CONSTRUCTION OF 2,6-TRANS PYRANS VIA PRINS CYCLIZATION AND ITS APPLICATION TOWARDS THE TOTAL SYNTHESIS OF METHYL SARCOPHYTOATE

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES
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CONSTRUCTION OF 2,6-TRANS PYRANS VIA PRINS CYCLIZATION AND ITS APPLICATION TOWARDS THE TOTAL SYNTHESIS OF METHYL SARCOPHYTOATE

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<table>
<thead>
<tr>
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<td>δ</td>
<td>chemical shift</td>
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<tr>
<td>°C</td>
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<td>acetyl</td>
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<td>aq</td>
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**SUMMARY**

Prins cyclization reaction involving a homoallylic alcohol with aldehyde is one of the most efficient methods to synthesize tetrahydropyran rings. However, due to the strong 1,3-diaxial interaction, the 2,6-cis tetrahydropyran moiety was formed preferably in most cases. The emphasis of this thesis is focused on the evolution of a convenient catalytic Prins cyclization for the construction of 2,6-trans pyranyl motifs and its application towards the total synthesis of natural product.

In the first introduction chapter, a summary of established methodologies in the formation of 2,6-trans pyranyl ring system was outlined, ranging from venerable oxo-Michael addition to recently emerging transition metal-catalyzed cyclization. Especially, the strategy of silyl-terminated cyclization onto oxocarbenium ions was thoroughly and intensively discussed. With the increasing demand for more convergent and versatile method, we developed an indium(III) catalyzed Prins cyclization method for synthesizing 2,6-trans dihydropyrans using α-alkoxycarbonyl allenic alcohols and aldehydes. It was believed that the utility of combining allenic alcohol and alkoxy carbonyl group led to the highly 2,6-trans diastereoselectivity on a basis of electronic and steric effect, detailed in Chapter 2.

![Chemical Reaction](image)

The final chapter of this thesis documents our efforts towards the synthesis of methyl sarcophytoate involving the Diels-Alder precursors, the diene unit and methyl sarcoate, which was displayed in two parts respectively.
In part A, the HWE reaction leading to the RCM precursor of methyl sarcoate came up with failure, may due to the deleterious reactivity of ketone, which bears the potential culpable functionality, $\alpha,\beta$-unsaturated ester. Then the strategy was changed to introduce the isopropyl moiety using the asymmetric Michael addition prior to the HWE reaction.

In part B, the skeleton structure of the diene unit 3 was successfully constructed using Prins cyclization of allenic alcohol, Cu(I)-promoted coupling reaction of triflate with Grignard reagent, HWE olefination, indium-mediated Barbier-type allylation in aqueous media as the key steps.
In our continuous efforts to explore new methodologies, we described a novel carbon-carbon bond-forming reaction of aliphatic terminal alkynes with aldehydes in the presence of In(OTf)$_3$ and trimethylsilyl halide for the synthesis of 1,3-dihalo-1-ene in the Appendix.

\[
R^1\text{C} = \text{C} + R^2\text{CHO} \xrightarrow{\text{In(OTf)$_3$, TMSX}} \xrightarrow{4\text{Å MS}, 0\text{oC, CH}_2\text{Cl}_2, 4\text{ h}} X\text{-C} = \text{C} \quad X = \text{Br, Cl}
\]

R$^1$, R$^2$ = aliphatic
CHAPTER 1

Strategies for the Construction of
2,6-trans Pyranyl Rings
1.1 Introduction

Functionalized pyranyl rings are featured prominently in a wide variety of biologically active natural products and functional molecules. Therefore, much attention has been focused on the development of new synthetic methods aimed at the efficient construction of pyrans with a range of oxidation levels, some of which were incorporated in the total synthesis of natural products. In particular, trans 2,6-disubstituted pyranyl unit was commonly embedded in a large number of natural products, examples included Laulimalide, Aspergillide A, Prugosene A, Sorangicin A, Swinhohide A and their analogues. Those complex metabolites displayed impressive bioactivity, including antifungal, antibacterial activity and cytotoxicity.

Figure 1.1 Examples of natural products containing 2,6-trans pyranyl moiety

In spite of general methods to access pyranyl moiety available, no specific review about 2,6-trans pyrans was reported so far. In this chapter, we have confined our efforts to summarize the chemists’ contributions for the construction of only 2,6-trans pyrans and their applications in natural products syntheses.

1.2 Cyclization onto Oxocarbenium Ions

Oxocarbenium ions with a carboxyl substituent on the cationic carbon atom have been implicated as versatile and highly reactive electrophilic intermediates in organic synthesis. Especially, the vinylsilane-terminated cyclizations of oxocarbenium ions for the efficient construction of oxygenated heterocycles have been widely studied in the past decades. Speckamp utilized this key intermediate to build the 2,6-trans dihydropyrans (DHP) through intramolecular cyclization of (E)-vinylsilane. The observed 2,6-trans diastereoselectivity can be reasonably explained by more stable cyclization conformation featuring an assisting silyl function in axial orientation, derived from oxonia-Cope rearrangement followed by a chair-chair interconversion (Scheme 1.1).

---

In 2004, Yu also discovered a similar method for synthesis of 2,6-trans pyrans from the α-acetoxy acetal catalyzed by (iPrO)$_2$Ti(NTf)$_2$. The chemical transformation involved the oxa-Cope rearrangement and subsequent intramolecular allylic transfer reaction into the oxocarbenium ion (Scheme 1.2).

Actually, this steric compression strategy was employed in the synthetic study towards Okadaic acid. When anti-silyl ether was subjected to the intramolecular Silyl-Modified Sakurai condensation, the 2,6-trans DHP was cyclized from the favourable transition state, whereas, the disfavoured one suffered from severe 1,3-diaxal interactions between the TMS group and the ethyl moiety (Scheme 1.3).

---

With the further utilization of vinylsilane-terminated cyclizations, Panek developed an efficient method to synthesize stereochemically trans-2,6-DHPs in high selectivity via [4+2]-annulations of anti-(E)-β-hydroxycrotylsilanes and aldehydes.\textsuperscript{12} A pseudo-axial orientation for the silyl group has been proposed for effective σ-π overlap in the cyclization step. Considered from both steric and electronic effects, the major trans-trans diastereomer was rationalized through an anti-$S_E'$ addition in the boat-like transition state, which positioned the bulky silyl group and the neighbouring ester substituent in anti orientation to each other. In addition, the stabilization of oxycarbenium ions by conjugated aldehydes could improve the diastereoselectivity through an electron-delocalization resonance effect. This expedient method to access complementary DHPs was elegantly used for the synthesis of many natural products, including leucascandrolide A,\textsuperscript{13} callipeltoside A,\textsuperscript{14} kerdomycin,\textsuperscript{15} herboxidiene/GEX 1A,\textsuperscript{16} neopeltolide,\textsuperscript{17} and brevisamide.\textsuperscript{18}

In the course of the total synthesis of apicularen A, Panek observed that the functional group X directly affected the sense and magnitude of diastereoselectivity. In the case of X = OMe, annulations of crotylsilane resulted in the formation of 2,6-trans DHP as the major isomer. The process can be interpreted through a twist boat-like transition state, in which the electrostatic attraction between the nonbonding lone pair of electrons of methyl ether and the positively charged oxocarbenium, resided on the carbon atom, stabilized the conformer and accelerated the reaction (Scheme 1.5).

---

Scheme 1.4

Scheme 1.5

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Later, Panek employed (Z)-crotylsilanes to construct complementary DHPs for the extension of this area. The annulations of syn-(Z)-crotylsilanes and aldehyde afforded 2,6-trans DHPs, which has been used for the total synthesis of bistramide A (Scheme 1.6).²⁰

![Scheme 1.6](image)

1.3 Oxy-Michael Type Addition

Oxy-Michael addition, based on the cyclization of the alcohol onto the α,β-unsaturated carbonyl compounds, represents a powerful strategy for the synthesis of pyrans. The rationale for this pathway is through regioselective 6-exo-ring closure from the common cyclization precursor δ-hydroxy alkene. It has been proven that the diastereoselectivity of the cyclization process is strongly influenced by the experimental conditions, protecting groups on the α-hydroxyl function and alkene geometry.²¹

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For instance, in 1993, Kibayashi and Machinaga exploited the intramolecular Michael cyclization of (E)-acrylate as a key step in the synthesis of (+)-decarestrictine L possessing a 2,6-trans-THP moiety (Scheme 1.7).\textsuperscript{22} The undesired cis adduct was not observed due to the unfavourable transition states A and B destabilized by 1,3-diaxial interaction and 1,3-allylic strain, respectively. Subsequently, the energetically most favourable conformer D, with both sterically larger substituents in axial orientation, provided the 2,6-trans THP ring.

![Scheme 1.7](image_url)

**Scheme 1.7**

Schneider disclosed a base-catalyzed oxa-conjugated addition of enantiopure 7-hydroxy-2-enimides to give rise to predominantly trans-THPs.\textsuperscript{23} It was indicated that the stereogenic centers in the chain controlled stereoselectivity of the cyclization while the chiral auxiliary oxazolidinone had only a supportive effect. Surprisingly, reversal of the stereochemistry in the cyclization was observed by using hydroxyenoate instead of the enimide (Scheme 1.8). PM3 calculation revealed that stereoelectronic effect arose from the molecular orbital interaction between the lone pair of the oxygen and the


anti bonding π* orbital of the conjugate double bond, accounting for the resultant kinetic control for the imides and thermodynamic control for the esters.

Scheme 1.8

(E)-Hydroxyacrylate was found to be converted into 2,6-trans-THP via an oxy-Michael addition in excellent diastereoselectivity (Scheme 1.9).

Another appealing example of oxy-Michael addition is the formation of pyranyl ring in the formal total synthesis of (−)-apicularen A. As shown in Scheme 1.10, interestingly, both epimers of α,β-unsaturated ketone in the presence of Amberlyst-15 afforded the same thermodynamically controlled product via transannular conjugated addition.

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1.4 Nucleophilic Addition onto the Cyclic Oxonium

Lewis acid-catalyzed addition to anomic centres of carbohydrates proved to involve the generation of oxo-carbenium ions, which may be trapped with a variety of activated nucleophiles in the axial side due to the anomic effect from the ring oxygen.\(^{26}\) This general expeditious route for the diastereoselective installation on cyclic oxoniums mainly invokes three typical reactions, Mukaiyama-aldol reaction, Ferrier rearrangement\(^ {27}\) and Hosomi-Sakurai reaction.\(^ {28}\) Owing to the ease of functionalization depending on the attacking nucleophiles, this strategy was frequently applied in the synthesis of natural products.

Swinholide A, characterized by four 2,6-trans pyran ring systems (shown in Figure 1.1), inspired numerous synthetic efforts in 1990s.\(^ {29}\) Peterson

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was the first to complete the total synthesis of this complex molecule.\(^{30}\) In his strategy, a variant of Ferrier rearrangement, subsequently allowed the stereocontrolled introduction of aldehydic side-chain with silyl enol ether, afforded 2,6-trans DHP in high diastereoselectivity (d.r. > 97:3). Meanwhile, treatment of cyclic acetal with allylttrimethylsilane and catalytic TMSOTf led to the rapid and exclusive formation of 2,6-trans-THP via kinetically controlled axial attack on the intermediate oxocarbenium ion (Scheme 1.11).

Scheme 1.11

The 2,6-trans THP core embedded in leucascandrolide A was assembled by a diastereofacial condensation of diacetate with silyl enol ether via a Mukaiyama-aldol process (Scheme 1.12).\(^{31}\) An (E)-unsaturated ketone fragment was directly installed promoted by ZnCl\(_2\) in high yield and excellent diastereoselectivity.

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With the same strategy, Brabander introduced an axial nitrile into the pyranyl acetate with trimethylsilyl cyanide mediated by ZnI$_2$ in the synthesis of psymphederin (Scheme 1.13).$^{32}$

In the formal total synthesis of (+)-zincophorin, Hsung developed a urea directed Stork-Crabtree hydrogenation of DHP derived from a hetero [4+2] cycloaddition of a chiral allenamide to form the DHP ring, followed by addition of (E)-crotylsilane from the anomerically favourable axial trajectory to the likely oxocarbenium intermediate generated in situ to give the crotylation products (Scheme 1.14).$^{33}$

---


Recently, Taylor addressed three-step sequence to 2,6-trans DHPs: electrophile-induced ether transfer, cyclization and functionalization, which was successfully implemented for the asymmetric formal synthesis of swinholide A (Scheme 1.15).\textsuperscript{34} It was envisaged that the oxocarbenium ion intermediate was generated via the ionization of glycal, followed by addition of nucleophile to produce the Ferrier rearrangement product.

Apart from these parallel methods to prepare 2,6-trans pyranyl moiety, a tandem allylation/cyanation of δ-hydroxy-α,β-unsaturated aldehydes promoted by InBr\textsubscript{3} was demonstrated by Yadav (Scheme 1.16).\textsuperscript{35} The reaction proceeded to give 2,6-trans DHP as single diastereoisomer, through activation of aldehyde by InBr\textsubscript{3} and subsequently formation of an oxonium intermediate in which


stereoelectronic and/or steric factors dictated the direction of the incoming nucleophile.

![Scheme 1.16](image)

The attacking groups are not limited to soft nucleophiles, hydride also can be used to trap the oxonium ion intermediate.\(^\text{36}\) DIBAL-H reduction of the bicycle ketal afforded the 2,6-trans DHP with retention of configuration.\(^\text{37}\) The stereoselectivity was attributed to coordination of aluminium reagent to O3-ketal oxygen, as a result of the formation of oxonium ion, subsequently S\(_\text{N}1\) attacked by the hydride source from the syn face to the cleaved C-O bond. The power of this methodology for rapid assemblage of 2,6-trans pyranyl system was elegantly proved in the total synthesis of (+)-leucascandrolide A macrolactone (Scheme 1.17).\(^\text{38}\)

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1.5 Ring Closing Metathesis

Ring closing metathesis promoted by the Grubbs catalyst is identified as a useful tool to gain access to 2,6-trans pyranyl systems. The tandem sequence of glycolate Claisen rearrangement/ring closing metathesis provided 2,6-trans DHP-2-carboxylate. Mechanistically, the relative stereochemistry seemed to arise from chelation control over enolate geometry and π-facial preference dictated by the chair-like transition state (Scheme 1.18).

Moreover, a direct route to 2,6-trans pyrans based on stereospecific rhodium-catalyzed allylic esterification with secondary alkenyl alcohols in

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conjunction with ring closing metathesis has been disclosed by Evans (Scheme 1.19).\textsuperscript{41} In this case, the copper(I) alkoxide with trimethylphosphite presumably promoted the rapid nucleophilic attack of the rhodium–allyl intermediate prior to the $\pi$-$\sigma$-$\pi$ isomerisation.

![Scheme 1.19](image)

### 1.6 Mukaiyama-Michael Reaction

More recently our group discovered a simple InCl$_3$-cataylzed Mukaiyama-Michael reaction between silyl enol ether and $\alpha,\beta$-unsaturated dihydropyranone under neat conditions.\textsuperscript{42} Tetrahydropyranones were produced as the sole 2,6-\textit{trans}-adducts in most cases. In view of the stability of the transition state, the diastereoselectivity was elucidated by the formation of preferential chair conformation (Scheme 1.20).

![Scheme 1.20](image)


1.7 Transition Metal-catalyzed Cyclization

In addition to the venerable methodologies mentioned above, transition metal was introduced into this field recently, based on the principle of coordination with olefins. Transition metal-catalyzed intramolecular cyclization provides a straightforward approach to pyranyl ring system.

Palladium(II) catalyst exhibits an electrophilic character, resulting in the formation of π-complex with olefin, which can be easily trapped by nucleophiles. The 2,6-trans THP from unactivated olefin were generated by PdCl$_2$(CH$_3$CN)$_2$-catalyzed intramolecular cyclization via a $\text{syn-S_N2'}$ type process. According to the observed stereochemical outcome, in the case of (E)-diol, the single isomer was formed from the favourable conformation without severe 1,3-allylic strain. However, under the same condition, (Z)-diol gave a 1:1 mixture of diastereoisomers because either 1,3-diaxial repulsive interactions or 1,3-allylic strain existed in two competing conformations (Scheme 1.21).

Scheme 1.21

This methodology has been applied in the total synthesis of natural product. The diol was allowed for Pd(II)-catalyzed ring formation in a 6-endo-trig fashion to give the 2,6-trans DHP core required for the elaboration of (-)-laulimalide (Scheme 1.22).\textsuperscript{44} It was predicted that the olefinic carbon atom was attacked by the hydroxyl group from the Re-face.

![Scheme 1.22](image)

Furthermore, Trost developed a tandem coupling cyclization of silyl-substituted alkyne and terminal alkene tethering a leaving group.\textsuperscript{45} In this reaction system, the palladium catalyst played the dual roles: to generate π-allyl species; to promote the ionization of newly formed allylic group. As presented in Scheme 1.23, the configuration of the THP was stereocontrolled by the chiral diphosphine ligand.

![Scheme 1.23](image)

The mercury(II)-mediated electrophilic ring-opening reactions of cyclopropylcarbinol derivatives also provides an efficient strategy for the


synthesis of 2,6-trans pyranyl rings. In this substrate-controlled process, the diastereoselectivity relied on the anchimeric assisted oxymercuration by the internal hydroxyl group and nucleophilic backside attack of the δ-OH, proceeding with inversion of configuration at the stereocenter. Upon hydrolysis and subsequent reductive demercuration, the functionalized pyrans were obtained in high region- and diastereo- selectivity. The synthetic utility of this mercury-mediated cyclization was investigated in the total synthesis of zincophorin (Scheme 1.24).  

Scheme 1.24

1.8 Summary

With the discovery of structurally novel natural products containing 2,6-trans pyranyl ring systems, a diversity array of strategies have already been established and successfully applied in the total synthesis of natural products. Besides the methodologies introduced above, ranging from venerable oxo-Michael addition to recently emerging transition metal-catalyzed cyclization, some other handful of efficient approaches to 2,6-trans pyrans was not included.

It is noteworthy that, as a typical example of cyclization onto oxocarbenium ion, Prins cyclization is one of most efficient multi-component reactions to form pyrans. Moreover, in combination with other reactions, a cascade reaction involving Pinacol rearrangement, Mukaiyama-alold, Ritter reaction, Friedel-Crafts, have also been developed. However, there are limited reports via silyl-terminated Prins reactions to directly synthesize 2,6-trans pyrans. Thus, it still remains an increasing demand for more convergent and versatile method to construct 2,6-trans pyranyl cores.

CHAPTER 2

Diastereoselective Synthesis of 2,6-trans dihydropyrans via Prins Cyclization
2.1 Introduction

THPs are ubiquitous structural features of many natural products. Indeed, several methods are available to synthesize THP rings. Among the many popular methods available, the Prins cyclization involving homoallylic alcohols with aldehydes is one of the most efficient methods. However, the 2,6-cis THP moiety was preferably formed in most cases, which could be attributed to the strong 1,3-diaxial interaction. The sp² hybridized carbon at C4 was trapped from favouring equatorial position due to delocalization.

Scheme 2.1 Formation of the 2,6-cis THP ring

Convenient methodologies for high diastereoselective synthesis of 2,6-trans pyrans have not established yet via Prins cyclization. The origin of Prins cyclization for construction of 2,6-trans pyranyl motifs derived from our previous work. Our group demonstrated that α-alkoxy tethered homoallylic alcohol can undergo Prins cyclization with various aldehydes catalyzed by indium(III) triflate to afford the 2,6-trans THPs, albeit with low selectivity (cis/trans = 50/50). The results were explained by the competition between the

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electronic and steric effect. As shown in Scheme 2.2, the carbonyl group adopting the β-position established the oxo-carbenium ion in the chair-like transition state, hereby forcing the carbonyl group to adopt the axial orientation. Meanwhile, the severe 1,3-diaxial interaction existed to compete two isomeric configurations.

![Scheme 2.2](image)

**Scheme 2.2** Electronic inductive effects on oxonium cations

From our previous work, based on the concept that the lone pairs of the alkoxy functionalities could successfully stabilized the oxo-carbenium ion, we developed a highly efficient Prins cyclization for synthesizing 2,6-trans DHPs using allenic alcohols and aldehydes promoted by an indium catalyst.

### 2.1.1 Reported metal-mediated reactions of α-allenic alcohol with aldehyde

α-Allenic alcohols have been proven to be versatile and useful synthons in organic synthesis due to its unique reactivity and the ease of conversion into compounds with other functional groups, like 1,3-diene, 57 2,5-dihydrofurans, 58 α,β-unsaturated enones 59 and amino alcohol. 60 Several methods have been

developed for synthesis of α-allenic alcohol from aldehyde via allenylation reactions with propargyl halide, \(^{61}\) propargyltin \(^{62}\) or propargylsilane compounds. \(^{63}\)

Aldol-type addition of allenyl carbinols with aldehydes mediated by oxo-vanadium complex was reported by Trost. \(^{64}\) The transformation may undergo intramolecular 1,3-oxygen transposition to generate enolate and subsequent aldol-type condensation, as illustrated in Scheme 2.3. Yo and co-workers also disclosed that this interesting chemical transformation could be promoted by InCl\(_3\). \(^{65}\)

![Scheme 2.3 Aldol-type addition of allenyl carbinols with aldehydes](image)

Similarly, with allyl transfer reaction mediated by 2-oxonia [3,3]-sigmatropic rearrangement, silicon-assisted propargyl transfer to carbonyl compounds was reported by our group. \(^{66}\) In the presence of aldehyde and Lewis acid catalyst, the rearrangement from α-allenic alcohol to homopropargylic alcohol could be accomplished (Scheme 2.4).


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DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

Scheme 2.4 Propargyl transfer to carbonyl compounds

2.1.2 Aim of the study and synthetic strategy

During the development of diversity-oriented methods to construct functionalised THP rings in the context of the synthesis of natural products, we became interested in the diastereoselective synthesis of 2,6-trans pyranyl motifs via Prins cyclization. Since the year 2002, our research group have been paying our efforts for developing the efficient construction of THP rings towards natural product synthesis. As one of the most convergent and efficient reactions for the formation of THP rings, Prins cyclization has been improved by several groups for its drawback on epimerization of the starting homoallylic alcohol. A symmetrical 2-oxonia Cope rearrangement was proposed to account for the racemisation of the products (Scheme 2.5).

Scheme 2.5 Epimerization Process

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This problem was overcome with addition of trimethylsilyl halides at low temperature in the presence of mild Lewis acid for trapping the carbocation to suppress the epimerization.\(^{71}\) The strategy was successfully applied in formal synthesis of (+)-SCH 351448 with 65% yield and excellent 2,6-cis-selectivity in the key step (Scheme 2.6).\(^{72}\)

\[\text{Scheme 2.6 Formal synthesis of (+)-SCH 351448 through InBr}_3\text{-mediated Prins cyclization}\]

Multicomponent Prins cyclizations involving similar kinds of substrates and aldehydes as well as Lewis acid have drawn a considerable attention since they constitute a powerful tool to construct six-membered heterocycles.\(^{73}\) Besides for the traditional homoallylic alcohol, other substrates were exploited in the Prins cyclization, such as homopropargyl alcohols,\(^{74}\) sulphur- and nitrogen-containing analogues.\(^{75}\) Surprisingly, to our knowledge, no example of Prins cyclization involving allenic alcohol has been reported.


With this in mind, we envisioned that removal of the 1,3-diaxial interaction by using $\alpha$-allenic alcohols instead of the homoallylic alcohols may lead to higher 2,6-trans selectivity (Scheme 2.7). On the other hand, the ester group would stabilize the oxocarbenium ion to suppress the allylic transfer process. Herein we described a highly efficient Prins cyclization method for synthesizing 2,6-trans DHPs using $\alpha$-allenic alcohols and aldehydes promoted by an indium salt catalyst.

Scheme 2.7 Proposed cyclization pathway using allenic alcohol through a distorted chair transition state

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2.2 Prins Cyclization of Allenic Alcohols with Aldehydes

In our first approach, the substrate of ester substituted α-allenic alcohol has been successfully prepared in two steps from the commercial available di-n-butyl tartrate (Scheme 2.8). Oxidation of di-n-butyl tartrate with periodic acid afforded n-butyl glyoxylate. Under the conditions established by our group,\(^{76}\) indium-mediated allenylation of n-butyl glyoxylate with 1-bromo-2-butyne in aqueous media produced the desired product 1 in good yield and excellent regioselectivity.

Scheme 2.8 Preparation of the α-allenic alcohol 1

Initial efforts were focused on the reactions of α-methylalllenic alcohol (Table 2.1, substrate 1) bearing an n-butyl ester group with a wide range of aldehydes in the presence of In(OTf)\(_3\) (0.1 equiv) and TMSBr (1.2 equiv) in CH\(_2\)Cl\(_2\) (0.1 M) at 0 °C. Previously, possible side reactions have been described between α-allenic alcohols and aldehydes promoted by Lewis acid. Therefore, to prevent from generating possible aldol-type adducts described above,\(^{64,65}\) the reactions were performed at low temperature with dropwise addition of diluted allenic alcohols using syringe pump over a period of 1 h. The results are summarized in Table 2.1.

Table 2.1 Cyclization of methylallenic alcohol 1 with aldehydes$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>time (h)</th>
<th>products (yield, %)$^c$</th>
<th>$dr$ (trans: cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2</td>
<td>2a (84) 2a’ (12)</td>
<td>87:13$^d$</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2</td>
<td>2b (75) 2b’ (6)</td>
<td>93:7$^d$</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1.5</td>
<td>2alc’ (84)</td>
<td>92:8$^d$</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1.5</td>
<td>2d (73) 2d’ (8)</td>
<td>90:10$^d$</td>
</tr>
<tr>
<td>5</td>
<td>phenyl</td>
<td>2</td>
<td>2e (70) 2e’ (13)</td>
<td>84:16$^d$</td>
</tr>
<tr>
<td>6</td>
<td>phenyl</td>
<td>3</td>
<td>2f (75) 2f’ (8)</td>
<td>89:11$^d$</td>
</tr>
</tbody>
</table>

$^a$ Reactions were performed with 1 (0.3 mmol, dissolved in 1 mL CH$_2$Cl$_2$, syringe pump addition), aldehyde (0.36 mmol), TMSBr (0.36 mmol) and In(OTf)$_3$ (0.03 mmol) in CH$_2$Cl$_2$ (2 mL) at 0 °C. $^b$ Stereochemistry assigned by NOESY experiments. $^c$ Isolated yield based on allenic alcohol. $^d$ Determined by isolated yields of respective isomers. $^e$ Determined by $^1$H NMR.

In all cases, the expected 4-halo-2,3,6-tetrasubstituted DHPs were obtained in good yields (Table 2.1, entries 1 to 6). Expectedly excellent diastereoselectivity was observed giving the 2,6-trans isomer as major one. The reactions with primary and sterically hindered aldehydes proceeded smoothly and the rate of the reaction was not affected by the bulkiness of the aldehydes (Table 2.1, entries 1 to 4). Furthermore, even the less reactive benzaldehyde$^{77}$ could afford the desired product which implied that the reaction was insensitive to the electronic influences of the substrates (Table 2.1, entry 6). The findings also showed that the use of aliphatic or aromatic aldehydes had no apparent effect on the diastereoselectivity.

It is worthy to note that the major isomers of tetrasubstituted DHPs were found to have the 2,6-trans relative stereochemistries as assigned by NOESY experiments (Figure 2.1).

**Figure 2.1** NOEs observed in NOSEY spectra of 2f and 2f’

The relative stereochemistry of one of the cyclization products (2f) was further confirmed by a single crystal X-ray structure as depicted in Figure 2.2. The figure showed that the relative stereochemistry of 2, 6 position protons were in the trans-configuration.

**Figure 2.2** Crystal structure of compound 2f

With these intriguing results, we further explored the reactions using bulky silicon-substituted allenic alcohol (Table 2.2, substrate 3) under the same conditions as stated above. To our delight, the Prins cyclization proceeded smoothly to afford the desired products with excellent diastereoselectivities (up to > 99:1). In addition, both aliphatic and aromatic aldehydes gave the desired DHPs in good yields and excellent diastereoselectivity (Table 2.2, entries 1 to 8).
**Table 2.2** Prins cyclization of trimethylsilyllallenic alcohol with aldehydes$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>time (h)</th>
<th>yield (%)$^c$</th>
<th>$dr$</th>
<th>trans/cis$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>4a</td>
<td>1</td>
<td>90</td>
<td></td>
<td>96:4</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>4b</td>
<td>1.5</td>
<td>84</td>
<td></td>
<td>96:4</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>4c</td>
<td>1</td>
<td>86</td>
<td></td>
<td>94:6</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>4d</td>
<td>1.5</td>
<td>82</td>
<td></td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>4e</td>
<td>1.5</td>
<td>80</td>
<td></td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>4f</td>
<td>2</td>
<td>83</td>
<td></td>
<td>93:7</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>4g</td>
<td>2.5</td>
<td>68</td>
<td></td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>4h</td>
<td>3</td>
<td>64</td>
<td></td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

For the conditions, see Table 1, footnote a. $^b$ Stereochemistry assigned by NOESY experiments. $^c$ Isolated yield based on allenic alcohol. $^d$ The trans/cis ratios were determined by $^1$H NMR.

Of mechanistic interest, we carried out the reaction of alkyl substituted allenic alcohol 5 with cyclohexanecarboxaldehyde (Table 2.3). Treatment of cyclohexyl substituted allenic alcohol with the aldehyde using the standard conditions afforded dicyclohexyl DHP 6 in good yield (Table 2.3, entry 1), but the relative diastereochrometry showed the 2,6-cis configuration, confirmed by NOESY. No cross-over product 7 was detected. The same product was obtained when phenethyl allenic alcohol was used. The yield was improved when an excess amount of aldehyde was added (Table 2.3, entry 3). In order to investigate whether the Lewis acid activation would influence the reaction outcome or not, addition of MgBr$_2$, FeCl$_3$ or AlCl$_3$ to the reaction mixture were
carried out (Table 2.3, entries 4 to 6). In the presence of FeCl$_3$, the DHP 6 was formed in moderate yield while complex reaction mixture was obtained with no trace of the cyclized product in the presence of MgBr$_2$ or AlCl$_3$. The unexpected product in the reactions indicated that some transformation possibly occurred between allenic alcohol and aldehyde.

Table 2.3 Reactions of alkyl substituted allenic alcohol with cyclohexanecarboxaldehyde$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>X</th>
<th>conditions</th>
<th>product 6 (yield, %)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Br</td>
<td>In(OTf)$_3$, TMSBr</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Br</td>
<td>In(OTf)$_3$, TMSBr</td>
<td>11</td>
</tr>
<tr>
<td>3$^b$</td>
<td></td>
<td>Br</td>
<td>In(OTf)$_3$, TMSBr</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Br</td>
<td>MgBr$_2$</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Cl</td>
<td>FeCl$_3$</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Cl</td>
<td>AlCl$_3$</td>
<td>trace</td>
</tr>
</tbody>
</table>

$^a$All reactions were carried out with 5 (0.3 mmol) and cyclohexanecarboxaldehyde (0.33 mmol) in CH$_2$Cl$_2$ (3 mL) at 0 °C unless otherwise stated. $^b$3 equivalent of aldehyde was used. $^c$Isolated yields are reported.

A plausible mechanism was proposed to account for this phenomenon (as shown in Scheme 2.9). During this process, homopropargylic transfer reaction occurred before the Prins cyclization reaction. This is consistent with the result we observed previously.$^{66}$ Subsequently, Prins-type cyclization of homopropargylic alcohol III with another equivalent of cyclohexanecarbox-
aldehyde took place,\textsuperscript{74} leading to the unexpected product 6. However, the ester substituted allenic alcohols (substrates 1 and 3) underwent Prins cyclization without any detection of the homopropargylic transfer product.

![Scheme 2.9 Proposed mechanism of cyclization of alkyl substituted allenic alcohol with aldehyde](image)

The carboalkoxyl group adjacent to the allenic alcohol moiety performed two functions: (1) stereoelectronic induction to form the desired intermediate I (Scheme 2.7) with 2,6-\textit{trans} configuration through stabilization of the oxo-carbenium ion and (2) efficient suppression of the unwanted oxonia-Cope rearrangement due to the electron withdrawing property of the ester functional group, as suggested by Roush.\textsuperscript{78} As a consequence, the reactive intermediate I favoured the direct Prins cyclization prior to oxonia-Cope rearrangement.

### 2.3 Conclusion

In conclusion, we have developed a general method which allows easy access to 2,6-\textit{trans} pyranyl motifs. Prins cyclization using carboalkoxyl allenic alcohols is the key to the success of this method. The ester group provides an

anomeric effect\textsuperscript{79} as well as lone pair stabilization\textsuperscript{80} of the oxocarbenium ion intermediate. It also suppresses the propargyl transfer process. The use of the allenic alcohols instead of the homoallylic alcohols removes the 1,3-diaxial steric repulsion of the ester group with hydrogen through a distorted six-membered ring transition state, thus promoting the ester group to adopt the axial orientation preferentially. We believe that this method of tuning the stereoelectronic versus steric effect to direct the reaction pathway will become a prevailing strategy in organic synthesis. The ester functional group in the product has the advantages of being convertible to other functional groups such as alcohols, alkenes, etc.


2.4 Experimental Section

General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware. Commercial solvents and reagents were used without further purification except for CH₂Cl₂ was freshly distilled from CaH₂. Aldehydes were freshly distilled before using.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Columns were typically packed as slurry and equilibrated with hexane prior to use.

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Liquid samples were examined as film between NaCl or KBr salt plates. Proton nuclear magnetic resonance (¹H NMR) and carbon nuclear magnetic resonance (¹³C NMR) spectroscopy were performed on a Bruker Advance 300, 400 and 500 NMR spectrometers. Chemical shifts ¹H NMR spectra are reported as in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0) and relative to the signal of chloroform-d (J = 7.264, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); ddd (doublet of doublets of doublets); dddd (doublet of doublets of doublets of doublets); dt (doublet of triplets); m (multiplets) and etc. The number of protons (n) for a given resonance is indicated by nH. Coupling
constants are reported as a $J$ value in Hz. Carbon nuclear magnetic resonance spectra ($^{13}$C NMR) are reported as d in units of parts per million (ppm) downfield from SiMe$_4$ ($\delta$ 0.0) and relative to the signal of chloroform-$d$ ($J$ = 77.03, triplet).

High resolution mass spectral analysis (HRMS) was performed on Water Q-TOF Premier mass spectrometer (Thermo Electron Corporation).

X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer.

**General Procedure for Prins Cyclization reactions of Allenic Alcohols and Aldehydes**

**Preparation of $n$-butyl glyoxylate**

$$\text{n-BuO} \overset{\text{OH}}{\text{O}} \overset{\text{O}}{\text{O}} \overset{\text{OH}}{\text{Bu-n}} \xrightleftharpoons{\text{H}_2\text{IO}_4, \text{Et}_2\text{O}, 0 \,^\circ\text{C}} \text{2 n-BuO} \overset{\text{O}}{\text{O}} \overset{\text{H}}{\text{H}}$$

To a solution of di-$n$-butyl tartrate (2.62 g, 10 mmol) in dry ether (60 mL) cooled was added periodic acid (2.28 g, 10 mmol) in portions over 1 h under N$_2$ at 0 °C. The resulting reaction was stirred for 4 h, decanted from the solid precipitate, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The residue was distilled under reduced pressure to give $n$-butyl glyoxylate (2.45 g) as a viscous oil in 94% yield; bp 55-63 °C/12 mmHg.

**Preparation of butyl 2-hydroxy-3-methylpenta-3,4-dienoate (Method A)**

$$\text{n-BuO} \overset{\text{O}}{\text{O}} \overset{\text{H}}{\text{H}} + \text{Me} \overset{\text{Br}}{\text{=C=C}} \xrightarrow{\text{In}, \text{THF/NaHCl (sat aq)}} 0 \,^\circ\text{C to rt} \text{n-BuO} \overset{\text{O}}{\text{O}} \overset{\text{Me}}{\text{Me}}$$
1-Bromo-2-butyn (1.33 g, 10 mmol, 2.0 equiv) was added to a mixture of n-butyl glyoxylate (0.65 g, 5 mmol, 1.0 equiv) and indium power (1.15 g, 10 mmol, 2.0 equiv) in THF/NH$_4$Cl (aq sat) (1:5, 20 mL) at 0 °C with vigorous stirring. After 0.5 h, the mixture was warmed to room temperature and kept for another 6 h, and finally quenched with 20 mL of 1 M HCl solution. The aq. layer was extracted with ethyl acetate (30 mL × 3). The combined organic extracts were washed with sat aq NaCl, dried over anhydrous MgSO$_4$, concentrated under vacuum, and purified by flash gel column chromatography to provide 1 (0.76 g, 83% yield) of as clear oil.

R$_f$: 0.30 (Hexane: Ethyl acetate = 4:1)

$^1$H NMR (300 MHz, CDCl$_3$): 4.79 – 4.83 (m, 2H), 4.56 (s, 1H), 4.13 – 4.25 (m, 2H), 3.03 (s, 1H), 1.72 (t, $J = 3.2$ Hz, 3H), 1.59 – 1.69 (m, 2H), 1.32 – 1.44 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 3H)

$^{13}$C NMR (75.4 MHz, CDCl$_3$): 206.6, 173.3, 97.9, 77.1, 72.3, 65.8, 30.6, 19.0, 14.3, 13.6

HRMS (ESI): m/z calculated for C$_{10}$H$_{16}$NaO$_3$ [M + Na]$^+$: 207.0997, Found: 207.0988

FTIR (NaCl): ν 3462, 2961, 2874, 1962, 1732, 1462, 1273, 1198, 1080, 850 cm$^{-1}$

Procedure for the Prins cyclization of allenic alcohol and aldehyde
To an oven dried 10 mL round-bottom flask with a magnetic stirring bar was added indium(III) triflate (16.9 mg, 0.03 mmol, 0.1 equiv) in 2 mL anhydrous CH₂Cl₂. The mixture was allowed to cool to 0 °C prior to addition of trimethylsilyl bromide (55.1 mg, 0.36 mmol, 1.2 equiv). Cyclohexanecarboxaldehyde (40.4 mg, 0.36 mmol, 1.2 equiv) was added within 5 min. Then a solution of butyl 2-hydroxy-3-methylpenta-3,4-dienoate (1, 55.3 mg, 0.3 mmol, 1.0 equiv) dissolved in 1 mL anhydrous CH₂Cl₂ was added using syringe pump addition over a period of 1 h. The reaction was stirred at 0 °C for 2 h, warming up to room temperature. The mixture was quenched with saturated NaHCO₃ aq. solution (10 mL). The aqueous layer was extracted with Et₂O (10 mL × 3). The combined organic layers were washed with water, sat aq NaCl, and dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The residue crude product was purified by flash column chromatography to afford dihydropyran 2a (90.6 mg) and 2a’ (12.9 mg) as colorless oil.

(2,6-trans)-Butyl 4-bromo-6-cyclohexyl-3-methyl-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 84%

Rᶠ: 0.46 (Hexane: Diethyl ether = 8:1)

¹H NMR (400 MHz, CDCl₃): 4.57 (s, 1H), 4.15 (t, J = 6.6 Hz, 2H), 3.90 (ddd, J = 3.7, 7.1, 10.5 Hz, 1H), 2.19 – 2.56 (m, 2H), 1.95 (d, J = 12.9 Hz, 1H), 1.88 (s,
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

3H), 1.61 – 1.75 (m, 6H), 1.35 – 1.46 (m, 3H), 1.13 – 1.26 (m, 3H), 0.98 – 1.08 (m, 2H), 0.94 (t, \( J = 7.4 \) Hz, 3H)

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 170.3, 128.2, 119.6, 77.5, 76.1, 65.1, 42.2, 38.7, 30.6, 28.8, 28.1, 26.5, 26.0, 25.9, 19.4, 19.2, 13.7

HRMS (ESI): m/z calculated for C\(_{17}\)H\(_{27}\)BrNaO\(_3\) [M + Na]^+: 381.1041, Found: 381.1031

FTIR (NaCl): ν 2926, 2853, 1732, 1454, 1383, 1346, 1305, 1280, 1179, 1130, 1063, 1020, 972, 831, 737 cm\(^{-1}\)

(2,6-cis)-Butyl 4-bromo-6-cyclohexyl-3-methyl-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 12%

R\(_f\): 0.40 (Hexane: Diethyl ether = 8:1)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): 4.63 (s, 1H), 4.13 – 4.22 (m, 2H), 4.31 – 4.37 (m, 1H), 2.19 – 2.68 (m, 2H), 1.97 (d, \( J = 12.4 \) Hz, 1H), 1.74 (s, 3H), 1.62 – 1.72 (m, 6H), 1.46 – 1.54 (m, 1H), 1.34 – 1.44 (m, 2H), 1.09 – 1.25 (m, 4H), 0.96 – 1.01 (m, 1H), 0.94 (t, \( J = 7.4 \) Hz, 3H)

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 169.3, 128.3, 119.5, 80.1, 79.2, 65.3, 42.0, 38.9, 30.5, 29.1, 28.1, 26.4, 26.0, 25.8, 19.1, 17.5, 13.7

HRMS (ESI): m/z calculated for C\(_{17}\)H\(_{27}\)BrNaO\(_3\) [M + Na]^+: 381.1041, Found: 381.1047
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

FTIR (NaCl): $\nu$ 2930, 2855, 1732, 1678, 1607, 1369, 1344, 1250, 1219, 1169, 1069, 756 cm$^{-1}$

(2,6-trans)-Butyl 4-bromo-3-methyl-6-(pentan-3-yl)-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 75%

R$_f$: 0.48 (Hexane: Diethyl ether = 8:1)

$^1$H NMR (400 MHz, CDCl$_3$): 4.60 (s, 1H), 4.12 – 4.19 (m, 3H), 2.19 – 2.63 (m, 2H), 1.91 (s, 3H), 1.64 – 1.71 (m, 2H), 1.22 – 1.56 (m, 7H), 0.89 – 0.98 (m, 9H)

$^{13}$C NMR (100 MHz, CDCl$_3$): 170.3, 128.2, 119.6, 77.5, 73.6, 65.1, 45.3, 38.6, 30.6, 21.1, 21.0, 19.3, 19.2, 13.7, 11.3, 11.1

HRMS (ESI): m/z calculated for C$_{16}$H$_{27}$BrNaO$_3$ [M + Na]$^+$: 369.1041, Found: 369.1040

FTIR (NaCl): $\nu$ 2961, 2874, 1744, 1462, 1381, 1221, 1179, 1128, 1099, 1020, 972, 792 cm$^{-1}$

(2,6-cis)-Butyl 4-bromo-3-methyl-6-(pentan-3-yl)-5,6-dihydro-2H-pyran-2-carboxylate
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

Yield (%): 6%

R_f: 0.45 (Hexane: Diethyl ether = 8:1)

^1^H NMR (400 MHz, CDCl$_3$): 4.64 (s, 1H), 4.17 (t, \( J = 6.6 \text{ Hz} \), 2H), 3.56 – 3.63 (m, 1H), 2.18 – 2.75 (m, 2H), 1.77 (s, 3H), 1.63 – 1.68 (m, 2H), 1.37 – 1.56 (m, 6H), 1.21 – 1.29 (m, 1H), 0.87 – 0.98 (m, 9H)

^1^C NMR (100 MHz, CDCl$_3$): 169.3, 128.2, 119.5, 80.1, 76.5, 65.3, 44.7, 38.5, 30.5, 21.3, 21.0, 19.1, 17.5, 13.7, 11.1, 11.0

HRMS (ESI): m/z calculated for C$_{16}$H$_{27}$BrNaO$_3$ [M + Na]$^+$: 369.1041, Found: 369.1040

FTIR (NaCl): v 2961, 2874, 1738, 1462, 1381, 1279, 1177, 1121, 1099, 1022, 972, 758 cm$^{-1}$

(2,6-trans)-Butyl 4-bromo-6-tert-butyl-3-methyl-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 84%, dr (trans/cis) = 92:8

R_f: 0.53 (Hexane: Diethyl ether = 8:1)

^1^H NMR (400 MHz, CDCl$_3$): 4.58 (s, 1H), 4.09 – 4.18 (m, 2H), 3.81 (dd, \( J = 3.5, 10.9 \text{ Hz} \), 1H), 2.12 – 2.59 (m, 2H), 1.87 (s, 3H), 1.61 – 1.68 (m, 2H), 1.34 – 1.43 (m, 2H), 0.93 (s, 3H), 0.91 (s, 9H)

^1^C NMR (100 MHz, CDCl$_3$): 170.2, 128.1, 119.9, 79.0, 77.7, 65.0, 36.2, 33.7, 30.6, 25.5 × 3, 19.3, 19.2, 13.6
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

HRMS (ESI): m/z calculated for C_{15}H_{25}^{79}BrNaO_3 [M + Na]^+: 355.0885, Found: 355.0862

FTIR (NaCl): ν 2958, 2872, 1734, 1678, 1396, 1365, 1300, 1242, 1179, 1128, 1107, 1015, 966, 837, 737 cm\(^{-1}\)

\chem{(2,6-trans)-Butyl} \quad \text{4-bromo-6-isobutyl-3-methyl-5,6-dihydro-2H-pyranyl-2-carboxylate}

Yield (%): 73%

R\text{f}: 0.44 (Hexane: Diethyl ether = 8:1)

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): 4.56 (s, 1H), 4.22 – 4.29 (m, 1H), 4.15 (t, J = 6.6 Hz, 2H), 2.23 – 2.44 (m, 2H), 1.88 (s, 3H), 1.79 – 1.86 (m, 1H), 1.61 – 1.68 (m, 2H), 1.47 – 1.55 (m, 1H), 1.34 – 1.43 (m, 2H), 1.20 – 1.28 (m, 1H), 0.91 – 0.95 (m, 9H)

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 170.3, 128.1, 119.0, 77.4, 70.4, 65.1, 44.6, 41.6, 30.6, 24.3, 23.2, 22.3, 19.3, 19.2, 13.7

HRMS (ESI): m/z calculated for C_{15}H_{25}^{79}BrNaO_3 [M + Na]^+: 355.0885, Found: 355.0885

FTIR (NaCl): ν 2957, 2872, 1732, 1682, 1468, 1383, 1342, 1269, 1225, 1179, 1126, 1101, 1069, 970, 802 cm\(^{-1}\)

\chem{(2,6-cis)-Butyl} \quad \text{4-bromo-6-isobutyl-3-methyl-5,6-dihydro-2H-pyranyl-2-carboxylate}
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

Yield (%): 8%

R_f: 0.41 (Hexane: Diethyl ether = 8:1)

$^1$H NMR (400 MHz, CDCl$_3$): 4.66 (s, 1H), 4.13 – 4.23 (m, 2H), 3.66 – 3.74 (m, 1H), 2.18 – 2.64 (m, 2H), 1.75 – 1.83 (m, 1H), 1.77 (s, 3H), 1.62 – 1.69 (m, 3H), 1.36 – 1.43 (m, 2H), 1.28 – 1.35 (m, 1H), 0.91 – 0.98 (m, 9H)

$^{13}$C NMR (100 MHz, CDCl$_3$): 169.3, 128.3, 119.0, 80.0, 73.4, 65.4, 43.9, 41.6, 30.5, 24.3, 22.9, 22.4, 19.1, 17.5, 13.7

HRMS (ESI): m/z calculated for C$_{15}$H$_{25}$BrNaO$_3$ [M + Na]$^+$: 355.0885, Found: 355.0878

FTIR (NaCl): $\nu$ 2959, 2872, 1732, 1682, 1614, 1470, 1454, 1371, 1252, 1229, 1171, 1142, 1069, 988, 891 cm$^{-1}$

(2,6-trans)-Butyl 4-bromo-3-methyl-6-phenethyl-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 70%

R_f: 0.46 (Hexane: Diethyl ether = 8:1)

$^1$H NMR (400 MHz, CDCl$_3$): 7.18 – 7.31 (m, 5H), 4.63 (s, 1H), 4.21 – 4.27 (m, 1H), 4.18 (t, J = 6.7 Hz, 2H), 2.84 – 2.92 (m, 1H), 2.66 – 2.73 (m, 1H), 2.25 –
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

2.57 (m, 2H), 1.91 (s, 3H), 1.76 – 1.89 (m, 2H), 1.62 – 1.69 (m, 2H), 1.36 – 1.46 (m, 2H), 0.96 (t, \( J = 7.4 \) Hz, 3H)

\( ^{13} \)C NMR (100 MHz, CDCl\(_3\)): 170.2, 141.9, 128.4, 128.4, 128.4, 125.9, 118.8, 77.4, 71.7, 65.2, 41.1, 37.1, 31.6, 30.6, 19.4, 19.2, 13.7

HRMS (ESI): m/z calculated for C\(_{19}\)H\(_{25}\)BrNaO\(_3\) \([\text{M + Na}]^+\): 403.0885, Found: 403.0899

FTIR (NaCl): \( \nu \) 3061, 3026, 2959, 2872, 1742, 1668, 1603, 1495, 1454, 1383, 1352, 1248, 1223, 1179, 1128, 1115, 1059, 974, 910, 735, 700 cm\(^{-1}\)

\((2,6\text{-cis})\)-Butyl 4-bromo-3-methyl-6-phenethyl-5,6-dihydro-2\(H\)-pyran-2-carboxylate

Yield (%): 13%

R\(_f\): 0.39 (Hexane: Diethyl ether = 8:1)

\( ^1 \)H NMR (400 MHz, CDCl\(_3\)): 7.26 – 7.30 (m, 2H), 7.17 – 7.21 (m, 3H), 4.65 (s, 1H), 4.15 – 4.25 (m, 2H), 3.54 – 3.63 (m, 1H), 2.18 – 2.82 (m, 4H), 1.93 – 2.05 (m, 1H), 1.64 – 1.85 (m, 6H), 1.36 – 1.48 (m, 2H), 0.95 (t, \( J = 7.4 \) Hz, 3H)

\( ^{13} \)C NMR (100 MHz, CDCl\(_3\)): 169.2, 141.5, 128.5, 128.4, 128.3, 125.9, 118.8, 79.9, 73.9, 65.4, 41.2, 36.3, 31.3, 30.5, 19.1, 17.5, 13.7

HRMS (ESI): m/z calculated for C\(_{19}\)H\(_{25}\)BrNaO\(_3\) \([\text{M + Na}]^+\): 403.0885, Found: 403.0878

FTIR (NaCl): \( \nu \) 3061, 3026, 2959, 2872, 1738, 1682, 1603, 1495, 1454, 1381, 1368, 1250, 1215, 1179, 1117, 1067, 983, 910, 750, 700 cm\(^{-1}\)
(2,6-trans)-Butyl 4-bromo-3-methyl-6-phenyl-5,6-dihydro-2H-pyran-2-carboxylate

m. p. 36-37 °C; Yield (%): 75%

Rf: 0.39 (Hexane: Diethyl ether = 8:1)

$^1$H NMR (400 MHz, CDCl$_3$): 7.28 – 7.41 (m, 5H), 5.31 (dd, $J = 3.7$, 10.5 Hz, 1H), 4.75 (s, 1H), 4.19 (t, $J = 6.8$ Hz, 2H), 2.68 – 2.89 (m, 2H), 1.95 (s, 3H), 1.63 – 1.70 (m, 2H), 1.35 – 1.44 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 3H)

$^{13}$C NMR (100 MHz, CDCl$_3$): 170.2, 140.4, 128.6, 128.1, 128.0, 126.2, 118.7, 77.7, 73.8, 65.3, 42.3, 30.6, 19.2, 19.1, 13.7

HRMS (ESI): m/z calculated for C$_{17}$H$_{21}$BrNaO$_3$ [M + Na]$^+$: 375.0572, Found: 375.0558

FTIR (NaCl): $\nu$ 3063, 3032, 2959, 2872, 1738, 1668, 1495, 1454, 1275, 1179, 1126, 1101, 1012, 820, 760, 700 cm$^{-1}$

(2,6-cis)-Butyl 4-bromo-3-methyl-6-phenyl-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 8%

Rf: 0.38 (Hexane: Diethyl ether = 8:1)
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

\[^{1}\text{H} \text{NMR} \text{ (} 400 \text{ MHz, } \text{CDCl}_3 \text{): } 7.28 – 7.41 \text{ (m, } 5\text{H}), 4.88 \text{ (d, } J = 0.9 \text{ Hz, } 1\text{H}), 4.71 \text{ (dd, } J = 3.2, 10.7 \text{ Hz, } 1\text{H}), 4.20 \text{ (t, } J = 6.7 \text{ Hz, } 2\text{H}), 2.90 – 2.99 \text{ (m, } 1\text{H}), 2.68 \text{ (d, } J = 16.9 \text{ Hz, } 1\text{H}), 1.83 \text{ (s, } 3\text{H}), 1.64 – 1.71 \text{ (m, } 2\text{H}), 1.37 – 1.46 \text{ (m, } 2\text{H}), 0.95 \text{ (t, } J = 7.4 \text{ Hz, } 3\text{H})

\[^{13}\text{C} \text{NMR} \text{ (} 100 \text{ MHz, } \text{CDCl}_3 \text{): } 169.0, 140.2, 128.5, 128.3, 128.1, 126.0, 118.5, 80.2, 76.5, 65.5, 43.1, 30.5, 19.1, 17.7, 13.7

HRMS (ESI): m/z calculated for C\(_{17}\)H\(_{21}\)BrNaO\(_3\) [M + Na]\(^+\): 375.0572, Found: 375.0555

FTIR (NaCl): \(\nu\) 3065, 3036, 2959, 2872, 1738, 1614, 1454, 1277, 1179, 1123, 1103, 1055, 1021, 970, 756, 700 cm\(^{-1}\)

**Preparation of butyl 2-hydroxy-3-(trimethylsilyl)penta-3,4-dienoate (Method B)**

\[
\begin{align*}
\text{n-BuO} & \quad \text{CO}_2H \\
\text{TMS} & \quad \text{Br} \\
\text{THF/H}_2\text{O} & \quad \text{In} \quad \text{r.t.} \\
\text{n-BuO} & \quad \text{CO}_2H \\
\text{TMS} & \quad \text{OH}
\end{align*}
\]

To a suspension of indium power (1.15 g, 10 mmol, 2.0 equiv) in H\(_2\)O/THF (5:1, 10 mL) was added \(n\)-butyl glyoxylate (0.65 g, 5 mmol, 1.0 equiv) and then trimethylsilyl propargyl bromide (1.91 g, 10 mmol, 2.0 equiv). The mixture was vigorously stirred at rt for 8 h. Standard workup and purified by flash silica gel column chromatograph gave \(3\) (0.67 g, 55%) as clear oil.

R\(_f\): 0.42 (Hexane: Ethyl acetate = 4:1)

\[^{1}\text{H} \text{NMR} \text{ (} 400 \text{ MHz, } \text{CDCl}_3 \text{): } 4.67 \text{ (t, } J = 2.1 \text{ Hz, } 1\text{H}), 4.53 – 4.59 \text{ (m, } 2\text{H}), 4.12 – 4.23 \text{ (m, } 2\text{H}), 2.78 \text{ (br, } 1\text{H}), 1.61 – 1.68 \text{ (m, } 2\text{H}), 1.34 – 1.43 \text{ (m, } 2\text{H}), 0.93 \text{ (t, } J = 7.4 \text{ Hz, } 3\text{H}), 0.16 \text{ (s, } 9\text{H})
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

$^{13}$C NMR (100 MHz, CDCl$_3$): 209.0, 173.7, 96.5, 72.0, 70.5, 65.5, 30.6, 19.0, 13.6, -1.0

HRMS (ESI): $m/z$ calculated for C$_{12}$H$_{23}$O$_3$Si [M + H]$^+$: 243.1416, Found: 243.1424

FTIR (NaCl): $\nu$ 3470, 3065, 2959, 2874, 1932, 1730, 1630, 1458, 1406, 1381, 1248, 1205, 1082, 1035, 843, 760, 696 cm$^{-1}$

(2,6-trans)-Butyl 4-bromo-6-cyclohexyl-3-(trimethylsilyl)-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 90%, $dr$ (trans/cis) = 96:4

R$_f$: 0.67 (Hexane: Diethyl ether = 8:1)

$^1$H NMR (400 MHz, CDCl$_3$): 4.78 (s, 1H), 4.09 – 4.21 (m, 2H), 3.46 (ddd, $J$ = 3.8, 6.8, 10.6 Hz, 1H), 2.59 (ddd, $J$ = 1.9, 10.6, 17.6 Hz, 1H), 3.42 (dd, $J$ = 3.8, 17.6 Hz, 1H), 1.94 (d, $J$ = 13.0 Hz, 1H), 1.69 – 1.74 (m, 2H), 1.62 – 1.67 (m, 4H), 1.35 – 1.45 (m, 3H), 1.13 – 1.26 (m, 5H), 0.94 (t, $J$ = 7.4 Hz, 3H), 0.24 (s, 9H)

$^{13}$C NMR (100 MHz, CDCl$_3$): 170.6, 134.1, 132.1, 77.6, 75.8, 65.3, 42.3, 41.0, 30.6, 28.6, 27.9, 26.4, 25.9, 25.8, 19.1, 13.6, -1.0

HRMS (ESI): $m/z$ calculated for C$_{19}$H$_{34}$BrO$_3$Si [M + H]$^+$: 439.1280, Found: 439.1276

FTIR (NaCl): $\nu$ 2928, 2853, 1734, 1667, 1611, 1450, 1306, 1248, 1182, 1126, 1070, 935, 885, 843, 762, 689 cm$^{-1}$
(2,6-trans)-Butyl 4-bromo-6-(pentan-3-yl)-3-(trimethylsilyl)-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 84%, dr (trans/cis) = 96:4

Rf: 0.51 (Hexane: Diethyl ether = 8:1)

$^1$H NMR (400 MHz, CDCl$_3$): 4.78 (d, $J = 1.7$ Hz, 1H), 4.15 (t, $J = 6.8$ Hz, 2H), 3.66 – 3.71 (m, 1H), 2.61 (ddd, $J = 2.0$, 10.7, 17.5 Hz, 1H), 2.41 (dd, $J = 3.7$, 17.5 Hz, 1H), 1.62 – 1.69 (m, 2H), 1.34 – 1.54 (m, 5H), 1.18 – 1.32 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H), 0.86 (t, $J = 7.4$ Hz, 6H), 0.24 (s, 9H)

$^{13}$C NMR (100 MHz, CDCl$_3$): 170.6, 134.0, 132.1, 77.6, 73.2, 65.3, 45.3, 41.0, 30.6, 20.8, 20.7, 19.1, 13.6, 11.2, 11.0, -1.0

HRMS (ESI): $m/z$ calculated for C$_{18}$H$_{34}$BrO$_3$Si [M + H]$^+$: 405.1461, Found: 405.1450

FTIR (NaCl): ν 2959, 2874, 1732, 1612, 1462, 1422, 1381, 1304, 1248, 1180, 1125, 1069, 1024, 934, 843, 762 cm$^{-1}$

(2,6-trans)-Butyl 4-bromo-6-tert-butyl-3-(trimethylsilyl)-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 86%, dr (trans/cis) = 94:6
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

R_f: 0.67 (Hexane: Diethyl ether = 8:1)

^1^H NMR (400 MHz, CDCl_3): 4.80 (d, J = 1.8 Hz, 1H), 4.08 – 4.19 (m, 2H), 3.37 (dd, J = 3.6, 11.0 Hz, 1H), 2.62 (ddd, J = 2.0, 11.0, 17.5 Hz, 1H), 2.38 (dd, J = 3.6, 17.5 Hz, 1H), 1.62 – 1.69 (m, 2H), 1.35 – 1.44 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.24 (s, 9H)

^1^3^C NMR (100 MHz, CDCl_3): 170.6, 133.9, 132.4, 78.9, 77.9, 65.3, 38.5, 33.7, 30.6, 25.3 × 3, 19.1, 13.6, -1.0

HRMS (ESI): m/z calculated for C_{17}H_{32}^{79}BrO_3Si [M + H]^+: 391.1304, Found: 391.1304

FTIR (NaCl): v 2957, 2872, 1734, 1612, 1466, 1396, 1366, 1296, 1296, 1248, 1180, 1128, 1086, 1059, 920, 841, 762, 689 cm^{-1}

(2,6-trans)-Butyl 4-bromo-6-octyl-3-(trimethylsilyl)-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 82%, dr (trans/cis) = >99:1

R_f: 0.64 (Hexane: Diethyl ether = 8:1)

^1^H NMR (400 MHz, CDCl_3): 4.78 (s, 1H), 4.09 – 4.21 (m, 2H), 3.67 – 3.74 (m, 1H), 2.42 – 2.55 (m, 2H), 1.62 – 1.69 (m, 2H), 1.35 – 1.55 (m, 4H), 1.26 (apparent s, 12H), 0.94 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 6.6 Hz, 3H), 0.24 (s, 9H)

^1^3^C NMR (100 MHz, CDCl_3): 170.5, 134.1, 131.6, 77.5, 71.8, 65.3, 43.4, 35.4, 31.9, 30.6, 29.5, 29.5, 29.2, 25.0, 22.7, 19.1, 14.1, 13.6, -1.0
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

HRMS (ESI): \( m/z \) calculated for C\(_{21}\)H\(_{40}\)\(^{79}\)BrO\(_3\)Si [M + H]\(^+\): 447.1930, Found: 447.1925

FTIR (NaCl): \( \nu \) 2930, 2857, 1726, 1610, 1458, 1215, 1124, 1067, 843, 756 cm\(^{-1}\)

\((2,6\text{-trans})\)-Butyl 4-bromo-6-isobutyl-3-(trimethylsilyl)-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 80%, \( dr \) (trans/cis) = >99:1

\( R_f \): 0.49 (Hexane: Diethyl ether = 8:1)

\(^1\)H NMR (500 MHz, CDCl\(_3\)): 4.76 (d, \( J = 1.5 \) Hz, 1H), 4.11 – 4.18 (m, 2H), 3.81 (ddd, \( J = 4.0, 8.6, 12.9 \) Hz, 1H), 2.41 – 2.49 (m, 2H), 1.76 – 1.85 (m, 1H), 1.62 – 1.68 (m, 2H), 1.45 – 1.51 (m, 1H), 1.36 – 1.42 (m, 2H), 1.15 – 1.24 (m, 1H), 0.86 – 0.94 (m, 9H), 0.23 (s, 9H)

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): 170.5, 134.0, 131.6, 77.5, 70.0, 65.3, 44.7, 43.8, 30.6, 24.2, 23.2, 22.2, 19.1, 13.7, -1.0

HRMS (ESI): \( m/z \) calculated for C\(_{17}\)H\(_{32}\)\(^{79}\)BrO\(_3\)Si [M + H]\(^+\): 391.1304, Found: 391.1279

FTIR (NaCl): \( \nu \) 2957, 2872, 1732, 1614, 1468, 1381, 1368, 1306, 1248, 1180, 1123, 1067, 1034, 932, 843, 762 cm\(^{-1}\)
(2,6-trans)-Butyl 4-bromo-6-phenethyl-3-(trimethylsilyl)-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 83%, \( dr (\text{trans/cis}) = 93:7 \)

\( R_f = 0.59 \) (Hexane: Diethyl ether = 8:1)

\(^1\)H NMR (500 MHz, CDCl\(_3\)): 7.29 – 7.32 (m, 2H), 7.20 – 7.23 (m, 3H), 4.86 (d, \( J = 1.5 \) Hz, 1H), 4.14 – 4.23 (m, 2H), 3.81 (ddd, \( J = 4.1 \) Hz, 8.1, 12.1 Hz, 1H), 2.86 (ddd, \( J = 5.4, 10.0, 14.3 \) Hz, 1H), 2.65 – 2.72 (m, 1H), 2.60 (ddd, \( J = 1.9, 10.4, 17.6 \) Hz, 1H), 2.51 (dd, \( J = 3.9, 17.6 \) Hz, 1H), 1.78 – 1.92 (m, 2H), 1.66 – 1.71 (m, 2H), 1.40 – 1.47 (m, 2H), 0.98 (t, \( J = 7.4 \) Hz, 3H), 0.29 (s, 9H)

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): 170.4, 141.7, 134.1, 131.3, 128.4, 128.3, 125.9, 77.6, 71.1, 65.4, 43.3, 37.2, 31.3, 30.6, 19.1, 13.7, -0.9

HRMS (ESI): \( m/z \) calculated for \( C_{21}H_{32}^{79}\text{BrO}_3\text{Si} [M + H]^+ \): 439.1304, Found: 439.1300

FTIR (NaCl): \( \nu \) 3063, 3019, 2958, 2874, 1730, 1612, 1454, 1301, 1250, 1215, 1184, 1123, 1069, 1030, 843, 756, 700 cm\(^{-1}\)

(2,6-trans)-Butyl 4-bromo-6-phenyl-3-(trimethylsilyl)-5,6-dihydro-2H-pyran-2-carboxylate

Yield (%): 68%, \( dr (\text{trans/cis}) = >99:1 \)
DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION

R<sub>f</sub>: 0.42 (Hexane: Diethyl ether = 8:1)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.28 – 7.38 (m, 5H), 4.95 (d, <i>J</i> = 1.4 Hz, 1H), 4.85 (dd, <i>J</i> = 4.0, 10.5 Hz, 1H), 4.12 – 4.23 (m, 2H), 2.87 (ddd, <i>J</i> = 1.9, 10.5, 17.6 Hz, 1H), 2.75 (dd, <i>J</i> = 4.1, 17.6 Hz, 1H), 1.62 – 1.69 (m, 2H), 1.32 – 1.41 (m, 2H), 0.91 (t, <i>J</i> = 7.4 Hz, 3H), 0.29 (s, 9H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 170.3, 140.5, 134.0, 131.1, 128.5, 128.0, 125.9, 77.9, 73.4, 65.5, 44.6, 30.5, 19.0, 13.6, -0.9

HRMS (ESI): <i>m/z</i> calculated for C<sub>19</sub>H<sub>27</sub>BrNaO<sub>3</sub>Si [M + Na]<sup>+</sup>: 433.0811, Found: 433.0795

FTIR (NaCl): <i>ν</i> 3063, 3032, 2958, 2872, 1730, 1611, 1496, 1452, 1309, 1248, 1182, 1123, 1069, 885, 842, 754, 698 cm<sup>-1</sup>

<sup>2</sup>H<sub>pyran-2-carboxylate</sub>

(2,6-trans)-Butyl 4-bromo-6-(3-nitrophenyl)-3-(trimethylsilyl)-5,6-dihydro-2H-pyran-2-carboxylate

R<sub>f</sub>: 0.40 (Hexane: Diethyl ether = 8:1)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 8.24 (s, 1H), 8.15 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.66 (d, <i>J</i> = 7.8 Hz, 1H), 7.53 (t, <i>J</i> = 7.9 Hz, 1H), 4.98 – 5.01 (m, 2H), 4.12 – 2.23 (m, 2H), 2.75 – 2.86 (m, 2H), 1.62 – 1.69 (m, 2H), 1.31 – 1.41 (m, 2H), 0.89 (t, <i>J</i> = 7.4 Hz, 3H), 0.29 (s, 9H)

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 169.9, 148.4, 142.7, 134.3, 131.8, 130.0, 129.5, 122.9, 120.9, 77.7, 72.1, 65.6, 44.2, 30.5, 19.0, 13.6, -0.9
HRMS (ESI): \( m/z \) calculated for C\(_{19}\)H\(_{27}\)\(^{79}\)BrNO\(_5\)Si [M + H]^+: 456.0842, Found: 456.0851

FTIR (NaCl): \( \nu \) 3092, 2959, 2874, 1732, 1614, 1537, 1531, 1348, 1247, 1184, 1124, 1174, 924, 843, 810, 762, 737, 691 cm\(^{-1}\)

1-Phenyl-4-(trimethylsilyl)hexa-4,5-dien-3-ol

Compound 5 was prepared according to the method B.

\[
\text{Ph} \quad \text{OH} \quad \text{TMS}
\]

Yield (%): 82%

R\(_f\): 0.39 (Hexane: Ethyl acetate = 4:1)

\(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.29 – 7.34 (m, 2H), 7.19 – 7.24 (m, 3H), 4.56 – 4.65 (m, 2H), 4.23 (s, 1H), 2.68 – 2.89 (m, 2H), 1.88 – 2.08 (m, 2H), 1.83 (d, \( J = 5.6 \) Hz, 1H), 0.19 (s, 9H)

\(^{13}\)C NMR (75.4 MHz, CDCl\(_3\)): 207.3, 142.1, 128.5, 128.4, 125.8, 100.6, 72.1, 70.0, 39.7, 32.1, -0.8

((2,6-cis)-4-Bromo-2,6-dicyclohexyl-5,6-dihydro-2H-pyran-3-y)trimethylsilane

\[
\text{TMS} \quad \text{Br} \\
\text{C} \quad \text{C} \quad \text{C} \\
\text{O} \quad \text{O} \quad \text{O}
\]

Yield (%): 71%, \( dr \) (cis/trans) = 99:1

R\(_f\): 0.60 (Hexane)
$^1$H NMR (300 MHz, CDCl$_3$): 4.14 (s, 1H), 3.15 (ddd, $J = 3.4$, 6.4, 9.6 Hz, 1H), 2.31 – 2.49 (m, 2H), 1.87 (d, $J = 12.8$ Hz, 1H), 1.62 – 1.74 (m, 7H), 1.48 – 1.54 (m, 2H), 0.88 – 1.44 (m, 12H), 0.24 (s, 9H)

$^{13}$C NMR (100 MHz, CDCl$_3$): 138.1, 130.0, 83.1, 77.3, 43.0, 42.6, 42.4, 30.6, 28.8, 28.4, 27.1, 26.7, 26.5 × 2, 26.2, 26.1, 24.8, 0.1

HRMS (ESI): $m/z$ calculated for C$_{20}$H$_{36}$BrOSi [M + H]$^+$: 399.1719, Found: 399.1702

FTIR (NaCl): ν 2926, 2851, 1672, 1601, 1450, 1354, 1250, 1115, 1072, 1006, 932, 893, 840, 760 cm$^{-1}$
CHAPTER 3

Research Towards the Total Synthesis of Methyl Sarcophytoate
3.1 Introduction

Marine natural products as drug candidates possess specific chemical structures and remarkable biological activities. Soft corals of the genus *Sarcophyton* are a family of Alcynoiidae which are proven to be a rich source of cembrane dimmers, featured by a 14-6-14 membered tricyclic backbone of tetraterpenoids. Biscembranoids were mainly isolated out from the marine soft coral genus of *Sarcophyton* (*S. glaucum*, *S. tortuosum*, *S. latum* and *S. elegans*), with the exception of isobiscembranoids, which were isolated from a soft coral *Lobophytum pauciflorum* more recently.

Up to now, 33 kinds of unusual biscembranoids have been discovered from the coral *Sarcophyton*. In 1986, methyl isosartortuoate was isolated from *S. tortuosum* Tixier-Durivault collected in the South China Sea by Su and Clardy, which was the first example of biscembranoids bearing 14-membered carbocyclic cembranes. This was followed by the isolation of a related compound, methyl sartotuoate, from the same soft coral by the same group. Subsequently, two other biscembranoids, named methyl sarcophytoate (1) and methyl chlorosarcophytoate, were isolated from the Okinawan soft coral *S. glaucum* by Kakisawa, while the absolute configuration of 1 was elucidated.

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by means of difference CD spectrum using a lanthanide reagent. In 1993, methyl neosartortuate acetate was isolated from the Australian soft coral *S. tortuosum* by Bowden, in which the relative stereochemistry of the epoxide moiety at C26/C27 was corrected by Guo.

![Methyl Sarcophytoate (1)](image1)

![Bisglaucumide G](image2)

![Methyl Neosartortuate Acetate](image3)

![Bisglaucumide A R = H](image4)

![Bisglaucumide B R = Ac](image5)

![Methyl Chlorosarcophytoate](image6)

![Methyl Sarcoate (2)](image7)

**Figure 3.1** Biscembranoids containing methyl sarcoate (2)

During the following 10 years, there was no additional report on the isolation of biscembranoids. However, on the basis of extensive spectroscopic analysis, more and more uncommon biscembranoids were discovered from soft corals of the genus *Sarcophyton* over recent years, including nyalolide (*S. glaucum* and *elegans*), methyl tortuoates A–D (*S. tortuosum*), bisglaucumlides A–K (*S. glaucum* and *elegans*), methyl neosartortuates A–D (*S. tortuosum*), bisglaucumlides A–K (*S. glaucum* and *elegans*), methyl tortuoates A–D (*S. tortuosum*), bisglaucumlides A–K (*S. glaucum* and *elegans*).
glaucum), ximaolides A–G (S. tortuosum), bislatumlides A and B (S. latum), desacetylnyalolide, diepoxynyalolide and dioxanyalolide (S. elegans).

![Methyl Sartortuoate](image1)

![Nyalolide Desacetylnyalolide](image2)

![Methyl Tortuoate A](image3)

![Bisglaucumilides C](image4)

![Bisglaucumilides F](image5)

![Ximaolide F](image6)

![Bisglaucumilides I](image7)

![Bislatumlide A](image8)

![Bislatumlide B](image9)

![Bisglaucumilides D](image10)

**Figure 3.2** Biscembranoids containing pyranyl motifs


The isolated biscembranoids have exhibited an impressive range of biological properties, including *in vitro* cytotoxicity against several tumor cell lines, antimicrobial activity against *Escherichia coli* and lethality against the brine shrimp *Artemia salina*.

Inspected from the complex and unique framework of these 33 compounds, the common structural feature among the dimeric cembranes is that the biscembranoids could be biogenetically derived through a probable Diels-Alder addition of two different cembranoid units. Macro cyclic cembranetype dienophile and diene were presumed as the precursors of the biscembranoids, for examples of methyl sarcophytoate (1), ximaolides and bislatumlides, which were originated from methyl sarcoate (2), methyl tortuosoate and isosarcophytonolide, respectively (Scheme 3.1).

![Scheme 4.1 Biogenesis of biscembranoids by Diels–Alder addition](image-url)
According to structures of the dienophiles of the biscembranoids, these 33 compounds were classified into three groups: methyl sarcoate, methyl tortuosoate and isosarcophytonolide including their double-bond isomers in the diterpenes. Noteworthy is that the bridgehead C1/C2 of two proposed cembranes in all biscembranoids (apart from bislatumlides) bears the same cis-configuration. The relative stereochemistry is suggested via the transition state of endo cycloaddition with respect to the α,β-unsaturated ester in the Diels-Alder reaction, as shown in Scheme 3.2. In contrast, exo cycloaddition would involve an impossibly encumbered transition state. This addition mode not only explains the stereochemistry of the bridgehead but also the trans-geometry of the carbomethoxyl group relative to the doubly allyl bridgehead proton (on C21).

Scheme 3.2 Configuration of the biscembranoid cyclohexene core
3.2 Previous Synthetic Work

Due to their structural novelties and potential bioactivities, total syntheses on cembranoids have been conducted by many chemists in the past decades. A variety of synthetic methods have been developed for the construction of the 14-membered cembranoid cores. Many of these strategies have been based on the intramolecular Nozaki-Hiyama-Kishi reaction,95 McMurry coupling,96 Stille cross-coupling,97 Friedel-Crafts acylation,98 radical macrocyclization,99 ring closure metathesis (RCM),100 [2,3]-Wittig ring contraction101 and Horner-Wadsworth-Emmons (HWE) olefination,102 etc.

In contrast, synthetic approaches towards the closely related natural bisembranoids have only attracted the attention of two research groups, Xu’s

group and Nakata’s group. Particularly, Nakata and coworkers accomplished an elegant total synthesis of methyl sarcophytoate 1 by an intermolecular Diels-Alder reaction, along with the asymmetric syntheses of both the diene unit 3 and the dienophile unit 2 (methyl sarcoate), initiated from the early 1990s. The chemical synthesis further confirmed the possibility of the biogenesis of biscembranoids via Diels–Alder addition.

In the total synthesis of methyl sarcoate 2, the key intermediate 6 could be constructed by the dithiane coupling of the dithiane 4 with the allyl bromide 5. After introduction of isopropenyl moiety using the Grignard reagent 8, the compound 12 could be formed by the Kosugi-Migita-Stille coupling between tributyl(vinyl)tin 11 and acid chloride 10 derived from the ester 9. The olefin 13 was cyclized to yield methyl sarcoate 3 by RCM in the presence of the Grubbs second-generation catalyst 14.


Scheme 3.3 Total synthesis of methyl sarcoate 2

Starting from geraniol 15, allyl alcohol 16 was converted to epoxy alcohol 17 via Sharpless asymmetric epoxidation (SAE) followed by RCM using the Grubbs catalyst 14 to afford β,γ-unsaturated δ-lactone 19. The following six-step transformation including Wittig reaction, SAE, and Parikh-Doering oxidation provided epoxy aldehyde 20.

Aldol reaction of 20 with t-butyl acetate produced alcohol 21 followed by silylation, DIBAL-H reduction, Wittig reaction, DIBAL-H reduction, 6-exo-tet cyclization and acetonization. SAE of 23 unexpectedly afforded only β-epoxide, which was deoxygenated via iodination, reduction and further converted into the cyclization precursor 24 by deprotection of the PMB ether followed by phenylsulfdation. The epoxy allyl sulfide 24 was transformed into the acetonide-protected diene unit 25 by the following four-step reactions.
involving \( n \)-BuLi-\( Bu_2Mg \)-mediated Ito-Kodama cyclization, oxidation of sulfide, \( syn \) \( \beta \)-elimination and dehydration. The deprotection of 25 with PPTS afforded the unstable 14-membered diene unit 3.

Scheme 3.4 Synthesis of the diene unit 3

Due to the high instability of 3 under Lewis acid promoted conditions, the precursor 25 was chosen as the diene unit for the final Deils-Alder reaction. At 100 °C for 1.5 days, the desired adduct 26 and its 4Z-isomer 27 were obtained in 22% and 27% yields, respectively. Finally, the acetonide group in 26 was deprotected with aq. AcOH to afford methyl sarcophytoate 1 in 50% yield. Interestingly, Nakata found that methyl sarcoate 2 and 27 could be isomerized into the corresponding product 28 and 26.
Inspired by the hypothetical biogenesis of bicembranoids and Nataka’s achievement, we initiated our synthetic project towards methyl sarcophytoate 1 from synthesizing methyl sarcoate 2 and the diene unit 3 separately.

Scheme 3.5
Part A. Towards Synthesis of Methyl Sarcoate

3.3 Retrosynthetic Analysis of Methyl Sarcoate

We anticipated that methyl sarcoate 2 would be constructed from 29 via RCM, which have been successfully employed in the formation of macrocycles. Two general approaches towards the synthesis of the common precursor 29 were outlined in Scheme 3.6. Both of them addressed HWE olefination, Micheal addition and Grignard reaction as key steps in different sequences. In approach (a), we intended to construct 29 through HWE olefination of the ketone 31 with the phosphonate 32, followed by the installation of the isopropenyl and isopropyl moiety. Approach (b) revealed the introduction of the isopropenyl and isopropyl moiety prior to HWE olefination of 33 with the same phosphonate 32 to construct 29.

Scheme 3.6 Retrosynthetic analysis of methyl sarcoate 2

3.4 Preliminary Studies

3.4.1 Approach (A) towards the precursor 29

According to the synthetic strategy, we began the synthesis of the phosphonate segment 32 with commercially available ethyl acetoacetate 34, as showed in Scheme 3.7.

![Scheme 3.7 Synthesis of the phosphonate segment 32](image)

Allylation of 34 followed by saponification and subsequent decarboxylation provided ketone 35 in good over yield.\(^{107}\) 35 was subjected to HWE reaction with triethyl phosphonoacetate to give the \(\alpha,\beta\)-unsaturated ester 36a in 68% yield and mixtures of region-isomers (\(E/Z = 76/24\)). An alternative method using trimethyl phosphonoacetate afforded the corresponding ester 36b in lower yield.\(^{108}\) Reduction of mixtures 36a with DIBAL-H produced alcohol, which upon oxidation with Dess-Martin periodinane (DMP) afforded the aldehyde 37. Treatment of aldehyde 37 with diethyl methylphosphonate anion gave the \(\beta\)-hydroxy phosphonate 38, followed by DMP oxidation resulted the

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\(^{108}\) No reaction was observed when 35 was treated with Wittig reagent \(\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}\).
desired β-keto phosphonate 32. Fortunately, the E/Z isomers could be separated by flash chromatography and the major E-isomer was obtained in 49% purified yield.

After successful synthesis of the β-keto phosphonate 32, we proceeded to synthesize the ketone 31 (Scheme 3.8). The known ketone 40\(^\text{109}\) was easily accessible from acetol 39. The TiCl\(_4/\text{n-Bu}_3\text{N}\) mediated direct cross Aldol addition\(^\text{110}\) of 40 and acrolein promoted by catalytic TMSCl led to the desired adduct 41. A cross metathesis (CM) of 41 with methyl acrylate in the presence of 4 mol% of Grubbs second-generation catalyst 14 proceeded smoothly to give α,β-unsaturated ester 42 in 82% yield. Subsequent protection of the alcohol 42 delivered TBS ether 31 in 95% yield.

![Scheme 3.8 Synthesis of ketone 31](image)

Actually, initial study for olefin CM was conducted with methyl acrylate and 43, which was derived from alcohol 41, however, the desired product was obtained in 37% yield together with 60% yield of the recovered starting material 43 (Scheme 3.9).

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Scheme 3.9

With both fragments 31 and 32 in hand, we then sought to investigate their HWE olefination (Scheme 3.10). Unfortunately, no traces of product 30 was observed under a variety of conditions, like activated Ba(OH)$_2$-THF,$^{111}$ NaH-toluene,$^{112}$ n-BuLi-THF, LiCl-DIEPA-CH$_3$CN,$^{113}$ LiHMDS-THF ranging from -78 °C to reflux temperature. In most cases, the ketone 31 was decomposed while the β-keto phosphonate 32 was recovered quantitatively.

Scheme 3.10

Other attempts to HWE reaction of 31 with the less reactive β-siloxy phosphonate 38 under either Paterson’s or base-induced conditions failed completely, only resulting in the decomposition of the starting material 31 (Scheme 3.11).

Upon the failure of all attempts to construct 30 using 31, we suspected that the $\alpha,\beta$-unsaturated ester in 31 might be the culpable functionality. Additionally, we are apprehensive that the HWE reaction involving the ketone 31 might be problematic due to its steric effect, resulting in the reaction could not be performed under mild condition. As before, we examined HWE olefination on simple structural ketone 40 as a studying model. We are quite pleased to find that treatment of 40 with $\beta$-ketophosphonate 32 using sodium hydride as base in toluene at 50 °C provided the desired product as a mixture of $E/Z$ isomers (Scheme 3.12).

The deleterious reactivity was attributed to $\alpha,\beta$-unsaturated ester moiety in 31, therefore, we turned our attention to prepare the saturated precursor 33 for HWE reaction. In view of the building blocks of 29, the isopropenyl moiety should be introduced into the fragment prior to HWE olefination.

3.4.2 Approach (B) towards the precursor 33
The synthesis of the key building block 33 commenced with monoprotection of 1,2-ethanediol 46 to afford alcohol 47, which was subjected to Swern oxidation\(^{114}\) followed by a Wittig reaction to furnish \(\alpha,\beta\)-unsaturated ester 48 in 48% yield.

![Scheme 3.13]

As a model study, by means of a symmetric Michael addition of Grignard reagent to \(\alpha,\beta\)-unsaturated ester 48, the isopropyl moiety was introduced into 48 to give 49. DIBAL-H reduction and subsequent Grignard reaction produced the diastereomers 50. Then silylation and selective desilylation followed by DMP oxidation of the primary alcohol 52 led to

aldehyde 53. Under modified Paterson’s conditions,¹¹⁵ treatment of methyl ketone 40 with c-Hex₂BCl in the presence of N,N-diisopropylethylamine, resulted in regiocontrolled formation of the less substituted dicyclohexylboron enolate, which reacted with aldehyde 53 provided the desired aldol adduct 54 in 70% yield (Scheme 3.13). Resylation of the secondary alcohol 54 with TBSOTf afforded the ketone 33 in 71% yield.

Part B. Towards Synthesis of the Diene unit 3

3.5 Retrosynthetic Analysis of the Diene Unit 3

The diene unit 3 of methyl sarcophytoate possesses several challenging synthetic structural features, including 2,6-trans-pyranyl moiety, conjugated triene and 1,2-syn-diol. Actually, a variety of currently isolated biscembranoids incorporate five and six-membered ethers as a consequence of transannular cyclization events. Typically 2,6-trans-pyranyl moieties with a variety of oxidation levels were the common features among them, as shown in Figure 3.2.

In the Chapter 2, we have developed a synthetically viable Prins cyclization of allenic alcohols bearing a α-carboalkoxy group for diastereoselective synthesis of 2,6-trans pyranyl motifs. To apply this methodology to the total synthesis of biologically active natural products, we would like to introduce our efforts towards the construction of structural skeleton of diene unit 3 of methyl sarcophytoate 1.

Several investigations have been focused on strategies for the elaboration of the 2,6-trans pyran cores in total synthesis of natural products. But to our best knowledge, there is few reports to afford 2,6-trans pyranyl moiety using Prins cyclization strategies, although multiple examples employing Prins cyclization approach to form 2,6-cis pyranyl rings have been emerged as a key step in natural products synthesis.\(^\text{116}\)

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Our retrosynthetic analysis of diene unit 3 was outlined in Scheme 3.14. We envisaged that the disconnections of cyclic 1,2-syn diol via intramolecular low valent titanium-induced McMurry coupling from the keto aldehyde 55 (Scheme 3.14). 117 Macrocyclization precursor 55 would rise from indium-mediated Barbier-type allylation reaction of aldehyde 57 with β-substituted allylic bromide 56 in aqueous media, followed by hydration at C21/C34 leading to the triene motif. α,β- Unsaturated aldehyde 57 could be constructed by HWE olefination from the corresponding ketone 58. The diastereoselective Prins cyclization applied to α-carboalkoxyl allenic alcohol would generate 2,6-trans dihydropyrain 59 by further elongation at the C25 position.

Scheme 3.14 Retrosynthetic analysis of the diene unit 3

The retrosynthetic analysis described above led to a strategy that has the advantages of convergency and requires only a few invariable protecting groups. Especially noteworthy is the possibility of avoiding protection-deprotection
process such as the hydroxyl group on C32 and C33 positions, which would simplify the overall procedures. However, it does provide evident challenges to this plan, such as the problem of stereocontrol over the McMurry coupling reaction that a mixture of four stereoisomeric diols might yield.118 These considerations would be discussed in the experimental execution of this synthetic plan.

3.6 Results and Discussion

3.6.1 Construction of allylation precursor

The construction of DHP core initiated from the preparation of cyclization precursor 60 via indium-mediated allenylation reaction of isopropyl glyoxylate 62, derived from oxidation of commercially available diisopropyl L-tartrate 61, and propargylic bromide in aqueous media. Under previous conditions mentioned in Chapter 2, the Prins cyclization between α-carboalkoxyl allenic alcohol 60 with tiglic aldehyde\(^\text{119}\) proceeded to produce the 2,6-trans dihydropyran 63 with high diastereoselectivity (\(\text{trans/cis} = 96/4\)), although in moderate yield (45%). Reduction using LiBH\(_4\) of the ester 63 provided the alcohol 64.

The oxidative cleavage of olefinic bonds represented a convenient method to convert olefins into the corresponding carbonyl compounds in organic synthesis. A number of traditional approaches have been employed to carry out these operations including ozonolysis (O\(_3\), -78 °C), Johnso-Lemieux oxidation (OsO\(_4\), NaIO\(_4\), rt),\(^\text{120}\) Upjohn dihydroxylation/diol cleavage (i. NMO, OsO\(_4\), >2 eqquiv H\(_2\)O; ii. NaIO\(_4\) or Pb(OAc)\(_4\))\(^\text{121}\) and other improved methods.\(^\text{122}\) After meeting with the failure for ozonolysis of the alkene 64, we

\(^\text{119}\) This study was initially attempted using a variety of highly functionalized α-oxoaldehydes with α-allenic alcohol 60 promoted by Lewis acids (InX\(_3\), TiX\(_4\), BX\(_3\)), such as , however, no corresponding DHP were formed. Employment of the acetal also gave the negative result.


employed Nicolaou’s conditions\textsuperscript{123} to successfully provide the desired ketone 65 in 93% yield with the intraannular double bond C27-C28 unaffected.

Protection of the carboxyl group of 65 as 1,3-dioxane using trimethylene glycol in the presence of p-TSA and triethyl orthoformate afforded ketal 66 in 94% yield. Triflation of the free hydroxyl group of 66, subsequently by Cul-catalyzed coupling reaction with Grignard reagent 67 to install a methylallyl moiety,\textsuperscript{124} provided 68 in 59% yield over 2 steps. Alkene

\textbf{Scheme 3.15}

Protection of the carboxyl group of 65 as 1,3-dioxane using trimethylene glycol in the presence of p-TSA and triethyl orthoformate afforded ketal 66 in 94% yield. Triflation of the free hydroxyl group of 66, subsequently by Cul-catalyzed coupling reaction with Grignard reagent 67 to install a methylallyl moiety,\textsuperscript{124} provided 68 in 59% yield over 2 steps. Alkene

\textbf{Scheme 3.15}

Protection of the carboxyl group of 65 as 1,3-dioxane using trimethylene glycol in the presence of p-TSA and triethyl orthoformate afforded ketal 66 in 94% yield. Triflation of the free hydroxyl group of 66, subsequently by Cul-catalyzed coupling reaction with Grignard reagent 67 to install a methylallyl moiety,\textsuperscript{124} provided 68 in 59% yield over 2 steps. Alkene

was subjected to the Nicolaou’s condition, providing 58 in 93% yield.\textsuperscript{125} A two-step protocol involving HWE olefination and DIBAL-H reduction were employed to afford an E/Z (81/19) mixture of inseparable diastereomers 59.

DMP oxidation of the allylic alcohol 59 furnished the α,β-unsaturated aldehyde 57.\textsuperscript{126} Fortunately, the diastereomers could be separated after column chromatography and the desired E-isomer was obtained in 66% over yield (3 steps) from 58. The diastereoselectivity was moderate due to the steric hindrance and modest reactivity of ketone 58. In addition, the relative stereochemistries were confirmed by X-ray structures of E and Z isomers 57 (Scheme 3.16).

\textsuperscript{125} An alternative strategy to access the ketone 58 from the alcohol 66 was abandoned, as shown below. A three-step sequence consisting of oxidation, Wittig reaction and conjugated reduction of α,β-unsaturated ketone was proposed to furnish the ketone 58. Much to our surprise, the corresponding aldehyde was not produced via selective oxidation using various conditions involving Swern oxidation, DMP, PCC, Parikh-Doering oxidation, cat. TPAP/NMO. In fact, meanwhile, the proton on C26 was oxidized to hydroxyl group when the oxidation of the hydroxyl group of 66 was observed. A possible pathway could account for this process based on the allylic C-H bond oxidation. It is well know that benzylic carbon atoms could be oxidized by a variety of oxidants, like CrO\textsubscript{3}, CAN, DDQ, O\textsubscript{3}, providing an oxo-carbenium ion, subsequently captured by nucleophile depending on the reaction conditions, resulting in formation of the acetal. We believed that a similar transformation also proceeded through oxo-carbenium mechanism in our reaction system.


\textsuperscript{126} All attempts to attach an acrolein moiety directly through olefin cross metathesis of alkene 68 did not give the desired α,β-unsaturated aldehyde 57. The parallel reactions were performed using acrolein and its analogue crotonaldehyde with 68 induced by Hoveyda-Grubbs catalyst in different solvents (CH\textsubscript{2}Cl\textsubscript{2}, toluene, PhCF\textsubscript{3}) and no trace of product 57 was detected.
After the success synthesis of allylation precursor 57, we moved forward to synthesize the allylic bromide 56 (Scheme 3.17). The synthesis of fragment 56 began with monoprotection as a TBS ether, followed by Swern oxidation without the aldehyde purification and Wittig reaction to provide single $E$-isomer 71 in 70% overall yield (3 steps). DIBAL-H reduction of the ester 71 afforded the alcohol 72, which was further converted to allylic bromide 56 using a combination of CBr₄ and PPh₃.

**Scheme 3.16**

**Scheme 3.17**
3.6.2 Allylation reaction

With the assembly fragment \(\alpha,\beta\)-unsaturated aldehyde 57 and allylic bromide 56 in hand, we proceeded to investigate the critical Barbier-type allylation reaction according to our synthetic plan. Previously, the efficient metal-mediated regioselective allylation had been established by many groups including ours when indium, zinc and tin were employed in aqueous media.\(^{127}\) Apart from the exceptions that the \(\alpha\)-adduct was obtained as major product in a few specific conditions, such as Lewis acids,\(^{128}\) some allylic metal reagents,\(^{129}\) or a certain amount of \(\text{H}_2\text{O}\) performed,\(^{130}\) the allylation of carbonyl compounds with \(\alpha\)-substituted allylic halides occurred specifically at the \(\gamma\)-position. Actually, this strategy has been widely applied to construct complicated molecules owing to the ease and convenience of operation.\(^{131}\)

To investigate the reactivity of indium-mediated allylation with aldehyde 57, several protected allylic bromide were screened under a variety of conditions. The results were summarized in Table 3.1. Tetrahydropyranyl substrate was found to be decomposed even in mild condition (entry 1), while TIPS protecting group was stable enough, however, the reaction cannot


proceeded when the solution was warmed up to 70 °C (entry 2). Employing the allylic bromide bearing TBS protecting group in the organic solvent (DMF) could not undergo allylation (entry 6). Much to our delight, the use of lanthanide(III) triflate as an additive, which had been proven to increase the rate and selectivity of the indium-mediated allylation reaction,\textsuperscript{132} gave an expected mixture of two epimers of C21 alcohol 73 as γ-adduct in 77% yield.

Table 3.1 Screening of reactivity of allylation reactions

<table>
<thead>
<tr>
<th>entries</th>
<th>R</th>
<th>conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>THF/H₂O, rt</td>
<td>56 decomposed</td>
</tr>
<tr>
<td>2</td>
<td>TIPS</td>
<td>THF/H₂O, 70 °C</td>
<td>SM recovered</td>
</tr>
<tr>
<td>3</td>
<td>TIPS</td>
<td>THF/H₂O, La(OTf)₃, rt</td>
<td>SM recovered</td>
</tr>
<tr>
<td>4</td>
<td>TBS</td>
<td>THF/H₂O, rt</td>
<td>SM recovered</td>
</tr>
<tr>
<td>5</td>
<td>TBS</td>
<td>THF/H₂O, 70 °C</td>
<td>56 decomposed</td>
</tr>
<tr>
<td>6</td>
<td>TBS</td>
<td>DMF, rt</td>
<td>SM recovered</td>
</tr>
<tr>
<td>7</td>
<td>TBS</td>
<td>THF/H₂O, La(OTf)₃, rt</td>
<td>77 (58/42)</td>
</tr>
</tbody>
</table>

3.7 Conclusions

The HWE reaction has emerged as a powerful strategy to construct C=C bond in the synthesis of the macrocyclic natural products. In our approach to synthesis of methyl sarcoate 2, although various conditions were screened between the β-ketophosphonate 32 and ketone 31, no olefinaton product 30 was observed. Encouraged by the model study performed, we hope the installation of the isopropyl moiety via the asymmetric conjugate addition prior to the HWE reaction would overcome the deleterious reactivity of 31, which bears α,β-unsaturated ester as the potential culpable functionality. According to the approach (b), the ketone 33 has been prepared successfully, and further investigation into synthesis of methyl sarcoate is underway indicated in the Scheme 3.18, involving HWE olefination, desilylation, Swern oxidation, Pinnick oxidation, methylation and ring closing metathesis.

![Scheme 3.18](image)

In addition, the skeleton structure of the diene unit 3 of methyl sarcophytoate has been successfully constructed in short linear steps. The Prins cyclization facilitated efficient access to the 2,6-trans dihydropyranyl backbone
CuI promoted coupling reaction of the triflate with Grignard reagent introduced the methylallyl moiety at C25 smoothly. The two fragments 56 and 57 were assembled for C21-C34 formation using indium-mediated allylation reaction. Further study, involving dehydration, debromination, deprotection and McMurry coupling reactions towards the total synthesis of methyl sarcophytoate is still ongoing in our laboratory (Scheme 3.19), involving dehydration, debromination, deprotection and McMurry coupling.
3.8 Experimental Section

**Hex-5-en-2-one (35)**

```
  Me   O
  |    |
  |    OEt
  |    Me
  34  \ 1) NaH, BrCH=CH₂, THF, reflux
       O
  |    |
  |    O
  |    Me
  35  2) 10% NaOH, rt
       3) 50% H₂SO₄, reflux
```

To a suspension of sodium hydride (60% in mineral oil, 2.60 g, 0.065 mol, 1.3 equiv) in THF (200 mL) was added dropwise ethyl acetoacetate (8.23 mL, 0.065 mol, 1.3 equiv). The resulting solution was stirred at rt for 30 min and ally bromide (4.33 mL, 0.05 mol, 1 equiv) was added over 30 min. The reaction mixture was stirred for 1 h and further stirred under reflux for 4 h.

Then the solution was cooled to rt and solvent was removed under vacuum. The residue was dissolved in 10% aq NaOH solution (50 mL) and the mixture was stirred at rt for 24 h.

After that, the solution was acidified with 50% H₂SO₄ solution (20 mL) and was heated to reflux for 2 h. The reaction mixture was cooled to rt and extracted with Et₂O (50 mL × 3). The combined organic layer was washed with sat aq NaHCO₃ solution and sat aq NaCl, dried over MgSO₄. Concentration afforded methyl ketone 35 (2.94 g) as a yellow oil, which was used without further purification.

Yield (%): 60%

Rₚ: 0.27 (Hexane/Ethyl acetate = 8/1)

**(E)-Ethyl 3-methylhepta-2,6-dienoate (36a)**

```
  Me   O
  |    |
  |    O
  |    Me
  35  \ 1) (EtO)₂POCH₂CO₂Et, NaH, toluene, reflux
       O
  |    |
  |    O
  |    Me
  36a
```

81
Sodium hydride (60% in mineral oil, 1.50 g, 0.0375 mol, 1.5 equiv) was taken up in dry toluene (150 mL) and cooled to 0 °C. Triethyl phosphonoacetate (6.94 mL, 0.035 mol, 1.4 equiv) was added cautiously as hydrogen was evolved. After 15 min, a solution of the above crude methyl ketone 35 (2.45 g, 0.025 mol, 1 equiv) in toluene (5 mL) was added via syringe. The reaction mixture was refluxed for 10 h and quenched with sat aq NH₄Cl solution (100 mL). The layers were separated and the aqueous phase was extracted with Et₂O (100 mL × 3). The combined organic layers were washed with sat aq NaCl, dried over MgSO₄, and concentrated in vacuo. Purification by flash chromatography afforded mixtures of 36a (2.86 g).

Yield (%): 68% (E/Z = 76/24)

Rf: 0.38 (Hexane/Ethyl acetate: 8/1)

¹H NMR (400 MHz, CDCl₃): δ 5.70 – 5.87 (m, 1H), 5.66 (s, 1H), 5.00 (dd, J = 20.1, 13.4 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 2.22 (d, J = 2.8 Hz, 4H), 2.15 (s, 3H), 1.28 (d, J = 7.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 166.8, 159.0, 137.3, 115.9, 115.3, 59.5, 40.2, 31.5, 18.7, 14.3.


FTIR (KBr): ν 3079, 2980, 2938, 1717, 1649, 1446, 1223, 1150, 1043 cm⁻¹

(E)-Methyl 3-methylhepta-2,6-dienoate (36b)

![Chemical Structure](image)

¹H NMR (400 MHz, CDCl₃): δ 5.69 – 5.87 (m, 1H), 5.67 (s, 1H), 5.95 – 5.07 (m, 2H), 3.67 (s, 3H), 2.23 (d, J = 2.9 Hz, 4H), 2.15 (d, J = 1.2 Hz, 3H).
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 167.2, 159.4, 137.2, 115.5, 115.3, 50.8, 40.1, 31.5, 18.8.

\(\text{(E)-3-Methylhepta-2,6-dien-1-ol}\)

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{DIBAL-H} & \quad \text{CH}_2\text{Cl}_2, \text{-78} \degree\text{C} \\
\text{Me} & \quad \text{OH} & \quad \text{Me}
\end{align*}
\]

To a solution of the ester 36a (2.52 g, 0.015 mol, 1 equiv) in CH\(_2\)Cl\(_2\) (150 mL) at -78 °C was slowly added DIBAL-H (1.0 M in toluene, 30.0 mL, 2 equiv). The resulting solution was stirred at -78 °C for 2 h and quenched with MeOH (10 mL). The mixture was warmed to ambient temperature and stirred for 4 h after adding sat potassium sodium tartrate (50 mL). The layer was separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (100 mL \(\times\) 3). The combined organic layers were washed with sat aq NaCl and dried over Na\(_2\)SO\(_4\). Concentration \textit{in vacuo} and purification by flash chromatography afforded the alcohol (1.67 g) as a colorless oil.

Yield (%): 88%

R\(_f\): 0.29 (Hexane/Ethyl acetate: 2/1)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.73 – 5.83 (m, 1H), 5.40 (t, \(J = 6.4\) Hz, 1H), 4.92 – 5.02 (m, 2H), 4.12 (d, \(J = 6.4\) Hz, 2H), 2.07 – 2.19 (m, 4H), 1.65 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 139.0, 138.3, 123.7, 114.6, 59.2, 38.8, 31.9, 16.2.

HRMS (ESI): m/z calculated for C\(_8\)H\(_{15}\)O [M + H]\(^+\): 127.1123, found: 127.1129.

FTIR (KBr): \(\nu\) 3355, 3079, 2976, 2927, 1641, 1450, 995 cm\(^{-1}\)
(E)-3-Methylhepta-2,6-dienal (37)

To a stirred solution of the alcohol (1.51 g, 0.012 mol, 1 equiv) in CH$_2$Cl$_2$ (60 mL) was added NaHCO$_3$ (4.03 g, 0.048 mol, 4 equiv) and Dess-Martin periodinane (10.18 g, 0.024 mol, 2 equiv) in one portion. The resulting solution was stirred at rt for 2 h. The solid was filtered through a short silica column using CH$_2$Cl$_2$. The filtrate was concentrated in vacuo to give the aldehyde 37 (0.92 g), which was used immediately in the next step.

Yield (%): 62%

R$_f$: 0.43 (Hexane/Ethyl acetate: 4/1)

$^1$H NMR (500 MHz, CDCl$_3$): δ 9.97 (d, $J = 8.0$ Hz, 1H), 5.86 (d, $J = 8.0$ Hz, 1H), 5.72 – 5.80 (m, 1H), 4.97 – 5.05 (m, 2H), 2.25 – 2.30 (m, 4H), 2.15 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 191.2, 163.1, 136.8, 127.6, 115.7, 39.7, 31.2, 17.6.

HRMS (ESI): m/z calculated for C$_8$H$_{13}$O [M + H]$^+$: 125.0966, found: 125.0966.

FTIR (KBr): ν 3079, 2935, 1689, 1641, 1251, 1165 cm$^{-1}$

(E)-Diethyl 2-hydroxy-4-methylocta-3,7-dienylphosphonate (38)

To a solution of diethyl methylphosphonate (1.17 g, 7.7 mmol, 1.1 equiv) in anhydrous THF (40 mL) at -78 °C was added dropwise n-BuLi (1.6 M in hexane, 5.25 mL, 8.4 mmol, 1.2 equiv). The mixture was stirred at -78 °C for 20
min, then a solution of aldehyde 37 (0.87 g, 7.0 mmol, 1 equiv) in THF (5 mL) was added slowly. The reaction mixture was stirred for 1 h while warming up. The reaction was quenched by sat aq NH₄Cl (30 mL). The aqueous phase was extracted with EtOAc (50 mL × 3) and the combined organic phase was washed with sat aq NaCl, dried over Na₂SO₄. Concentration in vacuo and purification by flash chromatography provided 38 (1.61 g).

Yield (%): 83%

R_f: 0.22 (Ethyl acetate)

¹H NMR (400 MHz, CDCl₃): δ 5.70 – 5.80 (m, 1H), 5.23 (d, J = 8.2 Hz, 1H), 4.90 – 5.01 (m, 2H), 4.70 – 4.78 (m, 1H), 4.05 – 4.13 (m, 4H), 3.31 (br, 1H), 2.94 – 2.15 (m, 6H), 1.66 (s, 3H), 1.28 – 1.33 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 138.1, 137.9 (d, J = 1.5 Hz), 127.1 (d, J = 16.0 Hz), 114.6, 63.6 (d, J = 4.2 Hz), 61.8 (d, J = 6.6 Hz), 38.6, 34.1 (d, J = 134.8 Hz), 31.8, 23.2, 16.4 (d, J = 3.8 Hz).


FTIR (KBr): ν 3334, 3077, 2983, 2931, 1640, 1443, 1393, 1222, 1030, 994 cm⁻¹

(E)-Diethyl 4-methyl-2-oxoocta-3,7-dienylphosphonate (32)

To a stirred solution of the β-hydroxyphosphate 38 (1.52 g, 5.5 mmol, 1 equiv) in CH₂Cl₂ (30 mL) was added NaHCO₃ (1.85 g, 22.0 mmol, 4 equiv) and Dess-Martin periodinane (4.67 g, 11.0 mmol, 2 equiv) in one portion. The resulting solution was stirred at rt for 2 h before quenched with sat aq NaHCO₃.
(20 mL). The aqueous layer was extracted with EtOAc (30 mL × 3) and the combined organic phase was washed with sat aq NaCl, dried over Na₂SO₄. Concentration in vacuo and purification by flash chromatography provided β-keto phosphonate E-32 (0.74 g) and Z-isomer (0.23 g).

![Image of E-32](image_url)

Yield (%): 49%

Rf: 0.17 (Ethyl acetate/Hexane = 2/1)

$^1$H NMR (400 MHz, CDCl₃): δ 6.23 (s, 1H), 5.72 – 5.87 (m, 1H), 4.93 – 5.06 (m, 2H), 4.09 – 4.17 (m, 4H), 3.05 (d, J = 22.5 Hz, 2H), 2.24 (d, J = 2.8 Hz, 4H), 2.14 (d, J = 1.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl₃): δ 190.9 (d, J = 5.8 Hz), 160.6, 137.1, 123.5, 115.4, 62.4 (d, J = 6.4 Hz), 40.5, 31.5, 25.7, 19.6, 16.3 (d, J = 6.2 Hz).


FTIR (KBr): ν 3078, 2983, 2931, 1724, 1683, 1615, 1252, 1027, 970 cm$^{-1}$

(Z)-Diethyl 4-methyl-2-oxoocta-3,7-dienylphosphonate

![Image of Z-isomer](image_url)

Yield (%): 15%

Rf: 0.25 (Ethyl acetate/Hexane = 2/1)
RESEARCH TOWARDS THE TOTAL SYNTHESIS OF METHYL SARCOPHYTOATE

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.19 (s, 1H), 5.59 – 5.70 (m, 1H), 4.96 – 5.02 (m, 2H), 4.13 (dq, $J$ = 14.2, 7.2 Hz, 4H), 3.08 (d, $J$ = 22.5 Hz, 2H), 2.18 – 2.24 (m, 4H), 2.06 (s, 3H), 1.31 (t, $J$ = 7.2 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 190.9 (d, $J$ = 6.0 Hz), 162.6, 135.8, 124.4, 116.6, 62.4 (d, $J$ = 6.4 Hz), 49.8, 44.0 (d, $J$ = 126.4 Hz), 37.1, 16.6, 16.4 (d, $J$ = 6.1 Hz).

HRMS (ESI): m/z calculated for C$_{13}$H$_{24}$O$_4$P [M + H]$^+$: 275.1412, found: 275.1407.

FTIR (KBr): $\nu$ 3078, 2980, 2927, 1725, 1683, 1615, 1252, 1025, 999 cm$^{-1}$

1-(tert-Butyldimethylsilyloxy)propan-2-one (40)

<chemical structure>

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.13 (s, 2H), 2.15 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 209.2, 69.6, 26.0, 25.8 × 3, 18.3, -5.5 × 2.

tert-Butyldimethylchlorosilane (3.32 g, 0.022 mol, 1.1 equiv) was added to a solution of hydroxyacetone 39 (95%, 1.56 g, 0.02 mol, 1 equiv) and imidazole (2.04 g, 0.03 mol, 1.5 equiv) in CH$_2$Cl$_2$ (40 mL). The reaction mixture was stirred at rt for 6 h and quenched with H$_2$O (20 mL). The mixture was extracted with CH$_2$Cl$_2$ (30 mL × 3) and the organic layer was dried over Na$_2$SO$_4$. Concentration in vacuo and purification by flash chromatography provided 40 (3.05 g) as a colorless oil.

Yield (%): 81%

R$_f$: 0.32 (Hexane/Ethyl acetate: 8/1)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.13 (s, 2H), 2.15 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H).
HRMS (ESI): m/z calculated for C₉H₂₁O₂Si [M + H]⁺: 189.1311, found: 189.1312.

FTIR (KBr): ν 2957, 2933, 1719, 1473, 1364, 1258, 1119 cm⁻¹

1-(tert-Butyldimethylsilyloxy)-4-hydroxyhex-5-en-2-one (41)

TiCl₄ (1.0 M in CH₂Cl₂, 21.0 mL, 0.021 mol, 1.4 equiv) was added slowly to a stirred solution of 40 (2.83 g, 0.015 mol, 1 equiv) in anhydrous CH₂Cl₂ (30 mL) at -78 °C under a N₂ atmosphere. TMSI (0.10 mL, 0.75 mmol, 0.05 equiv) and n-Bu₃N (5.0 mL, 0.021 mol, 1.4 equiv) was successively added to the mixture, which was stirred for 30 min. Acrolein (1.2 mL, 0.018 mol, 1.2 equiv) was added to the mixture followed by stirred at -78 °C for 2 h. The reaction mixture was quenched with H₂O (20 mL) and extracted with Et₂O (30 mL × 3). The combined organic layer was washed with sat aq NaCl, dried over Na₂SO₄ and concentrated. The obtained residue was purified by flash chromatography to give 41 (1.54 g).

Yield (%): 42%

Rf: 0.21 (Hexane/Ethyl acetate: 4/1)

¹H NMR (400 MHz, CDCl₃): δ 5.88 (ddd, J = 16.6, 10.5, 5.5 Hz, 1H), 5.29 (d, J = 16.6 Hz, 1H), 5.13 (d, J = 10.5 Hz, 1H), 4.58 (apparent s, 1H), 4.18 (s, 2H), 2.95 (br, 1H), 2.69 – 2.79 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 211.0, 139.1, 115.1, 69.7, 68.5, 44.9, 25.8 × 3, 18.3, -5.5 × 2.
HRMS (ESI): m/z calculated for C_{12}H_{25}O_{3}Si [M + H]^+: 245.1573, found: 245.1574.

FTIR (KBr): ν 3417, 2956, 2930, 2858, 1719, 1472, 1256, 1106, 778 cm\(^{-1}\)

\((E)\)-Methyl 7-(tert-butyldimethylsilyloxy)-4-hydroxy-6-oxohept-2-enoate (42)

To a solution of 41 (1.22 g, 5 mmol, 1 equiv) in anhydrous CH\(_2\)Cl\(_2\) (40 mL) was added the Grubbs second-generation catalyst (0.1698 g, 0.2 mmol, 0.04 equiv) followed by freshly distilled methyl acrylate (2.25 mL, 25 mmol, 5 equiv) under an Ar atmosphere. The reaction was allowed to reflux for 4 h and then concentrated in vacuo. The residual crude product was purified by flash chromatography to afford the desired α,β-unsaturated ester 42 (1.24 g) as a colorless oil.

Yield (%): 82%

R\(_f\): 0.53 (Hexane/Ethyl acetate: 4/1)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 6.90 (dd, J = 15.6, 4.2 Hz, 1H), 6.13 (dd, J = 15.6, 1.9 Hz, 1H), 4.77 (apparent s, 1H), 4.17 (s, 2H), 3.74 (s, 3H), 3.22 (br, 1H), 2.84 (dd, J = 17.9, 3.4 Hz, 1H), 2.74 (dd, J = 17.9, 8.8 Hz, 1H), 0.91 (s, 9H), 0.09 (s, 6H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 210.7, 166.9, 148.1, 120.5, 69.5, 66.6, 51.7, 44.2, 25.7 × 3, 18.3, -5.5 × 2.
RESEARCH TOWARDS THE TOTAL SYNTHESIS OF METHYL SARCOPHYTOATE

HRMS (ESI): m/z calculated for $\text{C}_{14}\text{H}_{27}\text{O}_5\text{Si} [\text{M + H}]^+$: 303.1628, found: 303.1624.

FTIR (KBr): $\nu$ 3334, 2956, 2927, 2856, 1714, 1439, 1282, 1067 cm$^{-1}$

$(E)$-Methyl 4,7-bis(tert-butyldimethylsilyloxy)-6-oxohept-2-enoate (31)

![Reaction Scheme]

tert-Butyldimethylchlorosilane (0.90 g, 6 mmol, 1.5 equiv) was added to a stirred solution of 42 (1.21 g, 4 mmol, 1 equiv), DMAP (24.4 mg, 0.2 mmol, 0.05 equiv) and imidazole (0.41 g, 6 mmol, 1.5 equiv) in DMF (30 mL). The reaction mixture was stirred at rt overnight and quenched with H$_2$O (20 mL). The mixture was extracted with Et$_2$O (30 mL $\times$ 3) and the organic layer was dried over Na$_2$SO$_4$. Concentration in vacuo and purification by flash chromatography provided 31 (1.58 g) as a colorless oil.

Yield (%): 95%

$R_f$: 0.45 (Hexane/Ethyl acetate: 8/1)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.94 (dd, $J = 15.6$, 4.8 Hz, 1H), 6.03 (dd, $J = 15.6$, 1.6 Hz, 1H), 4.81 – 4.86 (m, 1H), 4.15 (d, $J = 0.5$ Hz, 2H), 3.73 (s, 3H), 2.80 (dd, $J = 16.4$, 7.2 Hz, 1H), 2.58 (dd, $J = 16.4$, 5.5 Hz, 1H), 0.91 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 207.5, 166.9, 149.9, 120.0, 70.0, 67.8, 51.6, 46.0, 25.8 x 6, 18.3, 18.1, -4.6, -5.2, -5.5, -5.5.

HRMS (ESI): m/z calculated for $\text{C}_{20}\text{H}_{40}\text{O}_5\text{Si}_2\text{Na} [\text{M + Na}]^+$: 439.2312, found: 439.2310.
FTIR (KBr): ν 2956, 2931, 2858, 1727, 1472, 1256, 1166, 837, 778 cm⁻¹

2,2,3,3,10,10,11,11-Octamethyl-8-vinyl-4,9-dioxo-3,10-disiladodecan-6-one (43)

\[
\begin{align*}
\text{41} & \xrightarrow{\text{TBSCI imidazole, cat. DMAP}} \text{CH}_2\text{Cl}_2, \text{rt} \rightarrow \text{43}
\end{align*}
\]

\textit{tert}-Butyldimethylchlorosilane (45.2 mg, 0.3 mmol, 1.5 equiv) was added to a solution of 41 (48.9 mg, 0.2 mmol, 1 equiv), DMAP (1.2 mg, 0.01 mmol, 0.05 equiv) and imidazole (27.2 mg, 0.4 mmol, 2 equiv) in CH₂Cl₂ (5 mL). The reaction mixture was stirred at rt for 24 h and quenched with H₂O (10 mL). The mixture was extracted with Et₂O (10 mL × 3) and the organic layer was dried over Na₂SO₄. Concentration \textit{in vacuo} and purification by flash chromatography provided 43 (64.5 mg) as a colorless oil.

Yield (%): 90%
Rₚ: 0.48 (Hexane/Ethyl acetate: 8/1)

\(^1\)H NMR (400 MHz, CDCl₃): δ 5.82 (ddd, J = 16.6, 10.4, 6.0 Hz, 1H), 5.21 (d, J = 16.6 Hz, 1H), 5.05 (d, J = 10.4 Hz, 1H), 4.62 – 4.66 (m, 1H), 4.18 (s, 2H), 2.71 (dd, J = 15.3, 7.4 Hz, 1H), 2.51 (dd, J = 15.3, 5.2 Hz, 1H), 0.91 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl₃): δ 207.93, 140.50, 114.38, 70.26, 70.10, 46.88, 25.80 × 6, 18.34, 18.11, -4.45, -5.07, -5.42, -5.46.

HRMS (ESI): m/z calculated for C₁₈H₃₈O₃Si₂Na [M + Na]⁺: 381.2257, found: 381.2254.

FTIR (KBr): ν 2957, 2930, 2858, 1724, 1473, 1256, 1087, 837, 777 cm⁻¹
To a solution of 43 (43.0 mg, 0.12 mmol, 1 equiv) in anhydrous CH$_2$Cl$_2$ (2 mL) was added the Grubbs second-generation catalyst (4.1 mg, 0.0048 mmol, 0.04 equiv) followed by freshly distilled methyl acrylate (51.7 mg, 0.6 mmol, 5 equiv) under an Ar atmosphere. The reaction was allowed to reflux for 10 h and then concentrated \textit{in vacuo}. The residual crude product was purified by flash chromatography to afford the desired $\alpha,\beta$-unsaturated ester 42 (18.5 mg) in 37% yield and 60% 43 (25.5 mg) recovered.

\textbf{($E$)-Diethyl 2-(\textit{tert}-butyldimethylsilyloxy)-4-methylocta-3,7-dienylphosphonate (44)}

$\textit{tert}$-Butyldimethylchlorosilane (90.4 mg, 0.6 mmol, 1.2 equiv) was added to a solution of 36 (138.2 mg, 0.5 mmol, 1 equiv), DMAP (3.1 mg, 0.025 mmol, 0.05 equiv) and imidazole (51.1 mg, 0.75 mmol, 1.5 equiv) in CH$_2$Cl$_2$ (5 mL). The reaction mixture was stirred at rt for 12 h and quenched with H$_2$O (10 mL). The mixture was extracted with Et$_2$O (10 mL x 3) and the organic layer was dried over Na$_2$SO$_4$. Concentration \textit{in vacuo} and purification by flash chromatography provided $E$-44 (113.3 mg) and $Z$-44 (21.5 mg) in 58% and 11% yield, respectively.
R_f: 0.35 (Hexane/Ethyl acetate: 1/1)

^1^H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 5.78 (ddt, \( J = 16.8, 10.2, 6.4 \) Hz, 1H), 5.16 (dd, \( J = 8.9, 1.1 \) Hz, 1H), 4.91 – 5.02 (m, 2H), 4.72 – 4.80 (m, 1H), 4.00 – 4.08 (m, 4H), 2.09 – 2.18 (m, 3H), 2.02 – 2.06 (m, 2H), 1.87 – 1.97 (m, 1H), 1.65 (s, 3H), 1.29 (td, \( J = 7.1, 2.0 \) Hz, 6H), 0.85 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).

^13^C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta \) 138.3, 135.1, 128.7 (\( J = 9.4 \) Hz), 114.6, 65.2, 61.3 (d, \( J = 5.2 \) Hz), 38.7, 35.1 × 2 (\( J = 135.3 \) Hz), 31.8, 25.8 × 3, 18.0, 16.6 × 2, 16.4 (\( J = 5.5 \) Hz), -4.5 × 2 (\( J = 50.9 \) Hz).

HRMS (ESI): m/z calculated for C\textsubscript{19}H\textsubscript{39}O\textsubscript{4}PSiNa [M + Na]^+: 413.2253, found: 413.2257.

FTIR (KBr): \( \nu \) 2957, 2930, 2857, 1721, 1641, 1251, 1031, 836, 776 cm\textsuperscript{-1}

\((2E,5E)-1-(\text{tert-Butyldimethylsilyloxy})-2,6\text{-dimethyldeca-2,5,9-trien-4-one}\) (45)

Sodium hydride (60% in mineral oil, 4.8 mg, 0.12 mmol, 1.2 equiv) was taken up in dry toluene (1 mL) and cooled to 0 \(^\circ\)C. \( \beta \)-keto phosphonate 32 (32.9 mg, 0.12 mmol, 1.2 equiv) was added cautiously as hydrogen was evolved. After 15 min, a solution of the ketone 40 (18.8 mg, 0.1 mmol, 1 equiv) in toluene (0.5 mL) was added via syringe. The reaction mixture was stirred at 50 \(^\circ\)C for 8 h and quenched with sat aq NH\textsubscript{4}Cl (5 mL). The layers were separated and the aqueous phase was extracted with Et\textsubscript{2}O (10 mL × 3). The combined organic layers were washed with sat aq NaCl, dried over MgSO\textsubscript{4}, and
concentrated in vacuo. Purification by flash chromatography afforded mixtures of 36a (20.4 g).

Yield (%): 66% (E/Z = 88/12)

R_f: 0.36 (Hexane/Ethyl acetate: 8/1)

^1^H NMR (400 MHz, CDCl\textsubscript{3}): δ 6.36 (s, 1H), 6.09 (s, 1H), 5.75 – 5.87 (m, 1H), 4.97 – 4.06 (m, 2H), 4.10 (s, 2H), 2.23 (apparent s, 4H), 2.17 (s, 3H), 2.04 (s, 3H), 0.93 (s, 9H), 0.09 (s, 6H).

^13^C NMR (100 MHz, CDCl\textsubscript{3}): δ 192.0, 157.1, 155.0, 137.5, 126.1, 122.8, 115.2, 67.2, 40.5, 31.7, 25.9 × 3, 19.2, 15.8, -5.4 × 2.

HRMS (ESI): m/z calculated for C\textsubscript{18}H\textsubscript{32}O\textsubscript{2}SiNa [M + Na]^+: 331.2069, found: 331.2075.

FTIR (KBr): ν 3080, 2956, 2930, 2858, 1673, 1631, 1254, 1126, 838, 779 cm\textsuperscript{-1}

2-(tert-Butyldimethylsilyloxy)ethanol (47)

\[
\begin{align*}
\text{HO} & \text{OH} \\
\text{46} & \text{TBSCI} \\
\text{imidazole, CH}_2\text{Cl}_2, \text{rt} & \text{HO} \text{OTBS} \\
\text{47} &
\end{align*}
\]

tert-Butyldimethylchlorosilane (9.04 g, 0.06 mol, 1 equiv) was added to a stirred solution of ethane-1,2-diol (18.62 g, 0.3 mol, 5 equiv), DMAP (0.29 g, 2.4 mmol, 0.04 equiv) and Et\textsubscript{3}N (46 mL, 0.33 mol, 5.5 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (320 mL) under a N\textsubscript{2} atmosphere at 0 °C. The resulting mixture was stirred at rt for 12 h and quenched with sat aq NaHCO\textsubscript{3} (100 mL). The organic layer was washed with sat aq NaCl, dried over MgSO\textsubscript{4} and concentrated under reduced pressure. Purification by flash chromatography afforded the silylation product 47 (9.10 g) as a colorless oil.

Yield (%): 86%
RESEARCH TOWARDS THE TOTAL SYNTHESIS OF METHYL SARCOPHYTOATE

R<sub>f</sub>: 0.33 (Hexane/Ethyl acetate: 4/1)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.68 – 3.71 (m, 2H), 3.60 – 3.64 (m, 2H), 2.21 (t, J = 6.0 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 6H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 64.1, 63.7, 25.9 × 3, 18.3, -5.4 × 2.

HRMS (ESI): m/z calculated for C<sub>8</sub>H<sub>20</sub>O<sub>2</sub>SiNa [M + Na]<sup>+</sup>: 199.1130, found: 199.1137.

FTIR (KBr): ν 3440, 2956, 2931, 2858, 1472, 1464, 1257, 1116, 1060, 835, 776 cm<sup>-1</sup>

(E)-Methyl 4-(tert-butyldimethylsilyloxy)but-2-enoate (48)

To a solution of oxalyl chloride (5.20 mL, 0.06 mol, 1.2 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (400 mL) cooled to -78 °C was added dropwise a solution of DMSO (4.61 mL, 0.065 mol, 1.3 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). After 15 min, a solution of alcohol 47 (8.82 g, 0.05 mol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added. The reaction solution was stirred at -78 °C for 45 min. Et<sub>3</sub>N (35 mL, 0.25 mol, 5 equiv) was added in one portion and the resulting mixture was allowed to warm up to rt over 1 h. Triphenylphosphoranylidene acetate (20.06 g, 0.06 mol, 1.2 equiv) was added and the reaction was stirred at rt for overnight and refluxed for an additional 2 h. After that, the reaction mixture was cooled to rt and quenched with sat aq NH<sub>4</sub>Cl (150 mL). The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (150 mL × 3). The combined organic extracts were washed with sat aq NaCl and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and
concentrated in vacuo. The residue was purified by flash chromatography to afford the desired E-product (9.03 g).

Yield (%): 78%

Rf: 0.42 (Hexane/Ethyl acetate: 8/1)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.99 (dt, $J = 15.5, 3.4$ Hz, 1H), 6.09 (dt, $J = 15.5, 2.2$ Hz, 1H), 4.32 (dd, $J = 3.4, 2.2$ Hz, 2H), 3.73 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 167.1, 147.7, 119.2, 62.1, 51.5, 25.8 × 3, 18.3, -5.5 × 2.

HRMS (ESI): m/z calculated for C$_{11}$H$_{22}$O$_3$SiNa [M + Na]$^+$: 253.1236, found: 253.1241.

FTIR (KBr): ν 2956, 2930, 2857, 1724, 1663, 1437, 1300, 1137, 836, 777 cm$^{-1}$

**Methyl 3-((tert-butyldimethylsilyloxy)methyl)-4-methylpentanoate (49)**

To a mixture of the ester 48 (8.90 g, 38.6 mmol, 1 equiv) and CuI (0.5518 g, 2.9 mmol, 0.075 equiv) in anhydrous Et$_2$O (300 mL) was added dropwise iso-propylmagnesium chloride (2.0 M in Et$_2$O, 48 mL, 2.5 equiv) over 3 h at -78 °C. After stirring for 18 h, the reaction mixture was quenched by cold MeOH (20 mL) and sat aq NH$_4$Cl (80 mL). The aqueous layer was extracted with Et$_2$O (50 mL × 3). The combined organic extracts were washed with sat aq NaCl, dried over anhydrous MgSO$_4$, concentrated under vacuum, purified by flash silica gel column chromatography to provide 49 (8.20 g) as a clear oil.

Yield (%): 77%
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.65 (s, 3H), 3.56 (ddd, $J = 16.3, 10.1, 5.8$ Hz, 2H), 2.25 – 2.37 (m, 2H), 1.86 – 1.93 (m, 1H), 1.78 (m, 1H), 0.85 – 0.89 (m, 15H), 0.02 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 174.3, 63.5, 51.3, 43.4, 33.4, 28.2, 25.9 × 3, 19.9, 19.3, 18.2, -5.5, -5.6.

5-((tert-Butyldimethylsilyloxy)methyl)-2,6-dimethylhept-1-en-3-ol (50)

![Chemical Structure]

To a solution of the ester 49 (8.03 g, 29.3 mmol, 1 equiv) in hexane (200 mL) at -78 °C was added DIBAL-H (pre-cooled to -78 °C, 1.0 M in heptane, 33.2 mL, 32.2 mmol, 1.1 equiv) carefully over at least 2 portions. The resulting solution was stirred at -78 °C for 1 h and quenched with MeOH (10 mL). The mixture was warmed to ambient temperature and stirred for 4 h after adding sat aq potassium sodium tartrate (50 mL). The layer was separated and the aqueous layer was extracted with Et$_2$O (100 mL × 3). The combined organic layers were washed with sat aq NaCl and dried over Na$_2$SO$_4$. Concentration in vacuo afforded the crude aldehyde without further purification.

To a solution of the previous residue in Et$_2$O (300 mL) at -40 °C was added dropwise isopropenylmagnesium bromine (0.5 M in THF, 117 mL, 58.5 mmol, 2 equiv). The reaction mixture was stirred at -40 °C for 2 h and quenched with MeOH (10 mL) and sat aq NH$_4$Cl (100 mL) prior to warm to rt. The layer was separated and the aqueous layer was extracted with Et$_2$O (100 mL × 3). The combined organic layers were washed with sat aq NaCl and dried
over Na$_2$SO$_4$. Concentration in vacuo and purification by flash chromatography afforded the alcohol 50 (5.54 g) as a colorless oil.

Yield (%): 66% ($dr = 50:50$)

$^1$H NMR (diastereomers, 500 MHz, CDCl$_3$): $\delta$ 4.99 (s, 1H), 4.98 (s, 1H), 4.83 (s, 1H), 4.79 (s, 1H), 4.19 (dd, $J = 10.7$, 5.3 Hz, 1H), 3.99 (d, $J = 9.5$ Hz, 1H), 3.93 (d, $J = 2.5$ Hz, 1H), 3.68 (ddd, $J = 19.0$, 9.8, 3.8 Hz, 2H), 3.56 (dd, $J = 9.9$, 6.9 Hz, 1H), 3.48 (t, $J = 9.3$ Hz, 1H), 3.17 (d, $J = 4.6$ Hz, 1H), 1.74 (s, 3H), 1.73 (s, 3H), 1.67 – 1.70 (m, 1H), 1.66 (dd, $J = 5.9$, 2.8 Hz, 1H), 1.60 – 1.62 (m, 2H), 1.52 – 1.59 (m, 2H), 0.85 – 0.93 (m, 30H), 0.09 (s, 6H), 0.08 (s, 6H).

$^{13}$C NMR (diastereomers, 125 MHz, CDCl$_3$): $\delta$ 148.3, 147.9, 110.3, 110.1, 76.1, 72.9, 66.4, 65.3, 45.3, 42.2, 37.1, 35.5, 30.4, 29.5, 25.9 × 3, 25.9 × 3, 19.9, 19.9, 19.6, 19.0, 18.6, 18.3, 18.3, 17.7, -5.5, -5.5, -5.5, -5.5.

6,10,10-Triisopropyl-2,2,3,3,11-pentamethyl-8-(prop-1-en-2-yl)-4,9-dioxo-3,10-disiladodecane (51)

Triisopropylsilyl trifluoromethanesulfonate (3.23 mL, 12 mmol, 1.2 equiv) was added dropwise to a stirred solution of 50 (2.87 g, 10 mmol, 1 equiv) and 2,6-lutidine (1.75 mL, 15 mmol, 1.5 equiv) in CH$_2$Cl$_2$ (80 mL) under a N$_2$ atmosphere at -78 °C. The resulting mixture was stirred at -78 °C for 1 h and diluted with CH$_2$Cl$_2$ (50 mL) and sat aq NaCl (40 mL). The organic layer was separated and dried over Na$_2$SO$_4$. Concentration in vacuo and purification by flash chromatography afforded 51 (2.44 g) as a colorless oil.
Yield (%): 55% (dr = 50:50)

$^1$H NMR (diastereomers, 400 MHz, CDCl$_3$): $\delta$ 4.84 (s, 1H), 4.80 (s, 1H), 4.80 (s, 1H), 4.78 (s, 1H), 4.22 – 4.29 (m, 2H), 3.67 (s, 1H), 3.56 – 3.59 (m, 1H), 3.45 – 3.50 (m, 2H), 1.80 – 1.93 (m, 2H), 1.70 (s, 3H), 1.69 (s, 3H), 1.37 – 1.56 (m, 5H), 1.27 – 1.18 (m, 1H), 1.06 (s, 36H), 0.94 – 0.82 (m, 36H), 0.03 (s, 6H), 0.02 (s, 6H).

$^{13}$C NMR (diastereomers, 100 MHz, CDCl$_3$): $\delta$ 147.7, 147.1, 112.0, 111.2, 76.3, 76.2, 63.6, 63.6, 42.4, 42.2, 34.2, 33.4, 27.9, 27.5, 26.0, 25.9, 25.9, 20.2, 19.2, 18.6, 18.2, 18.1, 18.1, 16.7, 15.9, 12.5, 12.4, -5.4, -5.5.

2-Isopropyl-5-methyl-4-(triisopropylsilyloxy)hex-5-en-1-ol (52)

The silyl ether 51 (2.21 g, 5 mmol, 1 equiv) and camphor-10-sulfonic acid (0.1152 g, 0.5 mmol, 0.1 equiv) in the solution of CH$_2$Cl$_2$/MeOH (v:v = 1:1, 50 mL) was stirred for 10 h at rt. After the starting material was consumed monitored by TLC, the reaction mixture was treated with Et$_3$N (0.70 mL, 5 mmol, 1 equiv) and concentrated in vacuo. The residue was purified by flash chromatography to afford 52 (1.08 g) as a colorless oil.

Yield (%): 66% (dr = 50:50)

$^1$H NMR (diastereomers, 400 MHz, CDCl$_3$): $\delta$ 5.01 (s, 1H), 4.92 (s, 1H), 4.84 (s, 1H), 4.81 (s, 1H), 4.36 (t, $J$ = 4.7 Hz, 1H), 4.27 (dd, $J$ = 8.4, 5.7 Hz, 1H), 3.51 – 3.63 (m, 4H), 3.44 – 3.50 (m, 1H), 3.06 (dd, $J$ = 8.4, 3.6 Hz, 1H), 1.71 – 1.89 (m, 4H), 1.70 (s, 3H), 1.67 (s, 3H), 1.38 – 1.62 (m, 6H), 1.32 – 1.38 (m, 2H), 1.03 – 1.10 (m, 38H), 0.91 – 0.83 (m, 12H).
$^{13}$C NMR (diastereomers, 100 MHz, CDCl$_3$): $\delta$ 147.2, 145.6, 112.0, 111.9, 76.5, 75.5, 65.4, 64.1, 42.8, 41.9, 35.4, 34.1, 30.1, 28.4, 20.1, 19.6, 19.1, 18.8, 18.5, 18.3, 18.1, 18.1, 18.0, 18.0, 17.7, 16.2, 12.4, 12.3.

8-Hydroxy-9,13,13-triisopropyl-2,2,3,3,14-pentamethyl-11-(prop-1-en-2-yl)-4,12-dioxa-3,13-dilsilapentadecan-6-one (54)

To a stirred solution of the alcohol 52 (0.3286 g, 1 mmol, 1 equiv) in CH$_2$Cl$_2$ (10 mL) was added NaHCO$_3$ (0.2520 g, 3 mmol, 3 equiv) and Dess-Martin periodinane (0.6362 g, 1.5 mmol, 1.5 equiv) in one portion. The resulting solution was stirred at 0 °C for 1.5 h and concentrated in vacuo. The residue was flashed through a short silica gel column to provide the aldehyde 53 (0.2870 g, 88%), which was used immediately in the next step.

To a stirred solution of the ketone 40 (0.2483 g, 1.3 mmol, 1.5 equiv) in Et$_2$O (8 mL) was added sequentially N,N-diisopropylethylamine (0.68 mL, 3.96 mmol, 4.5 equiv) and chlorodicyclohexylborane (1 M in hexanes, 2.64 mL, 2.64 mmol, 3.0 equiv) at 0 °C. After 30 min, the reaction mixture was cooled to -78 °C and treated with a solution of freshly prepared aldehyde 53 (0.2870 g, 0.88 mmol, 1 equiv) in Et$_2$O (1 mL). After 6 h, the mixture was quenched by MeOH (2 mL) and sat aq NH$_4$Cl (10 mL). The aqueous phase was extracted with Et$_2$O (10 mL × 3), washed with sat aq NaCl and dried over MgSO$_4$. Concentration in vacuo and purification by flash chromatography provided the aldol adduct 54 (0.3170 g).
Yield (%): 70% \((dr = 50:50)\)

\(^1\)H NMR (diastereomers, 400 MHz, CDCl\(_3\)): \(\delta 4.84\) (s, 2H), \(4.80\) (s, 2H), \(4.29\) – \(4.35\) (m, 2H), \(4.20\) (s, 1H), \(4.19\) (s, 2H), \(4.14\) (s, 4H), \(4.05\) – \(4.09\) (m, 1H), \(3.01\) (s, 1H), \(2.63\) (d, \(J = 6.0\) Hz, 4H), \(2.16\) (s, 6H), \(1.75\) – \(1.82\) (m, 2H), \(1.70\) (d, \(J = 4.5\) Hz, 4H), \(1.41\) – \(1.62\) (m, 6H), \(1.28\) – \(1.36\) (m, 2H), \(1.00\) – \(1.08\) (m, 36H), \(0.91\) (d, \(J = 7.2\) Hz, 30H), \(0.08\) (s, 12H).

\(^{13}\)C NMR (diastereomers, 100 MHz, CDCl\(_3\)): \(\delta 211.7, 209.2, 147.4, 147.2, 112.1, 111.9, 77.2, 69.8, 69.7, 69.6, 69.3, 68.6, 45.2, 44.9, 44.0, 42.7, 33.5, 32.6, 28.5, 28.2, 26.0, 25.8, 25.8, 21.5, 20.8, 19.3, 18.4, 18.3, 18.3, 18.2, 18.2, 18.1, 18.1, 16.6, 16.2, 13.2, 12.5, 12.5, -5.5, -5.5, -5.5.

8-(\textit{tert}-Butyldimethylsilyloxy)-9,13,13-triisopropyl-2,2,3,3,14-pentamethyl-11-(prop-1-en-2-yl)-4,12-dioxa-3,13-disila pentadecan-6-one (33)

\textit{tert}-Butyldimethylsilyl trifluoromethanesulfonate 54 (0.21 mL, 0.9 mmol, 1.5 equiv) was added dropwise to a stirred solution of 54 (0.3090 g, 0.6 mmol, 1 equiv) and 2,6-lutidine (0.14 mL, 1.2 mmol, 2 equiv) in CH\(_2\)Cl\(_2\) (6 mL) under a N\(_2\) atmosphere at -40 °C. The resulting mixture was stirred at -40 °C for 2 h and diluted with CH\(_2\)Cl\(_2\) (10 mL) and sat aq NaCl (10 mL). The organic layer was separated and dried over Na\(_2\)SO\(_4\). Concentration \textit{in vacuo} and purification by flash chromatography afforded 33 (0.2680 g) as a colorless oil.

Yield (%): 71% \((dr = 50:50)\)
RESEARCH TOWARDS THE TOTAL SYNTHESIS OF M ETHYL SARCOPHYTOATE

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.90 (s, 1H), 4.85 (s, 1H), 4.36 – 4.47 (m, 1H), 4.24 (dd, $J$ = 9.6, 4.7 Hz, 1H), 4.12 (s, 2H), 3.54 (s, 1H), 2.84 (dd, $J$ = 16.8, 8.8 Hz, 1H), 2.40 (dd, $J$ = 16.8, 2.5 Hz, 1H), 1.95 – 2.07 (m, 1H), 1.70 (s, 3H), 1.48 – 1.61 (m, 2H), 1.36 (dd, $J$ = 9.6, 4.9 Hz, 1H), 1.28 (ddd, $J$ = 9.4, 7.9, 3.7 Hz, 2H), 0.98 – 1.15 (m, 24H), 0.79 – 0.96 (m, 18H), 0.09 (s, 3H), 0.08 (s, 3H), 0.02 (s, 3H), -0.04 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 209.1, 146.6, 112.9, 75.8, 70.0, 68.6, 45.4, 42.1, 32.9, 25.9 × 6, 22.9, 19.7, 18.1 × 3, 18.0 × 2, 15.7, 12.4 × 3, 11.8, -4.4, -4.7, -5.5, -5.5.

Isopropyl 2-hydroxy-3-methylpenta-3,4-dienoate (60)

To a solution of diisopropyl L-tartrate (2.34g, 10 mmol, 1 equiv) in dry Et$_2$O (60 mL) cooled was added periodic acid (2.28 g, 10 mmol, 1 equiv) in portions over 1 h under N$_2$ at 0 °C. The resulting reaction was stirred for 4 h, decanted from the solid precipitate, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to give a yellow oil. The crude residue product 62 was directly used for next step without purification.

To a suspension of indium powder (172.2 mg, 1.5 mmol, 1.5 equiv) in 3 mL THF/ sat aq NH$_4$Cl (v/v, 1:1) was added isopropyl glyoxalate 62 (116.1 mg, 1 mmol, 1 equiv) and then 1-bromo-but-2-yn (200.0 mg, 1.5 mmol, 1.5 equiv) at 0 °C. The mixture was allowed to warm to rt and vigorously stirred under N$_2$ for overnight. After the completion of the reaction, the resulting mixture was
quenched with 5 mL 1M HCl solution. The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic extracts were washed with sat aq NaCl, dried over anhydrous MgSO₄, concentrated under vacuum, purified by flash silica gel column chromatography to provide 60 (112.0 mg) as a clear oil. Yield: 66%

Rᵣ: 0.21 (Hexane: Ethyl acetate = 8:1)

¹H NMR (400 MHz, CDCl₃): 5.09 (hept, J = 6.3 Hz, 1H), 4.85 – 4.74 (m, 2H), 4.50 (d, J = 7.3 Hz, 1H), 3.07 (d, J = 7.3 Hz, 1H), 1.71 (t, J = 3.2 Hz, 3H), 1.27 (t, J = 6.3 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃): 206.6, 172.6, 98.0, 77.0, 72.3, 69.9, 21.7, 14.4.


FTIR (KBr): ν 3425, 2984, 2938, 2882, 1962, 1724, 1431, 1376, 1236, 1105 857 cm⁻¹

(2,6-trans)-Isopropyl 4-bromo-6-((E)-but-2-en-2-yl)-3-methyl-5,6-dihydro-2H-pyran-2-carboxylate (63)

To an oven dried 10 mL round-bottom flask with a magnetic stirring bar was added indium(III) triflate (84.3 mg, 0.15 mmol, 0.15 equiv) and 0.2 g 4 Å molecular sieves in 8 mL anhydrous CH₂Cl₂. The mixture was allowed to cool to -10 °C prior to addition of trimethylsilyl bromide (0.40 mL, 3 mmol, 3 equiv). Tiglic aldehyde (0.12 mL, 1.2 mmol, 1.2 equiv) was added within 5 min. Then
a solution of isopropyl 2-hydroxy-3-methylpent-3,4-dienoate 60 (170.2 mg, 1 mmol, 1 equiv) dissolved in 2 mL anhydrous CH₂Cl₂ was added using syringe pump addition over a period of 1 h. The reaction was stirred at -10 °C for 72 h, then slowly warmed up to room temperature and kept for 1 h. The mixture was quenched with sat aq NaHCO₃ (10 mL). The aqueous layer was extracted with Et₂O (15 mL x 3). The combined organic layers were washed with sat aq NaCl, and dried over anhydrous MgSO₄, filtered and concentrated \textit{in vacuo}. The residue crude product was purified by flash column chromatography to afford 63 (168.0 mg) as a pale yellow colorless oil.

Yield: 53%

Rᵣ: 0.44 (Hexane: Ethyl acetate = 8:1)

$^{1}$H NMR (300 MHz, CDCl₃): 5.60 (q, $J = 6.8$ Hz, 1H), 5.07 (dt, $J = 12.5$, 6.3 Hz, 1H), 4.65 (dd, $J = 10.7$, 3.4 Hz, 1H), 4.59 (s, 1H), 2.80 – 2.64 (m, 1H), 2.39 (d, $J = 17.9$ Hz, 1H), 1.89 (s, 4H), 1.66 (s, 3H), 1.63 (d, $J = 6.8$ Hz, 3H), 1.28 (d, $J = 6.3$ Hz, 7H).

$^{13}$C NMR (75.4 MHz, CDCl₃): 169.8, 134.2, 127.9, 122.6, 119.1, 77.4, 76.7, 69.1, 39.3, 21.8, 19.3, 13.2, 11.8.


FTIR (KBr): ν 2981, 2934, 2921, 1733, 1454, 1374, 1282, 1180, 1105 cm⁻¹

(2,6-trans)-4-Bromo-6-((E)-but-2-en-2-yl)-3-methyl-5,6-dihydro-2H-pyran-2-yl)methanol (64)
To a solution of the ester 63 (0.9520 g, 3 mmol, 1 equiv) in 20 mL anhydrous Et₂O at 0 °C was added lithium borohydride (2M in THF solution, 3.75 mL, 2.5 equiv). The mixture was allowed to warm to rt and kept for 12 h. After the completion of the reaction monitored by TLC, the reaction mixture was quenched by sat aq NH₄Cl cautiously. The layers were separated and the aqueous solution was extracted with Et₂O (15 mL × 3), the combined organic extracts were dried over MgSO₄, concentrated under vacuum, purified by flash silica gel column chromatography to provide 64 (0.6901 g) as a colorless oil.

Yield: 88%

Rf: 0.46 (Hexane: Ethyl acetate = 2:1)

¹H NMR (400 MHz, CDCl₃): 5.53 (q, J = 6.8 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.74 (dd, J = 11.6, 8.9 Hz, 1H), 3.66 (dd, J = 11.6, 2.2 Hz, 1H), 2.72 – 2.62 (m, 1H), 2.38 (d, J = 16.4 Hz, 2H), 1.75 (s, 3H), 1.63 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): 134.2, 129.8, 121.9, 117.7, 78.7, 74.0, 61.5, 39.7, 18.9, 13.1, 12.0.

HRMS (ESI): m/z calculated for C₁₁H₁₇O₂⁷⁹BrNa [M + Na]⁺: 283.0310, found: 283.0307.

FTIR (KBr): v 3440, 2920, 2885, 2863, 1672, 1442, 1380, 1091, 1048 cm⁻¹

1-(2,6-trans)-4-Bromo-6-(hydroxymethyl)-5-methyl-3,6-dihydro-2H-pyran-2-yl)ethanone (65)
To a solution of the alkene 64 (0.6530 g, 2.5 mmol, 1 equiv) in 25 mL acetone/water (v/v, 10:1) was added 2,6-lutidine (0.58 mL, 5 mmol, 2 equiv), NMO (50 wt. % in H₂O, 0.78 mL, 3.75 mmol, 1.5 equiv), and osmium tetraoxide (4 wt. % in H₂O, 0.32 mL, 0.05 mmol, 0.02 equiv). The reaction mixture was stirred vigorously for 6 h before iodobenzene diacetate (1.2080 g, 3.75 mmol, 1.5 equiv) was added in one portion. After stirring for 4 h, the reaction was quenched with sat aq sodium thiosulfate (10 mL). The mixture was extracted with EtOAc (20 mL × 3), washed with sat aq CuSO₄ (20 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude residue was purified by flash column chromatography to give 65 (0.5785 g) as a colorless oil.

Yield: 93%

R⁰: 0.18 (Hexane: Ethyl acetate = 2:1)

¹H NMR (400 MHz, CDCl₃): δ 4.40 (t, J = 6.2 Hz, 1H), 4.27 (t, J = 4.3 Hz, 1H), 3.73 (d, J = 2.0 Hz, 1H), 3.72 (s, 1H), 2.80 (br, 1H), 2.63 – 2.65 (m, 2H), 2.19 (s, 3H), 1.75 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): 207.1, 130.3, 116.0, 79.2, 75.3, 61.9, 36.4, 25.9, 19.0.


FTIR (KBr): ν 3447, 2923, 2892, 1721, 1670, 1354, 1277, 1107 cm⁻¹
To a stirred solution of the ketone 65 (0.5480 g, 2.2 mmol, 1 equiv) in 20 mL anhydrous toluene was added 1,3-propanediol (0.5022 g, 6.6 mmol, 3 equiv), triethyl orthoformate (1.10 mL, 6.6 mmol, 3 equiv) and p-TSA (41.8 mg, 0.22 mmol, 0.1 equiv). The reaction mixture was stirred for 8 h. The reaction was quenched with sat aq NaHCO₃ (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with sat aq NaCl, dried over MgSO₄, concentration under vacuum and purified by flash column chromatography to afford the product 66 (0.6355 g) as a colorless oil.

Yield: 94%

Rᵣ: 0.20 (Hexane: Ethyl acetate = 1:1)

¹H NMR (400 MHz, CDCl₃): δ 4.26 (d, J = 9.0 Hz, 1H), 4.00 (qd, J = 11.4, 3.0 Hz, 2H), 3.88 (dd, J = 10.3, 3.3 Hz, 3H), 3.74 – 3.79 (m, 1H), 3.68 (dd, J = 11.4, 3.0 Hz, 1H), 2.74 – 2.83 (m, 1H), 2.47 (d, J = 17.1 Hz, 1H), 2.32 (br, 1H), 1.91 – 2.02 (m, 1H), 1.75 (s, 3H), 1.48 (s, 3H), 1.45 (t, J = 3.0 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): 129.7, 118.1, 98.4, 78.9, 73.0, 61.0, 59.9, 59.7, 35.3, 25.5, 18.9, 15.0.


FTIR (KBr): ν 3447, 2949, 2925, 2880, 1718, 1670, 1354, 1254, 1157, 1057, 733 cm⁻¹
RESEARCH TOWARDS THE TOTAL SYNTHESIS OF METHYL SARCOPHYTOATE

2-((2,6-trans)-4-Bromo-5-methyl-6-(3-methylbut-3-enyl)-3,6-dihydro-2H-pyran-2-yl)-2-methyl-1,3-dioxane (68)

To a solution of the alcohol 66 (0.2150 g, 0.7 mmol, 1 equiv) in CH$_2$Cl$_2$ (8 mL) at -78 °C was added 2,6-ludidine (0.16 mL, 1.4 mmol, 3 equiv) and trifluoromethanesulfonic anhydride (0.17 mL, 1.1 mmol, 1.5 equiv). The reaction mixture was stirred at -78 °C for 1 h then slowly warmed up to rt before the reaction was quenched with sat aq NaHCO$_3$ (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (10 mL × 3), washed with sat aq NaCl, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give the crude triflate which was immediately used in the next reaction without further purification.

To a solution of methylallylmagnesium chloride 67 (0.5 M in THF, 14 mL, 7 mmol, 10 equiv) in THF at -78 °C was added copper(I) iodide (0.6666 g, 3.5 mmol, 5 equiv). Then the reaction mixture was warmed to 0 °C and cooled back to -40 °C. A solution of the triflate intermediate in THF (2mL) was added dropwise into the suspension. After stirring for 1 h, the reaction mixture was allowed to warm to room temperature over a period of 2 h with stirring. The mixture was treated with saturated NH$_4$Cl solution (10 mL) at 0 °C. The aqueous phase was extracted with EtOAc (20 mL × 3) and the combined organic extracts were dried over Na$_2$SO$_4$. Concentration and flash chromatography provided 68 (0.1423 g) as a colorless oil.

Yield: 59%

R$_f$: 0.28 (Hexane: Ethyl acetate = 4:1)
RESEARCH TOWARDS THE TOTAL SYNTHESIS OF METHYL SARCOPHYTOATE

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.72 (s, 1H), 4.70 (s, 1H), 4.10 (d, $J$ = 10.1 Hz, 1H), 3.95 – 4.05 (m, 2H), 3.81 – 3.94 (m, 2H), 3.78 (dd, $J$ = 10.1, 3.7 Hz, 1H), 2.90 (dd, $J$ = 16.2, 11.4 Hz, 1H), 2.45 (d, $J$ = 17.2 Hz, 1H), 2.29 (ddd, $J$ = 14.7, 10.1, 4.8 Hz, 1H), 2.04 – 2.12 (m, 1H), 1.96 (ddd, $J$ = 17.2, 11.4, 5.7 Hz, 1H), 1.70 – 1.77 (m, 8H), 1.52 (s, 3H), 1.41 – 1.46 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): 145.3, 133.3, 116.8, 110.3, 98.5, 78.2, 72.5, 60.0, 59.6, 34.9, 34.2, 29.0, 25.7, 22.6, 19.3, 16.1.


FTIR (KBr): $\nu$ 3075, 2963, 2927, 2875, 1714, 1450, 1368, 1254, 1156, 1110, 968 cm$^{-1}$

4-((2,6-trans)-4-Bromo-3-methyl-6-(2-methyl-1,3-dioxan-2-yl)-5,6-dihydro-2H-pyran-2-yl)butan-2-one (58)

To a solution of the alkene 68 (124.3 mg, 0.36 mmol, 1 equiv) in 4 mL acetone/water (v/v, 10:1) was added 2,6-lutidine (0.08 mL, 0.72 mmol, 2 equiv), NMO (50 wt. % in H$_2$O, 0.11 mL, 0.54 mmol, 1.5 equiv), and osmium tetraoxide (4 wt. % in H$_2$O, 0.05 mL, 0.0072 mmol, 0.02 equiv). The mixture was stirred vigorously for 4 h the iodobenzene diacetate (0.54 mmol, 1.5 equiv) was added. After stirring for 2 h, the reaction was quenched with sat aq sodium thiosulfate (10 mL). The mixture was extracted with EtOAc (10 mL x 3), washed with sat aq CuSO$_4$ (20 mL), dried over Na$_2$SO$_4$, and concentrated in
vacuo. The crude residue was purified by flash column chromatography to give 116.8 mg of the product 58.

Yield: 93%

$^1$H NMR (400 MHz, CDCl$_3$): 3.92 – 4.05 (m, 3H), 3.83 (dd, $J = 13.6$, 10.6 Hz, 2H), 3.72 (dd, $J = 10.5$, 3.7 Hz, 1H), 2.80 (dd, $J = 17.1$, 10.6 Hz, 1H), 2.62 (dd, $J = 10.3$, 5.0 Hz, 2H), 2.41 (d, $J = 17.1$ Hz, 1H), 2.13 (s, 3H), 1.88 – 1.97 (m, 2H), 1.7 – 1.82 (m, 1H), 1.74 (s, 3H), 1.45 (s, 3H), 1.41 – 1.42 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): 208.3, 133.1, 116.8, 98.4, 77.5, 72.4, 59.9, 59.6, 39.5, 35.0, 30.2, 25.6, 24.4, 19.2, 15.7.

**(E)-Ethyl 5-((2,6-trans)-4-bromo-3-methyl-6-(2-methyl-1,3-dioxan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-3-methylpent-2-enoate**

Sodium hydride (60% in mineral oil, 19.2 mg, 0.48 mmol, 1.5 equiv) was taken up in dry toluene (3 mL) and cooled to 0 °C. Triethyl phosphonoacetate (0.09 mL, 0.45 mmol, 1.4 equiv) was added cautiously as hydrogen was evolved. After 15 min, a solution of the ketone 58 (0.1111 g, 0.32 mmol, 1 equiv) in toluene (0.5 mL) was added via syringe. The reaction mixture was refluxed for 8 h and quenched with sat aq NH$_4$Cl (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with sat aq NaCl, dried over MgSO$_4$, and concentrated in vacuo. Purification by flash chromatography afforded mixtures of the ester (0.1150 g).
Yield: 86% \((E/Z = 81/19)\)

\[^1^H\text{NMR (400 MHz, CDCl}_3\text{): }\delta 5.68\text{ (s, 1H)}, 4.13\text{ (t, } J = 7.0\text{ Hz, 2H)}, 4.06\text{ (d, } J = 10.4, 3.7\text{ Hz, 1H)}, 3.95 -- 4.01\text{ (m, 2H)}, 3.81 -- 3.89\text{ (m, 2H)}, 3.74\text{ (dd, } J = 10.4, 3.7\text{ Hz, 1H)}, 2.84 -- 2.91\text{ (m, 1H)}, 2.39 -- 2.47\text{ (m, 2H)}, 2.18 -- 2.24\text{ (m, 1H)}, 2.16\text{ (s, 3H)}, 1.97\text{ (qd, } J = 11.4, 5.6\text{ Hz, 1H)}, 1.73 -- 1.81\text{ (m, 2H)}, 1.73\text{ (s, 3H)}, 1.51\text{ (s, 3H)}, 1.43\text{ (dt, } J = 13.3, 2.6\text{ Hz, 1H)}, 1.26\text{ (t, } J = 7.0\text{ Hz, 3H)}.\]

\((E)-5-((2,6-trans)-4-Bromo-3-methyl-6-(2-methyl-1,3-dioxan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-3-methylpent-2-en-1-ol\) (59)

To a solution of the ester \((0.1043\text{ g, 0.25 mmol, 1 equiv})\) in \(\text{CH}_2\text{Cl}_2\) \((2.5\text{ mL})\) at \(-78\text{ °C}\) was slowly added DIBAL-H \((1.0\text{ M in toluene, 0.50 mL, 2 equiv})\). The resulting solution was stirred at \(-78\text{ °C}\) for 1 h and quenched with MeOH \((0.5\text{ mL})\). The mixture was warmed to ambient temperature and stirred for 2 h after adding sat aq potassium sodium tartrate \((5\text{ mL})\). The layer was separated and the aqueous layer was extracted with EtOAc \((10\text{ mL} \times 3)\). The combined organic layers were washed with sat aq NaCl and dried over \(\text{Na}_2\text{SO}_4\). Concentration \textit{in vacuo} and purification by flash chromatography afforded the alcohol 59 \((94.0\text{ mg})\) as a colorless oil.

Yield: 99% \((E/Z = 81/19)\)

\[^1^H\text{NMR (400 MHz, CDCl}_3\text{): }\delta 5.44\text{ (dt, } J = 6.9, 1.1\text{ Hz, 1H)}, 4.10 -- 4.15\text{ (m, 2H)}, 4.04 -- 4.08\text{ (m, 1H)}, 3.95 -- 4.02\text{ (m, 2H)}, 3.81 -- 3.90\text{ (m, 2H)}, 3.76\text{ (dd, } J = 13.3, 2.6\text{ Hz, 1H)}, 1.51\text{ (s, 3H)}, 1.43\text{ (dt, } J = 13.3, 2.6\text{ Hz, 1H)}, 1.26\text{ (t, } J = 7.0\text{ Hz, 3H}).\]
= 10.4, 3.8 Hz, 1H), 2.85 – 2.91 (m, 1H), 2.44 (dd, J = 17.3, 1.6 Hz, 1H), 2.25 – 2.36 (m, 1H), 2.05 – 2.14 (m, 1H), 1.92 – 2.02 (m, 1H), 1.73 (apparent s, 3H), 1.68 (s, 3H), 1.52 (s, 3H), 1.25 (d, J = 1.6 Hz, 3H).

5-((2,6-trans)-4-Bromo-3-methyl-6-(2-methyl-1,3-dioxan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-3-methylpent-2-enal (57)

To a stirred solution of the alcohol 59 (82.6 mg, 0.22 mmol, 1 equiv) in CH₂Cl₂ (2 mL) was added NaHCO₃ (73.9 mg, 0.88 mmol, 4 equiv) and Dess-Martin periodinane (186.6 mg, 0.44 mmol, 2 equiv) in one portion. The resulting solution was stirred at rt for 1.5 h before quenched with sat aq NaHCO₃ (5 mL). The aqueous layer was extracted with Et₂O (10 mL × 3) and the combined organic phase was washed with sat aq NaCl, dried over Na₂SO₄. Concentration in vacuo and purification by flash chromatography provided α,β-unsaturated aldehyde E-57 (64.0 mg) and Z-57 (14.9 g).

Yield: 78% (E); m.p. 116 – 117 °C.

Rf : 0.26 (Hexane: Ethyl acetate = 2:1)

¹H NMR (400 MHz, CDCl₃): δ 9.98 (d, J = 8.0 Hz, 1H), 5.90 (d, J = 8.0 Hz, 1H), 4.08 (d, J = 10.1 Hz, 1H), 4.00 (qd, J = 11.7, 2.9 Hz, 2H), 3.81 – 3.90 (m, 2H), 3.74 (dd, J = 10.4, 3.7 Hz, 1H), 2.82 – 2.90 (m, 1H), 2.49 – 2.57 (m, 1H), 2.46 (d, J = 17.4 Hz, 1H), 2.24 – 2.31 (m, 1H), 2.18 (s, 3H), 1.91 – 2.03 (m, 1H), 1.77 – 1.82 (m, 2H), 1.74 (s, 3H), 1.50 (s, 3H), 1.41 – 1.46 (m, 1H).
$^{13}$C NMR (100 MHz, CDCl$_3$): 191.1, 163.2, 132.7, 127.5, 117.2, 98.4, 77.7, 72.9, 60.0, 59.7, 37.0, 34.9, 28.5, 25.6, 19.3, 17.8, 15.7.

HRMS (ESI): $m/z$ calculated for C$_{17}$H$_{25}$O$_4$-BrNa [M + Na]$^+$: 395.0834, found: 395.0843.

FTIR (KBr): 3055, 2987, 2959, 2874, 1668, 1156, 1110, 736 cm$^{-1}$

Yield: 18% (Z); m.p. 84 – 86 °C.

$R_f$: 0.33 (Hexane: Ethyl acetate = 2:1)

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.95 (d, $J = 8.1$ Hz, 1H), 5.80 (d, $J = 8.1$ Hz, 1H), 3.89 – 4.03 (m, 3H), 3.76 – 3.81 (m, 2H), 3.71 (dd, $J = 10.6$, 3.7 Hz, 1H), 2.62 – 2.76 (m, 3H), 2.37 (d, $J = 15.8$ Hz, 1H), 1.86 – 1.97 (m, 1H), 1.92 (s, 3H), 1.73 – 1.79 (m, 2H), 1.67 (s, 3H), 1.41 (s, 3H), 1.32 – 1.39 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): 191.6, 162.8, 132.7, 129.1, 117.0, 98.5, 77.4, 73.1, 59.8, 59.6, 35.2, 29.4, 29.0, 25.6, 24.8, 19.2, 14.8.

HRMS (ESI): $m/z$ calculated for C$_{17}$H$_{25}$O$_4$-BrNa [M + Na]$^+$: 395.0834, found: 395.0842.

FTIR (KBr): 3058, 2976, 2958, 2876, 1668, 1265, 1155, 1110, 739 cm$^{-1}$

3-(tert-Butyldimethylsilyloxy)propan-1-ol (69)

$\text{TBSCI} \xrightarrow{\text{imidazole, CH}_2\text{Cl}_2, \text{rt}} \text{TBSO} \xrightarrow{\text{OH}}$ 69

tert-Butyldimethylchlorosilane (7.54 g, 0.05 mol, 1 equiv) was added to a stirred solution of 1,3-propanediol (7.61 g, 0.1 mol, 2 equiv), imidazole (3.40 g, 0.05 mol, 1 equiv) in CH$_2$Cl$_2$ (200 mL) under a N$_2$ atmosphere at 0 °C. The resulting mixture was stirred at rt for 20 h and the organic layer was washed with H$_2$O twice, dried over MgSO$_4$ and concentrated under reduced pressure.
Purification by flash chromatography afforded the monosilyl protected diol 69 (7.92 g) as a colorless oil.

Yield: 83%

R_f: 0.30 (Hexane: Ethyl acetate = 4:1)

^1^H NMR (500 MHz, CDCl_3): 3.82 (t, J = 5.6 Hz, 2H), 3.79 (dd, J = 10.9, 5.4 Hz, 2H), 2.66 (t, J = 5.4 Hz, 1H), 1.80 – 1.74 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H).

^1^C NMR (125 MHz, CDCl_3): 62.9, 62.4, 34.2, 25.9 × 3, 18.2, -5.5 × 2.


FTIR (KBr): ν 3382, 2955, 2935, 2857, 1472, 1361, 1257, 1067, 835, 775 cm⁻¹

***(E)-Methyl 5-(tert-butyldimethylsilyloxy)-2-methylpent-2-enoate (71)***

To a solution of oxalyl chloride (3.38 mL, 0.039 mol, 1.3 equiv) in CH_2Cl_2 (250 mL) cooled to -78 °C was added dropwise DMSO (3.19 mL, 0.045 mol, 1.5 equiv). After 15 min, a solution of alcohol 69 (5.71 g, 0.03 mol, 1 equiv) in CH_2Cl_2 (10 mL) was added. The reaction solution was stirred at -78 °C for 45 min. Et₃N (20.92 mL, 0.15 mol, 5 equiv) was added in one portion and the resulting mixture was allowed to warm up to rt over 1 h. Methyl (triphenylphosphoranylidene)propionate(14.63 g, 0.042 mol, 1.4 equiv) was added and the reaction was stirred at rt for overnight and refluxed for an additional 2 h. After that, the reaction mixture was cooled to rt and quenched with sat aq NH_4Cl (100 mL). The organic layer was separated and the aqueous
layer was extracted with CH$_2$Cl$_2$ (100 mL × 3). The combined organic extracts were washed with sat aq NaCl and dried over Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. The residue was purified by flash chromatography to afford the desired \textit{E}-product 71 (6.52 g).

Yield: 84%

R$_f$: 0.31 (Hexane: Diethyl ether = 20:1)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.77 (t, $J$ = 7.0 Hz, 1H), 3.73 (s, 3H), 3.69 (t, $J$ = 7.0 Hz, 2H), 2.40 (q, $J$ = 7.0 Hz, 2H), 1.84 (s, 3H), 0.88 (s, 10H), 0.05 (s, 7H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.5, 138.9, 129.0, 61.7, 51.7, 32.4, 25.9 × 3, 18.3, 12.6, -5.3 × 2.

HRMS (ESI): $m/z$ calculated for C$_{13}$H$_{26}$O$_3$SiNa [M + Na]$^+$: 281.1549, found: 281.1540.

FTIR (KBr): ν 2955, 2930, 2857, 1718, 1437, 1256, 1102, 836, 776 cm$^{-1}$

\textbf{(E)-5-(tert-Butyldimethylsilyloxy)-2-methylpent-2-en-1-ol (72)}

To a solution of the ester 71 (6.20 g, 0.024 mol, 1 equiv) in CH$_2$Cl$_2$ (200 mL) at -78 °C was slowly added DIBAL-H (1.0 M in toluene, 60.0 mL, 0.06 mol mL, 2.5 equiv). The resulting solution was stirred at -78 °C for 2 h and quenched with MeOH (5 mL). The mixture was warmed to ambient temperature and stirred for 4 h after adding sat aq potassium sodium tartrate (50 mL). The layer was separated and the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with sat aq NaCl and
dried over Na\textsubscript{2}SO\textsubscript{4}. Concentration \textit{in vacuo} and purification by flash chromatography afforded the alcohol 72 (4.82 g) as a colorless oil.

Yield: 87%

R\textsubscript{f}: 0.33 (Hexane: Ethyl acetate = 4:1)

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 5.42 (t, \( J = 7.1 \) Hz, 1H), 4.00 (s, 2H), 3.61 (t, \( J = 7.1 \) Hz, 2H), 2.27 (q, \( J = 7.1 \) Hz, 2H), 1.68 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta \) 136.6, 122.1, 68.8, 62.8, 31.5, 26.0 \times 3, 18.4, 13.8, -5.4 \times 2.

HRMS (ESI): \( m/z \) calculated for C\textsubscript{12}H\textsubscript{26}O\textsubscript{2}SiNa [M + Na]\textsuperscript{+}: 253.1600, found: 253.1609.

FTIR (KBr): \( \nu \) 3396, 2955, 2929, 2857, 1472, 1255, 1095, 836, 775 cm\textsuperscript{-1}

\((E)-(5\text{-Bromo-4-methylpent-3-enyloxy})(\text{tert-butyl})\text{dimethylsilane (56)}\)

To a stirred solution of the alcohol 72 (3.45 g, 0.015 mol, 1 equiv) and Ph\textsubscript{3}P (4.72 g, 0.018 mol, 1.2 equiv) in CH\textsubscript{3}CN at 0 \( ^{\circ} \)C was added CBr\textsubscript{4} (5.97 g, 0.018 mol, 1.2 equiv). The reaction mixture was stirred for 10 min and then at rt for 15 min. The resultant mixture was filtered through a short silica gel column and washed with the eluent (hexane: diethyl ether 10:1). The combined filtrate was concentrated \textit{in vacuo} to afford the desired product 56 as a colorless oil (3.01 g).

Yield: 68%

R\textsubscript{f}: 0.35 (Hexane: diethyl ether = 8:1)
$^{1}$H NMR (400 MHz, CDCl$_3$): δ 5.62 (t, $J = 7.0$ Hz, 1H), 3.97 (s, 2H), 3.62 (t, $J = 6.8$ Hz, 2H), 2.26 (td, $J = 7.0$, 2.9 Hz, 3H), 1.80 – 1.75 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 133.6, 127.7, 62.2, 41.4, 32.1, 25.9 × 3, 18.3, 14.8, -5.3 × 2.

HRMS (ESI): $m/z$ calculated for C$_{12}$H$_{26}$OSi$_7$Br [M + H]$^+$: 293.0936, found: 293.293.0931.

FTIR (KBr): ν 2955, 2928, 2885, 2856, 1471, 1256, 1103, 836, 775 cm$^{-1}$

(E)-2-(5-Bromo-4-methylpent-3-enyloxy)tetrahydro-2H-pyran

![Chemical Structure](image)

$^{1}$H NMR (400 MHz, CDCl$_3$): δ 5.64 (t, $J = 7.1$ Hz, 1H), 4.57 (d, $J = 4.1$ Hz, 1H), 3.97 (s, 2H), 3.85 (ddd, $J = 11.1$, 7.8, 3.2 Hz, 1H), 3.73 (dt, $J = 9.5$, 7.0 Hz, 1H), 3.48 (dd, $J = 10.8$, 4.9 Hz, 1H), 3.41 (dt, $J = 9.5$, 6.8 Hz, 1H), 2.33 (q, $J = 7.0$ Hz, 2H), 1.85 – 1.79 (m, 1H), 1.77 (s, 3H), 1.71 (dt, $J = 12.9$, 3.2 Hz, 1H), 1.61 – 1.47 (m, 4H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 133.8, 127.6, 98.8, 66.3, 62.3, 41.4, 30.7, 29.0, 25.4, 19.6, 14.8.

(E)-(5-Bromo-4-methylpent-3-enyloxy)triisopropylsilane

![Chemical Structure](image)

$R_f$: 0.35 (Hexane: diethyl ether = 8:1)
RESEARCH TOWARDS THE TOTAL SYNTHESIS OF METHYL SARCOPHYTOATE

$^1$H NMR (400 MHz, CDCl$_3$): δ 5.66 (t, $J = 7.2$ Hz, 1H), 3.97 (s, 2H), 3.70 (t, $J = 6.8$ Hz, 2H), 2.29 (q, $J = 6.8$ Hz, 2H), 1.78 (d, $J = 0.5$ Hz, 3H), 1.04 – 1.07 (m, 21H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 133.5, 127.8, 62.5, 41.5, 32.3, 18.0 × 6, 14.8, 12.0 × 3.

HRMS (ESI): $m/z$ calculated for C$_{15}$H$_{32}$OSi$_7$Br $[M + H]^+$. 335.1406, Found: 335.1408.

FTIR (KBr): ν 2958, 2940, 292, 2865, 1464, 1383, 1207, 1107, 882, 681 cm$^{-1}$

(E)-8-((2,6-trans)-4-Bromo-3-methyl-6-(2-methyl-1,3-dioxan-2-yl)-5,6-dihydro-2H-pyran-2-yl)-3-(2-(tert-butyldimethylsilyloxy)ethyl)-2,6-dimethylocta-1,5-dien-4-ol (73)

![Reaction Scheme]

To a stirred solution of allyl bromide 56 (22.0 mg, 0.075 mmol, 1.5 equiv) in THF/H$_2$O (0.1 mL/0.1 mL, 1:1) was added indium power (11.4 mg, 0.1 mmol, 2 equiv). After vigorous stirring for 15 min at rt, La(OTf)$_3$ (29.3 mg, 0.05 mmol, 1 equiv) and aldehyde E-57 (16.8 mg, 0.05 mmol, 1 equiv) was added sequentially. Then the reaction mixture was stirred for 4 h. Et$_2$O (5 mL) was added to dilute the reaction mixture followed by sat aq NH$_4$Cl (5 mL) to quench the reaction. The mixture was extracted with Et$_2$O (10 mL × 3). The combined organic layers were washed with sat aq NaCl and dried over MgSO$_4$. 

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Concentration in vacuo and purification by flash chromatography afforded the \( \gamma \)-adduct 73 (20.4 mg) as a colorless oil.

Yield: 77%

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 5.20 (d, \( J = 8.8 \) Hz, 1H), 4.78 (s, 1H), 4.70 (s, 1H), 4.27 (t, \( J = 8.1 \) Hz, 1H), 3.95 – 4.10 (m, 2H), 3.81 – 3.91 (m, 2H), 3.77 (td, \( J = 10.4, 4.0 \) Hz, 2H), 3.65 – 3.70 (m, 1H), 3.52 – 3.58 (m, 1H), 2.84 – 2.95 (m, 1H), 2.44 (d, \( J = 17.3 \) Hz, 1H), 2.18 – 2.26 (m, 2H), 2.01 – 2.13 (m, 1H), 1.83 – 1.95 (m, 2H), 1.73 (s, 3H), 1.72 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.50 – 1.52 (m, 2H), 1.43 – 1.47 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

\(^{13}\)C NMR (mixtures, 100 MHz, CDCl\(_3\)): \( \delta \) 145.6, 144.6, 139.6, 139.6, 138.0, 137.8, 133.3, 133.3, 133.2, 127.1, 126.9, 126.5, 126.3, 116.9, 116.8, 116.8, 115.6, 112.5, 98.5, 98.5, 98.5, 78.3, 78.3, 78.2, 77.2, 72.6, 72.5, 72.3, 69.9, 69.8, 68.7, 61.8, 61.3, 60.0, 59.6, 51.4, 51.4, 51.2, 51.1, 36.1, 36.1, 36.0, 35.0, 34.9, 32.7, 32.7, 31.7, 29.4, 29.3, 29.1, 25.9, 25.7, 21.1, 21.0, 19.3, 19.3, 18.7, 18.3, 17.2, 17.1, 16.9, 16.8, 16.1, 16.1, 16.0, -5.4, -5.4.
Single crystal X-ray diffraction analysis of *E*−57

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<th>Property</th>
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<td>Empirical formula</td>
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<tr>
<td>Wavelength</td>
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<td>b = 9.2445(8) Å  β = 93.772(4)°</td>
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<td></td>
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<td>Independent reflections</td>
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<td>Full-matrix least-squares on F\textsuperscript{2}</td>
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<td>Data / restraints / parameters</td>
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<td>R indices (all data)</td>
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<td>Largest diff. peak and hole</td>
<td>1.464 and -1.434 e.Å\textsuperscript{-3}</td>
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</table>
Single crystal X-ray diffraction analysis of Z-57

Empirical formula \( \text{C}_{17} \text{H}_{25} \text{Br O}_4 \)
Formula weight 373.28
Temperature 103(2) K
Wavelength 0.71073 Å
Crystal system Monoclinic
Space group P2(1)/n
Unit cell dimensions
\[a = 10.5779(6) \text{ Å} \quad \alpha = 90^\circ.\]
\[b = 9.0056(6) \text{ Å} \quad \beta = 95.934(2)^\circ.\]
\[c = 17.8232(12) \text{ Å} \quad \gamma = 90^\circ.\]
Volume 1688.75(19) Å\(^3\)
Z 4
Density (calculated) 1.468 Mg/m\(^3\)
Absorption coefficient 2.449 mm\(^{-1}\)
F(000) 776
Crystal size 0.40 x 0.40 x 0.30 mm\(^3\)
Theta range for data collection 2.15 to 28.38°.
Index ranges
\(-14 < h < 11, -10 < k < 12, -23 < l < 23\)
Reflections collected 22353
Independent reflections 4202 [R(int) = 0.0490]
Completeness to theta = 28.38° 99.5 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.5269 and 0.4408
Refinement method Full-matrix least-squares on F\(^2\)
Data / restraints / parameters 4202 / 0 / 202
Goodness-of-fit on F\(^2\) 1.037
Final R indices [I>2sigma(I)] R1 = 0.0358, wR2 = 0.0663
R indices (all data) R1 = 0.0585, wR2 = 0.0743
Largest diff. peak and hole 0.456 and -0.643 e.Å\(^{-3}\)
A Novel Indium-mediated Carbon-Carbon Bond-forming Reaction: Synthesis of 1,3-dihalo-1-ene
A.1 Introduction

As air and moisture-tolerant Lewis acids, indium(III) complexes have evoked considerable attention for their high chemoselectivity and reactivity to catalyze carbon-carbon bond-forming reactions, including aldol reactions, Diels-Alder reaction, Prins cyclization, ene reactions, Friedel-Crafts reactions, etc. Due to indium’s low first ionization potential, many authors have highlighted useful advantages over conventional metal salts in terms of its inertness and selectivity in organic synthesis. In particular, it was found that indium(III) species had remarkable property of activating carbonyl compounds and terminal alkynes (Scheme A.1). Furthermore, indium(III) salts successfully catalyzed the conversion of propargylic alcohols or silyl ether into polycyclic products. Corey suggested that the indium(III) might coordinate with π-electrons of terminal alkynes by bidentate complexation with the π_x and π_y.

orbitals, and the effect was also operative with the other heavy metals that showed high π affinity [e.g., Hg(II) and Tl(III)].

Scheme A.1 Alkynylation via dual activation of both carbonyl compounds and alkynes in combination with a catalytic amount of metal salt and amine base

Interestingly, although coupling reaction of alkynes and carbonyls have been extensively studied in organic transformations as they generate new carbon-carbon bonds, the alkynylation products were obtained via addition of alkyne to carbonyls in most cases. Other progress were made on formation of 1,4-pentadiene and α,β-unsaturated ketones including Baylis–Hillman reactions (Scheme A.2). Therefore, the discovery of novel carbon-carbon

bond-forming reaction between alkyne and carbonyl offers plenty of room for further exploration.

Scheme A.2 Coupling reactions of alkynes and carbonyls

Recently, we disclosed an efficient system of combining catalytic indium(III) complex and stoichiometric trimethylsilyl halide for Prins cyclization as Lewis acid as well as proton scavenger. In fact, the first use of combination of indium species and halotrimethylsilane was employed in activation of O-trimethylsilyl monothioacetals a decade ago. Mukaiyama et al. mentioned that neither indium(III) chloride nor chlorotrimethylsilane was effective alone and the reaction proceeded only when indium(III) chloride and chlorotrimethylsilane were combined. In this system, the halotrimethylsilane was believed to enhance the acidity of indium salt through generation of cationic species. In addition, other applications of this catalyst system in the literature reports included aza-Michael addition, Hosomi-Sakurai reaction, reductive Friedel-Crafts alkylation, deoxygenative halogenations.


A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3-DIHALO-1-ENE

deoxygentative allylation,\textsuperscript{152} reductive deoxygenation,\textsuperscript{153} alkylation of alcohols,\textsuperscript{154} etc (Figure A.1).

\begin{center}
\textbf{Figure A.1} A variety of reactions catalyzed by indium(III) complex and halotrimethylsilane
\end{center}

In addition, the use of organoindium compounds was employed in a variety of coupling reactions.\textsuperscript{155} Baba discovered the InBr$_3$-mediated addition of ketene silyl acetals to alkynes to provide alkenylindiums.\textsuperscript{156} The alkyne was activated by InBr$_3$, leading to the ketene silyl acetal attacked by the $\delta^+$ on the internal carbon atom of alkyne. The carboindation adduct was formed in anti fashion.

In continuation of these studies, we attempted to utilize this system into the reaction of terminal alkyne and aldehyde. To our delight, a hitherto unknown coupling reaction under this mild condition was discovered resulting in preparation of 1,3-dihalo-1-enes. These functionalized 1,3-dihalo-1-ene compounds are potentially useful intermediates because they can be transformed to a variety of synthetic reagents through coupling, substitution, and elimination reactions.
A.2 Coupling Reaction of Terminal Alkyne and Aldehyde using Indium(III) Triflate as Catalyst

Initially, we examined the reaction of 1-octyne (1a) with 3-phenylpropionaldehyde (2a) in the presence of 10 mol% indium(III) triflate and 1 equiv of bromotrimethylsilane in CH_2Cl_2 at 0 °C. To our surprise, the unexpected product α-bromoallyl bromide (3a) was generated as sole coupling adduct while compound 4 was not detected from crude ^1H NMR (Scheme A.4). The major isomer of 3a was Z-configuration, characterized by NOSEY. Satisfyingly, the yield of 3a could be improved to 52% by employing excess of bromotrimethylsilane in the reaction system.

![Scheme A.4](image)

Table A.1 summarized the results for the reactions of 1-octyne with a variety of aliphatic aldehydes under this condition. Derivatives of α-bromoallyl bromides were generated in moderate to good yield (Table A.1, entries 1-6). In all cases, the desired 1,3-dibromo-1-enes were obtained predominantly in Z-configuration. Employing chlorotrimethylsilane as a nucleophile instead of bromotrimethylsilane also gave the corresponding 3g in moderate yield and higher stereoselectivity in comparison to the bromide (Table A.1, entries 7 and 8).

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157 The alkyne 1a was added to the reaction mixture prior to aldehyde 2a, and detailed procedure can be found in Experimental Section.

158 The desired products have less stability during column chromatography packed with silica gel or neutralized aluminum oxide, thus, the relative low yields of products may be due to the partial decomposition while the crude ^1H NMR spectroscopy showed the reactions proceeded smoothly.
3). This is probably due to the fact that the chloride is a relatively less active nucleophile and Z isomer was obtained as the thermodynamic product. Aromatic aldehydes such as benzaldehyde and p-nitrobenzaldehyde were examined, however, only traces of desired products were observed. In addition, the ketones were not appropriate substrates under the reaction conditions.

**Table A.1** Reactions of 1-octyne and aldehydes in the presence of In(OTf)₃ and TMSX (X = Cl, Br)

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCHO</th>
<th>X</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Z/E</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>PhCHO</td>
<td>Br</td>
<td>(3a)</td>
<td>52</td>
<td>76/24</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Br</td>
<td>(3b)</td>
<td>82</td>
<td>82/18</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Br</td>
<td>(3c)</td>
<td>78</td>
<td>83/17</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Br</td>
<td>(3d)</td>
<td>49</td>
<td>66/34</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Br</td>
<td>(3e)</td>
<td>66</td>
<td>62/38</td>
</tr>
<tr>
<td>6</td>
<td>PhCHO</td>
<td>Br</td>
<td>(3f)</td>
<td>11</td>
<td>74/26</td>
</tr>
<tr>
<td>7⁻</td>
<td>PhCHO</td>
<td>Cl</td>
<td>(3g)</td>
<td>50</td>
<td>86/14</td>
</tr>
</tbody>
</table>

⁻ Reactions were performed with 1a (0.4 mmol), aldehydes 2 (0.56 mmol), TMSBr (1.0 mmol), 4Å MS (0.08 g) and In(OTf)₃ (0.04 mmol) in CH₂Cl₂ (5 mL) at 0 °C for 4 h. ⁻ Isolated yield based on 1a. ⁻ Determined by ¹H NMR and NOESY. ² 20 mol% of In(OTf)₃ was loaded.

Subsequently, several terminal alkynes were treated with aliphatic aldehydes using the combination of In(OTf)₃ and trimethylsilyl halide (Table A.2). The corresponding 1,3-dihalo-1-enes were produced in the yields from 45% to 85%. In most cases, the reactions were found to afford Z-isomers as major

¹⁵⁹ When the catalyst loading of In(OTf)₃ increased to 20 mol%, the reaction went to completion.

128
products except for compounds 3j, 3l and 3m (Table A.2, entries 3, 5 and 6). Interestingly, when the reactions were performed with TMSCl as proton scavenger, E-vinyl chloride products were mainly obtained (Table A.2, entries 7 to 9), which may imply that the process was under thermodynamic control.

**Table A.2** Reactions of terminal alkynes and aldehydes in the presence of In(OTf)$_3$ and TMSX (X = Cl, Br)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Aldehyde</th>
<th>X</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
<th>Z/E$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1b)</td>
<td>2a</td>
<td>Br</td>
<td>3h</td>
<td>47</td>
<td>69/31</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>Br</td>
<td>3i</td>
<td>62</td>
<td>88/12</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>2a</td>
<td>Br</td>
<td>3j</td>
<td>78</td>
<td>44/56</td>
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<tr>
<td>4</td>
<td>1c</td>
<td>2b</td>
<td>Br</td>
<td>3k</td>
<td>85</td>
<td>59/41</td>
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<tr>
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<td>2a</td>
<td>Br</td>
<td>3l</td>
<td>51</td>
<td>22/78</td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>2b</td>
<td>Br</td>
<td>3m</td>
<td>45</td>
<td>25/75</td>
</tr>
<tr>
<td>7$^d$</td>
<td>1b</td>
<td>2a</td>
<td>Cl</td>
<td>3n</td>
<td>45</td>
<td>85/15</td>
</tr>
<tr>
<td>8$^d$</td>
<td>1c</td>
<td>2a</td>
<td>Cl</td>
<td>3o</td>
<td>50</td>
<td>86/14</td>
</tr>
<tr>
<td>9$^d$</td>
<td>1d</td>
<td>2a</td>
<td>Cl</td>
<td>3p</td>
<td>56</td>
<td>87/13</td>
</tr>
</tbody>
</table>

$^a$ For the conditions, see Table A.1, footnote a. $^b$ Isolated yield based on 1. $^c$ Determined by $^1$H NMR and NOESY. $^d$ 20 mol% of In(OTf)$_3$ was added.

Treatment of 1-octyne with 3-phenylpropionaldehyde in the presence of InBr$_3$ and TMSBr, also produced the desired product 3a in lower yield (36%) but with better stereoselectivity (Z/E = 88/12). The reactions in the absence of either InBr$_3$ or TMSBr under the standard conditions did not yield the product 3a. Alternative halide sources, like NaBr, LiBr, TIPSCl, TBSCl and TESCl
instead of TMSX were screened, but they either gave no conversion or low yield of desired product when 1-octyne and 3-phenylpropionaldehyde were employed in the presence of In(OTf)$_3$.

**A.3 Conclusion**

In summary, we have developed a novel carbon-carbon bond-forming reaction of aliphatic terminal alkynes with aldehydes in the presence of In(OTf)$_3$ and trimethylsilyl halide to give 1,3-dihalo-1-ene. Efforts to elucidate the reaction mechanism and further extension of the scope are currently underway.
A.4 Experimental Section

General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware. Commercial solvents and reagents were used without further purification except for CH$_2$Cl$_2$ was freshly distilled from CaH$_2$. Aldehydes were freshly distilled before using.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Columns were typically packed as slurry and equilibrated with hexane prior to use.

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Liquid samples were examined as film between KBr salt plates. Proton nuclear magnetic resonance (\textsuperscript{1}H NMR) and carbon nuclear magnetic resonance (\textsuperscript{13}C NMR) spectroscopy were performed on a Bruker Advance 300, 400 and 500 NMR spectrometers. Chemical shifts \textsuperscript{1}H NMR spectra are reported as in units of parts per million (ppm) downfield from SiMe$_4$ (\textsuperscript{δ} 0.0) and relative to the signal of chloroform-\textit{d} (\textit{J} = 7.264, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); ddd (doublet of doublets of doublets); dddd (doublet of doublets of doublets of doublets); dt (doublet of triplets); m (multiplets) and etc. The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as
A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3-DIHALO-1-ENE

a J value in Hz. Carbon nuclear magnetic resonance spectra (\(^{13}\)C NMR) are reported as d in units of parts per million (ppm) downfield from SiMe\(_4\) (δ 0.0) and relative to the signal of chloroform-d (J = 77.03, triplet).

High resolution mass spectral analysis (HRMS) was performed on Water Q-TOF Premier mass spectrometer (Thermo Electron Corporation).

**General Procedure for carbon-carbon bond-forming reactions of terminal alkynes and aldehydes**

To a solution of indium(III) triflate (22.5 mg, 0.04 mmol, 0.1 equiv) and powered 4 Å molecular sieves (0.08 g) in 4 mL anhydrous CH\(_2\)Cl\(_2\) at 0 °C was added bromotrimethylsilane (0.13 mL, 1.0 mmol, 2.5 equiv). After stirring for 5 min, a solution of 1-octyne (44.1 mg, 0.4 mmol, 1 equiv) in 0.5 mL CH\(_2\)Cl\(_2\) was added within 3 min via syringe. After 5 min, a solution of 3-phenylpropionaldehyde (75.1 mg, 0.56 mmol, 1.4 equiv) in 1 mL CH\(_2\)Cl\(_2\) was added slowly over 5 min. The reaction mixture was stirred for 4 h at 0 °C. The reaction was quenched with sat aq NaHCO\(_3\) (8 mL) and warmed to rt. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (10 mL × 3). The combined organic layer was washed with sat aq NaCl, dried over anhydrous Na\(_2\)SO\(_4\), filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography through a short column to afford 1\(\text{a}\) (80.7 mg) as a pale yellow oil.

**\((Z)-(3,5\text{-Dibromoundec-4-enyl})\text{benzene}\)**

\(\text{Yield (%): 52% (Z/E} = 76/24)\)
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R_f: 0.60 (Hexane)

$^1$H NMR (500 MHz, CDCl₃): δ 7.29 – 7.32 (m, 2H), 7.20-7.23 (m, 3H), 5.93 (d, $J$ = 9.8 Hz, 1H), 4.88 (dt, $J$ = 9.8, 7.1 Hz, 1H), 2.69 – 2.78 (m, 2H), 2.47 (t, $J$ = 7.3 Hz, 2H), 2.25 – 2.33 (m, 1H), 2.13 – 2.22 (m, 1H), 1.54 – 1.58 (m, 2H), 1.25 – 1.36 (m, 6H), 0.91 (t, $J$ = 6.9 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl₃): δ 140.5, 132.0, 129.7, 128.5, 128.5, 126.2, 52.5, 41.4, 40.6, 33.8, 31.49, 28.0, 27.9, 22.6, 14.1.

HRMS (ESI): m/z calculated for $C_{17}H_{25}$Br$_{81}$Br [M + H]$^+$: 389.0303, found: 389.0320.

FTIR (KBr): ν 3063, 3027, 2954, 2930, 2858, 1645, 1496, 1454, 1198, 748, 699 cm$^{-1}$.

(Z)-4,6-Dibromo-2-methyldodec-5-ene

Yield (%): 82% (Z/E = 82/18)

R_f: 0.63 (Hexane)

$^1$H NMR (400 MHz, CDCl₃): δ 5.85 (d, $J$ = 9.9 Hz, 1H), 4.96 (dt, $J$ = 9.9, 7.2 Hz, 1H), 2.45 (t, $J$ = 7.4 Hz, 2H), 1.84 – 1.91 (m, 1H), 1.67 – 1.77 (m, 1H), 1.54 – 1.58 (m, 1H), 1.28 (apparent s, 8H), 0.87 – 0.93 (m, 9H).

$^{13}$C NMR (100 MHz, CDCl₃): δ 131.4, 130.2, 51.8, 48.0, 41.4, 31.5, 28.0, 27.8, 26.9, 22.5, 22.2 × 2, 14.0.

HRMS (ESI): m/z calculated for $C_{13}H_{25}$Br$_{81}$Br [M + H]$^+$: 341.0303, found: 341.0322.

FTIR (KBr): ν 2957, 2930, 2859, 1646, 1466, 1173, 1058, 877, 726, 665 cm$^{-1}$.
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**(Z)-3,5-Dibromo-2,2-dimethylundec-4-ene**

![Chemical Structure of (Z)-3,5-Dibromo-2,2-dimethylundec-4-ene]

Yield (%): 78% (Z/E = 83/17)

R<sub>f</sub>: 0.65 (Hexane)

$^1$H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.95 (d, $J = 10.4$ Hz, 1H), 4.82 (d, $J = 10.4$ Hz, 1H), 2.47 (t, $J = 7.3$ Hz, 2H), 1.54 – 1.58 (m, 2H), 1.30 (apparent s, 6H), 1.07 (s, 9H), 0.89 (t, $J = 5.3$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl<sub>3</sub>): δ 131.6, 127.4, 66.0, 41.6, 35.9, 31.5, 28.0, 27.9, 27.1 × 3, 22.6, 14.0.

HRMS (ESI): m/z calculated for C<sub>13</sub>H<sub>2</sub>Br<sup>79</sup>Br<sup>81</sup>Br [M + H]<sup>+</sup>: 341.0303, found: 341.0297.

FTIR (KBr): ν 2959, 2930, 2859, 1643, 1464, 1368, 1153, 900, 846, 693 cm<sup>-1</sup>

**(Z)-5,7-Dibromotridec-6-ene**

![Chemical Structure of (Z)-5,7-Dibromotridec-6-ene]

Yield (%): 49% (Z/E = 66/34)

R<sub>f</sub>: 0.55 (Hexane)

$^1$H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.87 (d, $J = 9.8$ Hz, 1H), 4.88 (dt, $J = 9.8$, 7.2 Hz, 1H), 2.45 (t, $J = 7.2$ Hz, 2H), 1.93 – 2.02 (m, 1H), 1.81 – 1.91 (m, 1H), 1.55 – 1.58 (m, 2H), 1.28 – 1.44 (m, 10H), 0.87 – 0.93 (m, 6H).
A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF
1,3-DIHALO-1-ENE

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 131.4, 130.0, 53.2, 41.4, 38.7, 31.5, 29.7, 28.0,
27.8, 22.5, 22.1, 14.0, 13.9.

HRMS (ESI): m/z calculated for C$_{13}$H$_{25}^{79}$Br$_{81}$Br [M + H]$^+$: 341.0303, found:
341.0310.

FTIR (KBr): $\nu$ 2957, 2930, 2860, 1647, 1459, 1064, 844, 665 cm$^{-1}$

(Z)-7,9-Dibromoheptadec-7-ene

![Chemical structure of (Z)-7,9-Dibromoheptadec-7-ene]

Yield (%): 66% ($Z/E = 62/38$)

R$_f$: 0.55 (Hexane)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.86 (d, $J = 9.8$ Hz, 1H), 4.88 (dt, $J = 9.8$, 7.2
Hz, 1H), 2.39 – 2.51 (m, 2H), 1.92 – 1.99 (m, 1H), 1.81 – 1.90 (m, 1H), 1.54 –
1.60 (m, 2H), 1.28 (apparent s, 18H), 0.87 – 0.90 (m, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 131.4, 130.1, 53.2, 41.4, 39.0, 31.8, 31.5, 29.4,
29.2, 28.9, 28.0, 27.8, 27.6, 22.6, 22.5, 14.1, 14.0.

HRMS (ESI): m/z calculated for C$_{17}$H$_{32}^{79}$Br$_{81}$BrNa [M + Na]$^+$: 419.0748, found:
419.0739.

FTIR (KBr): $\nu$ 2956, 2926, 2856, 1646, 1466, 1069, 845, 735 cm$^{-1}$

(Z)-(2,4-Dibromodec-3-enyl)benzene

![Chemical structure of (Z)-(2,4-Dibromodec-3-enyl)benzene]

Yield (%): 11% ($Z/E = 74/26$)
A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3-DIHALO-1-ENE

\[ \text{Rf: } 0.43 \text{ (Hexane)} \]

\[^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.16 - 7.32 \text{ (m, 5H), 5.90 (d, } J = 9.8 \text{ Hz, 1H), 5.12 (dt, } J = 9.8, 7.2 \text{ Hz, 1H), 3.17 - 3.32 \text{ (m, 2H), 2.41 (t, } J = 7.2 \text{ Hz, 2H), 1.45 - 1.52 \text{ (m, 2H), 1.17 - 1.27 \text{ (m, 6H), 0.88 (t, } J = 6.9 \text{ Hz, 3H).} \]

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta 137.5, 132.2, 129.3, 129.2, 128.4, 127.0, 52.4, 45.1, 41.3, 31.5, 27.8, 27.7, 22.5, 14.1. \]

HRMS (ESI): m/z calculated for \( \text{C}_{16}\text{H}_{23}^{79}\text{Br}^{81}\text{Br} [\text{M + H}]^+: 375.0146, \) found: 375.0144.

FTIR (KBr): \( \nu 3063, 3029, 2955, 2930, 2858, 1645, 1496, 1454, 1031, 842, 749, 699 \text{ cm}^{-1} \)

\((Z)-(3,5\text{-Dichloroundec-4-enyl})\text{benzene}\)

\[ \text{Yield (\%): 50\% (Z/E = 86/14)} \]

\[ \text{Rf: } 0.36 \text{ (Hexane)} \]

\[^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.29 - 7.33 \text{ (m, 2H), 7.20 - 7.23(m, 3H), 5.64 (d, } J = 9.4 \text{ Hz, 1H), 4.85 (dt, } J = 9.4, 7.0 \text{ Hz, 1H), 2.69 - 2.85 \text{ (m, 2H), 2.35 (t, } J = 7.4 \text{ Hz, 2H), 2.05 - 2.24 \text{ (m, 2H), 1.53 - 1.58 \text{ (m, 2H), 1.25 - 1.35 \text{ (m, 6H), 0.90 (t, } J = 6.7 \text{ Hz, 3H).} \]

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta 140.7, 138.2, 128.5 \times 2, 128.5, 126.2, 57.8, 40.0, 39.3, 32.6, 31.5, 28.2, 27.1, 22.6, 14.1. \]

HRMS (ESI): m/z calculated for \( \text{C}_{17}\text{H}_{25}^{35}\text{Cl}_2 [\text{M + H}]^+: 299.1333, \) found: 299.1347.
A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3-DIHALO-1-ENE

FTIR (KBr): \( \nu \) 3064, 3027, 2955, 2930, 2858, 1654, 1603, 1497, 1454, 1030, 749, 699 cm\(^{-1}\)

(Z)-(3,5-Dibromomon-4-enyl)benzene

Yield (%): 47% (Z/E = 69/31)

\( R_f: \) 0.38 (Hexane)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.29 – 7.32 (m, 2H), 7.19 – 7.23 (m, 3H), 5.93 (d, \( J = 9.8 \) Hz, 1H), 4.88 (dt, \( J = 9.8, 7.1 \) Hz, 1H), 2.68 – 2.83 (m, 2H), 2.48 (t, \( J = 7.3 \) Hz, 2H), 2.14 – 2.23 (m, 2H), 1.53 – 1.60 (m, 2H), 1.27 – 1.38 (m, 2H), 0.93 (t, \( J = 7.4 \) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 140.5, 131.9, 129.7, 128.5, 128.5, 126.2, 52.5, 41.1, 40.5, 33.8, 30.0, 21.5, 13.8.

HRMS (ESI): \( m/z \) calculated for C\(_{15}\)H\(_{20}\)\(^{79}\)Br\(^{81}\)BrNa [M + Na]\(^+\): 382.9809, found: 382.9808.

FTIR (KBr): \( \nu \) 3027, 2957, 2930, 2860, 1645, 1603, 1497, 1454, 1075, 848, 749, 699 cm\(^{-1}\)

(Z)-4,6-Dibromo-2-methyldec-5-ene

Yield (%): 62% (Z/E = 88/12)

\( R_f: \) 0.55 (Hexane)
A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3-DIHALO-1-ENE

1H NMR (400 MHz, CDCl3): δ 5.85 (d, J = 9.8 Hz, 1H), 4.95 (dt, J = 9.8, 7.4 Hz, 1H), 2.46 (t, J = 7.3 Hz, 2H), 1.82 – 1.91 (m, 1H), 1.67 – 1.79 (m, 2H), 1.46 – 1.55 (m, 2H), 1.27 – 1.34 (m, 2H), 0.89 – 0.95 (m, 9H).

13C NMR (100 MHz, CDCl3): δ 131.3, 130.2, 51.9, 48.0, 41.1, 30.0, 26.9, 22.2, 22.1, 21.5, 13.8.


FTIR (KBr): ν 2952, 2932, 2871, 1647, 1466, 1369, 1090, 846, 746, 616 cm⁻¹

(E)-(3,5-Dibromohept-3-ene-1,7-diyl)dibenzene

Yield (%): 78% (Z/E = 44/56)

Rf: 0.48 (Hexane/diethyl ether = 20/1)

1H NMR (400 MHz, CDCl3): δ 7.14 – 7.35(m, 10H), 6.15 (d, J = 10.8 Hz, 1H), 4.34 (ddd, J = 10.8, 8.3, 5.7 Hz, 1H), 3.87 – 2.97 (m, 2H), 2.76 – 2.85 (m, 2H), 2.54 – 2.72 (m, 2H), 1.98 – 2.06 (m, 1H), 1.71 – 1.80 (m, 1H).

13C NMR (100 MHz, CDCl3): δ 140.3, 140.1, 134.0, 130.8, 129.5, 128.7, 128.7, 128.6, 128.5, 128.5, 126.5, 126.3, 49.3, 43.3, 40.4, 38.4, 34.2, 33.7, 33.5.


FTIR (KBr): ν 3084, 3061, 3026, 2927, 2860, 1635, 1453, 1075, 749, 698 cm⁻¹

(Z)-(3,5-Dibromo-7-methyloct-3-enyl)benzene

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A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3-DIHALO-1-ENE

![Chemical structure](https://via.placeholder.com/150)

Yield (%): 85% \((Z/E = 59/41)\)

\(R_f\): 0.33 (Hexane)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.19 – 7.35 (m, 5H), 5.74 (d, \(J = 9.8\) Hz, 1H), 4.92 (dt, \(J = 9.8, 7.7\) Hz, 1H), 2.90 – 2.94 (m, 2H), 2.77 – 2.81 (m, 2H), 1.74 – 1.84 (m, 1H), 1.62 – 1.71 (m, 1H), 1.42 – 1.50 (m, 1H), 0.89 (d, \(J = 6.6\) Hz, 6H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 140.0, 131.3, 128.6, 128.6, 128.4, 126.3, 51.4, 47.9, 43.3, 34.1, 26.7, 22.3, 22.0.

HRMS (ESI): m/z calculated for \(C_{15}H_{20}{ }^{79}\)Br\(^{81}\)BrNa [M + Na]\(^+\): 382.9809, found: 382.9831.

FTIR (KBr): \(\nu\) 3027, 2957, 2930, 2869, 1645, 1496, 1454, 1368, 1180, 1030, 748, 699 cm\(^{-1}\)

(\(E\))-(2,4-Dibromohex-2-ene-1,6-diyl)dibenzene

![Chemical structure](https://via.placeholder.com/150)

Yield (%): 51% \((Z/E = 22/78)\)

\(R_f\): 0.10 (Hexane)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.20 – 7.42 (m, 10H), 6.35 (d, \(J = 10.9\) Hz, 1H), 4.80 (dt, \(J = 10.9, 7.0\) Hz, 1H), 3.74 – 3.86 (m, 2H), 2.84 (t, \(J = 7.4\) Hz, 2H), 2.31 – 2.43 (m, 1H), 2.31 – 2.17 (m, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 140.0, 136.6, 134.1, 129.1, 128.8, 128.7 \(\times\) 2, 128.5, 127.1, 126.5, 48.8, 42.0, 40.7, 33.6.
A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3-DIHALO-1-ENE

HRMS (ESI): m/z calculated for C_{18}H_{19}^{79}\text{Br}^{81}\text{Br} [M + H]^+; 394.9833, found: 394.9835.

FTIR (KBr): ν 3062, 3027, 2927, 2860, 1635, 1603, 1495, 1453, 1077, 1030, 909, 735, 698 cm\(^{-1}\)

\((E)-(2,4\text{-Dibromo-6-methylhept-2-enyl})\text{benzene}\)

![Structure of (E)-(2,4-Dibromo-6-methylhept-2-enyl)benzene]

Yield (%): 45\% (Z/E = 25/75)

R\(_f\): 0.37 (Hexane)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.23 – 7.41 (m, 5H), 6.28 (d, \(J = 10.8\) Hz, 1H), 4.90 (dt, \(J = 10.8, 7.3\) Hz, 1H), 3.66 – 4.00 (m, 2H), 1.91 – 1.99 (m, 1H), 1.73 – 1.86 (m, 2H), 0.94 – 0.98 (m, 6H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 136.6, 134.9, 131.9, 128.8, 128.7, 127.1, 48.4, 48.2, 41.9, 26.7, 22.2, 22.0.

HRMS (ESI): m/z calculated for C\(_{14}\)H\(_{19}\)^{79}\text{Br}^{81}\text{Br} [M + H]^+; 346.9833, found: 346.9844.

FTIR (KBr): ν 3063, 3029, 2958, 2930, 2870, 1634, 1602, 1369, 1172, 1076, 750, 697 cm\(^{-1}\)

\((Z)-(3,5\text{-Dichloronon-4-enyl})\text{benzene}\)

![Structure of (Z)-(3,5-Dichloronon-4-enyl)benzene]

Yield (%): 45\% (Z/E = 85/15)
A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3-DIHALO-1-ENE

R_f: 0.32 (Hexane)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.21 – 7.26 (m, 2H), 7.10 – 7.17 (m, 3H), 5.58 (d, $J = 9.4$ Hz, 1H), 4.78 (dt, $J = 9.4$, 7.0 Hz, 1H), 2.62 – 2.78 (m, 2H), 2.29 (t, $J = 7.4$ Hz, 2H), 2.00 – 2.15 (m, 2H), 1.45 – 1.53 (m, 2H), 1.23 – 1.32 (m, 2H), 0.87 (t, $J = 7.3$ Hz, 4H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.7, 138.2, 128.5, 128.5, 126.2, 126.1, 57.7, 40.0, 39.0, 32.6, 29.2, 21.6, 13.8.

HRMS (ESI): m/z calculated for $C_{15}H_{21}^{35}Cl_2$ [M + H]$^+$: 271.1020, found: 271.1031.

FTIR (KBr): v 3064, 3027, 2957, 2932, 2861, 1654, 1497, 1454, 1030, 698, 665 cm$^{-1}$(Z)-(3,5-Dichlorohept-3-ene-1,7-diyl)dibenzene

Yield (%): 50% (Z/E = 86/14)

R_f: 0.41 (Hexane/diethyl ether = 20/1)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.11 – 7.29(m, 10H), 5.50 (d, $J = 9.2$ Hz, 1H), 4.76 (dt, $J = 9.2$, 7.0 Hz, 1H), 2.86 (t, $J = 7.4$ Hz, 2H), 2.57 – 2.67 (m, 4H), 1.93 – 2.09 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.7, 140.127, 136.8, 128.6, 128.5 × 4, 127.2, 126.3, 126.14, 57.4, 41.2, 39.9, 33.5, 32.4.

HRMS (ESI): m/z calculated for $C_{19}H_{21}^{35}Cl_2$ [M + H]$^+$: 319.1020, found: 319.1021.
A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3-DIHALO-1-ENE

FTIR (KBr): $\nu$ 3063, 3027, 2949, 2929, 2861, 1655, 1603, 1595, 1454, 1069, 1030, 848, 749, 699 cm$^{-1}$

(Z)-(2,4-Dichlorohex-2-ene-1,6-diyldibenzene

Yield (%): 56% (Z/E = 87/13)

R$_f$: 0.42 (Hexane/diethyl ether = 20/1)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.28 – 7.34 (m, 4H), 7.16 – 7.21 (m, 6H), 5.68 (d, $J = 9.4$ Hz, 1H), 4.82 (dt, $J = 9.4, 7.2$ Hz, 1H), 3.63 (s, 2H), 2.66 – 2.82 (m, 2H), 2.05 – 2.21 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.6, 136.6, 136.4, 129.0, 128.7, 128.5, 128.5, 127.9, 127.2, 126.2, 57.5, 45.5, 39.9, 32.6.

HRMS (ESI): m/z calculated for C$_{18}$H$_{19}^{35}$Cl$_2$ [M + H]$^+$: 305.0864, found: 305.0868.

FTIR (KBr): $\nu$ 3063, 3027, 2927, 2862, 1654, 1602, 1496, 1453, 1074, 1030, 750, 698 cm$^{-1}$
List of Publications


Conferences
