Construction of 2,6-trans pyrans via Prins cyclization and its application towards the total synthesis of methyl sarcophytoate

Hu, Xuhong

2011

Hu, X. H. (2011). Construction of 2,6-trans pyrans via Prins cyclization and its application towards the total synthesis of methyl sarcophytoate. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/47588>

<https://doi.org/10.32657/10356/47588>

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

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

**HU XUHONG
SCHOOL OF PHYSICAL AND MATHEMATICAL
SCIENCES
2011**

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

HU XUHONG

School of Physical and Mathematical Sciences

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

2011

ACKNOWLEDGEMENTS

Firstly, I would like to express my most sincere appreciation to my supervisor, Professor Loh Teck Peng for his continuous encouragement and invaluable guidance throughout my Ph.D study. His insistent and creative approach to the science of organic chemistry has influenced me profoundly. His enthusiasm and aspirations for research has also inspired me to go further.

I would also like to thank my former advisor, Professor Yang Hua Zheng for her excellent teaching and training during my graduate study in Nankai University.

Special thanks are extended to Dr Liu Feng, Dr Zhao Yu Jun, Dr Wang Shun Yi, Dr Xu Yun He, Dr Wang Peng, Dr Zhao Jun Feng, Mr Li Bin, Mr Luo Hai Qing for their invaluable discussions and sharing of knowledge. I would also like to express my gratitude to Dr Sreekumar Pankajakshan for his patient and careful proof reading of my thesis.

My gratitude to all my lab friends Dr Zhou Hai, Dr Lu Jun, Dr Zhang Yun Xiao, Dr Zhang Li, Dr Zhu Ming Kui, Mr Yin Peng, Mr Wen Zhen Kang, Mr Zhao Kai, Mr Mageshi Sampath, Mr Tian Jie Sheng, Mr Yang Yong Sheng and Miss Xu Feng Xia for helping me in every aspects during my postgraduate studies. I also thank my diligent and promising summer research students Thia Yi Ping Larissa, Cai Yong, Chen Xin Ying, Farhan Aizuddin Bin Hamza for their assistance rendered in the accomplishment of my projects.

I would also like to thank the support staffs in Nanyang Technological

University, namely Ms Chen Xiao Ping and Ms Hum Wei Mei Celine for administrative assistance, Ms Goh Ee Ling for assistance with NMR equipment, Ms Zhu Wen Wei for assistance with Mass Spectroscopy equipment as well as Dr Li Yong Xin for assistance with X-ray crystal diffractometer.

Finally, I would also like to thank my family for their continual support, encouragement and many sacrifices that they have made to ensure that I can focus my intent concentration on the four years' project.

TABLE OF CONTENTS

Acknowledgements	i
Table of Contents	iii
List of Abbreviations	v
Summary	viii
CHAPTER 1: STRATEGIES FOR THE CONSTRUCTION OF 2,6-TRANS PYRANYL RINGS	
1.1 Introduction	1
1.2 Cyclization onto Oxocarbenium Ions	2
1.3 Oxy-Michael Type Addition	6
1.4 Nucleophilic Addition onto the Cyclic Oxonium	9
1.5 Ring Closing Metathesis	14
1.6 Mukaiyama-Michael Reaction	15
1.7 Transition Metal-catalyzed Cyclization	16
1.8 Summary	18
CHAPTER 2: DIASTEREOSELECTIVE SYNTHESIS OF 2,6-TRANS DIHYDROPYRANS VIA PRINS CYCLIZATION	
2.1 Introduction	20
2.2 Prins Cyclization of Allenic Alcohols with Aldehydes	26
2.3 Conclusion	31
2.4 Experimental Section	33
CHAPTER 3: RESEARCH TOWARDS THE TOTAL SYNTHESIS OF METHYL SARCOPHYTOATE	
3.1 Introduction	53
3.2 Previous synthetic work	58
Part A. Towards synthesis of methyl sarcoate	
3.3 Retrosynthetic Analysis of Methyl Sarcoate	63
3.4 Preliminary studies	64
	iii

Part B. Towards Synthesis of the Diene Unit 3	
3.5 Retrosynthetic Analysis of the Diene Unit 3	70
3.6 Results and Discussion	73
3.7 Conclusions	79
3.8 Experimental Section	81
APPENDIX: A NOVEL INDIUM-MEDIATED CARBON-CARBON BOND-FORMING REACTION: SYNTHESIS OF 1,3- DIHALO-1-ENE	
A.1 Introduction	122
A.2 Coupling Reaction of Terminal Alkyne and Aldehyde using Indium (III) Triflate as Catalyst	127
A.3 Conclusion	130
A.4 Experimental Section	131
List of Publications	143

LIST OF ABBREVIATIONS

δ	chemical shift
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
Ar	aryl
aq	aqueous
BINAP	2,2'-diphenylphosphino-1, 1'-binaphthyl
Bn	benzyl
BOM	benzyloxymethyl
Bz	benzoyl
calcd	calculated
CH_2Cl_2	dichloromethane
CDCl_3	deuterated chloroform
cm^{-1}	inverse centimeter
Cy	cyclohexanyl
d	doublet
DIBAL-H	diisobutylaluminium hydride
dd	doublet of doublets
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DIPEA	diisopropylethylamine
dt	doublet of triplets
ee	enantiomeric excess
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
FTIR	fourier transform infrared spectrometry

g	gram
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
<i>i</i> -Pr	isopropyl
LiHMDS	lithium hexamethyldisilazane
M	molar concentration
m	multiplet
m/z	mass per charge ratio
M ⁺	parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MOM	methoxymethyl
MeOH	methanol
MHz	mega hertz
min	minute(s)
mL	milliliter(s)
mmol	millimole
mol%	mole percent
MS	mass spectrometry
<i>n</i> -Bu	<i>n</i> -butyl
NMO	4-methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
Ph	phenyl
PMP	<i>p</i> -methoxyphenyl
ppm	parts per million
PPTS	pyridium <i>p</i> -toluenesulfonate

<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
Py	pyridine
q	quartet
R _f	retention factor
rt	room temperature
s	singlet
sat	saturated
t	triplet
TBDPS	<i>tert</i> -butyldiphenyl silyl
TBS	<i>tert</i> -butyldimethyl silyl
^t Bu	<i>tert</i> -butyl
THF	tetrahydrofuran
TIP	Triisopropyl silyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TLC	thin layer chromatography
UV	ultraviolet
vol	volume

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 alkoxycarbonyl group led to the highly 2,6-*trans* diastereoselectivity on a basis of electronic and steric effect, detailed in Chapter 2.

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, α,β -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 $\text{In}(\text{OTf})_3$ and trimethylsilyl halide for the synthesis of 1,3-dihalo-1-ene in the Appendix.

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,¹ Aspergillide A,² Prugosene A,³ Sorangicin A,⁴ Swinholide A⁵ 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

¹ Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J. *J. Org. Chem.* **1988**, *53*, 3644–3646.

² Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225–228.

³ Lang, G.; Wiese, J.; Schmaljohann, R.; Imhoff, J. F. *Tetrahedron* **2007**, *63*, 11844–11849.

⁴ Jansen, R.; Wary, V.; Irschik, H.; Reichenbach, H.; Höfle, G. *Tetrahedron Lett.* **1985**, *26*, 6031–6034.

⁵ Kashman, Y.; Carmely, S. *Tetrahedron Lett.* **1985**, *26*, 511–514.

In spite of general methods to access pyranyl moiety available,⁶ 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

Oxocarbeniumium ions with a carboxyl substituent on the cationic carbon atom have been implicated as versatile and highly reactive electrophilic intermediates in organic synthesis.⁷ Especially, the vinylsilane-terminated cyclizations of oxocarbenium ions for the efficient construction of oxygenated heterocycles have been widely studied in the past decades.⁸ Speckamp utilized this key intermediate to build the 2,6-*trans* dihydropyrans (DHP) through intramolecular cyclization of (*E*)-vinylsilane.⁹ 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).

⁶ For reviews on the synthesis of tetrahydropyrans (THP), see: (a) Larrosa, I.; Romea, P.; Urrutia, F. *Tetrahedron* **2008**, *64*, 2683–2723. (b) Clarke, P. A.; Santos, S. E. *J. Org. Chem.* **2006**, *71*, 2045–2053. (c) Tang, Y.; Oppenheimer, J.; Song, Z.; You, L.; Zhang, X.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10785–10813. (d) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301–2323. (e) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362.

⁷ (a) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115–7128. (b) Horenstein, B. A.; Bruner, M. *J. Am. Chem. Soc.* **1996**, *118*, 10371–10379. (c) Martichonok, V.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 1702–1706.

⁸ (a) Castañeda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695–5707. (b) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386–4399. (c) Berger, D.; Overman, L. E. *Synlett* **1992**, 811–813. (d) Sakamoto, Y.; Tamegai, K.; Nakata, T. *Org. Lett.* **2002**, *4*, 675–678.

⁹ Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426–3427.

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)₂Ti(NTf)₂.¹⁰ The chemical transformation involved the oxa-Cope rearrangement and subsequent intramolecular allylic transfer reaction into the oxocarbenium ion (Scheme 1.2).

Scheme 1.2

Actually, this steric compression strategy was employed in the synthetic study towards Okadaic acid.¹¹ 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-diaxial interactions between the TMS group and the ethyl moiety (Scheme 1.3).

¹⁰ Yu, C. M.; Shin, M. S.; Cho, E. Y. *Bull. Korean Chem. Soc.* **2004**, 25, 1625–1626.

¹¹ Markó I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, 38, 2899–2902.

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.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,¹³ callipeltoside A,¹⁴ kendomycin,¹⁵ herboxidiene/GEX 1A,¹⁶ neopeltolide,¹⁷ and brevisamide.¹⁸

¹² Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836–9837.

¹³ (a) Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 3995–3998. (b) Su, Q.; Panek, J. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 1223–1225. (c) Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem.* **2007**, *72*, 2–24.

¹⁴ (a) Huang, H.; Panek, J. S. *Org. Lett.* **2004**, *6*, 4383–4385. (b) Huang, H.; Panek, J. S. *Org. Lett.* **2003**, *5*, 1991–1993.

¹⁵ (a) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529–1532. (b) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008**, *10*, 3813–3816.

¹⁶ Zhang, Y.; Panek, J. S. *Org. Lett.* **2007**, *9*, 3141–3143.

¹⁷ Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 9211–9214.

Scheme 1.4

In the course of the total synthesis of apicularen A,¹⁹ 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 1.5

¹⁸ Lee, J.; Panek, J. S. *Org. Lett.* **2009**, *11*, 4390–4393.

¹⁹ Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430.

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

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

²⁰ (a) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, 7, 3231–3234. (b) Lowe, J. T.; Wrona, I. E.; Panek, J. S. *Org. Lett.* **2007**, 9, 327–330. (c) Wrona, I. E.; Lowe, J. T.; Turbyville, T. J.; Johnson, T. R.; Beignet, J.; Beutler, J. A.; Panek, J. S. *J. Org. Chem.* **2009**, 74, 1897–1916.

²¹ (a) Mart ́n, V. S.; Nu ́ñez, M. T.; Ramirez, M. A.; Solar, M. A. *Tetrahedron Lett.* **1990**, 31, 763–766. (b) Mart ́n, V. S.; Palaz ́n, J. M. *Tetrahedron Lett.* **1992**, 33, 2399–2402. (c) Gung, B. W.; Francis, M. B. *J. Org. Chem.* **1993**, 58, 6177–6179. (d) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Org. Chem., Perkin Trans. 1* **1996**, 967–969. (e) Betancort, J. M.; Mart ́n, V. S.; Padr ́n, J. M.; Palaz ́n, J. M.; Ram ́rez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, 62, 4570–4583. (f) Ram ́rez, M. A.; Padr ́n, J. M.; Palaz ́n, J. M.; Mart ́n, V. S. *J. Org. Chem.* **1997**, 62, 4584–4590. (g) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, 4, 481–484. (h) De Brabander, J. K.; Soltani, O. *Org. Lett.* **2005**, 7, 2791–2793. (i) De Brabander, J. K.; Pan, Y. *Synlett* **2006**, 853–856.

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).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

Schneider disclosed a base-catalyzed oxa-conjugated addition of enantiopure 7-hydroxy-2-enimides to give rise to predominantly *trans*-THPs.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 enamide (Scheme 1.8). PM3 calculation revealed that stereoelectronic effect arose from the molecular orbital interaction between the lone pair of the oxygen and the

²² Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, 34, 5739–5742.

²³ Schneider, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **2000**, 73–82.

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).²⁴ The acrylate moiety was forced to reside on an axial position in order to form the favourable chair-like transition state, which simultaneously maximized the capacity of chelating with K^+ cation, with the model proposed by Martín.^{20e}

Scheme 1.9

Another appealing example of oxy-Michael addition is the formation of pyranyl ring in the formal total synthesis of (-)-apicularen A.²⁵ 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.

²⁴ Vares, L.; Rein, T. *J. Org. Chem.* **2002**, 67, 7226–7237.

²⁵ (a) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, 6, 1289–1292. (b) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2002**, 43, 8507–8510.

Scheme 1.10

1.4 Nucleophilic Addition onto the Cyclic Oxonium

Lewis acid-catalyzed addition to anomeric 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 anomeric 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 rearrangement²⁷ 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

²⁶ (a) Dawe, R. D. *J. Chem. Soc. Chem. Commun.* **1981**, 1180–1181. (b) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978. (c) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3803–3805. (d) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082–2089. (e) Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.* **1992**, *51*, 7911–7914. (f) Herscovici, J.; Boumaiza, L.; Antonakis, K. *J. Org. Chem.* **1992**, *57*, 2476–2480. (g) Osobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665–2676.

²⁷ (a) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443–5449. (b) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570–575.

²⁸ (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, *29*, 2589–2592. (b) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383–2386.

²⁹ (a) Patron, A. P.; Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Nicolaou, K. C. *J. Chem. Soc. Chem. Commun.* **1994**, 1147–1150. (b) Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Patron, A. P.; Nicolaou, K. C. *J. Chem. Soc. Chem. Commun.* **1994**, 1151–1152. (c) Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khatuya, H.; Richter, P. K.; Bertinato, P. *J. Am. Chem. Soc.* **1996**, *118*, 3059–3060. (d) Nakata, T.; Komatsu, T.; Nagasawa, K.; Yamada, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 8225–8228.

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 allyltrimethylsilane 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 ZnCl₂ in high yield and excellent diastereoselectivity.

³⁰ Paterson, I.; Smith, J. D. *J. Org. Chem.* **1992**, *57*, 3261–3264. (b) Paterson, I.; Cumming, J. G. *Tetrahedron Lett.* **1992**, *33*, 2847–2850. (c) Paterson, I.; Yeung, K. S. *Tetrahedron Lett.* **1993**, *34*, 5347–5350. (d) Paterson, I.; Smith, J. D.; *Tetrahedron Lett.* **1993**, *34*, 5351–5354. (f) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A.; Yeung, K. S. *Tetrahedron Lett.* **1994**, *35*, 3405–3408. (g) Paterson, I.; Smith, J. D.; Ward, R. A.; Cumming, J. G. *J. Am. Chem. Soc.* **1994**, *116*, 2615–2616. (h) Paterson, I.; Yeung, K. S.; Ward, R. A.; Cumming, J. G.; Smith, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 9391–9392. (i) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lambole, S. *Tetrahedron* **1995**, *51*, 9393–9412. (j) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413–9436. (k) Paterson, I.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K. S. *Tetrahedron* **1995**, *51*, 9437–9466. (l) Paterson, I.; Yeung, K. S.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Lambole, S. *Tetrahedron* **1995**, *51*, 9467–9486.

³¹ (A) Williams, D. R.; Patnaik, S.; Plummer, S. V. *Org. Lett.* **2003**, *5*, 5035–5038. (b) Paterson, I.; Tudge, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 343–347. (c) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833–6849.

Scheme 1.12

With the same strategy, Brabander introduced an axial nitrile into the pyranyl acetate with trimethylsilyl cyanide mediated by ZnI_2 in the synthesis of psympederin (Scheme 1.13).³²

Scheme 1.13

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

³² Jiang, X.; Williams, N.; De Brabander, J. K. *Org. Lett.* **2007**, 9, 227–230.

³³ (a) Song, Z.; Hsung, R. P. *Org. Lett.* **2007**, 9, 2199–2202; (b) Song, Z.; Hsung, R. P.; Lu, T.; Lohse, A. G. *J. Org. Chem.* **2007**, 72, 9722–9731. (c) Song, Z.; Lohse, A. G.; Hsung, R. P. *Nat. Prod. Rep.* **2009**, 26, 560–571.

Scheme 1.14

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).³⁴ It was envisaged that the oxocarbenium ion intermediate was generated *via* the ionization of glycol, followed by addition of nucleophile to produce the Ferrier rearrangement product.

Scheme 1.15

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_3 was demonstrated by Yadav (Scheme 1.16).³⁵ The reaction proceeded to give 2,6-*trans* DHP as single diastereoisomer, through activation of aldehyde by InBr_3 and subsequently formation of an oxonium intermediate in which

³⁴ Kartika, R.; Frein, J. D.; Taylor, R. E. *J. Org. Chem.* **2008**, 73, 5592–5594.

³⁵ Yadav, J. S.; Sunitha, V.; Reddy, B. V. S.; Das, P. P.; Gyanchander, E. *Tetrahedron Lett.* **2008**, 49, 855–857.

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

Scheme 1.16

The attacking groups are not limited to soft nucleophiles, hydride also can be used to trap the oxonium ion intermediate.³⁶ DIBAL-H reduction of the bicycle ketal afforded the 2,6-*trans* DHP with retention of configuration.³⁷ The stereoselectivity was attributed to coordination of aluminium reagent to O3-ketal oxygen, as a result of the formation of oxonium ion, subsequently $\text{S}_{\text{N}}1$ 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).³⁸

³⁶ (a) Kotsuki, H. *Synlett* **1992**, 97–106. (b) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *46*, 4595–4612.

³⁷ Bogaczyk, S.; Brescia, M. R.; Shimshock, Y. C.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 4352–4355.

³⁸ Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641–4644.

Scheme 1.17

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.³⁹ The tandem sequence of glycolate Claisen rearrangement/ring closing metathesis provided 2,6-*trans* DHP-2-carboxylate.⁴⁰ 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).

Scheme 1.18

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

³⁹ (a) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, 63, 8626–8627.

⁴⁰ Burke, S. D.; Ng, R. A.; Morrison, J. A.; Alberti, M. J. *J. Org. Chem.* **1998**, 63, 3160–3161.

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

Scheme 1.19

1.6 Mukaiyama-Michael Reaction

More recently our group discovered a simple InCl_3 -catalyzed Mukaiyama-Michael reaction between silyl enol ether and α,β -unsaturated dihydropyranone under neat conditions.⁴² Tetrahydropyranones were produced as the sole 2,6-*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

⁴¹ Evans, P. A.; Leahy, D. K.; Andrews, W. J.; Uruguchi, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4788–4791.

⁴² Chua, S. S.; Alni, A.; Chan, L. T. J.; Yamane, M.; Loh, T. P. *Tetrahedron* **2011**, *67*, 5079–5082.

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 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 $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ -catalyzed intramolecular cyclization *via* a *syn*- $\text{S}_{\text{N}}2'$ type process.⁴³ 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

⁴³ Kawai, N.; Lagrange, J. M.; Ohimi, M.; Uenishi, J. *J. Org. Chem.* **2006**, 71, 4530–4537.

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).⁴⁴ It was predicted that the olefinic carbon atom was attacked by the hydroxyl group from the *Re*-face.

Scheme 1.22

Furthermore, Trost developed a tandem coupling cyclization of silyl-substituted alkyne and terminal alkene tethering a leaving group.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

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

⁴⁴ Uenishi, J.; Ohmi, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2756–2760.

⁴⁵ Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128*, 6745–6754.

synthesis of 2,6-*trans* pyranyl rings.⁴⁶ 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).⁴⁷

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.⁴⁸

⁴⁶ Meyer, C.; Blanchard, N.; Defosseux, M.; Cossy, J. *Acc. Chem. Res.* **2003**, *36*, 766–772.

⁴⁷ (a) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626–4647. (b) Cossy, J.; Blanchard, N.; Defosseux, M.; Meyer, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 2144–2146.

⁴⁸ (a) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2665–2667. (b) Flamme, E. M.; Roush, W. R. *Beilstein J. Org. Chem.* **2005**, *1*, doi:10.1186/1860-5397-1-7.

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.⁴⁹ Moreover, in combination with other reactions, a cascade reaction involving Pinacol rearrangement,⁵⁰ Mukaiyama-aldol,⁵¹ Ritter reaction,⁵² Friedel-Crafts,⁵³ 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.

⁴⁹ For reviews, see: (a) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925–957. (b) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413–445.

⁵⁰ (a) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748–4749. (b) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033–9044. (c) Cohen, F.; MacMillan, D. W. C.; Overman, L. E.; Romero, A. *Org. Lett.* **2001**, *3*, 1225–1228. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157. (e) Overman, L. E.; Velthuisen, E. J. *J. Org. Chem.* **2006**, *71*, 1581–1587.

⁵¹ (a) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421. (b) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3163–3166. (c) Li, H.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 7194–7195. (d) Li, H.; Loh, T. P. *Org. Lett.* **2010**, *12*, 2679–2681.

⁵² (a) Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480–16481. (b) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Reddy, G. M. *Tetrahedron Lett.* **2007**, *48*, 4903–4906. (c) Reddy, U. C.; Raju, B. R.; Kumar, E. K. P.; Saikia, A. K. *J. Org. Chem.* **2008**, *73*, 1628–1630. (d) Reddy, B. V. S.; Ramesh, K.; Ganesh, A. V.; Kumar, G. G. K. S. N.; Yadav, J. S.; Gré, R. *Tetrahedron Lett.* **2011**, *52*, 495–498.

⁵³ (a) Yang, X. F.; Wang, M.; Zhang, Y.; Li, C. J. *Synlett* **2005**, 1912–1916. (b) Basavaiah, D.; Reddy, K. R. *Org. Lett.* **2007**, *9*, 57–60. (c) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605–2608.

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.⁵⁴ The sp^2 hybridized carbon at C4 was trapped from favouring equatorial position due to delocalization.⁵⁵

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.⁵⁶ 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

⁵⁴ (a) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, 39, 7271–7274. (b) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, 66, 4679–4686. (c) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, 126, 9904–9905. (d) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, 5, 3883–3885. (e) Yang, X. F.; Mague, J. T.; Li, C. J. *J. Org. Chem.* **2001**, 66, 739–747.

⁵⁵ Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, 128, 1680–1682.

⁵⁶ Chan, K. P.; Seow, A. H.; Loh, T. P. *Tetrahedron Lett.* **2007**, 48, 37–41.

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 Electronic inductive effects on oxonium cations

From our previous work, based on the concept that the lone pairs of the alkoxy functionalities could successfully stabilize 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 enones⁵⁹ and amino alcohol.⁶⁰ Several methods have been

⁵⁷ (a) Cho, Y. S.; Jun, B. K.; Pae, A. N.; Cha, J. W.; Koh, H. Y.; Chang, M. Y.; Han, S. Y. *Synthesis*, **2004**, 16, 2620–2624. (b) Emos, D.; Kim, S. H.; Lee, P. H. *Bull. Korean Chem. Soc.* **2010**, 31, 645–649.

⁵⁸ (a) Hoffmann-Roder, A.; Krause, N. *Org. Lett.* **2001**, 3, 2537–2538. (b) Emos, D. Kang, D.; Lee, P. H. *J. Org. Chem.* **2010**, 75, 7447–7450.

⁵⁹ Kang, S. K.; Ko, B. S.; Lee, D. M. *Synth. Commun.* **2002**, 32, 3263–3271.

⁶⁰ Friesen, R. W. *Tetrahedron Lett.* **1990**, 31, 4249–4252.

developed for synthesis of α -allenic alcohol from aldehyde *via* allenylation reactions with propargyl halide,⁶¹ propargyltin⁶² 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

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).

⁶¹ (a) Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 13042–13043. (b) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 496–497. (c) Inoue, M.; Nakata, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 252–255. (d) Yi, X. H.; Meng, Y.; Hua, X. G.; Li, C. J. *J. Org. Chem.* **1998**, *63*, 7472–7480. (e) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207–3210.

⁶² (a) Yu, C. M.; Yoon, S. K.; Lee, S. J.; Lee, J. Y.; Kim, S. S. *Chem. Commun.* **1998**, 2749–2750.

⁶³ Buckle, M. J. C.; Fleming, I.; Gil, S.; Pang, K. L. C. *Org. Biomol. Chem.* **2004**, *2*, 749–769.

⁶⁴ Trost, B. M.; Jonasson, C.; Wuchrer, M. *J. Am. Chem. Soc.* **2001**, *123*, 12736–12737.

⁶⁵ Yu, C. M.; Kim, Y. M.; Kim, J. M. *Synlett* **2003**, 1518–1520.

⁶⁶ Lee, K. C.; Lin, M. J.; Loh, T. P. *Chem. Commun.* **2004**, 2456–2457.

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,⁶⁷ we became interested in the diastereoselective synthesis of 2,6-*trans* pyranyl motifs *via* Prins cyclization. Since the year 2002,⁶⁸ 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.⁶⁹ A symmetrical 2-oxonia Cope rearrangement was proposed to account for the racemisation of the products (Scheme 2.5).⁷⁰

Scheme 2.5 Epimerization Process

⁶⁷ Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053.

⁶⁸ (a) Loh, T. P.; Yang, J. Y.; Feng, L. C.; Zhou, Y. *Tetrahedron Lett.* **2002**, 43, 7193–7196. (b) Zhou, H.; Loh, T. P. *Tetrahedron Lett.* **2009**, 50, 4368–4371.

⁶⁹ (a) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, 50, 7115–7128. (b) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, 4, 3919–3922. (c) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, 4, 577–580.

⁷⁰ Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem. Int. Ed.* **2001**, 40, 2921–2922.

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

Scheme 2.6 Formal synthesis of (+)-SCH 351448 through InBr_3 -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.

⁷¹ Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, 7, 4491–4494.

⁷² Chan, K. P.; Ling, Y. H.; Loh, T. P. *Chem. Commun.* **2007**, 939–941.

⁷³ (a) Ghosh, A. K.; Shin, D.; Schiltz, G. *Heterocycles* **2002**, 58, 659–666. (b) Cao, H.; Jiang, H. F.; Qi, C. R.; Yao, W. J.; Chen, H. J. *Tetrahedron Lett.* **2009**, 50, 1209–1214.

⁷⁴ (a) Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, 8, 1633–1636. (b) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, 5, 1979–1982. (c) Chavre, S. N.; Choo, H.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S. *Org. Lett.* **2006**, 8, 3617–3619.

⁷⁵ (a) Huang, H.; Spande, T. F.; Panek, J. S. *J. Am. Chem. Soc.* **2003**, 125, 626–627. (b) Dobbs, A. P.; Guesn, S. J. J.; Martinovi, S. M.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, 68, 7880–7883. (c) Dobbs, A. P.; Guesn, S. J. J. *Synlett* **2005**, 2101–2103. (d) Dobbs, A. P.; Guesn, S. J. J.; Hursthouse, M. B.; Coles, S. J. *Synlett* **2003**, 11, 1740–1742. (e) Carballo, R. M.; Ramírez, M. A.; Rodríguez, M. L.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, 8, 3837–3840. (f) Carballo, R. M.; Valdomir, G.; Purino, M.; Martín, V. S.; Padrón, J. I. *Eur. J. Org.*

With this in mind, we envisioned that removal of the 1,3-diaxial interaction by using α -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 α -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

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 -methylallenic alcohol (Table 2.1, substrate **1**) bearing an *n*-butyl ester group with a wide range of aldehydes in the presence of $\text{In}(\text{OTf})_3$ (0.1 equiv) and TMSBr (1.2 equiv) in CH_2Cl_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.

⁷⁶ Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, 125, 13042–13043.

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

entry	R	time (h)	products (yield, %) ^c		<i>dr</i> (<i>trans</i> : <i>cis</i>)
1		2	2a (84)	2a' (12)	87:13 ^d
2		2	2b (75)	2b' (6)	93:7 ^d
3		1.5	2c/c' (84)		92:8 ^e
4		1.5	2d (73)	2d' (8)	90:10 ^d
5		2	2e (70)	2e' (13)	84:16 ^d
6		3	2f (75)	2f' (8)	89:11 ^d

^a Reactions were performed with **1** (0.3 mmol, dissolved in 1 mL CH₂Cl₂, syringe pump addition), aldehyde (0.36 mmol), TMSBr (0.36 mmol) and In(OTf)₃ (0.03 mmol) in CH₂Cl₂ (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 ¹H 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 benzaldehyde⁷⁷ 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.

⁷⁷ Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768–5774.

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 NOESY 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 trimethylsilylallenenic alcohol with aldehydes^a

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <p>(1 equiv) 3</p> </div> <div>+</div> <div style="text-align: center;"> <p>(1.2 equiv)</p> </div> <div style="text-align: center;"> <p>In(OTf)₃ (10 mol %) TMSBr (1.2 equiv) CH₂Cl₂ (0.1 M) 0 °C</p> </div> <div style="text-align: center;"> <p>2,6-<i>trans</i> 4a-g^b</p> </div> </div>					
entry	R	product	time (h)	yield (%) ^c	<i>dr</i> <i>trans/cis</i> ^d
1		4a	1	90	96:4
2		4b	1.5	84	96:4
3		4c	1	86	94:6
4		4d	1.5	82	>99:1
5		4e	1.5	80	>99:1
6		4f	2	83	93:7
7		4g	2.5	68	>99:1
8		4h	3	64	>99:1

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

Of mechanistic interest, we carried out the reaction of alkyl substituted allenenic alcohol **5** with cyclohexanecarboxaldehyde (Table 2.3). Treatment of cyclohexyl substituted allenenic alcohol with the aldehyde using the standard conditions afforded dicyclohexyl DHP **6** in good yield (Table 2.3, entry 1), but the relative diastereochemistry showed the 2,6-*cis* configuration, confirmed by NOESY. No cross-over product **7** was detected. The same product was obtained when phenethyl allenenic 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 MgBr₂, FeCl₃ or AlCl₃ 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

entry	R	X	conditions	product 6 (yield, %) ^c
1		Br	$\text{In}(\text{OTf})_3$, TMSBr	63
2		Br	$\text{In}(\text{OTf})_3$, TMSBr	11
3 ^b		Br	$\text{In}(\text{OTf})_3$, TMSBr	71
4		Br	MgBr_2	trace
5		Cl	FeCl_3	44
6		Cl	AlCl_3	trace

^aAll reactions were carried out with **5** (0.3 mmol) and cyclohexanecarboxaldehyde (0.33 mmol) in CH_2Cl_2 (3 mL) at 0 °C unless otherwise stated. ^b3 equivalent of aldehyde was used. ^cIsolated 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,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

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-*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.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-*trans* pyranyl motifs. Prins cyclization using carboalkoxyl allenic alcohols is the key to the success of this method. The ester group provides an

⁷⁸ Roush, W. R.; Dilley, G. T. *Synlett* **2001**, 955–959.

anomeric effect⁷⁹ as well as lone pair stabilization⁸⁰ 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.

⁷⁹ (a) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322–5323. (b) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528. (c) Mulzer, J.; Meyer, F.; Buschmann, J.; Luger, P. *Tetrahedron Lett.* **1995**, *36*, 3503–3506.

⁸⁰ (a) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692–10697. (b) Loh, T. P.; Wang, R. B.; Sim, K. Y. *Tetrahedron Lett.* **1996**, *37*, 2989–2992.

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 CH_2Cl_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 NaCl or KBr salt plates. Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C 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 SiMe_4 (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 δ 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).

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

General Procedure for Prins Cyclization reactions of Allenic Alcohols and Aldehydes

Preparation of *n*-butyl glyoxylate

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 $^\circ\text{C}$. The resulting reaction was stirred for 4 h, decanted from the solid precipitate, dried over Na_2SO_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 $^\circ\text{C}/12$ mmHg.

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

1-Bromo-2-butyne (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/NH₄Cl (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 MgSO₄, 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)

¹H NMR (300 MHz, CDCl₃): 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)

¹³C NMR (75.4 MHz, CDCl₃): 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 C₁₀H₁₆NaO₃ [M + Na]⁺: 207.0997, Found: 207.0988

FTIR (NaCl): ν 3462, 2961, 2874, 1962, 1732, 1462, 1273, 1198, 1080, 850 cm⁻¹

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 CH_2Cl_2 . The mixture was allowed to cool to 0 °C prior to addition of trimethylsilylbromide (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 CH_2Cl_2 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 NaHCO_3 aq. solution (10 mL). The aqueous layer was extracted with Et_2O (10 mL $\times$ 3). The combined organic layers were washed with water, sat aq NaCl , and dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The residue crude product was purified by flash column chromatography to afford dihydropyrans **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%

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

^1H NMR (400 MHz, CDCl_3): 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,

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 $\text{C}_{17}\text{H}_{27}^{79}\text{BrNaO}_3$ $[\text{M} + \text{Na}]^+$: 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)

^1H 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 $\text{C}_{17}\text{H}_{27}^{79}\text{BrNaO}_3$ $[\text{M} + \text{Na}]^+$: 381.1041, Found: 381.1047

FTIR (NaCl): ν 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-2*H*-pyran-2-carboxylate

Yield (%): 75%

R_f : 0.48 (Hexane: Diethyl ether = 8:1)

^1H 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 $\text{C}_{16}\text{H}_{27}^{79}\text{BrNaO}_3$ $[\text{M} + \text{Na}]^+$: 369.1041, Found: 369.1040

FTIR (NaCl): ν 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-2*H*-pyran-2-carboxylate

Yield (%): 6%

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

¹H NMR (400 MHz, CDCl₃): 4.64 (s, 1H), 4.17 (t, *J* = 6.6 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)

¹³C NMR (100 MHz, CDCl₃): 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 C₁₆H₂₇⁷⁹BrNaO₃ [M + Na]⁺: 369.1041, Found: 369.1040

FTIR (NaCl): ν 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)

¹H NMR (400 MHz, CDCl₃): 4.58 (s, 1H), 4.09 – 4.18 (m, 2H), 3.81 (dd, *J* = 3.5, 10.9 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)

¹³C NMR (100 MHz, CDCl₃): 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

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, 1466, 1396, 1365, 1300, 1242, 1179, 1128, 1107, 1015, 966, 837, 737 cm^{-1}

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

Yield (%): 73%

R_f : 0.44 (Hexane: Diethyl ether = 8:1)

1H NMR (400 MHz, $CDCl_3$): 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)

^{13}C NMR (100 MHz, $CDCl_3$): 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}

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

Yield (%): 8%

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

¹H NMR (400 MHz, CDCl₃): 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)

¹³C NMR (100 MHz, CDCl₃): 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 C₁₅H₂₅⁷⁹BrNaO₃ [M + Na]⁺: 355.0885, Found: 355.0878

FTIR (NaCl): ν 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)

¹H NMR (400 MHz, CDCl₃): 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 –

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 $\text{C}_{19}\text{H}_{25}^{79}\text{BrNaO}_3$ $[\text{M} + \text{Na}]^+$: 403.0885, Found: 403.0899

FTIR (NaCl): ν 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-*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)

^1H 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 $\text{C}_{19}\text{H}_{25}^{79}\text{BrNaO}_3$ $[\text{M} + \text{Na}]^+$: 403.0885, Found: 403.0878

FTIR (NaCl): ν 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%

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

¹H NMR (400 MHz, CDCl₃): 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)

¹³C NMR (100 MHz, CDCl₃): 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 C₁₇H₂₁⁷⁹BrNaO₃ [M + Na]⁺: 375.0572, Found: 375.0558

FTIR (NaCl): ν 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%

R_f: 0.38 (Hexane: Diethyl ether = 8:1)

^1H NMR (400 MHz, CDCl_3): 7.28 – 7.41 (m, 5H), 4.88 (d, $J = 0.9$ Hz, 1H), 4.71 (dd, $J = 3.2, 10.7$ Hz, 1H), 4.20 (t, $J = 6.7$ Hz, 2H), 2.90 – 2.99 (m, 1H), 2.68 (d, $J = 16.9$ Hz, 1H), 1.83 (s, 3H), 1.64 – 1.71 (m, 2H), 1.37 – 1.46 (m, 2H), 0.95 (t, $J = 7.4$ Hz, 3H)

^{13}C NMR (100 MHz, CDCl_3): 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 $\text{C}_{17}\text{H}_{21}^{79}\text{BrNaO}_3$ $[\text{M} + \text{Na}]^+$: 375.0572, Found: 375.0555

FTIR (NaCl): ν 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)

To a suspension of indium power (1.15 g, 10 mmol, 2.0 equiv) in $\text{H}_2\text{O}/\text{THF}$ (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)

^1H NMR (400 MHz, CDCl_3): 4.67 (t, $J = 2.1$ Hz, 1H), 4.53 – 4.59 (m, 2H), 4.12 – 4.23 (m, 2H), 2.78 (br, 1H), 1.61 – 1.68 (m, 2H), 1.34 – 1.43 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 3H), 0.16 (s, 9H)

^{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 $\text{C}_{12}\text{H}_{23}\text{O}_3\text{Si}$ $[\text{M} + \text{H}]^+$: 243.1416, Found: 243.1424

FTIR (NaCl): ν 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)

^1H 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 $\text{C}_{19}\text{H}_{34}^{79}\text{BrO}_3\text{Si}$ $[\text{M} + \text{H}]^+$: 439.1280, Found: 439.1276

FTIR (NaCl): ν 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

*R*_f: 0.51 (Hexane: Diethyl ether = 8:1)

¹H NMR (400 MHz, CDCl₃): 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)

¹³C NMR (100 MHz, CDCl₃): 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 C₁₈H₃₄⁷⁹BrO₃Si [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

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

¹H NMR (400 MHz, CDCl₃): 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)

¹³C NMR (100 MHz, CDCl₃): 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 C₁₇H₃₂⁷⁹BrO₃Si [M + H]⁺: 391.1304, Found: 391.1304

FTIR (NaCl): ν 2957, 2872, 1734, 1612, 1466, 1396, 1366, 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-2*H*-pyran-2-carboxylate

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

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

¹H NMR (400 MHz, CDCl₃): 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)

¹³C NMR (100 MHz, CDCl₃): 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

HRMS (ESI): m/z calculated for $C_{21}H_{40}^{79}BrO_3Si$ $[M + H]^+$: 447.1930, Found: 447.1925

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

(2,6-*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)

1H 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 $C_{17}H_{32}^{79}BrO_3Si$ $[M + H]^+$: 391.1304, Found: 391.1279

FTIR (NaCl): ν 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* (*trans/cis*) = 93:7

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

¹H NMR (500 MHz, CDCl₃): 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)

¹³C NMR (125 MHz, CDCl₃): 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 C₂₁H₃₂⁷⁹BrO₃Si [M + H]⁺: 439.1304, Found: 439.1300

FTIR (NaCl): ν 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* (*trans/cis*) = >99:1

R_f: 0.42 (Hexane: Diethyl ether = 8:1)

¹H NMR (400 MHz, CDCl₃): 7.28 – 7.38 (m, 5H), 4.95 (d, *J* = 1.4 Hz, 1H), 4.85 (dd, *J* = 4.0, 10.5 Hz, 1H), 4.12 – 4.23 (m, 2H), 2.87 (ddd, *J* = 1.9, 10.5, 17.6 Hz, 1H), 2.75 (dd, *J* = 4.1, 17.6 Hz, 1H), 1.62 – 1.69 (m, 2H), 1.32 – 1.41 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.29 (s, 9H)

¹³C NMR (100 MHz, CDCl₃): 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): *m/z* calculated for C₁₉H₂₇⁷⁹BrNaO₃Si [M + Na]⁺: 433.0811, Found: 433.0795

FTIR (NaCl): ν 3063, 3032, 2958, 2872, 1730, 1611, 1496, 1452, 1309, 1248, 1182, 1123, 1069, 885, 842, 754, 698 cm⁻¹

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

Yield (%): 64%, *dr* (*trans/cis*) = >99:1

R_f: 0.40 (Hexane: Diethyl ether = 8:1)

¹H NMR (400 MHz, CDCl₃): 8.24 (s, 1H), 8.15 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 4.98 – 5.01 (m, 2H), 4.12 – 4.23 (m, 2H), 2.75 – 2.86 (m, 2H), 1.62 – 1.69 (m, 2H), 1.31 – 1.41 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.29 (s, 9H)

¹³C NMR (100 MHz, CDCl₃): 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 $C_{19}H_{27}^{79}BrNO_5Si$ $[M + H]^+$: 456.0842, Found: 456.0851

FTIR (NaCl): ν 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.

Yield (%): 82%

R_f : 0.39 (Hexane: Ethyl acetate = 4:1)

1H 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-yl)trimethylsilane

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

R_f : 0.60 (Hexane)

^1H 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 $\text{C}_{20}\text{H}_{36}^{79}\text{BrOSi}$ $[\text{M} + \text{H}]^+$: 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.⁸¹ Soft corals of the genus *Sarcophyton* are a family of Alcyoniidae 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.⁸²

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,⁸³ 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.⁸⁴ Subsequently, two other biscembranoids, named methyl sarcophytoate (**1**) and methyl chlorosarcophytoate, were isolated from the Okinawan soft coral *S. glaucum* by Kakisawa,⁸⁵ while the absolute configuration of **1** was elucidated

⁸¹ For annual reviews of marine natural products, see: (a) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2011**, 28, 196–268. (b) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2010**, 27, 165–237. (c) Blunt, J. W.; Copp, B. R.; Hu, W. P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2009**, 26, 170–244. (d) Blunt, J. W.; Copp, B. R.; Hu, W. P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2008**, 25, 35–94. (e) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, 23, 26–78.

⁸² (a) Yang, P.; Lv, Y.; van Ofwegen, L.; Proksch, P.; Lin, W. *Org. Lett.* **2010**, 12, 2484–2487. (b) Yang, P.; Deng, Z.; van Ofwegen, L.; Proksch, P.; Lin, W. *Chem. Pharm. Bull.* **2010**, 58, 1591–1595. (c) Yang, P.; Deng, Z.; van Ofwegen, L.; Proksch, P.; Lin, W. *Mar. Drugs* **2010**, 8, 2837–2848.

⁸³ Su, J.; Long, K.; Pang, T.; He, C.; Clardy, J. *J. Am. Chem. Soc.* **1986**, 108, 177–178.

⁸⁴ Su, J.; Long, K.; Peng, T.; Zeng, L.; Zheng, Q.; Lin, X. *Sci. Sin. ser. B* **1988**, 29, 1172–1184.

⁸⁵ Kusumi, T.; Igari, M.; Ishitsuka, M. O.; Ichikawa, A.; Itezono, Y.; Nakayama, N.; Kakisawa, H. *J. Org. Chem.* **1990**, 55, 6286–6289.

by means of difference CD spectrum using a lanthanide reagent.⁸⁶ In 1993, methyl neosartortuate acetate was isolated from the Australian soft coral *S. tortuosum* by Bowden,⁸⁷ in which the relative stereochemistry of the epoxide moiety at C26/C27 was corrected by Guo.⁸⁸

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*),⁸⁹ methyl tortuoates A–D (*S. tortuosum*),⁹⁰ bisglaucumlides A–K (*S.*

⁸⁶ Ishitsuka, M. O.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1991**, 32, 6595–6596.

⁸⁷ Leone, P. A.; Bowden, B. F.; Carroll, A. R.; Coll, J. C.; Meehan, G. V. *J. Nat. Prod.* **1993**, 56, 521–526.

⁸⁸ Jia, R.; Guo, Y. W.; Chen, P.; Yang, Y. M.; Mollo, E.; Gavagnin, M.; Cimino, G. *J. Nat. Prod.* **2007**, 70, 1158–1166.

⁸⁹ Feller, M.; Rudi, A.; Berer, N.; Goldberg, I.; Stein, Z.; Benayahu, Y.; Schleyer, M.; Kashman, Y. *J. Nat. Prod.* **2004**, 67, 1303–1308.

⁹⁰ (a) Zeng, L. M.; Lan, W. J.; Su, J. Y.; Zhang, G. W.; Feng, X. L.; Liang, Y. J.; Yang, X. P. *J. Nat. Prod.* **2004**, 67, 1915–1918. (b) Lan, W. J.; Li, H. J.; Yan, S. J.; Su, J. Y.; Zeng, L. M. *J. Asian Nat. prod. Res.* **2007**, 9, 267–271. (c) Lan, W. J.; Wang, S. L.; Li, H. J. *Nat. Prod. Commun.* **2009**, 4, 1193–1196.

glaucum),⁹¹ ximaolides A–G (*S. tortuosum*),^{105,92} bislatumlides A and B (*S. latum*),⁹³ desacetylnyalolide, diepoxynyalolide and dioxanyalolide (*S. elegans*).⁹⁴

Figure 3.2 Biscembranoids containing pyranyl motifs

⁹¹ (a) Iwagawa, T.; Hashimoto, K.; Okamura, H.; Kurawaki, J.; Nakatani, M.; Hou, D. X.; Fujii, M.; Doe, M.; Morimoto, Y.; Takemura, K. *J. Nat. Prod.* **2006**, *69*, 1130–1133. (b) Iwagawa, T.; Hashimoto, K.; Yokogawa, Y.; Okamura, H.; Nakatani, M.; Doe, M.; Morimoto, Y.; Takemura, K. *J. Nat. Prod.* **2009**, *72*, 946–949.

⁹² Jia, R.; Guo, Y. W.; Mollo, E.; Gavagnin, M.; Cimino, G. *Helv. Chim. Acta.* **2008**, *91*, 2069–2074.

⁹³ Yan, X. H.; Gavagnin, M.; Cimino, G.; Guo, Y. W. *Tetrahedron Lett.* **2007**, *48*, 5313–5316.

⁹⁴ Bishara, A.; Rudi, A.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **2007**, *70*, 1951–1954.

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. Macrocyclic cembrane-type 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

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 biscembranoids have only attracted the attention of two research groups, Xu's

⁹⁵ Paquette, L. A.; Rayner, C. M.; Doherty, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 4078–4079. (b) Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910–3926. (c) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926–3936. (d) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165–169. (e) Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345–347. (f) Huang, Q.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 543–545. (g) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901–5904. (h) Tang, B.; Bray, C. D.; Pattenden, G. *Tetrahedron Lett.* **2006**, *47*, 6401–6404. (i) Tang, B.; Bray, C. D.; Pattenden, G. *Org. Biomol. Chem.* **2009**, *7*, 4448–4457. (j) Kimbrough, T. J.; Roethle, P. A.; Mayer, P.; Trauner, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 2619–2621. (k) Tang, B.; Bray, C. D.; Pattenden, G.; Rogers, J. *Tetrahedron* **2010**, *66*, 2492–2500.

⁹⁶ (a) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8928–8929. (b) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942–6949. (c) Dauben, W. G.; Wang, T.; Stephens, R. W. *Tetrahedron Lett.* **1990**, *31*, 2392–2396. (d) Yue, X.; Li, Y. *Synthesis* **1996**, 736–740. (e) Li, Y.; Liu, Z.; Lan, J.; Li, J.; Peng, L.; Li, W. Z.; Li, Y.; Chan, A. S. C. *Tetrahedron Lett.* **2000**, *41*, 7465–7469. (f) Liu, Z.; Li, W. Z.; Li, Y. *Tetrahedron: Asymm.* **2001**, *12*, 95–100. (g) Zhang, T.; Liu, Z.; Li, Y. *Synthesis* **2001**, 393–298. (h) Liu, Z.; Peng, L.; Li, W. Z.; Li, Y. *Synlett* **2003**, 1977–1980.

⁹⁷ (a) Cases, M.; Gonzalez-Lopez de Turiso, F.; Pattenden, G. *Synlett* **2001**, 1869–1872. (b) Zhang, F.; Peng, L.; Zhang, T.; Mei, T.; Liu, H.; Li, Y. *Synth. Commun.* **2003**, *33*, 3761–3770. (c) Cases, M.; Gonzalez-Lopez de Turiso, F.; Hadjisoteriou, M. S.; Pattenden, G. *Org. Biomol. Chem.* **2005**, *3*, 2786–2804.

⁹⁸ Kato, T.; Suzuki, M.; Kobayashi, T. *J. Org. Chem.* **1980**, *45*, 1126–1130.

⁹⁹ (a) Cox, N. J. G.; Pattenden, G. *Tetrahedron Lett.* **1989**, *30*, 621–624. (b) Astley, M. P.; Pattenden, G. *Synlett* **1991**, 335–336. (c) Astley, M. P.; Pattenden, G. *Synthesis* **1992**, 101–105.

¹⁰⁰ (a) Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7314–7316. (b) Tietze, L. F.; Brazel, C. C.; Hölsken, S.; Magull, J.; Ringe, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 5246–5249. (c) Gaich, T.; Weinstabl, H.; Mulzer, J. *Synlett* **2009**, 1357–1366.

¹⁰¹ Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729–5735.

¹⁰² Marshall, J. A.; Dehoff, B. S. *Tetrahedron* **1987**, *43*, 4849–4860.

group¹⁰³ and Nakata's group.¹⁰⁴ 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.¹⁰⁵ 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**.

¹⁰³ (a) Liao, X.; Xu, X. *Tetrahedron Lett.* **2000**, *41*, 4641–4644. (b) Gao, Y.; Nan, F.; Xu, X. *Tetrahedron Lett.* **2000**, *41*, 4811–4841. (c) Hong, Z.; Chen, X.; Xu, X. *Tetrahedron Lett.* **2003**, *44*, 485–488. (d) Hong, Z.; Xu, X. *Tetrahedron Lett.* **2003**, *44*, 489–491. (e) Liu, P.; Xu, X. *Tetrahedron Lett.* **2004**, *45*, 5163–5166. (f) Yao, H.; Gao, Y.; Liu, P.; Sun, B.; Xu, X. *Synlett* **2007**, 571–574. (g) Yao, H.; Gao, Y.; Liu, P.; Xu, X. *Chin. J. Chem.* **2009**, *27*, 2025–2030.

¹⁰⁴ (a) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Synlett* **1997**, 899–902. (b) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1417–1429. (c) Ichige, T.; Kamimura, S.; Mayumi, K.; Sakamoto, Y.; Terashita, S.; Ohteki, E.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2005**, *46*, 1263–1267. (d) Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Am. Chem. Soc.* **2007**, *129*, 9862–9863. (e) Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Org. Chem.* **2009**, *74*, 230–243.

¹⁰⁵ (a) Nakata, M.; Yasuda, M.; Suzuki, S.; Ohba, S. *Synlett* **1994**, 71–74. (b) Nakata, M.; Yasuda, M.; Kawakita, J. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2607–2610.

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** expectedly 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 phenylsulfidation. The epoxy allyl sulfide **24** was transformed into the acetonide-protected diene unit **25** by the following four-step reactions

involving *n*-BuLi-Bu₂Mg-mediated Ito-Kodama cyclization, oxidation of sulfide, *syn* β -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 Diels-Alder reaction. At 100 °C for 1.5 days, the desired adduct **26** and its 4*Z*-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**.

Scheme 3.5

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.

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.¹⁰⁶ 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**

¹⁰⁶ Magauer, T.; Martin, H. J.; Mulzer, J. *Chem. Eur. J.* **2010**, *16*, 507–519. (b) Smith, A. B., III.; Bosanac, T.; Basu, K. *J. Am. Chem. Soc.* **2009**, *131*, 2348–2358. (c) Keck, G. E.; Giles, R. L.; Cee, V. J.; Wager, C. A.; Yu, T.; Kraft, M. B. *J. Org. Chem.* **2008**, *73*, 9675–9691. (d) Nicolaou, K. C.; Sun, Y. P.; Guduru, R.; Banerji, B.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2008**, *130*, 3633–3644.

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**

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 α,β-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 β-hydroxy phosphonate **38**, followed by DMP oxidation resulted the

¹⁰⁷ Storcken, R. P. M.; Panella, L.; van Delft, F. L.; Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2007**, *349*, 161–164.

¹⁰⁸ No reaction was observed when **35** was treated with Wittig reagent $\text{Ph}_3\text{P=CHCO}_2\text{Me}$.

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**¹⁰⁹ was easily accessible from acetol **39**. The $\text{TiCl}_4/n\text{-Bu}_3\text{N}$ mediated direct cross Aldol addition¹¹⁰ 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**

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).

¹⁰⁹ Kozikowski, A. P.; Okita, M.; Kabayashi, M.; Floss, H. G. *J. Org. Chem.* **1988**, 53, 863–869.

¹¹⁰ Yoshida, Y.; Matsumoto, N.; Hamasaki, R.; Tanabe, Y. *Tetrahedron Lett.* **1999**, 40, 4227–4230.

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 $n\text{-BuLi}$ -THF, LiCl -DIEPA- CH_3CN ,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).

¹¹¹ Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett* **1993**, 774–776.

¹¹² Smith, A. B., III.; Dorsey, B. D.; Visnick, M.; Matsuya, M.; Malamas, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 3110–3112.

¹¹³ Blanchette, M. A.; Choy, W.; Davis, J. T.; Essinfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

Scheme 3.11

Upon the failure of all attempts to construct **30** using **31**, we suspected that the α,β -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 β -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).

Scheme 3.12 Model study

The deleterious reactivity was attributed to α,β -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 oxidation¹¹⁴ followed by a Wittig reaction to furnish α,β -unsaturated ester **48** in 48% yield.

Scheme 3.13

As a model study, by means of a symmetric Michael addition of Grignard reagent to α,β -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

¹¹⁴ Mancuso, A. J.; Huang, S. L.; Swern, D.; *J. Org. Chem.* **1978**, *43*, 2480–2482.

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). Resilylation of the secondary alcohol **54** with TBSOTf afforded the ketone **33** in 71% yield.

¹¹⁵ Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, 37, 8585–8588.

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 -carboalkoxyl 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.¹¹⁶

¹¹⁶ For a review of Prins macrocyclization strategy, see: Crane, E. A.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 8316–8326. For recent representative applications in the synthesis of natural products, see: (a) Wender, P. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 9228–9231. (b) Tenenbaum, J. M.; Morris, W. J.; Custar, D. W.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 5892–5895. (c) Woo, S. K.; Lee, E. *J. Am. Chem. Soc.* **2010**, *132*, 4564–4565. (d) Yadav, J. S.; Kumar, G. G. K. S. N. *Tetrahedron* **2010**, *66*, 480–487. (e) Gesinski, M. R.; Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2009**, *11*, 5342–5345. (f) Custar, D. W.; Zabawa, T. P.; Hines, J.; Crews, C. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 12406–12414. (g) Vintonyak, V. V.; Kunze, B.; Sasse, F.; Maier, M. E. *Chem. Eur. J.* **2008**, *14*, 11132–11140. (h) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177–13181. (i) Cheung, L. L.; Marumoto,

Our retrosynthetic analysis of diene unit **3** was outline 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* dihydropyran **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

S.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 3101–3104. (j) Wender, P. A.; Dechristopher, B. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 6658–6659. (k) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 3242–3244. (l) Seden, P. T.; Charmant, P. H. J.; Wills, C. L. *Org. Lett.* **2008**, *10*, 1637–1640.

¹¹⁷ McMurry reported that intramolecular coupling reactions of an open-chain oxo aldehydes preceded on treatment with as solution of $\text{TiCl}_3/\text{Zn-Cu}$ couple under inert atmosphere in DME to give large-ring cycloalkenes at reflux temperature (see rf.: McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655–2656.) and large-ring cyclic 1,2-diols at low temperature (see rf.: McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169–1172.).

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.

¹¹⁸ Williams, D. R.; Heidebrecht, R. W. *J. Am. Chem. Soc.* **2003**, *125*, 1843–1850.

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 aldehyde¹¹⁹ proceeded to produce the 2,6-*trans* dihydropyran **63** with high diastereoselectivity (*trans/cis* = 96/4), although in moderate yield (45%). Reduction using LiBH₄ 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 (O₃, -78 °C), Johnso-Lemieux oxidation (OsO₄, NaIO₄, rt),¹²⁰ Upjohn dihydroxylation/diol cleavage (i. NMO, OsO₄, >2 equiv H₂O; ii. NaIO₄ or Pb(OAc)₄)¹²¹ and other improved methods.¹²² After meeting with the failure for ozonolysis of the alkene **64**, we

¹¹⁹ This study was initially attempted using a variety of highly functionalized α -oxoaldehydes with α -allenic alcohol **60** promoted by Lewis acids (InX₃, TiX₄, BX₃), such as , however, no corresponding DHP were formed. Employment of the acetal also gave the negative result.

¹²⁰ Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.

¹²¹ Vanrheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973–1976.

¹²² (a) Miyamoto, K.; Sei, Y.; Yamaguchi, K.; Ochiai, M. *J. Am. Chem. Soc.* **2009**, *131*, 1382–1383. (b) Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.* **2006**, *8*, 693–696. (c) Ho, C. M.; Yu, W. Y.; Che, C. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 3303–3307. (d) Yu, W.;

employed Nicolaou's conditions¹²³ to successfully provide the desired ketone **65** in 93% yield with the intraannular double bond C27-C28 unaffected.

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 CuI-catalyzed coupling reaction with Grignard reagent **67** to install a methylallyl moiety,¹²⁴ provided **68** in 59% yield over 2 steps. Alkene

Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219. (e) Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824–3825.

¹²³ Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552–1555.

¹²⁴ Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1989**, *30*, 1281–1284.

68 was subjected to the Nicolaou's condition, providing **58** in 93% yield.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**.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).

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 known that benzylic carbon atoms could be oxidized by a variety of oxidants, like CrO_3 , CAN, DDQ, O_2 , 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.

For the examples of oxidation of benzylic carbon atoms, see: (a) Gatta, F.; Settimj. G. *J. Heterocyclic Chem.* **1983**, 20, 1267–1270. (b) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 23, 885–888. (c) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 23, 889–892. (d) Isobe, K.; Takeda, N.; Mohri, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1989**, 37, 3390–3392. (e) Xu, Y. C.; Lebeau, E.; Gillard, J. W.; Attardo, G. *Tetrahedron Lett.* **1993**, 34, 3841–3844. (f) Nising, C. F.; Ohnemüller, U. K.; Friedrich, A.; Lesch, B.; Steiner, J.; Schnöckel, H.; Nieger, M.; Bräse, S. *Chem. Eur. J.* **2006**, 12, 3647–3654.

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_2Cl_2 , toluene, PhCF_3) and no trace of product **57** was detected.

Scheme 3.16

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% over 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 CBr_4 and PPh_3 .

Scheme 3.17

3.6.2 Allylation reaction

With the assembly fragment α,β -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 α -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 H₂O performed,¹³⁰ the allylation of carbonyl compounds with α -substituted allylic halides occurred specifically at the γ -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

¹²⁷ (a) Isaac, M. B.; Chan, T. H. *Tetrahedron Lett.* **1995**, *36*, 8957–8960. (b) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228–3229. (c) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927–3930. (d) Loh, T. P. Yin, Z.; Song, H. Y.; Tan, K. L. *Tetrahedron Lett.* **2003**, *44*, 911–914.

¹²⁸ Ito, A.; Kishida, M.; Kurusu, Y.; Masuyama, Y. *J. Org. Chem.* **2000**, *65*, 494–498.

¹²⁹ (a) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955–8956. (b) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *116*, 6130–6141. (c) Guo, B. S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710–4711.

¹³⁰ (a) Tan, K. T.; Chng, S. S.; Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 2958–2963. (b) Loh, T. P.; Tan, K. T.; Yang, J. Y.; Xiang, C. L. *Tetrahedron Lett.* **2001**, *42*, 8701–8703. (c) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Tetrahedron Lett.* **2001**, *42*, 8705–8708.

¹³¹ For application of indium-mediated allylation in natural products syntheses, see, (a) Lee, K. C.; Loh, T. P. *Chem. Commun.* **2006**, 4209–4211. (b) Huang, J. M.; Xu, K. C.; Loh, T. P. *Synthesis* **2003**, 755–764. (c) Loh, T. P.; Song, H. Y. *Synlett* **2002**, 2119–2121. (d) Coleman, R. S.; Gurralla, S. R.; Mitra, S.; Rao, A. *J. Org. Chem.* **2005**, *70*, 8932–8941. (e) Hansen, F. G.; Bundgaard, E.; Madsen, R. *J. Org. Chem.* **2005**, *70*, 10139–10142. (f) Skaanderup, P. R.; Madsen, R. *J. Org. Chem.* **2003**, *68*, 2115–2112. (g) Liu, Y.; Wang, J.; Li, H.; Wu, J.; Feng, G.; Dai, W. M. *Synlett* **2010**, 2184–2188.

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,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

entries	R	conditions	yield (%)
1		THF/H ₂ O, rt	56 decomposed
2	TIPS	THF/H ₂ O, 70 °C	SM recovered
3	TIPS	THF/H ₂ O, La(OTf) ₃ , rt	SM recovered
4	TBS	THF/H ₂ O, rt	SM recovered
5	TBS	THF/H ₂ O, 70 °C	56 decomposed
6	TBS	DMF, rt	SM recovered
7	TBS	THF/H ₂ O, La(OTf) ₃ , rt	77 (58/42)

¹³² (a) Ho, S. C. D.; Sim, K. Y.; Loh, T. P. *Synlett* **1996**, 263–264.; (b) Loh, T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett.* **1998**, 39, 1453–1456.

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 olefination 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

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

63 in high diastereoselectivity. CuI promoted coupling reaction of the triflate with Grignard reagent **67** 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.

Scheme 3.19

3.8 Experimental Section

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

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 allyl 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%

R_f: 0.27 (Hexane/Ethyl acetate = 8/1)

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

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)

R_f: 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.

HRMS (ESI): *m/z* calculated for C₁₀H₁₇O₂ [*M* + H]⁺: 169.1229, found: 169.1226.

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

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

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): δ 167.2, 159.4, 137.2, 115.5, 115.3, 50.8, 40.1, 31.5, 18.8.

(E)-3-Methylhepta-2,6-dien-1-ol

To a solution of the ester **36a** (2.52 g, 0.015 mol, 1 equiv) in CH_2Cl_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_2Cl_2 (100 mL $\times$ 3). The combined organic layers were washed with sat aq NaCl and dried over Na_2SO_4 . Concentration *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)

^1H NMR (400 MHz, CDCl_3): δ 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): δ 139.0, 138.3, 123.7, 114.6, 59.2, 38.8, 31.9, 16.2.

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

FTIR (KBr): ν 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_2Cl_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_2Cl_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)

^1H 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 $\text{C}_8\text{H}_{13}\text{O}$ $[\text{M} + \text{H}]^+$: 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 $n\text{-BuLi}$ (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 NH_4Cl (30 mL). The aqueous phase was extracted with EtOAc (50 mL $\times$ 3) and the combined organic phase was washed with sat aq NaCl, dried over Na_2SO_4 . 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, CDCl_3): 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).

^{13}C NMR (100 MHz, CDCl_3): 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).

HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_{26}\text{O}_4\text{P}$ $[\text{M} + \text{H}]^+$: 277.1569, found: 277.1571.

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 CH_2Cl_2 (30 mL) was added NaHCO_3 (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 NaHCO_3

(20 mL). The aqueous layer was extracted with EtOAc (30 mL $\times$ 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).

Yield (%): 49%

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

¹H 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).

¹³C 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).

HRMS (ESI): m/z calculated for C₁₃H₂₄O₄P [M + H]⁺: 275.1412, found: 275.1406.

FTIR (KBr): ν 3078, 2983, 2931, 1724, 1683, 1615, 1252, 1027, 970 cm⁻¹

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

Yield (%): 15%

R_f: 0.25 (Ethyl acetate/Hexane = 2/1)

^1H NMR (400 MHz, CDCl_3): δ 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): δ 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 $\text{C}_{13}\text{H}_{24}\text{O}_4\text{P}$ $[\text{M} + \text{H}]^+$: 275.1412, found: 275.1407.

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

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

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_2Cl_2 (40 mL). The reaction mixture was stirred at rt for 6 h and quenched with H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (30 mL $\times$ 3) and the organic layer was dried over Na_2SO_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)

^1H NMR (400 MHz, CDCl_3): δ 4.13 (s, 2H), 2.15 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 209.2, 69.6, 26.0, 25.8 $\times$ 3, 18.3, -5.5 $\times$ 2.

HRMS (ESI): m/z calculated for $C_9H_{21}O_2Si$ $[M + H]^+$: 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)

$TiCl_4$ (1.0 M in CH_2Cl_2 , 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 CH_2Cl_2 (30 mL) at $-78\text{ }^\circ C$ under a N_2 atmosphere. $TMSCl$ (0.10 mL, 0.75 mmol, 0.05 equiv) and $n\text{-Bu}_3N$ (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 $-78\text{ }^\circ C$ for 2 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with Et_2O (30 mL $\times$ 3). The combined organic layer was washed with sat aq $NaCl$, dried over Na_2SO_4 and concentrated. The obtained residue was purified by flash chromatography to give **41** (1.54 g).

Yield (%): 42%

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

1H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{25}O_3Si$ $[M + H]^+$: 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_2Cl_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)

1H 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 .

HRMS (ESI): m/z calculated for $C_{14}H_{27}O_5Si$ $[M + H]^+$: 303.1628, found: 303.1624.

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

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

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_2O (20 mL). The mixture was extracted with Et_2O (30 mL $\times$ 3) and the organic layer was dried over Na_2SO_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)

1H NMR (400 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 207.5, 166.9, 149.9, 120.0, 70.0, 67.8, 51.6, 46.0, 25.8 $\times$ 6, 18.3, 18.1, -4.6, -5.2, -5.5, -5.5.

HRMS (ESI): m/z calculated for $C_{20}H_{40}O_5Si_2Na$ $[M + Na]^+$: 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-dioxa-3,10-disiladodecan-6-one

(43)

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 CH_2Cl_2 (5 mL). The reaction mixture was stirred at rt for 24 h and quenched with H_2O (10 mL). The mixture was extracted with Et_2O (10 mL $\times$ 3) and the organic layer was dried over Na_2SO_4 . Concentration *in vacuo* and purification by flash chromatography provided **43** (64.5 mg) as a colorless oil.

Yield (%): 90%

R_f : 0.48 (Hexane/Ethyl acetate: 8/1)

^1H NMR (400 MHz, CDCl_3): 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, CDCl_3): δ 207.93, 140.50, 114.38, 70.26, 70.10, 46.88, 25.80 $\times$ 6, 18.34, 18.11, -4.45, -5.07, -5.42, -5.46.

HRMS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{38}\text{O}_3\text{Si}_2\text{Na}$ $[\text{M} + \text{Na}]^+$: 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_2Cl_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 *in vacuo*. The residual crude product was purified by flash chromatography to afford the desired α,β -unsaturated ester **42** (18.5 mg) in 37% yield and 60% **43** (25.5 mg) recovered.

(E)-Diethyl 2-(tert-butyldimethylsilyloxy)-4-methylocta-3,7-dienylphosphonate (44)

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_2Cl_2 (5 mL). The reaction mixture was stirred at rt for 12 h and quenched with H_2O (10 mL). The mixture was extracted with Et_2O (10 mL $\times$ 3) and the organic layer was dried over Na_2SO_4 . Concentration *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)

¹H NMR (400 MHz, CDCl₃): δ 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).

¹³C NMR (100 MHz, CDCl₃): δ 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 C₁₉H₃₉O₄PSiNa [M + Na]⁺: 413.2253, found: 413.2257.

FTIR (KBr): ν 2957, 2930, 2857, 1721, 1641, 1251, 1031, 836, 776 cm⁻¹

(2*E*,5*E*)-1-(*tert*-Butyldimethylsilyloxy)-2,6-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 °C. β-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 °C for 8 h and quenched with sat aq NH₄Cl (5 mL). The layers were separated and the aqueous phase was extracted with Et₂O (10 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** (20.4 g).

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

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

^1H NMR (400 MHz, CDCl_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_3): δ 192.0, 157.1, 155.0, 137.5, 126.1, 122.8, 115.2, 67.2, 40.5, 31.7, 25.9 $\times$ 3, 19.2, 15.8, -5.4 $\times$ 2.

HRMS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{32}\text{O}_2\text{SiNa}$ $[\text{M} + \text{Na}]^+$: 331.2069, found: 331.2075.

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

2-(*tert*-Butyldimethylsilyloxy)ethanol (**47**)

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_3N (46 mL, 0.33 mol, 5.5 equiv) in CH_2Cl_2 (320 mL) under a N_2 atmosphere at 0 $^\circ\text{C}$. The resulting mixture was stirred at rt for 12 h and quenched with sat aq NaHCO_3 (100 mL). The organic layer was washed with sat aq NaCl , dried over MgSO_4 and concentrated under reduced pressure. Purification by flash chromatography afforded the silylation product **47** (9.10 g) as a colorless oil.

Yield (%): 86%

R_f: 0.33 (Hexane/Ethyl acetate: 4/1)

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100 MHz, CDCl₃): δ 64.1, 63.7, 25.9 × 3, 18.3, -5.4 × 2.

HRMS (ESI): *m/z* calculated for C₈H₂₀O₂SiNa [M + Na]⁺: 199.1130, found: 199.1137.

FTIR (KBr): ν 3440, 2956, 2931, 2858, 1472, 1464, 1257, 1116, 1060, 835, 776 cm⁻¹

(*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 CH₂Cl₂ (400 mL) cooled to -78 °C was added dropwise a solution of DMSO (4.61 mL, 0.065 mol, 1.3 equiv) in CH₂Cl₂ (10 mL). After 15 min, a solution of alcohol **47** (8.82 g, 0.05 mol, 1 equiv) in CH₂Cl₂ (20 mL) was added. The reaction solution was stirred at -78 °C for 45 min. Et₃N (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 NH₄Cl (150 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (150 mL × 3). The combined organic extracts were washed with sat aq NaCl and dried over Na₂SO₄, filtered and

concentrated *in vacuo*. The residue was purified by flash chromatography to afford the desired *E*-product (9.03 g).

Yield (%): 78%

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

¹H NMR (400 MHz, CDCl₃): δ 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).

¹³C NMR (100 MHz, CDCl₃): δ 167.1, 147.7, 119.2, 62.1, 51.5, 25.8 × 3, 18.3, -5.5 × 2.

HRMS (ESI): *m/z* calculated for C₁₁H₂₂O₃SiNa [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 Et₂O (300 mL) was added dropwise isopropylmagnesium chloride (2.0 M in Et₂O, 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 NH₄Cl (80 mL). The aqueous layer was extracted with Et₂O (50 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 **49** (8.20 g) as a clear oil.

Yield (%): 77%

^1H NMR (400 MHz, CDCl_3): δ 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): δ 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**)

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_2O (100 mL $\times$ 3). The combined organic layers were washed with sat aq NaCl and dried over Na_2SO_4 . Concentration *in vacuo* afforded the crude aldehyde without further purification.

To a solution of the previous residue in Et_2O (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_4Cl (100 mL) prior to warm to rt. The layer was separated and the aqueous layer was extracted with Et_2O (100 mL $\times$ 3). The combined organic layers were washed with sat aq NaCl and dried

over Na₂SO₄. Concentration *in vacuo* and purification by flash chromatography afforded the alcohol **50** (5.54 g) as a colorless oil.

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

¹H NMR (diastereomers, 500 MHz, CDCl₃): δ 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).

¹³C NMR (diastereomers, 125 MHz, CDCl₃): δ 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 CH₂Cl₂ (80 mL) under a N₂ atmosphere at -78 °C. The resulting mixture was stirred at -78 °C for 1 h and diluted with CH₂Cl₂ (50 mL) and sat aq NaCl (40 mL). The organic layer was separated and dried over Na₂SO₄. Concentration *in vacuo* and purification by flash chromatography afforded **51** (2.44 g) as a colorless oil.

^{13}C NMR (diastereomers, 100 MHz, CDCl_3): δ 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, 18.1, 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-dioxo-3,13-disilapentadecan-6-one (54)

To a stirred solution of the alcohol **52** (0.3286 g, 1 mmol, 1 equiv) in CH_2Cl_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_2O (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_2O (1 mL). After 6 h, the mixture was quenched by MeOH (2 mL) and sat aq NH_4Cl (10 mL). The aqueous phase was extracted with Et_2O (10 mL $\times$ 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)

^1H NMR (diastereomers, 400 MHz, CDCl_3): δ 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): δ 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-(*tert*-Butyldimethylsilyloxy)-9,13,13-triisopropyl-2,2,3,3,14-pentamethyl-11-(prop-1-en-2-yl)-4,12-dioxo-3,13-disilapentadecan-6-one (33)

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_2Cl_2 (6 mL) under a N_2 atmosphere at $-40\text{ }^\circ\text{C}$. The resulting mixture was stirred at $-40\text{ }^\circ\text{C}$ for 2 h and diluted with CH_2Cl_2 (10 mL) and sat aq NaCl (10 mL). The organic layer was separated and dried over Na_2SO_4 . Concentration *in vacuo* and purification by flash chromatography afforded **33** (0.2680 g) as a colorless oil.

Yield (%): 71% (*dr* = 50:50)

^1H NMR (400 MHz, CDCl_3): δ 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): δ 209.1, 146.6, 112.9, 75.8, 70.0, 68.6, 45.4, 42.1, 32.9, 25.9 $\times 6$, 22.9, 19.7, 18.1 $\times 3$, 18.1 $\times 3$, 18.0 $\times 2$, 15.7, 12.4 $\times 3$, 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_2O (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_2SO_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_4Cl (v/v, 1:1) was added isopropyl glyoxalate **62** (116.1 mg, 1 mmol, 1 equiv) and then 1-bromo-2-butyne (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 $\times$ 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%

R_f: 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.

HRMS (ESI): *m/z* calculated for C₉H₁₄O₃Na [M + Na]⁺: 193.0841, found: 193.0850.

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-methylpenta-3,4-dienoate **60** (170.2 mg, 1 mmol, 1 equiv) dissolved in 2 mL anhydrous CH_2Cl_2 was added using syringe pump addition over a period of 1 h. The reaction was stirred at $-10\text{ }^\circ\text{C}$ for 72 h, then slowly warmed up to room temperature and kept for 1 h. The mixture was quenched with sat aq NaHCO_3 (10 mL). The aqueous layer was extracted with Et_2O (15 mL $\times$ 3). The combined organic layers were washed with sat aq NaCl , and dried over anhydrous MgSO_4 , filtered and concentrated *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%

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

^1H NMR (300 MHz, CDCl_3): 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, CDCl_3): 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.

HRMS (ESI): m/z calculated for $\text{C}_{14}\text{H}_{21}\text{O}_3^{79}\text{BrNa}$ $[\text{M} + \text{Na}]^+$: 339.0572, found: 339.0566.

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%

R_f: 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): ν 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 tetroxide (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 $\times$ 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%

R_f: 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.

HRMS (ESI): m/z calculated for C₉H₁₃O₃⁷⁹BrNa [M + Na]⁺: 270.9946, found: 270.9946.

FTIR (KBr): ν 3447, 2923, 2892, 1721, 1670, 1354, 1277, 1107 cm⁻¹

((2,6-*trans*)-4-Bromo-3-methyl-6-(2-methyl-1,3-dioxan-2-yl)-5,6-dihydro-2H-pyran-2-yl)methanol (66**)**

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%

R_f : 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.

HRMS (ESI): *m/z* calculated for C₁₂H₁₉O₄⁷⁹BrNa [M + Na]⁺: 329.0364, found: 329.0370.

FTIR (KBr): ν 3447, 2949, 2925, 2880, 1718, 1670, 1354, 1254, 1157, 1057, 733 cm⁻¹

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_2Cl_2 (8 mL) at $-78\text{ }^\circ\text{C}$ was added 2,6-lutidine (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 $-78\text{ }^\circ\text{C}$ 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_2Cl_2 (10 mL $\times$ 3), washed with sat aq NaCl, dried over Na_2SO_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 $-78\text{ }^\circ\text{C}$ was added copper(I) iodide (0.6666 g, 3.5 mmol, 5 equiv). Then the reaction mixture was warmed to $0\text{ }^\circ\text{C}$ and cooled back to $-40\text{ }^\circ\text{C}$. A solution of the triflate intermediate in THF (2 mL) 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_4Cl solution (10 mL) at $0\text{ }^\circ\text{C}$. The aqueous phase was extracted with EtOAc (20 mL $\times$ 3) and the combined organic extracts were dried over Na_2SO_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)

^1H NMR (400 MHz, CDCl_3): δ 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, $J = 10.4, 3.7$ 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.

HRMS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{25}\text{O}_3^{79}\text{BrNa}$ $[\text{M} + \text{Na}]^+$: 367.0885, found: 367.0882.

FTIR (KBr): ν 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_2O , 0.11 mL, 0.54 mmol, 1.5 equiv), and osmium tetroxide (4 wt. % in H_2O , 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 $\times$ 3), washed with sat aq CuSO_4 (20 mL), dried over Na_2SO_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%

^1H 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_4Cl (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (10 mL $\times$ 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)

¹H NMR (400 MHz, CDCl₃): δ 5.68 (s, 1H), 4.13 (t, *J* = 7.0 Hz, 2H), 4.06 (d, *J* = 10.4 Hz, 1H), 3.95 – 4.01 (m, 2H), 3.81 – 3.89 (m, 2H), 3.74 (dd, *J* = 10.4, 3.7 Hz, 1H), 2.84 – 2.91 (m, 1H), 2.39 – 2.47 (m, 2H), 2.18 – 2.24 (m, 1H), 2.16 (s, 3H), 1.97 (qd, *J* = 11.4, 5.6 Hz, 1H), 1.73 – 1.81 (m, 2H), 1.73 (s, 3H), 1.51 (s, 3H), 1.43 (dt, *J* = 13.3, 2.6 Hz, 1H), 1.26 (t, *J* = 7.0 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 g, 0.25 mmol, 1 equiv) in CH₂Cl₂ (2.5 mL) at -78 °C was slowly added DIBAL-H (1.0 M in toluene, 0.50 mL, 2 equiv). The resulting solution was stirred at -78 °C for 1 h and quenched with MeOH (0.5 mL). The mixture was warmed to ambient temperature and stirred for 2 h after adding sat aq potassium sodium tartrate (5 mL). The layer was separated and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with sat aq NaCl and dried over Na₂SO₄. Concentration *in vacuo* and purification by flash chromatography afforded the alcohol **59** (94.0 mg) as a colorless oil.

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

¹H NMR (400 MHz, CDCl₃): δ 5.44 (dt, *J* = 6.9, 1.1 Hz, 1H), 4.10 – 4.15 (m, 2H), 4.04 – 4.08 (m, 1H), 3.95 – 4.02 (m, 2H), 3.81 – 3.90 (m, 2H), 3.76 (dd, *J*

= 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 CH_2Cl_2 (2 mL) was added NaHCO_3 (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 NaHCO_3 (5 mL). The aqueous layer was extracted with Et_2O (10 mL $\times$ 3) and the combined organic phase was washed with sat aq NaCl , dried over Na_2SO_4 . 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.

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

^1H NMR (400 MHz, CDCl_3): 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 $\text{C}_{17}\text{H}_{25}\text{O}_4^{79}\text{BrNa}$ $[\text{M} + \text{Na}]^+$: 395.0834, found: 395.0843.

FTIR (KBr): ν 3055, 2987, 2959, 2874, 1668, 1265, 1156, 1110, 736 cm^{-1}

Yield: 18% (Z); m.p. 84 – 86 $^\circ\text{C}$.

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

^1H 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 $\text{C}_{17}\text{H}_{25}\text{O}_4^{79}\text{BrNa}$ $[\text{M} + \text{Na}]^+$: 395.0834, found: 395.0842.

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

3-(*tert*-Butyldimethylsilyloxy)propan-1-ol (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_2Cl_2 (200 mL) under a N_2 atmosphere at 0 $^\circ\text{C}$. The resulting mixture was stirred at rt for 20 h and the organic layer was washed with H_2O 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)

¹H NMR (500 MHz, CDCl₃): 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).

¹³C NMR (125 MHz, CDCl₃): 62.9, 62.4, 34.2, 25.9 × 3, 18.2, -5.5 × 2.

HRMS (ESI): *m/z* calculated for C₉H₂₂O₂SiNa [M + Na]⁺: 213.1287, found: 213.1278.

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 CH₂Cl₂ (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 CH₂Cl₂ (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 NH₄Cl (100 mL). The organic layer was separated and the aqueous

layer was extracted with CH_2Cl_2 (100 mL $\times$ 3). The combined organic extracts were washed with sat aq NaCl and dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to afford the desired *E*-product **71** (6.52 g).

Yield: 84%

R_f : 0.31 (Hexane: Diethyl ether = 20:1)

^1H NMR (400 MHz, CDCl_3): δ 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): δ 168.5, 138.9, 129.0, 61.7, 51.7, 32.4, 25.9 $\times$ 3, 18.3, 12.6, -5.3 $\times$ 2.

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

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

(*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_2Cl_2 (200 mL) at $-78\text{ }^\circ\text{C}$ 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 $-78\text{ }^\circ\text{C}$ 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 $\times$ 3). The combined organic layers were washed with sat aq NaCl and

dried over Na_2SO_4 . Concentration *in vacuo* and purification by flash chromatography afforded the alcohol **72** (4.82 g) as a colorless oil.

Yield: 87%

R_f : 0.33 (Hexane: Ethyl acetate = 4:1)

^1H NMR (400 MHz, CDCl_3): δ 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).

^{13}C NMR (100 MHz, CDCl_3): δ 136.6, 122.1, 68.8, 62.8, 31.5, 26.0×3 , 18.4, 13.8, -5.4×2 .

HRMS (ESI): m/z calculated for $\text{C}_{12}\text{H}_{26}\text{O}_2\text{SiNa}$ $[\text{M} + \text{Na}]^+$: 253.1600, found: 253.1609.

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

(E)-(5-Bromo-4-methylpent-3-enyloxy)(tert-butyl)dimethylsilane (56)

To a stirred solution of the alcohol **72** (3.45 g, 0.015 mol, 1 equiv) and Ph_3P (4.72 g, 0.018 mol, 1.2 equiv) in CH_3CN at 0 $^\circ\text{C}$ was added CBr_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 *in vacuo* to afford the desired product **56** as a colorless oil (3.01 g).

Yield: 68%

R_f : 0.35 (Hexane: diethyl ether = 8:1)

^1H 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 $\text{C}_{12}\text{H}_{26}\text{OSi}^{79}\text{Br}$ $[\text{M} + \text{H}]^+$: 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

^1H 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

R_f : 0.35 (Hexane: diethyl ether = 8:1)

^1H 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 $\times$ 6, 14.8, 12.0 $\times$ 3.

HRMS (ESI): m/z calculated for $\text{C}_{15}\text{H}_{32}\text{OSi}^{79}\text{Br}$ $[\text{M} + \text{H}]^+$: 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)

To a stirred solution of allyl bromide **56** (22.0 mg, 0.075 mmol, 1.5 equiv) in $\text{THF}/\text{H}_2\text{O}$ (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, $\text{La}(\text{OTf})_3$ (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_2O (5 mL) was added to dilute the reaction mixture followed by sat aq NH_4Cl (5 mL) to quench the reaction. The mixture was extracted with Et_2O (10 mL $\times$ 3). The combined organic layers were washed with sat aq NaCl and dried over MgSO_4 .

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

Yield: 77%

^1H NMR (400 MHz, CDCl_3): δ 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): δ 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

Empirical formula	C ₁₇ H ₂₅ 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 = 10.5477(9) Å α = 90 ° b = 9.2445(8) Å β = 93.772(4) ° c = 17.7246(14) Å γ = 90 °
Volume	1724.6(2) Å ³
Z	4
Density (calculated)	1.438 Mg/m ³
Absorption coefficient	2.399 mm ⁻¹
F(000)	776
Crystal size	0.40 x 0.30 x 0.30 mm ³
Theta range for data collection	2.19 to 26.58 °
Index ranges	-13 ≤ h ≤ 12, -11 ≤ k ≤ 11, -
	22 ≤ l ≤ 22
Reflections collected	21239
Independent reflections	3553 [R(int) = 0.0683]
Completeness to theta = 26.58 °	98.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.5331 and 0.4471
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3553 / 0 / 202
Goodness-of-fit on F ²	1.049
Final R indices [I > 2σ(I)]	R1 = 0.0521, wR2 = 0.1336
R indices (all data)	R1 = 0.0764, wR2 = 0.1517
Largest diff. peak and hole	1.464 and -1.434 e.Å ⁻³

Single crystal X-ray diffraction analysis of **Z-57**

Empirical formula	C ₁₇ H ₂₅ 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) Å α = 90 ° b = 9.0056(6) Å β = 95.934(2) ° c = 17.8232(12) Å γ = 90 °
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 > 2σ(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

APPENDIX

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,¹³³ indium(III) complexes have evoked considerable attention for their high chemoselectivity and reactivity to catalyze carbon-carbon bond-forming reactions, including aldol reactions,¹³⁴ Diels-Alder reaction,¹³⁵ Prins cyclization,¹³⁶ ene reactions,¹³⁷ Friedel-Crafts reactions,¹³⁸ 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.¹³⁹ In particular, it was found that indium(III) species had remarkable property of activating carbonyl compounds and terminal alkynes (Scheme A.1).¹⁴⁰ 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

¹³³ (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149–11176. (b) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739–2749. (c) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Curr. Org. Chem.* **2003**, *7*, 1661–1689

¹³⁴ (a) Loh, T. P.; Huang, J. M.; Goh, S. H.; Vittal, J. J. *Org. Lett.* **2000**, *2*, 1291–1294; (b) Zhao, J. F.; Tan, B. H.; Loh, T. P. *Chem. Sci.* **2011**, *2*, 349–352.

¹³⁵ (a) Ali, T.; Chauhan, K. K.; Frost, C. G. *Tetrahedron Lett.* **1999**, *40*, 5621–5624. (b) Prajapati, D.; Laskar, D. D.; Sandhu, J. S. *Tetrahedron Lett.* **2000**, *41*, 8639–8643. (c) Yanai, H.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 7087–7093.

¹³⁶ Dobbs, A. P.; Guesne, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880–7883. (b) Cho, Y. S.; Kim, H. Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M. Y. *Org. Lett.* **2002**, *4*, 2025–2028.

¹³⁷ (a) Loh, T. P.; Yang, J. Y.; Feng, L. C.; Zhou, Y. *Tetrahedron Lett.* **2002**, *43*, 7193–7196. (b) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 6244–6246.

¹³⁸ (a) Chapman, C. J.; Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Tetrahedron Lett.* **2001**, *42*, 773–775. (b) Ding, R.; Zhang, H. B.; Chen, Y. J.; Liu, L.; Wang, D.; Li, C. J. *Synlett* **2004**, 555–557.

¹³⁹ (a) Cintas, P. *Synlett* **1995**, 1087–1096. (b) Frost, C. G.; Hartley, J. P. *Mini Rev. Org. Chem.* **2004**, *1*, 1–7. (c) Ghosh, R.; Maiti, S. *J. Mol. Cat. A: Chem.* **2007**, *264*, 1–8. (d) Augé, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764.

¹⁴⁰ (a) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363–1366. (b) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573–1574. (c) Tsuchimoto, T.; Hatanaka, K.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2003**, 2454–2455. (c) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002–13003. (d) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527–1530. (e) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 1336–1340.

orbitals, and the effect was also operative with the other heavy metals that showed high π affinity [e.g., Hg(II) and Tl(III)].¹⁴¹

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.¹⁴² Other progresses were made on formation of 1,4-pentadiene¹⁴³ and α,β -unsaturated ketones¹⁴⁴ including Baylis–Hillman reactions¹⁴⁵ (Scheme A.2). Therefore, the discovery of novel carbon-carbon

¹⁴¹ Surendra, K.; Qiu, W.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724–9726.

¹⁴² For a review, see: (a) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983. For recently representative examples, see: (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688. (b) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807. (c) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J.; *J. Am. Chem. Soc.* **2006**, *128*, 8–9. (d) Gao, G.; Xie, R. G.; Pu, L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *15*, 5417–5420. (e) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760–13761. (f) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636–12637. (g) Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z. *Org. Lett.* **2004**, *6*, 4147–4149. (h) Ooi, T.; Miura, T.; Ohmatsu, K.; Saito, A.; Maruoka, K. *Org. Biomol. Chem.* **2004**, *2*, 3312–3319.

¹⁴³ (a) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2002**, *4*, 1491–1493. (b) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2002**, *4*, 3415–3417. (c) Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Gupta, M. K.; Biswas, S. K. *Tetrahedron Lett.* **2005**, *46*, 1161–1163.

¹⁴⁴ (a) Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **2002**, *43*, 1613–1615. (b) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **2005**, *70*, 57–62.

¹⁴⁵ (a) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 2358–2360. (b) Senapati, B. K.; Hwang, G. S.; Lee, S.; Ryu, D. H. *Angew. Chem. Int. Ed.* **2009**, *48*, 4398–4401. (c) Wei, H. X.; Kim, S. H.; Caputo, T. D.; Purkiss, S. W.; Li, G.

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.¹⁴⁶ In fact, the first use of combination of indium species and halotrimethylsilane was employed in activation of O-trimethylsilyl monothioacetals a decade ago.¹⁴⁷ 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 addition¹⁴⁸, Hosomi-Sakurai reaction,¹⁴⁹ reductive Friedel-Crafts alkylation,¹⁵⁰ deoxygenative halogenations,¹⁵¹

Tetrahedron **2000**, 56, 2397–2401. (d) Chen, D.; Timmons, C.; Liu, J. Y.; Headley, A.; Li, G. *Eur. J. Org. Chem.* **2004**, 3330–3335. (e) Shi, M.; Wang, C. *Tetrahedron* **2002**, 58, 9063–9074.

¹⁴⁶ (a) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, 7, 4491–4494. (b) Liu, F.; Loh, T. P. *Org. Lett.* **2007**, 9, 2063–2066.

¹⁴⁷ Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1990**, 2239–2242.

¹⁴⁸ (a) (b) Yang, L.; Xu, L. W.; Xia, C. G. *Tetrahedron Lett.* **2007**, 48, 1599–1603.

¹⁴⁹ (a) Lee, P. H.; Lee, K.; Sung, S.; Chang, S. *J. Org. Chem.* **2001**, 66, 8646–8649. (b) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578–1581. (c) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, 58, 8227–8235.

¹⁵⁰ Miyai, T.; Onishi, Y.; Baba, A. *Tetrahedron* **1999**, 55, 1017–1026.

deoxygenative allylation,¹⁵² reductive deoxygenation,¹⁵³ alkylation of alcohols,¹⁵⁴ etc (Figure A.1).

Figure A.1 A variety of reactions catalyzed by indium(III) complex and halotrimethylsilane

In addition, the use of organoindium compounds was employed in a variety of coupling reactions.¹⁵⁵ Baba discovered the InBr_3 -mediated addition of ketene silyl acetals to alkynes to provide alkenylindiums.¹⁵⁶ The alkyne was activated by InBr_3 , leading to the ketene silyl acetal attacked by the δ^+ on the internal carbon atom of alkyne. The carboindation adduct was formed in *anti* fashion.

¹⁵¹ Onishi, Y.; Ogawa, D.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13690–13691.

¹⁵² Yasuda, M.; Onishi, Y.; Ito, T.; Baba, A. *Tetrahedron Lett.* **2000**, *41*, 2425–2428.

¹⁵³ (a) Miyai, T.; Ueba, M.; Baba, A. *Synlett* **1999**, 182–184. (b) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741–7744.

¹⁵⁴ (a) Saito, T.; Yasuda, M.; Baba, A. *Synlett* **2005**, 1737–1739. (b) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516–8522.

¹⁵⁵ (a) Shen, Z. L.; Lai, Y. C.; Wong, C. H. A.; Goh, K. K. K.; Yang, Y. S.; Cheong, H. L.; Loh, T. P. *Org. Lett.* **2011**, *13*, 422–425. (b) Shen, Z. L.; Goh, K. K. K.; Yang, Y. S.; Lai, Y. C.; Wong, C. H. A.; Cheong, H. L.; Loh, T. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 511–514. (c) Shen, Z. L.; Goh, K. K. K.; Cheong, H. L.; Wong, C. H. A.; Lai, Y. C.; Yang, Y. S.; Loh, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 15852–15855. (d) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4555–4558.

¹⁵⁶ Nishimoto, Y.; Moritoh, R.; Yasuda, M.; Baba, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 4577–4580.

Scheme A.3

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 CH₂Cl₂ at 0 °C.¹⁵⁷ 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

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).¹⁵⁸ 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

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).¹⁵⁹ 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)

Entry	RCHO	X	Product	Yield (%) ^b	Z/E ^c
1	Ph-CH ₂ -CHO (2a)	Br	(3a)	52	76/24
2	CH ₃ -CH ₂ -CH ₂ -CHO (2b)	Br	(3b)	82	82/18
3	(CH ₃) ₃ C-CHO (2c)	Br	(3c)	78	83/17
4	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CHO (2d)	Br	(3d)	49	66/34
5	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CHO (2e)	Br	(3e)	66	62/38
6	Ph-CH ₂ -CHO (2f)	Br	(3f)	11	74/26
7 ^d	Ph-CH ₂ -CHO (2a)	Cl	(3g)	50	86/14

^a Reactions were performed with **1a** (0.4 mmol), aldehydes **2** (0.56 mmol), TMSBr (1.0 mmol), 4 Å MS (0.08 g) and In(OTf)₃ (0.04 mmol) in CH₂Cl₂ (5 mL) at 0 °C for 4 h. ^b Isolated yield based on **1a**. ^c Determined by ¹H NMR and NOESY. ^d 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.

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)

$ \begin{array}{c} \text{R}^2\text{—}\equiv\text{—} \\ (1 \text{ equiv}) \\ \mathbf{1b\sim d} \end{array} + \begin{array}{c} \text{R}^1\text{CHO} \\ (1.4 \text{ equiv}) \\ \mathbf{2a\sim b} \end{array} \xrightarrow[4 \text{ \AA MS, } 0^\circ\text{C, CH}_2\text{Cl}_2, 4 \text{ h}]{\text{In(OTf)}_3 (10 \text{ mol\%}) \\ \text{TMSX (2.5 equiv)}} \begin{array}{c} \text{X} \quad \text{X} \\ \diagdown \quad \diagup \\ \text{R}^2\text{—C=C—C—R}^1 \\ \mathbf{3h\sim p} \end{array} $						
Entry	Alkyne	Aldehyde	X	Product	Yield (%) ^b	<i>Z/E</i> ^c
1	(1b)	2a	Br	3h	47	69/31
2	1b	2b	Br	3i	62	88/12
3	(1c)	2a	Br	3j	78	44/56
4	1c	2b	Br	3k	85	59/41
5	(1d)	2a	Br	3l	51	22/78
6	1d	2b	Br	3m	45	25/75
7 ^d	1b	2a	Cl	3n	45	85/15
8 ^d	1c	2a	Cl	3o	50	86/14
9 ^d	1d	2a	Cl	3p	56	87/13

^a For the conditions, see Table A.1, footnote a. ^b Isolated yield based on **1**. ^c Determined by ¹H NMR and NOESY. ^d 20 mol% of In(OTf)₃ was added.

Treatment of 1-octyne with 3-phenylpropionaldehyde in the presence of InBr₃ 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 InBr₃ 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 $\text{In}(\text{OTf})_3$.

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 $\text{In}(\text{OTf})_3$ 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_2Cl_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 (^1H NMR) and carbon nuclear magnetic resonance (^{13}C 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 SiMe_4 (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 δ 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_2Cl_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_2Cl_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_2Cl_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_2Cl_2 (10 mL $\times$ 3). The combined organic layer was washed with sat aq NaCl , dried over anhydrous Na_2SO_4 , filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography through a short column to afford **1a** (80.7 mg) as a pale yellow oil.

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

Yield (%): 52% ($Z/E = 76/24$)

R_f: 0.60 (Hexane)

¹H 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).

¹³C 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 C₁₇H₂₅⁷⁹Br⁸¹Br [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)

¹H 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).

¹³C 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 C₁₃H₂₅⁷⁹Br⁸¹Br [M + H]⁺: 341.0303, found: 341.0322.

FTIR (KBr): ν 2957, 2930, 2859, 1646, 1466, 1173, 1058, 877, 726, 665 cm⁻¹

(Z)-3,5-Dibromo-2,2-dimethylundec-4-ene

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

*R*_f: 0.65 (Hexane)

¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100 MHz, CDCl₃): 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 C₁₃H₂₅⁷⁹Br⁸¹Br [*M* + *H*]⁺: 341.0303, found: 341.0297.

FTIR (KBr): ν 2959, 2930, 2859, 1643, 1464, 1368, 1153, 900, 846, 693 cm⁻¹

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

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

*R*_f: 0.55 (Hexane)

¹H NMR (400 MHz, CDCl₃): 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).

^{13}C NMR (100 MHz, CDCl_3): δ 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 $\text{C}_{13}\text{H}_{25}^{79}\text{Br}^{81}\text{Br}$ $[\text{M} + \text{H}]^+$: 341.0303, found: 341.0310.

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

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

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

R_f : 0.55 (Hexane)

^1H NMR (400 MHz, CDCl_3): δ 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): δ 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 $\text{C}_{17}\text{H}_{32}^{79}\text{Br}^{81}\text{BrNa}$ $[\text{M} + \text{Na}]^+$: 419.0748, found: 419.0739.

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

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

Yield (%): 11% ($Z/E = 74/26$)

R_f: 0.43 (Hexane)

¹H NMR (400 MHz, CDCl₃): δ 7.16 – 7.32 (m, 5H), 5.90 (d, *J* = 9.8 Hz, 1H), 5.12 (dt, *J* = 9.8, 7.2 Hz, 1H), 3.17 – 3.32 (m, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.45 – 1.52 (m, 2H), 1.17 – 1.27 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 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 C₁₆H₂₃⁷⁹Br⁸¹Br [M + H]⁺: 375.0146, found: 375.0144.

FTIR (KBr): ν 3063, 3029, 2955, 2930, 2858, 1645, 1496, 1454, 1031, 842, 749, 699 cm⁻¹

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

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

R_f: 0.36 (Hexane)

¹H NMR (400 MHz, CDCl₃): δ 7.29 – 7.33 (m, 2H), 7.20 – 7.23 (m, 3H), 5.64 (d, *J* = 9.4 Hz, 1H), 4.85 (dt, *J* = 9.4, 7.0 Hz, 1H), 2.69 – 2.85 (m, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.05 – 2.24 (m, 2H), 1.53 – 1.58 (m, 2H), 1.25 – 1.35 (m, 6H), 0.90 (t, *J* = 6.7 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 140.7, 138.2, 128.5 × 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 C₁₇H₂₅³⁵Cl₂ [M + H]⁺: 299.1333, found: 299.1347.

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

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

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

R_f : 0.38 (Hexane)

^1H NMR (400 MHz, CDCl_3): δ 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): δ 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 $\text{C}_{15}\text{H}_{20}^{79}\text{Br}^{81}\text{BrNa}$ [$\text{M} + \text{Na}$] $^+$: 382.9809, found: 382.9808.

FTIR (KBr): ν 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)

^1H NMR (400 MHz, CDCl_3): 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).

^{13}C NMR (100 MHz, CDCl_3): δ 131.3, 130.2, 51.9, 48.0, 41.1, 30.0, 26.9, 22.2, 22.1, 21.5, 13.8.

HRMS (ESI): m/z calculated for $\text{C}_{11}\text{H}_{21}^{79}\text{Br}^{81}\text{Br}$ $[\text{M} + \text{H}]^+$: 312.9990, found: 312.9980.

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% ($Z/E = 44/56$)

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

^1H NMR (400 MHz, CDCl_3): 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).

^{13}C NMR (100 MHz, CDCl_3): 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.

HRMS (ESI): m/z calculated for $\text{C}_{19}\text{H}_{21}^{79}\text{Br}^{81}\text{Br}$ $[\text{M} + \text{H}]^+$: 408.9990, found: 408.9992.

FTIR (KBr): ν 3084, 3061, 3026, 2927, 2860, 1635, 1453, 1075, 749, 698 cm^{-1}

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

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

*R*_f: 0.33 (Hexane)

¹H NMR (400 MHz, CDCl₃): δ 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).

¹³C NMR (100 MHz, CDCl₃): δ 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 C₁₅H₂₀⁷⁹Br⁸¹BrNa [M + Na]⁺: 382.9809, found: 382.9831.

FTIR (KBr): ν 3027, 2957, 2930, 2869, 1645, 1496, 1454, 1368, 1180, 1030, 748, 699 cm⁻¹

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

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

*R*_f: 0.10 (Hexane)

¹H NMR (400 MHz, CDCl₃): δ 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).

¹³C NMR (100 MHz, CDCl₃): δ 140.0, 136.6, 134.1, 129.1, 128.8, 128.7 × 2, 128.5, 127.1, 126.5, 48.8, 42.0, 40.7, 33.6.

HRMS (ESI): m/z calculated for $C_{18}H_{19}^{79}Br^{81}Br$ $[M + H]^+$: 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-Dibromo-6-methylhept-2-enyl)benzene

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

R_f : 0.37 (Hexane)

1H 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 $C_{14}H_{19}^{79}Br^{81}Br$ $[M + H]^+$: 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-Dichloronon-4-enyl)benzene

Yield (%): 45% ($Z/E = 85/15$)

R_f: 0.32 (Hexane)

¹H NMR (400 MHz, CDCl₃): δ 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).

¹³C NMR (100 MHz, CDCl₃): δ 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 C₁₅H₂₁³⁵Cl₂ [M + H]⁺: 271.1020, found: 271.1031.

FTIR (KBr): ν 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)

¹H NMR (400 MHz, CDCl₃): δ 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).

¹³C NMR (100 MHz, CDCl₃): δ 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 C₁₉H₂₁³⁵Cl₂ [M + H]⁺: 319.1020, found: 319.1021.

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

(Z)-(2,4-Dichlorohex-2-ene-1,6-diyl)dibenzene

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

R_f : 0.42 (Hexane/diethyl ether = 20/1)

^1H NMR (400 MHz, CDCl_3): δ 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): δ 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 $\text{C}_{18}\text{H}_{19}^{35}\text{Cl}_2$ [$\text{M} + \text{H}$] $^+$: 305.0864, found: 305.0868.

FTIR (KBr): ν 3063, 3027, 2927, 2862, 1654, 1602, 1496, 1453, 1074, 1030, 750, 698 cm^{-1}

List of Publications

1. Hu Xu-Hong, Liu Feng, Loh Teck-Peng. Stereoelectronic versus Steric Tuning in the Prins Cyclization Reaction: Synthesis of 2,6-*trans* Pyranyl Motifs. *Organic Letters*, **2009**, *11*, 1741–1743.
2. Luo Hai-Qing, Hu Xu-Hong, Loh Teck-Peng. Highly Stereocontrolled Synthesis of Fluorinated 2,6-*trans* Dihydropyrans *via* Prins Cyclization. *Tetrahedron Letters*, **2010**, *51*, 1041–1043.

Conferences

1. Hu Xu-Hong, Loh Teck-Peng. Stereoelectronic vs. Steric Tuning in the Prins Cyclization Reaction: Synthesis of 2,6-*trans* Pyranyl Motifs. *6th Asian-European Symposium on Metal Mediated Efficient Reactions*, June 7–9, **2010**, Singapore.
2. Hu Xu-Hong, Loh Teck-Peng. Stereoelectronic vs. Steric Tuning in the Prins Cyclization Reaction: Synthesis of 2,6-*trans* Pyranyl Motifs. *241st ACS National Meeting, Anaheim, CA*, March 27–31, **2011**, United States.