Synthesis of curvulone B and allahabadolactone, and the development of a diastereoselective Tsuji-Trost cyclisation

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ALLAHABADOLACTONE, AND THE DEVELOPMENT
OF A DIASTEREOSELECTIVE TSUJI-TROST
CYCLISATION**

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SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

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DEVELOPMENT OF A DIASTEREOSELECTIVE
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Abstract

The first chapter describes the synthesis of curvulone B featuring a strategy of cross metathesis and oxa-Michael addition in the construction of the desired *cis*-THP ring. This strategy is one of the most effective tools in the synthesis of THP rings containing natural products. *o*-Chlorobenzyl ether was developed as a new protecting group for alcohols and proved to be a reliable protecting group under Lewis acidic condition.

Chapter two describes the development of a diastereoselective Tsuji-Trost cyclisation. This method was applied in the synthesis of multi-substituent six-membered rings.

Chapter three describes the total synthesis of allahabadolactone A though a route featuring alkyne hydroboration, stereospecific Suzuki coupling and an intramolecular Diels-Alder (IMDA) reaction. This work confirmed the superiority of the aldehyde as an electron withdrawing group for the IMDA reaction and, for the first time, demonstrated the unsuitability of the alkyne substituent in the IMDA reaction. Also, the absolute stereochemistry of allahabadolactone A was confirmed by the synthesis. Meanwhile, a new Rh catalyst was prepared with (2-furyl)₃P ligand, which could be utilized efficiently in the hydroboration of terminal alkynes.

List of Abbreviations

Ac	acetyl
Aq	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
COD	cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DHP	dihydropyran
DIBAL-H	diisobutylaluminium hydride
DMAP	<i>N,N</i> -(dimethyl-4-amino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene

HMDS	<i>N,N</i> -bis(trimethylsilyl)amide
HOMO	highest occupied molecular orbital
IBX	2-iodoxybenzoic acid
IMDA	intramolecular Diels-Alder
LA	Lewis Acid
LDA	lithium diisopropylamide
LG	leaving group
LUMO	lowest unoccupied molecular orbital
MOM	methoxymethyl
Nu	nucleophile
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
Ns	nosyl
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
Pin	pinacolato
i-Pr	isopropyl
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl

TBS	<i>tert</i> -butyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetra- <i>n</i> -propylammonium perruthenate
Ts	tosyl

Chapter 1

1.1 Introduction

The study of the isolation and synthesis of metabolites of marine microorganisms has always been very appealing in organic research due to the biological activities found in the organic secondary metabolites produced by them.¹ Curvularin-type macrolides, for example, have shown multiple biological effects, such as anti-tumor, anti-fungal and cytotoxicity against certain cancer cell lines. The biological activities of some of these macrolides were tested against the organisms - *Bacillus megaterium*, *Microbotryum violaceum*, *Septoria tritici* and *Chlorella fusca*.²

Recently, Krohn and Kurtan discovered two new Curvularin metabolites – Curvulone A **1.1** and Curvulone B **1.2**— isolated from the fungus *Curvularia* sp. found in the red marine alga *Gracilaria*.² Curvulone B, the first derivative from this organism to be discovered bearing a tetrahydropyran ring, demonstrated the strongest anti-bacterial and anti-fungal functions among those reported curvularins.¹

Scheme 1-1. Curvulone A **1.1** and Curvulone B **1.2**

1.2 Cross metathesis and Oxa-Michael tandem reaction

The six-membered oxygenated heterocycle, known as tetrahydropyran (THP), is one of the most common structural constituents in natural products.³ It is widely ranging from simple carbohydrates to functional metabolites in nature.³ A lot of THP containing natural products are found with useful biological activities.³ For example, eribulin mesylate has been approved as a clinical drug.³ Hence, many chemists and biologists have gained interest in THP rings due to their unique structures and potent biological activities.

In addition, with the different functionalities and stereogenic centers present in and around the THP ring, the synthesis of stereodefined THP rings has drawn much attention among organic chemists.⁴ For instance, one of the major challenges faced by chemists would be synthesizing the 2,6-substituted THP ring, which is the most common motif in THP ring derivatives. Various methodologies, such as the Prins reaction, ring closing metathesis, intramolecular radical cyclization, transition metal catalyzed alkoxycarbonylation and hetero Diels–Alder cyclisation, have been established for the efficient construction of THP rings.⁵ Among these methods, intramolecular oxa-Michael reaction is a unique and versatile tool to build THP rings since the stereochemical outcome of the reaction greatly depends on the reactivity of the substrate and the conditions employed.³ In general, the *cis* product is the thermodynamic product because its bis-equatorial conformation.⁷ Under basic conditions, the formation of a 2,6-*trans*-THP ring is kinetically favored at low temperature, whereas the *trans*-THP ring could be provided directly under thermodynamic conditions. And *trans*-THP could be isomerized to *cis* isomer under thermodynamic conditions (Scheme 1-2).⁷

Scheme 1-2 oxa-Michael addition under basic conditions

Under mild acidic conditions, the cyclisation will proceed to afford a thermodynamically favored 2,6-*cis*-disubstituted THP ring, which is also the kinetically favored product though a chair-like transition state, especially if the electron withdrawing group is a ketone.⁶ In the transition state, the protonated enone species would be formed under acidic condition and the TS-*trans* would be disfavored due to the steric hindrance between the protonated enone and the axial proton. Excellent stereoselectivity could generally be anticipated with a sufficiently electrophilic Michael acceptor, such as ketone or thioester while an ester group would not be preferred due to its unreactivity (Scheme 1-3).⁷

Scheme 1-3 oxa-Michael addition under acidic conditions

Cross metathesis has emerged as a powerful and convenient technique for the formation of carbon-carbon double bonds.⁸ The advantages of adopting Cross metathesis are using catalysts that are commercially available, its high tolerance to most of the functional groups, high efficiency under mild conditions and atom economy compared to the traditional olefination reactions.^{9,10} Hence, it has become one of the most important strategies among the various types of olefin formation.

The combination of the above-mentioned strategies can simply afford the synthesis of THP rings by connecting the conjugate acceptor and a hydroxyl containing side chain with cross metathesis followed by oxa-Michael cyclisation. This tandem strategy can simply be extended to the scope of the synthesis of 2,6-disubstituted THP rings. Several reports from this laboratory with this elegant strategy have also proved its possibility.⁴ In the

synthesis of (-)-diospongins A, the Michael acceptor was obtained by a cross metathesis reaction in the presence of the Grubbs II catalyst. Then a tandem deprotection and oxa-Michael addition under acidic conditions afforded the desired natural product as a single stereoisomer (Scheme 1-4).⁴ In the formal synthesis of clavosolide, the same strategy was applied to prepare the core structure of THP ring motif but a more robust Hoveyda-Grubbs II catalyst was selected due to the steric hindrance of the methyl group at the allylic position (Scheme 1-4).⁴

Scheme 1-4. Metathesis-Michael strategy for the synthesis of diospongins A and clavosolide

1.3 Previous Work

Takahashi *et al.* first reported the total synthesis of curvulone B in 2012 (Scheme 1-5).¹¹ They initially started with the ester compound which was transformed to the aldehyde in several steps.¹¹ The α , β -unsaturated ketone was generated after vinylation with a Grignard reagent followed by oxidation. Cross metathesis was employed to an olefin, containing a hydroxyl group, forming the precursor of the THP ring.¹¹ Due to the presence of an acid sensitive acetal group in their synthesis, the THP ring was synthesized under basic conditions affording a mixture of diastereoisomers while the *trans* THP product was slightly favored despite being higher energy under their conditions. Extra steps had to be employed in order to isomerize the *trans*-THP ring to desired *cis*-THP ring.¹¹ The strategy of protection of the benzyl aldehyde and isomerization of the THP ring inevitably led to poor step economy. Therefore, a more effective strategy with higher stereoselectivity had to be developed.¹¹

Scheme 1-5. Total synthesis of curvulone B by Takahashi *et al.* Reagents and conditions: (a) vinyl MgCl, THF, 0 °C; (b) TPAP, NMO, CH₂Cl₂, r.t.; (c) Grubbs II, CH₂Cl₂, 40 °C; (d) TBAF, THF, r.t.; (e) *t*-BuOK, THF, r.t.; (f) Jones' oxidation, 0 °C; CH₂N₂, Et₂O, r.t.; Pd(OH)₂, H₂, EtOAc, r.t.

A former member in our group developed a more concise strategy to synthesize curvulone B (Scheme 1-6).¹² The α,β -unsaturated carbonyl group, introduced by Friedel–Crafts acylation and a simple elimination, would then be used for cross metathesis. The desired *cis* THP ring was successfully obtained as a single diastereoisomer in the presence of amberlyst-15. Unfortunately, this strategy was limited due to the low yield in the Friedel–Crafts acylation arising from the deprotection of the benzyl groups. This was caused by the formation of a benzyl cation mediated by the Lewis acid (Scheme 1-7). Under the Lewis acidic conditions, the lone pair of electrons on the oxygen atom of the protected phenol will coordinate to the Lewis acid leading to the formation of the benzyl cation. In order to

increase the stability of the benzyl protecting group under Lewis acidic conditions, our strategy was to modify the aromatic ring of the benzyl group to change its electronic properties. In particular, adding electron-withdrawing substituents could reduce the stabilization of the carbocation.

Scheme 1-6. Total synthesis of Curvulone B by Guanying. Reagents and conditions: (a) CO, $i\text{-Pr}_2\text{NEt}$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, MeOH, reflux; (b) SnCl_4 , $\text{Cl}(\text{CH}_2)_2\text{COCl}$, CH_2Cl_2 , 0°C , 40%; (c) Et_3N ; CH_2Cl_2 , r.t.; (d) Grubbs II, C_6F_6 , **1.12**; (e) Amberlyst-15; MeOH, r.t.; (f) $\text{Pd}(\text{OH})_2$, H_2 , EtOAc, r.t.

Scheme 1-7. Decomposition of the benzyl protecting group.

The use of substituted benzyl groups has been very well established for protecting hydroxyl groups.¹⁴ For example, the *p*-methoxyl benzyl ether (PMB) can be used in the protection of alcohols. Moreover, due to the electron donating effect of the methoxy group at the *para* position, such protecting group can undergo mild oxidation using DDQ more easily than the non-substituted benzyl group. And, more importantly, this kind of group could undergo more facile acidic cleavage due to the better stabilized carbocation

Buchwald *et al.* reported halobenzyl ethers as protecting groups (Scheme 1-8). These groups could be converted into a variety of arylamines through cross-coupling reactions, which could be easily deprotected on treatment with Lewis acids or protic acids.¹⁸

Scheme 1-8 halobenzyl ether protecting groups by Buchwald

In order to disfavour the formation of benzyl cation in our case, the electron density of the aromatic ring should be decreased to increase the energy of the cation. The electronic properties of the aromatic ring can generally be modified by conjugation effect or inductive effect of a substituent.

Another group member employed the *p*-chlorobenzyl ether as the protecting group and hypothesized that the electron withdrawing effect of the chlorine atom at the *para* position could decrease the electron density of the benzyl protecting system.¹³ This would destabilize the benzyl cation so as to inhibit the debenzylation in the Friedel–Crafts acylation reaction. Though this method only improved the yield of the Friedel–Crafts acylation reaction from 40% to 42%, it gave us a clue on how to change the situation.

We began our synthesis of curvulone B with *p*-nitrobenzyl as the protecting group in the hope that the mesoionic effect of the nitro group can improve its electron withdrawing ability, which would hence be more effective than the *para*-chlorobenzyl protecting group. To our delight, the yield of the Friedel–Crafts acylation improved to 80% following the condition developed by Guanying, which indeed proved our previous hypothesis. However, we later realized that the nitro protecting group caused difficulty in driving the cross metathesis reaction. Due to the poor solubility of the starting material containing the two nitro groups, the cross metathesis reaction could not proceed even with the use of robust Hoveyda–Grubbs II

catalyst and a more active Grela-Hoveyda II catalyst. Therefore, there is a need to change to another protecting group for the synthesis of curvulone B.

The *para* chloro decreased the electron density of the aromatic ring modestly because the inductive effect depends considerably on the distance between the substituents and the reactive position. Inductive effect is minimized when the substituent lies in the *para* position. In order to increase the electron withdrawing effect and maintain the solubility simultaneously, our plan was to switch the chloro to the *ortho* position.

1.4 Results and Discussion

Scheme 1-9. Synthesis of curvulone B. Reagents and Conditions (a) SOCl_2 , MeOH, 90%; (b) *o*-chlorobenzyl chloride, K_2CO_3 , KI, acetone, 99%; (c) LiAlH_4 , THF, 0 °C, 97%; (d) SOCl_2 , pyridine, CH_2Cl_2 , 0 °C 98%; (e) CO, *i*- Pr_2NEt , $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, MeOH, 91%. PG= *o*-chlorobenzyl

Following the previous procedure in scheme 1-7 that developed by Guanying, we obtained the key intermediate **1.9** in high yield (Scheme 1-9). Starting with commercially available 3,5-dihydroxybenzoic acid, the ester **1.5** was prepared through esterification with thionyl chloride in methanol. The hydroxyl groups were then protected with *o*-chlorobenzyl chloride. In addition, 5 mol% KI was added to the reaction in order to generate *o*-chlorobenzyl iodide *in situ* to accelerate benzyl ether formation. The work-up procedure was easy – the product precipitated from H₂O and was obtained by filtration– and hence provided another advantage for the reaction. Protected ester **1.6** was then reduced with LiAlH₄ at 0 °C, followed by chlorination with thionyl chloride to afford benzyl chloride **1.8**. Benzyl chloride **1.8** underwent a palladium catalyzed carbonylation to give ester **1.9** under CO pressure in a balloon while no reaction of the *o*-chlorobenzyl group was observed. A reported alternative to carbonylation to introduce the ester group from the corresponding benzyl chloride is first substitution with cyanide, followed by hydrolysis then esterification.¹⁹

Scheme 1-10. Synthesis of curvulone B Reagents and conditions (s) SnCl₄, Cl(CH₂)₂COCl, CH₂Cl₂, 0 °C, 89%; (b) Et₃N; CH₂Cl₂, r.t. 95%; PG= *o*-chlorobenzyl

After several attempts with different Lewis acids, tin(IV) chloride was found to be the best choice for the Friedel-Crafts acylation in the previous research.¹² It was found that low temperature can also decrease debenzylation. In addition, a low concentration of tin(IV) was beneficial for the Friedel-Crafts acylation, as a high concentration of tin(IV) would drive the debenzylation. As expected, the yield of Friedel-Crafts acylation with the *o*-chlorobenzyl protecting group improved to 89% (Scheme 1-10), which validates our hypothesis that the *o*-chlorobenzyl can prevent the decomposition more effectively due to its strong inductive effect.

Scheme 1-11. Synthesis of curvulone B. Reagents and conditions (a) Mg, THF, reflux; (b) CuI, **1.16**, THF, -78 °C, 75%; (c) TBSCl, imidazole, CH₂Cl₂, r.t., 98%.

Following the conditions in Guanying's synthesis, the terminal alkene **1.15** was prepared from epoxide opening of (*R*)-propylene oxide **1.16** with Grignard reagent **1.14** prepared from 4-bromobutene **1.13** with activated magnesium.¹⁵ Grignard reagent **1.14** attacked the epoxide at the less hindered position in the presence of CuI. The TBS ether **1.12** was easily

generated from the alcohol **1.15** by treatment with TBSCl and imidazole (Scheme 1-11). In our previous study,¹² the bulky TBS protecting group was used to prevent the coordination of the hydroxyl group to the Ru center of the metathesis catalyst increasing the cross metathesis yield, which is in consistent with Takahashi's work.¹¹ A easier workup also benefited from the TBS group because the free alcohol was quite volatile.

Jacobsen's catalyst was employed to recover the (*R*)-propylene oxide **16** from hydrolytic kinetic resolution (HKR) of (+/-) propylene oxide (Scheme 1-12).¹⁶ The (*R*)-propylene oxide was collected via simple distillation. Jacobsen's catalyst, a chiral Co(III) complex, is effective to give the desired unreacted epoxide and 1,2-diol with high enantioselectivity.¹⁶ A few drops of AcOH were added to activate the (*R, R*)-Co(III) pre-catalyst to generate the Co(III)OAc complex which achieved the HKR of the (+/-) propylene oxide in the presence of water. The (*R, R*)-catalyst would selectively open the (*S*)- propylene oxide as a nucleophile giving (*S*)-propylene diol.¹⁶

Scheme 1-12. HKR of the propylene oxide

Since we had both of the cross metathesis precursors in hand, we were going to examine the cross metathesis reaction. According to Grubbs'

classification, the terminal alkene and vinyl ketone belong to type I and type II olefin respectively for cross metathesis. In our previous work, Grubbs second generation catalyst afforded the best yield in hexafluorobenzene. Grela has suggested that C_6F_6 has a better π -stacking effect with the NHC ligands in the catalyst that can stabilize the ruthenium complex.¹⁷ These conditions were not desirable for *o*-chlorobenzyl protected compound due to the poor solubility in C_6F_6 . A previous study also indicated that a kinetic factor played an important role in this transformation so a higher temperature was preferred for the reaction. In order to increase the temperature, a high boiling point solvent, dichloroethane (DCE), was used as the solvent and a good yield of 85% was obtained. The yield of cross metathesis decreased to 50% in CH_2Cl_2 and the unsaturated ketone was insoluble in toluene. The reaction was carried out with a continuous flow of nitrogen to remove the ethylene generated (Scheme 1-13).

Scheme 1-13. Synthesis of curvulone B Reagents and conditions (a) 10 mol% Grubbs II, **1.12**, DCE, 85%. (b) Amberlyst-15, MeOH, 88%. PG= *o*-chlorobenzyl

The TBS group was deprotected and the THP ring was concurrently generated via oxa-Michael intramolecular addition in a tandem reaction under the acidic conditions with amberlyst-15 in methanol (Scheme 1-13). Amberlyst-15 has been widely applied in organic synthesis. It is a powerful and environmentally friendly polymer acid and can be easily removed by filtration and reused. The THP ring was obtained directly as a single *cis* diastereoisomer as the oxa-Michael reaction formed a stable chair conformation with the substituents at the equatorial positions. In comparison, Takahashi *et al.* synthesized the THP ring under mildly basic conditions, which led to a mixture favouring the *trans* isomer. Our approach to access the THP ring in the synthesis of curvulone B was superior.

Scheme 1-14 Deprotection Reagents and conditions (a) $\text{Pd}(\text{OH})_2$, EtOAc, H_2 , 81%.

PG=*o*-chlorobenzyl

Finally the natural product curvulone B was obtained by debenzylation over 20% $\text{Pd}(\text{OH})_2$ under hydrogen in a yield of 92% (Scheme 1-14). In addition, the carbon-chlorine bond of *o*-chlorobenzyl was not reduced because *o*-chlorotoluene was observed in the ^1H NMR spectrum of the crude material.

The ^1H NMR (Figure 1-1) and ^{13}C NMR of the natural product synthesized were consistent with the data from the paper reporting the isolation of curvulone B by Krohn *et. al.*¹ The optical rotation was measured to be -19 (*c* 0.28, EtOH) which was close to the reported value of $[\alpha]_{\text{D}}^{25}$ -22 (*c* 0.27, EtOH).¹

Figure 1-1 ^1H NMR spectrum of curvulone B

1.5 Summary

We achieved an efficient synthesis of curvulone B in 10 steps with 39% overall yield. The cross metathesis and oxa-Michael addition strategy afforded the 2,6-*cis*-THP ring stereoselectively. The *o*-chlorobenzyl group was first introduced and proved to be a reliable protecting group under Lewis acidic conditions. We believe *o*-chlorobenzyl should prove to be a useful protecting group for organic synthesis due to its more deactivating than the *p*-chloro analogue.

1.6 Experimental

All reactions were run under nitrogen gas atmosphere with oven-dried

glassware. Anhydrous toluene, THF and Et₂O were distilled from sodium metal. The other solvents and reagents were used as received. Column chromatography was carried out on silica gel 230-400 mesh, and analytical TLC on glass plates (silica gel 60, F254). All ¹H NMR spectra were recorded on a JEOL ECA 400 MHz or Bruker Advance DPX at 400 MHz in CDCl₃ solutions. ¹³C NMR spectra were recorded in CDCl₃ on the same instruments at the corresponding frequency. Chemical shifts are recorded in ppm and coupling constants are recorded in Hz.

Methyl 3,5-dihydroxybenzoate 1.5

Thionyl chloride (1.14 mL, 15.6 mmol) was added cautiously to a solution of 3,5-dihydroxybenzoperoxoic acid (2.0 g, 13.0 mmol) in anhydrous methanol (20 mL) at room temperature. After refluxing for 2h, methanol was removed by rotary evaporation and the residue was washed with methanol (5 mL x 2). The solid was dried under high vacuum.

¹H NMR (400 MHz, CDCl₃): δ 7.09 (d, *J* = 2.3 Hz, 2H), 6.56 (t, *J* = 2.8 Hz, 1H), 4.92 (s, 2H), 3.91 (s, 3H).

All data are consistent with that reported in literature.¹⁹

Methyl 3,5-bis(2-chlorobenzyloxy)benzoate 1.6

Ester **1.5** (1g, 5.95 mmol), *o*-chlorobenzyl chloride (1.51 mL, 11.9 mmol), K_2CO_3 (1.64 g, 11.9 mmol) and KI (50 mg, 0.3 mmol) were mixed in acetone (40 mL). The mixture was heated at reflux overnight. The reaction was cooled and filtered, washing with acetone (10 mL). The solution was concentrated by rotary evaporation and the residue was dried *in vacuo* to a beige solid (2.48 g, 100%).

R_f = 0.52 (1:3 EtOAc–hexane). m.p.: 86–88 °C

1H NMR (400 MHz, $CDCl_3$): δ 7.51–7.18 (m, 8H), 6.84 (t, J = 2.52 Hz, 1H), 5.19 (s, 4H), 3.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 159.6, 134.3, 132.79, 132.3, 129.5, 129.2, 128.9, 127.1, 108.7, 107.1, 67.4, 52.5.

IR (neat): 2357, 1721, 1593, 1304, 1173, 1045, 767 cm^{-1} .

MS (ESI): m/z = 415.1 $[M(^{35}Cl)+H]^+$

HRMS (ESI): m/z calcd for $C_{22}H_{19}^{35}Cl_2O_3$ $[M+H]^+$: 415.0868; found: 415.0901.

(3,5-bis(2-chlorobenzoyloxy)phenyl)methanol 1.7

LiAlH₄ (0.45 g, 11.9 mmol) was added portionwise to the solution of ester **1.6** (2.48 g, 5.95 mmol) in anhydrous THF (100mL) at 0 °C under a continuous N₂ flow. The reaction was stirred for 30 min at 0 °C. The reaction was quenched with H₂O (0.25 mL) at 0 °C and washed with 15% NaOH (0.25 mL) and H₂O (0.75 mL). The white suspension was dried over MgSO₄ and filtered through celite. A colorless solid was collected by rotary evaporation (2.25 g, 97%).

*R*_f = 0.21 (1:3 EtOAc–hexane). m.p.: 101–103 °C

¹H NMR (400 MHz, CDCl₃): δ 7.51–7.17 (m, 8H), 6.65 (s, 2H), 6.57 (s, 1H), 5.15 (s, 4H), 4.65 (s, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 160.0, 143.8, 134.7, 132.8, 129.5, 129.2, 129.0, 127.1, 106.0, 101.3, 67.3, 65.1.

IR (neat): 3233, 3175, 1609, 1169, 1015, 968, 934, 806, 737 cm⁻¹.

MS (ESI): *m/z* = 389.0 [M+H]⁺

HRMS (ESI): *m/z* calcd for C₂₁H₂₀³⁵Cl₂O₂+H: 387.0919; found: 387.0959;

(3,5-bis((2-chlorobenzyl)oxy)phenyl) Chloride **1.8**

Pyridine (0.46 mL, 5.65 mmol) was added to a solution of alcohol **1.8** (2.20 g, 5.65 mmol) in CH₂Cl₂ (20 mL). Thionyl chloride (0.41 mL, 5.65 mmol) was added dropwise to the mixture at 0 °C and the reaction was stirred for 3 h at room temperature. The mixture was neutralised with aq. HCl (2 M) and extracted with CH₂Cl₂ (3 × 20 mL). The organic layers were combined, dried over MgSO₄ and concentrated *in vacuo*. The residue was dried under high vacuum to give chloride **1.8** as a faint yellow solid (2.08 g, 98%).

R_f = 0.57 (1:3 EtOAc–hexane). m.p.: 82~85 °C

¹H NMR (400 MHz, CDCl₃): δ 7.56-7.27 (m, 8H), 6.68 (s, 2H), 6.60 (s, 1H), 5.16 (s, 4H), 4.54 (s, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 160.1, 140.0, 134.6, 132.9, 129.7, 129.3, 129.1, 127.2, 108.1, 102.3, 67.5, 46.4.

IR (neat): 1601, 1300, 1211, 1177, 1069, 1049, 833, 744, 714 cm⁻¹.

MS (ESI): m/z = 406.9 [M+H]⁺.

HRMS (ESI): m/z calcd for C₂₁H₁₇³⁵Cl₃O+H: 405.0580; found: 405.0299.

Methyl 2-(3,5-bis((2-chlorobenzyl)oxy) phenyl) acetate **1.9**

A solution of chloride **1.8** (1.67 g, 4.10 mmol), *i*-Pr₂NEt (0.86 mL, 4.92 mmol) Pd(PPh₃)₂Cl₂ (57 mg, 0.082 mmol) in methanol (50 mL) was flushed with CO and the mixture was heated at reflux under CO (in balloon) overnight. The mixture was concentrated and purified by flash

chromatography on silica eluting with 25% EtOAc/ Hexane to give ester **1.9** as a colorless solid (1.60 g, 91%).

R_f = 0.28 (1:3 EtOAc–hexane). m.p.: 90–92 °C

^1H NMR (400 MHz, CDCl_3): δ 7.56–7.24 (m, 8H), 6.57 (s, 3H), 5.14 (s, 4H), 3.69 (s, 3H), 3.58 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 171.9, 160.0, 136.5, 134.3, 132.8, 129.6, 129.2, 129.1, 127.2, 109.0, 101.0, 67.4, 52.3, 41.6.

IR (neat): 1720, 1603, 1301, 1177, 1048 cm^{-1}

MS (ESI): m/z = 431.0 $[\text{M}+\text{H}]^+$

HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{20}\text{O}_4^{35}\text{Cl}_2+\text{Na}$: 451.0844; found: 451.0834.

Methyl 2-(2-(3-chloropropanoyl)-3,5-bis((2-chlorobenzyl)oxy)phenyl)acetate **1.10**

A solution of SnCl_4 (1.81 mL, 1.81 mmol, 1M in CH_2Cl_2) was added to a solution of 3-chloropropionyl chloride (173 μL , 1.81 mmol) in anhydrous CH_2Cl_2 (60 mL) at -78 °C. A solution of ester **1.9** (650 mg, 1.51 mmol) in 20 mL CH_2Cl_2 was added dropwise into the mixture at -78 °C. The mixture was stirred at -40 °C overnight under nitrogen and quenched with Et_3N (0.36 mL). The mixture was warmed to room temperature and washed with saturated aqueous NH_4Cl solution (10 mL). The organic layers were

separated and the aqueous layer was extracted with CH₂Cl₂ (10 × 3 mL). The combined organic layers were dried over MgSO₄ and concentrated to give a colorless solid (0.70 g, 89%).

R_f = 0.31 (1:3 EtOAc–hexane). m.p.: 96–98 °C

¹H NMR (400 MHz, CDCl₃): δ 7.50–7.23 (m, 8H), 6.55 (s, 1H), 6.51 (s, 1H), 5.15 (s, 4H), 3.75 (t, *J* = 7.08, 2H), 3.71–3.67 (m, 5H), 3.36 (t, *J* = 6.86, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 202.5, 171.7, 160.8, 158.3, 135.8, 134.0, 133.5, 133.2, 132.9, 129.8, 129.8, 129.6, 129.5, 129.2, 129.0, 127.3, 127.2, 123.4, 110.3, 99.3, 68.2, 67.4, 52.2, 47.1, 39.4, 39.0.

IR (neat): 1740, 1682, 1604, 1578, 1323, 1292, 1169, 1092, 1049, 760, 725 cm⁻¹

MS (ESI): *m/z* = 545.1 [M+Na]⁺,

HRMS (ESI): *m/z* calcd for C₂₆H₂₃³⁵Cl₃O₅+H: 519.0897; found: 519.0874.

Methyl 2-(2-acryloyl-3,5-bis(2-chlorobenzyloxy)phenyl)acetate **1.11**

Et₃N (0.34 mL, 2.43 mmol) was added to a solution of ketone **1.10** (633 mg, 1.21 mmol) in anhydrous CH₂Cl₂ (25 mL) at room temperature. The solution was stirred for 6 h and quenched by aq. NH₄Cl (10 mL). The aqueous layers were extracted with CH₂Cl₂ (10 × 3 mL) and the combined organic layers were dried over MgSO₄ and concentrated under reduce

pressure. Purification by flash chromatography on silica with 25% ethyl acetate/hexane gave **1.11** as a white solid (559 mg, 95%).

R_f = 0.25 (1:3 EtOAc–hexane). m.p.: 97–100 °C

^1H NMR (400 MHz, CDCl_3): δ 7.54–7.25 (m, 8H), 6.79 (dd, J =17.4, 10.5 Hz, 1H), 6.57 (d, J =4.12 Hz, 2H), 6.16 (dd, J =17.4, 1.4 Hz, 1H), 5.83 (dd, J =10.5, 1.4 Hz, 1H), 5.18 (s, 2H), 5.14 (s, 2H), 3.70–3.66 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 109.7, 171.4, 171.2, 160.6, 158.0, 138.2, 135.6, 134.1, 134.0, 132.9, 132.3, 129.6, 129.4, 129.3, 129.2, 129.1, 128.9, 128.6, 127.2, 127.1, 122.9, 109.7, 99.5, 67.8, 67.4, 60.5, 52.1, 38.7, 21.1, 14.3.

IR (neat): 2342, 1740, 1667, 1601, 1177, 748 cm^{-1} .

MS (ESI): m/z = 484.9 $[\text{M}+\text{H}]^+$,

HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{22}^{35}\text{Cl}_2\text{O}_5+\text{H}$: 485.0923; found: 485.0955.

(*R*)-hept-6-en-2-ol 1.15

Bromo-but-1-ene **1.13** (2.04 mL, 20.0 mmol) was added dropwise to a mixture of Mg turnings (1.46 g, 60.0 mmol) and a crystal piece of iodine in anhydrous THF (30 mL) under N_2 over 0.5 h. The mixture was heated at reflux for 3 h. The prepared Grignard solution **1.14** was transferred to a solution of (*R*)-propylene oxide (0.7 mL, 10.0 mmol) and copper iodide (190 mg, 1.0 mmol) in THF (10 mL) at -78°C under nitrogen. The mixture was stirred overnight at -40°C and quenched with aq. NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (20 mL x3) and the combined organic

layers were dried over MgSO_4 and concentrated in *vacuo* to give **1.15** as a colorless liquid (850 mg, 75%).

^1H NMR (400 MHz, CDCl_3): δ 5.81 (ddt, $J=17.2, 10.5, 6.9$ Hz, 1H), 4.99 (m, 2H), 3.81 (s, 1H), 2.08 (m, 2H), 1.56-1.27 (m, 5H), 1.19 (d, $J=6.0$ Hz, 3 H).

All data are consistent with that reported in literature.²⁰

(*R*)-tert-butyl(hept-6-en-2-yloxy)dimethylsilane 1.12

tert-Butyldimethylsilyl chloride (396 mg, 2.63 mmol), imidazole (238 mg, 3.50 mmol) and **1.15** (200 mg, 1.75 mmol) were mixed in anhydrous THF (2 mL) at 0 °C. The mixture was stirred overnight at room temperature and then quenched with aq. NH_4Cl (2 mL). The mixture was extracted with Et_2O (5 x 3 mL). The combined organic layers were dried over MgSO_4 and concentrated by rotary evaporation to yield **1.12** as a colorless liquid.

$[\alpha]_{\text{D}}^{21}$ -11.4 (c 0.80, MeOH)

^1H NMR (400 MHz, CDCl_3): δ 5.81 (ddt, $J=17.2, 10.5, 6.4$ Hz, 1H), 4.97 (m, 2H), 3.78 (m, 1H), 2.04 (m, 2H), 1.50-1.32 (m, 4H), 1.12 (d, $J=6.0$ Hz), 0.92 (s, 3H), 0.884 (s, 9H), 0.107 (s, 3H).

All data are consistent with that reported in literature.²¹

(*R,E*)-methyl 2-(3,5-bis(2-chlorobenzyloxy)-2-(7-((*tert*-butyldimethylsilyl)oxy)oct-2 enoyl phenyl) acetate **1.17**

Ketone **1.11** (1 g, 2.05 mmol) and alkene **1.12** (945 mg, 4.10 mmol) was dissolved in 1,2-dichloroethane (3 mL). Nitrogen was continuously flowed through the system during the reaction. Grubbs II catalyst (180 mg, 0.205 mmol) in 1,2-dichloroethane (2 mL) was added in five portions at 90 min interval at 70 °C. The mixture was cooled and filtered through celite. The solution was evaporated and the residue was purified by flash chromatography on silica eluting with 20% ethyl acetate/hexane gave **1.17** as a colorless oil (1.2 g, 85%).

$[\alpha]_D^{21}$ -3.3 (*c* 0.80, EtOH); R_f = 0.43 (1:4 EtOAc–hexane).

^1H NMR (400 MHz, CDCl_3): δ 7.56-7.24 (m, 8H), 6.75 (dt, J =16.0, 6.9 Hz, 1H), 6.58 (s, 2H), 6.48 (d, J =15.6 Hz, 1H), 5.18 (s, 2H), 5.13 (s, 2H), 3.74 (m, 1H), 3.70 (s, 3H), 3.58 (s, 2H), 2.19 (m, 2H), 1.53-1.13 (m, 4H), 1.08 (d, J =6.4 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 197.0, 171.6, 160.4, 157.7, 149.9, 135.3, 134.3, 133.1, 132.5, 132.3, 129.7, 129.6, 129.5, 129.4, 129.2, 128.7, 127.3, 127.2, 123.8, 109.5, 99.7, 68.5, 67.7, 67.5, 52.3, 39.4, 38.8, 32.8, 26.1, 24.4, 24.0, 18.3, -4.1, -4.5.

IR (neat): 1740, 1647, 1633, 1176 cm^{-1} .

MS (ESI): m/z = 685.0 $[\text{M}+\text{H}]^+$.

HRMS (ESI): m/z calcd for $C_{37}H_{46}O_6^{35}Cl_2Si+H$: 687.2667; found: 687.2697

Methyl 2-(3,5-bis(2-chlorobenzyloxy)-2-(2-((2*S*,6*R*)-6-methyltetrahydro-2*H*-pyran-2-yl)acetyl) phenyl) acetate **1.18**

Compound **1.17** (100 mg, 0.146 mmol) and amberlyst-15 (60 mg) was mixed in MeOH (5 mL). The mixture was stirred overnight, filtered through celite, and the solution was concentrated by rotary evaporation. The crude was purified by flash chromatography on silica eluting with 20% ethyl acetate/hexane to give **1.18** as a colorless oil (69 mg, 88%).

$[\alpha]_D^{21}$ -18.3 (c 0.4, EtOH); R_f = 0.27 (1:4 EtOAc–hexane).

1H NMR (400 MHz, $CDCl_3$): δ 7.52-7.25 (m, 8H), 6.52 (d, J =2.8 Hz, 2H), 5.15 (s, 4H), 3.85 (m, 1H), 3.70 (s, 3H), 3.62 (s, 2H), 3.37 (m, 1H), 3.06 (dd, J =16.0, 7.8 Hz, 1H), 2.95 (dd, J =16.5, 5.5 Hz, 1H), 1.72-1.70 (m, 1H), 1.57-1.47 (m, 4H), 1.12-1.09 (m, 1H), 1.08 (d, J =6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 172.0, 160.4, 157.8, 135.3, 134.2, 134.0, 133.0, 132.9, 129.7, 129.6, 129.5, 129.4, 129.3, 127.3, 124.9, 109.8, 99.3, 74.9, 68.1, 67.4, 52.2, 51.6, 39.0, 33.2, 31.3, 23.8, 22.3.

MS (ESI): m/z = 593.3 $[M+Na]^+$, 571.0 $[M+H]^+$.

HRMS (ESI): m/z calcd for $C_{31}H_{32}O_6^{35}Cl^{37}Cl+H$: 573.1803; found: 573.1853

Curvulone B 1.2

A mixture of compound **1.18** (69 mg, 0.128 mmol) and $Pd(OH)_2$ on carbon (30 mg) in ethyl acetate (5 mL) was flushed with hydrogen and then stirred overnight under hydrogen (balloon). The mixture was filtered through celite and concentrated by rotary evaporation. Purification by flash chromatography on silica eluting with 50% ethyl acetate/hexane gave **1.2** as a colorless oil (42 mg, 81%)

$[a]_D^{21}$ -19 ($c=0.28$, EtOH)

1H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 6.27 (d, $J=2.3$ Hz, 1H), 6.20 (d, 2.3 Hz, 1H), 4.14 (m, 1H), 3.91 (d, $J=16.5$ Hz, 1H), 3.70 (s, 3H), 3.56 (m, 1H), 3.51 (d, $J=16.5$ Hz, 1H), 3.30 (dd, $J=14.2, 10.3$ Hz, 1H), 2.57 (dd, $J=14.3, 3.2$ Hz, 1H), 1.85 (m, 1H), 1.66 (m, 1H), 1.60 (m, 1H), 1.57 (m, 1H), 1.44 (m, 1H), 1.27 (m, 1H), 1.16 (d, $J=5.9$ Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 172.4, 159.5, 159.4, 135.8, 120.9, 111.7, 104.1, 77.9, 74.9, 52.1, 49.0, 39.7, 32.7, 30.7, 23.1, 21.5.

References

1. Krohn, K.; Biele, C.; Aust, H. J.; Draeger, S.; Schulz, B. *J. Nat. Prod.* **1999**, *62*, 629;
2. Dai, J.; Krohn, K.; Pescitelli, G.; Kerti, G.; Papp, T. *Eur. J. Org. Chem.* **2010**, 6928;
3. (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309; (b) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301;
4. (a) Bates, R. W., Song, P. *Tetrahedron* **2007**, *63*, 4497; (b) Bates, R. W.; Song, P. *Synthesis* **2010**, 2935; (c) Bressy, C.; Allais, F.; Cossy, J., *Synlett* **2006**, 3455.
5. (a) Fuwa, H. *Heterocycles* **2012**, *86*, 1255; (b) Larossa, I.; Romea, P.; Urp í F. *Tetrahedron* **2008**, *64*, 2683; (c) Clarke, P. A.; Santos, S., *Eur. J. Org. Chem.* **2006**, *9*, 2045.
6. (a) Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1589. (b) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919;
7. Nising, C. F.; Br äse, S. *Chem. Soc. Rev.* **2012**, *41*, 988;
8. Chatterjee, A. K.; Choi, T-L.; Sander, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360;
9. Guillena, G.; Yus, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358;
10. Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681;
11. Takahashi, S.; Akita, Y.; Nakamura, T.; Koshino, H. *Tetrahedron: Asymmetry* **2012**, *23*, 952;
12. Zhou, G. Y. Final Year Project, Nanyang Technological University, **2012**.
13. Kang, Dave, Z. H. Summer Research Project, Nanyang Technological

University, **2013**.

14. Wuts, P. G. M; Greene, T. W. *Greene's Protective Groups in Organic Synthesis, Fourth Edition*; Wiley, **2006**.
15. Gould, A. E; Furrow, M. E; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, 124, 1307.
16. Samojlowicz, C.; Bieniek, M.; Zarecki, A.; Kadyrov, R.; Grela, K., *Chem. Comm.* **2008**, 47, 6282
17. Plante, O.; Buchwald, S. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, 122, 7148.
18. Tarbell, D. S.; Wargotz, B. *J. Am. Chem. Soc.* **1954**, 76, 5761.
19. Hofmann, A.; Graf, C.; Kung, S.-H.; Kim, M.; Peng, X.; El-Aama, R.; Rühl, E. *Synthesis* **2010**, 2010, 1150.
20. von Delius, M.; Le, C. M.; Dong, V. M. *J. Am. Chem. Soc.* **2012**, 134, 15022.
21. Seo, S.-Y.; Jung, J.-K.; Paek, S.-M.; Lee, Y.-S.; Kim, S.-H.; Suh, Y.-G. *Tetrahedron Lett.* **2006**, 47, 6527.

Chapter 2

2.1 Introduction of Tsuji- Trost reaction

The transition metal catalyzed allylic substitution, known as the Tsuji-Trost reaction, is one of the most versatile bond formation reactions in organic synthesis.¹ In 1965, Tsuji reported the first alkylation of π -allyl palladium complexes with nucleophiles, such as malonates, to form a C-C bond.² This is the first example in which the transition metal intermediate acted as an electrophile while in the traditional palladium catalyzed cross coupling reactions, the metalated intermediates usually worked as nucleophiles generated from the oxidative addition step. The Trost group subsequently developed this novel reaction into a catalytic version³ and utilized it in asymmetric synthesis.⁴ Since then numerous contributions have been made, especially in terms of leaving groups, transition metal catalysts and ligands, in this field of the Tsuji-Trost reaction.⁴ Due to the high regio- and stereoselectivity of the Tsuji-Trost reaction, it has been widely used in the total synthesis of natural products.⁵

In the generally accepted mechanism (scheme 2-1), the Pd(0) species coordinates to the alkene first. A π -allyl palladium complex is formed through oxidative addition with the expulsion of the leaving group. The product is then generated by the nucleophilic attack on the electrophilic π -allyl palladium complex with concomitant reduction of the palladium species, completing the catalytic cycle.

Scheme 2-1 Mechanism of the Tsuji-Trost reaction

Normally, the formation of the π -allyl complex is disfavored in the reversible process due to thermodynamic issues.⁶ In order to drive the equilibrium in the direction of the π -allyl complex, the most popular method is to put a good leaving group on the allylic position.⁷ Generation of the π -allyl complex is then favored owing to the irreversibility of formation of the allylic substrate.⁶ Research in this field was fruitful and several classical allylic substrates are presented in Scheme 2-2. Due to stability issues, allylic halides are generally not good choices while allylic acetates are commonly used due to their availability and reactivity. In addition, carbonate was introduced as a leaving group by Tsuji. The use of carbonate allows the reaction to proceed under neutral conditions without influence

on the base-sensitive functional groups present in the molecule because the corresponding alkoxide formed *in situ* through decarboxylation is able to take part in the deprotonation.⁸ Thus, no base needs to be added. Vinyl epoxides behave similarly.

Scheme 2-2 General Substrates for Tsuji-Trost reaction

Among the transition metals applied in this reaction, palladium catalysts indeed play a dominant role. Recently, research on other transition metals, such as Ir, Fe, Mo, Cu and Rh, has become competitive and can show unique characteristics in the Tsuji-Trost reaction.⁹

There are numerous examples that Tsuji-Trost reaction played an important role in the efficient and stereoselective construction of complex natural products.

Overman *et. al* successfully finished the enantioselective synthesis of strychnine – a remarkable alkaloid of historical importance.⁵ The first key step of this synthesis was an enantioselective Tsuji-Trost reaction of a cyclopentene derivative (Scheme 2-3). This step was emphasized because of the net stereochemical outcome and exclusive displacement of the

carbonate group in the presence of the acetate group.

Scheme 2-3 Tsuji-Trost reaction in the synthesis of strychnine

Reagents and conditions: $\text{Pd}_2(\text{dba})_3$, PPh_3 , NaH , THF.

In the synthesis of FR 1828877 reported by Sorensen and co-workers, the Tsuji-Trost macrocyclization was employed for the construction of the pivotal macrocycle intermediate (Scheme 2-4).⁵ On treatment with palladium catalyst, the allylic carbonate substrate underwent oxidative addition promoted by the expulsion of CO_2 and releasing the methoxide which deprotonated the β -ketoester moiety, thus enabling the macrocyclisation. This work showed the elegance of Tsuji-Trost reaction in the formation of macrocycles.

Scheme 2-4 Tsuji-Trost reaction in the synthesis of FR 1828877.

Reagents and conditions: $\text{Pd}_2(\text{dba})_3$, THF, 45 °C, 80%.

2.2 Tsuji-Trost ring-closing reaction

The intramolecular Tsuji-Trost reaction is one of the most attractive synthetic methods for ring formation due to its good competence and flexibility.⁵ It has been applied in the synthesis of several natural products with good selectivity and functional group tolerance.⁵

The synthesis of six-membered rings with multiple functional groups is an important topic, since they are vitally important intermediates and structural features for natural products and drugs.⁵ Hence, using the intramolecular Tsuji-Trost reaction to generate such rings is appealing for a number of reasons, including step-economy, as well as both regio and stereoselectivity. There have been several reports of the formation of six-membered rings with the Tsuji-Trost reaction. Tsuji group reported a Pd-catalyzed cyclisation to give a substituted cyclohexanone (Scheme 2-5) with some asymmetric induction.¹⁰ The allylic alcohol was first protected as a THP ether under acidic conditions.¹⁰ The protected alcohol underwent Wacker oxidation and then reacted with dimethyl carbonate to generate the β -ketoester substituent.¹⁰ The carbonate group was then formed from the THP group through two steps. The Tsuji-Trost cyclisation finally afforded the six-membered ring in the presence of palladium catalyst and chiral phosphine ligand.¹⁰ After decarboxylation, the optical activity of the ketone compound was obtained in up to 48% e.e.¹⁰ The allylic carbonate was found to be more active than the corresponding allylic acetate in this

transformation.¹⁰ However, competitive *O*-allylation also occurred.¹¹

Scheme 2-5 Tsuji-Trost cyclisation reaction a. DHP, acid, CH₂Cl₂; b. PdCl₂, CuCl, O₂, DMF; c. (MeO)₂CO, NaH, benzene; d. *p*-TsOH, MeOH; e. ClCO₂Me, py., benzene; f. Pd(OAc)₂, (*S*)-(*R*)-BPPFA; g. NaCl, DMSO.

The Tsuji group then carried out the same cyclisation in the presence of NaH. The sodium salt prevented the *O*-allylation product from forming (Scheme 2-6).¹¹ The sodium cation is believed to be chelated by the enolate to generate a stable six-membered ring intermediate which would exert a blocking effect on the oxygen position.

Scheme 2-6 Tsuji-Trost cyclisation with NaH

2.3 Study on the synthesis of briaranes

The briaranes are a group of several hundred marine natural products.¹² Interesting biological activities have been claimed for a number of the natural products in this family. In addition, they possess a synthetically challenging bicyclic [8.4.0] ring system with a lactone connected to the ten membered ring.¹² Due to their structural complexity and the biological activity, there has been some efforts towards the synthesis of these molecules.

Procter *et.al.* reported a Cr(II)-mediated cyclization to install the bicyclic [8.4.0] structure (Scheme 2-7).¹³ The synthesis started from a 1,4-addition of the Grignard reagent to conjugated ketone.¹³ Reagent **2.7.1** was used as an equivalent to a Michael acceptor to give the substituted cyclohexanone. The ketone and ester group were reduced to alcohols and the primary alcohol was selectively protected as a TBS ether group. The acetal group in the side chain was then transformed into ketone under acidic conditions, followed by an iodovinylation in the presence of Cr(II). The allylic alcohol derivative was then installed in a sequence of deprotection and oxidation. A Cr(II) mediated cyclisation was developed to install the ten membered ring. This method was effective in constructing the [8.4.0] moiety but suffered some drawbacks. It is quite difficult to perform asymmetric synthesis in the scheme and the use of toxic Cr(II) made it environmentally unfriendly.

Scheme 2-7 Cr(II)-mediated cyclization by Procter. Reagents and conditions: a. CuI, TMEDA, TMSCl; b. 1) MeLi, **2.7.1**, THF; 2) CCl₄, CaCO₃, reflux; c. 1) LiAlH₄, Et₂O; 2) H₂SO₄; 3) TBSCl, Et₃N, DMAP, THF; d. 1) MeI, AgO; 2) CrCl₂, CHI₃, THF; e. 1) HF, MeCN; 2) MnO₂, CH₂Cl₂; f. CrCl₂, NiCl₂, DMSO.

Ito and Iguchi *et. al.* reported a synthetic study of pachyclavulide B, which is a briarane-type diterpenoid with a bicyclic [8.4.0] structure (Scheme 2-8).¹⁴ The synthesis began with Birch reduction of 2,6-dimethylbenzoic acid, followed by esterification with diazomethane. Shi epoxidation with reagent **2.8.1** was employed to introduce the epoxide and the ester was reduced to the alcohol, followed by a protection with TBDPS group. The allylic alcohol was obtained from the epoxide opening reaction on treatment with Et₂AlTMP, which reacted with the alkene in the presence of NIS to give the

iodo compound. The challenging quaternary carbon on the ring was introduced by an intramolecular radical cyclisation with good diastereoselectivity. The acetal group was oxidized to give lactone with the help of Jones reagent. The α -hydroxyl group was introduced use of the Davis reagent, and the lactone was reduced to afford the triol, which subsequently underwent oxidative cleavage to give the aldehyde on treatment with NaIO_4 . The diol product was obtained by a diastereoselective Grignard addition reaction. This is the only enantioselective approach so far. The asymmetric epoxidation gave good enantioselectivity and all the desired stereogenic centers on the six-membered ring could be installed effectively. However, the low yield and high loading of the catalyst in the asymmetric epoxidation step limited the application of this method.

Scheme 2-8 Towards the synthesis of pachyclavulide B. Reagents and conditions: a.

1) Na, NH₃, EtOH; 2) CH₂N₂, Et₂O; b **2.8.1**, oxone, MeCN-DMM; c.1) DIBAL-H, toluene; 2) TBDPSCl, imidazole, CH₂Cl₂; d. Et₂AlTMP, toluene; e. ethyl vinyl ether, NIS, CH₂Cl₂; f. 1) Bu₃SnH, AIBN, toluene; 2) Jones reagent, acetone; g. 1) TBAF, THF; 2) LDA, 2-(phenylsulfonyl)-3-phenyloxaziridine, THF; 3) TBDPSCl, imidazole, DMF; h. 1) LiAlH₄, THF; 2) NaIO₄, THF, H₂O; i. vinylmagnesium chloride, THF.

Harned *et al.* reported a concise synthetic route to the multi-substituent six membered ring of the briarane diterpenoids (Scheme 2-9).¹⁵ In their synthesis, the salicylate ester underwent oxidative dearomatization with reagent **2.9.1** to give a dienone substrate, which was subjected to a

conjugate addition with a metalated TMS-acetylene species in a highly diastereoselective manner, followed by *in situ* methylation. The acetylide added *syn* to the OMe group and the methyl group was installed *syn* to the alkyne group. The stereochemistry of the alkylation was under Curtin-Hammett-type control as proposed by Harned.¹⁵ The methoxy group was eliminated in the presence of zinc dust. The alcohol was obtained from the reduction of the ketone as a ratio of 1:1.3 of two diastereoisomers. The desired isomer was separated by silica-gel chromatography and the ester underwent a sequence of reduction and reoxidation to give the aldehyde intermediate. This scheme allowed that all the stereocenters on the six-membered ring could be introduced in a few steps but the low yield of several steps and poor diastereoselectivity in a ratio of 1:1.3 of the reduction of the ketone are issues that remain to be addressed.

Scheme 2-9 Synthetic route of multi-substituent six membered ring by Harned. Reagents

and conditions: a. **2.9.1**, MeOH; b. 1) TMS-acetylene, Et₂AlCl, 2). MeI, K₂CO₃, 18-c-6; c. Zn, AcOH; d. NaBH₄, Y(OTf)₃, MeOH, d.r.=1:1.3; e. 1) LiAlH₄, Et₂O; 2) TEMPO, PhI(OAc)₂

Crimmins *et al.* reported a route to prepare the six-membered ring utilizing dianionic Claisen rearrangement and ring-closing metathesis (Scheme 2-10).¹⁵ In this route, the hydroxyester was prepared in a few steps by utilizing Evans auxiliary. An Ireland-Claisen rearrangement was applied to establish the quaternary carbon next to the carbonyl group. The ester group was transformed into allylic alcohol easily. On treatment with Grubb II catalyst, the desired six-membered ring product was obtained in a good yield. This strategy allowed a fast construction of the six-membered ring with all the stereogenic centers installed. However, the hydroxyester had to be prepared with auxiliary and extra steps had to be employed to obtain the desired allylic alcohol in a good diastereoselectivity.

Scheme 2-10 Reagents and conditions: a.1. LiHMDS, toluene/THF; 2. CH₂N₂, Et₂O; b.

1. TBSOTf, 2,6-lutidine, CH₂Cl₂; 2. *i*-Bu₂AlH, CH₂Cl₂; c. (COCl)₂, DMSO, Et₃N, CH₂Cl₂; 2 allylmagnesium bromide, Et₂O; d. 5 mol% Grubbs II, toluene; 2. TBAF, CH₂Cl₂.

A synthesis of the northern hemisphere of the briaranes was reported by this laboratory (Scheme 2-11).¹⁶ The six membered ring was derived from the Diels-Alder reaction of the sulfonyl diene with excellent diastereoselectivity in a ratio of 15:1. After deconjugation of the alkene, oxidative desulfonylation provided the ketone. Diastereoselective reduction of the ketone gave an allylic alcohol which was subjected to a Johnson-Claisen rearrangement to install the quaternary center. Iodocyclisation allowed lactone formation. Further transformations then allowed Keck allylation for installation of the carbon side chain.

Scheme 2-11 Synthesis of the northern hemisphere of briaranes

While one synthetic challenge arises from the construction of the ten

membered ring, another is provided by the highly substituted six membered ring. The Diels-Alder approach employed earlier in this laboratory¹⁶ was effective in generating such a ring but suffered from a number of drawbacks. Not only would developing an asymmetric version be difficult, the scheme is somewhat atom inefficient and the key Diels-Alder reaction requires rather brutal conditions because it involves the combination of two π -systems that are both electron poor. An alternative way to construct the six membered ring might be via an intramolecular Tsuji-Trost reaction. If we consider the advanced intermediate previously reported by this laboratory, an alternative retrosynthetic analysis could involve several redox adjustments around the ring, installation of the side chain by nucleophilic addition and formation of the silyl ether functionality based upon alkene oxidative cleavage (Scheme 2-12). This would lead to a simplified cyclohexanone intermediate which includes a β -ketoester moiety. The methyl group α to the ester could be envisioned to be installed by an axial alkylation reaction under stereoelectronic control. For such selectivity, it would be necessary for the vinyl group and the other methyl group to both be equatorial. This disconnection would then reveal an intramolecular Tsuji-Trost reaction i.e. cyclisation of β -ketoester. It might be anticipated that a chair transition state would deliver the required bis-equatorial stereochemistry.

Scheme 2-12 Retrosynthetic plan

Just such a diastereoselective Tsuji-trost cyclisation was employed in this laboratory in a formal synthesis of swainsonine (Scheme 2-13).¹⁷ Treatment of the allylic acetate with a palladium(0) catalyst in the presence of base gave the piperidine in good yield as a 10:1 mixture of stereoisomers, favouring the desired isomer. This was then carried through to the known swainsonine intermediate.

Scheme 2-13 Formal synthesis of swainsonine

Hence, we were interested to investigate the diastereoselectivity of the intramolecular Tsuji-Trost cyclisation before applying this methodology to the synthesis of the natural products. We hope that the cyclisation would undergo thorough a chair-like transition state to give a *trans* product.

2.4 Results and Discussion

Scheme 2-14 Synthesis of the acid **2.3**. Reagents and conditions a. 1) H_2O_2 , MeOH; 2) CuSO_4 , FeSO_4 , H_2O ; 63% overall yield

Initially, we intended to work with racemic material and ultimately would be able to use optically pure material derived from citronellene. The acid **2.3** was prepared from 4-methylcyclohexanone with H_2O_2 with the help of Fe^{2+} and Cu^{2+} (Scheme 2-14) in a yield of 63%.¹⁸ The mechanism of this reaction was proposed by Kochi.¹⁶ The hydrogen peroxide first reacted with ketone (Scheme 2-15) to form a hydroperoxy acetal. The peroxide bond was cleaved by the ferrous ions to give an alkoxy radical.²⁰ The alkoxy radical has a dramatic effect on weakening the unreactive neighboring carbon-carbon according to Evans' work.²¹ The homolytic cleavage of the C-C bond resulted in the formation of the carbonyl group and an alkyl radical which was transformed into an olefin through a beta-hydride elimination in the presence of cupric ions.²² This reaction provided rapid access to useful quantities of the acid.

Scheme 2-15 Mechanism of the ring opening reaction.

Cross metathesis to generate allylic substrate

Scheme 2-16

Table 2-1

Entry ^a	R ^b	Catalyst ^c	Yield
1	R=CO ₂ Me	Grubbs II	25%
2	R=CO ₂ Me	H-G II	73%
3	R=Ac	Grubbs II	20%

a. 200 mg **2.3** in 6 mL toluene; b. 1.5 eq. to acid **2.3**; c. 5 mol% loading

After getting the acid, the next step was to prepare the allylic substrate **2.4** for the Tsuji-Trost reaction. Cross metathesis with a 1,4-butanediol derivative could simply afford the desired product (Scheme 2-16). In this reaction, the carbonate partner was found to be more reactive than the acetate (Entry 1 vs 3), which was also observed in the Tsuji-Trost reaction by Tsuji.⁸ However, low yields were obtained using the Grubbs-II catalyst. We believe that this is due to the extra steric hindrance caused by the methyl group at the allylic position of the olefin. This effect has been observed

before in this laboratory.²³ HG-II was, therefore, employed as the catalyst. This catalyst is known to be more robust than the Grubbs' catalysts and the reaction times can be extended. A good yield of 73% was obtained in this reaction after a reaction time of 12 h. The diol derivatives were employed in this reaction as the corresponding allylic alcohol derivatives undergo facile homo-metathesis.²⁴ 2H multiplets at 5.67-5.54 ppm was observed for the internal alkene protons. A doublet at 4.58 ppm was assigned to the allylic protons. A singlet at 3.78 was characteristic of the methoxy proton.

Preparation of the malonate

Scheme 2-17

With the corresponding allylic carbonate in hand, it was necessary to convert it to the β -ketoester **2.5** (Scheme 2-17). Following Masamune's procedure,²⁵ the acid was first reacted with 1,1'-carbonyldiimidazole (CDI) to give the activated intermediate **I-5** (Scheme 2-18). This underwent a Claisen condensation with the mono-methyl malonate magnesium salt generated *in situ* from the corresponding potassium salt with MgCl_2 . Decarboxylation *in situ* furnished the β -keto ester with a good yield of 88%. For the formation of **I-5**, the CDI deprotonated the carboxylic acid and then reacted with the carboxylate to give the acetic anhydride intermediate

losing one equivalent imidazole at the same time. The imidazole reacted with the acetic anhydride to give the intermediate **I-5**.

At the same time, we also tried to prepare **2.5** by reaction of the acid chloride with Meldrum's acid (Scheme 2-18). However, no desired product was obtained and only starting material was recovered.

According to its ^1H NMR spectrum, the product existed in its keto form surprising to have no enol form observable. Two singlet peaks at 3.78 and 3.72 ppm were observed for the two methoxy groups. A singlet at 3.42 ppm was observed for the two protons between the keto and ester units.

Scheme 2-18

Tsuji-Trost Reaction

Scheme 2-19

Table 2-2

Entry ^a	Catalyst ^b	Additive	Result	Yield
1	Pd(PPh ₃) ₄	-	2.7	95%
2	Pd(OAc) ₂ +PPh ₃	-	2.7	73%
3	DppfPdCl ₂	5 mol% Et ₃ N	Starting material	-
4	DppePdCl ₂	5 mol% Et ₃ N	Starting material	-
5	[Ir(COD)Cl] ₂ +P(OPh) ₃	-	Starting material	-
6 ^c	Pd(PPh ₃) ₄	-	2.7	90%
7	Pd(PPh ₃) ₄	2eq. NaH	2.6	60%
8	Pd(OAc) ₂ +PPh ₃	2eq. NaH	2.6	77%
9	Pd(OAc) ₂ +PPh ₃	2eq. tBuOK	2.8	85%
10	Pd(OAc) ₂ +PPh ₃	2eq. nBuLi	2.8	70%

a. All reactions were carried out in THF at room temperature and stirred overnight. b.

[M] = 5 mol%. c. The reaction was carried out in methanol.

We initially submitted the β -keto ester to the Tsuji-Trost reaction with $\text{Pd}(\text{PPh}_3)_4$ and $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ under neutral conditions in THF. However, only the *O*-allylation product **2.7** was obtained (Entries 1 and 2). The structure of **2.7** was deduced from its ^1H and ^{13}C NMR spectra. The signals characteristic of a terminal alkene at 5.80 and 5.28 ppm were observed in the ^1H NMR spectrum. The H α to the ester was observed at 5.32 ppm. No signals corresponding to a ketone group were observed in the ^{13}C NMR spectrum. A similar result was also observed in the total synthesis of (-)-Fusarisetin A by Li.²⁶ Since the *O*-allylation product could re-enter into a Tsuji-Trost reaction, it was subjected to Trost's conditions²⁴ in hoping to achieve *C*-allylation product but only starting material was recovered.

Several bidentate palladium catalysts were also used. However, no useful results were obtained and only starting material was recovered (Entry 3 and 4). An Ir catalyst was also introduced in this reaction as it has been reported that they favor the formation of the *C*-branched allylation products according to Takeuchi²⁸ and You²⁹. We submitted the β -ketoester to this reaction in methanol hoping that hydrogen bonding between the enolate and the carbonyl group can prevent the *O*-allylation from occurring. However, the undesired product *O*-allylation product was still obtained (Entry 6).

Hence, in order to prevent *O*-allylation, a metal cation was introduced. The reaction was carried out with NaH, *t*-BuOK and *n*-BuLi. Gratifyingly, the reaction using NaH gave the desired *C*-allylation product **2.6** (Entry 7 and

8) while, surprisingly, the other reactions yielded the undesired eight-membered ring product **2.8** (Entry 9 and 10). The C-allylation product **2.6** exists entirely as an enol according to its NMR spectrum (Figure 2-1). The enol hydroxyl proton was observed as a sharp singlet at 12.41 ppm. Protons characteristic of a terminal alkene were also observed. In the ^1H NMR spectrum of **2.8**, two internal olefin peaks at 5.59 and 5.47 ppm were observed instead of a vinyl group. The coupling constant of the dd peak at 5.47 ppm is 16.0, 8.2 Hz, indicating that the product is a *trans*-cyclooctene. The formation of compound **2.8** is surprising. The formation of eight membered rings is often found to be difficult due to transannular strain.

Scheme 2-20 Tsuji-Trost cyclisation

For the mechanism of this ring closure (Scheme 2-20), the Pd catalyst first coordinated with the allylic carbonate to generate the π -allyl palladium complex, release the CO_2 and the methoxide generated deprotonates the ketoester. Both the C and O in the β -ketoester motif are nucleophilic under basic conditions. Reactions proceeding through pathway **a** would generate the six membered ring product **2.6** and the one through **b** would form O-allylation product **2.7**. The nucleophilic carbon attacking the far position of the allylic complex through pathway **c** would explain the formation of the

eight membered ring product **2.8**.

Scheme 2-21

We also tested the cyclisation with substrate **2.9**, which was prepared in a good yield as a single β -ketoester isomer under the previous conditions (Scheme 2-21). The Tsuji-Trost reaction of **2.9** would provide the six membered ring together with a methyl group at the α position to the ester. However, no *C*-allylation product was observed under the condition that worked for the substrate without a methyl group. This is likely to be due to the extra steric hindrance from the extra methyl group.

Figure 2-3

Interestingly, the product **2.6** was obtained as a single diastereoisomer. For the purposes of our synthesis, it was essential to determine the relative stereochemistry of the product. As assignment of the proton signals in the ^1H NMR spectrum was not obvious, a COSY experiment was carried out (Figure 2-1 and 2-2). The signal at δ 5.72 ppm due to the internal vinyl proton was clearly correlated to the signal at δ 3.13 ppm. This signal could, therefore, be assigned to proton H_3 . The coupling constant between H_3 and H_4 was then calculated as 5.0 Hz based on the *dd* H_3 peak. According to the Karplus relationship, H_3 and H_4 might be in a relationship of either *ax*/*eq* or *eq*/*eq*. In order to confirm the stereochemistry of H_4 , the coupling relationship between H_4 and the geminal pair of H_1 and H_2 had to be

determined. Due to the complexity of the signal at 1.78 ppm (H_4), a homonuclear-decoupling experiment was carried out to simplify the spectrum (figure 2-3). The proton H_4 at δ 1.78 appeared as a *ddd* peak after proton irradiation at the methyl group (figure 2-3). The coupling constants between H_4 and H_1 , H_2 were calculated as 6 Hz and 12 Hz. These results indicate that the relationship between H_4 and H_1 is *ax/ax* according to the Karplus relationship. Therefore H_4 is an axial proton and H_3 is equatorial proton. Hence, these coupling constants clearly proved that the methyl group and the vinyl group are *cis* to each other (Scheme 2-22).

Scheme 2-22 Coupling constant

Interestingly, this result was opposite to our initial hypothesis. We hypothesize that the cyclisation would proceed through a half-chair like transition state in which the allylic complex would prefer to take over the axial position due to $A^{1,2}$ strain between the π -allyl complex and the ester group (Scheme 2-23).³⁰

Scheme 2-23

2.5 Summary and future work

In conclusion, we have developed an effective method to diastereoselectively provide the intermediate **2.6** using the intramolecular Tsuji-Trost cyclisation. In the future, we hope to apply it into the total synthesis of natural products. While the stereochemical outcome is opposite to that desired for the synthesis of the briarane natural products, there are other natural products with this pattern.

For example, 14-hydroxy-6,12-muuroloadien-15-oic acid **2.23.1** was isolated from *Eremophila mitchellii* from Australia.³¹ It is recognized as an uncommon scaffold to build novel drug-like screening libraries.³¹ In the target molecule **2.23.1**, the methyl group at the left ring is *cis* to the right

ring. It could be assembled with the help of our finding (Scheme 2-24). The **2.23.1** could be prepared from **2.23.2** through a ring opening of cyclopropane. The cyclopropane group should arise from ester **2.23.3** though a regioselective Kulinkovich reaction.³² Compound **2.23.3** could be prepared by ring closing metathesis and selective hydrogenation of **2.23.4**. Horner-Wadsworth-Emmons olefination of **2.23.5** could furnish the precursor for metathesis. Aldehyde **2.23.5** would be derived from the Tsuji-Trost product **2.6** though a sequence of Pd catalyzed carbonylation, selective alkene reduction and selective ester reduction.

Scheme 2-24 Retrosynthetic plan

Experimental

All reactions were run under nitrogen gas atmosphere with oven-dried glassware. Anhydrous toluene, THF and Et₂O were distilled from sodium metal. The other solvents and reagents were used as received. Column chromatography was carried out on silica gel 230-400 mesh, and analytical TLC on glass plates (silica gel 60, F254). All ¹H NMR spectra were recorded on a JEOL ECA 400 MHz or Bruker Advance DPX at 400 MHz in CDCl₃ solutions. ¹³C NMR spectra were recorded in CDCl₃ on the same instruments at the corresponding frequency. Chemical shifts are recorded in ppm and coupling constants are recorded in Hz.

4-methylhex-5-enoic acid 2.3

H₂O₂ solution (30% in water, 18 mL, 17.8 mmol) was added slowly to a solution of 4-methylcyclohexan-1-one (10 g, 89.2 mmol) in methanol (10 mL) at room temperature. After stirring for 1 h, the solution was transferred slowly into a solution of FeSO₄·6H₂O (24.8 g, 89.2 mmol) and CuSO₄·5H₂O (22.3 g, 89.2 mmol) in water (80 mL) and the mixture was stirred overnight at room temperature. The mixture was extracted with Et₂O (3×40 mL) and the combined organic solution was washed with aq. NaOH (2 M, 3×20 mL). The aqueous phase was acidified to pH2 with aq. HCl and was extracted with ethyl acetate (3×30 mL). The combined organic solution was washed with brine, dried over MgSO₄ and concentrated under reduced

pressure. The colorless oil **2.3** (7.2 g, 63%) was used directly without further purification.

¹H NMR (400 MHz, CDCl₃) δ 5.64 (ddd, 1H, *J*=17.7, 10.3, 7.8 Hz), 5.01-4.96 (m, 2H), 2.40-2.28 (m, 2H), 2.20-2.13 (m, 1H), 1.73-1.54 (m, 2H), 1.02 (d, *J*=6.7 Hz, 3H).

All data are consistent with that reported in literature.³³

(E)-7-((methoxycarbonyl)oxy)-4-methylhept-5-enoic acid 2.4

The acid **2.3** (1.00g, 7.80 mmol) and (*Z*)-but-2-ene-1,4-diyl dimethyl bis(carbonate) (2.39 g, 11.7 mmol) and HG-II (244 mg, 0.39 mmol) was mixed in toluene (30 mL). The mixture was stirred at 80 °C overnight under a flow of N₂. Upon completion of the reaction, the mixture was cooled to room temperature and purified by column chromatography on silica gel (20% -50% EA/Hex) to give the desired product **2.4** as a colorless oil (1.23 g, 73%)

¹H NMR (400 MHz, CDCl₃) δ 5.67-5.54 (m, 2H), 4.58 (d, *J*=5.8 Hz, 2H), 3.78 (s, 3H), 2.35-2.31 (m, 2H), 2.25-2.18 (m, 1H), 1.72-1.59 (m, 2H), 1.01 (d, *J*=5.5 Hz, 3H).

IR(neat) cm⁻¹: 3439, 2953, 2922, 2852, 2725, 2090, 1749, 1637, 1462, 1377.

MS (ESI): *m/z* = 239.31 [M + Na]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₁₀H₁₇O₅: 217.1076; found: 217.1094.

potassium 3-methoxy-3-oxopropanoate

KOH (2.12 g, 37.85 mmol) was added to a solution of dimethyl malonate

(5.00 g, 37.85 mmol) in methanol (20 mL) at 0 °C. After stirring 30 min, the mixture was warmed to room temperature and stirred for 4 h further. The solvent was removed under reduced pressure and the crude was dried under vacuum for 6 h. A white solid was obtained (5.85 g, 99%)

methyl (E)-9-((methoxycarbonyl)oxy)-6-methyl-3-oxonon-7-enoate 2.5

1,1'-Carbonyldiimidazole (448 mg, 2.76 mmol) was added to solution of acid **2.4** (500 mg, 2.31 mmol) in THF (10 mL) at room temperature. The mixture was stirred for 1 h, then potassium 3-methoxy-3-oxopropanoate (540 mg, 3.45 mmol) and MgCl₂ (220 mg, 2.31 mmol) were added. The mixture was stirred overnight. Aq. NH₄Cl was added to the reaction and the mixture was extracted with Et₂O (3×10 mL). The combined organic layer was washed with brine, dried over MgSO₄. The solution was concentrated in *vacuo*. The crude product was purified by column chromatography (20% EA/Hex) to give **5** (550 mg, 88%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 5.63-5.51 (m, 2H), 4.56 (d, *J*=5.2 Hz, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.42 (s, 2H), 2.52-2.48 (m, 2H), 2.20-2.12 (m, 1H), 1.67-1.52 (m, 2H), 1.00 (d, *J*=6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 202.7, 167.8, 155.8, 141.6, 123.0, 68.6, 55.0, 52.6, 49.3, 40.9, 36.2, 29.9, 20.4.

IR(neat) cm⁻¹: 3396, 2958, 2872, 1746, 1668, 1647, 1628, 1443, 1387, 1269.

MS (ESI): *m/z* = 295.44 [M + Na]⁺.

HRMS (EI): *m/z* [M + Na]⁺ calcd for C₁₃H₂₀O₆Na: 295.1158; found:

295.1144.

methyl 2-hydroxy-5-methyl-6-vinylcyclohex-1-ene-1-carboxylate 2.6

NaH (60% in mineral oil, 58 mg, 1.46 mmol) was added to a solution of compound **2.5** (200 mg, 0.73 mmol) in THF (10 mL) under N₂ at room temperature. After stirring for 30 minutes, Pd(OAc)₂ (8.2 mg, 0.037 mmol) and PPh₃ (28.8 mg, 0.11 mmol) were added to the mixture. The mixture was stirred for 1 h at room temperature. Aq. NH₄Cl (5 mL) was added and the mixture was extracted with Et₂O (3 × 10 mL). The combined organic solution was washed with brine, dried over MgSO₄ and the solution was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (20% EA/Hex) to afford **2.6** as a colorless oil (112 mg, 0.57 mmol, 77%)

¹H NMR (400 MHz, CDCl₃) δ 12.41 (s, 1H), 5.72 (ddd, J=17.1, 10.2, 7.4 Hz, 1H), 5.10-4.91 (m, 2H), 3.71 (s, 3H), 3.13 (dd, J=7.3, 5.0 Hz, 2H), 2.36-2.31 (m, 2H), 1.80-1.72 (m, 1H), 1.51-1.46 (m, 2H), 0.94 (d, J=6.9 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 173.3, 173.1, 137.6, 116.7, 100.7, 51.6, 41.6, 32.4, 29.6, 24.9, 19.5.

IR(neat) cm⁻¹: 3446, 3076, 2999, 2954, 2929, 2872, 1751, 1716, 1649, 1612, 1440, 1267, 1215.

MS (ESI): *m/z* = 197.27 [M + H]⁺.

HRMS (EI): *m/z* [M + Na]⁺ calcd for C₁₁H₁₆O₃Na: 219.0997; found:

219.0985.

References

1. Trost, B. M.; Van Vranken, D. L., *Chem. Rev.* **1996**, *96*, 395.
2. Tsuji, J.; Takahashi, H.; Morikawa, M., *Tetrahedron Lett.* **1965**, *6*, 4387.
3. Trost, B. M.; Fullerton, T. J., *J. Am. Chem. Soc.* **1973**, *95*, 292.
4. Trost, B. M.; Crawley, M. L., *Chem. Rev.* **2003**, *103*, 2921.
5. (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D., *Angew. Chem., Int. Ed.* **2005**, *44* , 4442; (b) S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1993**, *115*, 9293; (c) S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1995**, *117*, 5776; (d) D. A. Vosburg, C. D. Vanderwal, E. J. Sorensen, *J. Am. Chem. Soc.* **2002**, *124*, 4552.
6. Amatore, C.; Jutand, A.; Meyer, G.; Mottier, L., *Chem. – Eur. J.* **1999**, *5* , 466.
7. Amatore, C.; Bahsoun, A. A.; Jutand, A.; Mensah, L.; Meyer, G.; Ricard, L., *Organometallics* **2005**, *24*, 1569.
8. Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K., *J. Org. Chem* **1985**, *50* , 152.
9. Kzmaier, U. *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*, Springer: New York, **2011**
10. Yamamoto, K.; Tsuji, J., *Tetrahedron Lett.* **1982**, *23* , 3089.
11. Yamamoto, K.; Deguchi, R.; Ogimura, Y.; Tsuji, J., *Chem. Lett.* **1984**, *13* , 1657.

12. (a) Sung, P.-J.; Chang, P.-C.; Fang, L.-S.; Sheu, J.-H.; Chen, W.-C.; Chen, Y.-P.; Lin, M. R. *Heterocycles* **2005**, *65*, 195; (b) Sung, P.-J.; Sheu, J.-H.; Wang, W.-H.; Fang, L.-S.; Chung, H.-M.; Pai, C.-H.; Su, Y. D.; Tsai, W.-T.; Chen, B.-Y.; Lin, M.-R.; Li, G.-Y. *Heterocycles* **2008**, *75*, 2627
13. Roe, M. B.; Whittaker, M.; Procter, G., *Tetrahedron Lett.* **1995**, *36*, 8103
14. Iwasaki, J.; Ito, H.; Nakamura, M.; Iguchi, K., *Tetrahedron Lett.* **2006**, *47*, 1483.
15. (a). Moon, N. G.; Harned, A. M., *Org. Lett.* **2015**, *17*, 221. (b). Moon, N. G.; Harned, A. M., *Org. Biomol. Chem.* **2017**, *15*, 1876. (c) Crimmins, M. T.; Zhang, Y.; Williams, P. S., *Org. Lett.* **2017**, *19*, 3907
16. Bates, R. W.; Pinsa, A.; Kan, X., *Tetrahedron* **2010**, *66* , 6340.
17. Bates, R. W.; Dewey, M. R.; Tang, C. H.; bte Safii, S.; Hong, Y.; Hsieh, J. K. H.; Siah, P. S., *Synlett* **2011**, *22* , 2053.
18. Ogibin, Y. N.; Starostin, E. K.; Aleksandrov, A. V.; Pivnitsky, K. K.; Nikishin, G. I., *Synthesis* **1994**, *1994* , 901.
19. H. E.; De La Mare.; J. K. Kochi.; and F. F. Rust., *J. Am. Chem. Soc.* **1963**, *85*, 1437
20. Rawlinson, G. S. D. J., *Organic Peroxides*. Wiley-Interscience: New York, **1971**; Vol. 2.
21. Evans, D. A.; Baillargeon, D. J., *Tetrahedron Lett.* **1978**, *19* , 3315.
22. (a) Cekovic, Z.; Green, M. M., *J. Am. Chem. Soc.* **1974**, *96* , 3000; (b) Kochi, J. K. *J. Am. Chem. Soc.* **1963**, *85*, 1958.
23. Bates, R. W.; Song, P., *Synthesis* **2010**, *2010* , 2935.
24. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H., *J. Am. Chem. Soc.*

2003, 125 , 11360.

25. Brooks, D. W.; Lu, L. D. L.; Masamune, S. *Angew. Chem., Int. Ed.* **1979**, 18 , 72.

26. Deng, J.; Zhu, B.; Lu, Z.; Yu, H.; Li, A., *J. Am. Chem. Soc.* **2012**, 134 , 920.

27. Trost, B. M.; Runge, T. A.; Jungheim, L. N., *J. Am. Chem. Soc.* **1980**, 102 , 2840.

28. Takeuchi, R.; Kashio, M., *J. Am. Chem. Soc.* **1998**, 120 , 8647.

29. He, H.; Zheng, X.-J.; Li, Y.; Dai, L.-X.; You, S.-L., *Org. Lett.* **2007**, 9 , 4339.

30. Johnson, F. *Chem.Rev.* **1968**, 68, 375.

31. Barnes, E. C.; Choomuenwai, V.; Andrews, K. T.; Quinn, R. J.; Davis, R. A., *Org. Bio. Chem.* **2012**, 10 , 4015.

32. Kulinkovich, O. G.; Kozyrkov, Y. Y.; Bekish, A. V.; Matiushenkov, E. A. *Synthesis*, **2005**, 10, 1713.

33. Starostin, E. K.;D. B. Furman,D. B.; Ignatenko, A. V.; Barkova, A. P.; Nikishin, G. I. *Russ. Chem. Bull., Int. Ed.*, **2006**, 55, 2016.

Chapter 3

3.1 Introduction

3.1.1 Allahabadolactone A

Allahabadolactones A **3.1** and B are secondary metabolites isolated from *Aspergillus allahabadii* BCC45335, an endophytic fungi isolated from the root of *Cinnamomum subavenum* in Thailand.¹ They were found to display modest bioactivities, such as cytotoxic activity.¹ Genus *Aspergillus* is known as an abundant source of biological active natural products from which a great deal of secondary metabolites with various bioactivities have recently been isolated.² The structure of allahabadolactone A was established based on spectroscopic analysis and the absolute stereochemistry was determined by employing the X-ray crystallographic analysis with Mosher's ester analysis.¹

Scheme 3-1 Allahabadolactone A

From a structural point of view, allahabadolactone A possesses an unsaturated *trans*-decalin with a substituted five-membered lactone appended to the unsaturated ring. It contains seven stereogenic centres in

total - five of them are located on the decalin including a quaternary one, and another two spread in the substituted lactone. The skeleton of the unsaturated *trans*-decalin with the same methyl substituent has been found in several natural products, such as equisetin,³ fusarisetin,⁴ oblongolide,⁵ phomasetin,³ cryptocin,⁶ paecilosetin⁷ and aspermytin.⁸ Synthesis of these molecules will be discussed in the part **3.1.5**.

3.1.2 Biosynthetic discussion

A biosynthetic pathway for the allahabadolactones (Scheme 3-2) was proposed by the authors featuring an intramolecular Diels–Alder reaction and lactone formation via C-H bond oxidation.¹ A late stage methylation and dehydration gave the allahabadolactones.

Scheme 3-2 Plausible biosynthetic pathway

The Diels–Alder reaction is a powerful and efficient tool to build the cyclohexene motif in organic synthesis. It is generally accepted that the reaction proceeds through a [4+2] pericyclic transition state in a concerted

manner.⁹ Frontier molecular orbital theory can be used to describe and understand this reaction.¹⁰ The pericyclic reaction proceeds via a concerted HOMO_{diene} – LUMO_{dienophile} interaction in the transition state.¹¹ Increasing the electrophilicity of the dienophile or nucleophilicity of the diene would benefit the cycloaddition by strengthening the interaction of the HOMO_{diene} – LUMO_{dienophile} interaction.¹²

Research on enzyme-mediated transformations has demonstrated the capability of enzymes in a handful of reaction types.¹³ However, examples of pericyclic reactions catalyzed by enzymes are extremely infrequent.¹⁴ A controversy associated with the existence of Diels–Alderase has emerged.¹⁵ Despite Diels–Alderase having been proposed as a key step in the biosynthesis of a number of secondary metabolites, identification of the enzymatic processes poses significant challenges.¹⁵ Several works have contributed to give a suggestion in the field of the putative Diels–Alderase.¹⁵⁻¹⁶

An enzyme-mediated decalin framework formation has been suggested in the biosynthesis of lovastatin by Vederas, Hutchinson and co-workers (Scheme 3-3).¹⁷ In order to test the involvement of the lovastatin nonaketide synthase in the construction of decalin motif, the enzyme LovB (lovastatin nonaketide synthase) was submitted to a model system.¹⁷ The corresponding *endo*-product was obtained. The substrate underwent an IMDA cyclization to yield a *cis*-decalin (*exo* adduct) and *trans*-decalin

(*endo* adduct) at a 1:1 ratio in the absence of the synthase and formation of another diastereomeric product (*endo-2*) was observed in a 15:15:1=*exo*:*endo-1*:*endo-2* ratio in the presence of LovB.¹⁷ This is the first example to declare that the decalin structure was constructed mediated by an enzyme in a putative Diels–Alders reaction. However, Williams has asserted that the lack of more detailed biophysical characterization for the proteins made it difficult to prove the construction of the decalin ring system from a pericyclic, concerted transition state mechanism, also the lack of proof of a concerted transition state for the enzymatic process.¹⁵

Scheme 3-3 Model system of biosynthesis of lovastatin

Parallel to this, in the aforementioned biosynthetic assumption of allahabadolactone, the *trans* decalin moiety was also proposed to be built

though an intramolecular Diels-Alderase reaction.

Different from the decalin moiety, the construction of the lactone motif is difficult in a C–H oxidation manner that proposed in the biosynthetic pathway.¹ Though several work has been reported in this field, it remains a challenge to selectively introduce functional groups though C-H oxidation, especially in fully saturated systems.¹⁸ In the practice of synthesis, we often look at alternative strategies.¹⁹

3.1.3 Retrosynthesis of Allahabadolactone A

To the best of our knowledge, no total synthesis of allahabadolactone A has been reported. Due to the complexity of the structure and biological activity, we were inspired to attempt the enantioselective synthesis of this molecule.

Scheme 3-4 Retrosynthetic plan

In our retrosynthetic plan (Scheme 3-4), the skeleton of the molecule would be installed via an intramolecular Diels–Alder (IMDA) reaction and electrophile-induced ring closure as the key steps. The lactone moiety would be introduced via an electrophilically induced ring closure of the carboxylic acid and the alkene. The stereochemical outcome of the IMDA reaction was expected to be controlled by the stereogenic centre bearing a methyl group at C8. The precursor for the proposed IMDA reaction was going to be prepared by Suzuki cross-coupling reaction of a vinyl boronate

and halopolyene side chain. Propylene oxide or an equivalent was chosen to introduce the stereogenic center in the side chain by ring opening with trimethylsilyl acetylene.²⁰ 1,2-Dichloroethylene would be utilized as a bridge to connect the boronate moiety and the chiral synthon chain. Citronellal is an ideal synthon from the chiral pool with a methyl group to build the carbon skeleton of the vinyl boronate for the cross-coupling reaction.

3.1.3 Chiral Pool Source–Citronellal

Chiral pool is a term referred to a stock of abundant chiral synthons generated by nature.²¹ It usually contains amino acids, carbohydrates, hydroxyl acids and terpenes.²² The chiral pool synthesis is an effective and economical strategy to prepare complex natural products owing to the low cost and rich chiralities of the materials in the pool.²² Numerous natural products have been synthesized by means of chiral pool synthesis.²³ One of the disadvantages using the chiral pool is that in many cases only one enantiomer is available. In the practice of synthesis with chiral pool material, new chiral centers are preferred to be introduced by diastereoselective reactions. Nowadays, many of the materials available in the chiral pool come from synthesis in industry rather than directly from nature.

Citronellal and its analogs citronellol and citronellene, are common acyclic

monoterpenoids and serve as important intermediates in organic synthesis.²⁴ Unlike most terpene sources in chiral pool, both the *R* and *S* enantiomers of them are commercially available. Citronellal can be prepared from geraniol by asymmetric synthesis.²⁴ Due to the flexibility and specificity of their structure, they have been widely employed as versatile building blocks in asymmetric synthesis especially when a stereogenic center bearing a methyl group is found in the target.²⁴

In the synthesis of pheromones (Scheme 3-5), citronellal is a key chiral source to build the structure with defined stereochemistry. In the synthesis of nepetalactone, Schreiber *et al.* described an approach to elucidate the structure from (*S*)-citronellal.²⁵ First, citronellal was oxidized into the dialdehyde mediated by selenium dioxide, followed by three more steps into the final products in a highly diastereoselective manner. The synthesis was featured by a diastereoselective enone cycloaddition reaction.

Scheme 3-5 Synthesis of nepetalactone by Schreiber. Reagents and conditions: (a). SeO_2 , BuOOH ; (b). MeNHPh ; (c). TsOH , $\text{THF}/\text{H}_2\text{O}$; (d) AgNO_3 , Celite, reflux.

Another important application of citronellal is in the synthesis of cyclic and

polycyclic compounds. Lee *et al.* reported a stereoselective synthesis of desethanoartemisin, which was a novel analogue of the artemisinin with potential antimalarial activity (Scheme 3-6).²⁶

Scheme 3-6 Synthesis of desethanoartemisin by Lee. Reagents and conditions: (a).1. ZnBr_2 ; 2. B_2H_6 , $\text{NaOH}/\text{H}_2\text{O}_2$; (b).1. Jones reagent; 2. CH_2N_2 ; (c) $\text{MeOCH}_2\text{PPh}_3\text{Cl}$, $n\text{BuLi}$; (d).1. CH_3CHO , $^1\text{O}_2$, rose Bengal, MeOH , $h\nu$; 2. HCl gas; 3. 60% HClO_4 .

3.1.4 1,2-Dichloroethylene

The 1,2-dichloroethylenes are interesting synthons because the two terminal functions could undergo cross coupling reactions selectively owing to the weak reactivity of the vinyl chlorides. Both the *E* or *Z* isomer are readily available in a pure form. They have been employed in the preparation of numerous useful intermediates in organic synthesis, such as the enediyne compounds. Due to the diverse bioactivities and the unique architectures, considerable efforts have been contributed into the field of synthesis of enediynes and several methods have been developed to build the enediyne moiety.²⁷ Among them, the route reported by Schreiber was

easy and elegant.²⁸ In the synthesis of esperamicin and calicheamicin class natural products, the enediynes were prepared from the cross coupling reactions of 1,2-dichloroethylene with two different alkynes selectively (Scheme 3-7).²⁸ However, previous work in this area has focused much more on the *cis* isomer compared to the *trans* isomer.²⁹ The stereospecific and chemoselective cross coupling reactions with 1,2-dichloroethylene inspired us to build the polyene for IMDA in this route.

Scheme 3-7 Sonogashira reaction with *Z*-1,2 dichloroethylene. Reagents and conditions:

(a). Pd(PPh₃)₄, CuI, propylamine; (b) **3.7.1** Pd(PPh₃)₄, CuI, propylamine.

3.1.5 Intramolecular Diels-Alder (IMDA) Reaction

The IMDA approach has been proven to be one of the most elegant and versatile strategies in organic synthesis, particularly for the synthesis of polycyclic complexes.³⁰ Numerous natural products have been prepared with this approach in a highly diastereoselective and predictable manner.³⁰ It is an atom economical reaction since all atoms in the starting material would appear in the product. It can generate up to four stereogenic centres

in a single step with excellent chemo-, regio- and diastereoselectivity.³¹ For example, in the synthesis of indanomycin by Ley, the tetrahydroindan moiety was built through an IMDA reaction with four new stereogenic centres installed (Scheme 3-8).³²

Scheme 3-8 Reagents and conditions: toluene, reflux.

In the preparation of this kind of mono-unsaturated *trans*-decalin skeleton with IMDA, the reaction would proceed through a chair-like transition state while the chiral methyl group will be disposed in an equatorial position. This strategy appears to be general and has been utilized in the total synthesis of several natural products.

Synthesis of oblongolide

In 1995, Shing *et al.* reported the synthesis of (-)-oblongolide **3.9.1** via an IMDA reaction as the key step (Scheme 3-9).³³

Scheme 3-9 Synthesis of oblongolide by Shing. Reagents and conditions: (a) (MeO)₂P(O)CH₂CH=CHCO₂Me, NaHMDS, THF, -78 °C; (b) DIBAL, THF, -78 °C; (c) 1,2-dichlorobenzene, sealed tube, 210 °C.

The synthetic route began with (–)-citronellol. It was converted into aldehyde **3.9.2** by sequential Lemieux-Johnson oxidation, Wittig reaction and PDC oxidation. The triene system **3.9.3** was installed by a Horner-Wadsworth-Emmons olefination and subsequent selective reduction by DIBAL afforded the precursor for IMDA **3.9.4**. After heating at in a sealed tube for 132 h, (–)-oblongolide **3.9.1** was obtained as a single diastereoisomer *via* an endo-equatorial transition state in which the methyl group adopting a pseudoequatorial position to control the stereochemistry.³³ In contrast to the intermolecular Diels-Alder reaction, in which the preferential *endo* selectivity is generally attributed to nonbonding secondary orbital interaction between the diene and dienophile,³⁴ the

stereoselectivity of IMDA under thermal condition is governed by the delicate steric effect of the transition state based on Roush' work.³⁵ In this work, attempts to accomplish the IMDA with Lewis acid met with failures due to the unreactivity of the ester precursor.³³ In order to improve the diastereoselectivity, high temperatures and long reaction time had to be adopted in order to convert the *exo* product to the *trans* product *via* a reversible IMDA reaction.^{30b}

Synthesis of equisetin by Dixon

Dixon *et.al.* reported a diastereoselective synthesis of equisetin *via* a Lewis-acid catalyzed IMDA reaction (Scheme 3-10).³⁶

Scheme 3-10 Synthesis of equisetin by Dixon. Reagent and conditions: (a) **3.10.2**, nBuLi, THF, -78 °C; (b) DMSO, (COCl)₂, Et₃N, CH₂Cl₂; (c) **3.10.5**, KHMDS, THF, -78 °C (d) LiClO₄, Et₂O

The preparation of aldehyde **3.10.1** was achieved in several expeditious conversions from citronellol. Horner-Wadsworth-Emmons olefination with phosphonate **3.10.2** and removal of the silyl group gave the triene **3.10.3** in a *E*: *Z*=17:1 ratio. The dienophile moiety was prepared from the aldehyde **3.10.4** though Horner-Wadsworth-Emmons reaction on treatment with the dilithio anion of **3.10.5** in a manner favoring the *E* isomer formation. The

IMDA reaction was performed under Lewis acidic conditions and the desired *trans* decalin motif was obtained in a good yield and diastereoselectivity. The strong reactivity of the dienophile part was attributed to the dicarbonyl unit because the Lewis acid would chelate more tightly than the corresponding mono-carbonyl compound. The excellent diastereocontrol was also from stereogenic center bearing the methyl group in the chair like transition state in which the *endo* approach between lithium activated dicarbonyl dienophile and the polyene was dominated by steric interaction. The final product equisetin was assembled in subsequent steps.

Synthesis of equisetin by Shishido

In 2001, Shishido *et al.* reported the enantioselective total synthesis of (–)-equisetin using as the key step a Me₃Al–mediated IMDA reaction (Scheme 3-11).³⁷

Scheme 3-11 Synthesis of equisetin by Shishido. Reagent and conditions: (a) dichloromethylboronic ester, CrCl₂, LiI, THF; (b) (*E*)-ethyl 3-iodoacrylate, Pd₂(dba)₃, PPh₃, aq. NaOH, THF; (c) DIBAL, THF, -78 °C (d) Me₃Al, CH₂Cl₂, 0 °C.

They started the synthesis with citronellal. Aldehyde **3.11.1** was assembled in high yield over a few steps. In contrast to Dixon's synthesis, their diene motif was introduced by a stepwise sequence of Takai-olefination and Suzuki cross coupling reaction. Conversion of **3.11.1** to vinyl pinacol boronate **3.11.2** in the presence CrCl₂ was carried out and the product underwent Suzuki coupling to afford **3.11.3**. The dienophile was installed on intermediate **3.11.4** in a sequence of de-protection, oxidation and Wittig olefination. After several attempts with the ester **3.11.5** for IMDA reaction, no encouraging results were obtained. They then examined the reaction with the corresponding aldehyde. IMDA product **3.11.6** was generated on

treatment of the aldehyde with Me_3Al in a yield of 75% and 8:1 diastereoselectivity. They also achieved the total synthesis of aspermytin using the same strategy.

This work indicated that the reactivity of the dienophile played an important role for the diastereoselectivity in this kind of IMDA reaction mediated by Lewis acid.

Synthesis of Fusarisetin A

Fusarisetin is a natural product with complex structure and diverse biological activities⁴. It could be assembled from equisetin.³⁸ The construction of the *trans* decalin skeleton was similar to the strategy employed in the synthesis of equisetin. In the synthesis reported by Li in 2011³⁹ and Gao in 2012,⁴⁰ similar intermediates to the one in Dixon's work mentioned above were chosen to build *trans*-decalin framework.

In Theodorakis' work, citronellal was converted into di-aldehyde **3.12.1** in a more step-economic approach (Scheme 3-12).⁴¹ Di-aldehyde **3.12.1** could be obtained easily by cross metathesis with methacrolein or allylic oxidation with a SeO_2/IBX system. A regioselective Wittig olefination with phosphonium salt **3.12.2** with the non-conjugated aldehyde in the presence of *n*BuLi afforded triene moiety **3.12.3** as mixture of *E*:*Z*=3:2 isomer in a good yield. A one pot photo-induced olefin isomerization and Lewis acid catalyzed IMDA reaction served to afford the desired unsaturated decalin

motif **3.12.4** efficiently. This approach showed the diversity of transformation and functionalization of citronellal due to the flexibility of the structure.

Scheme 3-12 Synthesis of Fusarisetin by Theodorakis. Reagent and conditions: (a) methacrolein, 5 mol% Grubbs-II or $\text{SeO}_2/\text{tBuOOH}$ then IBX; (b) 3.12.2, nBuLi , THF, -78°C ; (c) I_2 , sunlamp; then Et_2AlCl , -78°C .

3.1.6 Hydroboration

Since its development by Brown in 1956,⁴² hydroboration has become indispensable in organic synthesis because the corresponding boranes and boronates can be easily used to a variety of functionalities, such as alcohols and carboxylic acids.⁴³ Many methods have been developed for hydroboration, especially with transition metals.⁴⁴ Alkenyl boronates are expedient synthons for further derivatization among which the transformations into substituted alkenes through Suzuki cross-coupling reactions are widely applied in pharmaceutical and industrial processes.⁴⁵

Hydroboration of terminal alkynes plays a predominant role in the preparation for alkenyl boronates.⁴⁶ Compared to other methods, such as cross metathesis of alkenes,⁴⁷ cross coupling reaction of vinyl boronate,⁴⁸ hydroboration is frequently preferred due to several advantages, such as low toxicity, economic, mild conditions and readily availability of the reagents.⁴⁴

Catecholborane was used as the reagent for hydroboration initially and it could provide boronic acids after hydrolysis.⁴⁹ However, several drawbacks made it not an ideal choice, such as the undesired smell, tough workup and lack of methods for the purifying the vinyl boronic acid products. Several other borane derivatives have earned a good reputation. Among which pinacolboronates (PinBH) , introduced by Knochel, played a dominant role due to the moisture stability and easily handling.⁵⁰ In particular, pinacolatoboron derivatives are stable to silica gel and can be purified by chromatography. Knochel showed that vinyl Bpin derivatives can be prepared by thermal hydroboration.^{50a}

Hydroboration can be catalyzed by transition metal complexes.⁴⁴ Rhodium catalysts were one of the most popular among these complexes. Wilkinson catalyst can be used, although gives poor regioselectivity in several cases.⁵¹ Srebnik *et.al.* demonstrated that hydroboration of alkynes with PinBH catalyzed by $\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{Cl}$ gave better regioselectivity compared to the one catalyzed by Wilkinson catalyst.⁵¹

3.2 Results and Discussion

For our synthesis, we started with racemic citronellal. Enantiopure material was only employed in the final route.

3.2.1 Alkynylation of citronellal.

Scheme 3-13 Reagent and conditions: **3.4**, MeOH, K₂CO₃ 73% or 1) CBr₄, Zn, PPh₃; 2) *n*BuLi, -78 °C, 85%.

Citronellal was first treated with the Ohira–Bestmann reagent **3.4** or the Corey–Fuchs reagent to afford alkyne **3.3** in a yield of 73% or 85%, respectively (Scheme 3-13).

One carbon homologation to prepare alkynes from carbonyl compounds is a convenient pathway in organic synthesis.⁵² Corey and Fuchs developed an efficient and sample method to achieve this in two steps, which has been widely applied for the synthesis of various alkynes.⁵³ The aldehyde first proceeds though Ramirez olefination with ylide **3.14.1** to give dibromo-olefin **3.14.2**. Ylide **3.14.1** is generated in situ from CBr₄ and PPh₃ in the presence of Zn dust. The terminal alkyne is obtained by treatment of **3.14.2** with 2 equivalents *n*BuLi though a Fristch-Buttenberg-Weichell

rearrangement (Scheme 3-14).

Scheme 3-14

The Ohira–Bestmann reagent **3.4** is a modification of Seyferth–Gilbert reagent **3.15.1** (Scheme 3-15).⁵⁴ It can be easily prepared by using a diazo transfer reagent. Compared to the Seyferth–Gilbert reagent,⁵⁵ this modification allowed the reaction to proceed without strong bases and low temperatures, which indisputably expanded the substrate scope.

Scheme 3.15

For the mechanism of this reaction, the phosphonate **3.16.1** is generated *in situ* from **3.4** in the presence of K_2CO_3 in methanol and reacted with

aldehyde to give oxaphosphetane **3.16.3**. After a cycloelimination of **3.16.3**, the generated diazoalkene **3.16.4** would lose nitrogen to yield vinylidene **3.16.5** which produces the alkyne though through a Fritsch-Buttenberg-Weichell rearrangement, as in the Corey-Fuchs chemistry.

Scheme 3-16

Despite a higher yield obtained with Corey–Fuchs reaction, the harsh conditions, troublesome workup and poor atom economy make it an undesired choice comparing to the Ohira–Bestmann reagent.

In the ^1H NMR of the product, a triplet peak at 1.94 ppm with a coupling constant of $J=2.6$ Hz corresponded to the alkyne proton.

3.2.2 One pot Ozonolysis and Wittig olefination

Scheme 3-17 Reagent and conditions: 1. O_3 , CH_2Cl_2 , -78°C ; 2. $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Me}$, CH_2Cl_2 , reflux, 68%-77%.

With the alkyne **3.3** in hand, we examined the ozonolysis and Wittig olefination (Scheme 3-17). Comparing to Lemieux-Johnson oxidation,⁵⁶ ozonolysis is a more economical and green method. Alkenes can be easily oxidized into a variety of functional groups with O_3 and different workup procedures. Initially the alkene was submitted to ozonolysis conditions and PPh_3 was utilized as the reducing reagent in the workup. Surprisingly a nearly quantitative yield of PPh_3 was recovered and aldehyde product was obtained in low yield due to volatility. We then realized that the aldehyde could be formed without a reducing agent. This was confirmed by the ^1H NMR spectrum of the crude mixture. In order to solve the volatility problem, the ylide was directly added into the reaction mixture after ozonolysis. Much to our delight, this one pot procedure gave a yield of up to 77% for

1.00 g scale reaction. A reasonable yield of 68% was obtained when increasing to 3.00 g scale. The stereoisomeric ratio of *E/Z* isomers was found to be 20:1 by integration of the alkene protons at 6.75 ppm and 5.92 ppm in the ^1H NMR spectrum. In the ^1H NMR spectrum, the *trans*-isomer displayed a triplet peak at 6.75 ppm with a coupling constant of $J=7.3$ Hz for the alkene proton while a singlet peak at 3.73 ppm represented the methoxy group.

The ozonolysis could take place selectively in the alkene position without any disturbance of the alkyne because O_3 prefers to react with the electron rich functional group and in this reaction, the alkene with two methyl groups is more electron rich due to the electron donating effect of the methyl groups.

3.2.3 Hydroboration of Terminal Alkyne

Scheme 3-18 Reagent and conditions: PinBH, 2 mol% $\text{Rh}[(2\text{-furyl})_3\text{P}]_2(\text{CO})\text{Cl}$, toluene, 77%.

In order to prepare the alkenyl boronate **3.6**, our alkyne **3.5** was initially subjected to either the thermal conditions or catalytic conditions using $\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{Cl}$ or $\text{NiCp}(\text{PPh}_3)\text{Cl}$ reported by Srebnik.⁵¹ Neither gave us promising results. No reaction was observed under thermal conditions or with the Ni catalyst and an inseparable mixture of starting material and hydroboration product was delivered as a ratio of 1: 1 when the Rh catalyst was used. In the ^1H NMR spectrum of the crude material (Figure 3.1), the ratio of the alkene proton of the unsaturated ester system at 6.75 ppm and two protons of vinyl boronate at 6.60 and 5.45 ppm was 2:1:1, indicating that the starting material left and the hydroboration product existed in a 1:1 ratio.

Figure 3.1

At the same time, we also examined the hydroboration of alkyne with an oxygen containing group in the side chain (Scheme 3-19). A poor yield of 30% was obtained after heating at reflux overnight with $\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{Cl}$

since hydroboration in the presence of oxygen atom remains problematic in some cases probably due to a coordination effect.⁵⁷

Scheme 3-19 Reagent and conditions: **3.18.1**, 2 mol% Rh(CO)(PPh₃)₂Cl, CH₂Cl₂, 30%.

Unlike the corresponding hydrosilylation reaction, the mechanism of hydroboration catalyzed by transition metals remains unexplored. A Chalk-Harrod type mechanism has been proposed (Scheme 3-20).⁵⁸ In this mechanism, the active Rh catalyst is generated by a dissociation of a phosphine ligand. Oxidative addition of borane occurs to generate a rhodium hydride complex. Migratory insertion of alkyne into the rhodium hydride forms alkenyl rhodium boronate or alkenyl boronate rhodium hydride that undergoes reductive elimination to yield the product and releases the active rhodium catalyst to finish the cycle simultaneously.

Scheme 3-20 Mechanism of hydroboration

In Srebnik's work, high yields were obtained while one phosphine ligand of Wilkinson catalyst was replaced with CO due to the steric factor.⁵¹ Inspired by these facts, we wondered whether the reactivity of the rhodium catalyst could be enhanced when the PPh_3 was replaced by another ligand.

Scheme 3-21

Table 3.1

Entry	Ligand ^a	Ratio Rh/L	Time	Yield (%)
1	PPh ₃	1:2	o.n.	50 ^c
2	(<i>o</i> -tol) ₃ P	1:2	o.n	0
3	Cy ₃ P	1:2	0.5 h	37 ^c
4	[2,4,6-(MeO) ₃ C ₆ H ₂] ₃ P	1:2	o.n.	0
5	Ph ₃ As	1:2	1.5 h	43 ^c
6	(2-Furyl) ₃ P	1:2	2 h	76
7	(2-Furyl) ₃ P ^b	1:2	2 h	77
8	(2-Furyl) ₃ P	1:1	2 h	74
9	-	-	-	0

a. Conditions: 1 mol% = [Rh(CO)₂Cl]₂; 1.2 eq. PinBH; Ligand; toluene; catalyst was generated *in situ* unless otherwise stated.

b. Pre-formed Rh complex.

c. With inseparable impurity.

We tested the influence of the ligand on hydroboration with the racemic alkyne **3.5** (Scheme 3-21). The requisite analogues of Rh(CO)(PPh₃)₂Cl for hydroboration were generated *in situ* from [Rh(CO)₂Cl]₂ with the corresponding ligands. Only starting material was recovered when using (*o*-tol)₃P (Entry 2), tris(2,4,6-trimethoxyphenyl)phosphine (Entry 4) or in the absence of ligand (Entry 9). Tricyclohexylphosphine (Entry 3) and triphenylarsine (Entry 5) led to a low yield of an impure product. Bulky

phosphine ligands were found fruitless in our case and other smaller ligands were investigated. To our delight, tri(2-furyl)phosphine gave us a better yield with clean hydroboration product (Figure 3.2) in a short time (Entry 6). This may be due to its modest size and electron richness.

The use of this ligand was inspired by Farina's work on coupling reactions.⁵⁹ In the proposed mechanism, the reaction started from the generation of the real Rh catalyst species by dissociation of one phosphine ligand. We hypothesized that this species could be generated *in situ* by mixing the precatalyst Rh and the ligand in a ratio of 1:1. Reaction with a ratio of Rh:L=1:1 also afforded the desired product in a similar result (Entry 8) suggesting that the dissociation of a phosphine ligand happened initially for this reaction.

Figure 3.2

The $\text{Rh}[(2\text{-Furyl})_3\text{P}]_2(\text{CO})\text{Cl}$ complex could be easily prepared by the

method described by Wilkinson *et al.* for the triphenylphosphine complex and the structure was confirmed by X-ray crystallography (Figure 3.3).⁶⁰

Figure 3.3

We also checked our method for several kinds of terminal alkynes (Table 3.2). In all cases, the alkenyl boronates were obtained as single regio- and stereoisomers. We found that reactions using a condition of Rh:L=1:1 could be accomplished in a higher yield and shorter time in several cases (Entries 1 vs. 2; 4 vs. 5; 6 vs. 7).

Table 3.2

Entry ^a	Alkenyboronate	Ratio Rh/L	Time	Yield (%)
1	3.7	1:2	1 h	80
2	3.7	1:1	20 min	81
3	3.8	1:1	80 min	80
4	3.9	1:2	o.n.	72
5	3.9	1:1	1 h	80
6	3.10	1:2 ^b	o.n.	75
7	3.10	1:1	2.5 h	30
8	3.11	1:1	1.5 h	61

a. Reaction conditions: 1 mol% [Rh] = [Rh(CO)₂Cl]₂ 1.2 eq. PinBH; Ligand; Toluene;

b. Pre-formed Rh complex.

In addition, no reaction happened with internal alkynes **3.22.1**, **3.22.2** and **3.22.3**. A poor yield of about 10 % of **3.22.4** probably resulted from the deactivation of the catalyst due to the coordination of the substrate to the metal center. The catalyst could be applied in the hydroboration of terminal alkynes selectively.

Scheme 3-22

The outstanding activity of the catalyst with Fu_3P was attributed to a combination of steric and electronic effects that enriching the electron density of the Rh metal center while diminishing the size of the catalyst.⁶¹

3.2.4 Cyclic sulfate ring opening reaction

With the alkenyl boronate in hand, the vinyl chloride side chain **3.13** was prepared by a Sonogashira reaction with *trans*-1,2-dichloroethene.⁶²

Scheme 3-23

The alkynol **3.14** was obtained *via* a sequence of ring opening of cyclic sulfate and desilylation (Scheme 3-24).²⁰

Scheme 3-24 Reagent and conditions: (a). 1. SOCl_2 , CH_2Cl_2 , reflux; 2. NaIO_4 , RuCl_3 , $\text{MeCN}/\text{H}_2\text{O}$; (b). trimethylsilylacetylene, $n\text{BuLi}$, THF, -78°C ; (c). K_2CO_3 , MeOH .

The stereogenic center of alkynol **3.14** was going to be introduced from propylene oxide or an equivalent. Since the reaction of an epoxide with alkynyl lithium reagents usually requires a quite polar co-solvent or strong Lewis acid, such as $\text{BF}_3 \cdot \text{OEt}_2$ and this epoxide is quite volatile, the cyclic sulfate **3.16** was used instead.²⁰ Cyclic sulfates are more reactive epoxide-like substrates.⁶³ Since an investigation on the preparation from the

corresponding diol by Sharpless, ring opening reaction of cyclic sulfates with various nucleophiles have been studied.⁶³ A method of ring opening by an acetylide anion was described in this laboratory,²⁰ which was also applied in this laboratory in the synthesis of sedinine.⁶⁴

Cyclic sulfate **3.16** was produced from the corresponding diol **3.15** by Sharpless's one pot method.⁶³ The enantiopure diol **3.15** was supplied by a hydrolytic kinetic resolution (HKR) on treatment with Jacobsen's catalyst.⁶⁵ The HKR method was also carried out in the previous synthesis of curvulone B. Cyclic sulfate **3.15** was treated with the lithium acetylide anion generated from trimethylsilylacetylene with *n*BuLi. Removal of the TMS group in the product **3.17** with K₂CO₃ in methanol afforded the alkynol **3.14** efficiently in an overall yield of 72% from the diol.

3.2.5 Sonogashira reaction

Scheme 3-25 Reagent and conditions: (a) 5 mol% Pd(PPh₃)₄, 5 mol% CuI, Et₃N, THF; (b). TBSCl, imidazole, CH₂Cl₂.

Chloroenynes are quite useful building blocks in organic synthesis, which allow the synthesis of polyunsaturated compounds in a stereospecific way.⁶⁶ For the preparation of this kind of substrates, the most convenient approach

by far is the Sonogashira cross coupling of 1,2-dichloroethylenes with terminal alkynes.⁶⁷ Unlike some Wittig type reactions, which could also deliver an equivalent product but suffer from poor stereoselectivity, the Sonogashira reaction is highly chemo- and stereoselective.⁶⁸ After the coupling reaction, the chloroalkenes retain the same configuration. Since both the *E* and *Z* 1,2-dichloroethylenes are readily available, it is a general and stereodefined route.

For our reaction, the coupling reaction was carried out in the presence of $\text{Pd}(\text{PPh}_3)_4$ and CuI in THF. $\text{Pd}(\text{PPh}_3)_4$ was preferable in this case as the classic Sonogashira conditions with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ gave a poor 20% yield.⁶⁸ Three equivalents of *trans*-1,2-dichloroethylene was initially employed to yield the mono-coupling product in an excellent yield of 95%. Later modification allowed the amount of the ethene to be reduced to 1.5 equivalents. This indicates that the dichloride starting material is distinctly more reactive than the monochloride product. The alkynol **3.13** was easily protected with a TBS group under standard conditions.

The ^1H NMR displayed a doublet peak at 6.49 ppm with a coupling constant of $J=13.7$ Hz and a doublet of triplet at 5.92 ppm with coupling constant of $J=13.7, 2.3$ Hz for the two alkene protons. The 13.7 Hz coupling between the two vinyl protons indicates the retention of the *trans* geometry.

3.2.6 Suzuki cross coupling

Scheme 3-26 Reagent and conditions: 2 mol% Pd(OAc)₂, 4 mol% Sphos, NaOH, THF/H₂O, 70°C.

With both coupling partners in hand, the following step was the Suzuki cross-coupling reaction.

Coupling of a vinyl chloride represented a synthetic challenge under typical conditions due to the low activity of the carbon-chlorine bond towards oxidative addition. We tried the reaction with Pd(PPh₃)₄ or Pd(PPh₃)₂Cl₂ and, unsurprisingly, no coupling product was obtained. In order to drive the vinyl chloride towards oxidative addition, a more electron rich ligand was necessary. Since their introduction, dialkylbiarylphosphines have been widely developed in organic synthesis.⁶⁹ The formation of the monoligated [L₁Pd] intermediate was benefited from the bulky and electron donating character of the dialkylbiarylphosphine ligands.⁶⁹ Compared to [L₂Pd], the monocoordinated one is smaller in size and more electron rich allowing the oxidative addition happen faster.⁶⁹ In the synthesis of amphotericin B, the Burke group developed conditions to build polyenes *via* Suzuki cross-coupling with dialkylbiarylphosphine ligands.⁷⁰

When we screened conditions for ligands, K_2CO_3 was applied as the base, and the vinyl chloride substrate **3.18** was recovered (Entry 1-3) except in the case when SPhos was employed (Entry 4).

Table 3.3

Entry ^a	Catalyst	Result
1	5 mol% $Pd(PPh_3)_4$	3.18 recovered
2	5 mol% $Pd(PPh_3)_2Cl$	3.18 recovered
3	4 mol% XPhos+2 mol% $Pd(OAc)_2$	3.18 recovered
4	4 mol% SPhos+2 mol% $Pd(OAc)_2$	3.18 consumed

a. Conditions: 2 eq. K_2CO_3 , THF+ H_2O (1:1), 70 °C.

These results implied that oxidative addition with Sphos happened and we turned our attention to identifying a suitable base. At present, the choice of base for Suzuki is still empirical. After several attempts, the reaction with NaOH (Entry 4) gave us the desired product in a satisfying yield of 87% while the ester was not hydrolyzed under these conditions.

Table 3.4

Entry ^a	Bases	Yield
--------------------	-------	-------

1	Cs ₂ CO ₃	0
2	K ₂ CO ₃	0
3	Na ₂ HPO ₄	0
4	NaOH	87 %

Conditions: 2 eq. Base, 4 mol% SPhos+2 mol% Pd(OAc)₂, THF+H₂O (1:1), 70 °C.

3.2.7 IMDA reaction

For the key IMDA reaction, an *endo* product was expected that formed through a chair-like transition state with the methyl group at the equatorial position.

First Generation

Scheme 3-27 Reagent and conditions: 1) DIBAL-H, CH₂Cl₂, -78 °C; 2) DMP, CH₂Cl₂.

We initially checked the IMDA reaction with ester **3.19**. Under Lewis acidic conditions, no product was obtained due to the low reactivity of the dienophile. The electron-withdrawing ability of ester is weaker than that of an aldehyde. It was also observed that poor reactivity for the ester substrate

in the work of Li and Shishido.^{37, 39}

In order to improve the reactivity of the dienophile, the ester group was converted into the aldehyde in a sequence of reduction by DIBAL and reoxidation by DMP (Scheme 3-27). The IMDA reaction then proceeded with a variety of Lewis acids (Table 3.5), such as AlCl_3 and MeAlCl_2 . However, the diastereoselectivity of the product was poor. A 2:1 ratio of *endo/exo* isomers was obtained according to the integration of the two aldehyde peaks in the ^1H NMR spectrum. We presumed the major isomer was produced though *endo* selectivity.

Second Generation

A more reactive dienophile system was anticipated to improve the diastereoselectivity. A malonate type moiety was introduced for the IMDA reaction, anticipating that two carbonyl group could increase the reactivity of the dienophile.

Scheme 3-28 Reagent and conditions: (a) O_3 , methanol, 0 °C, then $NaBH_4$, 84%; (b) i. 1 mol% $[Rh(CO)Cl]_2$: Fu_3P =1:1, Bpin, 88%; ii $Pd(OAc)_2$, SPhos, NaOH, THF/ H_2O 85%; iii DMP, CH_2Cl_2 , 94%; (c) Dimethyl malonate, 0.2 eq. piperidine, 0.2 eq. AcOH, CH_2Cl_2 , 75%; (d) Meldrum's acid, 0.2 eq. piperidine, 0.2 eq. AcOH, CH_2Cl_2 , 82%.

The synthesis of the precursor was similar to our previous synthetic plan with a few modifications. The alkyne **3.3** was subjected to ozonolysis in methanol, followed by reduction with $NaBH_4$, as the corresponding

aldehyde performed poorly in the following hydroboration and Suzuki coupling reactions. Subsequent hydroboration, Suzuki coupling and reoxidation of the alcohol afforded the aldehyde **3.22**. The IMDA precursor was installed *via* Knoevenagel condensation with dimethyl malonate in the presence of sub-stoichiometric amount of piperidine and acetic acid. The Knoevenagel reaction has to be employed after the Suzuki reaction because the Knoevenagel reaction product would undergo hydrolysis under the Suzuki reaction condition. The precursor **3.23** underwent the IMDA reaction upon treatment with AlCl_3 at $-78\text{ }^\circ\text{C}$, proving that the two carbonyl dienophile was more reactive than allowing the reaction occurred at low temperature. To our disappointment, a mixture of diastereoisomers **3.24** was obtained again in a ratio of 2:1 (Table 3.5). Concurrently, the aldehyde **3.22** was treated with Meldrum's acid under Knoevenagel reaction condition. A tandem Knoevenagel-IMDA reaction, caused by the higher reactivity of the Meldrum's acid, once again led to the formation of an inseparable mixture of diastereoisomers **3.25** in a ratio of 2:1. The same result was obtained even at $-78\text{ }^\circ\text{C}$. This is in accordance with the higher reactivity of the Meldrum's acid compared to the malonate.⁷¹

Third Generation

Scheme 3-29 Reagent and conditions: (a). Red-Al, THF, reflux, 92%; (b). TBSCl, imidazole, CH₂Cl₂, 93%.

Given the drastic changes that we had made to the dienophile to no avail, we realized that the poor diastereoselectivity must result from the nature of the alkynyl moiety. To test our hypothesis, the alkynol **3.13** was treated with Red-Al to give dienol product **3.26** as a *E,E*-isomer. In contrast, reduction with LiAlH₄ in THF at reflux led to a complex mixture. In the ¹H NMR spectrum, a *dd* peak at 6.44 with *J*= 13.3, 10.6 Hz, a doublet peak at 6.14 with *J*= 13.3 Hz, a *dd* peak at 6.07 with *J*=15.6, 11.0 Hz and a *dt* peak at 5.71 with *J*=15.1, 7.3 Hz represent the diene protons. The coupling constant of the *dt* peak proved that the product was the *E, E* isomer. The purity of alkynol **3.13** was crucial to the success of the Red-Al mediated reduction because the presence of transition metal residues from the Sonogashira reaction would cause the reduction of the vinyl Cl bond instead. In order to remove the transition metal residues, a strategy of protection with TBSCl and imidazole and deprotection with amberlyst-15 was employed to purify alkynol **3.13**. Purification of the Sonogashira product

by cold finger distillation gave a modest yield of 40% owing to polymerization of the compound.

Scheme 3-28 Reagent and conditions: (a) $\text{Pd}(\text{OAc})_2$, SPhos, NaOH, THF/ H_2O , 87%; (b) DIBAL-H, CH_2Cl_2 , -78°C , 77%; (c) DMP, CH_2Cl_2 , 91%. (d) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 0°C 47% or AlCl_3 , CH_2Cl_2 , 0°C , 62%.

Gratifyingly, the Suzuki reaction with the TBS ether of dienol 3.27 afforded ester 3.28 in a yield of 87%. The precursor for IMDA reaction 3.30 was obtained in a sequence of reduction and reoxidation.

The unsaturated decalin framework was constructed as a single stereoisomer on treatment with $\text{BF}_3 \cdot \text{OEt}_2$ at 0°C . No reaction occurred at -78°C , a longer reaction time was required at -40°C and rapid

accomplishment of the reaction was observed at 0 °C. The TBS ether was cleaved at the same time. Further investigation allowed the yield of the reaction to be increased to 62% by replacing $\text{BF}_3 \cdot \text{OEt}_2$ with AlCl_3 , while the diastereoselectivity remained the same.

The results of the three approaches for the IMDA reaction are summarized in table **3.5**.

Table 3.5 Diels-Alder Reactions

Entry	Approach	Lewis acid	T/°C	Time	Result
1	I (CHO)	Me ₃ Al (1.5 eq)	-78	o.n.	No IMDA
			-40	o.n.	No IMDA
			0	o.n.	No IMDA
2		MeAlCl ₂ (1.0 eq)	-60	o.n.	No IMDA
			-40	o.n.	20% d.r.=2:1
3		AlCl ₃ (1.0 eq)	-78	o.n.	No IMDA
			-40	o.n.	30% d.r.=2:1
4		BF ₃ ·OEt ₂ (3.0 eq)	-78	o.n.	No IMDA
			-40	o.n.	Decomposition
5		SnCl ₄ (1.0 eq)	-10	o.n.	Trace d.r.=1:1
6		LiClO ₄ ^b (1.5 eq)	r.t.	o.n.	No IMDA
7	II	LiClO ₄ ^b (1.5 eq)	r.t.	o.n.	No IMDA
8		AlCl ₃ (1.5 eq)	-78	o.n.	42% d.r.=2:1
9	III	BF ₃ ·OEt ₂ (2.0 eq)	-78	o.n.	No IMDA
			-40	o.n.	47% single diastereoisomer
			0	1 h	47% single diastereoisomer
10		MeAlCl ₂ (2.0 eq)	-78	o.n.	No IMDA
			-40	o.n.	- ^c , single diastereoisomer
11		AlCl ₃ (2.0 eq)	0	1 h	62% single diastereoisomer

Conditions: a. 20 mg starting material, 5 mL CH₂Cl₂; b. Et₂O was used as solvent; c. a mixture of TBS and de-TBS product.

A model DFT calculation also indicated that the HOMO of the triene was 3.28 eV higher than that of the dienyne (Figure 3.4).⁷² In the Lewis acid

mediated Diels-Alder reaction, the dienophile becomes more electrophilic because the LUMO of the dienophile is lowered by the polarization of the conjugated alkene bond.¹² Secondary orbital interactions between the electron withdrawing group and the diene have been invoked to explain the relative stereochemistry. It may be suggested that the stronger secondary orbital interaction between the triene and the dienophile further stabilized the HOMO_{diene} – LUMO_{dienophile} interaction to enhance the stereoselectivity. In our case, however, secondary orbital interactions seem to fail to explain the difference of the diastereoselectivity between the triene and dienyne substrates because the selectivity remained the same even when a more reactive electron withdrawing group was employed.

Figure 3.4

An electrostatic effect can be hypothesized to explain the diastereoselectivity (Scheme 3-29). A repulsion in the *exo*-TS1 was one possibility for an electrostatic interaction. The alkene proton carries a partial positive charge because the C-H bonds are polarized towards the carbon atom. The carbon atom of the carbonyl group also carries a partial positive charge. The Coulombic repulsion between these two partial positive charges raises the *exo*-TS1 higher in energy. The IMDA with alkene substituents therefore prefer to proceed through the *endo*-TS1 to give the desired *trans*-decalin. The IMDA reaction with alkyne substituent decreased the energy difference between *exo*-TS2 and *endo*-TS2 leading formation of a mixture of diastereoisomers as this system has no corresponding interaction.

Scheme 3-29

3.2.8 Pinnick-Lindgren oxidation

Scheme 3-30 Reagent and conditions: 2-methyl-2-butene, NaClO_2 , NaH_2PO_4 , $\text{H}_2\text{O}/t\text{BuOH}$, 80%.

The aldehyde was oxidized to the corresponding carboxylic acid through a Pinnick oxidation (Scheme 3-30). Compared to other methods of oxidation, the Pinnick-Lindgren oxidation employs less toxic, occurs under mild conditions and is more functional group tolerant. Aldehyde **3.31** was oxidized to acid **3.32** in the presence of the free hydroxyl group.

Scheme 3-31

A mechanism was proposed by Kudesia (Scheme 3-31).⁷³ Under mild acidic conditions, the chlorite added to the aldehyde, followed by a pericyclic fragmentation to give the corresponding carboxylic acid and hypochlorous acid. 2-methyl-2-butene was used as a scavenger for the HOCl .

3.2.9 Electrophile induced cyclisation-elimination

Iodocyclisation has emerged as the most popular method in the electrophilic cyclization and it has been widely used to in the practice of total synthesis, especially the introduction of new stereogenic center.⁷⁴ For instance, an iodocyclisation has been employed in the synthesis of a briarane unit in this laboratory (Scheme 3-32).⁷⁴

Scheme 3-32

We were interested in this kind of cyclisation to generate the lactone and move the alkene to furnish the desired structure.⁷⁵ The iodocyclisation occurred on treatment with I₂ in the presence of aq. NaHCO₃ giving a single diastereoisomer based on ¹H NMR analysis.

Scheme 3-33 Reagent and conditions: a. I_2 , aq. $\text{NaHCO}_3/\text{THF}$, 85%; b. DBU, CH_2Cl_2

However, the later elimination with DBU gave a mixture in which the desired product was the minor isomer. Based on NMR analysis, the elimination was suspected to occur in both possible directions. In the ^1H NMR of the product, a *dt* peak at 5.25 ppm was observed which was assigned as H_1 and a *dd* peak at 4.46 was observed which was assigned as H_2 . A mixture of regioisomers **3.34** and **3.35** was obtained in a ratio of 5:2 according to the integration of the H_1 and H_2 . A similar observation has been reported by Bartlett.⁷⁶

Scheme 3-34 Reagent and conditions: a. PhSeNPhth, CH₂Cl₂; b. aq. H₂O₂, THF

Investigations on cyclisation mediated selenium reagents have achieved fruitful advantages in organic synthesis.^{75b, 77} A series of selenium reagents have been developed. In selenocyclisation, the ArSeX reagent reacts with an alkene to form an seleniranium ion intermediate, followed by stereospecific *anti* nucleophilic addition. The selenium motif can then be easily transferred into a variety of functional groups under mild conditions.⁷⁸

We anticipated that selenocyclization chemistry could afford the desired lactone. Commercially available ArSeCl was utilized for the cyclisation in the presence of Et₃N. The desired product was obtained in quite low yield probably due to undesirable secondary processes mediated by the halides but the reaction was chemoselective and only one stereoisomer was obtained. *N*-(phenylseleno)phthalimide was therefore prepared from ArSeCl and potassium phthalimide (Scheme 3-35) and gave a good result of 83% in the cyclisation presumably because there is now no source of

halide.⁷⁹ The product was obtained as a single diastereoisomer but at this stage the stereochemistry was not assigned.

Scheme 3-35

In the iodo- or selenocyclisation, the first step is the formation of a bridged cationic intermediate from the alkene and the electrophiles. We hypothesized that the carboxylate would capture the ion *via* pseudoequatorial intermediate **3.37** to provide the desired product (Scheme 3-36).

Scheme 3-36

The eliminated product was obtained on treatment with aqueous H_2O_2 solution.⁷⁸ The selenium cyclisation and elimination strategy gave the desired product in an 83% overall yield, with no trace of the regioisomer. The ^1H NMR and ^{13}C NMR data was excellent match with the data reported in literature, indicating that the selenocyclisation occurred in the desired

stereoselective approach. The optical rotation (+25.9, CHCl₃) matched that of the natural product in literature (+26.6 CHCl₃) almost perfectly.¹

Compared to the iodo-mediated elimination, the excellent selectivity of seleno-type elimination can be attributed to the pericyclic mechanism.

Scheme 3-37

The iodo-elimination proceeds through an E2 mechanism. Proton H_a may be more acidic due to the inductive effect of the oxygen, thus, a mixture of elimination regioisomers is obtained. Alternatively, in the selenium case, a pericyclic elimination operates. Hence the acidity of the protons is not a factor. Complete selectivity for the desired isomer can be attributed to dipolar repulsion between the selenoxide oxygen and the lactone oxygen. Thus, the selenoxide oxygen is oriented towards H_b and elimination only takes place in this direction

^1H NMR of the final product

^1H NMR of the allahabadolactone A

3.3 Conclusion

Scheme 3-38

The synthesis of allahabadolactone A was completed through a route featuring alkyne hydroboration, stereospecific Suzuki coupling and an IMDA reaction (Scheme 3-38). This work confirmed the superiority of the aldehyde as an electron withdrawing group for the IMDA reaction and, for the first time, demonstrated the unsuitability of the alkyne substituent in the IMDA reaction. Also, the absolute stereochemistry of allahabadolactone A was confirmed by the synthesis. Meanwhile, a new Rh catalyst was

prepared with (2-Furyl)₃P ligand, which could be utilized efficiently in the hydroboration of terminal alkynes.

Experimental

All reactions were run under nitrogen gas atmosphere with oven-dried glassware. Anhydrous toluene, THF and Et₂O were distilled from sodium metal. The other solvents and reagents were used as received. Column chromatography was carried out on silica gel 230-400 mesh, and analytical TLC on glass plates (silica gel 60, F254). All ¹H NMR spectra were recorded on a JEOL ECA 400 MHz or Bruker Advance DPX at 400 MHz in CDCl₃ solutions. ¹³C NMR spectra were recorded in CDCl₃ on the same instruments at the corresponding frequency. Chemical shifts are recorded in ppm and coupling constants are recorded in Hz.

(R)-4,8-Dimethylnon-7-en-1-yne 3.3

Method A: (*R*)-Citronellal (1.00 g, 6.48 mmol) was added to a mixture of diethyl (1-diazo-2-oxopropyl)phosphonate (1.87 g, 9.72 mmol) and K₂CO₃ (1.79 g, 12.96 mmol) in methanol (15 mL). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the H₂O (20 mL) was added. The mixture was extracted with

Et₂O (20 mL × 3). The combined organic layers were washed with brine, dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (10% EtOAc/Hexane) to afford a colourless oil (0.71 g, 73%).

Method B: PPh₃ (3.40 g, 12.96 mmol), Zn power (848 mg, 12.96 mmol) and CBr₄ (4.30 g, 12.96 mmol) was mixed in anhydrous CH₂Cl₂ (40 mL). The mixture was stirred overnight at room temperature under N₂. (*R*)-citronellal (1.00 g, 6.48 mmol) was added to the mixture and the reaction was stirred for 2 h and then quenched with H₂O (30 mL). The layers were extracted with CH₂Cl₂ (20 mL × 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to give a colourless oil (1.88 g, 94%). The oil was dissolved in anhydrous THF (15 mL) and the reaction was cooled to -78 °C. *n*BuLi (7.6 mL, 12.16 mmol, 1.6 M in hexane) was added dropwise to the reaction. After stirring for 2 h at -78 °C, the reaction was quenched with H₂O and warmed to room temperature. The mixture was extracted with Et₂O (10 mL × 3). The organic layers were combined, washed with brine and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (10% EtOAc/Hexane) to give a colourless oil (0.82 g, 90%).

¹H NMR (400 MHz, CDCl₃) δ 5.12-5.08 (m, 1H), 2.17 (ddd, J=16.5, 5.5,

2.8 Hz, 1H), 2.07 (ddd, $J=16.5, 6.9, 2.8$ Hz, 1H), 2.02-1.94 (m, 3H), 1.70-1.66 (m, 4H), 1.61 (s, 3H), 1.49-1.41 (m, 1H), 1.29-1.19 (m, 1H), 1.00 (d, $J=6.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 131.7, 124.7, 83.6, 69.3, 36.2, 32.2, 26.0, 25.9, 25.8, 19.5, 17.9.

All data are consistent with that reported in literature.⁸⁰

Methyl (*R,E*)-2,6-dimethylnon-2-en-8-ynoate **3.5**

O_3 in O_2 was bubbled through a solution of alkene **3.3** (3.00 g, 19.95 mmol) in CH_2Cl_2 at -78°C . When the reaction was done, the mixture was flushed with O_2 for 15 min. Methyl 2-(triphenylphosphoranylidene)propanoate (6.96 g, 19.95 mmol) was added to the solution at room temperature and the mixture was heated at reflux for 4 h. The reaction was cooled to room temperature and the volatile was removed under reduced pressure. The residue was taken up in the minimum amount of CH_2Cl_2 , and excess hexane was added. The precipitate was removed by filtration through celite, the filtrate was concentrated under reduced pressure and purified via column chromatography (10% EtOAc/Hexane) to give ester **3.5** as a colourless oil (2.64 g, 68%).

¹H NMR (400 MHz, CDCl₃) δ 6.75 (t, *J* = 7.3 Hz, 1H), 3.73 (s, 3H), 2.21–2.13 (m, 4H), 1.96 (t, *J* = 2.8 Hz, 1H), 1.84 (s, 3H), 1.72–1.67 (m, 1H), 1.62–1.56 (m, 1H), 1.41–1.25 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 168.8, 142.4, 127.9, 83.0, 69.7, 51.9, 34.7, 32.2, 26.4, 25.8, 19.5, 12.6.

IR(neat) cm⁻¹: 3302, 2114, 1713, 1651, 1265, 1096, 934.

MS (ESI): *m/z* = 217.99 [M + Na]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₁₂H₁₉O₂: 195.1385; found: 195.1383.

[α]_D²³ +4.1 (*c* 0.68, CHCl₃).

Methyl (R,2*E*,8*E*)-2,6-dimethyl-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nona-2,8-dienoate 3.6

Ester **3.5** (1.00 g, 5.15 mmol) and Rh[(2-furyl)₃P]₂(CO)Cl (0.10 mmol) were mixed in toluene (50 mL) under nitrogen. 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.89 mL, 6.18 mmol) was added. The mixture was stirred for 2 h at room temperature. The reaction was quenched with H₂O and the mixture was extracted with Et₂O (10 mL × 3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The

residue was purified by column chromatography (20% EtOAc/Hexane) to give the product as a colourless oil (1.28 g, 77%).

¹H NMR (400 MHz, CDCl₃) δ 6.73 (t, J=7.3 Hz, 1H), 6.57 (dt, J=17.9 Hz, 6.9 Hz, 1H), 5.42 (d, J=17.9 Hz, 1H), 3.72 (s, 3H), 2.20-2.12 (m, 2H), 1.82 (s, 3H), 1.63-1.42 (m, 3H), 1.27 (s, 12H), 0.90 (d, J= 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 168.9, 153.0, 142.8, 127.6, 83.2, 51.9, 43.6, 35.4, 32.3, 26.4, 25.0, 19.6, 12.5.

IR(neat) cm⁻¹: 3390, 2978, 2953, 2872, 1713, 1634, 1435, 1362, 1269, 1146, 1092.

MS (ESI): *m/z* = 323.92 [M + H]⁺.

HRMS (EI): *m/z* [M + Na]⁺ calcd for C₁₈H₃₁BO₄Na: 345.2213; found: 345.2221.

[α]_D²³ -1.8 (*c* 3.50, CHCl₃).

(S)-4-Methyl-1,3,2-dioxathiolane 2,2-dioxide 3.16

Thionyl chloride (5.75 mL, 80 mmol) was added slowly to a solution of (*S*)-propylene diol (5.0 g, 65 mmol) in CH₂Cl₂ (40 mL). The mixture was heated at reflux for 1h and cooled to 0 °C. H₂O (40 mL), acetonitrile (25 mL), ruthenium trichloride trihydrate (13 mg, 0.065 mmol) were added

sequentially. NaIO₄ (21 g, 100 mmol) was added portionwise to the mixture. The mixture was stirred for 1 h at room temperature and extracted with Et₂O (10 mL x 3). The combined organic layers were washed with aq. NaHCO₃, brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by distillation (70 °C at 0.5 mmHg) to give the product as a colourless oil (8.2 g, 90%).

¹H NMR (400 MHz, CDCl₃) δ 5.15-5.10 (m, 1H), 4.73 (dd, J=8.7, 6.0 Hz, 1H), 4.31 (t, J= 8.5 Hz, 1H), 1.60 (d, J=6.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 79.7, 74.2, 18.0.

All data are consistent with that reported in literature.²⁰

(S)-pent-4-yn-2-ol 3.14

n-BuLi (16.3 mL, 26.1 mmol, 1.6 M in hexane) was slowly added to a solution of trimethylsilylacetylene (3.69 mL, 26.1 mmol) in THF (50 mL) at -78 °C. After stirring for 30 min, a solution of cyclic sulfate **3.16** (3.00 g, 21.7 mmol) in THF (5 mL) was added *via* cannula. The mixture was warmed to room temperature and stirred for 1 h. H₂O (0.40 mL) and concentrated H₂SO₄ (0.35 mL) were added. The cloudy mixture was stirred

for 15 min and neutralized with aq. NaHCO₃. The mixture was extracted with Et₂O (20 mL × 3). The combined organic solution was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude compound was dissolved in MeOH (15 mL) and K₂CO₃ (4.50 g, 32.55 mmol) was added. The mixture was heated at reflux for 2 h and cooled to room temperature. H₂O (30 mL) was added to the mixture and it was extracted with CH₂Cl₂ (20 mL×3). The combine organic phase was washed with brine and dried over MgSO₄. The solvent was removed *in vacuo*. The product was obtained by distillation (45 °C at 6 mmHg) or column chromatography on silica gel (30% Et₂O/Hexane) as a colourless oil (1.46 g, 80%).

¹H NMR (400 MHz, CDCl₃) δ 4.00-3.95 (m, 1H), 2.44-2.29 (m, 2H), 2.05 (t, J=2.6 Hz, 1H), 1.27 (d, J=6.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 81.1, 71.1, 66.5, 29.2, 22.5.

All data are consistent with that reported in literature.²⁰

(*S,E*)-7-Chlorohept-6-en-4-yn-2-ol 3.13

Trans-1,2-dichloroethene (276 μL, 3.66 mmol), alcohol **3.14** (200 mg, 2.38

mmol), Pd(PPh₃)₄ (69 mg, 2.5 mol%), CuI (23 mg, 5 mol%) and Et₃N (663 μL, 4.76 mmol) were mixed in anhydrous THF (10 mL). The mixture was stirred overnight under N₂ and quenched with aq. NH₄Cl (10 mL). The mixture was extracted with Et₂O (10 mL × 3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (20% EtOAc/Hexane) to give a colourless oil (326 mg, 95 %).

¹H NMR (400 MHz, CDCl₃) δ 6.49 (d, J=13.7 Hz, 1H), 5.92 (dt, J=13.7, 2.3 Hz, 1H), 4.00-3.94 (m, 1H), 2.55-2.41 (m, 2H), 1.27 (d, J=6.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 130.0, 114.0, 89.5, 78.1, 66.5, 30.1, 22.6.

IR(neat) cm⁻¹: 3372, 3073, 2907, 2220, 1718, 1583, 1450, 1419, 1375, 1229, 1112, 1085, 939, 918.

MS (ESI): *m/z* = 145.19 [C₇H₁₉O³⁵Cl+H]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₇H₁₀O³⁵Cl: 145.0420; found: 145.0414.

[α]_D²³ +12.5 (*c* 3.00, CHCl₃).

(*S*,4*E*,6*E*)-7-Chlorohepta-4,6-dien-2-ol 3.26

Alcohol **3.13** (1.20 g, 8.30 mmol) was dissolved in anhydrous THF (15 mL).

Red-Al (3.36 mL, 11.19 mmol, 65% wt. in tol.) was slowly added to the solution at -78 °C and then the reaction was heated at reflux for 3 h. The mixture was cooled to 0 °C and quenched with H₂O. After adding HCl (5 ml, 2M), the mixture was extracted with Et₂O (10 mL × 3). The combined organic layers were washed with brine and dried over Na₂SO₄. After removing the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (20% EtOAc/Hexane) to give the product as a colourless oil (1.12 g, 92 %).

¹H NMR (400 MHz, CDCl₃) δ 6.44 (dd, J=13.3, 10.6 Hz, 1H), 6.14 (d, J=13.3 Hz, 1H), 6.07 (dd, J= 15.6, 11.0 Hz, 1H), 5.71 (dt, J= 15.1, 7.3 Hz, 1H), 3.90-3.83 (m, 1H), 2.31-2.17 (m, 2H), 1.21 (d, J=6.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 133.6, 131.5, 129.5, 120.0, 67.5, 42.7, 23.2.

IR(neat) cm⁻¹: 3372, 2970, 2928, 1653, 1583, 1456, 1375, 1285, 1117, 1074, 978, 937, 824.

MS (ESI): *m/z* = 147.27 [C₇H₁₁O³⁵Cl+H]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₇H₁₂O³⁵Cl: 147.0577; found: 147.0573.

[α]_D²³ +12.9 (*c* 1.00, CHCl₃).

***tert*-Butyl(((*S*,4*E*,6*E*)-7-chlorohepta-4,6-dien-2-yl)oxy)dimethylsilane**

3.27

The alcohol **3.26** (240 mg, 1.64 mmol), TBSCl (299 mg, 1.99 mmol) and imidazole (226 mg, 3.32 mmol) were mixed in CH₂Cl₂ (10 mL). After stirring for 2 h, the reaction was quenched with aq. NH₄Cl (10 mL). The mixture was extracted with Et₂O (10 mL × 3) and the combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel (10% EtOAc/Hexane) to give a colourless oil **3.27** (397 mg, 93%)

¹H NMR (400 MHz, CDCl₃) δ 6.42 (dd, *J*=13.3, 11.0 Hz, 1H), 6.09 (d, *J*=13.3 Hz, 1H), 5.99 (dd, *J*=15.6, 11.0 Hz, 1H), 5.70 (dt, *J*=15.1, 7.3 Hz, 1H), 3.87-3.80 (m, 1H), 2.25-2.13 (m, 2H), 1.12 (d, *J*=6.0 Hz, 3H), 0.88 (s, 9H), 0.04-0.03 (m, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 134.0, 132.8, 128.3, 119.0, 68.6, 43.2, 26.1, 23.8, 18.4, -4.3, -4.5.

IR(neat) cm⁻¹: 3422, 2955, 2857, 2100, 1653, 1638, 1472, 1375, 1256, 1126, 1080, 999, 977.

MS (ESI): *m/z* = 261.41 [C₁₃H₂₅O³⁵Cl + H]⁺.

HRMS (EI): *m/z* [M + Na]⁺ calcd for C₁₃H₂₅O³⁵ClNa: 283.1261; found: 283.1275.

[α]_D²³ +12.0 (*c* 0.20, CHCl₃).

Methyl (2*E*,6*R*,8*E*,10*E*,12*E*,15*S*)-15-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10,12-tetraenoate 3.28

Vinyl Cl **3.27** (500 mg, 1.92 mmol), Boronate **3.6** (620 mg, 1.92 mmol), NaOH (155 mg, 3.84 mmol), Pd(OAc)₂ (8.8 mg, 0.038 mmol) and Sphos (30 mg, 0.076 mmol) were mixed into a solution of THF/H₂O (20 mL, 1:1). The mixture was heated at 70 °C for 2 h under N₂. Aq. NH₄Cl (5 mL) was added and the mixture was extracted with Et₂O (10 mL × 3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude was purified by column chromatography on silica get (10% EtOAc/Hexane) to give a colourless oil (704 mg, 87%)

¹H NMR (400 MHz, CDCl₃) δ 6.74 (t, *J*=7.8 Hz, 1H), 6.11-5.98 (m, 4H), 5.68-5.59 (m, 2H), 3.86-3.80 (m, 1H), 3.73 (s, 3H), 2.28-2.07 (m, 4H), 2.00-1.93 (m, 1H), 1.83 (s, 3H), 1.55-1.43 (m, 2H), 1.30-1.19 (m, 2H), 1.12 (d, *J*=6.0 Hz, 3H), 0.94-0.83 (m, 12H), 0.04-0.03 (m, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 168.9, 142.9, 132.8, 132.7, 132.2, 131.3, 131.2, 131.1, 127.7, 69.0, 51.9, 43.5, 40.4, 35.4, 33.2, 26.5, 26.1, 23.8, 19.6, 18.4, 12.6, -4.3, -4.4.

¹H NMR (400 MHz, CDCl₃) δ 6.11-6.00 (m, 4H), 5.68-5.60 (m, 2H), 5.39 (t, J=7.3 Hz, 1H), 3.99 (d, J=5.0 Hz, 2H), 3.84-3.79 (m, 1H), 2.24-1.93 (m, 6H), 1.66 (s, 3H), 1.57-1.24 (m, 3H), 1.12 (d, J=6.0 Hz, 3H), 0.89-0.84 (m, 12H), 0.04-0.03 (m, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 134.8, 133.2, 132.7, 132.0, 131.4, 131.1, 131.0, 126.8, 69.3, 69.0, 43.5, 40.5, 36.5, 33.2, 26.1, 25.4, 23.8, 19.7, 18.4, 13.9, -4.3, -4.4.

IR(neat) cm⁻¹: 3356, 3013, 2955, 2928, 1689, 1644, 1641, 1462, 1375, 1254, 1128, 1082, 1043, 995, 835.

MS (ESI): *m/z* = 393.35 [M + H]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₂₄H₄₅O₂Si: 393.3189; found: 393.3182.

[α]_D²³ +9.0 (*c* 0.80, CHCl₃).

(2*E*,6*R*,8*E*,10*E*,12*E*,15*S*)-15-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10,12-tetraenal 3.30

DMP (1.86 g, 4.38 mmol) was added to a solution of the alcohol **3.29** (860 mg, 2.19 mmol) in CH₂Cl₂ (20 mL) and the mixture was stirred for 30 min at room temperature. The reaction was quenched with aq. NaHCO₃ (20 mL) and the mixture was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were dried over MgSO₄ and filtered through celite. The solvent was removed under reduced pressure and the crude mixture was purified by chromatography on silica gel (20% EtOAc/Hexane) to give the product as a colourless oil (780 mg, 91%).

¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 6.47 (t, J=7.3 Hz, 1H), 6.12-6.02 (m, 4H), 5.69-5.61 (m, 2H), 3.86-3.80 (m, 1H), 2.38-1.98 (m, 5H), 1.75 (s, 3H), 1.60-1.49 (m, 2H), 1.32-1.23 (m, 2H), 1.12 (d, J=5.9 Hz, 3H), 0.95-0.87 (m, 12H), 0.07-0.03 (m, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 195.6, 155.2, 139.4, 132.6, 132.5, 132.4, 131.4, 131.3, 131.2, 68.9, 43.5, 40.4, 35.2, 33.3, 26.9, 26.1, 23.8, 19.6, 18.4, 9.4, -4.3, -4.4.

IR(neat) cm⁻¹: 3422, 2957, 2928, 2857, 1726, 1690, 1639, 1462, 1375, 1256, 1128, 997, 835.

MS (ESI): *m/z* = 413.62 [M + Na]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₂₄H₄₃O₂Si: 391.3032; found: 391.3037.

[α]_D²³ +14.0 (*c* 0.80, CHCl₃).

(1*S*,2*R*,4*aS*,6*R*,8*aR*)-2-((*S,E*)-4-Hydroxypent-1-en-1-yl)-1,6-dimethyl-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalene-1-carbaldehyde **3.31**

AlCl₃ (136 mg, 1.02 mmol) was added to a solution of aldehyde **3.30** (200 mg, 0.51 mmol) in CH₂Cl₂ (10 mL) at 0 °C. After stirring for 1 h, the reaction was quenched with aq. NaHCO₃ (10 mL). The mixture was extracted with Et₂O (5 mL x 3). The combined organic phase was washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and the crude was purified by chromatography on silica gel (30% EtOAc/Hexane) to give the product as a colourless oil (88 mg, 62%).

¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 5.54-5.36 (m, 4H), 3.82-3.76 (m, 3H), 2.61-2.58 (m, 1H), 2.23-2.08 (m, 2H), 1.85-1.39 (m, 9H), 1.17 (d, J=5.9 Hz, 3H), 1.04 (s, 3H), 0.92 (d, J=6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 209.1, 132.6, 131.6, 129.8, 126.5, 67.4, 50.7, 49.2, 42.7, 41.8, 39.1, 37.6, 35.6, 33.4, 27.2, 23.0, 22.7, 14.3.

IR(neat) cm⁻¹: 3410, 2955, 2928, 2857, 1719, 1472, 1362, 1254, 1070, 837.

MS (ESI): *m/z* = 299.48 [M + Na]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₁₈H₂₉O₂: 277.2168; found: 277.2173.

$[\alpha]_D^{23} +211.6$ (c 0.50, CHCl_3).

(1*S*,2*R*,4*aS*,6*R*,8*aR*)-2-((*S,E*)-4-Hydroxypent-1-en-1-yl)-1,6-dimethyl-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalene-1-carboxylic acid **3.32**

NaH_2PO_4 (60 mg, 0.50 mmol), 2-methylbut-2-ene (172 μL , 1.62 mmol) was mixed in a solution of aldehyde **3.31** (100mg, 0.36 mmol) in $\text{tBuOH}/\text{H}_2\text{O}$ (8 mL, 3:1). NaClO_2 (82 mg, 0.90 mmol) was added to the mixture. The reaction was stirred for 4 h at room temperature. H_2O (10 mL) was added to the reaction, and the mixture was extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over MgSO_4 and the solvent was removed under reduced pressure. The acid was obtained by chromatography on silica gel (50% $\text{EtOAc}/\text{Hexane}$) as a colourless oil (117 mg, 80%).

^1H NMR (400 MHz, CDCl_3) δ 5.50-5.35 (m, 4H), 5.09 (br, 1H), 3.82-3.72 (m, 1H), 2.61 (dd, $J=8.7, 4.1$ Hz, 1H), 2.24-2.17 (m, 2H), 2.02-1.97 (m, 1H), 1.81-1.72 (m, 4H), 1.63-1.47 (m, 4H), 1.19-1.16 (m, 6H), 0.91 (d, $J=6.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 179.7, 135.7, 131.3, 127.6, 126.2, 67.3, 50.7, 49.6, 42.5, 42.0, 40.4, 38.3, 35.7, 33.6, 27.7, 22.7, 22.7, 16.8.

IR(neat) cm⁻¹: 3422, 2953, 2924, 2855, 1667, 1608, 1585, 1404, 1227, 1070, 995, 773.

MS (ESI): $m/z = 315.48$ $[M + Na]^+$.

HRMS (EI): m/z $[M + Na]^+$ calcd for C₁₈H₂₈O₃Na: 315.1936; found: 315.1928.

$[\alpha]_D^{23}$ +114.1 (*c* 0.80, CHCl₃).

(3*R*,3*aR*,5*aS*,7*R*,9*aR*,9*bS*)-3-((1*S*,3*S*)-3-Hydroxy-1-(phenylselenanyl)butyl)-7,9*b*-dimethyl-3*a*,5*a*,6,7,8,9,9*a*,9*b*-octahydronaphtho[1,2-*c*]furan-1(3*H*)-one 3.36

Potassium *N*-(phenylseleno)phthalimide (123 mg, 0.42 mmol) was added to a solution of acid **3.32** (60 mg, 0.21 mmol) in CH₂Cl₂. After stirring for 2 h, the solvent was removed under reduced pressure and excess hexane was added. The mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc/Hexane) to give the product as a colourless oil (157 mg, 83%)

¹H NMR (400 MHz, CDCl₃) δ 7.63-7.60 (m, 2H), 7.30-7.28 (m, 3H), 5.80-

5.76 (m, 1H), 5.61 (d, $J=10.1$ Hz, 1H), 4.37 (dd, $J=9.6, 5.0$ Hz, 1H), 4.32-4.26 (m, 1H), 2.50 (dd, $J=9.6, 4.6$ Hz, 1H), 1.94-1.77 (m, 5H), 1.71-1.63 (m, 2H), 1.48-1.47 (m, 2H), 1.31-1.24 (m, 5H), 1.12 (s, 3H), 0.90 (d, $J=6.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 179.0, 134.7, 134.6, 129.5, 129.3, 128.1, 122.7, 85.4, 65.7, 49.4, 46.7, 45.6, 41.8, 41.3, 40.5, 36.2, 35.3, 33.0, 25.7, 24.5, 22.6, 16.1.

IR(neat) cm^{-1} : 3441, 2928, 2367, 2097, 1772, 1636, 1558, 1466, 1375, 1265, 1125, 1022.

HRMS (EI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{32}\text{O}_3\text{SeNa}$: 471.1414; found: 471.1427.

MS (ESI): $m/z = 471.16$ $[\text{M} + \text{Na}]^+$.

$[\alpha]_{\text{D}}^{23}$ +50.5 (c 0.20, CHCl_3).

Allahabadolactone A 3.1

H_2O_2 (2 mL, 30% in H_2O) was added in to a solution of lactone **3.36** (157 mg, 0.35 mmol) in THF (5 mL). The reaction was stirred for 1 h at room temperature. After adding H_2O (5 mL), the mixture was extracted with Et_2O (5 mL x 3). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (25% EtOAc /Hexane) to give the product as a colourless oil (50 mg, 100%)

¹H NMR (400 MHz, CDCl₃) δ 5.91 (dd, J=15.6, 5.5 Hz, 1H), 5.72 (ddd, J=15.6, 7.3, 1.3 Hz, 1H), 5.66 (d, J=10.1 Hz, 1H), 5.55-5.49 (m, 1H), 4.47 (dd, J=10.2, 7.3 Hz, 1H), 4.39-4.35 (m, 1H), 2.35-2.32 (m, 1H), 1.95-1.78 (m, 4H), 1.53-1.41 (m, 1H), 1.31-1.20 (m, 1H), 1.30 (d, J=6.8 Hz, 3H), 1.14 (s, 3H), 0.91 (d, J=6.4 Hz, 3H), 0.97-0.76 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 179.5, 139.1, 135.2, 126.1, 121.0, 82.8, 68.0, 51.7, 44.9, 41.8, 40.3, 36.4, 35.3, 33.0, 25.7, 23.5, 22.6, 16.5.

[α]_D²³ +25.9 (*c* 0.08, CHCl₃).

(±)-4-Methylhept-6-yn-1-ol 3.21

O₃ in O₂ was bubbled through a solution of alkyne **3.3** (1.00 g, 6.65 mmol) in MeOH (40 mL) at room temperature. When all the starting material was consumed, O₂ was flushed through the solution for 10 min. The mixture was cooled to 0 °C and NaBH₄ was added portionwise. The reaction was stirred for 30 min before aq. NH₄Cl (5 mL) was added. The mixture was concentrated *in vacuo* and the mixture was extracted with CH₂Cl₂ (10 mL x 3). The combined organic layers were washed with brine, dried over MgSO₄ and the volatile was removed under reduced pressure. The crude

product was purified by column chromatography on silica gel (25% EtOAc/Hexane) to give alcohol (705 mg, 84%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 3.65 (t, J=6.4 Hz, 2H), 2.21-2.07 (m, 2H), 1.96 (t, J=2.3 Hz, 1H), 1.75-1.48 (m, 4H), 1.38-1.23 (m, 1H), 1.00 (d, J=6.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 83.3, 69.5, 63.4, 32.5, 32.1, 30.5, 26.0, 19.6.

All data are consistent with that reported in literature.⁸¹

(±)-(E)-4-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-1-ol 3.39

Tri(2-furyl)phosphine (18.4 mg, 0.08 mmol) and [Rh(CO)₂Cl]₂ (15.4 mg, 0.04mmol) were mixed in toluene (40 mL) at room temperature. A solution of alcohol **3.21** (500 mg, 3.96 mmol) in toluene (2 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.69 mL, 4.80 mmol) were added. The mixture was stirred for 2 h at room temperature. The reaction was quenched with H₂O and the mixture was extracted with Et₂O (10 mL x 3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc/Hexane) to give the product as a colourless oil (886 mg, 88%).

¹H NMR (400 MHz, CDCl₃) δ 6.59 (dt, J=17.9, 6.9 Hz, 1H), 5.42 (d, J=18.3 Hz, 1H), 3.64-3.60 (m, 2H), 2.21-2.14 (m, 1H), 2.05-1.97 (m, 1H), 1.64-1.48 (m, 4H), 1.43-1.34 (m, 1H), 1.26 (s, 12H), 0.90 (d, J=6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 153.4, 83.3, 63.5, 43.8, 32.8, 30.6, 25.0, 19.8.

IR(neat) cm⁻¹: 3397, 2976, 2929, 2870, 2247, 1734, 1636, 1456, 1362, 1144, 997.

MS (ESI): *m/z* = 255.32 [M + H]⁺.

HRMS (EI): *m/z* [M + Na]⁺ calcd for C₁₄H₂₇O₃Na: 277.1951; found: 277.1933.

(*S,E*)-tert-Butyl((7-chlorohept-6-en-4-yn-2-yl)oxy)dimethylsilane 3.18

Alcohol **3.13** (237 mg, 1.64 mmol), TBSCl (299 mg, 1.99 mmol) and imidazole (226 mg, 3.32 mmol) were mixed in CH₂Cl₂ (10 mL) at room temperature. The reaction was stirred for 2 h at r.t. After quenching with aq. NH₄Cl, the mixture was extracted with Et₂O (10 mL x 3). The combined organic solution was washed with brine, dried over Na₂SO₄ and filtered through celite. The volatile was removed under reduced pressure and the crude product was purified by column chromatography (25% EtOAc/Hexane) to give a colourless oil (399 mg, 94%).

¹H NMR (400 MHz, CDCl₃) δ 6.44 (d, J=14.2, 1H), 5.91 (dt, J=13.8, 2.3 Hz, 1H), 3.98- 3.93 (m, 1H), 2.45 (ddd, J=16.5, 6.0, 2.3 Hz, 1H), 2.34 (ddd, J=16.9, 6.8, 1.8 Hz, 1H), 1.21 (d, J=5.9 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 129.2, 114.4, 91.1, 67.7, 30.5, 26.0, 23.8, -4.7.

IR(neat) cm⁻¹: 2955, 2856, 2220, 1699, 1585, 1471, 1377, 1255, 1126. 999.

MS (ESI): *m/z* = 259.50 [M + H]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₁₃H₂₄OSi³⁵Cl: 259.1285; found: 259.1326.

[α]_D²³ +12.3 (*c* 0.30, CHCl₃).

(±)-(6*E*,8*E*,13*S*)-13-((*tert*-Butyldimethylsilyl)oxy)-4-methyltetradeca-6,8-dien-10-yn-1-ol 3.40

Alcohol **3.39** (500 mg, 1.76 mmol), Vinyl Chloride **3.18** (455 mg, 1.76 mmol), Pd(OAc)₂ (8 mg, 0.035 mmol), Sphos (29 mg, 0.070 mmol) and NaOH (142 mg, 3.52 mmol) were mixed in a solution of THF/H₂O (20 mL, 1:1) at room temperature. The reaction was stirred at 70 °C for 2 h. The mixture was cooled to room temperature and extracted with Et₂O (10 mL x

3). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered through celite. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (25% EtOAc/Hexane) to give the product as a colourless oil (502 mg, 85%).

^1H NMR (400 MHz, CDCl_3) δ 6.48 (dd, $J=15.6, 11.0$ Hz, 1H), 6.05 (dd, $J=15.1, 11.0$ Hz, 1H), 5.72 (dt, $J=15.1, 7.3$ Hz, 1H), 5.47 (d, $J=15.6$ Hz, 1H), 3.98-3.93 (m, 1H), 3.62 (t, $J=6.4$ Hz, 2H), 2.49 (ddd, $J=16.9, 5.9, 2.3$ Hz, 1H), 2.36 (ddd, $J=16.5, 6.9, 2.3$ Hz, 1H), 2.14-2.08 (m, 1H), 1.99-1.92 (m, 1H), 1.64-1.48 (m, 4H), 1.42-1.20 (m, 7H), 0.89 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.2, 135.6, 131.4, 109.7, 89.9, 81.5, 68.2, 63.5, 40.5, 33.3, 32.8, 30.8, 30.6, 26.1, 23.7, 19.7, 18.4, -4.4.

IR(neat) cm^{-1} : 3421, 3053, 2929, 2856, 2304, 2123, 1637, 1265, 987.

MS (ESI): $m/z = 351.59$ $[\text{M} + \text{H}]^+$.

HRMS (EI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{39}\text{O}_2\text{Si}$: 351.2719; found: 351.2715.

(±)-(6*E*,8*E*,13*S*)-13-((*tert*-Butyldimethylsilyl)oxy)-4-methyltetradeca-6,8-dien-10-ynal 3.22

Alcohol **3.40** (900 mg, 2.58 mmol) and DMP (1.63 g, 3.87 mmol) were mixed in CH₂Cl₂ (20 mL) at room temperature. The mixture was stirred for 30 min. After quenching with aq. NaHCO₃ (20 mL), the mixture was extracted with CH₂Cl₂ (10 mL x 3). The organic phase was washed with brine, dried over MgSO₄, filtered through celite and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc/Hexane) to give aldehyde (842 mg, 94%) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 9.76 (t, J=1.8 Hz, 1H), 6.48 (dd, J=15.6, 11.0 Hz, 1H), 6.06 (dd, J=15.1, 11.0 Hz, 1H), 5.70 (dt, J=15.1 Hz, 7.3 Hz, 1H), 5.49 (d, J= 15.6 Hz, 1H), 3.98-3.92 (m, 1H), 2.52-2.33 (m, 4H), 2.14-2.07 (m, 1H), 2.01-1.94 (m, 1H), 1.72- 1.39 (m, 3H), 1.22 (d, J=6.0 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 202.8, 141.0, 134.8, 131.7, 110.1, 90.1, 81.4, 68.2, 41.9, 40.2, 33.0, 30.8, 28.7, 26.1, 23.7, 19.5, 18.4, -4.5.

IR(neat) cm⁻¹: 2957, 2928, 2904, 2856, 2719, 2150, 1724, 1638, 1448, 1377, 1256, 1126, 986.

MS (ESI): *m/z* = 349.67 [M + H]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₂₁H₃₇O₂Si: 349.2563; found: 349.2594.

(±)-Dimethyl 2-((6E,8E,13S)-13-((*tert*-butyldimethylsilyl)oxy)-4-methyltetradeca-6,8-dien-10-yn-1-ylidene)malonate 3.23

Aldehyde **3.22** (500 mg, 1.50 mmol), dimethyl malonate (165 μ L, 1.50 mmol), piperidine (30 μ L, 0.30 mmol) and AcOH (17 μ L, 0.30 mmol) were mixed in CH₂Cl₂ (10 mL) at room temperature. The mixture was stirred for 4 h and the solvent was removed under reduce pressure. H₂O (5 mL) was added and the mixture was extracted with Et₂O (5 mL x 3). The organic phase was washed with aq. NaHCO₃, brine and dried over MgSO₄. The volatile was removed *in vacuo* and the crude was purified by column chromatography (25% EtOAc/Hexane) to give the product as a colourless oil (500 mg, 75%).

¹H NMR (400 MHz, CDCl₃) δ 7.01 (t, J=8.2 Hz, 1H), 6.47 (dd, J=15.6, 11.0 Hz, 1H), 6.05 (dd, J=15.1, 11.0 Hz, 1H), 5.69 (dt, J=15.1 Hz, 7.3 Hz, 1H), 5.48 (d, J=15.6 Hz, 1H), 3.97-3.93 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.51-2.27 (m, 4H), 2.11-2.04 (m, 1H), 1.97-1.93 (m, 1H), 1.57-1.43 (m, 2H), 1.32-1.22 (m, 7H), 0.89 (s, 9H), 0.07 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 166.3, 164.6, 150.7, 141.0, 135.0, 131.7, 127.9, 110.0, 89.8, 81.2, 68.2, 52.6, 52.5, 40.2, 35.1, 33.0, 30.8, 27.7, 26.1,

23.7, 19.5, 18.4, -4.5.

IR(neat) cm^{-1} : 3022, 2953, 2928, 2857, 2081, 1732, 1688, 1643, 1435, 1256, 1126, 995.

MS (ESI): m/z = 463.68 $[\text{M} + \text{H}]^+$.

HRMS (EI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{43}\text{O}_5\text{Si}$: 463.2880; found: 463.2866.

(±)-2-((*S*)-4-((*tert*-Butyldimethylsilyl)oxy)pent-1-yn-1-yl)-2',2',6-trimethyl-4a,5,6,7,8,8a-hexahydro-2H-spiro[naphthalene-1,5'-[1,3]dioxane]-4',6'-dione **3.25**

Meldrum's acid (365 mg, 2.53 mmol), aldehyde **3.22** (840 mg, 2.41 mmol) piperidine (48 μL , 0.48 mmol) and AcOH (28 μL , 0.48 mmol) were mixed in CH_2Cl_2 (10 mL). After stirring for 2h, the solvent was removed under reduce pressure. H_2O (10 mL) was added to the mixture and was extracted with Et_2O (10 mL x 3). The combined organic layers were washed with aq. NaHCO_3 , brine and dried over MgSO_4 . The solvent was removed under reduced pressrue and the crude was purified by column chromatography (25% EtOAc/Hexane) to give the product as colourless oil (942 mg, 82%).

(a mixture of diastereoisomer of endo/exo=2:1)

¹H NMR (400 MHz, CDCl₃) δ 5.68 (d, J = 10.1 Hz, 1H), 5.64– 5.60 (m, 1H), 3.93–3.88 (m, 1H), 3.58 (s, 1H), 2.25–2.17 (m, 2H), 2.00–1.86 (m, 2H), 1.64–1.54 (m, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.27–1.16 (m, 7H), 0.89–0.82 (m, 2H), 0.05 (s, 6H)

(±)-Methyl (2*E*,8*E*,10*E*,15*S*)-15-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10-trien-12-ynoate 3.19

It was prepared with the same procedure as for **3.28**

¹H NMR (400 MHz, CDCl₃) δ 6.73 (t, J=7.2 Hz, 1H), 6.45 (dd, J=15.6, 10.8 Hz, 1H), 6.04 (dd=15.6, 10.8 Hz, 1H), 5.70 (dt, J=15.6, 7.2 Hz, 1H), 5.48 (d, J=15.6 Hz, 1H), 3.97-3.93 (m, 1H), 3.73 (s, 3H), 2.52-2.33 (m, 3H), 2.19-1.92 (m, 4H), 1.83 (s, 3H), 1.62-1.39 (m, 2H), 1.29-1.22 (m, 3H), 0.89-0.78 (m, 12H), 0.08 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 168.9, 142.8, 141.1, 135.3, 131.5, 127.7, 109.9, 90.0, 81.5, 68.2, 51.9, 40.3, 35.5, 33.1, 30.8, 26.5, 26.1, 23.7, 19.6, 18.4, 12.6, -4.5.

IR(neat) cm⁻¹: 2955, 2929, 2737, 2253, 2214, 1715, 1653, 1458, 1437,

1257, 1128, 997.

MS (ESI): $m/z = 419.34$ $[M + H]^+$.

HRMS (EI): m/z $[M + H]^+$ calcd for $C_{25}H_{43}O_3Si$: 419.2981; found: 419.2998.

(±)-(2*E*,8*E*,10*E*,15*S*)-15-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10-trien-12-yn-1-ol 3.39

it was prepared with the same procedure as for **3.29**

1H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, $J=15.6, 11.0$ Hz, 1H), 6.04 (dd=15.1, 11.0 Hz, 1H), 5.70 (dt, $J=15.1, 7.2$ Hz, 1H), 5.47 (d, $J=15.6$ Hz, 1H), 5.38 (t, $J=7.4$ Hz, 1H), 3.99-3.3.91 (m, 3H), 2.52-2.32 (m, 2H), 2.13-1.89 (m, 4H), 1.66 (s, 3H), 1.59-1.28 (m, 3H), 1.23-1.08 (m, 6H), 0.87 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 135.7, 134.9, 131.3, 126.6, 109.6, 89.9, 81.4, 69.2, 68.2, 40.4, 36.5, 33.0, 30.8, 26.1, 25.4, 23.7, 19.7, 18.4, 13.9, -4.4.

IR(neat) cm^{-1} : 3412, 2955, 2929, 2258, 1654, 1434, 1370, 1259, 1128, 1097, 1080, 995, 910.

MS (ESI): $m/z = 391.73$ $[\text{M} + \text{H}]^+$.

HRMS (EI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{43}\text{O}_2\text{Si}$: 391.3032; found: 391.3037.

(±)-(2*E*,8*E*,10*E*,15*S*)-15-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylhexadeca-2,8,10-trien-12-ynal 3.20

It was prepared with the same procedure as for **3.30**

^1H NMR (400 MHz, CDCl_3) δ 9.39 (s, 1H), 6.51-6.45 (m, 2H), 6.05 (dd, $J = \text{dd} = 15.1, 11.0$ Hz, 1H), 5.72 (dt, $J = 15.1, 7.2$ Hz, 1H), 5.49 (d, $J = 15.6$ Hz, 1H), 3.98-3.91 (m, 1H), 2.52-2.33 (m, 4H), 2.18-1.93 (m, 2H), 1.74 (s, 3H), 1.67-1.48 (m, 3H), 1.28-1.18 (m, 6H), 0.89 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 195.4, 154.9, 140.9, 139.4, 134.8, 131.6, 110.0, 90.0, 81.3, 68.1, 40.2, 35.1, 33.1, 26.8, 26.0, 23.6, 19.5, 18.3, 9.3, -

4.5.

IR(neat) cm^{-1} : 2953, 2723, 2216, 1732, 1695, 1568, 1458, 1377, 1302, 1258, 1080, 999.

MS (ESI): $m/z = 389.62$ $[\text{M} + \text{H}]^+$.

HRMS (EI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{41}\text{O}_2\text{Si}$: 389.2876; found: 389.2879.

Rh[(2-furyl) $_3\text{P}$] $_2(\text{CO})\text{Cl}$

Tri(2-furyl)phosphine (474 mg, 2.04 mmol) and $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (200 mg, 0.51 mmol) were mixed in toluene (20 mL) at room temperature. A yellow precipitate appeared immediately. After stirring for 10 min, the mixture was cooled to 0 °C, filtered and washed with cold EtOH (10 mL $\times$ 2) and Et₂O (10 mL $\times$ 2). The pale yellow solid was obtained after drying by suction in air as a pale yellow cubic crystals;

yield: 640 mg (99%);

IR (neat) cm^{-1} : 2021, 1380, 1210, 1120, 1000, 720

mp 168–169 °C.

General Procedure for hydroboration.

Alkyne (1 mmol) in toluene (1 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1, 174 μL , 1.2 mmol) were added to a solution of Rh[(2-

furyl)₃P]₂(CO)Cl (6.34 mg, 0.02 mmol) in toluene (10 mL). The mixture was stirred under N₂ at room temperature. After quenching with H₂O, the mixture was extracted with Et₂O. The combined organic layers were dried over MgSO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography

(E)-4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane 3.7

¹H NMR (400 MHz, CDCl₃): δ = 7.48–7.26 (m, 6 H), 6.17 (d, J = 16.0 Hz, 1 H), 1.32 (s, 12 H).

¹³C NMR (100 MHz, CDCl₃): δ = 149.7, 137.7, 129.1, 128.7, 127.2, 116.5 (br), 83.6, 24.7.

yield: 369 mg, 81%.

All data are consistent with that reported in literature.⁸²

(E)-2-[4-(Methoxymethoxy)pent-1-enyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3.10

¹H NMR (400 MHz, CDCl₃): δ = 1.14 (d, J = 5.9 Hz, 3 H), 1.23 (s, 12 H), 2.43–2.24 (m, 2 H), 3.20 (s, 3 H), 3.80–3.75 (m, 1 H), 4.65–4.58 (m, 2 H), 5.47 (d, J = 16.0 Hz, 1 H), 6.62–6.54 (m, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 20.4, 25.0, 43.6, 55.4, 72.4, 83.2, 95.0, 121.5 (br), 150.4.

IR (neat) cm^{-1} : 2976, 2929, 2887, 1635, 1466, 1400, 1363, 1321, 1146, 1130, 1101, 1038, 970, 918, 849

MS (ESI): $m/z = 257$.

HRMS (EI): m/z $[M + H]^+$ calcd for $\text{C}_{13}\text{H}_{26}\text{BO}_4$: 257.1924; found: 257.1937.

yield: 299 mg, 75%.

(E)-2-(Hex-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3.8

^1H NMR (400 MHz, CDCl_3): $\delta = 0.88$ (t, $J = 7.3$ Hz, 3 H), 1.42–1.26 (m, 16 H), 2.15 (dt, $J = 6.8, 6.4$ Hz, 2 H), 5.42 (d, $J = 16.0$ Hz, 1 H), 6.3 (dt, $J = 16.0, 6.8$ Hz, 1 H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.1, 22.5, 25.0, 30.6, 35.7, 83.2, 118.8$ (br), 154.9.

yield: 1.030 g, 80%.

All data are consistent with that reported in literature.⁸³

(E)-tert-Butyldimethyl[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyloxy]silane 3.9

^1H NMR (400 MHz, CDCl_3): $\delta = 0.06$ (s, 6 H), 0.91 (s, 12 H), 1.27 (s, 9 H), 4.24 (dd, $J = 3.6, 1.4$ Hz, 2 H), 5.75 (dd, $J = 18.0, 1.8$ Hz, 1 H), 6.67 (dt, $J = 18.0, 3.6$ Hz, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = -5.1, 18.7, 25.0, 26.2, 83.4, 152.4.

yield: 280 mg, 80%.

All data are consistent with that reported in literature.⁸⁴

(E)-2-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but- 3-en-2-ol 3.11

¹H NMR (400 MHz, CDCl₃): δ = 1.29–1.17 (m, 18 H), 1.72 (br, 1 H), 5.59 (d, J = 20.0 Hz, 1 H), 6.69 (d, J = 20.0 Hz, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.8, 29.3, 72.0, 83.5, 113.7 (br), 160.0.
yield: 306 mg, 61%.

All data are consistent with that reported in literature.⁸⁵

References

1. Sadorn, K.; Saepua, S.; Boonyuen, N.; Laksanacharoen, P.; Rachtawee, P.; Prabpai, S.; Kongsaree, P.; Pittayakhajonwut, P., *Tetrahedron* **2016**, *72*, 489.
2. Chen, M.; Shao, C.-L.; Meng, H.; She, Z.-G.; Wang, C.-Y., *J. Nat. Prod.* **2014**, *77*, 2720.
3. Singh, S. B.; Zink, D. L.; Goetz, M. A.; Dombrowski, A. W.; Polishook, J. D.; Hazuda, D. J., *Tetrahedron Lett.* **1998**, *39*, 2243.
4. Jang, J.-H.; Asami, Y.; Jang, J.-P.; Kim, S.-O.; Moon, D. O.; Shin, K.-S.; Hashizume, D.; Muroi, M.; Saito, T.; Oh, H.; Kim, B. Y.; Osada, H.; Ahn, J. S., *J. Am. Chem. Soc.*

2011, *133*, 6865.

5. Begley, M. J.; Grove, J. F., *J. Chem. Soc., Perkin Trans. 1* **1985**, 861.
6. Li, J. Y.; Strobel, G.; Harper, J.; Lobkovsky, E.; Clardy, J., *Org. Lett.* **2000**, *2*, 767.
7. Lang, G.; Blunt, J. W.; Cummings, N. J.; Cole, A. L. J.; Munro, M. H. G., *J. Nat. Prod.* **2005**, *68*, 810.
8. Tsukamoto, S.; Miura, S.; Yamashita, Y.; Ohta, T., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 417.
9. Sauer, J.; Sustmann, R., *Angew. Chem. Int. Ed.* **1980**, *19*, 779.
10. Houk, K. N., *J. Am. Chem. Soc.* **1973**, *95*, 4092.
11. Black, K.; Liu, P.; Xu, L.; Doubleday, C.; Houk, K. N., *Proc. Nat. Aca. Sci.* **2012**, *109*, 12860.
12. Inukai, T.; Kojima, T., *J. Org. Chem.* **1966**, *31*, 1121.
13. Kamal, A.; Azhar, M. A.; Krishnaji, T.; Malik, M. S.; Azeeza, S., *Coord. Chem. Rev.* **2008**, *252*, 569.
14. Stocking, E. M.; Williams, R. M., *Angew. Chem. Int. Ed.* **2003**, *42*, 3078.
15. Klas, K.; Tsukamoto, S.; Sherman, D. H.; Williams, R. M., *J. Org. Chem.* **2015**, *80*, 11672.
16. Campbell, C. D.; Vederas, J. C., *Biopolymers* **2010**, *93*, 755.
17. Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D. J.; Van den Heever, J. P.; Hutchinson, C. R.; Vederas, J. C., *J. Am. Chem. Soc.* **2000**, *122*, 11519.
18. Chen, M. S.; White, M. C., *Science* **2007**, *318*, 783.
19. Murray, R. W.; Jeyaraman, R.; Mohan, L., *J. Am. Chem. Soc.* **1986**, *108*, 2470.

20. Bates, R. W.; Maiti, T. B., *Synth. Commun.* **2003**, *33*, 633.
21. Hanessian, S. G., Bradley M., *Design and Strategy in Organic Synthesis From the Chiron Approach to Catalysis*. WileyVCH, Weinheim: 2013.
22. Blaser, H. U., *Chem. Rev.* **1992**, *92*, 935.
23. (a) Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J., *Chem. Rev.* **2017**, 11753; (b) Urabe, D.; Asaba, T.; Inoue, M., *Chem. Rev.* **2015**, *115*, 9207.
24. Lenardão, E. J.; Botteselle, G. V.; de Azambuja, F.; Perin, G.; Jacob, R. G., *Tetrahedron* **2007**, *63*, 6671.
25. Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B., *J. Am. Chem. Soc.* **1986**, *108*, 8274.
26. Imakura, Y.; Yokoi, T.; Yamagishi, T.; Koyama, J.; Hu, H.; McPhail, D. R.; McPhail, A. T.; Lee, K.-H., *J. Chem. Soc., Chem. Commun.* **1988**, 372.
27. Nicolaou, K. C.; Smith, A. L.; Yue, E. W., *Proc. Nat. Aca. Sci.* **1993**, *90*, 5881.
28. Schreiber, S. L.; Kiessling, L. L., *J. Am. Chem. Soc.* **1988**, *110*, 631.
29. Ratovelomanana, V.; Linstrumelle, G., *Tetrahedron Lett.* **1981**, *22*, 315.
30. (a) Craig, D., *Chem. Soc. Rev.* **1987**, *16*, 187; (b) Takao, K.-i.; Munakata, R.; Tadano, K.-i., *Chem. Rev.* **2005**, *105*, 4779; (c) Heravi, M. M.; Vavsari, V. F., *RSC Adv.* **2015**, *5*, 50890.
31. Fallis, A. G., *Acc. Chem. Res.* **1999**, *32*, 464.
32. Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J., *J. Org. Chem.* **1984**, *49*, 3503.
33. Shing, T. K. M.; Yang, J., *J. Org. Chem.* **1995**, *60*, 5785.
34. Sauer, J., *Angew. Chem. Int. Ed.* **1967**, *6*, 16.

35. Roush, W. R.; Hall, S. E., *J. Am. Chem. Soc.* **1981**, *103*, 5200.
36. Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodriguez, F., *Org. Lett.* **2000**, *2*, 3611.
37. Yuki, K.; Shindo, M.; Shishido, K., *Tetrahedron Lett.* **2001**, *42*, 2517.
38. Huang, J.; Fang, L.; Long, R.; Shi, L.-L.; Shen, H.-J.; Li, C.-c.; Yang, Z., *Org. Lett.* **2013**, *15*, 4018.
39. Deng, J.; Zhu, B.; Lu, Z.; Yu, H.; Li, A., *J. Am. Chem. Soc.* **2012**, *134*, 920.
40. Yin, J.; Wang, C.; Kong, L.; Cai, S.; Gao, S., *Angew. Chem. Int. Ed.* **2012**, *51*, 7786.
41. (a) Xu, J.; Caro-Diaz, E. J. E.; Trzoss, L.; Theodorakis, E. A., *J. Am. Chem. Soc.* **2012**, *134*, 5072; (b) Xu, J.; Caro-Diaz, E. J. E.; Lacoske, M. H.; Hung, C.-I.; Jamora, C.; Theodorakis, E. A., *Chem. Sci.* **2012**, *3*, 3378.
42. Brown, H. C.; Rao, B. C. S., *J. Am. Chem. Soc.* **1956**, *78*, 5694.
43. (a) Brown, H.; Rao, B. C., *J. Org. Chem.* **1957**, *22*, 1137; (b) Batey, R. A.; MacKay, D. B.; Santhakumar, V., *J. Am. Chem. Soc.* **1999**, *121*, 5075.
44. Beletskaya, I.; Pelter, A., *Tetrahedron* **1997**, *53*, 4957.
45. Miyaoura, N.; Suzuki, A., *Chem. Rev.* **1995**, *95*, 2457.
46. Barbeyron, R.; Benedetti, E.; Cossy, J.; Vasseur, J.-J.; Arseniyadis, S.; Smietana, M., *Tetrahedron* **2014**, *70*, 8431.
47. Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2013**, *135*, 6026.
48. Itami, K.; Tonogaki, K.; Ohashi, Y.; Yoshida, J.-i., *Org. Lett.* **2004**, *6*, 4093.
49. Brown, H. C.; Gupta, S. K., *J. Am. Chem. Soc.* **1972**, *94*, 4370.
50. (a) Tucker, C. E.; Davidson, J.; Knochel, P., *J. Org. Chem.* **1992**, *57*, 3482; (b)

- Woods, W. G.; Strong, P. L., *J. Am. Chem. Soc.* **1966**, *88*, 4667.
51. Pereira, S.; Srebnik, M., *Tetrahedron Lett.* **1996**, *37*, 3283.
52. Habrant, D.; Rauhala, V.; Koskinen, A. M. P., *Chem. Soc. Rev.* **2010**, *39*, 2007.
53. Corey, E. J.; Fuchs, P. L., *Tetrahedron Lett.* **1972**, *13*, 3769.
54. Ohira, S., *Synth. Commun.* **1989**, *19*, 561.
55. Seyferth, D.; Marmor, R. S., *Tetrahedron Lett.* **1970**, *11*, 2493.
56. Pappo, R.; Allen, J. D. S.; Lemieux, R. U.; Johnson, W. S., *J. Org. Chem.* **1956**, *21*, 478.
57. Pereira, S.; Srebnik, M., *Organometallics* **1995**, *14*, 3127.
58. Chalk, A. J.; Harrod, J. F., *J. Am. Chem. Soc.* **1965**, *87*, 16.
59. Farina, V.; Krishnan, B., *J. Am. Chem. Soc.* **1991**, *113*, 9585.
60. The CCDC number is 1501278.
61. Andersen, N. G.; Keay, B. A., *Chem. Rev.* **2001**, *101*, 997.
62. Alami, M.; Crousse, B.; Linstrumelle, G., *Tetrahedron Lett.* **1994**, *35*, 3543.
63. Gao, Y.; Sharpless, K. B., *J. Am. Chem. Soc.* **1988**, *110*, 7538.
64. Bates, R. W.; Lu, Y., *Org. Lett.* **2010**, *12*, 3938.
65. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2002**, *124*, 1307.
66. Alami, M.; Peyrat, J.-F.; Brion, J.-D., *Synthesis* **2000**, *2000*, 1499.
67. Crousse, B.; Alami, M.; Linstrumelle, G., *Tetrahedron Lett.* **1997**, *38*, 5297.
68. Alami, M.; Peyrat, J.-F.; Brion, J.-D., *Tetrahedron Lett.* **2002**, *43*, 3007.
69. Martin, R.; Buchwald, S. L., *Acc. Chem. Res.* **2008**, *41*, 1461.

70. Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D., *J. Am. Chem. Soc.* **2008**, *130*, 466.
71. Ivanov, A. S., *Chem. Soc. Rev.* **2008**, *37*, 789.
72. The calculation was done by Csokas, D. in this laboratory.
73. Kudesia, P. V., *Bull. Soc. Chim. Belg* **1972**, *81*, 623.
74. Bates, R. W.; Pinsa, A.; Kan, X., *Tetrahedron* **2010**, *66*, 6340.
75. (a) Cardillo, G.; Orena, M., *Tetrahedron* **1990**, *46*, 3321; (b) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N., *Tetrahedron* **2004**, *60*, 5273.
76. Holmes, C. P.; Bartlett, P. A., *J. Org. Chem.* **1989**, *54*, 98.
77. Paulmier, C., *Selenium Reagents and Intermediates in Organic Synthesis*. Pergamon Press: Oxford, 1986.
78. Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F., *J. Am. Chem. Soc.* **1979**, *101*, 3884.
79. Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A., *Tetrahedron* **1985**, *41*, 4835.
80. Liu, C.; Zeng, Z.; Chen, R.; Jiang, X.; Wang, Y.; Zhang, Y., *Org. Lett.* **2016**, *18*, 624.
81. Nicolaou, K. C.; Shah, A. A.; Korman, H.; Khan, T.; Shi, L.; Worawalai, W.; Theodorakis, E. A., *Angew. Chem. Int. Ed.* **2015**, *54*, 9203.
82. Ojha, D. P.; Prabhu, K. R., *Org. Lett.* **2016**, *18*, 432.
83. Yoo, K. S.; Yoon, C. H.; Jung, K. W., *J. Am. Chem. Soc.* **2006**, *128*, 16384.
84. Tanaka, K.; Ohashi, W.; Okada, H.; Chujo, Y., *Tetrahedron Lett.* **2014**, *55*, 1635.
85. Morrill, C.; Grubbs, R. H., *J. Org. Chem.* **2003**, *68*, 6031.

Summary

In summary, the total synthesis of curvulone B and allahabadolactone A were achieved in a short and efficient route. A new Rh catalyzed was prepared and applied in the hydroboration of terminal alkynes. A diastereoselective intramolecular Tsuji-Trost cyclisation was built towards the synthesis of natural products.

In the future work, we will apply this Tsuji-Trost methodology in the total synthesis of natural products and study on the selectivity of the 8-membered ring product which was found in this reaction.