer was obtained with *t*BuOK at -78°C (entry 89). When the reaction was conducted at RT the *trans* isomer became the major isomer in a 0.2:1 ratio (entry 90).

Figure 71 Interrogation of 2,3-THP model substrate with bases.

Table 8

Entry	Base	Solvent	T	t	Conversion	Selectivity (cis:trans)
89.	<i>t</i> BuOK	THF	-78°C	2h	100%	1:0.1
90.	<i>t</i> BuOK	THF	RT	3h	100%	0.2:1
91.	TBAF	THF	RT	15h	0%	-
92.	TBAF	THF	reflux	2h	0%	-
93.	TBAF	THF	reflux	2d	100%	0.6:1
94.	DBU	THF	RT	15h	0%	-
95.	DBU	THF	reflux	15h	0%	-

0.2 equivalent of the *t*BuOK and 1 equivalent of the non-alkoxide (TBAF, DBU) were used

Finally, the next group of experiments was aimed to investigate the possibility of the isomerisation of the less stable isomer with TBAF and DBU (Figure 72). All four cases showed the exact same reactivity pattern, which was also in full accordance with the observation in 2,6-THP case. There was no isomerisation with TBAF at RT, but it could be effected at reflux. This clearly indicates that the cyclisation was always under kinetic control at ambient temperature. In contrast, DBU was not able to provoke the isomerisation of the kinetic product neither at RT nor at reflux. It follows that the formation of the *cis* isomer as a major product resulted from kinetic control.

	2,6-<i>trans</i> (eq-ax) 4		2,5-<i>cis</i> (eq-ax) 15		2,4-<i>trans</i> (eq-ax) 17		2,3-<i>cis</i> (eq-ax) 20	
	R.T.	reflux	R.T.	reflux	R.T.	reflux	R.T.	reflux
DBU	×	×	×	×	×	×	×	×
TBAF	×	✓	×	✓	×	✓	×	✓

Figure 72 Examination of thermodynamic equilibration with DBU and TBAF.

These are a few selected examples to demonstrate the diversity of kinetic and thermodynamic control with regard to temperature and base (Figure 73). The *trans* 2,6-THP could be formed at low temperature with *t*BuOK. The reaction was evidently under kinetic control as by elevating the temperature the *trans* isomer began to undergo isomerisation. More interestingly, the *cis* isomer could be obtained under kinetic control by using DBU. The kinetic control was present even at elevated temperature as evidenced by the fact that the *trans* isomer did not display isomerisation with DBU at reflux. The reaction with TBAF gave the *trans* isomer as a major product at RT but resulted the *cis* isomer exclusively at an elevated temperature. The reaction at RT was found to be under kinetic control as there was no

equilibration when the pure *trans* isomer was exposed to TBAF at RT. However, the *trans* isomer was completely converted into the *cis* isomer at elevated temperature, which stands in contrast to result found in the case of the reaction with DBU. 2,5-THP displayed a time-dependant selectivity with *t*BuOK at RT. The reaction did not show clear kinetic or thermodynamic control since the initial ratio of *trans*:*cis* changed to a single *cis* upon prolonged stirring. A similar trend was observed for the reaction with TBAF in toluene although the ‘hidden’ isomerisation reaction was appeared to be much slower than that with *t*BuOK. The control experiment showed that the *trans* isomer could slowly isomerise in toluene at a moderately high temperature. The reaction to give 2,4-THP with TBAF was likely to be under thermodynamic control since the ratio of *trans*:*cis* at RT changed in favour of *cis* at reflux, indicating the presence of equilibrium. For the 2,3-THP showed the same trend accompanied with a decreased reactivity in cyclisation. The use of *t*BuOK at low temperature resulted in the equatorial-axial product, which could undergo isomerisation at ambient temperature.

Figure 73 Diversity of kinetic and thermodynamic control. Only the major isomer is shown.

3. Acid-catalysed *oxa*-Michael cyclisation

We were curious to know whether weak or strong acids can catalyse the *oxa*-Michael cyclisation. It turned out if the substrate is an unactivated ester the cyclisation does not take place in the presence of strong acid (Figure 74). *S. Ping* previous group member also observed the failure of acid catalysis while working on the synthesis of *Clavosolide*.⁴ However, once the carbonyl group becomes more electrophilic, for instance the substrate is an aldehyde, ketone or thioester the cyclisation proceeds smoothly even at RT.

Figure 74 Acid-catalysed attempts with enoate ester substrates.

Clarke et al. showed that the LUMO of the protonated oxoester was higher (1.43 eV) than that in the protonated thioester (1.06 eV), thereby making the LUMO of the thioester more accessible for nucleophiles in energy.¹⁹ This was manifested in the increased reactivity of the thioesters in the *oxa*-Michael cyclisation.

In parallel with the base-catalysed experiments, Annabel Ho Ph.D. candidate began to interrogate the substrates in which the alkene is activated by a ketone group as shown by the following examples (Figure 75). Her investigations have shown that the acid-catalysed *oxa*-

Michael cyclisation of α,β -unsaturated ketones is feasible under acidic conditions as opposed to the case of esters. Amberlyst-15 was used as a catalyst and all the cyclisation went to completion at RT overnight, giving the diequatorial product exclusively. Despite the fact that these are the more stable products, it does not necessarily mean that they were formed under thermodynamic control. To test this, a mixture of the 2,6-*cis* and 2,6-*trans* isomers was prepared by base-catalysed cyclisation (*t*BuOK). When this mixture was exposed to the same acidic conditions that was applied for the cyclisation reactions, no change was observed, which clearly meant these molecules did not equilibrate under acidic conditions. Consequently, the preference for the diequatorial products is the result of kinetic control as indicated by *Clarke* in the case of thioesters. It is of note that protection of OH group did not alter the observed selectivity. This means that the TSs of the stereo-determining step of the cyclisations with protected and unprotected substrates are the same. After deprotection in protic medium, the resultant intermediate is identical to the starting material of the cyclisation with unprotected substrates, which upon protonation undergoes cyclisation to furnish the *cis* isomer.

Figure 75 Acid-catalysed attempts with enone substrates.

In complete contrast, when the THP ring is embedded in a macrocycle ring then the thermodynamic control under acidic conditions is possible. This was demonstrated by *Rizzacasa et al.*²⁹ and *Boddy et al.*³¹.

The former group investigated a transannular conjugate addition to synthesise *Apicularen A*²⁹. Based on MM2 calculations performed on a model compound, the *trans* isomer was found to be lower in energy than the *cis* isomer (Figure 76).³⁰ The calculated order was in line with their experimental findings. The reaction promoted by Amberlyst-15 resulted in a mixture in favour of *trans* isomer at reflux (6:1). Nevertheless, when the cyclisation was

affected at RT, the major product was the *cis* isomer. These two control experiments proved the presence of thermodynamic control at an elevated temperature.

Figure 76 Transannular oxa-Michael cyclisation in the synthesis of *Apicularen A* by Rizzacasa *et al.* and relative MM2 energies of the isomers.

Boddy *et al.* devised a synthetic route to the macrocyclic core of *Neopeltolide* involving a transannular oxa-Michael cyclisation (Figure 77).³¹ The ester moiety was ineffective to bring about the cyclisation with acids, but the cyclisation took place when the relative position of the OH-group and Michael-acceptor was restructured to give a ketone-type acceptor. The authors performed DFT calculations at B3LYP/6-31++G** level of theory to identify the more stable form of the THP ring incorporated in the macrocycle ring. The *trans* THP was predicted to be in a twist-boat conformation lying 1.4 kcal/mol above the *cis* THP in a chair conformation. Their experimental results led to the same conclusion as the formation of the *cis* THP was dominant at an elevated temperature. Furthermore, the *trans* THP could be transformed into the more stable *cis* isomer under acidic conditions, giving identical diastereomer ratio. At the first glance, this is in contrast to the findings by Rizzacasa *et al.*³⁰ as the *trans* isomer was found to be thermodynamically favoured in their study. However, the two macrocycles differ in size; *Apicularen A* possesses the 9-membered ring system and *Neopeltolide* owns a 12-membered macrocycle ring. This has a significant effect on the stereochemical outcome of a

thermodynamically controlled reaction. Specifically, the size of the macrocycle can control the thermodynamic stability of the THP ring.

Figure 77 Transannular *oxa*-Michael cyclisation in the synthesis of *Neopeltolide* by Boddy *et al.* and relative B3LYP/6-31++G** energies of the isomers.

4. Relative configuration assignments of the THPs by NMR spectroscopy

The determination of the relative configurations was based on the coupling constants of the protons attached to $-\text{CH}_2\text{-CO}_2\text{Me}$ group and Ph group. In some cases, due to the complicated spin system, the coupling constants could not be extracted from the original peaks. Nevertheless, the homonuclear decoupling NMR experiment allowed for the simplification of the complex multiplets by irradiating specific protons, thereby eliminating the coupling from the irradiated proton. The proton-proton coupling constants of interest could be obtained by examining the resultant residual multiplets. When the coupling constants were compared to identify the stereochemistry the chair conformation was considered to be the most probable.

The *Karplus* equation has generally proved reliable to identify the stereochemistry of unstrained acyclic hydrocarbon systems.³² The equation is used for vicinal coupling, in which a H atom is coupled with another H atom through three covalent bonds. This provides an approximate value of vicinal H-H coupling constant as a function of their dihedral angle. When the dihedral angle is either 180° or 0° the vicinal H-H coupling is maximal (8-12 Hz). The vicinal H-H coupling is minimal (0 Hz) when the dihedral angle is 90° . Figure 78 provides a schematic illustration of coupling constants of cyclohexane deducted from the *Karplus* equation. In an idealized case, $J_{\text{ax-eq}}$ and $J_{\text{eq-eq}}$ of cyclohexane are anticipated to be identical as both have a dihedral angle of 60° . It should be noted that this dihedral angle is $\sim 57^\circ$ in reality due to the cyclic nature. More importantly, the substituted cyclohexanes become slightly flattened. This modifies the dihedral angle of $\text{H}_{\text{eq}}\text{-H}_{\text{eq}}$ to slightly higher than 60° ($\rightarrow$ smaller coupling constant), and $\text{H}_{\text{ax}}\text{-H}_{\text{eq}}$ to somewhat below 60° ($\rightarrow$ larger coupling constant). It should be noted that the coupling constants of 2-5 Hz are not sufficiently definitive to determine the relationship of H-H since the coupling constants can be slightly perturbed by the electronegativity of substituent and the distortion of the ring system. However, $\text{H}_{\text{eq}}\text{-H}_{\text{eq/ax}}$ and

H_{ax} - H_{ax} relationships are clearly distinguishable via coupling constants. Based on this well-proven protocol, we could identify the stereochemistry of all the isolated isomers.

Figure 78 Expected coupling constants of cyclohexane-like compounds based on the Karplus equation.

First, the 2,6-THPs were examined (Figure 79). With the aid of a COSY NMR experiment, the assignment of the proton attached to $-CH_2-CO_2Me$ group could be achieved. In the original 1H -NMR spectrums, an ambiguous multiplet was observed for the proton attached to the $-CH_2-CO_2Me$ group in both cases at 3.97 ppm (2,6-*cis*) and 4.22 ppm (2,6-*trans*), which ideally should be a *dddd*. By decoupling the CH_2 protons, the multiplets appeared to be simplified enough for further analysis. For the *cis* isomer, the equatorial position of the $-CH_2-CO_2Me$ group was apparent with the coupling constants of 11.3 Hz and 2.0 Hz. To confirm the equatorial position of the Ph group, the coupling pattern of the proton attached to the Ph group was examined. The original 1H -NMR showed a doublet of doublet at 4.40 ppm with coupling constants of 11.3 Hz and 2.2 Hz. Thus, the *cis* stereochemistry (eq-ax) of the two substituents was confirmed. The coupling constants of the proton attached to $-CH_2-CO_2Me$ group in the *trans* isomer were observed as a weighted average of the two conformers, the presence of which can be accounted for by the conformational equilibrium at RT. The 3.2 Hz corresponds to a H_{eq} - H_{ax} coupling. The 7.4 Hz arises from a mixture of H_{eq} - H_{eq} and H_{ax} - H_{ax} coupling constants due to the interconversion of the two conformers, which coincides with the time-scale of NMR spectroscopy. The proton attached to the Ph group was observed as an apparent triplet at 4.88 ppm. This can also be explained by the dynamic equilibrium of the two conformers, seeing the two diastereomeric protons as a simple CH_2 group accompanied with an average coupling constant.

2,6-THP

* observed coupling constant is weighted average of the two conformers
due to conformational equilibrium

Figure 79 Conclusive coupling constants of 2,6-*cis*- and 2,6-*trans*-THPs.

In the case of 2,5-THPs, the *trans* and the *cis* diastereomers were found to be an inseparable mixture, the *trans* isomer was obtained by driving the isomerisation to full completion at reflux. For that reason, only the *trans* isomer could be examined by NMR spectroscopy (Figure 80). Similarly, the identification of the proton attached to $-\text{CH}_2\text{-CO}_2\text{Me}$ group was done by a COSY NMR experiment. Its original peak at ~ 3.84 ppm was found to be a complicated multiplet. After decoupling CH_2 protons, the equatorial position of the $-\text{CH}_2\text{-CO}_2\text{Me}$ group was obvious. This was shown by the coupling constants of 11.0 Hz and 2.1 Hz of the neighbouring proton. The multiplicity of the CH_2 attached to the oxygen atom was then analysed to determine the spatial position of the Ph group. The protons in the CH_2 group are diastereotopic, hence they were observed as two separate peaks at 4.01 ppm and 3.45 ppm. The H_{ax} was seen as a triplet with a coupling constant of 11.3 Hz because the $\text{H}_{\text{ax}}\text{-H}_{\text{eq}}$ geminal coupling constant was coincidentally identical to the $\text{H}_{\text{ax}}\text{-H}_{\text{ax}}$ coupling constant. The H_{eq} was identified as a clear *ddd* with coupling constants of 11.3 Hz, 4.4 Hz and 2.3 Hz. The first coupling constant was a result of the geminal coupling, the second arguably indicated a $\text{H}_{\text{eq}}\text{-H}_{\text{ax}}$ relationship with the proton attached to the Ph group. Interestingly, the H_{eq} displayed a long-range W-coupling with 2.3 Hz. Taken all together, the *trans* stereochemistry (eq-eq) of the two substituents was verified.

Figure 80 Conclusive coupling constants of 2,5-*trans*-THP.

Gratifyingly, the coupling constants of the proton attached to the -CH₂-CO₂Me group was clearly identifiable from the ¹H-NMR spectrum of 2,4-*cis* (eq-eq) THP as a *dddd* at 3.90 ppm (Figure 81). The coupling constants of 10.4 Hz and 2.1 Hz reasonably indicated the H_{ax}-H_{eq} and H_{ax}-H_{ax} relationship, which also corresponded to the equatorial position of the -CH₂-CO₂Me group. However, there was a need to reduce the complex multiplicity of the proton attached to the Ph group by homonuclear decoupling the neighbouring CH₂ group. The resulting coupling constants 9.8 Hz and 2.3 Hz validated the Ph group in equatorial position. The 2,4-*trans* (eq-ax) isomer could not be thoroughly analysed as the two axial protons at 3.78 ppm overlapped with one another in the ¹H-NMR spectrum. However, the equatorial position of the Ph group could be confirmed by the coupling constants of 8.5 Hz and 3.8 Hz after homodecoupling the neighbouring CH₂ group at 1.89 ppm.

Figure 81 Conclusive coupling constants of 2,4-*cis*- and 2,4-*trans*-THPs.

The assignments of *cis* (ax-eq) - *trans* (eq-eq) stereochemistry for the 2,3-THPs also relied on the analysis of the coupling patterns (Figure 82). The protons attached to the -CH₂-CO₂Me group was by COSY NMR spectroscopy as previously. This proton in the ¹H-NMR spectrum of *cis* isomer was observed as *ddd* at 4.25 ppm. The coupling constants could be extracted as 9.3 Hz, 4.5 Hz and 3.5 Hz, and the latter was characteristic of H_{eq}-H_{ax} relationship. The proton attached to the Ph group was observed as an apparent quartet at 2.92 ppm. Similar to the 2,6-*trans* isomer, its coupling constant of 4.4 Hz was observed as a weighted average of the two conformers due to the rapid interconversion of the two conformers. In the case of the *trans* isomer, protons attached to the -CH₂-CO₂Me group showed a clear *ddd* at 3.92 ppm, thereby the coupling constants could be obtained from the original peak. The obtained coupling constants are as follows: 10 Hz, 8.9 Hz, and 3.5 Hz. The largest coupling constant corresponded to the H_{ax}-H_{ax} relationship, and the other two stemmed from the coupling with the -CH₂-CO₂Me. Since the conformational equilibrium was absent here, the coupling pattern of the proton attached to Ph group was rather conclusive to verify the *trans* relationship of the two adjacent substituents. This peak was observed as *td* at 2.52 ppm with coupling constants of 10.0 Hz and 4.1 Hz. The two coupling constants corresponding to H_{ax}-H_{ax} relationship was identical by chance, and the smaller coupling constant perfectly matched the anticipated H_{ax}-H_{eq} value.

2,3-THP

Figure 82 Conclusive coupling constants of 2,3-*cis*- and 2,3-*trans*-THPs.

5. Computational study of acid- and base-catalysed *oxa*-Michael cyclisation

Building on the work undertaken with strong bases at low temperature, our primary interest was to provide a suitable rationale for the observed *trans* selectivity. Under the premise that the selectivity originates due to the presence of the cation between the alkoxide and the carbonyl group, our computational effort expanded to the scrutiny of the transition states involving the cation. We also intended to examine how the coordination of THF to the cation affects each TS.

Intrigued by the exceptional *cis* selectivity outlined in the literature summary, this computational study also dealt with the origin of *cis* selectivity in the acid-catalysed cyclisations. Related test reactions were done by our Ph.D. fellow Annabel Ho. Initial studies focused on identifying possible transition states and test if the counter anion was pivotal in the model system. Then, our intention was to pinpoint the selectivity-determining factors and compared them with those in base-catalysed cyclisation.

First and foremost, we need to address the uncertainty regarding the structural parameters that may be crucial in determining the stereochemical outcome. Thus, some questions lying ahead of us must be dealt with such as the preference of *s-cis* or *s-trans* geometry in the enone moiety and the progression of the bond-forming distance in each TS. Although it has been showed that the perfect tetrahedral angle is not a prerequisite for the intramolecular cyclisation, we would like to test if there is any correlation between the trajectory and the order of the respective TSs in energy, as it previously was proposed.

This all was aimed to be executed by using state-of-the art DFT methods. Even more accurate (yet computationally very expensive) wavefunction-based methods do of course exist. However, DFT methods have shown excellent performance for closed shell organic molecules (both charged and neutral)³³. Besides, DFT is also the contemporary method of choice to study reaction mechanisms^{34,35,36}.

5.1. General details of computational method

We began the calculations by first obtaining the lowest energy conformers of the acyclic reactant. For the conformational analysis of the starting acyclic molecule, we applied Monte Carlo sampling using the standard OPLS_2005 force field, which was carried out in the *MacroModel* software by using with well-validated default settings for medium-size molecules.³⁷ Next, all the distinct conformers within 10 kcal/mol were optimised using Density Functional Theory (DFT) with the *Gaussian* 09 suite of programmes.³⁸ The lowest-energy structure was used as a reference point for constructing the thermodynamic profile of the cyclisation.

After due calibration, the dispersion-corrected hybrid ω B97X-D exchange-correlation functional was chosen in conjunction with the ‘triple- ξ ’ 6-311+G(d,p) basis-set.³⁹ To further increase the accuracy of the description of long-range interactions that arise from the solvent environment present and the loosely tied electrons of the alkoxide anion, diffuse and polarization functions were applied as well.

The SMD explicit solvation model was used to model the global solvation effects.⁴⁰ Harmonic vibrational frequency calculations were performed to confirm the nature of the obtained structures. No imaginary frequencies were found for all the minima reported. For the transition states (TSs) only one imaginary frequency was found.

To verify that the TSs obtained indeed do describe the actual process, the following verifications were done:

- Animation of the imaginary frequency in order to verify that they genuinely describe the bond formation process for the *oxa*-Michael cyclisation.
- The connection between the reactant and the product through a corresponding transition state was further confirmed by optimizing slightly altered bond distance between the

nucleophilic oxygen and the electrophilic β -carbon along the two directions which were associated with the imaginary frequency found in the vibrational frequency calculation.

- IRC (Intrinsic Reaction Coordinate) calculations which confirmed that the desired internal cyclisation indeed did happen. These calculations thus aid us in ascertaining that the transition states correspond to the investigated intramolecular cyclisation.

Considering the general inaccuracy in computing entropies due to (a) the ideal-gas approximation used in the partition functions, and (b) rigid-rotor approximations, and also, that no significant structural change occurs in the course of an intramolecular *oxa*-Michael cyclisation, we utilized the enthalpy as a reference point, as opposed to the free-energies.

After geometry optimization, single point energies were calculated for all the structures applying the larger 6-311++G(3df,3pd) basis-set. The ultrafine integration grid was used to enhance the accuracy of the numerical integration in all the DFT calculations. Having applied the above-mentioned parameters, the enthalpy was calculated according to the following formula:

$$H(\text{corrected}) = E(\omega\text{b97xd}/6\text{-}311\text{++G}(3\text{df},3\text{pd})/\text{SMD}) + \text{Thermal correction to Enthalpy}(\omega\text{b97xd}/6\text{-}311\text{+G}(\text{d},\text{p})/\text{SMD}).$$

5.2. Results and discussion of computational study of base-catalysed cyclisation

Initial studies were focused on possible transition states. The twist-boat-like transition states leading to both products were regarded as negligible alternatives considering the notable energy difference between the chair and the twist-boat conformers, particularly in the absence of any stabilizing effect in the twist-boat TSs.⁴¹ As our experimental results had shown that the role of the cation was insignificant in controlling the stereochemistry, hence, no cations were included in our initial calculations. Our initial computational study began with a systematic scan around the bond between the β - and the γ -carbon atom in the bare THP-enolate, and then the structure having the highest energy was used to locate further transition states. The two lowest TSs are shown in the enthalpy profile of the reaction along with the corresponding enolates (Figure 83). Some other important structural parameters are also given. The (*E*)-2,6-*trans* transition state is 0.3 kcal/mol lower than the (*E*)-2,6-*cis* transition state, which adequately reflects the observed diastereoselectivity albeit, the question still remains open as to the origin of the selectivity. It is worthwhile to note that the geometry of the enolate greatly influences the order of the TSs in enthalpy, namely, the (*Z*)-enolate found to be consistently unfavoured when compared to the (*E*)-enolate by 0.5 kcal/mol. This can be rationalized as arising from the 1,3-allylic strain present between the MeO- and the α -C-H groups (2.45 Å in (*Z*)-enolates, as opposed to 2.61 Å in (*E*)-enolates) (Figure 84 (A)).

Besides, once the products were formed the relative stability became the reverse. In contrast to the trend in the TSs, the (*E*)-2,6-*cis* THP enolate was computed to be more stable than the (*E*)-2,6-*trans* THP enolate by 0.9 kcal/mol. This is aligned with the general expectation and can be accounted for by the resultant 1,3-diaxial repulsion in the (*E*)-2,6-*trans* THP product. This also shows that the employed computational method reasonably predicts the relative stability of the entities involved in the cyclisation.

Figure 83 Computed enthalpy profile for the base-catalysed oxa-Michael cyclisation. (*E*)-2,6-*trans* and (*E*)-2,6-*cis* TS with key structural parameters indicated.

Notably, all the transition states have a long bond-forming distance of 2.3-2.4 Å, indicating an early transition state ($\Delta_{\text{bond length}}(\text{TS-product}) = 0.9 \text{ Å}$), which is consistent with the previously reported transition states. Based on the long $O(-)\cdots C(\beta)$ distance and the experimental outcome, the 1,3-diaxial effect is arguably insignificant under kinetic control in the base catalysed cyclisation. The question of why the *trans* product is favoured remains. We, therefore, attempted to interrogate the transition states for a reason. Interestingly, the Bürgi–Dunitz trajectory is closer to the tetrahedral angle in the (*E*)-2,6-*cis* transition state (*cis* TS: 107.8°), which stands in contrast to the findings from the *Schneider* (*cis* Ts: 99° , *trans* TS: 104°)¹⁶ and the *Yonemitsu* groups (*trans* TS: 101.6° *cis* TS: 113.6°)¹⁴. It can be concluded that the intention of the nucleophile to precisely follow the Bürgi–Dunitz trajectory is not a stereo-discriminating factor⁴². We also examined the possibility of hyperconjugative interaction

between the equatorial C(γ)-H and the double bond in both TSs. However, we did not find any significant change in the bond length neither when compared to the other two equatorial C-H bonds in the carbon chain, nor to one another.⁴³ NBO calculations were also performed, which also showed the absence of hyperconjugative effects.

Figure 84 (A) Transition states having 1,3-allylic strain. (B) (*E*)-2,6-*cis/trans* TSs in chelation model.

We became interested to see whether the same trend can be experienced if the alkali cation is located between the oxygens as previously postulated in the chelation model¹³. We found that the (*E*)-2,6-*trans* arrangement remained the lowest amongst the possible transition states (Figure 84 (B)). Thus, the computational and experimental results are in agreement that the cation itself, which was widely thought to be the reason for the *trans* selectivity, does not play a crucial role in the selectivity.

In an attempt to elucidate the cause for *trans* selectivity under basic conditions, we scrutinize possible electrostatic factors. The NBO of the TSs charges were computed at the ω b97xd/6-311++G(3df,3pd) level of theory. In both TSs, the alkoxide O atom and the α -C atom in the acceptor fragment possess NBO charges of -0.88 and -0.45 or -0.46. Hence, an electrostatic repulsion between the partially negative atoms is anticipated. The only significant difference between the (*E*)-2,6-*cis* and (*E*)-2,6-*trans* TS appears to be the distance between the alkoxide O atom and the α -C atom. This distance in (*E*)-2,6-*cis* TS is 0.1 Å shorter, implying enhanced destabilisation effect by adverse electrostatic repulsion.

Figure 85 Electrostatic interaction in $(E)\text{-}2,6\text{-}trans$ and $(E)\text{-}2,6\text{-}cis$ TS. The key NBO charges are indicated. Majority of H atoms is omitted for clarity.

Given the ~ 13 kcal/mol energy barrier of the reverse reaction, it is very unlikely the isomerisation into the *cis* isomer noticeably affects the overall selectivity at -78°C within the timeframe of our experiments. However, the isomerization reaction, which arises from the collapse of the enolate to afford the acyclic form, becomes rapidly predominant at higher temperature resulting in reverse selectivity (Figure 86). As can be seen in the enthalpy profile, the overall thermodynamic product of the cyclisation would be the $(E)\text{-}2,6\text{-}cis\text{-THP}$, which is 0.9 kcal/mol lower in energy than the $(E)\text{-}2,6\text{-}trans\text{-THP}$. These experimental and computational results accord with the tenet that the cyclisation is under kinetic control at low temperature, particularly at -78°C , whilst whereas thermodynamic control governs the stereochemical outcome at higher temperature, commonly above 0°C .

Figure 86 Isomerisation driven by thermodynamic control.

Such a change in the selectivity at elevated temperature is attributable to the unfavourable 1,3-diaxial interaction present in the *trans* product, for instance in the case of 2,6-

tetrahydropyrans, which seems to be the major driving force for the isomerisation. The most notable aspect of this phenomenon is that it appears strikingly general irrespective of other substituents on the rest of the ring when strong base is applied (Figure 51,6).

The cyclisations triggered by F^- or DBU are more complicated. Since these two bases are less basic than *t*BuOM, they may tightly bind to the OH-group in the course of the cyclisation. This also may result that the deprotonation and the cyclisation is a synchronous process. For that reason, the simplified bare anion TSs cannot be used to elucidate the origin of stereoselectivity.

Furthermore, as we did not see any notable selectivity pattern in the literature review for the cyclisations with F^- at ambient temperature (Figure 53), where we can assume a kinetic control, this type of reaction was not worthy of further computational investigation. In this case, the origin of the selectivity seems to be substrate-specific and a greater number of possible transition states with lesser-distinct structural differences could be expected. However, we showed that the cyclisation with TBAF becomes thermodynamically controlled at an elevated temperature, always favouring the more stable 2,6-*cis* product.

The reactions with DBU exhibited an 2,6-*cis* selectivity not only in the literature review (Figure 49) but also in our investigation. However, the selectivity was found to be low (*cis:trans* 1:0.5). Thus, computations cannot quantitatively reproduce the selectivity considering the relatively minor energy differences between the plausible TSs. The key revelation emerging from experimentation with DBU is that the DBU-catalysed reactions proved to be under kinetic control even at reflux.

5.3 Results and discussion of computational study of acid-catalysed cyclisation

The activation enthalpies of the acid-catalysed cyclisation were calculated to be 4.6 kcal/mol for the 26*transZ* TS and 4.1 kcal/mol for the 26*cisZ* TS (Figure 87), which is consistent with the observed diastereoselectivity (*cis* only). We found that the O-protonated products formed in the cyclisation were indeed stable intermediates (converged structural optimisation by DFT, having 1.56 Å O(H)-C bond distance in the THP) without including the counter anions. As all acids appear to give the same stereochemical outcome, the role of the counter ion was disregarded. Ring-opening reaction of the protonated tetrahydropyrans were also computationally not observed.¹⁹ We presume that the proton transfer between the O_{ring}-H and the enol carbon possesses a virtually negligible energy barrier considering the close proximity of the proton and the enol carbon, and the amount of enthalpy liberated through the proton transfer. Therefore, the cyclisation and the proton transfer can take place nearly simultaneously, which leads directly to the final products under kinetic control. In the case of the *trans* TS, the (*Z*)-isomer was found to be lower by 0.78 kcal/mol than the (*E*)-geometry in the enol. Likewise, of the *cis*-(*Z*) and *cis*-(*E*) TSs the former was always the lower ($\Delta H=0.15$ kcal/mol). The Bürgi–Dunitz trajectory is closer to tetrahedral angle in the 26*cisE* TS (103.6°) than that in 26*transZ* TS (107.1°). However, it has been shown that this factor is likely to be insignificant in the intramolecular cyclisation.⁴² Importantly, the OH...C(β) distance was shortened up to 1.9 Å, thereby reducing this bond length difference between the TS and the O-protonated product ($\Delta_{\text{bond length}}(\text{TS-product}) = 0.4$ Å). This reveals that the acid-catalyzed cyclisation takes place via a late-transition state as opposed to the base-catalyzed cyclisation (*vide supra*). As Clarke *et al.* has pointed out, there has been no tangible explanation for the *cis* preference in the acid-catalysed *oxa*-Michael cyclisation.¹⁹ In their study, the energy difference between the *trans* and the *cis* TS was rationalized to be a result of an increased pseudo-1,3 diaxial steric clash between the hydrogen and the electrophilic Michael acceptor in the *trans* TS. This is in full

agreement with our computational findings and explanation, however, this is only the case because of the relatively short bond-forming distance in the TSs and the consequent importance of the early-transition state. This, we believe, is the essence of understanding the origin of the stereocontrol.

Figure 87 Computed enthalpy profile for the acid-catalysed oxa-Michael cyclisation. 26cisE TS and 26transZ TSs with key structural parameters indicated.

5.4 Reflection on the earliness-lateness nature of the transition states and the stereochemical consequences

The computational studies revealed that the base-catalysed cyclisation tend to take place through an early-TS, as opposed to the acid-catalysed cyclisation, TS of which is rather late. We would like to quantitatively discuss this phenomenon. The question we raised is what causes the earliness and the lateness in the TSs.

The mechanism of the base-catalysed cyclisation involves a nucleophilic attack of the alkoxide anion to the electrophilic β -carbon to furnish the cyclisation product. The electron shell of the nucleophilic anion is reasonably more diffuse than a neutral hydroxyl group. It may follow that the bond formation between the alkoxide and the carbon atom occurs farther away than that in a neutral case. In other words, the alkoxide anion has a longer arm to reach the β -carbon of the double bond. By contrast, the acid-catalysed cyclisation begins with the protonation of the carbonyl group, thereby increasing the electrophilicity of the β -carbon⁴⁴. Hence, the β -carbon becomes more receptive to nucleophiles and the LUMO of the Michael-acceptor becomes slightly more contracted as well as lower in energy.⁴⁵ Due to the slightly decreased LUMO coefficients on the β -carbon and the neutral state of the hydroxyl group, the nucleophile is required to approach the carbon closer to initiate the bond formation. This proposed qualitative explanation is outlined in Figure 88.

Figure 88 Qualitative description of the origin of the earliness-lateness in the TSs.

Finding similar examples when the bond length is determinative in diastereoselection is a great challenge. However, one of the most illustrative examples is the relationship of the bond length and the level of diastereoselectivity in aldol reactions.^{46,47} The reactions with boron enolates generally display greater selectivity than the respective lithium enolate. This may be in part due to the significantly shorter B-O bond (1.5-1.6 Å) in comparison with the Li-O bond (1.9-2.0 Å), which enables a tighter and more organized TSs.⁴⁸ The significance of the substituent-ligand and the substituent-substituent interaction may be anticipated to be inversely proportional to M-O bond length, and directly proportional to the size of the metal ligand in the former case (Figure 89).

Figure 89 Schematic illustration of diastereoselective aldol reaction. M: B, Li.

6. Conclusion of the studies on acid- and base-catalysed oxa-Michael cyclisation

We have experimentally proved that the metal cation is not criteria for *trans* selectivity in the base-catalysed cyclisation at low temperature. The chelation model is therefore incorrect in the explanation of *trans* selectivity. The preference for the formation of equatorial-axial product at low temperature is indeed general as the same pattern applies to the 2,5-; 2,4-; 2,3-isomers as well.

The TSs of the base- and the acid-catalysed cyclisations differ in one respect. The bond-forming distance is appeared to be the game changer in selectivity. The long O-C distance eliminated the significance of the classical 1,3-diaxial interactions in the base-catalysed cyclisation. However, the substantially shorter distance gave rise to this repulsive interaction in the acid-catalyzed reaction, which is manifested in an exclusive *cis* selectivity under kinetic control. Earlier, the selectivity of acid-catalysed cyclisation was believed to be controlled by orbital overlapping,¹² in contrast, we propose that the high selectivity of the acid-catalyzed reactions is rooted in the short bond-forming distance, which enhances the 1,3-diaxial clash in the product-like TS.

On the basis of the structural information obtained thus far, electrostatic effects are likely to be the main contributor to the *trans* selectivity in the base-catalyzed oxa-Michael cyclisation.

We are delighted with the cautionary note of the present study about selectivity-determining factors and intrigued about the avenues this study will open for further the mechanistic investigation in the intramolecular oxa-Michael cyclisation.

We also hope that these findings will stimulate the rethinking of the importance of ‘lateness-earliness’ in transition states and more attention will be paid to it when it comes to elucidating selectivity in organic reactions

7. Experimental section

General information

Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware. Anhydrous DCM was freshly distilled from CaH_2 under nitrogen, anhydrous THF was freshly distilled from sodium metal and benzophenone under nitrogen, anhydrous toluene was freshly distilled from sodium metal under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. Column chromatography was conducted with Merck silica gel (230-400 mesh). All the chemicals were obtained from commercial sources and used as received without purification unless indicated otherwise. [18]-Crown-6 and [15]-Crown-5 were purchased from Alfa Aesar. [18]-Crown-6 were recrystallized according to the literature procedure⁴⁹. The THF solutions of *t*BuOM (M:K,Na) in Sure/Seal™ bottles were purchased from Sigma Aldrich. NMR spectra were recorded on JEOL ECA 400SL (400MHz), JEOL ECA 400 (400MHz) and Bruker AV400 (400 MHz) spectrometers in CDCl_3 solutions. Chemical shifts are given in ppm (referenced to the residual chloroform ^1H -spectrum 7.26 ppm, ^{13}C -spectrum: 77.16 ppm) and coupling constants in Hz. In the cases of severely overlapping peaks, the integration of individual peaks is assumed to be the expected value. FTIR spectra were recorded on Shimadzu IRPrestige-21 using KBr plate. Only the most intense and/or diagnostic IR peaks are reported. High-resolution mass spectrometry (HRMS) measurements were performed on Micromass® Q-ToF Premier™ (ESI-TOF) employing electrospray ionization technique (ESI) in methanol solutions.

General procedure for *t*BuOK catalyzed cyclisation

To a solution of alcohol (0.1 mmol) in dry THF (1 ml) was added $t\text{BuOK}$ in THF solution (0.2 eqv.) at -78°C dropwise placing the needle against the wall of the round-bottom flask. The reaction was stirred for 45 mins at -78°C then quenched by adding aqueous NH_4Cl solution (1 ml). The mixture was allowed to warm to room temperature and diluted with diethyl ether (2 ml) while stirring. The organic phase was separated, and the aqueous phase was extracted with diethyl-ether (2 ml) twice. The combined organic phase was dried over Na_2SO_4 , then filtered through a silica/Celite pad washing with diethyl-ether, and finally concentrated *in vacuo* to yield a yellow oil.

General procedure for $t\text{BuOK}$ catalyzed cyclisation in the presence [18]-Crown-6

To a solution of [18]-Crown-6 (0.1 mmol, 1 eqv.) in dry THF (0.5 ml) was added $t\text{BuOK}$ in THF solution (0.2 eqv.) at room temperature and stirred for 15 mins. The mixture was cooled down to -78°C and stirred for 10 mins. A solution of alcohol (0.1 mmol, 1 eqv.) in dry THF (0.5 ml) was added dropwise placing the needle against the wall of the round-bottom flask. The reaction was stirred for 45 mins at -78°C then quenched by adding aqueous NH_4Cl solution (1 ml). The mixture was allowed to warm to room temperature and diluted with diethyl-ether (2 ml) while stirring. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 ml) twice. The combined organic phase was dried over Na_2SO_4 , then

filtered through a silica/Celite pad washing with diethyl-ether, and finally concentrated *in vacuo* to yield a yellow oil.

General procedure for TBAF or DBU catalyzed cyclisation

To a solution of alcohol (0.1 mmol, 1 eqv.) in dry THF (1 ml) was added TBAF (1 eqv.) or DBU (1 eqv.) in one portion at room temperature and stirred for 15 hours. The crude mixture was then filtered through a silica/Celite pad washing with diethyl ether, and finally concentrated *in vacuo* to yield a yellow oil.

General method for cross-metathesis reaction

To a solution of the titled compound (1.1 mmol, 1 eqv.) in dry DCM was added methyl acrylate (3.4 mmol, 3 eqv.) under gentle nitrogen flow. After 15 mins, a solution of Grubbs-II (0.06 mmol, 0.05 eqv. $c = 0.05 \text{ mol/dm}^3$) in dry DCM was added dropwise at reflux. The reaction was monitored by TLC (hexane:ethyl acetate 80:20), upon completion (2-4 h) the reaction was left open to air overnight. Purification of the crude mixture by flash column chromatography (gradient, 95:5, 90:10, 80:10, 70:10 hexane:ethyl acetate) furnished the respective *oxa*-Michael precursor as a transparent oil. Yields: 2,6-THP precursor: 93%, 2,5-THP precursor: 75%, 2,4-THP precursor: 80%, 2,3-THP precursor: 86%

2,6-disubstituted THP**(*E*)-methyl 7-hydroxy-7-phenylhept-2-enoate (3)**

¹H NMR (400 MHz, CDCl₃): 7.26-7.38 (m, 5H), 6.92 (dt, *J* = 15.6, 7.0 Hz, 1H), 5.79 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.66-4.70 (m, 1H), 3.12 (s, 3H), 2.21 (qd, *J* = 7.0, 1.5 Hz, 2H), 1.56-1.86 (m, 3H), 1.40-1.52 (m, 1H)

¹³C NMR (100 MHz, CDCl₃): 24.39, 32.15, 51.55, 74.51, 121.33, 125.97, 127.83, 128.68, 144.68, 149.22, 167.22

IR (cm⁻¹): 1647, 1431, 1273, 1200, 1147, 569

HRMS: Calculated for C₁₄H₁₉O₃ (M+H)⁺: 235.1334, Found: 235.1330

***trans* methyl 2-(6-phenyltetrahydro-2*H*-pyran-2-yl)acetate (4)**

¹H NMR (400 MHz, CDCl₃): 7.24-7.27 (m, 1H), 7.33-7.39 (m, 4H), 4.88 (t, *J* = 5.7 Hz, 1H), 4.20-4.26 (m, 1H), 3.70 (s, 3H), 2.75 (dd, *J* = 14.7, 8.6 Hz, 1H), 2.50 (dd, *J* = 14.7, 5.7 Hz, 1H), 1.87-2.03 (m, 2H), 1.66-1.78 (m, 3H), 1.45-1.53 (m, 1H)

¹³C NMR (100 MHz, CDCl₃): 18.88, 29.48, 29.95, 39.37, 51.81, 68.82, 72.96, 126.68, 127.19, 128.51, 141.61, 171.98

IR (cm^{-1}): 1738, 1495, 1435, 1346, 1287, 1262, 1202, 1173, 1142, 1094, 1072, 1020, 793, 756, 727, 7000

HRMS: Calculated for $\text{C}_{14}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$)⁺: 235.1334, Found: 235.1332

***cis* methyl 2-(6-phenyltetrahydro-2*H*-pyran-2-yl)acetate (5)**

¹H NMR (400 MHz, CDCl_3): 7.22-7.25 (m, 1H), 7.29-7.34 (m, 4H), 4.40 (dd, $J = 11.3, 2.2$ Hz, 1H), 3.95-4.01 (m, 1H), 3.68 (s, 3H), 2.66 (dd $J = 15.1, 7.1$ Hz, 1H), 2.48 (dd, $J = 15.1, 6.0$ Hz, 1H), 1.92-1.99 (m, 1H), 1.84-1.87 (m, 1H), 1.71-1.78 (m, 2H), 1.44-1.56 (m, 1H), 1.29-1.42 (m, 1H)

¹³C NMR (100 MHz, CDCl_3): 23.79, 30.94, 33.18, 41.55, 51.56, 74.73, 79.63, 125.74, 127.16, 128.18, 143.12, 171.79

IR (cm^{-1}): 1740, 1645, 1491, 1437, 1198, 1086, 1044, 926, 754, 698, 522

HRMS: Calculated for $\text{C}_{14}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$)⁺: 235.1334, Found: 235.1335

2,5-disubstituted THP

(*E*)-methyl 7-hydroxy-6-phenylhept-2-enoate (12)

¹H NMR (400 MHz, CDCl₃): 7.19-7.21 (m, 2H), 7.25-7.28 (m, 1H), 7.33-7.36 (m, 2H), 6.91 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.76 (dt, *J* = 15.7, 1.6 Hz, 1H), 3.74 (br d, *J* = 6.8 Hz, 2H), 2.8 (dtd, *J* = 11.5, 6.6, 5.0 Hz, 1H), 2.07-2.13 (m, 2H), 1.89 (dddd, *J* = 13.6, 8.8, 7.0, 5.0 Hz, 1H), 1.75 (dddd, *J* = 13.6, 10.1, 8.1, 6.6 Hz, 1H)

¹³C NMR (100 MHz, CDCl₃): 29.99, 30.34, 48.14, 51.57, 67.52, 121.36, 127.20, 128.18, 128.99, 141.46, 149.01, 167.17

IR (cm⁻¹): 1746, 1651, 1107, 1088, 698, 515

HRMS: Calculated for C₁₄H₁₉O₃ (M+H)⁺: 235.1334 Found: 235.1337

***trans* methyl 2-(5-phenyltetrahydro-2*H*-pyran-2-yl)acetate (16)¹**

¹H NMR (400 MHz, CDCl₃): 7.18-7.33 (m, 5H), 4.01 (ddd, *J* = 11.3, 4.4, 2.3 Hz, 1H), 3.81-3.88 (m, 1H), 3.46 (t, *J* = 11.3 Hz, 1H), 2.78-2.85 (m, 1H), 2.59 (dd, *J* = 15.2, 7.8 Hz, 1H), 2.47 (dd, *J* = 15.2, 5.2 Hz, 1H), 2.03-2.07 (m, 1H), 1.76-1.86 (m, 2H), 1.50-1.57 (m, 1H)

¹³C NMR (100 MHz, CDCl₃): 30.56, 31.72, 41.49, 42.69, 52.00, 74.06, 74.37, 126.95, 127.57, 128.78, 142.28, 172.06

IR (cm⁻¹): 1738, 1636, 1493, 1437, 1196, 1163, 1109, 1086, 1007, 758, 700, 527

HRMS: Calculated for C₁₄H₁₉O₃ (M+H)⁺: 235.1334, Found: 235.1338

¹ 2,5-*trans* and *cis* diastereomers were found to be an inseparable mixture, *trans* was obtained by driving the isomerisation to full completion at reflux.

2,4-disubstituted THP**(E)-methyl 7-hydroxy-5-phenylhept-2-enoate (14)**

¹H NMR (400 MHz, CDCl₃): 7.16-7.23 (m, 3H), 7.29-7.32 (m, 2H), 6.82 (dt, *J* = 15.6, 7.3 Hz, 1H), 5.77 (dt, *J* = 15.6, 1.5 Hz, 1H), 3.68 (s, 3H), 3.52-3.59 (m, 1H), 3.42-3.49 (m, 1H), 2.88-2.95 (m, 1H), 2.53 (td, *J* = 7.3, 1.4 Hz, 2H), 1.97 (dddd, *J* = 14.1, 7.7, 6.8, 4.8 Hz, 1H), 1.82 (dddd, *J* = 14.1, 10.2, 6.1, 5.3 Hz, 1H), 1.20 (t, *J* = 5.2 Hz)

¹³C NMR (100 MHz, CDCl₃): 38.83, 39.76, 41.75, 60.87, 122.61, 126.84, 127.63, 128.84, 143.58, 147.27, 166.96

IR (cm⁻¹): 1697, 1651, 1495, 1435, 1277, 1211, 1159, 1041, 986, 764, 702, 553

HRMS: Calculated for C₁₄H₁₉O₃ (M+H)⁺: 235.1334, Found: 235.1335

***trans* methyl 2-(4-phenyltetrahydro-2*H*-pyran-2-yl)acetate (17)**

¹H NMR (400 MHz, CDCl₃): 7.20-7.35 (m, 5H), 4.35 (dt, *J* = 10.2, 5.4 Hz, 1H), 3.73-3.85 (m, 2H), 3.71 (s, 3H), 3.02-3.11 (m, 1H), 2.83 (dd, *J* = 14.9, 8.4 Hz, 1H), 2.53 (dd, *J* = 14.9, 5.9 Hz, 1H), 2.10 (ddd, *J* = 13.5, 8.8, 4.3 Hz, 1H), 1.89-1.93 (m, 2H), 1.78 (dt, *J* = 13.5, 4.8 Hz, 1H)

^{13}C NMR (100 MHz, CDCl_3): 32.23, 35.31, 35.83, 38.25, 51.92, 62.46, 69.93, 126.37, 127.30, 128.68, 144.60, 171.89

IR (cm^{-1}): 1738, 1634, 1440, 1385, 1260, 1204, 1153, 1086, 1034, 766, 700, 500

HRMS: Calculated for $\text{C}_{14}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 235.1334, Found: 235.1331

***cis* methyl 2-(4-phenyltetrahydro-2*H*-pyran-2-yl)acetate (18)**

^1H NMR (400 MHz, CDCl_3): 7.20-7.35 (m, 5H), 4.11 (dt, $J = 6.1, 3.4$ Hz, 1H), 3.90 (dddd, $J = 10.4, 7.9, 5.2, 2.1$ Hz, 1H), 3.70 (s, 3H), 3.60 (m, 1H), 2.78-2.86 (m, 1H), 2.60 (dd, $J = 15.2, 7.9$ Hz, 1H), 2.45 (dd, $J = 15.2, 5.2$ Hz, 1H), 1.88-1.91 (m, 2H), 1.76 (m, 2H), 1.49 (q, $J = 12.5$ Hz, 1H)

^{13}C NMR (100 MHz, CDCl_3): 33.26, 39.18, 41.54, 41.65, 51.89, 68.45, 74.42, 126.58, 126.88, 128.70, 145.50, 171.85

IR (cm^{-1}): 1730, 1603, 1495, 1435, 1381, 1310, 1283, 1202, 1155, 1126, 1084, 1007, 760, 700, 532

HRMS: Calculated for $\text{C}_{14}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 235.1334, Found: 235.1329

2,3-disubstituted THP**(E)-methyl 7-hydroxy-4-phenylhept-2-enoate (9)**

¹H NMR (400 MHz, CDCl₃): 7.30-7.33 (m, 2H), 7.21-7.26 (m, 1H), 7.17-7.19 (m, 2H), 7.07 (dd, *J* = 15.6, 7.9 Hz, 1H), 5.80 (dt, *J* = 15.7, 1.2 Hz, 1H), 3.71 (s, H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.41 (q, *J* = 7.6 Hz, 1H), 1.79-1.94 (m, 2H), 1.44-1.62 (m, 2H)

¹³C NMR (100 MHz, CDCl₃): 30.72, 31.24, 48.40, 51.66, 62.74, 120.64, 127.05, 127.85, 128.92, 141.98, 151.93, 167.19

IR (cm⁻¹): 1715, 1645, 1495, 1454, 1435, 1275, 1173, 1057, 737, 700, 517

HRMS: Calculated for C₁₄H₁₉O₃ (M+H)⁺: 235.1334, Found: 235.1332

***cis* methyl 2-(3-phenyltetrahydro-2H-pyran-2-yl)acetate (19)**

¹H NMR (400 MHz, CDCl₃): 7.41-7.42 (m, 2H), 7.20-7.32 (m, 3H), 4.25 (ddd, *J* = 9.3, 4.5, 3.5 Hz, 1H), 4.04-4.10 (m, 1H), 3.62-3.68 (m, 2H), 3.63 (s, 3H), 2.92 (q, *J* = 4.4 Hz, 1H), 2.56 (dd, *J* = 15.6, 9.3 Hz, 1H), 2.15 (dd, *J* = 15.6, 4.5 Hz, 1H), 1.99-2.05 (m, 1H), 1.84-1.92 (m, 2H), 1.41-1.48 (m, 1H)

¹³C NMR (100 MHz, CDCl₃): 21.72, 29.23, 37.75, 43.44, 51.81, 67.38, 76.43, 126.51, 128.40, 129.40, 142.05, 172.36

IR (cm^{-1}): 1748, 1645, 1602, 1495, 1435, 1371, 1317, 1258, 1192, 1167, 1082, 1003, 762, 706, 488

HRMS: Calculated for $\text{C}_{14}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$) $^{+}$: 235.1334, Found: 235.1332

***trans* methyl 2-(3-phenyltetrahydro-2*H*-pyran-2-yl)acetate (20)**

^1H NMR (400 MHz, CDCl_3): 7.17-7.32 (m, 3H), 7.26-7.32 (m, 2H), 4.04-4.08 (m, 1H), 3.92 (ddd, $J = 10.0, 8.9, 3.5$ Hz, 1H), 3.58-3.61 (m, 1H), 2.52 (td, $J = 10.0, 4.1$ Hz, 1H), 2.30 (dd, $J = 15.2, 8.9$ Hz, 1H), 2.23 (dd, $J = 15.2, 3.5$ Hz, 1H), 1.99-2.00 (m, 1H), 1.66-1.83 (m, 3H)

^{13}C NMR (100 MHz, CDCl_3): 26.39, 32.27, 39.54, 48.57, 51.73, 68.69, 79.06, 127.01, 127.90, 128.87, 142.68, 171.34

IR (cm^{-1}): 1742, 1634, 1493, 1435 1375, 1290, 1204, 1163, 1107, 1078, 1047, 760, 703, 530

HRMS: Calculated for $\text{C}_{14}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$) $^{+}$: 235.1334, Found: 235.1345

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9. NMR Spectra

X : parts per Million : 1H

Chapter 3 SYNTHESIS OF THE PROPOSED STRUCTURE OF *CRYPTOCONCATONE H*

1. Introduction

1.1. Brief introduction of natural products isolated from *Cryptocarya* species

Cryptocarya is a genus of evergreen trees, in the family of *Lauraceae*. More than 350 species of this genus have been described in tropical and subtropical regions. A large number of phytochemical studies resulted in the isolation of different secondary metabolites from this species, most importantly, α -pyrone derivatives^{1,2,3,4}, flavonoids^{5,6,7}, and several alkaloids^{8,9}.

In the early 90's, *Leete et al.* investigated the possible biosynthetic pathways of the formation of the *Psilotinin* natural product by isotopic-labelling experiment.¹⁰ Phenylalanine was found to be the starting building-block, which upon deamination produced cinnamic acid. As is well known, the co-enzyme A ester of cinnamic acid serves an entry point for the biosynthesis of various polyketides¹¹ and fatty acids¹² (Figure 90). The most common chain elongation is done with the aid of malonyl-CoA while liberating CO₂. The NADPH converts the ketone into hydroxyl group followed by dehydration, which sets the stage for enzymatic ring closure. It was hypothesized that an enzyme protonates the γ -carbon atom to initiate the attack of carboxyl group on the δ -position, furnishing α -pyrone moiety. Besides, the sequences of the chain extension with malonyl-CoA could result in the formation of various polyketides containing α -pyrone fragment, such as *cryptofolione*, *goniothalamine*, *kurzilactone*, *strictifolione* and different *cryptomoscatone* derivatives (Figure 91, 92). These natural products were isolated from various *Cryptocarya* species.

Figure 90

The α -pyrone-containing natural product family, which were isolated from *Cryptocarya* genus, are shown in Figure 91 along with a comprehensive list of their currently available total syntheses, which we do not aim to comprehensively discuss herein.

Kurzilactone was isolated from the leaves of *Cryptocarya kurzii*, which is an indigenous species in Malaysia.¹³ This natural product exhibits significant cytotoxicity against the KB human carcinoma cell line. Originally, only a provisional stereochemical assignment by NMR spectroscopy was reported; both stereogenic centers bearing hydroxyl groups in the side chain were assigned a *syn*-relationship, but a corrected *anti*-relationship was later reported on the basis of a synthetic study.¹⁴

Cryptomoscatone D2, which was isolated from the stem bark of *Cryptocarya moschata*,¹⁵ exhibited antiproliferative activity against non-infected human cervical carcinoma C33A, human lung's fibroblast MRC-5 and HPV-infected HeLa, SiHa cell lines.¹⁶ In addition, the structurally nearly identical (*Z*)-*cryptomoscatone D2* bearing *cis* geometry was found to be a G2-checkpoint inhibitor in human breast carcinoma (MCF-7) cell line.¹⁷ This member of *cryptomoscatone* family was isolated from *Cryptocarya concinna* tree.¹⁵ The last member of D-series is *cryptomoscatone D1*. The stereochemical relationship of the hydroxyl moieties was

initially determined to be all *syn* with the aid of NMR- and CD- spectroscopy.¹⁵ By its total synthesis,¹⁸ the stereochemistry was revised to be *syn-anti*.

Cryptofolione was extracted from stem bark of different species of *Cryptocarya*, such as *Cryptocarya myrtifolia*¹⁹ and *Cryptocarya moschata*¹⁵. This polyketide displayed a considerable activity against trypomastigotes of *Trypanosoma cruzi*, reducing the number of the parasites by one third in a concentration of 250 µg/mL.²⁰ In addition, it also showed a mild leishmancidal inhibitory effect. Despite the extensive CD- and ¹³C-NMR analysis, the absolute stereochemistry of the *anti*-diol unit remained unestablished.¹⁵ The exact structure was confirmed when its two isomers were synthesized.²¹

Cryptocaryalactone was isolated from *Cryptocarya bourdilloni*.^{22,23} The structure of was established by its synthesis.^{24,25} This natural product appeared to be a natural germinator with no effect on corn.

Strictifolione, which showed antifungal activity,^{26,27} was isolated from the stem bark of *Cryptocarya strictifolia* that grows in the rainforest of West Kalimantan, Indonesia.²⁸ Shortly after its isolation, the relative and the absolute configuration were reassigned by the same group who isolated it through its first total synthesis.²⁹

Goniothalamine was first isolated from the dried bark of *Cryptocarya caloneura*,³⁰ and later was discovered in a variety of other tropical-subtropical plants, such as *Cryptocarya moschata*¹⁵, *Bryonopsis laciniosa*³¹, and different *Goniothalamus*³² species. Its stereogenic centre was initially assigned to be (*S*)-configuration.³⁰ The revision of (*S*)-stereochemistry was only made a decade later.¹⁵ In terms of biological properties, it shows *in vitro* cytotoxic activity^{33,34} via inducing apoptosis in breast carcinoma MDA-MB-23, T47D, MCF-7, human cervical carcinoma HeLa, gastric carcinoma HGC-27, leukaemia carcinoma HL-60 and ovarian carcinoma Caov-3.³⁵ It was also found to be highly effective against the mosquito larvae.³¹ It

was shown that the (*E*)-geometry of the styrol group was essential for its antiproliferative activity.

Although it has not been fully proved the presence of the α,β -unsaturated lactone, which acts as a Michael-acceptor, is believed to be the root cause of their observed pharmacological effects.

Figure 91

The next subgroup of this natural product family has a tetrahydropyran ring embedded in the carbon chain (Figure 92).

Obolactone was isolated from *Cryptocarya obovate*.⁷ Its relative configuration was first determined by crystallographic analysis, and then its absolute stereochemistry was established by CD-analysis. *Obolactone* exhibited potent cytotoxicity against KB cells with a noticeable $IC_{50} = 3 \mu M^2$. More interestingly, it also acted against *Trypanosoma brucei*, which is associated with African sleeping sickness.²

In 2000, *Yoshida et al.* isolated a series of *cryptopyranmoscatones*, namely A1, A2, A3, B1, B2, and B4 members, from the branch of stem bark of *Cryptocarya moschata* tree found in Southeastern region of Brazil.¹⁵ This class of natural products contains a tetrahydropyran ring which, other than B2, features *trans* stereochemistry. The total syntheses of these natural products have been recently disclosed. To the best of our knowledge, there has been no biological evaluation of the *cryptopyranmoscatone* family.

Figure 92

More recently, in *Nakagawa-Goto, K.*'s group six new lactone derivatives containing a unique spiro[3.5]nonane moiety, were isolated from *Cryptocarya laevigata* (Figure 93).³⁶ This class of natural products was logically named *cryptolaevilactone*. Their structure was determined based on the observed COSY, HMBC, and NOESY correlations. The absolute stereochemistry assignment was also supported by their experimental ECD spectrum.

Figure 93

In 2016, *Luo et al.* disclosed ten new styryl α,β -unsaturated lactones from the leaves and the twigs of *Cryptocarya concinna* found in subtropical mainland China.³⁷ Representatives structures of the isolated natural products can be seen in Figure 94. Their structures were said to be elucidated by HRESIMS, various NMR experiments as well as chemical derivatization. As part of their quest for new anti-inflammatory agents, their inhibition activity of NO production, which was induced by LPS in RAW 264.7 macrophages in their biological assay, was investigated. Their study showed that the newly isolated natural products displayed notable NO-inhibitory effect, as a result, they were claimed to be worthy of further investigation as potential anti-inflammatory agents in the future.

In their isolation study, one of the natural products named *cryptoconcatone H 1* was found to possess a tetrahydropyran core. The relative stereochemistry of proton 2, 6 was assigned as *cis* based on their ROESY correlations with proton 4. The correlation of proton 2, 6 with one another was not mentioned, which would have further corroborated the *cis* stereochemistry. No coupling constants of protons 2, 6 were provided, and no decoupling experiment was done to determine them. Moreover, the ROESY spectrum in question was not

reported. Considering the lack of a detailed stereochemical assignment of the THP core, we believed it was worth the synthetic effort to confirm the stereochemistry.

Figure 94

As it was mentioned in the previous paragraph, it is not uncommon that initial structural assignment is incorrect^{38,39} even with the aid of several cutting-edge NMR methods^{40,41,42}. This further supported our effort aimed at the synthesis of the reported compound.

It was not only us who were intrigued by the possibility of a structural revision of the THP-containing natural product. To the best of our knowledge, there was no reported synthetic study of the natural product at the commencement of this total synthesis project. However, shortly after this project was launched, *Pilli et al.* reported the synthesis of two *cryptoconcatone H* isomers guided by DP4+ calculations (Figure 95).⁴³ Prior to the calculation of DP4+ probabilities,^{44,45} a systematic conformational search in the gas phase was performed for the 8 plausible diastereomers using MMFF force field. The lowest energy conformer (within 10 kcal/mol) were optimized at B3LYP/6-31G* level of theory. Ultimately, the Boltzmann-averaged shielding tensors were calculated utilizing the gauge including atomic orbitals method (GIAO) at mPW1PW91/6-31+G** level of theory employing PCM solvent model. The obtained tensors were used to calculate the probability of a proposed structure. Based on their calculations, compound **8** having *trans*-THP core was proposed to be the most probable for *cryptoconcatone H*. As they assumed the absolute configuration of C-4' (pyranone ring) was

misassigned by *Luo et al.*,³⁷ the two epimers were synthesized by a sequential usage of *Krische*'s asymmetric allylation method (Figure 95). The *trans*-THP was constructed via a Pd(II)-mediated cyclisation. After a few functional group manipulations, the desired isomers were obtained. The isomer **9** showed a closely matching ¹H and ¹³C NMR data but the specific optical rotation was found to be the opposite. Thus, they proposed that the correct structure of the isolated natural product was very likely to be the enantiomer of compound **9**. Nevertheless, the reported structure has not been as yet synthesized. It is worth noting that *Pilli*'s approach can be regarded as unique since a stereochemical revision is generally initiated by the synthesis of the reported structure, rather than by calculating the most probable structure of the natural product.

Figure 95

2. Results and Discussion

2.1. The motive of our synthetic effort and the main elements of the target

The initial uncertainty of the stereochemistry of the tetrahydropyran ring prompted us to embark on a synthesis of the reported structure of *Cryptoconcatone H*.³⁷ At the commencement of this total synthesis project, there was no reported synthesis for this natural product. Thus, the purpose of the present study was to design a concise synthetic route and to provide a synthetic evidence in order for its structural elucidation to be clarified. The synthesis described here benefits from an effective strategy rather than a methodological advancement. The natural product could be dissected into four distinctive moieties (Figure 96). One of those is the separate dihydro-pyranone attached to the main *cis*-tetrahydropyran core via a CH₂ linker. The latter incorporates an embedded *anti*-diol moiety and the pendant styrol fragment, which can be derived from a much simple starting material cinnamaldehyde.

Figure 96

2.2 Retrosynthetic analysis of *Cryptoconcatone H*

Our initial retrosynthesis of *Cryptoconcatone H* **1** is outlined in Figure 97. The ring closing-metathesis is a common retrosynthetic approach towards the construction of dihydro-pyranone. The required intermediate **10** can be accessed by acylation of the allyl-alcohol with acryloyl chloride. The chiral allyl alcohol moiety **11** can be introduced upon asymmetric allylation of the corresponding aldehyde **12**. Building on the findings of our previous investigation, we intend to utilize the acid-catalysed intramolecular Michael cyclisation as a facile method to construct the *cis*-tetrahydropyran core **12**. This is envisioned by using precursor **13**, which can be originated from the regioselective cross-metathesis reaction of the diol **14** with crotonaldehyde. The introduction of *anti* stereochemistry of the diol **15** can be controlled by exploiting the existing stereogenic centre that is expected to participate in an intramolecular group transfer with a suitable reagent. This approach provides us two potential synthetic routes to construct the required configuration. A convenient procedure for establishing the stereogenic centre in question involves the reaction of aldehyde **15** with allyl-zinc reagent, giving the diol **14** in one step (*route A*). An alternative, the diastereoselective reduction of β -hydroxy ketone can be employed to furnish the desired *anti* product (*route B*). In the former case, the aldehyde **15** can be resulted from the reduction of compound **16** bearing a thiazolidinethione chiral auxiliary. The displacement of thioxothiazolidinone with *N,O*-dimethylhydroxylamine can give access to Weinreb-amide **18** which can be converted into the corresponding ketoalcohol **17**. Having the alcohol in β -position can set the stage for a diastereoselective reduction of the ketone group in favour of the *anti* diol. Lastly, the intermediate **16** can be accessible by an asymmetric aldol condensation of the commercially available cinnamaldehyde and acylated-thioxothiazolidinone.

Figure 97

2.3. Synthetic attempts

Our synthetic endeavour commenced with preparation of the chiral auxiliary that enables the installation of the first stereogenic center. It was prepared over three steps, as shown in Figure 98. The aminoalcohol **21** was acquired as the sole product by treatment of L-phenylalanine **20** with BH_3 generated *in situ* by NaBH_4 in the presence of BF_3 etherate (80%). Subsequent exposure of **21** to carbon disulfide under basic conditions at reflux provided the desired thioxothiazolidinone ring **22** in an excellent yield (93%).⁴⁶ Finally, compound **22** could readily be converted into its acylated derivative **23** using acetyl chloride (68%).

Figure 98

This sequence to prepare the chiral auxiliary could be conducted on a 20-gram scale, which provided ample material for the subsequent asymmetric aldol reaction (Figure 99).

Figure 99

Table 9

Entry	Equivalents	t	Conversion	d.r.
1.	1.2 eqv. TiCl_4 / 1.2 eqv. DIPEA	2h	61%	7 : 1
2.	1.2 eqv. TiCl_4 (toluene solution) / 1.2 eqv. DIPEA	2h	50%	5.5 : 1
3.	1.2 eqv. TiCl_4 / 1.2 eqv. DIPEA	O.N.	42%	5 : 1
4.	1.8 eqv. TiCl_4 (toluene solution) / 1.8 eqv. DIPEA	2h	40%	2 : 1
5.	1.5 eqv. TiCl_4 (toluene solution) / 1.1 eqv. Spartein	2h	50%	2 : 1
6.	1.5 eqv. TiCl_4 (toluene solution) / 1.1 eqv. DIPEA	2h	42%	0.65:1
7.	1.8 eqv. TiCl_4 / 2.4 eqv. DIPEA	3.5h	36%	1 : 1

We first performed the reaction in accordance with a reported protocol for the asymmetric aldol reaction by *Yadav et al.*⁴⁷ The authors conducted reaction at -78°C using 1.2 eqv. of TiCl_4 and DIPEA, which yielded the desired product in a 9:1 diastereomer ratio in a good yield (83%). While producing sufficient amount of aldol product for further experimentation, we were not able to reproduce the reported conversion and selectivity in our hands (entry 1). The low conversion associated with preparing the aldol product was exacerbated by the fact that the selectivity was not satisfactory considering the early stage of the synthesis. This shortcoming prompted us to conduct a series of optimization reactions. In order to avoid the formation of local hotspots, we conducted the reaction by the slow addition of a solution of cinnamaldehyde in DCM to the enolate at -78°C . The toluene solution of TiCl_4 was used to test if the presence of a non-polar solvent influences either the conversion or the selectivity. Slightly decreased conversion and selectivity was observed under this condition (entry 2). Even when the reaction was left to stir overnight at -78°C neither of them improved (entry 3). Next, we increased the equivalence of TiCl_4 and DIPEA, but it led to a significantly

decreased selectivity (entry 4). Following an *Organic Synthesis* procedure established by *Crimmins et al.*, Sparteine was used as a base with a slight excess of TiCl_4 .⁴⁶ Unfortunately, this condition could not bring any improvement for the conversion and the selectivity (entry 5). The modified version of this procedure, which employed DIPEA but using the same number of equivalents as previously, also failed to enhance the conversion, only a slight increase in selectivity was observed (entry 6). Finally, we used a large excess of DIPEA, which resulted in a 1:1 mixture of the two diastereomers (entry 7).

The latter was in agreement with the general observation that use of excess base favours the formation of the opposite diastereomer.^{48,49} In both transition states, the electrophilic aldehyde is accommodated at the opposite side of the benzyl substituent for the avoidance of steric clash. It is proposed that in the absence of base the thiocarbonyl group coordinates to the titanium displacing a chloride anion and the reaction, therefore, takes place through a chelation-controlled TS to give *anti* isomer as a major product. By contrast, this chelation is no longer favoured when excess base is used. This leads to a non-chelated and dipole minimized TS, which give rise to *syn* product (Figure 100).^{50,51}

Figure 100

The diminished selectivity was not unexpected either. For the asymmetric aldol reaction with thiazolidinethione chiral auxiliary, high selectivity can be obtained when substrates bearing α -substituent are used, which is not typically the case for substrates devoid of substituent in α -position (Figure 101).

Figure 101

In spite of an extensive optimization, the conversion and the selectivity did not improve. Best results were obtained when the original protocol was employed (entry 1).⁴⁷

At the outset, we intended to get access to the diol **14** through a Barbier reaction.^{52,53,54} The most striking feature of this reaction is that the carbon-carbon bond formation takes places in aqueous medium. Nevertheless, the mechanism is not fully understood. Furthermore, better performance can be witnessed when saturated aqueous solution of NH_4Cl is used as co-solvent.

We attempted to prepare aldehyde **15** by the reductive cleavage of the chiral auxiliary with DIBAL-H. Only a high excess of DIBAL-H could drive the reaction to completion (Figure 102). Use of 2 eqv. was not effective to reduce all quantity of SM. In the case of more than 2 eqv. of DIBAL-H, the SM disappeared but an unidentified intermediate was detected in the crude NMR spectrum.

Figure 102

Table 10

Entry	Equivalents	t	Conversion	Crude NMR
8.	2 eqv. DIBAL-H	30min	~ 70%	SM, product unidentified intermediate
9.	3 eqv. DIBAL-H	30min	100%	product, unidentified intermediate
10.	12 eqv. DIBAL-H	30min	100%	product only
11.	6 eqv. DIBAL-H	30min	-	unidentified intermediate

As a control experiment to test if we can reproduce the reported modification in the literature, the hydroxyl group in intermediate **16** was protected as its TBS-ether to give

compound **25**, which was then subjected to reduction with 1 eqv. of DIBAL-H (Figure 103). The reaction resulted in a starting material-product 2:1 ratio. In parallel, the reductive cleavage of thiazolidinethione **16** with LiAlH_4 could be accomplished without incident, which would have enabled us to apply *Krische*'s asymmetric allylation strategy to establish the *anti*-diol **14**.⁵⁵ These two bypass experiments suggested that the capricious behaviour of the reduction may have arisen from the uncertain quality of DIBAL-H reagent we had. Apart from that, we had enough aldehyde in hand to attempt the Barbier reaction.

Figure 103

The first attempt was done according to the original *Luche* procedure, but the selectivity turned out to be moderate (Figure 104).⁵⁴ At this point, we thought that the low selectivity could be attributable to the presence of thiazolidinethione by coordinating to zinc. The aldehyde **15** was suspected to be unstable on purification thus we used the crude mixture of the reduction for the Barbier reaction at first. Interestingly, the reaction with the purified aldehyde was found to be less selective. Applying preformed allyl-zinc reagent had no effect on the diastereoselectivity. Use of indium led to significantly reduced selectivity. By and large, the Barbier reaction proved to be rather inefficient at delivering synthetically useful selectivity, hence, we next turned our attention to *route B*.

Figure 104

Table 11

Entry	Conditions	<i>T</i>	<i>t</i>	Selectivity
12.	thione 28 was present / Zn added portionwise	0°C	2h	1:0.53
13.	Aldehyde 15 only/ Zn added portionwise	0°C to RT	O.N.	1:0.72
14.	thione 28 was present / preformation of Zn-allyl	0°C to RT	O.N.	1:0.64
15.	thione 28 was present / In added portionwise	0°C to RT	O.N.	1:1

By analogy to Weinreb ketone synthesis, we believed that the addition of allyl Grignard reagent to intermediate **16**, followed by a mild acidic workup could result in the direct formation of the ketoalcohol **17** (Figure 105). Such a transformation was unprecedented in the literature, but we deemed this experiment worthy of an attempt as it could shorten the synthesis. The reaction was performed at -78°C with 2.5 eqv. Grignard reagent, resulting in an excellent conversion.

Figure 105

Although the desired ketoalcohol **17** was formed the thioxothiazolidinone by-product **28** could not be removed from the mixture by column chromatography, which would have been imperative prior to *Evans–Saksena* reduction, because standard silica-gel chromatography brought about the facile isomerisation of product **29** (Figure 106).

Figure 106

Thus, we opted for the use of the common *N,O*-dimethylhydroxylamine to introduce the allyl moiety through its Weinreb amide (Figure 107).⁴⁹ Exposure of compound **16** to *N,O*-dimethylhydroxylamine hydrochloride in the presence of excess trimethylaluminum furnished the desired Weinreb amide **18** in full conversion. Likewise, treating **16** with hydrochloride salt of the Weinreb amine and imidazole gave the amide in an acceptable yield (67%). Due to its ease of execution, the latter was chosen as the optimal route to scale up. The next task was to introduce the allyl moiety while the facile isomerisation to a more stable enone is circumvented. With Et₂O as a solvent, the reaction exhibited a very low conversion at ambient temperature, but no isomerisation product was detected in the crude NMR spectrum. Once the solvent was changed to THF, the reaction proceeded with ease at -20°C, yielding the desired ketoalcohol **17** in an excellent yield (98%). The rationale for this is that the monoanionic species is virtually insoluble in Et₂O, but has a sufficient degree of solubility in THF to allow for the nucleophilic attack of allyl-Grignard in solution. Most importantly, by use of 2.5 eqv. allylmagnesium chloride the replacement of the amide was feasible without the need for protection of the alcohol group.

Figure 107

Elaboration of the second stereogenic centre was accomplished by *Evans–Saksena* reduction.⁵⁶ It is proposed that the reduction, which leads predominantly to *anti* product, is controlled by chelation involving 6-membered ring TS depicted in Figure 108. The AcOH is presumed to facilitate the ligand exchange on the boron atom.

Figure 108

Key to the success of this diastereoselective reduction is that the reducing agent is required to be of high purity. Accordingly, we set out to prepare the tetramethylammonium triacetoxymethylborohydride following the original procedure of *Evans et al.* (Figure 109),⁵⁶ except the benzene solvent was changed to the less harmful toluene. Sodium borohydride was dissolved in 25% aqueous tetramethylammonium hydroxide followed by a simple filtration to isolate the product Me_4NBH_4 . Next, exposure to 3.5 eqv. of acetic acid resulted in the displacement of hydrides with acetate. We note that the latter was performed in Schlenk flask equipped with a Schlenk filter, which allowed for convenient handling of the extremely hygroscopic product. After the reaction, the excess of toluene was removed in vacuum and the reducing agent was stored in the Schlenk flask.

Figure 109

The reduction was conducted in absolute MeCN at -35°C under nitrogen atmosphere (Figure 110). This reaction proceeded with exceptionally high selectivity as virtually no *syn* diol could be isolated. Gratifyingly, no isomerisation reaction was observed under the applied acidic condition. As expected, the reduction proceeded with better performance when freshly

prepared tetramethylammonium triacetoxyborohydride was used. In other case, either no reduction occurred, or the selectivity was significantly diminished.

Figure 110

As shown in our retrosynthesis (Figure 97), we intended to elaborate the enone moiety by a regioselective cross-metathesis. We speculated that the cross-metathesis of the unprotected diol **14** could take place exclusively at the less hindered alkene moiety under mild condition (Figure 111). To our surprise, the first attempt with 5% Grubbs II catalyst in DCM at RT resulted in the formation of the tetrahydropyran ring **31** *in situ* within 4.5 hours (27%). After column chromatography we could isolate a minor product that corresponded to the acyclic enal compound **30**. This indicated that the cyclisation could possibly be catalysed by the somewhat Lewis-acidic Grubbs catalyst or its decomposition product. Capitalizing on this observation, we employed an extended reaction time, but unfortunately with no beneficial effect, as only decomposition was observed. Careful inspection of the ^1H -NMR spectrum of the crude mixture revealed that formation of cinnamaldehyde also occurred. The reaction was repeated in a way that the inert atmosphere was discontinued after 4.5 hours in order to degrade the catalyst while in the hope that Ru-residue exerts some catalytic effect towards cyclisation. This approached only led to the formation of acyclic enal compound **30** in a very poor yield (16%). It is worth mentioning that none of the experiments resulted in the formation of the intramolecular ring-closing metathesis product.

Figure 111

Table 12

Entry	Equivalents of crotonaldehyde	t	Product
16.	30 eqv.	4.5h	<i>in situ</i> cyclised THP (27%)
17.	3 eqv.	O.N.	decomposition
18.	30 eqv.	4.5h then stirred O.N. open to air	acyclic enone-diol (16%)

As this cross-metathesis reaction was particularly problematic under the circumstances applied, we look through the literature in search of an optimal condition for this regioselective metathesis. We found two essential studies contributing to this field. *Cossy et al.* investigated the behaviour of a series of dienols in cross-metathesis reaction.⁵⁷ Their preliminary study showed the allylic and homoallylic olefins had a similar reactivity when the dienol was unprotected (Figure 112). Because of the unselective metathesis, dienols were converted into their acetate, which allowed for cross-metathesis with high degree of regioselectivity. This approach was then successfully utilized in the synthesis of the C1-C14 fragment of *Amphidinol* 3 natural product.⁵⁸

Figure 112

The regioselectivity was thought to result from the deactivated nature of the allylic double bond, which is due to the proximity of the electron-withdrawing acetate group. They also assumed that the complex **32** was formed, which was deemed a dead-end in the catalytic cycle.

Soon afterwards, *Fuwa et al.* showcased a regioselective cross-metathesis of a selectively protected diene-1,3-diol in the synthesis of (+)-*Neopeltolide*.⁵⁹ They found that the protection of the allylic alcohol was indispensable for the successful regioselective replacement (Figure 113). Doing so, the two double bonds were sufficiently differentiated to furnish the desired enal product **34**. Regioselectivity of the cross-metathesis reaction is best described by assuming the formation of a ruthenium alkylidene complex, in which a H-bond is present between the unprotected hydroxyl group and the chlorine atoms attached to ruthenium (Figure 113). They reasoned that the desired cross-metathesis reaction is more facile, because in the event of ring-closing metathesis, the requisite ruthenacyclobutane **33** would resort to break the H-bond or adopt a strained conformation.

Figure 113

It is of note that RCM was the dominant reaction pathway without protection of allylic alcohol, which resulted in the corresponding 6-membered ring **35** as a major product. This

clearly shows that the OH-group has a significant directing effect in the metathesis reaction. The formation of the alkylidene complex on the allylic-side is immensely favourable when the OH-group is not protected.

Due to the intractability of diol **14** in the selective cross-metathesis, we opted for an alternative synthetic approach in which the hydroxyl groups were protected as their acetonide (Figure 114). Use of excess of polymer supported pyridinium *p*-toluenesulfonate gave rise to the formation of **37** side-product. The desired acetonide **36** was isolated in a low yield (30%) after column chromatography. 0.02 eqv. of pyridinium *p*-toluenesulfonate in dry acetone was best suited for the introduction of acetonide protecting group.⁶⁰ The full conversion could be obtained within 4 hours at RT, resulting in the protected alcohol in a good yield (77%).

The *anti* stereochemistry of the diol **14** was further confirmed by inspection of the chemical shifts of the two acetonide methyl carbons in the ¹³C-NMR spectrum. It is well-documented that the acetonide of an *anti*-diol exists in twist-boat confirmation to avoid 1,3-diaxial repulsion.⁶¹ In our case, 25.7 ppm and 24.9 ppm chemical shifts of the methyl groups were convincingly characteristic of the acetonide of *anti*-1,3-diol (Figure 114).^{62,63,64}

Figure 114

The protection of the diol as its acetonide allowed for selective cross-metathesis with crotonaldehyde at the less hindered alkene fragment with the help of Grubbs II catalyst, giving the unsaturated aldehyde **38** in a good yield (70%) (Figure 115).

Figure 115

Our next objective was to construct the *cis* tetrahydropyran. We found that subjecting the acetonide **38** to camphorsulfonic acid with one drop of water was inefficient to bring about the desired cyclisation (Figure 116).⁶⁵ To our delight, the tandem deprotection – *oxa*-Michael cyclisation could be accomplished by using catalytic amount of aqueous HCl, giving rise to *cis* THP ring **31** exclusively in an excellent yield (86%).⁶⁶ Pleasingly, there was no the need for further optimisation. With the aldehyde **31** in hand, the stage was set for the establishment of the remaining stereogenic centre. Prior to that, the protection of the alcohol with TBS was achieved by using a standard condition.

Figure 116

Figure 117

At this stage, the stereochemical assignment of the formed THP ring **39** could be determined. Protection of the free OH-group resulted in interpretable multiplicity patterns (Figure 117) using a 400 MHz NMR instrument. The determination of the relative configurations was based on the coupling constants of the protons attached to -CH₂-CHO, styryl- and the γ -OTBS groups. By decoupling the methylene protons in -CH₂-CHO group, the multiplet at 3.96 ppm appeared to be simplified enough for further analysis. The equatorial position of the -CH₂-CHO group was evident displaying the coupling constants of 11.4 Hz and 3.1 Hz. The proton attached to the styryl moiety (H_{ax(1)}) was observed as *dddd* at 4.03 ppm. A thorough analysis of this multiplicity revealed the coupling constants of 11.5 Hz, 5.9 Hz, 2.0 Hz and 1.6 Hz. The 11.5 Hz in conjunction with 2.0 Hz was unquestionably characteristic of H_{eq}-H_{ax} relationship. In addition, the two coupling constants of H_{ax(2)} corresponding to H_{ax}-H_{ax} relationship were coincidentally identical (11.5 Hz), which manifested as an apparent quartet at 1.42 ppm. The 1.6 Hz

corresponded to an allylic coupling and 5.9 Hz arose from the coupling with the neighbouring proton on the styrol fragment. Lastly, the proton adjacent to OTBS-group was identified as a clear *tt* with coupling constants of 11.5 Hz and 4.7 Hz. This was in line with the previously observed coupling constants, and further confirmed the *anti*-diol relationship embedded in the THP scaffold.

As a consequence of having the aldehyde functionality, this synthetic route enabled for the divergent synthesis of *Cryptoconcatone H* epimers **40**, **41** (Figure 118). Different catalyst systems were tested in a quest to get access to both isomers with synthetically reasonable selectivity.

Figure 118

Although Barbier allylation has been demonstrated with high diastereoselectivity^{67,68,69,70} through chelation control^{65,71} employing this class of reaction failed to delivery any reasonable selectivity (Table 13). The original Barbier conditions,⁷² which required for RT to proceed at a reasonable rate, gave a 1:0.6 mixture in favour of isomer **41** (entry 19.). It has been showed that the reaction temperature can be lowered when indium is used as a metal source in the presence of acid.⁷³ Hence, the aldehyde **39** was treated with a mixture of In and allyl bromide at -20°C using 4 eqv. of acetic acid.⁷⁴ The reaction showed a slightly improved 1:0.4 selectivity (entry 20.).^{75,76} In the hope of obtaining an increased selectivity, the reaction was then performed at -78°C, but the reaction did not proceed at this given temperature. The reaction was allowed to warm to -40°C. Despite the allylation taking place, it gave invariably low selectivity (entry 21.).

Table 13

Entry	metal source	allyl source	T	t	conversion	selectivity 41:40
19.	Zn (NH ₄ Cl)	allyl bromide (2 eqv.)	RT	overnight	100%	1:0.5
20.	In (AcOH)	allyl bromide (2 eqv.)	-20°C	overnight	100%	1:0.6
21.	In (AcOH)	allyl bromide (2 eqv.)	-40°C	overnight	100%	1:0.6

The observed selectivity can be rationalized by a combination of chelation model^{77,78} and Fürst-Plattner rule⁷⁹ (Figure 119). The chelated species, in which titanium cation resides between the oxygen of THP and the aldehyde group, adopts a cyclohexene-like conformation. In this particular case, an intramolecular attack can be proposed, but the intermolecular version would result the same stereochemical outcome as well. The nucleophilic attack of the aldehyde group can take place by the allyl group approaching at either the top or the bottom face. Both directions yield the trans-diaxial product initially. However, the twist-boat conformation of TS is higher in energy than the chair-like arrangement, which is primarily a consequence of the torsional strain formed in twist-boat TS.

Figure 119

We next turned our attention toward the lesser-applied Keck reaction (Table 14).⁸⁰ The catalyst is a chiral BINOL-complex in which the Lewis acidic centrum is a titanium cation. The catalyst initiates an allyl addition in a stereoselective fashion, and the stereochemistry of the forming stereogenic center can be predicted based on the choice of catalyst. Initial attempts applying the original Keck's condition with allyltributyltin resulted in no product formation

(entry 22,23.).^{81,82} Tetraallyltin was found to be the optimal allyl source as in its presence full conversion was obtained within 5 hours even at -40°C (entry 25).⁸³ Allyltrimethylsilane was also appeared to be a suitable reagent at RT (entry 27). Keck allylation and its modified versions were rather unselective in our case (entry 27,28).⁸⁴ Surprisingly, the same 1:0.6 diastereomer ratio was obtained in each case, irrespective of whether the configuration of the BINOL ligand was (*R*) or (*S*). This indicated that the chiral ligand was not involved in the process of stereoinduction. Furthermore, the major product was the same as that obtained in Barbier reaction.

Based on the invariable diastereomeric ratio, we propose that the stereoinduction is chelation-controlled rather than ligand-assisted process (Figure 120). The origin of observed selectivity can be explained in a similar fashion as that in the Barbier reaction. In this case, the nucleophilic addition of the tetraallyltin occurs in an intermolecular fashion leading to trans-diaxial product. As previously mentioned, the twist-boat TS is high in energy compared to chair TS, which determines the overall diastereomeric ratio.

Figure 120

Table 14

Entry	catalyst system	allyl source	T	t	conversion	selectivity 41:40
22.	Ti(OPr) ₄ / (R)-BINOL	allyltributylstannane (1.1 eqv.)	-40°C to -30°C to -20°C	3d	no reaction	-
23.	Ti(OPr) ₄ / (R)-BINOL	allyltributylstannane (1.1 eqv.)	RT	overnight	no reaction	-
24.	Ti(OPr) ₄ / (R)-BINOL / iPrOH	tetraallyltin (1.5 eqv.)	RT	3h	100%	1:0.6
25.	Ti(OPr) ₄ / (R)-BINOL / iPrOH	tetraallyltin (1.5 eqv.)	-40°C	5h	100%	1:0.6
26.	Ti(OPr) ₄ / (S)-BINOL / iPrOH	tetraallyltin (1.5 eqv.)	-40°C	5h	100%	1:0.6
27.	TiF ₄ / (R)-BINOL	allyltrimethylsilane (1.5 eqv.)	0°C to RT	overnight	100%	1:0.6
28.	TiF ₄ / (R)-BINOL	tetraallyltin (1.5 eqv.)	0°C to RT	overnight	100%	1:0.6
29.	TiCl ₄	tetraallyltin (1.1 eqv.)	-78°C	15min	decomposed	-
30.	TiCl ₄	allyltrimethylsilane (1.1 eqv.)	-78°C	15min	decomposed	-
31.	[Ir(COD)Cl] ₂ / (R)-BINAP	allyl acetate (10 eqv.)	100°C	14h	80%	0.4:1
32.	[Ir(COD)Cl] ₂ / (S)-BINAP	allyl acetate (10 eqv.)	100°C	27.5h	70%	1:0.125
33.	[Ir(COD)Cl] ₂ / (S)-Cl-MeO-BIPHEP	allyl acetate (10 eqv.)	100°C	27.5h	50%	1:0.125

Building on the success of chelation controlled THP functionalisation in the synthesis of *spirastrrellolide A* by *Paterson et al.*,⁸⁵ we treated the aldehyde **39** with tetraallyltin in the presence of TiCl₄ at -78°C. Unfortunately, there was no identifiable product in the mixture after 15 mins (entry 29, 30). This was likely to be a result of the highly reactive nature of TiCl₄ that gave rise to a complete decomposition of the aldehyde starting material.

Although many efforts were made to optimise the Keck allylation, the selectivity was still far from being practical. We, therefore, resorted to examine another asymmetric allylation method. A variety of synthetic methodologies exist to establish allyl alcohol moiety in an asymmetric fashion. Most of these procedures involve achiral starting materials and chiral reagents or catalyst. However, when employing these protocols, the chiral induction can be greatly influenced by the existing stereogenic centers of the intermediate at an advanced stage of the synthesis.⁸⁶ One of these catalytic methods that overcomes this issue is the iridium-catalysed allylation of carbonyl group developed by *Krische* and co-workers.^{87,88,89,90} This has been well-demonstrated by a number of examples in the total synthesis of different polyketides.^{55,43,91,92,93,94,95}

The explanation of the high consistency in stereoinduction is as follows (Figure 121). The proposed stereochemical model is based on the coordination features revealed by the X-ray structure of C,O-benzoate complex.⁹⁶ This is the active form of the catalyst and often generated

in situ. In the preferred mode of coordination, the C-H group of an aldehyde is faced towards the phenyl fragment of the ligand, presumably giving rise to a C-H- π preferential interaction.⁹⁷ Thus, the bulky group is projected away from the catalytic centre to avoid any interference. This accounts for the exceptional substrate tolerance. Furthermore, this mode of coordination of the carbonyl group to the iridium centre allows the addition to proceed via a chair-like TS with the allyl group.

Figure 121

An important feature of this asymmetric allylation is the alcohol and aldehyde can equally be employed as a starting material (Table 14).⁹⁸ In the case of the aldehyde, *i*PrOH is required that acts as a reducing agent to regenerate the active form of the catalyst.

To confirm the model discussed above, (*S*)- and (*R*)-BINAP were both tested. Use of the ligands with opposite configuration resulted in a mixture of diastereomers, but major isomer was found to be different in each case. The observed stereochemistry of the major product was in line with proposed stereochemical model as well as the literature precedents. Accordingly, the (*S*)-BINAP yielded isomer **41** in a 1:0.125 ratio (entry 32), in contrast, (*R*)-BINAP gave an increased proportion of the requisite isomer **40** (entry 31). The reactions were conducted in accordance with the standard Krische protocol. In the reaction, 5% [Ir(COD)Cl]₂ and 20%

3-chloro-4-nitrobenzoic acid were used to generate the active form of catalyst in the presence of 2 eqv. *i*PrOH and 0.4 eqv. Cs₂CO₃. Besides, 10 eqv. allyl acetate was added and the reaction was performed at 100°C under inert atmosphere. Unfortunately, the conversion with BINAP was not 100% but the selectivity was satisfying. In an attempt to increase the catalytic efficiency, (*S*)-Cl-MeO-BIPHEP was also tested. The desired allyl alcohol was then isolated in the same ratio as that observed with (*S*)-BINAP, but the conversion was far less (entry 33). At this stage, we could isolate the diastereomers by column chromatography so that we had ample amount of the two intermediates to attempt to complete the synthesis. It is of note that all the allylation reactions proceeded with no erosion of stereochemical integrity at the *cis*-THP ring.

It is worth pointing out the possible reason for why the Ti-based catalysts have shown poor selectivity. It is likely that the Ti cation Lewis acid is highly inclined to engage in chelation with this particular compound, giving rise to an enhancement of substrate control over reagent control. In contrast, due to the relatively softer and more highly ligated Ir centre of the Krische catalyst the chelation is less likely to form, and this may account for the better selectivity obtained with this catalytic system.

While different routes are possible to access the dihydro pyranone we chose to construct it by a sequence of acylation and cross-metathesis reactions (Figure 122). The exposure of both allylic alcohols **40**, **41** to 3 eqv. of acryloyl chloride in the presence of NEt₃ at RT furnished the desired products. This type of acylation reaction with acryloyl chloride often displays moderate yield, which may be the result of the sensitive enoate ester. For that reason, the acylation product **42**, **43** was not purified by column chromatography but used directly in the following step (reported yields refer to the isolated crude mixture after work-up).

The crude mixture was subsequently subjected to ring-closing metathesis using 0.1 eqv. of Grubbs I catalyst. The reaction was performed at RT in abs. DCM under gentle nitrogen flow. After 2 hours, the TLC showed a full conversion. We first utilized TBAF to implement

the deprotection reaction. It was with great sadness that the reaction only showed a complex mixture rather than the targeted natural product. We reasoned that the fluoride anion initiated unidentifiable side reactions considering its rather enhanced basicity. To circumvent this downside, we opted for the buffered version of F⁻ anion.⁹⁹ Accordingly, HF·py allowed the desired deprotection to proceed smoothly. The latter reaction was performed with due precaution in a plastic container at RT. This two-operation sequence allowed us to complete the synthesis of the reported structure of *Cryptoconcatone H* **1** and its epimer **44** in a single pass.

Figure 122

2.4 Computational study of acid-catalysed *oxa*-Michael cyclisation with γ -OH substrate

The cyclisation of this particular intermediate **38** differs from the previously investigated instances in one major aspect. The precursor possesses a γ -OH group that may alter the TSs leading to the major *cis* isomer. Although *Clarke et al.* previously concluded that there is no stabilizing effect via H-bonding of γ -OH for a boat-like TS in the case of acid-catalysed reaction,¹⁰⁰ we yet intended to investigate the viability of a boat-like TS by our computational method. This would allow us to confirm that the above-mentioned conclusion is independent of the level of theory applied.

Our computational approach herein was identical to that described in the previous chapter (section 5.1.). The ω B97X-D density functional was used in conjunction with the 6-311+G(d,p) basis-set. The SMD explicit solvation model was employed to model the global solvation effects (THF). For the TSs, only one imaginary frequency was found by harmonic vibrational frequency calculations, which confirmed transition state nature of the obtained structure. Enthalpy was used to compare the relative order of TSs.

TSs found for the cyclisation of interest are shown in Figure 123. The relative order of chair- and boat-TSs is in full agreement with that reported by *Clarke et al.*, namely the chair-like TSs were found to be systematically lower than the boat-like TSs.¹⁰⁰ Therefore, we can corroborate the idea that no stabilizing effect of γ -OH operates in the acid-catalysed *oxa*-Michael cyclisation. In addition, (*E*)-geometry of the enal was always more favourable in energy than (*Z*)-geometry, which we previously rationalised by the allylic-strain in (*Z*)-enals. Most importantly, all the TSs show an early bond-forming distance between the OH- group and the β -carbon. This is in line with our hypothesis of the acid-catalysed cyclisation proceeding via early-TS, in which the avoidance of 1,3-diaxial repulsion is the stereo-determining factor.

Figure 123

2.6 Comparison of NMR spectrums of our synthetic sample and the isolated natural product

None of the ^1H -NMR spectra of our synthesized isomers **1**, **44** was consistent with the data reported for the natural product (Figure 124). This clearly shows that the structure originally proposed for the natural product is incorrect.³⁷ ^1H -NMR spectrums of **1**, **44** shows a number of distinct differences, markedly the region of CH-O group. As can be seen in the reported spectrum, two protons overlap with each other at 4.80 ppm, one of them is the proton in the cyclic ester and the other one is presumably one of the protons adjacent to THP oxygen. In our case of *cis*-THP, only one proton, the proton in the cyclic ester, appears at 4.70-4.80 ppm. In addition, our study further provides evidence that stereochemical revision proposed by *Pilli et al.* is most likely to be correct.

Figure 124

3. Conclusion

In conclusion, an efficient synthesis of the proposed structure of *Cryptoconcatone H* has been achieved utilizing a tandem deprotection – intramolecular oxa-Michael cyclisation to establish the cis-THP ring.

The clear difference between the NMR data of the synthetic sample and the one reported for the isolated natural product confirm that the proposed structure **1** is incorrect.

4. Experimental section

(*R,E*)-3-hydroxy-*N*-methoxy-*N*-methyl-5-phenylpent-4-enamide (**18**)

To a solution of (*R,E*)-1-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-5-phenylpent-4-en-1-one **16** (1 eqv., 20.0 mmol, 7.8 g) in abs. DCM (85 ml) was added *N,O*-dimethylhydroxylamine hydrochloride (1 eqv., 20.0 mmol, 1.98 g) in one portion followed by imidazole (3 eqv., 60.0 mmol, 4.08 g). After stirring for 2 h at RT, the reaction was filtered through a pad of Celite® washed with DCM, and concentrated *in vacuo*. Purification *via* silica gel flash chromatography (80→50% EtOAc/Hexane) afforded **18** (3.15 g) as a colorless oil. Yield: 67%

¹H NMR (400 MHz, CDCl₃): 7.38-7.40 (m, 2H), 7.30-7.34 (m, 2H), 7.22-7.26 (m, 1H), 6.68 (dd, *J* = 16.0, 0.9 Hz, 1H), 6.26 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.76 (m, 1H), 3.99 (*J* = 3.4 Hz, 1H), 3.70 (s, 3H), 3.21 (s, 3H), 2.80 (d, *J* = 16.6 Hz, 1H), 2.68 (dd, *J* = 16.6, 9.0 Hz, 1H)

¹³C NMR (100 MHz, CDCl₃): 173.3, 136.8, 130.6, 130.5, 128.7, 127.8, 126.6, 68.9, 61.5, 38.6, 32.0

IR (cm⁻¹): 1643, 1447, 1387, 1196, 1113, 970, 750, 694

HRMS: Calculated for C₁₃H₁₇NO₃Na (M+Na)⁺: 258.1106, Found: 258.1110

[α]_D²¹: -12.9 (*c* = 0.17, CHCl₃)

(*R,E*)-6-hydroxy-8-phenylocta-1,7-dien-4-one (17)

To a solution of (*R,E*)-3-hydroxy-*N*-methoxy-*N*-methyl-5-phenylpent-4-enamide **18** (1 eqv., 13.4 mmol, 3.15 g) in abs. THF (45 ml) was added 2 M THF solution of allylmagnesium chloride (2.5 eqv., 33.5 mmol, 16.75 ml) dropwise under nitrogen atmosphere at -20°C. The reaction was vigorously stirred for 1 h then quenched by adding saturated NH₄Cl solution dropwise at -20°C, and stirred for 15 min and then at RT for another 15 min. The mixture was diluted with Et₂O, and the aqueous phase was extracted with EtOAc (2X). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material **17** (2.84 g) was directly used in the next step without further purification. Yield: 98%

¹H NMR (400 MHz, CDCl₃): 7.36-7.39 (m, 2H), 7.29-7.33 (m, 2H), 7.22-7.25 (m, 1H), 6.63 (dd, *J* = 16.0, 1.3 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.91 (ddt, *J* = 17.2, 10.2, 6.9 Hz, 1H), 5.22 (dq, *J* = 10.2, 1.4 Hz, 1H), 5.17 (dq, *J* = 17.2, 1.4 Hz, 1H), 4.76 (qd, *J* = 6.8, 1.3 Hz, 1H), 3.22 (dt, *J* = 6.9, 1.4 Hz, 2H), 2.77 (d, *J* = 6.8 Hz, 2H)

¹³C NMR (100 MHz, CDCl₃): 200.1, 144.5, 136.7, 131.3, 130.5, 130.3, 128.64, 127.8, 126.6, 68.7, 46.1, 18.5

IR (cm⁻¹): 1655, 1630, 1493, 1441, 1290, 1198, 1042, 968, 750, 694

HRMS: Calculated for C₁₄H₁₇O₂ (M+H)⁺: 217.1229, Found: 217.1232

[α]_D²¹: 6.1 (*c* = 0.65, CHCl₃)

(3*R*,5*S*,*E*)-1-phenylocta-1,7-diene-3,5-diol (**14**)

To a solution of tetramethylammonium triacetoxymethylborohydride (8 eqv., 78.4 mmol, 20.6 g) in abs. MeCN (40 ml) was added anhydrous acetic acid (43 ml) at 0°C and the mixture was stirred for 30 min. The mixture was cooled to -35 °C, and then a solution of (*R,E*)-6-hydroxy-8-phenylocta-1,7-dien-4-one (**17**) (1 eqv., 9.8 mmol, 2.12 g) in abs. MeCN (30 ml) was added dropwise. The mixture was stirred under nitrogen atmosphere at -35 °C overnight. The reaction was quenched by adding saturated NaHCO₃ solution slowly at such a rate as to keep the internal temperature between -35-(-20) °C while vigorously stirred. When the mixture became completely frozen, it was gradually warmed to RT and addition of saturated NaHCO₃ solution was continued until the pH of the mixture reached ~8, which was monitored by universal pH indicator paper. The mixture was diluted with DCM, and the aqueous phase was extracted with DCM (4X). The combined organic layers were over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified *via* silica gel flash chromatography (20% EtOAc/Hexane) to yield **14** (1.69 g) as a colorless oil. Yield: 79%

Remark: tetramethylammonium triacetoxymethylborohydride (Me₄NBH(OAc)₃) was prepared according to the original procedure of *Evans et al.*⁵⁶ and stored in the Schlenk flask used. To achieve high diastereoselectivity and conversion, the reducing agent was required to be freshly prepared and used within ~2 weeks.

¹H NMR (400 MHz, CDCl₃): 7.38-7.40 (m, 2H), 7.30-7.34 (m, 2H), 7.22-7.26 (m, 1H), 6.64 (dd, *J* = 15.9, 1.3 Hz, 1H), 6.28 (dd, *J* = 15.9, 6.0 Hz, 1H), 5.81 (dddd, *J* = 11.9, 9.6, 7.7, 6.7 Hz, 1H), 5.14-5.18 (m, 2H), 4.64-4.68 (m, 1H), 4.01-4.08 (m, 1H), 2.25-2.34 (m, 2H), 1.80-1.84 (m, 2H)

^{13}C NMR (100 MHz, CDCl_3): 136.8, 134.5, 132.1, 130.0, 128.7, 127.7, 126.6, 118.5, 70.4, 68.3, 42.2 (peak at 42.2 ppm is most likely due to two carbon peaks)

IR (cm^{-1}): 1645, 1495, 914, 748, 692

HRMS: Calculated for $\text{C}_{14}\text{H}_{19}\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 219.1385, Found: 219.1382

$[\alpha]_{\text{D}}^{21}$: 28.4 ($c = 0.21$, CHCl_3)

(4*S*,6*R*)-4-allyl-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxane (**36**)

(3*R*,5*S*,*E*)-1-phenylocta-1,7-diene-3,5-diol **14** (1 eqv., 7.7 mmol, 1.69 g) was dissolved in abs. acetone (50 ml) and 2,2-dimethoxypropane (6 eqv., 46 mmol, 5.7 ml) was added in one portion followed by pyridinium *p*-toluenesulfonate (0.02 eqv., 0.15 mmol, 39 mg). The reaction was stirred overnight and then quenched by addition of saturated NaHCO_3 solution. The layers were separated, and the organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to afford **36** (1.53 g mg) as a colorless oil. The isolated product required no further purification and was directly used in the next step. Yield: 77%

^1H NMR (400 MHz, CDCl_3): 7.37-7.39 (m, 2H), 7.28-7.32 (m, 2H), 7.21-7.26 (m, 1H), 6.56 (dd, $J = 16.0, 1.0$ Hz, 1H), 6.23 (dd, $J = 16.0, 6.3$ Hz, 1H), 5.82 (ddt, $J = 17.2, 10.2, 6.9$ Hz, 1H), 5.07-5.15 (m, 2H), 4.51 (dtd, $J = 9.0, 6.3, 1.0$ Hz, 1H), 3.96 (dq, $J = 9.0, 6.3$ Hz, 1H), 2.36 (dt, $J = 13.5, 6.3$ Hz, 1H), 2.24 (dt, 13.5, 6.3 1H), 1.87 (ddd, $J = 13.0, 9.0, 6.0$ Hz, 1H) 1.78 (ddd, $J = 13.0, 9.0, 6.0$ Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H)

^{13}C NMR (100 MHz, CDCl_3): 136.9, 134.3, 130.6, 130.1, 128.6, 127.7, 126.5, 117.2, 100.6, 68.0, 66.2, 40.3, 37.4, 25.7, 24.9

IR (cm^{-1}): 1714, 1643, 1599, 1487, 966, 916, 748, 694

HRMS: Calculated for $\text{C}_{17}\text{H}_{23}\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 259.1698, Found: 259.1695

$[\alpha]_{\text{D}}^{21}$: 10.6 ($c = 0.5$, CHCl_3)

(*E*)-4-((4*S*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)but-2-enal (**38**)

To a solution of (4*S*,6*R*)-4-allyl-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxane **36** (1 eqv. 2.59 mmol, 670 mg) in abs. toluene (19 ml) was added crotonaldehyde (3 eqv., 7.78 mmol, 645 μL) in one portion under gentle nitrogen flow. After stirring for 15 min, a solution of Grubbs-II catalyst (0.05 eqv., 0.130 mmol, 107 mg) in abs. toluene (37 ml) was added dropwise *via* syringe (3.8 ml/h) at reflux while the gentle nitrogen flow was continuously maintained. The reaction mixture was stirred at reflux until no starting material remained (4 h) based on TLC (eluent: 20% EtOAc/Hexane). Upon completion, the reaction mixture was concentrated *in vacuo* and subsequently subjected to silica gel flash column chromatography (99 $\rightarrow$ 10% EtOAc/Hexane). The product **38** (519 mg) was isolated as a yellowish oil. Yield: 70%

Remarks: crotonaldehyde (bp: 104 $^{\circ}\text{C}$) was purified by fractionally distillation under nitrogen using a Vigreux column.

^1H NMR (400 MHz, CDCl_3): 9.53 (d, $J = 7.7$ Hz, 1H), 7.37-7.39 (m, 2H), 7.29-7.33 (m, 2H), 7.21-7.26 (m, 1H), 6.86 (dt, $J = 15.7, 6.6$ Hz, 1H), 6.56 (dd, $J = 15.5, 1.0$ Hz, 1H), 6.21 (dd, J

= 15.5, 6.4 Hz, 1H), 6.22 (ddt, J = 15.7, 7.7, 1.3 Hz, 1H), 4.53 (dtd, J = 9.0, 6.4, 1.0 Hz, 1H), 4.08 (ddt, J = 9.0, 7.6, 6.4 Hz, 1H), 2.50-2.63 (m, 2H), 1.91 (ddd, J = 13.0, 9.0, 6.4 Hz, 1H), 1.80 (ddd, J = 13.0, 9.0, 6.4 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H)

^{13}C NMR (100 MHz, CDCl_3): 194.0, 154.1, 136.7, 134.9, 130.9, 129.5, 128.7, 127.9, 126.6, 100.9, 67.8, 65.2, 38.9, 37.8, 25.5, 25.0

IR (cm^{-1}): 1645, 1495, 1454, 1267, 1169, 1071, 972, 750, 700

HRMS: Calculated for $\text{C}_{18}\text{H}_{23}\text{O}_3$ ($\text{M}+\text{H}$) $^{+}$: 287.1647, Found: 287.1645

$[\alpha]_{\text{D}}^{21}$: -5.8 (c = 0.17, CHCl_3)

2-((2*S*,4*S*,6*R*)-4-hydroxy-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)acetaldehyde (**31**)

To a solution of (*E*)-4-((4*S*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)but-2-enal **38** (1 eqv., 1.76 mmol, 505 mg). in bench THF (33 ml) was added 2N aqueous HCl solution (0.02 eqv, 0.32 mmol, 160 μL) at RT. The reaction was stirred overnight and then quenched by adding solid NaHCO_3 (2 eqv. with respect to HCl, 0.64 mmol, 57 mg). The mixture was diluted with Et_2O , and the aqueous phase was extracted with EtOAc (2X). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The isolated product **31** (372 mg) required no further purification and was directly used in the next step. Yield: 86%

^1H NMR (400 MHz, CDCl_3): 9.82 (t, J = 2.0 Hz, 1H), 7.39-7.35 (m, 2H), 7.29-7.31 (m, 2H), 7.22-7.26 (m, 1H), 6.58 (d, J = 16.0, 1.3 Hz, 1H), 6.18 (dd, J = 16.0, 5.8 Hz, 1H), 4.06 (ddt, 11.5, 5.8, 1.3 Hz 1H), 3.91-4.02 (m, 2H), 2.75 (ddd, J = 16.7, 7.5, 2.0 Hz, 1H), 2.57 (ddd, J =

16.7, 5.0, 2.0 Hz, 1H), 2.11 (ddt, $J = 11.5, 5.8, 2.0$ Hz, 1H), 2.05 ($J = 11.5, 5.8, 2.0$ Hz, 1H), 1.38 (q, 11.5 Hz, 1H), 1.30 (q, 11.5 Hz, 1H)

^{13}C NMR (100 MHz, CDCl_3): 200.9, 136.7, 130.8, 129.1, 128.7, 127.9, 126.6, 76.3, 70.9, 67.8, 49.6, 41.0, 40.7

IR (cm^{-1}): 2359, 1688, 1495, 1454, 1385, 1225, 968, 750, 694

HRMS: Calculated for $\text{C}_{15}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}^+$): 247.1334, Found: 247.1331

$[\alpha]_{\text{D}}^{21}$: -16.4 ($c = 0.45$, CHCl_3)

2-((2*S*,4*S*,6*R*)-4-((tert-butyldimethylsilyl)oxy)-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)acetaldehyde (**39**)

To a solution of 2-((2*S*,4*S*,6*R*)-4-hydroxy-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)acetaldehyde **31** (1 eqv., 1.45 mmol, 356 mg) in abs. DCM (12 mL) was added imidazole (5 eqv., 7.25 mmol, 494 mg) at 0°C, followed by TBSCl (1.1 eqv. 1.6 mmol, 240 mg). The mixture was stirred at RT for 0.5 h and quenched by adding saturated NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with DCM (2X). The combined organic layers were washed with water (1X) and brine (1X), and dried over anhydrous Na_2SO_4 . Evaporation of the solvent under reduced pressure followed by silica gel flash column chromatography (99→95→10% EtOAc/Hexane) afforded **39** (355 mg). Yield: 68%

^1H NMR (400 MHz, CDCl_3): 9.83 (dd, $J = 1.8, 2.4$ Hz, 1H), 7.36-7.38 (m, 2H), 7.28-7.32 (m, 2H), 7.21-7.26 (m, 1H), 6.57 (d, $J = 15.9, 1.6$ Hz, 1H), 6.17 (dd, $J = 15.9, 5.9$ Hz, 1H), 4.03

(dddd, $J = 11.5, 5.9, 2.0, 1.6$ Hz, 1H), 3.94-4.00 (m, 1H), 3.88 (tt, $J = 11.5, 4.7$ Hz, 1H), 2.72 (ddd, $J = 16.6, 7.5, 2.4$ Hz, 1H), 2.55 (ddd, $J = 16.6, 4.9, 1.8$ Hz, 1H), 1.96 (ddt, $J = 11.5, 5.9, 2.0$ Hz, 1H), 1.90 (ddt, $J = 11.5, 5.9, 2.0$ Hz, 1H), 1.44 (q, $J = 11.5$ Hz, 1H), 1.35 (q, $J = 11.5$ Hz, 1H)

^{13}C NMR (100 MHz, CDCl_3): 201.1, 136.8, 130.6, 129.4, 128.7, 127.8, 126.6, 76.4, 71.0, 68.4, 49.7, 41.6, 41.3, 25.9, 18.2, -4.4

IR (cm^{-1}): 2953, 2857, 1728, 1599, 1578, 1387, 1360, 1319, 1254, 1207, 1072, 1005, 966, 912, 837, 755, 735, 692, 669

HRMS: Calculated for $\text{C}_{21}\text{H}_{33}\text{O}_3\text{Si}$ ($\text{M}+\text{H}$) $^+$: 361.2199, Found: 361.2192

$[\alpha]_{\text{D}}^{21}$: -22.4 ($c = 0.16$, CHCl_3)

General procedure for Keck allylation

(*S*)-or (*R*)-BINOL (0.2 eqv., 0.028 mmol, 8.0 mg) was weighed into a round-bottom-flask and abs. DCM (0.5 ml) was added under nitrogen atmosphere. Next, titanium(IV) isopropoxide (0.1 eqv., 0.014 mmol, 4.2 μL) was added *via* automatic pipette under nitrogen flow secured by inverted-funnel followed by abs. *i*-propanol (3 eqv., 0.42 mmol, 32 μL). At this point, the solution turned orange. The mixture was stirred for 1 h at RT. Subsequently, and tetraallyltin (1.5 eqv., 0.21 mmol, 48 μL) was added followed by a solution of the aldehyde **39** (1 eqv., 0.14 mmol, 50 mg) in abs. DCM (0.1 ml) at the required temperature. Upon completion, the reaction

mixture was filtered through a pad of Celite[®] washed with DCM. Evaporation of the solvent under reduced pressure followed by silica gel flash column chromatography (99→98→95% EtOAc/Hexane) afforded the titled compounds.

General procedure for Barbier allylation

To a solution of the aldehyde **39** (1 eqv., 0.14 mmol, 50 mg) in a mixture of THF (0.1 ml) and saturated aqueous NH₄Cl (0.4 ml) was added activated Zn powder (2 eqv., 0.28 mmol, 18 mg) in one portion and purged with nitrogen. The allyl bromide (2 eqv., 0.28 mmol, 24 μ L) was then added dropwise at RT and the reaction was stirred overnight. The reaction mixture was filtered through a pad of Celite[®] washed with EtOAc. Evaporation of the solvent under reduced pressure followed by silica gel flash column chromatography (99→98→95% EtOAc/Hexane) afforded the titled compounds.

General procedure for Krische allylation

A solution of aldehyde **39** (1 eqv., 0.14 mmol, 50 mg) in abs. THF (0.5 mL) was added to a sealed tube charged with [Ir(cod)Cl]₂ (0.05 eqv., 0.007 mmol, 4.7 mg), (*R*)-BINAP (0.1 eqv., 0.014 mmol, 8.7 mg), Cs₂CO₃ (0.4 eqv., 0.056 mmol, 18.3 mg), 4-Cl-3-NO₂-BzOH (0.2 eqv., 0.028 mmol, 5.3 mg), and allyl acetate (10 eqv., 1.4 mmol, 151 μ L) under nitrogen atmosphere. The reaction mixture stirred under inert atmosphere at 100 °C for 14 h and then concentrated *in vacuo*. Purification of the resultant crude mixture by silica gel flash column chromatography (99→98→95% EtOAc/Hexane) afforded the titled compounds.

(*S*)-1-((2*R*,4*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)pent-4-en-2-ol (**40**)

^1H NMR (400 MHz, CDCl_3): 7.34-7.36 (m, 2H), 7.28-7.31 (m, 2H), 7.21-7.26 (m, 1H), 6.54 (d, $J = 16.0$ Hz, 1H), 6.16 (dd, $J = 16.0, 6.1$ Hz, 1H), 5.84 (ddt, $J = 17.2, 10.2, 7.1$ Hz, 1H), 5.07-5.12 (m, 2H), 4.02-4.06 (m, 1H), 3.80-3.95 (m, 1H), 3.84 (tt, $J = 11.3, 4.7$ Hz, 1H), 3.65-3.71 (m, 1H), 2.17-2.32 (m, 2H), 1.95 (ddt, $J = 11.3, 4.7, 2.0$ Hz, 1H), 1.82 (ddt, $J = 11.3, 4.7, 2.0$ Hz, 1H), 1.63-1.75 (m, 2H), 1.42 (q, $J = 11.3$ Hz, 1H), 1.34 (q, $J = 11.3$ Hz, 1H)

^{13}C NMR (100 MHz, CDCl_3): 136.7, 135.1, 130.8, 129.4, 128.7, 127.9, 126.6, 117.4, 76.6, 71.4, 68.4, 42.1, 42.0, 41.9, 41.7, 26.0, 18.2, -4.4 (one carbon peak may be obscured beneath the peak of CDCl_3 solvent)

IR (cm^{-1}): 1472, 1360, 1254, 1072, 964, 914, 837, 775, 747, 692

HRMS: Calculated for $\text{C}_{24}\text{H}_{39}\text{O}_3\text{Si}$ ($\text{M}+\text{H}$) $^+$: 404.2747, Found: 404.2750

$[\alpha]_{\text{D}}^{21}$: 15.6 ($c = 0.67$, CHCl_3)

(2*R*)-1-((4*S*)-4-((tert-butyldimethylsilyl)oxy)-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)pent-4-en-2-ol (**41**)

^1H NMR (400 MHz, CDCl_3): 7.22-7.37 (m, 5H), 6.55 (d, $J = 16.0$ Hz, 1H), 6.18 (dd, $J = 16.0, 6.0$ Hz, 1H), 5.84 (ddt, $J = 17.3, 10.4, 7.3$ Hz, 1H), 5.10-5.15 (m, 2H), 3.99-4.03 (m, 1H), 3.81-3.90 (m, 1H), 3.73-3.78 (m, 1H), 2.60 (d, $J = 4.0$ Hz, 1H), 2.23-2.28 (m, 2H), 1.94 (ddt, $J = 11.2, 4.5, 2.3$ Hz, 1H), 1.65-1.80 (m, 3H), 1.41 (q, $J = 11.2$ Hz, 1H), 1.41 (q, $J = 11.2$ Hz, 1H)

^{13}C NMR (100 MHz, CDCl_3): 136.8, 135.1, 130.5, 129.8, 128.7, 127.8, 126.6, 117.9, 76.5, 73.4, 68.8, 67.8, 42.3, 42.0, 41.8, 41.5, 26.0, 18.3, -4.4

IR (cm^{-1}): 1480, 1370, 1253, 1074, 964, 914, 837, 775, 746, 692

HRMS: Calculated for $\text{C}_{24}\text{H}_{39}\text{O}_3\text{Si}$ ($\text{M}+\text{H}^+$): 404.2747, Found: 404.2749

$[\alpha]_{\text{D}}^{21}$: 32.4 ($c = 0.75$, CHCl_3)

(*S*)-6-(((2*S*,4*S*,6*R*)-4-hydroxy-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)methyl)-5,6-dihydro-2*H*-pyran-2-one (**44**)

To a solution of the alcohol **41** (1 eqv., 0.05 mmol, 20 mg) in abs. DCM (0.5 ml) was sequentially added triethylamine (6 eqv., 0.3 mmol, 42 μL) and acryloyl chloride (3 eqv., 0.15 mmol, 12 μL) at 0 °C and stirred for 10 min. The reaction mixture was then stirred for additional 2 h at RT. The reaction was then quenched with brine (0.5 mL) and extracted with DCM (2X). The combined organic layers were dried over anhydrous NaSO_4 and concentrated *via* reduced pressure. The isolated crude mixture was used in the next step without further purification (at this point, the reported yields (see reaction arrows) refer to the isolated crude mixture after work-up). Next, to a solution of the unsaturated ester (1 eqv. 0.038 mmol, 17.3 mg) in abs. DCM (3 ml) was added a solution of Grubbs-I catalyst (0.1 eqv., 0.0038 mmol, 3.4 mg) in abs. DCM (200 μL) dropwise *via* syringe at reflux while a gentle nitrogen flow was continuously maintained. The reaction mixture was stirred at reflux until no starting material remained (2 h) based on TLC (eluent: 50% EtOAc/Hexane). Upon completion, the reaction mixture was transferred into a plastic vial and HF Pyridine (~1 eqv., 0.0038 mmol, 98 μL , $c = 70\%$) was

added at 0 °C *via* automatic pipette equipped with plastic head. The reaction was then stirred at RT for 1 h. To quench the remaining HF, the mixture was treated with silica gel. Evaporation of the solvent *via* reduced pressure followed by silica gel column chromatography (50→100% EtOAc/Hexane then 5% MeOH/EtOAc) afforded the titled compound **44** (9 mg) as a yellowish gum. Yield: 57% (over 3 steps)

Safety Warning: Precaution should be taken while working with HF·Pyridine. It is highly toxic and corrosive. Symptoms of HF exposure are often delayed for several hours. The caused injury is extremely painful and slow healing is expected.

¹H NMR (400 MHz, CDCl₃): 7.37-7.39 (m, 2H), 7.29-7.32 (m, 2H), 7.21-7.23 (m, 1H), 6.87 (ddd, *J* = 9.6, 6.0, 2.7 Hz, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.0 Hz, 1H), 6.01-6.04 (m, 1H), 4.74-4.81 (m, 1H), 4.02-4.07 (m, 1H), 3.93 (tt, *J* = 11.3, 4.3 Hz, 1H), 3.78-3.85 (m, 1H), 2.63-2.39 (m, 2H), 2.09-2.12 (m, 1H), 1.83-1.96 (m, 3H), 1.37 (q, *J* = 11.3 Hz, 2H)

¹³C NMR (100 MHz, CDCl₃): 164.6, 145.3, 136.8, 130.8, 129.4, 128.7, 127.9, 126.6, 121.6, 76.0, 74.6, 71.0, 68.0, 41.9, 41.4, 41.2, 30.1

IR (cm⁻¹): 1634, 1371, 1260, 1053, 1030 818, 748, 694, 503

HRMS: Calculated for C₁₉H₂₃O₄ (M+H)⁺: 315.1596, Found: 315.1601

[α]_D²¹: 21.2 (*c* 0.51, MeOH)

(*R*)-6-(((2*S*,4*S*,6*R*)-4-hydroxy-6-((*E*)-styryl)tetrahydro-2*H*-pyran-2-yl)methyl)-5,6-dihydro-2*H*-pyran-2-one (**1**)

Product **1** (5 mg) was obtained as a yellowish gum from alcohol **40** (1 eqv., 0.05 mmol, 20 mg) in an identical protocol which was described for the final product **44**. Yield: 32% (over 3 steps)

¹H NMR (400 MHz, CDCl₃): 7.37-7.39 (m, 2H), 7.29-7.33 (m, 2H), 7.22-7.6 (m, 1H), 6.89 (ddd, $J = 9.5, 6.0, 2.5$ Hz, 1H), 6.57 (d, $J = 16.0$ Hz, 1H), 6.18 (dd, $J = 16.0, 6.0$ Hz, 1H), 6.02 (br dd, $J = 9.5, 2.4$ Hz, 1H), 4.67 (dtd, $J = 11.3, 6.0, 4.5$ Hz, 1H), 3.99-4.03 (m, 1H), 3.87-3.95 (m, 1H), 3.71-3.77 (m, 1H), 2.37-2.39 (m, 2H), 2.15-2.22 (m, 1H), 2.10 (ddt, $J = 11.3, 4.5, 2.0$ Hz, 1H), 2.04 (ddt, $J = 11.3, 4.5, 2.0$ Hz, 1H), 1.86-1.93 (m, 1H), 1.38 (q, $J = 11.3$ Hz, 1H), 1.29 (q, $J = 11.3$ Hz, 1H)

¹³C NMR (100 MHz, CDCl₃): 164.6, 145.5, 136.8, 130.6, 129.4, 128.7, 127.9, 126.6, 121.4, 76.2, 75.1, 71.5, 68.0, 41.3, 40.8, 40.5, 29.4

IR (cm⁻¹): 1638, 1379, 1258, 1063, 1038, 880, 809, 747, 694, 515

HRMS: Calculated for C₁₉H₂₃O₄ (M+H)⁺: 315.1596, Found: 315.1607

[α]_D²¹: 4.2 (*c* 0.44, CHCl₃)

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6. NMR Spectra