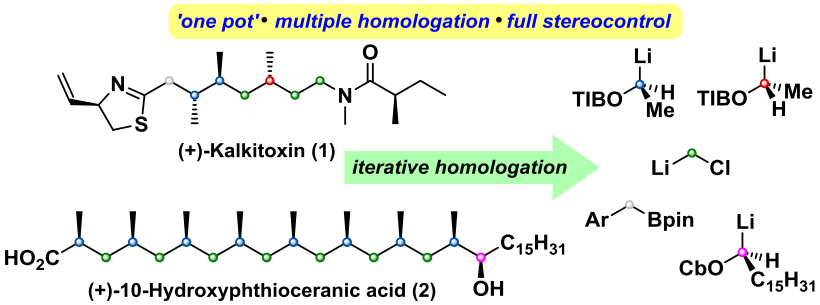
## 1. WORK PROGRESS AND ACHIEVEMENTS DURING THE PERIOD

### • A summary of progress towards objectives and details for each task;

In Nature, a vast array of complex biomolecules, including peptides, oligonucleotides, oligosaccharides and polyketides has been manufactured through enzymatic iterative assembly of simple building blocks. The archetypical example is polyketide synthesis where a simple thioester is subjected to a series of enzymatic reactions, undergoing chain extension, dehydration, or reduction multiple times until the target molecule is formed.[1] Inspired by this strategy, a broad variety of iterative methods has been developed to provide an efficient access to complex molecules. Aggarwal and co-workers have developed an efficient method for the iterative, reagent-controlled homologation of a boronic ester.[2] This process enabled the conversion of a simple boronic ester into a molecule bearing 10 contiguous methyl substituents with full stereocontrol in an effectively "one-pot" process. Different stereoisomers could be obtained simply by controlling the sequence of reagent addition. According to the research proposal, we proposed to apply this methodology to the synthesis of chemically and biologically useful molecules. Recently, we have demonstrated the power of the assembly-line synthesis strategy for the highly stereocontrolled synthesis of two different natural products, (+)-kalkitoxin **1** and (+)-hydroxyphthioceranic acid **2**.[3] The core of these complex molecules were constructed via iterative homologations of boronic esters using chiral lithiated benzoate esters and chloromethyllithium as key building blocks (Scheme 1).




**Scheme 1**. The synthesis of (+)-kalkitoxin and (+)-hydroxyphthioceranic acid by assembly-line synthesis

In the case of (+)-kalkitoxin, six iterative homologations were conducted on commercially available *p*-$MeOC_6H_4CH_2Bpin$ to build up the core of the molecule before the C–B bond was converted into the desired C–N bond, without purification of intermediates. In the case of (+)-10-hydroxyphthioceranic acid, 16 iterative homologations were conducted on *p*-$MeOC_6H_4Bpin$ with only four intermediate purifications before oxidation of the C–B bond to the desired alcohol.

Having demonstrated the application of the assembly-line synthesis strategy towards the synthesis of natural products with carbon chains bearing simple alkyl groups. However, most natural products contain polar functional groups, and being able to introduce hydroxyl groups with stereocontrol would greatly enhance the scope of this methodology. Thus we planned to construct polypropionates employing the assembly-line synthesis strategy. The polypropionates, which are characterized by sequences of

methyl- and hydroxy-bearing stereogenic centres, are attractive targets for synthetic organic chemists due to their broad spectrum of biological activities and structural complexity. In addition, most of them frequently contain the *anti,anti*-dipropionate stereotriad (Fig. 1), which remains notoriously challenging to synthesize with acceptable levels of diastereoselectivity by aldol or crotylmetal chemistry.

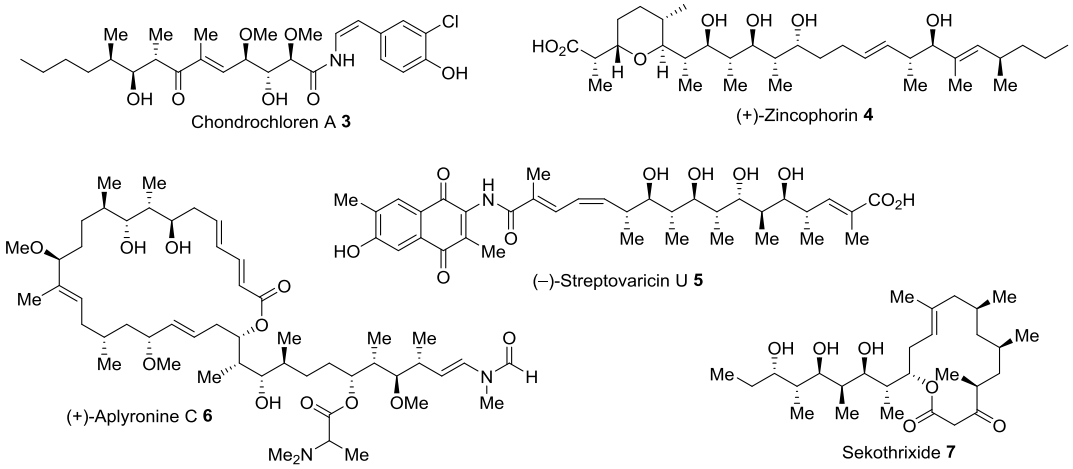
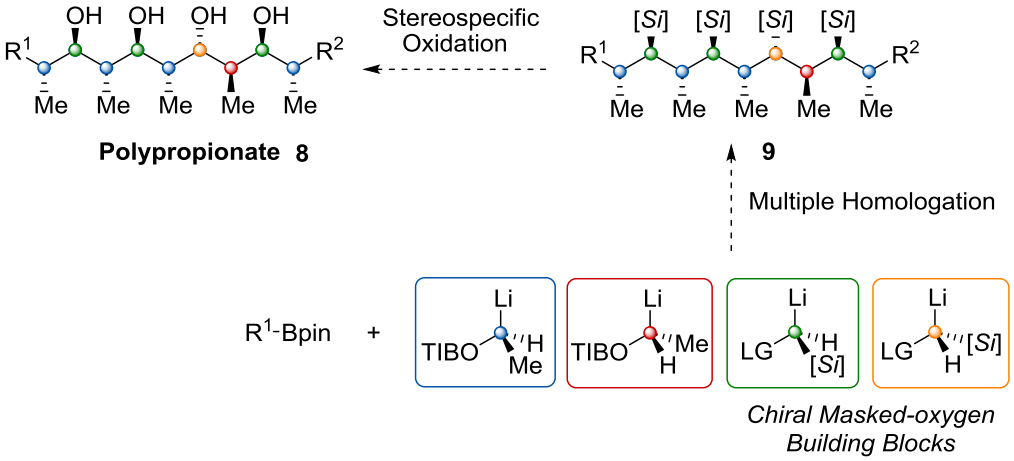


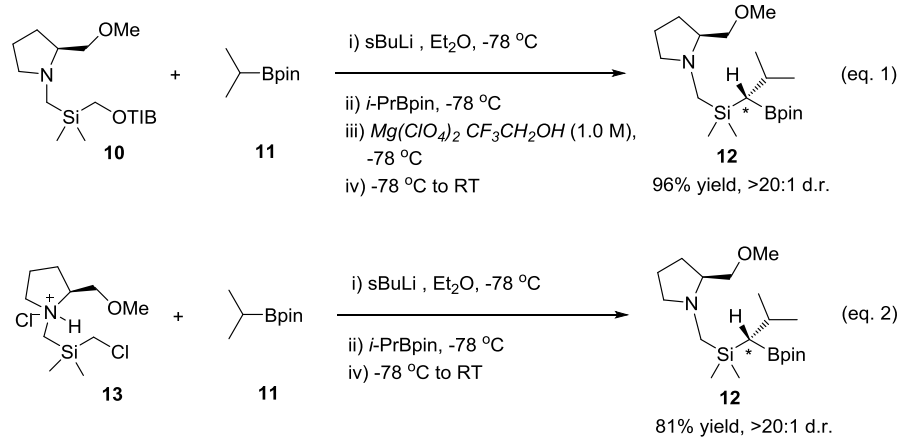

**Figure 1**. Representative examples of polypropionate-containing natural products.

We propose to synthesize polypropionate chains using iterative homologation methodology (Scheme 2). Novel α-silyl carbenoids will be used as masked-oxygen building blocks together with chiral lithiated benzoate esters in the iterative homologation process of boronic esters to incorporate multiple silyl groups and methyl side-groups into carbon chains with stereocontrol. Ultimately, carbon-silicon bonds will be oxidised stereospecifically leading to the desired polypropionate core **8**.To the best of our knowledge, our iterative method is totally dominated by reagent control, that is, no matched and mismatched effects are observed, thereby enabling us to synthesize different isomers with excellent levels of diastereoselectivity. Thus we should be able to provide a general solution to the long-standing problem associated with the synthesis of the *anti,anti*-dipropionate stereotriad by utilizing our iterative reagent-controlled strategy.



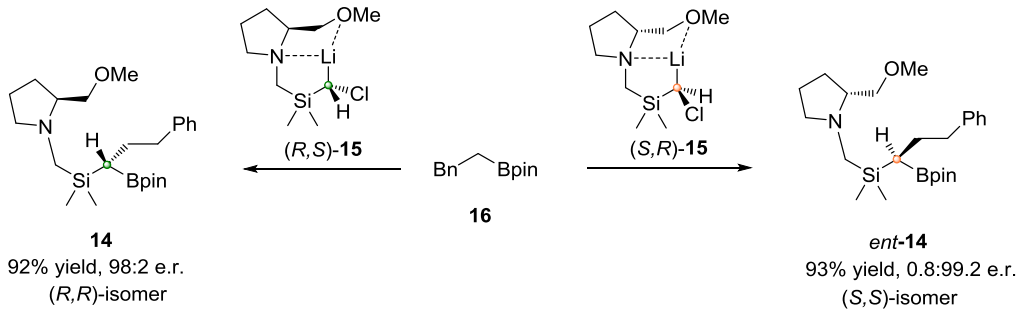

**Scheme 2**. Synthetic plan for polypropionate synthesis by assembly-line synthesis

After an extensive investigation, we then successfully developed new chiral silicon–containing building blocks serving as masked oxygen-functionality. Initially, we realized that α-silyl carbenoids are extremely configurationally unstable. By generating such lithiated intermediates in the presence of stoichiometric amounts of external chiral ligands (*e.g.* sparteine or bisoxazoline) led to the corresponding products being formed with no selectivity under the lithiation–borylation reaction.[4] However, the problem was solved by incorporating a chiral auxiliary side-arm into silyl moiety of carbenoid precusor.[5] The lithiated intermediate could be formed in high selectivity by dynamic thermodynamic resolution and it was subsequently treated with a boron reagent to afford a boronate complex intermediate. In the case of using a bulky OTIB group as a leaving group, it was found that Lewis acid, $Mg(ClO_4)_2$ in $CF_3CH_2OH$, was essential for triggering 1,2-migration of the boronate complex intermediate (Scheme 3, eq.1). On the other hand, 1,2-metallate rearrangement of the less hindered boronate complex possessing chlorine as a leaving group proceeded smoothly upon warming the reaction mixture to room temperature to provide the boronic ester **12** in good yield and with high diastereoselectivity (Scheme 3, eq.2).



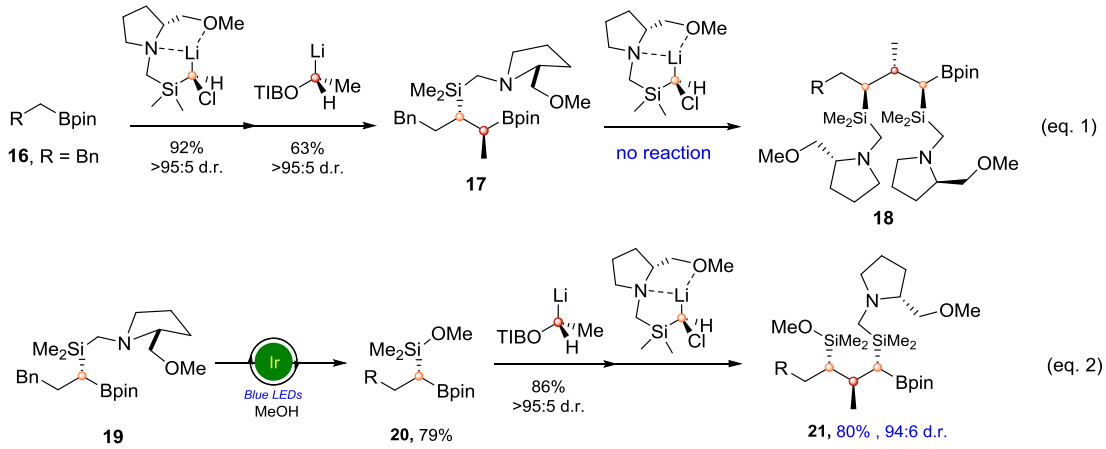

**Scheme 3.** Lithiation-borylation reaction of secondary boronic ester with chiral silane

Gratifyingly, both isomers of α-silyl carbenoids of type **15** could be efficiently generated with high diastereoselectivities by using either (*R*)- or (*S*)-(aminomethyl)silane building blocks (Scheme 4).



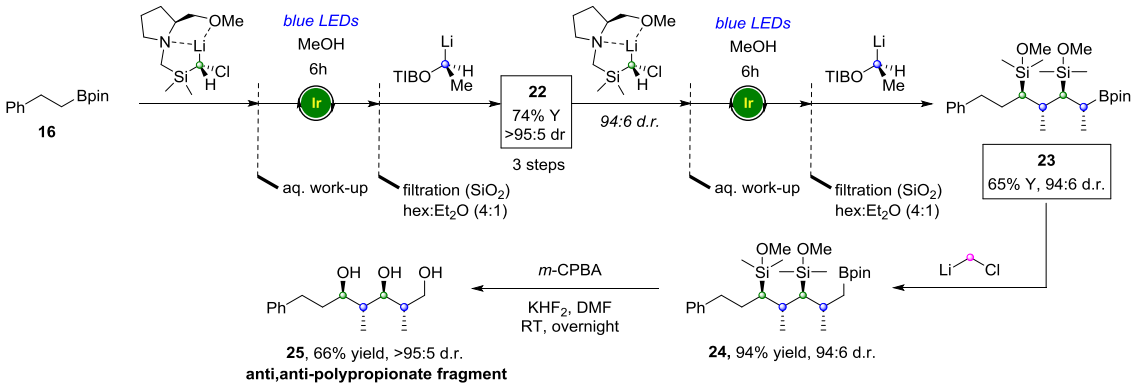

**Scheme 4.** Preparation of homologated boronic esters in both diastereoisomeric forms

With the suitable carbenoid building blocks in hand, we next demonstrated their utility in the assembly-line synthesis of polypropionates. Attempts to make the boronic ester **18** via triple homologation of a boronic ester using chiral chlorosilanes and lithiated benzoate ester initially proved problematic. No reaction was observed in the third homologation with chiral chlorosilane. Presumably, an intramolecular chelation of nitrogen atom of pyrrolidine moiety to boronic ester prevents the reaction with chiral carbenoid (Scheme 5, eq. 1). However, we were pleased to find that the chiral auxiliary side-arm in the homologated product **19** could be removed under visible light photo-redox conditions to afford the methoxysilane **20** in excellent yield.[6] Finally, the methoxysilane intermediate **20** was subjected to two consecutive homologations sequence to provide the desired product **21** in good yields and high stereocontrol (Scheme 5, eq. 2).



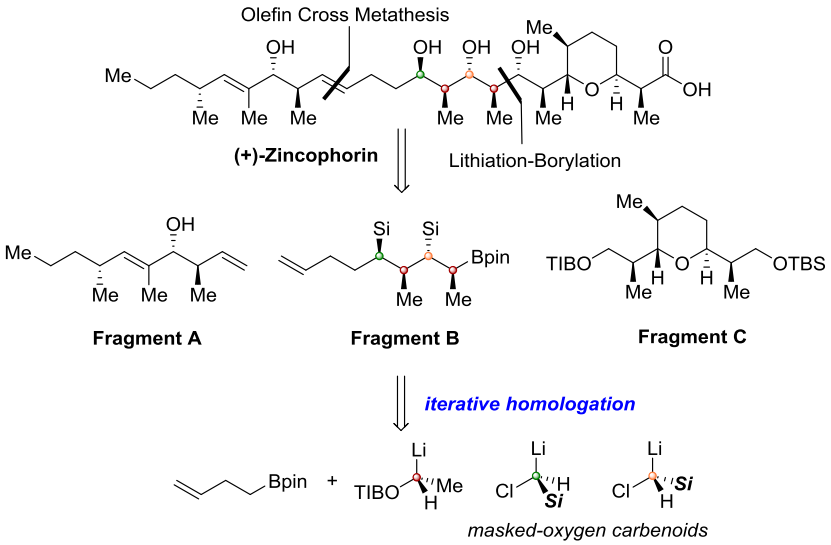

**Scheme 5.** The use of chiral chlorosilane building block in the assembly-line synthesis

An optimized protocol had to be developed for iterative homologation to ensure high fidelity. Therefore, we decided to execute iterative homologation sequence. In practice sequentially treating boronic ester **16** with chiral chlorosilane, followed by oxidative cleavage of α-aminosilyl moiety, and then homologation reaction with lithiated benzoate ester gave boronic ester **22** in 74% yield over 3 steps and with full stereocontrol. Repeating the same sequence with the intermediate **22** afforded boronic ester 23 in 65% yield and again with excellent stereocontrol. Moreover, Matteson one carbon homologation of **23** proceeded well in nearly quantitative yield.[7] Finally, carbon-silicon bonds could then be oxidised in stereospecific manner using *m*-CPBA and $KHF_2$ to provide the anti, anti-dipropionate fragment **25** in 66% yield.[8]




**Scheme 6.** The synthesis of polypropionate core

Having demonstrated a highly effective assembly-line synthesis protocol, we aim to apply this approach to polypropionate natural product synthesis. (+)-Zincophin was chosen as the next target. Our retrosynthetic analysis of (+)-Zincophin shows that it could be assembled from fragments A, B, and C (Scheme 7). In order to construct the fragment B, we planed to use the assembly-line synthesis starting from homoallylic boronic ester with different carbenoid building blocks in the appropriate order.




**Scheme 7.** Retrosynthetic analysis of (+)-zincophorin

## References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