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**NEW STRATEGY FOR DIENE SYNTHESIS:
APPLICATION IN TOTAL SYNTHESIS OF
PALMEROLIDE A**

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**SCHOOL OF PHYSICAL AND MATHEMATICAL
SCIENCES**

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**NEW STRATEGY FOR DIENE SYNTHESIS:
APPLICATION IN TOTAL SYNTHESIS OF
PALMEROLIDE A**

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LIST OF ABBREVIATIONS

δ	chemical shift
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
Ar	aryl
aq	aqueous
Bn	benzyl
Bz	benzoyl
calcd	calculated
CH_2Cl_2	dichloromethane
CDCl_3	deuterated chloroform
cm^{-1}	inverse centimeter
d	doublet
DIBAL-H	diisobutylaluminium hydride
dd	doublet of doublets
D-(-)-DIPT	D-(-)-diisopropyltartarate
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublet of triplets
1,2-DPPE	1,2-bis(diphenylphosphino)ethane
equiv.	equivalent(s)

ESI	electrospray ionization
Et	ethyl
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
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
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
NMP	<i>N</i> -methyl pyrrolidone
NOESY	nuclear overhauser enhancement spectroscopy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
Ph	phenyl
PivOH	pivalic acid
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> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> Bu	<i>tert</i> -butyl
THF	tetrahydrofuran
TIP	triisopropylsilyl

TLC	thin layer chromatography
TsCl	<i>p</i> -toluenesulfonyl chloride
UV	ultraviolet
vol	volume

SUMMARY

Palladium-catalyzed alkenylation offers one of the most efficient methods for the synthesis of functionalized butadienes. However, due to the need for pre-functionalization of reactants and undesirable formation of stoichiometric amount of waste in the reactions, these processes were rendered neither atom-economical nor environmentally benign. The emphasis of this thesis is focused on the design and development of a palladium-catalyzed cross-coupling reaction of unactivated alkenes with acrylates for the construction of 1,3-diene motifs and its application towards a total synthesis of the natural product, Palmerolide A.

In the first introduction chapter, a summary of established methodologies in the construction of 1,3-butadiene system is outlined, ranging from carbonyl olefination to recently emerging olefin metathesis. In particular, the strategy of transition metal-catalyzed alkenylation is thoroughly and intensively discussed. With the increasing demand for more atom- and step-economical methods, we have developed a direct and efficient palladium-catalyzed method for the cross-coupling of homoallylic and allylic alcohols with acrylates that produces dienic alcohols in moderate to high yields, and with good stereoselectivity. This atom-economical methodology offers a straightforward access to forge new $C(sp^2)-C(sp^2)$ bonds, which is detailed in Chapter 2.

The fragment **18**, could be readily accessible prepared *via* a boron-based allylation between **25** and **26**.

The aldehyde **25**, which contains the *E*-diene motif, could be readily accessed using our cross-coupling method between **21** and butyl acrylate **22**, followed by reduction of the ester to an alcohol. Conversion of the alcohol to a good leaving group, which is then reacted with a Grignard reagent or ester enolate to form the desired

aldehyde.

CHAPTER 1

Strategies for 1,3-Diene Synthesis

1.1 Introduction

1,3-Dienes are very important structural units in organic synthesis. They also serve as useful precursors for further transformations in Diels–Alder reaction¹ and polymerization². In addition, many natural products and pharmaceuticals contain diene building blocks such as Pateamine A,³ (–)-Dactylolide,⁴ (–)-Zampanolide,⁵ Palmerolide A,⁶ Chaxalactins A–C (1–3),⁷ Pyridinopyrone C,⁸ (+)-Curacin A,⁹ *etc.* Consequently, many research groups are focusing on establishing more efficient and convenient methods for preparation of this structural motif. Till now, a variety of methods have been established and some of them had been successfully applied in total synthesis of natural products. Depending on the type of bond cleaved and formed, these methods could be categorized into three general strategies: carbonyl olefination reactions, alkenylation through cross-coupling reactions catalyzed by transition metal and the third strategy is olefin metathesis. In this chapter, a summary of past efforts of chemists' contribution towards 1,3-diene synthesis is described.

¹Fringuelli, F.; Taticci, A. *Dienes in the Diels–Alder Reaction*; John Wiley and Sons: New York, **1990**.

²(a) Pragliola, S.; Cipriano, M.; Boccia, A. C.; Longo, P. *Macromol. Rapid Commun.* **2002**, 23, 356. (b) Kamahori, K.; Tada, S.; Ito, K.; Itsuno, S. *Macromolecules*. **1999**, 32, 541. (c) Friedmann, G.; Brosse, N. *Eur. Polym. J.* **1991**, 27, 747.

³Northcote, P. T.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron Lett.* **1991**, 32, 6411.

⁴Ding, F.; Jennings, M. P. *J. Org. Chem.* **2008**, 73, 5965.

⁵Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, 37, 5535.

⁶Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc.* **2006**, 128, 5630.

⁷Rateb, M. E.; Houssen, W. E.; Harrison, W. T. A.; Deng, H.; Okoro, C. K.; Asenjo, J. A.; Andrews, B. A.; Bull, A. T.; Goodfellow, M.; Ebel, R.; Jaspars, M. *J. Nat. Prod.* **2011**, 74, 1965.

⁸Fukuda, T.; Miller, E. D.; Clark, B. R.; Alnauman, A.; Murphy, C. D.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2011**, 74, 1773.

⁹Verdier-Pinard, P.; Lai, J.; Yoo, H. D.; Yu, J.; Marquez, B.; Nagle, D. G.; Nambu, M.; White, J. D.; Falck, J. R.; Gerwick, W. H.; Day, B. W.; Hamel, E. *Mol. Pharmacol.* **1998**, 53, 62.

Figure 1.1 Examples of natural products containing diene moiety

1.2 Recent Methods for Diene Synthesis

1.2.1 Carbonyl Olefination Reactions

Carbonyl olefination is a traditional method for the construction of C–C double bond. A preliminary report involving aldol and related carbonyl olefination reactions appeared in 1982.¹⁰ Several years later, more efficient strategies for the synthesis of 1,3-diene were developed. Examples include the phosphorus-based Wittig olefination,¹¹ Horner-Wadsworth-Emmons(HWE), Z-selective Still-Gennari modifications of HWE olefination,¹² sulfur-based Julia olefination,¹³ and silicon-based Peterson olefination.¹⁴ However, there is still a need to develop methodology for expanding substrate scope and controlling the stereoselectivity of the reactions. In 2010, Tian *et al.* reported a modification of the Wittig reaction of *N*-sulfonyl imines instead of aldehydes with semi-stabilized triphenylphosphoniumylides to form diene with greater than 99:1 stereoselectivity and in good yield (Scheme 1.1).¹⁵

Scheme 1.1

¹⁰(a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, 13, 1. (b) Mukaiyama, T. *Org. React.* **1982**, 28, 203.

¹¹Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 89, 863.

¹²Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405..

¹³(a) Paris, J. M. *Tetrahedron Lett.* **1973**, 4833. (b) Kim, G., Chu-Moyer, M. Y., Danishefsky, S. J., Schulte, G. K. *J. Am. Chem. Soc.* **1993**, 115, 30. (c) Smith, A. B., III, Brandt, B. M. *Org. Lett.* **2001**, 3, 1685. (d) Liu, P., Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, 123, 10772.

¹⁴(a) Peterson, D. J. *J. Org. Chem.* **1968**, 33, 780. (b) Van Staden, L. F., Gravestock, D., Ager, D. J. *Chem. Soc. Rev.* **2002**, 31, 195

¹⁵Dong, D. J.; Li, H. H.; Tian, S. K. *J. Am. Chem. Soc.* **2010**, 132, 5018

In the same year, Helquist developed a modified HWE reaction in one simple step (Scheme 1.2).¹⁶ This method provided an efficient and rapid access to 1,3-dienes.

Scheme 1.2

Also, He¹⁷ discovered a novel olefination of aldehydes with α -substituted allenates (Scheme 1.3) mediated by nucleophilic phosphines to prepare 1,2,3,4-tetrasubstituted 1,3-dienes in high chemo- and diastereoselectivity.

Scheme 1.3

1.2.2 Alkenylation

In the past decades, functionalized butadienes were mostly prepared *via* carbonyl olefination reactions, which have been reinforced by the investigations and

¹⁶Markiewicz, J. T.; Schauer, D. J.; Löffstedt, J.; Corden, S. J.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, 75, 2061

¹⁷Xu, S.; Zou, W.; Wu, G.; Song, H.; He, Z. *Org. Lett.* **2010**, 12, 3556.

development of transition metal-catalyzed cross-coupling reactions such as Negishi coupling,¹⁸ Stille cross-coupling¹⁹ and Heck alkenylation.²⁰ Recently, several interesting methods employing Pd- or Rh- catalyzed oxidative cross-coupling reactions to construct dienes have been developed. In 2005, Ma and coworkers established a highly regio- and stereoselective synthesis of 1,3-dienes. The reaction was catalyzed by Pd(PPh₃)₄ from easily available allenes and aryl halides (Scheme 1.4).²¹

In 2006, Skrydstrup disclosed a new variation of the Heck coupling reaction of unactivated vinyl tosylates with electron-deficient alkenes catalyzed by the combination of [PdCl₂(cod)]/ P(^tBu)₃HBF₄ and in the presence of Cy₂NMe (Scheme 1.5).²² In the case where R¹ is a large substituent such as *tert*-butyl or trimethylsilyl, isomerized coupling products were obtained in good to excellent yields (eq 2). This products were formed through an effective 1,2-migration of the alkenyl Pd(II) intermediate.

¹⁸(a) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, **2002**; Vol. 2, Part III, pp 213-1119. (b) Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233.

¹⁹Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508.

²⁰(a) Moritani, I.; Fujiwara, Y. *Synthesis* **1973**, 524. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (d) Fujiwara, Y.; Jia, C. *Pure Appl. Chem.* **2001**, *73*, 319. (e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (f) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (g) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (h) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (i) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (j) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395. (k) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170.

²¹Fu, C.; Ma, S. *Org. Lett.* **2005**, *7*, 1707.

²²Hansen, A. L.; Ebran, J. P.; Ahlquist, M.; Norrby, P. O.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3349.

Furthermore, under modified reaction conditions,²³ the use of Buchwald's dialkylbiarylphosphines, X-Phos, instead of P^tBu_3 not only promoted the reaction effectively, but is also suppressed the unwanted 1,2-migration. In the following year, Skrydstrup also found that an intermolecular ene-yne coupling of disubstituted acetylenes with electron-deficient alkenes²⁴ catalyzed by a Pd(II) hydride species, generated *in situ* from the phosphine ligand and Pd(II) source (Scheme 1.6). The 1,3-butadienes could be obtained with high yields and regioselectivities.

Shinokubo²⁵ developed an aryl rhodation/Heck-type addition to afford functionalized dienes by reacting aryl boronic acids with internal alkynes and acrylate

²³Ebran, J. P.; Hansen, A. L.; Gøsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931.

²⁴Lindhardt, A. T.; Mantel, M. L. H.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 2668.

²⁵Kurahashi, T.; Shinokubo, H.; Osuka, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 6336.

at ambient temperature in aqueous media (Scheme 1.7).

Molander and Yokoyama²⁶ reported a new efficient approach to trisubstituted 1,3-dienes *via* a one-pot sequential Suzuki-Miyaura cross-coupling reaction (Scheme 1.8). Treatment of 1,1-dibromoalkenes with alkenyltrifluoroborates in the presence of $\text{Pd}(\text{PPh}_3)_4$, followed by alkyltrifluoroborates provided the corresponding 1,3-dienes in excellent yield.

Jung²⁷ and co-workers developed a novel protocol for the reaction of alkenyl boron compounds with various alkenes *via* oxygen-promoted palladium-catalyzed cross-coupling to produce a variety of 1,3-dienes in good to excellent yields under mild reaction conditions (Scheme 1.9). Utilization of a catalytic bidentate nitrogen ligand facilitated the coupling reaction and prevented the precipitation of $\text{Pd}(0)$ *via* stabilization of the palladium(II) species to enhance reactivity of the palladium catalyst, resulting in high catalytic efficiency and selectivity. Different from Heck and Suzuki

²⁶Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, 71, 2493.

²⁷Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, 128, 16384.

coupling reactions, inclusive of their previous report,²⁸ a base was not required in Jung's reaction and the undesired homo-coupled product was also suppressed under this condition.

A highly efficient chelate-controlled intermolecular Heck reaction was reported by White²⁹ in 2008. They used various unactivated alkenes and aryltrifluoroborates or styrenylpinacolboronic esters, mediated by Pd(II)/sulfoxide catalyst, to produce 1,3-dienes with outstanding yields and excellent *E/Z* stereoselectivities.

Frantz³⁰ demonstrated a novel palladium-catalyzed elimination/isomerization reaction of substituted enoltriflates to provide the functionalized 1,3-butadienes in good yields (Scheme 1.11). On the basis of experimental results and mechanistic studies, a distinct catalytic pathway was proposed to account for the diene formation process: A cationic vinyl palladium(II) complex was formed through oxidative addition of the enoltriflate into Pd(0), followed by β -hydride elimination to provide

²⁸Yoon, C. H.; Yoo, K. S.; Yi, S. W.; Mishra, R. K.; Jung, K. W. *Org. Lett.* **2004**, 6, 4037.

²⁹Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, 130, 11270.

³⁰Crouch, I. T.; Dreier, T.; Frantz, D. E. *Angew. Chem. Int. Ed.* **2011**, 50, 6128.

the corresponding allenolate, which subsequently underwent hydropalladation and a second β -hydride elimination to form the conjugated diene.

Scheme 1.11

A novel oxidative cross-coupling reaction of vinyl carboxylates with acrylates was demonstrated by Ishii³¹ in 2004 (Scheme 1.12). The corresponding coupling products could be obtained in good yields by using catalytic $\text{Pd}(\text{OAc})_2$ combined with $\text{H}_4\text{PMo}_{11}\text{VO}_{40}/\text{O}_2$ as oxidants in acetic acid at 90 °C.

Scheme 1.12

Recently, our group³² disclosed a direct route to synthesize 1,3-dienes in moderate to good yield and stereoselectivities *via* palladium-catalyzed cross-coupling of α -methylstyrene with acrylates (Scheme 1.13). The reaction proceeded smoothly in the presence of 20 mol% $\text{Pd}(\text{OAc})_2$ and $\text{Cu}(\text{OAc})_2/\text{O}_2$ at 60 °C in a specific mixed solvent system consisting of DMSO/HOAc (1:1).

³¹Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, 6, 4623.

³²(a) Xu, Y. H.; Lu, J.; Loh, T. P. *J. Am. Soc. Chem.* **2009**, 131, 1372. (b) Xu, Y. H.; Wang, W. J.; Wen, Z. K.; Hartley, J. J.; Loh, T. P. *Tetrahedron Lett.* **2010**, 51, 3504.

Scheme 1.13

A further study³³ revealed that employment of enamide instead of α -methylstyrene with acrylate under similar conditions also afforded the corresponding coupling products with good yields and excellent stereoselectivities (Scheme 1.14). A mechanistic investigation showed that the treatment of enamide with $\text{Pd}(\text{OAc})_2$ in DMSO led to a six-membered cyclic vinylpalladium intermediate, which was isolated as a single crystal and characterized by X-ray analysis. Then the palladacycle underwent carbopalladation to construct the new C-C bond and subsequent β -hydride elimination to give the coupling product.

the palladacycle intermediate

Scheme 1.14

³³Xu, Y. H.; Chok, Y. K.; Loh, T. P. *Chem. Sci.* **2011**, 2, 1822.

Yu's group³⁴ demonstrated a complementary palladium-catalyzed cross-coupling reaction of α -oxoketenedithioacetals with acrylates and other terminal alkenes. A variety of 1,3-butadienes bearing multiple functional groups were successfully synthesized employing C–H bond activation.

Scheme 1.15

The Rh(III)-catalyzed cross-coupling of functionalized alkenes leading to the corresponding 1,3-butadienes was disclosed by Glorius³⁵ in 2011. This methodology could be applied to the formation of $\alpha,\beta,\gamma,\delta$ -unsaturated amino acids, which are valuable building blocks in the life sciences for further transformations.

Scheme 1.16

1.2.3 Olefin Metathesis

Olefin metathesis, its importance highlighted by the awarding of the 2005 Nobel

³⁴Yu, H.; Jin, W.; Sun, C.; Chen, J.; Du, W.; He, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2010**, 49, 5792.

³⁵Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem. Eur. J.* **2011**, 17, 7167.

Prize to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock “for the development of the metathesis method in organic synthesis,” has become one of the most powerful and versatile transformation for C–C double bond formation.³⁶ Based on the types of unsaturated hydrocarbons (alkene or alkyne) involved in the process, metathesis can be classified into three general categories: diene, diyne and enyne metathesis. Enyne metathesis has emerged as a powerful tool for 1,3-diene generation from reorganization of an alkene and an alkyne, although the regio- and stereoselectivity has limited the widespread application of this method.³⁷ In addition, there are several examples of ring closing metathesis for macrocyclic 1,3-diene construction.³⁸ However, to date, only a few reports have been documented for 1,3-diene synthesis using olefin cross-metathesis, owing to the low chemo- and diastereoselectivity.

In 2004, Grubbs³⁹ developed an efficient and mild approach for the synthesis of substituted 1,3-diene *via* olefin cross-metathesis (Scheme 1.17). Using a commercially available second-generation Grubbs catalyst the reactions proceeded smoothly to yield cross-metathesis product with high chemo- and diastereo-selectivity.

³⁶(a) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, **1997**. (b) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH, **2003**. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2037. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (e) Pariya, C.; Jayaprakash, K. N.; Sarkar, A. *Coord. Chem. Rev.* **1998**, *168*, 1. (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (g) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (h) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (i) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (j) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (k) Deshmukh, P. H.; Blechert, S. *Dalton Trans.* **2007**, 2479. (l) Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, 3327. (m) Calderon, N. *Acc. Chem. Res.* **1972**, *5*, 127.

³⁷(a) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509. (b) Diver, S. T. Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.

³⁸(a) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903. (b) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem., Int. Ed.* **2000**, *39*, 1664. (c) Wagner, J.; Cabrejas, L. M. M.; Grossmith, C. E.; Papageorgiou, C.; Senia, F.; Wagner, D.; France, J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 9255.

³⁹Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187.

Scheme 1.17

Later, Curran's group⁴⁰ demonstrated that cross-metathesis reactions of terminal and 1,2-disubstituted symmetrical alkenes with hexadienoates to afforded various (2*Z*,4*E*)-dienylesters with good yields and stereoselectivities. It is noteworthy that the less stable (*Z*)-1,2-disubstituted hexadienoates survived the cross metathesis without isomerization and the *Z*-geometry is retained in the product, while the newly formed C–C double bond is mainly or exclusively in the *E*-configuration. This methodology provided a rapid access to the C1–C9 fragment of (–)-dictyostatin and its analogues (Scheme 1.18)⁴¹.

⁴⁰Letts, G. M.; Curran, D. P. *Org. Lett.* **2007**, 9, 5.

⁴¹Fukui, Y.; Brućkner, A. M.; Shin, Y.; Balachandran, R.; Day, B. W.; Curran, D. P. *Org. Lett.* **2006**, 8, 301.

Scheme 1.18

1.3 Summary

Voluminous studies on the syntheses of functionalized 1,3-butadienes have been reported, thus providing satisfactory and efficient strategies for the total synthesis of natural products. However, the limited substrate scope and need for pre-functionalized substrates restricted application of these methodologies. Besides the methodologies introduced above, there are some other useful methods for preparation of 1,3-dienes, ranging from hydrogenation of 1,3-enynes,⁴² iterative hydroboration-protonolysis⁴³ of butadiynes, hydroboration of alkynes,⁴⁴ and Pd-catalyzed alkenyl-alkenyl coupling using other alternative metals such as Al, Zn, Zr, *etc.*⁴⁵

⁴²Jang, H. Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, 126, 4664. (b) Kong, J. R.; Cho, C. W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, 127, 11269. (c) Chen, M. Z.; Micalizio, G. C. *Org. Lett.* **2009**, 11, 4982.

⁴³Zweifel, G.; Polston, N. L. *J. Am. Chem. Soc.* **1970**, 92, 4068.

⁴⁴(a) Negishi, E.; Lew, G.; Yoshida, T. *J. Chem. Soc., Chem. Commun.* **1973**, 874. (b) Negishi, E.; Yoshida, T. *J. Chem. Soc., Chem. Commun.* **1973**, 606.

⁴⁵(a) Negishi, E. Palladium-Catalyzed Reactions Involving Reductive Elimination. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, **2002**; Vol. 2, Part III, pp 213-1119. (b) Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, 80, 233. (c) Miyaura, N.; Suzuki, A. *Chem.*

Among the aforementioned methods, the palladium-catalyzed C-H functionalization is the most highly atom- and step-economical strategy for diene synthesis. However, to our best knowledge, diene synthesis through Pd-catalyzed C-H functionalization is rare in view of the limited substrate scope and undesirable side reaction. Thus, there still remain demand for the development of more efficient and direct approach to construct the 1,3-diene motif.

CHAPTER 2

Synthesis of Functionalized Butadienes via Palladium m-Catalyzed Cross-Coupling

2.1 Introduction

Functionalized butadienes are ubiquitous structural motifs present in many natural products, and they are very useful building blocks in modern organic synthesis.⁴⁶ The construction of butadiene scaffolds is frequently accomplished *via* the Horner-Wadsworth-Emmons olefination reaction.⁴⁷ In recent years, with the development of transition-metal-catalyzed coupling reactions, many examples of butadiene synthesis that involved the use of Pd,⁴⁸ Rh⁴⁹ or Ru⁵⁰ complexes as catalyst have been reported. However, the need for pre-functionalizing the reactants and formation of undesirable stoichiometric amount of waste in the reactions have rendered these processes neither atom-economical nor environmentally benign.⁵¹ Consequently, the establishment of a catalytic protocol for the formation of the new C(*sp*²)-C(*sp*²) bond *via* direct C-H bond functionalization is necessary. Pioneering work on palladium-assisted stoichiometric and catalytic oxidative coupling of arenes

⁴⁶(a) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley-Interscience: New York, **1990**. (b) Luh, T. Y.; Wong, K.-T. *Synthesis* **1993**, 349. (c) Mehta, G.; Rao, H. S. P. In *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Eds.; John Wiley & Sons: New York, **1997**; Vol. 1, pp 359-480.

⁴⁷(a) Horner, L., Hoffmann, H., Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Horner, L., Hoffman, H., Wippel, H. G., Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (c) Wadsworth, W. S., Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

⁴⁸(a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384. (c) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (d) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270.

⁴⁹(a) Yotphan, S.; Bergman, R. G.; Ellman, J. E. *J. Am. Chem. Soc.* **2008**, *130*, 2452. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (c) Shibata, Y.; Otake, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2009**, *11*, 689.

⁵⁰(a) Mitsudo, T.; Zhang, S. W.; Nagao, M.; Watanabe, Y. *J. Chem. Soc. Chem. Commun.* **1991**, 598. (b) Yi, C. S.; Lee, D. W.; Chen, Y. *Organometallics* **1999**, *18*, 2043. (c) Kakiuchi, F.; Uetsuhara, T.; Tanaka, Y.; Chatani, N.; Murai, S. *J. Mol. Catal. A* **2002**, *182-183*, 511. (d) Nishimura, T.; Washitake, Y.; Uemura, S. *Adv. Synth. Catal.* **2007**, *349*, 2563.

⁵¹(a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (d) King, A. O.; Okukado, N.; Negishi, E. I. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (e) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (f) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866. (g) Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

with electron-deficient olefins was first reported by Fujiwara and co-workers.⁵² Building on those results, palladium-catalyzed direct C–H bond functionalization reactions are now employed in the synthesis of complex organic molecules.⁵³ To date, despite the efficiency of direct (hetero)aryl C–H bond functionalization reactions,⁵⁴ direct alkene-alkene coupling reactions *via* alkenyl C–H bond activation are rarely reported. That is primarily due to the inertness of the C–H bond in simple olefins, and the difficulties in promoting the desired cross-coupling over homo-coupling.⁵⁵ Till now, the limited success in such cross-coupling reactions are as follows: Ishii and co-workers reported the cross-coupling reaction of vinyl carboxylates with acrylates catalyzed by Pd(II) with vanadomolybdophosphoric acid.⁵⁶ Yu demonstrated the cross-coupling reactions of activated alkenes with acrylates to construct functionalized

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⁵⁶Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623

1,3-butadiene.⁵⁷ A rhodium-catalyzed oxidative C–H olefination of functionalized alkenes was also developed by Glorius and co-workers.⁵⁸

Figure 2.1

Although these systems provided very convenient and satisfactory strategies for the construction of dienes by olefination of alkenes through vinylic C–H functionalization, many of them suffer from limited substrate scope and the need for specific conditions. Most procedures require the use of alkenes containing activating or directing groups as substrates (Figure 2.1). Our group recently discovered the direct cross-coupling⁵⁹ (Scheme 2.1) between simple olefins to form dienes under mild conditions, without the need for directing group in the substrates.

Scheme 2.1

This method provided an enhanced substrate scope and diastereoselectivities

⁵⁷Yu, H.; Jin, W.; Sun, C.; Chen, J.; Du, W.; He, S.; Yu, Z. *Angew.Chem., Int. Ed.* **2010**, 49, 5792.

⁵⁸Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem. Eur. J.* **2011**, 17, 7167.

⁵⁹Xu, Y. H.; Lu, J.; Loh, T. P. *J. Am. Soc. Chem.* **2009**, 131, 1372.

compared to Ishii's report. A deuterium labeling study provided the coupling product with retention of the deuterium atoms, which indicates that a Pd π -allyl intermediate was not involved in this reaction. Based on this result, a possible mechanism was proposed in Figure 2.2.

Figure 2.2

Nevertheless, this reaction is plagued by a limited range of substrates that can be utilized and the yield as well as diastereoselectivity for aromatic olefin are moderate. For aliphatic olefins, poor yield, no diastereoselectivity, and high catalyst loading were encountered. All of these disadvantages limited the widespread application of this reaction. Therefore, we have extensively screened reaction conditions and reported the palladium-catalyzed cross-coupling reaction of aliphatic alkenes with acrylates to give the desired products in moderate yield and diastereoselectivity.

2.2 Results and Discussion

2.2.1 Diene construction through palladium-catalyzed cross-coupling reactions of protected homoallylic alcohols with acrylates.

Initially, using our previously reported conditions, the model reaction of **1** (1equiv.) with *n*-butyl acrylate (**2**, 2 equiv.) did not afford any desired product.⁵⁹ In our attempt to realize the coupling, different bidentate ligands were introduced to increase the catalytic reactivity of the palladium catalyst (Table 2.1 entries 1–12). The results showed that 1,10-phenanthroline was most efficient in promoting the cross-coupling reaction (Table 2.1, entry 5). Unfortunately, the stereoselectivity was low. From these results, it could be concluded that the Pd-nitrogen coordination angle, chelating length and steric environment are all vital to the coupling reaction. On the basis of these factors, phenanthroline was selected as the best choice for the coupling reaction. We think that the use of catalytic bidentate nitrogen ligand facilitated the coupling reaction and prevented precipitation of palladium black *via* stabilization of the palladium(0) species to enhance reactivity of the palladium catalyst, resulting in high catalytic efficiency. We reckoned that introduction of a bulky protecting group on the hydroxyl might help to improve the *E/Z* ratio of the product. Next, we examined different protecting groups for the hydroxyl group and the results of the coupling reaction are shown in Table 2.2. That was indeed the case as evidenced from the reaction of TIPS-protected substrate with *n*-butyl acrylate. A 75:25 ratio of the *E:Z* isomers was obtained even though the yield of the product was low (Table 2.2, entry 5).

Table 2.1 Screened ligand for the direct cross-coupling between olefins

Entry	R	L/additive	T (°C)	Solvent (1:1)	Yield (%)	E/Z (%) ^b
1	H	-	60	DMSO/HOAc	-	-
2	H	L1	60	DMSO/HOAc	23	50:50
3	H	L2	60	DMSO/HOAc	-	-
4	H	L3	60	DMSO/HOAc	-	-
5	H	L4	60	DMSO/HOAc	32	50:50
6	H	L5	60	DMSO/HOAc	16	50:50
7	H	L6	60	DMSO/HOAc	10	50:50
8	H	L7	60	DMSO/HOAc	11	50:50
9	H	L8	60	DMSO/HOAc	8	50:50
10	H	L9	60	DMSO/HOAc	-	-
11	H	L10	60	DMSO/HOAc	-	-
12	H	L11	60	DMSO/HOAc	-	-

Table 2.2 Screened protecting group for the coupling reaction

Entry	R	L/additive	T (°C)	Solvent (1:1)	Yield(%)	<i>E/Z</i> (%) ^b
1	Ac	L4	60	DMSO/HOAc	12	50:50
2	Bn	L4	60	DMSO/HOAc	15	55:45
3	Bz	L4	60	DMSO/HOAc	14	50:50
4	TBDPS	L4	60	DMSO/HOAc	11	55:45
5	TIPS	L4	60	DMSO/HOAc	17	75:25

To further improve the reaction yield and stereoselectivity, the catalyst loading, temperature, and choice of solvent were optimized as outlined in Table 2.3. Ultimately, we found that 10 mol% Pd(OAc)₂, 12 mol% 1,10-phenanthroline and 12 mol% AgSbF₆ as an additive, 2 equiv. Cu(OAc)₂ as an oxidant in NMP/PivOH (v/v, 1:1) at 120 °C for 24 h was most effective. For example, the desired coupling product was obtained in 82% yield with an *E:Z* ratio of 75:25 (Table 2.3, entry 9). Other oxidants, such as AgOAc, Ag₂O and benzoquinone, gave relative poor yields of the cross-coupling product.

Table 2.3. Optimization of various reaction conditions for the direct cross-coupling between olefins^a

Entry	L/additive	T (°C)	Solvent (1:1)	Yield (%)	E/Z (%) ^b
1	L4	60	DMSO/HOAc	17	75:25
2	L4	60	DMSO/PivOH	23	75:25
3	L4	90	DMSO/PivOH	30	75:25
4	L4	90	NMP/PivOH	39	75:25
5	L4	120	NMP/PivOH	65	75:25
6	L4/AgBF ₄	120	NMP/PivOH	68	75:25
7	L4/AgOTf	120	NMP/PivOH	62	75:25
8	L4/AgClO ₄	120	NMP/PivOH	59	75:25
9	L4/AgSbF₆	120	NMP/PivOH	82	75:25

^aThe reaction conditions are as follows: olefin 1 (0.3 mmol), *n*-butyl acrylate (0.6 mmol), Pd(OAc)₂ (10 mol%), ligand (12 mol%) and silver salt (12 mol%) in mixed solvent heated at the appointed temperature. ^bConfiguration of the product was confirmed by ¹H NMR after purification.

With the optimized coupling reaction conditions, we examined the scope of the reaction by examining the cross-coupling between a dozen of structurally diverse TIPS-protected homoallylic alcohols and *n*-butyl or ethyl acrylates. As shown in Table 2.4, all of the reactions gave the coupling products in moderate to good yields with moderate *E:Z* ratios.

Table 2.4. Exploration of the scope of various homoallylic alcohols towards direct coupling with *n*-butyl acrylate^a

^aThe reactions were carried out as follows: olefin **1** (0.3 mmol), *n*-butyl acrylate (0.6 mmol), Pd(OAc)₂ (10 mol%), 1,10-phenanthroline (12 mol%), Cu(OAc)₂ (0.6 mmol) and AgSbF₆ (12 mol%) in NMP/PivOH (v:v = 1:1) at 120 °C for 24 h. ^b The yields indicated in the table are isolated yields and the *E*:*Z* ratios were determined after purification of the product.

It was evident from the results that *n*-butyl acrylate reacted effectively to give the coupling product in a higher yield than ethyl acrylate, although there was no improvement in the *E*:*Z* ratio. Also, the reaction could tolerate the presence of a chloro atom in the 4-chlorophenyl group (**3i**), which permits further synthetic elaboration. Interestingly, the *E*/*Z* isomer ratio of the coupling reaction was affected by the nature

of the substituent on the carbinolic carbon of the homoallylic alcohol, For example, when the hydroxylated carbon atom bears either a phenyl group or a primary alkyl group, *E/Z* ratios of 75:25 (see Table 2.4, **3a**, **3a'**, **3b**, **3b'**, **3e**, **3g**, **3h**, **3i**, **3j**, **3l**) were observed for the corresponding products, products with higher *E/Z* ratios (80:20 and 86:14) were obtained when using substrates bearing secondary alkyl groups on the carbinolic carbon atom (**3c**, **3c'**, **3f**). Moreover, when the carbinolic carbon atom of the substrate bears a tertiary alkyl group (**3d** and **3d'**), the corresponding products were obtained with *E/Z* ratios of greater than 95:5, thus suggesting that steric bulk influences the stereochemical outcome of these reactions. These results may be attributed to the first step of C-H activation as shown in Scheme 2.2. The bulky TIPS and R affected the C-H activation occurred in the more preferred state **B**, which resulted in favourable *E* intermediate due to the steric hindrance.

Scheme 2.2

This hypothesis was proved by the results that when employing a primary TIPS protected homoallylic alcohol **1k** as the substrate, products **3k** and **3k'** were obtained with lower *E/Z* ratio. Based on these results and combined our previously reported direct coupling reaction, we proposed a mechanism of this coupling reaction, as shown

in Scheme 2.3. Initially, the terminal alkenyl-H was activated by $\text{Pd}(\text{OAc})_2$ to give a preferable *E* intermediate due to the effect of the bulky TIPS group. Treatment of butyl acrylate with intermediate **2** via carbopalladation constructed a new C-C bond, subsequently β -H elimination to afford the coupling product **4**. The $\text{Pd}(0)$ was reoxidized by $\text{Cu}(\text{OAc})_2$ to complete the catalytic cycle.

Scheme 2.3

2.2.2 Diene construction via palladium-catalyzed cross-coupling of allylic alcohol with *tert*-butyl acrylate.

Success of the above-mentioned cross-coupling reaction provided the basis for further expansion of the substrate scope. In view of the usefulness of dienic alcohols in organic synthesis,⁴⁶ we have also investigated the cross-coupling reaction of allylic alcohols with *tert*-butyl acrylate. Based on the conditions established earlier, we proceeded with further optimization for the reaction. As shown in Table 2.5, with the use of 20 mol% of $\text{Pd}(\text{OAc})_2$, 20 mol% 1,10-phenanthroline as ligand, and 20 mol% AgSbF_6 as additive, diene **6a** was obtained in good yield and stereoselectivity. Other aryl, alkyl and alkenyl substituted allylic alcohols were equally effective in producing

the dienic alcohols in moderate yield and stereoselectivity (Table 2.6). These results further demonstrated the versatility of our cross-coupling reaction.

Table 2.5. Cross-coupling between allylic alcohol and *tert*-butyl acrylate to form dienic alcohol

Entry	L/additive	T (°C)	Solvent (1:1)	Yield (%)	E/Z (%) ^b
1	AgBF ₄	80	DMSO/HOAc	56	83:17
2	AgOTf	80	DMSO/HOAc	48	83:17
3	AgClO ₄	80	DMSO/HOAc	39	83:17
4	AgSbF ₆	80	DMSO/HOAc	65	83:17
5	AgSbF₆	80	DMSO/PivOH	74	83:17
6	AgSbF ₆	80	NMP/PivOH	53	83:17
7	AgSbF ₆	100	DMSO/PivOH	57	83:17
8 ^a	AgSbF ₆	80	DMSO/PivOH	trace	--

^aThe hydroxyl group was protected by TIPS.

Table 2.6 Exploration of the scope of allylic alcohol towards direct coupling with *tert*-butyl acrylate

2.3 Conclusion

In conclusion, we have developed a direct and efficient palladium-catalyzed method for the cross-coupling of homoallylic and allylic alcohols with acrylates that produces dienic alcohols in moderate to high yields, and with good stereoselectivity. This atom-economical methodology offers a straightforward access to forge new $C(sp^2)-C(sp^2)$ bonds.

2.4 Experimental Section

General Methods

Commercial grade solvents and reagents were used without further purification. Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Hexane, ethyl acetate were fractionally distilled. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated 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 a basic solution of potassium permanganate or acidic solution of ceric molybdate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. IR spectra were recorded as thin films on NaCl plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral analysis (HRMS) was performed on Waters Q-ToF Premier Mass Spectrometer. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker Advance 300, 400 and 500 NMR spectrometer. Chemical shifts for ^1H NMR spectra 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* (δ 7.26, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); dt (doublets of triplet); or m (multiplets). 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* (δ 77.0, triplet).

General procedure for the synthesis of protected homoallylic alcohols **1a-1l**

1) A round bottomed flask charged with a solution of the 3-bromo-2-methylprop-1-ene (1.0 equiv) and indium (1.0 equiv) in THF/H₂O (1:1) was kept at room temperature with stirring. The aldehyde (1.0 equiv) was added to the solution and the resulting suspension was stirred for 10-24 h. Saturated NH₄Cl solution was added at 0 °C. The THF layer was separated from the aqueous layer, which was extracted with Et₂O for 3 times. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was directly used in the next step without further purification⁶⁰.

2) A solution of the homoallylic alcohol (1.0 equiv) in CH₂Cl₂ was added 2,6-lutidine (1.5 equiv) and TIPSOtF (1.2 equiv) at 0 °C. After stirring at 0 °C for 2 h, aq. NaHCO₃ was added followed by an extraction with ether. The combined organic extracts were washed with 1 M HCl and brine, dried and concentrated. The crude was purified by flash chromatography (silica gel, hexanes/EtOAc 20:1) to give the target product.

⁶⁰Wang, R. B.; Lim, C. H.; Tan, C. H.; Lim, B. K.; Sim, K. Y.; Loh, T. P. *Tetrahedron: Asymmetry*. **1995**, *6*, 1825.

General procedure for the synthesis of allylic alcohols of 4a-4g

2-Bromopropene (7.0 mmol, 1.0 equiv) in THF (9 mL) was added to magnesium turnings (8.4 mmol, 1.2 equiv) in THF (1 mL) under nitrogen, at such a rate so as to maintain a gentle reflux. After the addition, the mixture was heated under reflux for a further 1 h and then cooled in ice, the aldehyde (7.7 mmol, 1.1 equiv) was then slowly added in the reaction mixture. After a further 0.5 h the mixture was poured into saturated aqueous NH₄Cl (75 mL) and extracted with ether (3 × 50 mL). The extracts were combined, dried over Na₂SO₄ and evaporated under reduced pressure, and the residue was flash chromatographed (hexane/EtOAc = 15:1) to give the title compound.⁶¹

General procedure for the palladium-catalyzed cross-coupling of protected homoallylic alcohol with *n*-butyl acrylate.

A 5 mL round bottomed flask equipped with a magnetic stirring bar was added the substituted alkene (0.30 mmol), Pd(OAc)₂ (10 mol%, 0.03 mmol), Cu(OAc)₂ (0.6

⁶¹Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc. Perkin Trans. I* **1989**, 413.

mmol, 2.0 equiv), 1,10-phenanthroline (12 mol%, 0.036 mmol), AgSbF₆ (12 mol%, 0.036 mmol), *n*-butyl acrylate (0.6 mmol, 2.0 equiv) in 0.6 mL NMP/PivOH (v/v=1:1). The reaction mixture was stirred at 120 °C for 24 h. The mixture was cooled to room temperature, followed by the addition of saturated aqueous NaHCO₃ solution and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel to give the desired products.

General procedure for the palladium-catalyzed cross-coupling of allylic alcohol with *tert*-butyl acrylate.

To a 5 mL round bottomed flask equipped with a magnetic stirring bar was added the allylic alcohol (0.30 mmol), Pd(OAc)₂ (20 mol%, 0.06 mmol), Cu(OAc)₂ (0.6 mmol, 2.0 equiv), 1,10-phenanthroline (20 mol%, 0.06 mmol), AgSbF₆ (20 mol%, 0.06 mmol), *tert*-butyl acrylate (0.6 mmol, 2.0 equiv) in 0.6 mL DMSO/PivOH (v/v = 1:1). The reaction mixture was stirred at 80 °C for 48 h. The mixture was cooled to room temperature, followed by the addition of saturated aqueous NaHCO₃ solution and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was

purified *via* column chromatography on silica gel to give the desired products.

Characterization data for the protected homoallylic alcohols.

Triisopropyl((5-methyl-1-phenylhex-5-en-3-yl)oxy)silane (1a)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 84% yield: $R_f = 0.74$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.25 (t, $J = 7.5$ Hz, 2H), 7.18 – 7.12 (m, 3H), 4.79 (s, 1H), 4.76 (s, 1H), 4.07 (dq, $J = 10.1, 5.0$ Hz, 1H), 2.71 (td, $J = 10.8, 5.6$ Hz, 2H), 2.38 – 2.25 (m, 2H), 1.86 (ddt, $J = 13.5, 10.8, 5.3$ Hz, 1H), 1.78 – 1.69 (m, 4H), 1.11-1.08 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 142.87, 142.68, 128.36, 128.28, 125.57, 112.98, 70.28, 45.46, 38.07, 30.82, 22.92, 18.22, 12.68.

FTIR (NaCl, cm^{-1}): 3072.60, 3053.32, 2943.37, 2864.29, 1647.21, 1458.18, 1265.30, 1103.28, 1058.92, 883.40, 738.74.

HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{39}\text{OSi}$ $[\text{M}+\text{H}]^+$: 347.2770, found 347.2754.

Triisopropyl((3-methyl-1-phenylbut-3-en-1-yl)oxy)silane (1b)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 86% yield: $R_f = 0.71$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.12 (m, 5H), 4.94 – 4.79 (m, 1H), 4.68 (s, 1H), 4.52 (s, 1H), 2.58 (dd, $J = 13.1, 5.7$ Hz, 1H), 2.35 (dd, $J = 13.1, 7.5$ Hz, 1H), 1.61 (s, 3H), 1.15 – 0.84 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 145.20, 141.84, 127.76, 126.95, 126.28, 113.65, 74.66, 49.68, 23.28, 18.03, 17.95, 12.36.

FTIR (NaCl, cm^{-1}): 3072.60, 3028.24, 2941.44, 2864.29, 1647.21, 1492.90, 1462.04, 1454.33, 1382.96, 1365.60, 1265.30, 1091.71, 1064.71, 883.40, 740.67.

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{35}\text{OSi}$ $[\text{M}+\text{H}]^+$: 319.2457, found 319.2449.

((1-Cyclohexyl-3-methylbut-3-en-1-yl)oxy)Triisopropylsilane (1c)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 81% yield: $R_f = 0.68$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 4.76 (s, 1H), 4.73 (s, 1H), 3.87 (dd, $J = 9.9, 3.9$ Hz, 1H), 2.29 (dd, $J = 13.6, 8.2$ Hz, 1H), 2.18 (dd, $J = 13.6, 5.6$ Hz, 1H), 1.81 – 1.70 (m, 5H),

1.64 (t, $J = 13.4$ Hz, 3H), 1.46 – 1.14 (m, 6H), 1.08 (s, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 143.16, 112.60, 74.94, 42.86, 42.48, 29.68, 26.88, 26.76, 26.59, 26.18, 22.81, 18.32, 18.31, 13.02.

FTIR (NaCl, cm^{-1}): 2927.94, 2864.29, 1647.21, 1448.54, 1375.25, 1263.37, 1114.86, 1060.85, 1053.13, 883.40, 742.59.

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{41}\text{OSi}$ $[\text{M}+\text{H}]^+$: 325.2927, found 325.2940.

Triisopropyl((2,2,5-trimethylhex-5-en-3-yl)oxy)silane (1d)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 79% yield: $R_f = 0.66$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 4.77 (s, 1H), 4.76 (s, 1H), 3.83 – 3.73 (m, 1H), 2.42 (dd, $J = 15.1, 6.4$ Hz, 1H), 2.16 (dd, $J = 15.1, 4.6$ Hz, 1H), 1.77 (s, 3H), 1.10-1.09 (m, 21H), 0.93 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 144.02, 112.02, 78.08, 43.35, 37.01, 26.18, 22.96, 18.50, 18.46, 13.57.

FTIR (NaCl, cm^{-1}): 2945.30, 2866.22, 1647.21, 1463.97, 1390.68, 1361.74, 1263.37, 1097.50, 1028.06, 883.40, 800.46, 742.59.

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{39}\text{OSi}$ $[\text{M}+\text{H}]^+$: 299.2770, found 299.2780.

Triisopropyl((2-methyldodec-1-en-4-yl)oxy)silane (1e)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 83% yield: R_f = 0.69 (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 4.76 (s, 1H), 4.71 (s, 1H), 4.03 – 3.96 (m, 1H), 2.24 (qd, J = 13.5, 6.5 Hz, 2H), 1.74 (s, 3H), 1.46 – 1.20 (m, 14H), 1.09-1.07 (m, 21H), 0.89 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 143.07, 112.64, 70.87, 45.62, 36.32, 31.92, 29.93, 29.63, 29.30, 24.51, 23.04, 22.71, 18.22, 14.11, 12.71.

FTIR (NaCl, cm^{-1}): 3072.60, 3053.32, 2927.94, 2864.29, 1647.21, 1463.97, 1377.17, 1263.37, 1101.35, 1051.20, 1012.63, 883.40, 740.67, 677.01.

HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{47}\text{OSi}$ $[\text{M}+\text{H}]^+$: 355.3396, found 355.3406.

((5-Ethyl-2-methylhept-1-en-4-yl)oxy)Triisopropylsilane (1f)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 75% yield: R_f = 0.71 (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 4.76 (s, 1H), 4.72 (s, 1H), 4.17 – 4.08 (m, 1H), 2.28 (dd,

$J = 13.5, 7.6$ Hz, 1H), 2.17 (dd, $J = 13.5, 6.1$ Hz, 1H), 1.72 (s, 3H), 1.54 (td, $J = 13.8, 6.8$ Hz, 1H), 1.43 – 1.15 (m, 4H), 1.08-1.06 (m, 21H), 0.91 (td, $J = 7.4, 4.5$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 143.22, 112.75, 71.74, 46.41, 42.61, 22.73, 22.42, 21.65, 18.29, 13.03, 12.74, 12.63.

FTIR (NaCl, cm^{-1}): 3053.32, 2960.73, 2943.37, 2866.22, 1462.04, 1379.10, 1265.30, 1083.99, 1055.06, 883.40, 740.67, 705.95.

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{41}\text{OSi}$ $[\text{M}+\text{H}]^+$: 313.2927, found 313.2931.

Methyl 7-methyl-5-((triisopropylsilyl)oxy)oct-7-enoate (1g)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 80% yield: $R_f = 0.65$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 4.76 (s, 1H), 4.70 (s, 1H), 4.03-3.99 (m, 1H), 3.65 (s, 3H), 2.35 – 2.17 (m, 4H), 1.80 – 1.62 (m, 5H), 1.60 – 1.38 (m, 2H), 1.12 – 0.98 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 174.07, 142.65, 112.89, 70.30, 51.39, 45.37, 35.42, 34.32, 22.92, 19.96, 18.16, 12.61.

FTIR (NaCl, cm^{-1}): 3074.53, 2943.37, 2866.22, 1743.65, 1647.21, 1460.11, 1436.97, 1363.67, 1249.87, 1170.79, 1097.50, 883.40, 738.74.

HRMS (ESI) m/z calculated for $C_{19}H_{39}O_3Si$ $[M+H]^+$:343.2668, found 343.2674.

Triisopropyl((3-methyl-1-(p-tolyl)but-3-en-1-yl)oxy)silane (1h)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 82% yield: R_f = 0.81 (hexane : ethyl acetate = 10:1).

1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 7.8 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 4.85 (t, J = 6.6 Hz, 1H), 4.70 (s, 1H), 4.55 (s, 1H), 2.59 (dd, J = 13.1, 5.7 Hz, 1H), 2.40 – 2.31 (m, 4H), 1.64 (s, 3H), 1.06 – 0.95 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.22, 142.04, 136.33, 128.44, 126.16, 113.49, 74.45, 49.71, 23.28, 21.17, 18.05, 17.97, 12.37.

FTIR (NaCl, cm^{-1}): 3053.32, 2943.37, 2866.22, 1462.04, 1421.54, 1265.30, 1087.85, 1064.71, 997.20, 883.40, 740.67.

HRMS (ESI) m/z calculated for $C_{21}H_{37}OSi$ $[M+H]^+$:333.2614, found 333.2628.

((1-(4-Chlorophenyl)-3-methylbut-3-en-1-yl)oxy)Triisopropylsilane (1i)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 76% yield: $R_f = 0.79$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.17 (m, 4H), 4.84 (t, $J = 6.5$ Hz, 1H), 4.68 (s, 1H), 4.48 (s, 1H), 2.56 (dd, $J = 13.1, 5.1$ Hz, 1H), 2.32 (dd, $J = 13.0, 7.9$ Hz, 1H), 1.61 (s, 3H), 1.11 – 0.90 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 143.67, 141.28, 132.50, 127.94, 127.57, 114.02, 73.94, 49.56, 23.28, 17.99, 17.93, 12.28.

FTIR (NaCl, cm^{-1}): 3074.53, 3051.39, 2943.37, 2866.22, 1647.21, 1597.06, 1489.05, 1463.97, 1263.37, 1215.15, 1087.85, 1012.63, 883.40, 740.67.

HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{34}\text{OSiCl}$ $[\text{M}+\text{H}]^+$: 353.2067, found 353.2080.

Triisopropyl((3-methyl-1-(4-(trifluoromethyl)phenyl)but-3-en-1-yl)oxy)silane (1j)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 74% yield: $R_f = 0.80$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 8.1$ Hz, 2H), 7.41 (d, $J = 8.0$ Hz, 2H), 4.99 – 4.87 (m, 1H), 4.69 (s, 1H), 4.47 (s, 1H), 2.60 (dd, $J = 13.2, 5.3$ Hz, 1H), 2.35 (dd, $J = 13.2, 7.8$ Hz, 1H), 1.63 (s, 3H), 1.08 – 0.93 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 149.14, 141.02, 129.19 (q, $J = 32$ Hz), 126.48, 124.79

(q, $J = 4$ Hz), 124.32 (q, $J = 271$ Hz), 114.26, 74.03, 49.50, 23.29, 17.98, 17.92, 12.29.

FTIR (NaCl, cm^{-1}): 2943.37, 2866.22, 1647.21, 1618.28, 1463.97, 1325.10, 1265.30, 1165.00, 1126.43, 1066.64, 1016.49, 997.20, 883.40, 759.95.

HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{34}\text{OF}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 387.2331, found 387.2328.

Triisopropyl((3-methylbut-3-en-1-yl)oxy)silane (1k)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 75% yield: $R_f = 0.68$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 4.76 (s, 1H), 4.71 (s, 1H), 3.79 (t, $J = 7.1$ Hz, 2H), 2.28 (t, $J = 7.1$ Hz, 2H), 1.76 (s, 3H), 1.16 – 0.96 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 143.20, 111.41, 62.48, 41.30, 22.92, 18.01, 12.03.

FTIR (NaCl, cm^{-1}): 3074.53, 2943.37, 2866.22, 1649.14, 1458.18, 1381.03, 1247.94, 1205.51, 1105.21, 1068.56, 1012.63, 995.27, 918.12, 883.40, 773.46.

HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{31}\text{OSi}$ $[\text{M}+\text{H}]^+$: 243.2144, found 243.2152.

((1-(Benzyloxy)-4-methylpent-4-en-2-yl)oxy)Triisopropylsilane (1l)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 71% yield: $R_f = 0.65$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.21 (m, 5H), 4.77 (s, 1H), 4.73 (s, 1H), 4.51 (d, $J = 4.6$ Hz, 2H), 4.17 – 4.06 (m, 1H), 3.43 (d, $J = 5.1$ Hz, 2H), 2.36 (dd, $J = 13.7$, 7.0 Hz, 1H), 2.28 (dd, $J = 13.7$, 5.4 Hz, 1H), 1.76 (s, 3H), 1.13 – 1.00 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 142.46, 138.57, 128.22, 127.59, 127.39, 113.08, 74.17, 73.25, 70.40, 43.39, 23.27, 18.14, 18.12, 12.55.

FTIR (NaCl, cm^{-1}): 3053.32, 2943.37, 2891.30, 2866.22, 1647.21, 1496.76, 1454.33, 1265.30, 1107.14, 1093.64, 883.40, 740.67.

HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{39}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 363.2719, found 363.2720.

Characterization data for the products

(2*E*,4*E*)-Butyl 5-methyl-9-phenyl-7-((triisopropylsilyl)oxy)nona-2,4-dienoate (3a)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 75:25$) in 82% yield, ^1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.68$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.56 (dd, $J = 15.1$, 11.6 Hz, 1H), 7.32 – 7.06 (m, 5H), 6.03 (d, $J = 11.9$ Hz, 1H), 5.80 (d, $J = 15.2$ Hz, 1H), 4.28 – 4.02 (m, 3H), 2.76 – 2.60

(m, 2H), 2.46 – 2.37 (m, 2H), 1.91 (s, 3H), 1.86 – 1.69 (m, 2H), 1.67 – 1.63 (m, 2H), 1.47 – 1.32 (m, 2H), 1.08- 1.06(m , 21H), 0.94 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.67, 146.22, 142.34, 140.39, 128.35, 128.30, 125.86, 125.72, 119.48, 70.41, 64.07, 47.79, 38.55, 30.97, 30.77, 19.16, 18.17, 17.95, 13.71, 12.65.

FTIR (NaCl, cm^{-1}): 3053.32, 2958.80, 2943.37, 2866.22, 1705.07, 1633.71, 1610.56, 1494.83, 1462.04, 1384.89, 1307.74, 1265.30, 1159.22, 1087.85, 977.91, 883.40, 740.67.

HRMS (ESI) m/z calculated for $\text{C}_{29}\text{H}_{49}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$:473.3451, found 473.3439.

(2*E*,4*E*)-Ethyl 5-methyl-9-phenyl-7-((triisopropylsilyl)oxy)nona-2,4-dienoate (3a')

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 75:25$) in 68% yield, ^1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.66$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.56 (dd, $J = 15.1, 11.6$ Hz, 1H), 7.37 – 7.07 (m, 5H), 6.03 (d, $J = 11.8$ Hz, 1H), 5.79 (d, $J = 15.2$ Hz, 1H), 4.27 – 4.15 (m, 2H), 4.14 – 4.03 (m, 1H), 2.73-2.61 (m, 2H), 2.56 – 2.31 (m, 2H), 1.91 (s, 3H), 1.86 – 1.67 (m, 2H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.09-1.07 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.57, 146.26, 142.33, 140.43, 128.35, 128.29, 125.86, 125.72, 119.45, 70.39, 60.12, 47.78, 38.56, 30.96, 18.16, 17.94, 14.30, 12.64.

FTIR (NaCl, cm^{-1}): 3053.32 2943.37, 1701.22, 1633.71, 1456.26, 1367.53, 1265.30, 1097.50, 1060.85, 883.40, 738.74.

HRMS (ESI) m/z calculated for $\text{C}_{27}\text{H}_{45}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 445.3138, found 445.3141.

(2*E*,4*E*)-Butyl 5-methyl-7-phenyl-7-((triisopropylsilyl)oxy)hepta-2,4-dienoate (3b)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 75:25$) in 73% yield, ^1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.65$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.47 (dd, $J = 15.1, 11.7$ Hz, 1H), 7.32 – 7.16 (m, 5H), 5.80 (d, $J = 11.6$ Hz, 1H), 5.68 (d, $J = 15.2$ Hz, 1H), 4.89 (t, $J = 6.4$ Hz, 1H), 4.13 (t, $J = 6.7$ Hz, 2H), 2.63 (dd, $J = 12.8, 6.1$ Hz, 1H), 2.44 (dd, $J = 12.8, 6.6$ Hz, 1H), 1.77 (s, 3H), 1.69 – 1.59 (m, 2H), 1.46 – 1.34 (m, 2H), 1.05 – 0.92 (m, 24H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.73, 145.38, 144.69, 140.48, 127.90, 127.17, 126.54, 125.98, 119.24, 74.55, 64.04, 51.89, 30.75, 19.15, 18.49, 17.96, 17.87, 13.71, 12.27.

FTIR (NaCl, cm^{-1}): 3053.32, 2960.73, 2943.37, 2866.22, 1701.22, 1635.64, 1610.56, 1458.18, 1386.82, 1307.74, 1265.30, 1064.71, 883.40, 738.74.

HRMS (ESI) m/z calculated for $C_{27}H_{45}O_3Si$ $[M+H]^+$: 445.3138, found 445.3150.

(2*E*,4*E*)-Ethyl 5-methyl-7-phenyl-7-((triisopropylsilyl)oxy)hepta-2,4-dienoate (3b')

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 75:25$) in 65% yield, 1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.64$ (hexane : ethyl acetate = 10:1).

1H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, $J = 15.1, 11.7$ Hz, 1H), 7.36 – 7.09 (m, 5H), 5.79 (d, $J = 11.6$ Hz, 1H), 5.68 (d, $J = 15.2$ Hz, 1H), 4.89 (t, $J = 6.3$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.63 (dd, $J = 12.8, 6.1$ Hz, 1H), 2.44 (dd, $J = 12.8, 6.6$ Hz, 1H), 1.78 (s, 3H), 1.27 (t, $J = 6.9$ Hz, 3H), 1.13 – 0.81 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.56, 145.33, 144.65, 140.45, 127.87, 127.15, 126.53, 125.94, 119.23, 74.52, 60.03, 51.86, 18.47, 17.93, 17.85, 14.25, 12.25.

FTIR (NaCl, cm^{-1}): 3018.60, 2943.37, 2866.22, 1701.22, 1650.23, 1273.02, 1215.15, 1093.64, 756.10.

HRMS (ESI) m/z calculated for $C_{25}H_{41}O_3Si$ $[M+H]^+$: 417.2825, found 417.2841.

(2*E*,4*E*)-Butyl 7-cyclohexyl-5-methyl-7-((triisopropylsilyl)oxy)hepta-2,4-dienoate (3c)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture (*E/Z* = 80:20) in 65% yield, ^1H and ^{13}C NMR are described for the *E* isomer: R_f = 0.54 (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, J = 15.2, 11.6 Hz, 1H), 6.01 (d, J = 11.6 Hz, 1H), 5.77 (d, J = 15.1 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 3.96 – 3.76 (m, 1H), 2.52 – 2.14 (m, 2H), 1.88 (s, 3H), 1.81 – 1.55 (m, 7H), 1.47 – 1.27 (m, 2H), 1.24 – 1.10 (m, 7H), 1.07-1.04 (m, 21H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.76, 147.02, 140.60, 125.62, 119.07, 75.03, 64.03, 44.87, 43.46, 30.77, 28.72, 27.10, 26.76, 26.53, 19.16, 18.21, 17.79, 13.71, 12.96, 12.91.

FTIR (NaCl, cm^{-1}): 3053.32, 2958.80, 2929.87, 2864.29, 1701.22, 1633.71, 1463.97, 1450.47, 1265.30, 1205.51, 883.40, 740.67.

HRMS (ESI) m/z calculated for $\text{C}_{27}\text{H}_{51}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 451.3607, found 451.3628.

(2*E*,4*E*)-Ethyl 7-cyclohexyl-5-methyl-7-((triisopropylsilyl)oxy)hepta-2,4-dienoate (3c')

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture (*E/Z* = 80:20) in 56% yield, ^1H and ^{13}C NMR are described for the *E* isomer: R_f = 0.56 (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, J = 15.1, 11.7 Hz, 1H), 6.01 (d, J = 11.6 Hz, 1H), 5.76 (d, J = 15.1 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.87 (t, J = 5.7 Hz, 1H), 2.55 – 2.20 (m, 2H), 1.88 (s, 3H), 1.79 – 1.52 (m, 5H), 1.42 – 1.11 (m, 9H), 1.06-1.02 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.67, 147.06, 140.64, 125.62, 119.06, 75.02, 60.09, 44.87, 43.49, 28.70, 27.13, 26.76, 26.53, 18.21, 17.79, 14.29, 12.96, 12.92.

FTIR (NaCl, cm^{-1}): 2929.87, 2864.29, 1714.72, 1635.64, 1612.49, 1463.97, 1450.47, 1386.82, 1367.53, 979.84, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{25}\text{H}_{47}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 423.3294, found 423.3310.

(2*E*,4*E*)-Butyl 5,8,8-trimethyl-7-((triisopropylsilyl)oxy)nona-2,4-dienoate (3d)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture (*E/Z* > 95:5) in 64% yield, ^1H and ^{13}C NMR are described for the *E* isomer: R_f = 0.53 (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, J = 15.1, 11.7 Hz, 1H), 6.03 (d, J = 11.6 Hz, 1H), 5.77 (d, J = 15.1 Hz, 1H), 4.14 (t, J = 6.7 Hz, 2H), 3.77 (t, J = 5.6 Hz, 1H), 2.47

(dd, $J = 14.4, 5.5$ Hz, 1H), 2.26 (dd, $J = 14.4, 5.5$ Hz, 1H), 1.91 (s, 3H), 1.70 – 1.56 (m, 2H), 1.46 – 1.32 (m, 2H), 1.07-1.04 (d, $J = 3.7$ Hz, 21H), 0.89 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.73, 147.57, 140.49, 125.34, 119.10, 78.32, 64.07, 45.76, 36.92, 30.76, 26.13, 19.16, 18.41, 18.38, 17.62, 13.71, 13.56.

FTIR (NaCl, cm^{-1}): 3053.32, 2958.80, 2945.30, 1866.22, 1703.14, 1631.78, 1610.56, 1463.97, 1307.74, 1265.30, 1161.15, 1138.00, 979.84, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{25}\text{H}_{49}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 425.3451, found 425.3459.

(2*E*,4*E*)-Ethyl 5,8,8-trimethyl-7-((triisopropylsilyl)oxy)nona-2,4-dienoate (3d')

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z > 95:5$) in 53% yield, ^1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.55$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.54 (dd, $J = 15.1, 11.7$ Hz, 1H), 6.04 (d, $J = 11.6$ Hz, 1H), 5.76 (d, $J = 15.1$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.77 (t, $J = 5.6$ Hz, 1H), 2.47 (dd, $J = 14.4, 5.5$ Hz, 1H), 2.26 (dd, $J = 14.4, 5.5$ Hz, 1H), 1.91 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.08-1.05 (m, 21H), 0.89 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.65, 147.62, 140.53, 125.35, 119.11, 78.33, 60.13, 45.78, 36.93, 26.14, 18.42, 18.39, 17.63, 14.29, 13.57.

FTIR (NaCl, cm^{-1}): 2958.80, 2866.22, 1701.22, 1629.85, 1265.30, 1095.57, 742.59.

HRMS (ESI) m/z calculated for $\text{C}_{23}\text{H}_{45}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 397.3138, found 397.3156.

(2*E*,4*E*)-Butyl 5-methyl-7-((triisopropylsilyl)oxy)pentadeca-2,4-dienoate (3e)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 75:25$) in 67% yield, ^1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.58$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.55 (dd, $J = 15.1, 11.6$ Hz, 1H), 6.00 (d, $J = 11.4$ Hz, 1H), 5.77 (d, $J = 15.1$ Hz, 1H), 4.13 (t, $J = 6.7$ Hz, 2H), 4.03 – 3.92 (m, 1H), 2.53 – 2.20 (m, 2H), 1.89 (s, 3H), 1.67 – 1.58 (m, 2H), 1.45 – 1.38 (m, 2H), 1.26-1.22 (m, 14H), 1.05-1.03 (m, 21H), 0.93 (t, $J = 7.4$ Hz, 3H), 0.86 (t, $J = 6.5$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.75, 146.74, 140.58, 125.69, 119.15, 71.00, 64.03, 47.85, 36.81, 31.83, 30.78, 29.77, 29.51, 29.20, 26.95, 24.56, 22.64, 19.16, 18.13, 14.04, 13.69, 12.65.

FTIR (NaCl, cm^{-1}): 3055.24, 2956.87, 2929.87, 2866.22, 1708.93, 1635.64, 1460.11, 1267.23, 979.84, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{29}\text{H}_{57}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 481.4077, found 481.4087.

(2*E*,4*E*)-Butyl 8-ethyl-5-methyl-7-((triisopropylsilyl)oxy)deca-2,4-dienoate (3f)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture (*E/Z* = 86:14) in 77% yield, ¹H and ¹³C NMR are described for the *E* isomer: R_f = 0.61 (hexane : ethyl acetate = 10:1).

¹H NMR (400 MHz, CDCl₃) δ 7.53 (dd, *J* = 15.1, 11.6 Hz, 1H), 5.99 (d, *J* = 11.5 Hz, 1H), 5.76 (d, *J* = 15.1 Hz, 1H), 4.17 – 4.08 (m, 3H), 2.45 – 2.16 (m, 2H), 1.87 (s, 3H), 1.68 – 1.54 (m, 4H), 1.45 – 1.28 (m, 4H), 1.20 – 1.13 (m, 1H), 1.04-1.02 (m, *J* = 3.6 Hz, 21H), 0.96 – 0.85 (m, 9H).

¹³C NMR (100 MHz, CDCl₃) δ 167.74, 146.99, 140.56, 125.81, 119.05, 71.91, 64.02, 47.32, 44.33, 30.76, 22.17, 21.95, 19.15, 18.17, 18.15, 17.73, 13.68, 12.91, 12.64, 12.55.

FTIR (NaCl, cm^{-1}): 3053.32, 2960.73, 2945.30, 1703.14, 1633.71, 1463.97, 1421.54, 1309.67, 1265.30, 894.97, 883.40.

HRMS (ESI) m/z calculated for $C_{26}H_{51}O_3Si$ $[M+H]^+$: 439.3607, found 439.3618.

(2*E*,4*E*)-1-Butyl 11-methyl 5-methyl-7-((triisopropylsilyl)oxy)undeca-2,4-dienedioate (3g)

This compound was prepared by the general procedure described above and was

obtained as a colorless oil of inseparable mixture ($E/Z = 75:25$) in 62% yield, ^1H and ^{13}C NMR are described for the E isomer: $R_f = 0.51$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.55 (dd, $J = 15.1, 11.6$ Hz, 1H), 6.02 (d, $J = 11.7$ Hz, 1H), 5.80 (d, $J = 15.2$ Hz, 1H), 4.26 – 4.10 (m, 2H), 4.10 – 3.98 (m, 1H), 3.65 (s, 3H), 2.54 – 2.22 (m, 4H), 1.91 (s, 3H), 1.78 – 1.58 (m, 4H), 1.52 – 1.32 (m, 4H), 1.07-1.05 (m, 21H), 0.95 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 173.82, 167.63, 146.13, 140.37, 125.82, 119.44, 70.47, 64.02, 51.40, 47.63, 35.96, 34.12, 30.75, 19.99, 19.14, 18.10, 13.68, 12.66, 12.59.

FTIR (NaCl, cm^{-1}): 3018.60, 2958.80, 2943.37, 2866.22, 1739.79, 1724.36, 1701.22, 1635.64, 1610.56, 1382.96, 1363.67, 1265.30, 1215.15, 1159.22, 979.84, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{26}\text{H}_{49}\text{O}_5\text{Si}$ $[\text{M}+\text{H}]^+$: 469.3349, found 469.3360.

(2*E*,4*E*)-Butyl 5-methyl-7-(*p*-tolyl)-7-((triisopropylsilyl)oxy)hepta-2,4-dienoate (3h)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 75:25$) in 47% yield, ^1H and ^{13}C NMR are described for the E isomer: $R_f = 0.67$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.48 (dd, $J = 15.1, 11.7$ Hz, 1H), 7.31 – 6.92 (m, 4H), 5.82 (d, $J = 11.7$ Hz, 1H), 5.69 (d, $J = 15.1$ Hz, 1H), 4.86 (t, $J = 6.4$ Hz, 1H), 4.13 (t, J

= 6.7 Hz, 2H), 2.62 (dd, J = 12.8, 6.2 Hz, 1H), 2.41 (dd, J = 14.6, 8.0 Hz, 1H), 2.31 (s, 3H), 1.77 (s, 3H), 1.68 – 1.56 (m, 2H), 1.46 – 1.33 (m, 2H), 1.10 – 0.81 (m, 24H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.73, 145.65, 141.73, 140.54, 136.59, 128.55, 126.40, 125.85, 119.14, 74.36, 64.00, 51.95, 30.75, 21.10, 19.14, 18.47, 17.96, 17.89, 13.70, 12.28.

FTIR (NaCl, cm^{-1}): 2958.80, 2943.37, 2866.22, 1708.93, 1635.64, 1610.56, 1463.97, 1382.96, 1265.30, 1213.23, 1087.85, 1064.71, 995.27, 979.84, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{28}\text{H}_{47}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 459.3294, found 459.3310.

(2*E*,4*E*)-Butyl 7-(4-chlorophenyl)-5-methyl-7-((triisopropylsilyl)oxy)hepta-2,4-dienoate (3i)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture (E/Z = 75:25) in 46% yield. The stereochemistry was deduced by NOESY correlation analysis. ^1H and ^{13}C NMR are described for the *E* isomer: R_f = 0.65 (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.46 (dd, J = 15.1, 11.6 Hz, 1H), 7.33 – 6.97 (m, 4H), 5.78 (d, J = 11.6 Hz, 1H), 5.70 (d, J = 15.2 Hz, 1H), 4.88 (t, J = 6.3 Hz, 1H), 4.18 – 4.00 (m, 2H), 2.62 (dd, J = 12.9, 5.8 Hz, 1H), 2.41 (dd, J = 12.8, 6.9 Hz, 1H), 1.78 (s,

3H), 1.67 – 1.45 (m, 2H), 1.45 – 1.34 (m, 2H), 1.08 – 0.90 (m, 24H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.62, 144.64, 143.22, 140.20, 132.74, 128.11, 127.29, 126.76, 119.59, 73.84, 64.07, 51.76, 30.74, 19.14, 18.50, 17.94, 17.87, 13.70, 12.21.

FTIR (NaCl, cm^{-1}): 3053.32, 3020.53, 2958.80, 2943.37, 2866.22, 1705.07, 1633.71, 1610.56, 1463.97, 1384.89, 1307.74, 1265.30, 997.20, 979.84, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{27}\text{H}_{44}\text{O}_3\text{SiCl}$ $[\text{M}+\text{H}]^+$: 479.2748, found 479.2759.

(2*E*,4*E*)-Butyl 5-methyl-7-(4-(trifluoromethyl)phenyl)-7-((triisopropylsilyl)oxy)hepta-2,4-dienoate (3j)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture (*E/Z* = 75:25) in 37% yield, ^1H and ^{13}C NMR are described for the *E* isomer: R_f = 0.67 (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.62 – 7.30 (m, 5H), 5.77 (d, J = 11.6 Hz, 1H), 5.69 (d, J = 15.2 Hz, 1H), 4.98 (t, J = 6.3 Hz, 1H), 4.27 – 4.04 (m, 2H), 2.64 (dd, J = 12.9, 5.7 Hz, 1H), 2.44 (dd, J = 12.9, 6.7 Hz, 1H), 1.79 (s, 3H), 1.68 – 1.54 (m, 2H), 1.45 – 1.33 (m, 2H), 1.13 – 0.81 (m, 24H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.64, 148.71, 144.25, 140.11, 129.46 (q, $J = 32$ Hz), 126.95, 126.24, 124.98 (q, $J = 4$ Hz), 124.18 (q, $J = 270$ Hz), 119.78, 73.97, 64.13, 51.68, 30.75, 19.16, 18.52, 17.94, 17.88, 13.70, 12.25.

FTIR (NaCl, cm^{-1}): 3053.32, 3018.60, 2960.73, 2945.30, 2866.22, 1701.22, 1635.64, 1618.28, 1463.97, 1419.61, 1325.10, 1309.67, 1265.30, 1215.15, 1165.00, 1126.43, 979.84, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{28}\text{H}_{44}\text{O}_3\text{SiF}_3$ $[\text{M}+\text{H}]^+$: 513.3012, found 513.3006.

(2*E*,4*E*)-Butyl5-methyl-7-((triisopropylsilyl)oxy)hepta-2,4-dienoate (3k)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 67:33$) in 30% yield, ^1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.51$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.57 (dd, $J = 15.2, 11.5$ Hz, 1H), 6.02 (d, $J = 10.8$ Hz, 1H), 5.78 (d, $J = 15.2$ Hz, 1H), 4.14 (td, $J = 6.7, 3.2$ Hz, 2H), 3.79 (dt, $J = 9.7, 6.6$ Hz, 2H), 2.53 (t, $J = 6.6$ Hz, 1H), 2.36 (t, $J = 6.6$ Hz, 1H), 1.92 (s, 3H), 1.71 – 1.60 (m, 2H), 1.47 – 1.33 (m, 2H), 1.13 – 0.99 (m, 21H), 0.94 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.78, 147.00, 140.71, 124.78, 119.14, 64.06, 61.96, 43.54, 30.79, 19.18, 17.96, 13.73, 11.94, 11.91.

FTIR (NaCl, cm^{-1}): 3053.32, 2958.80, 2943.37, 2866.22, 1701.22, 1635.64, 1610.56, 1463.97, 1265.30, 1159.22, 1101.35, 979.84, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{41}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 369.2825, found 369.2838.

(2*E*,4*E*)-Butyl 7-acetoxy-5-methylhepta-2,4-dienoate (3k')

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 67:33$) in 32% yield, ^1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.25$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.52 (dd, $J = 25.9, 10.7$ Hz, 1H), 6.00 (d, $J = 11.5$ Hz, 1H), 5.80 (d, $J = 15.2$ Hz, 1H), 4.27 – 3.85 (m, 4H), 2.59 (t, $J = 6.7$ Hz, 1H), 2.44 (t, $J = 6.7$ Hz, 1H), 2.01 (s, 3H), 1.90 (s, 3H), 1.67 – 1.56 (m, 2H), 1.48 – 1.31 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (400 MHz, CDCl_3) δ 170.88, 167.48, 144.67, 140.13, 125.16, 120.06, 64.11, 62.05, 38.99, 30.74, 20.84, 19.13, 17.32, 13.69.

FTIR (NaCl, cm^{-1}): 3055.24, 2960.73, 2873.94, 1734.01, 1705.07, 1637.56, 1612.49, 1384.89, 1365.60, 1159.22, 1139.93, 738.74, 704.02.

HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{23}\text{O}_4$ $[\text{M}+\text{H}]^+$: 255.1596, found 255.1601.

(2*E*,4*E*)-Butyl 8-(benzyloxy)-5-methyl-7-((triisopropylsilyl)oxy)octa-2,4-dienoate (3l)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 75:25$) in 51% yield, ^1H and ^{13}C NMR are described for the E isomer: $R_f = 0.51$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.55 (dd, $J = 15.1, 11.7$ Hz, 1H), 7.38 – 7.23 (m, 5H), 6.04 (d, $J = 11.4$ Hz, 1H), 5.76 (d, $J = 15.1$ Hz, 1H), 4.49 (d, $J = 4.0$ Hz, 2H), 4.13 (dt, $J = 6.8, 4.4$ Hz, 3H), 3.50 – 3.28 (m, 2H), 2.65 – 2.32 (m, 2H), 1.93 (s, 3H), 1.70 – 1.61 (m, 2H), 1.47 – 1.34 (m, 2H), 1.05-1.03(m, 21H), 0.95 (t, $J = 7.6$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.77, 146.25, 140.58, 138.25, 128.30, 127.67, 127.56, 126.06, 119.23, 73.93, 73.33, 70.35, 64.07, 45.73, 30.80, 19.19, 18.33, 18.09, 18.07, 13.74, 12.53.

FTIR (NaCl, cm^{-1}): 3053.32, 3020.53, 2960.73, 2943.37, 2866.22, 1703.14, 1633.71, 1610.56, 1454.33, 1386.82, 1365.60, 1307.74, 1265.30, 979.84, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{29}\text{H}_{49}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 489.3400, found 489.3403.

(2*E*,4*E*)-*tert*-Butyl 6-hydroxy-5-methyl-6-phenylhexa-2,4-dienoate (6a)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 74% yield with $E/Z = 83:17$, and the E/Z isomer can be separated by column; The stereochemistry was deduced by NOESY correlation analysis. For the E isomer $R_f = 0.21$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.48 (dd, $J = 15.2, 11.6$ Hz, 1H), 7.38 – 7.19 (m, 5H), 6.46 (d, $J = 11.6$ Hz, 1H), 5.86 (d, $J = 15.2$ Hz, 1H), 5.13 (s, 1H), 2.67 (s, 1H), 1.70 (s, 3H), 1.48 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.77, 148.22, 141.40, 139.09, 128.44, 127.82, 126.51, 123.26, 122.54, 80.23, 78.36, 28.09, 13.69.

FTIR (NaCl, cm^{-1}): 3446.79, 3016.67, 2980.02, 1693.50, 1637.56, 1612.49, 1492.90, 1454.33, 1392.61, 1367.53, 1315.45, 1280.73, 1257.59, 1215.15, 979.84, 848.68.

HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{23}\text{O}_3$ $[\text{M}+\text{H}]^+$: 275.1647, found 275.1639.

The minor Z isomer was contaminated with an inseparable unknown compound (10%), $R_f = 0.24$ (hexane: ethyl acetate =10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.77 (dd, $J = 15.0, 11.8$ Hz, 1H), 7.43 – 7.22 (m, 5H), 6.11 (d, $J = 11.8$ Hz, 1H), 6.00 (s, 1H), 5.84 (d, $J = 15.0$ Hz, 1H), 2.23 (s, 1H), 1.74 (s, 3H), 1.50 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 166.69, 147.94, 141.40, 137.86, 128.35, 127.36, 125.71, 125.52, 123.45, 80.40, 70.99, 28.18, 18.37.

FTIR (NaCl, cm^{-1}): 3446.79, 3055.32, 2980.02, 2931.80, 1697.36, 1663.71, 1606.70, 1450.47, 1421.54, 1392.61, 1265.30, 1217.08, 894.97, 848.68.

HRMS (ESI) m/z calculated for $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1647, found 275.1655.

(2*E*,4*E*)-*tert*-Butyl 6-hydroxy-5-methyltrideca-2,4-dienoate (6b)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 80:20$) in 56% yield. 1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.43$ (hexane : ethyl acetate = 10:1).

1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, $J = 15.0, 11.7$ Hz, 1H), 6.13 (d, $J = 11.6$ Hz, 1H), 5.77 (d, $J = 15.2$ Hz, 1H), 4.06 (t, $J = 6.4$ Hz, 1H), 2.17 (s, 1H), 1.82 (s, 3H), 1.47 (s, 9H), 1.29-1.23 (m, 12H), 0.85 (t, $J = 6.5$ Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.82, 149.54, 139.14, 122.74, 122.70, 80.17, 76.88, 35.02, 31.73, 29.43, 29.16, 28.11, 25.50, 22.57, 14.01, 12.87.

FTIR (NaCl, cm^{-1}): 3446.79; 2927.94, 1695.43, 1685.79, 1637.56, 1367.53, 1313.52, 1282.66, 1215.15, 1151.50, 1138.00, 979.84, 755.10.

HRMS (ESI) m/z calculated for $C_{18}H_{33}O_3$ $[M+H]^+$: 297.2430, found 297.2440.

(2*E*,4*E*)-*tert*-Butyl 6-hydroxy-5-methyl-8-phenylocta-2,4-dienoate (6c)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture (*E/Z* = 80:20) in 58% yield, ^1H and ^{13}C NMR are described for the *E* isomer: R_f = 0.35 (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.49 (dd, J = 15.1, 11.6 Hz, 1H), 7.35 – 7.09 (m, 5H), 6.17 (d, J = 11.5 Hz, 1H), 5.80 (d, J = 15.2 Hz, 1H), 4.10 (t, J = 6.4 Hz, 1H), 2.75 – 2.52 (m, 2H), 2.16 (d, J = 17.0 Hz, 1H), 1.88 (dd, J = 8.5, 5.8 Hz, 2H), 1.85 (s, 3H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.78, 149.15, 141.56, 139.01, 128.35, 128.30, 125.85, 122.92, 122.88, 80.23, 75.99, 36.51, 31.75, 28.11, 12.98.

FTIR (NaCl, cm^{-1}): 3431.36, 3014.74, 2980.02, 2931.80, 1695.43, 1685.79, 1637.56, 1367.53, 1313.52, 1282.66, 1217.08, 1147.65, 979.84, 756.10.

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{27}\text{O}_3$ $[\text{M}+\text{H}]^+$: 303.1960, found 303.1952.

(2*E*,4*E*,7*E*)-*tert*-Butyl 6-hydroxy-5,7-dimethylnona-2,4,7-trienoate (6d)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture (*E/Z* = 84:16) in 50% yield, ^1H and ^{13}C NMR are described for the *E* isomer: R_f = 0.38 (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.48 (dd, $J = 15.0, 11.7$ Hz, 1H), 6.32 (d, $J = 11.6$ Hz, 1H), 5.80 (d, $J = 15.2$ Hz, 1H), 5.62 – 5.51 (m, 1H), 4.43(s, 1H), 1.70 (s, 3H), 1.61 (d, $J = 6.5$ Hz, 5H), 1.50 – 1.39 (m, 12H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.92, 147.35, 139.28, 135.24, 122.81, 122.56, 122.21, 81.24, 80.09, 28.09, 13.93, 13.18, 11.10.

FTIR (NaCl, cm^{-1}): 3446.79, 3014.74, 2980.02, 2931.80, 2920.23, 1693.50, 1635.64, 1612.49, 1456.26, 1392.61, 1367.53, 1313.52, 1280.73, 1215.15, 1149.57, 1136.07, 1049.28, 979.84, 848.68.

HRMS (ESI) m/z calculated for $\text{C}_{15}\text{H}_{25}\text{O}_3$ $[\text{M}+\text{H}]^+$: 253.1804, found 253.1799.

(2*E*,4*E*)-*tert*-Butyl 6-hydroxy-5-methyl-6-(4-(trifluoromethyl)phenyl)hexa-2,4-dienoate (6e)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 61% yield with $E/Z = 80:20$, and the E/Z isomer can be separated by column, for the E isomer $R_f = 0.25$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.66 – 7.39 (m, 5H), 6.45 (d, $J = 11.6$ Hz, 1H), 5.91 (d, $J = 15.2$ Hz, 1H), 5.26 (s, 1H), 2.16 (d, $J = 2.6$ Hz, 1H), 1.72 (s, 3H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.53, 147.02, 145.18, 138.53, 130.10 (q, $J = 32$ Hz), 126.73, 125.47 (q, $J = 4$ Hz), 124.30, 124.06 (q, $J = 270$ Hz), 123.86, 80.46, 78.14, 28.17, 13.29.

FTIR (NaCl, cm^{-1}): 3018.60, 2980.02, 2927.94, 1689.64, 1325.10, 1215.15, 1130.29, 1066.64, 756.10.

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{22}\text{O}_3\text{F}_3$ $[\text{M}+\text{H}]^+$: 343.1521, found 343.1515.

The minor *Z* isomer was contaminated with an inseparable unknown compound (10%), $R_f = 0.26$ (hexane: ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.74 (dd, $J = 14.9, 11.8$ Hz, 1H), 7.59 (d, $J = 8.2$ Hz, 2H), 7.48 (d, $J = 8.1$ Hz, 2H), 6.15 (d, $J = 11.8$ Hz, 1H), 6.05 (s, 1H), 5.88 (d, $J = 15.0$ Hz, 1H), 2.36 (s, 1H), 1.70 (s, 3H), 1.50 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.62, 146.99, 145.28, 137.32, 129.58 (q, $J = 32$ Hz), 126.29, 125.87, 125.27 (q, $J = 4$ Hz), 124.12 (q, $J = 270$ Hz), 124.08, 80.64, 70.33, 28.16, 18.13.

FTIR (NaCl, cm^{-1}): 3018.60, 1701.22, 1325.10, 1215.15, 756.10, 669.30.

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{22}\text{O}_3\text{F}_3$ $[\text{M}+\text{H}]^+$: 343.1521, found 343.1529.

(2*E*,4*E*)-*tert*-Butyl 6-hydroxy-6-(4-methoxyphenyl)-5-methylhexa-2,4-dienoate (6f)

This compound was prepared by the general procedure described above and was obtained as a colorless oil in 56% yield with $E/Z = 80:20$, and the E/Z isomer can be separated by column, for the E isomer $R_f = 0.21$ (hexane : ethyl acetate = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, $J = 15.2, 11.7$ Hz, 1H), 7.23 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.48 (d, $J = 11.5$ Hz, 1H), 5.87 (d, $J = 15.2$ Hz, 1H), 5.10 (s, 1H), 3.79 (s, 3H), 2.35 (s, 1H), 1.71 (s, 3H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.84, 159.34, 148.42, 139.19, 133.64, 127.94, 123.22, 122.16, 113.94, 80.25, 77.96, 55.28, 28.18, 14.03.

FTIR (NaCl, cm^{-1}): 3444.87, 2976.16, 2929.87, 1712.79, 1693.50, 1643.35, 1633.71, 1367.53, 1311.59, 1172.72, 1149.57, 1035.77, 981.77, 833.25.

HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+$: 305.1753, found 305.1742.

The minor Z isomer was contaminated with an inseparable unknown compound (10%), $R_f = 0.22$ (hexane: ethyl acetate =10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.76 (dd, $J = 15.0, 11.8$ Hz, 1H), 7.27 (d, $J = 10.6$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 6.09 (d, $J = 11.8$ Hz, 1H), 5.95 (s, 1H), 5.82 (d, $J = 15.0$ Hz, 1H), 3.80 (s, 3H), 2.05 (s, 1H), 1.75 (s, 3H), 1.50 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.71, 158.94, 148.19, 137.94, 133.59, 126.78, 125.45, 123.33, 113.79, 80.37, 70.87, 55.28, 28.21, 18.49.

FTIR (NaCl, cm^{-1}): 3016.67, 2978.09, 2927.94, 1699.29, 1510.26, 1301.95, 1249.87, 1215.15, 1147.65, 758.02, 667.37.

HRMS (ESI) m/z calculated for $C_{18}H_{25}O_4$ $[M+H]^+$: 305.1753, found 305.1752

(2*E*,4*E*)-*tert*-Butyl 6-hydroxy-5,7,7-trimethylocta-2,4-dienoate (6g)

This compound was prepared by the general procedure described above and was obtained as a colorless oil of inseparable mixture ($E/Z = 91:9$) in 53% yield, 1H and ^{13}C NMR are described for the *E* isomer: $R_f = 0.45$ (hexane : ethyl acetate = 10:1).

1H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, $J = 15.2, 11.6$ Hz, 1H), 6.08 (d, $J = 11.5$ Hz, 1H), 5.76 (d, $J = 15.2$ Hz, 1H), 3.80 (s, 1H), 1.89 (s, 3H), 1.46 (s, 9H), 0.90 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.81, 148.61, 138.89, 125.30, 122.55, 84.21, 80.13, 36.03, 28.09, 26.47, 15.61.

FTIR (NaCl, cm^{-1}): 3468.01, 3018.60, 2976.16, 2956.87, 1693.50, 1631.78, 1608.63, 1367.53, 1315.45, 1282.66, 1215.15, 1151.50, 1134.14, 979.84, 756.10.

HRMS (ESI) m/z calculated for $C_{15}H_{27}O_3$ $[M+H]^+$: 255.1960, found 255.1966.

CHAPTER 3

Research Towards the Total Synthesis of Palmerolide A

3.1 Introduction

Recently, Baker's⁶² group isolated a macrolide natural product from the antarctic marlin tunicate *Synoicum adareanum* and termed it palmerolide A. This macrolide exhibits strong cytotoxicity (LC_{50} = 18 nM) against the melanoma cancer cell line UACC-62, and displays selective antitumor activity against renal cancer cell line RXF 393 (LC_{50} = 6.5 μ M) and colon cancer cell line HCC- 2998 (LC_{50} = 6.5 μ M). From a synthetic viewpoint, palmerolide A is a challenging structure featuring a 20-membered α,β -unsaturated lactone ring with an enamide side chain, five chiral centers, a labile carbamate moiety, and a 1,3-diene motif within the macrocyclic core. On the basis of Mosher's ester stereochemical analysis and high-field NMR spectroscopic studies, the structure of palmerolide A was suggested to be **1a** (Figure 3.1). However, after De Brabander's first total synthesis⁶³ of the originally proposed structure **1a**, they found that it was a diastereomer of palmerolide A. Based on the synthesis results and spectral analysis, they deduced the correct structure of palmerolide A to be [*ent*-(19-*epi*-20-*epi*-**1a**)], as shown in **1b**. In fact, synthetic **1b** exhibited identical physical properties (¹H and ¹³C NMR, and MS) to the reported natural palmerolide A. In addition, the circular dichroism (CD) spectrum and sign of optical rotation of synthetic **1b** also proved identical to those of the reported natural product.

⁶²Diyabalanage, T. Amsler, C. D. James B. McClintock, J. B. Baker, B. J. *J. Am. Chem. Soc.* **2006**, 128, 5630.

⁶³Jiang, X. Liu, B. Lebreton, S. De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, 129, 6386.

Figure 3.1

3.2 Previous Synthetic Work

In view of its structural challenge and potential bioactivity, numerous total syntheses of palmerolide A have been reported since its isolation in 2006. In 2007, De Brabander reported the first total synthesis of the originally proposed palmerolide A and made a structure revision of the natural product. By means of Suzuki coupling between fragments **3** and **4**, the diene moiety was assembled, followed by Yamaguchi esterification with enoic acid **2**, and an intramolecular Horner-Wadsworth-Emmons olefination *via* a β -keto-phosphonate to complete the macrolide core (Scheme 3.1). Finally, Curtius rearrangement and isocyanate transformation with 2-Me-

propenylmagnesium provided the *N*-acyl dienamine⁶⁴ segment to furnish the molecule.

Scheme 3.1

Nicolaou⁶⁵ and co-workers demonstrated synthesis of the revised structure of palmerolide A, as well as the originally proposed structure and its enantiomer, *via* the Stille coupling of fragment **7** with **8**, followed by Yamaguchi esterification with **9**, and ring-closing metathesis to form the macrocycle. After several ensuing transformations, at last synthesis of the molecule was completed by an enamide coupling reaction (Scheme 3.2).

⁶⁴Wu, Y.; Liao, X.; Wang, R.; Xie, X. S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245.

⁶⁵(a) Nicolaou, K. C.; Guduru, R.; Sun, Y. P.; Banerji, B.; Chen, David, Y. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 5896. (b) Nicolaou, K. C.; Sun, Y. P.; Guduru, R.; Banerji, B.; Chen, David, Y. K. *J. Am. Chem. Soc.* **2008**, *130*, 3633.

Scheme 3.2

Recently, Hall⁶⁶ and co-workers successfully synthesized the revised palmerolide A by employing an asymmetric organoboron methodology for C–C bond construction developed in their laboratory. The retrosynthetic analysis (Scheme 3.3) highlights a B-alkyl Suzuki coupling between fragment **10** and **11**, followed by an intramolecular Yamaguchi esterification to close the macrocycle.

⁶⁶Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216.

Scheme 3.3 Retrosynthesis of the revised palmerolide A

Fragment **10** was obtained by application of their enantioselective crotylboration catalyzed by chiral Brønsted acid.⁶⁷ Fragment **11** was synthesized from pyran **12**, which was prepared from the alkenyl boronate substrate **13** via an unprecedented

⁶⁷(a) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (b) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (c) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236.

Claisen-Ireland [3,3]-sigmatropic rearrangement.⁶⁸ Besides the above mentioned total syntheses, four formal syntheses,⁶⁹ and a few partial synthetic methods have also been reported.⁷⁰

In this chapter, we will focus on the application of our Pd-catalyzed cross-coupling reaction to the construction of the 1,3-diene core of palmerolide A, and progress towards the total synthesis of the molecule.

3.3 Retrosynthetic Analysis of Palmerolide A

The proposed retrosynthesis of palmerolide A foresaw a connection of three fragments, involving the assembly of fragments **16** and **15** via a Wittig reaction to construct the C21 and C22 double bond, then an enamide coupling with fragment **14** to furnish the molecule. The macrocycle **16** can be derived from a ring-closing metathesis of fragment **17**, which can be prepared from **18** and **19** through Yamaguchi esterification. The fragment **18**, which embeds the *E*-dienic alcohol unit, could be readily accessed using our cross-coupling method between **21** and butyl acrylate (**22**), followed by several chemical transformations.

⁶⁸(a) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (b) Pietruszka, J.; Schöne, N. *Eur. J. Org. Chem.* **2004**, 5011.

⁶⁹(a) Pujari, S. A.; Gowrisankar, P.; Kaliappan, K. P. *Chem. Asian J.* **2011**, *6*, 3137. (b) Prasad, K. R.; Pawar, A. B. *Org. Lett.* **2011**, *13*, 4252. (c) Gowrisankar, P.; Pujari, S. A.; Kaliappan, K. P. *Chem. Eur. J.* **2010**, *16*, 5858. (d) Jaegel, J.; Maier, M. E. *Synthesis*. **2009**, *17*, 2881.

⁷⁰(a) Kaliappan, K. P.; Gowrisankar, P. *Synlett* **2007**, 1537. (b) Cantagrel, G.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2983. (c) Chandrasekhar, S.; Vijeender, K.; Chandrashekar, G.; Reddy, C. R. *Tetrahedron:Asymmetry* **2007**, *18*, 2473. (d) Jägel, J.; Schmauder, A.; Binanzer, M.; Maier, M. *Tetrahedron*. **2007**, *63*, 13006. (e) Jones, D. M.; Dudley, G. B. *Synlett* **2010**, 223. (f) Lebar, M. D.; Baker, B. J. *Tetrahedron*. **2010**, *66*, 1557.

Scheme 3.4

As depicted in Scheme 3.5, there are two general approaches for the synthesis of precursor **18**, both involving a S_N2 nucleophilic substitution as key step, albeit in

different sequences. In route A, we intended to assemble **18** through S_N2 nucleophilic substitution of the sulfonate intermediate **24** treated with LDA, followed by the addition of Cl-substituted **23**. Approach B revealed the formation of C12–C13 through a S_N2 substitution reaction of either the acetate **30** with Grignard reagent **29**, or the triflate **27** with ester enolate **28**, to construct aldehyde **25**, followed by the diastereo- and enantio-selective addition of [(Z)-γ-(methoxymethoxy)allyl]-(+)-diisopinocampheylborane⁷¹ to afford the corresponding fragment **18**.

Scheme 3.5

3.4 Preliminary Studies

3.4.1 Synthesis of dienoic acid **19**

⁷¹Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535.

For the synthesis of fragment **19**, we initially conducted the monoprotection of commercially available 1,5-diols **31** (Scheme 3.6). The primary alcohol was subjected to PCC oxidation to yield aldehyde **33**, allowing for Grignard reaction with vinyl magnesium bromide at -78°C to afford the allylic alcohol **34** in 70% yield. Sharpless kinetic resolution⁷² of alcohol **34** was carried out with D-(-)-DIPT, $t\text{BuOOH}$ and $\text{Ti}(\text{OPr})_4$ in the presence of CaH_2 at -22°C , providing the chiral allylic alcohol **35** (96% ee based on Mosher's ester derivative) in good yield. Upon treatment of the enantiomerically enriched allylic alcohol **35** with TIPSOTf gave the TIPS ether **36**. Selective cleavage of the primary TBS ether **36** and Dess-Martin oxidation, followed by Wittig reaction afforded the dienoate **38**, which could be easily transformed to dienoic acid **19** through saponification.

Scheme 3.6

⁷²(a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Mulzer, J.; Böhm, I.; Bats, J. W. *Tetrahedron Lett.* **1998**, *39*, 9643.

3.4.2 Synthesis of esterification precursor 18

3.4.2.1 Synthesis of sulfonate intermediate 24 (Route A)

Scheme 3.7 summarized the construction of the sulfonate intermediate **24** commencing from commercially available dimethyl-D-tartrate (**39**). Protection of the 1,2-diol **39** with 2,2-dimethoxypropane and subsequent selective mono reduction with NaBH₄ provided the primary alcohol **41**. Treatment of **41** with I₂ in the presence of PPh₃ and imidazole afforded the iodide **42**, which was converted into the corresponding sulfonate intermediate **24** using standard protocol in 85% yield.

Scheme 3.7

3.4.2.2 Synthesis of 1-chloro-2,4-diene substrate 23 (Route A)

The synthesis of diene substrate **20** employs the commercially available optically pure alcohol **43** (Scheme 3.8). As described in the literature, a three step protocol involving protection of **43** with PMB, reduction and Dess-Martin oxidation yielded the

corresponding aldehyde **44**.⁷³

Scheme 3.8

While numerous conditions for allylation of aldehyde **44** with

⁷³(a) Luo, J. L.; Li, H. M.; Wu, J. L.; Xing, X. L.; Dai, W. M. *Tetrahedron*. **2009**, 65, 6828. (b) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, 117, 12011. (c) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, 124, 6981.

methallyltrimethylsilane (**45**) were examined,⁷⁴ the diastereoselective allylation product **46** (91:9) could be obtained in moderate yield (65%) only by presumed chelation-control through hexa-coordinated tin intermediates,⁷⁵ which was then protected as the TIPS ether **47**. Subsequent selective cleavage of the primary PMB group and protection smoothly yielded⁷⁶ **48** in 79% yield over 2 steps. Applying the optimal condition described in the Chapter 2, the terminal alkene **48** was subjected to the direct coupling reaction. It is noteworthy that the Ac-substituted substrate proved to be the best choice for executing the coupling strategy, which in this case, the desired diene **20** was generated in moderate yield (69%) and a respectable 80:20 *E:Z* ratio. Further studies revealed that this reaction could routinely be conducted on a 10-mmol scale in 71% yield, without decrease in the *E/Z* selectivity.

According to our synthetic plan, we progressed toward the synthesis of fragment

⁷⁴We tried the reaction using boron trifluoride diethyl etherate as Lewis Acid, the allylation product was obtained in 70%, but *dr* was 50:50. When using TiCl₄ as the Lewis Acid, only trace allylation product was obtained.

⁷⁵We also changed the protecting group from PMB to TBDPS, but the yield and *dr* decreased dramatically.

⁷⁶Firstly the PMB-substituted alkene **47** allowed for the direct coupling reaction, however, the yield was quite low. Then we turned our attention to change the protecting group on the terminal position. Interestingly, the acetyl and benzoyl substituted intermediates **48** gave significant better results, as shown below.

18 from the coupling product **20** (Scheme 3.9). Deprotection of ester **20** under basic condition gave the corresponding free alcohol **49** in high yield. Subsequent protection of primary alcohol **49** afforded the TBDPS ether, which was subjected to DIBAL-H reduction to provide alcohol **51** in high yield. Fortunately, the resulting diastereomeric *syn*-**51** and *anti*-**51'** (91:9) could be separated by column chromatography, though the *E* and *Z* isomers (80:20) were inseparable.

With the allylic alcohol **51** in hand, we continued with the construction of fragment **18** according to the above-mentioned route A in Scheme 3.5. Unfortunately, all attempts to convert the hydroxyl group to either a chloride or a bromide, using methods such as PPh₃/CCl₄,⁷⁷ Me₂S/NCS,⁷⁸ MeSO₂Cl/LiCl/*s*-collidine,⁷⁹ C₅H₅N//MeSO₂Cl/LiCl,⁸⁰ 4-DMAP/*p*-tosyl chloride,⁸¹ CBr₄/1,2-DPPE,⁸² and CBr₄/PPh₃,⁸³ were proved futile (Scheme 3.9). In most cases, S_N2' products were observed from the crude ¹H NMR. So we decided to abandon the choice of route A to access fragment **18**.

⁷⁷Ohyoshi, T.; Miyazawa, Y.; Aoki, K.; Ohmura, S.; Asuma, Y.; Hayakawa, I.; Kigoshi, H. *Org. Lett.* **2011**, *13*, 2160.

⁷⁸Burghart-Stoll, H.; Kapferer, T.; Brückner, R. *Org. Lett.* **2011**, *13*, 1016.

⁷⁹Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

⁸⁰Zhao, Y. J.; Loh, T. P. *Org. Lett.* **2008**, *10*, 2143.

⁸¹Joo, J. E.; Lee, K. Y.; Pham, V. T.; Tian, Y. S.; Ham, W. H. *Org. Lett.* **2007**, *9*, 3627.

⁸²Ogawa, S.; Urabe, D.; Yokokura, Y.; Arai, H.; Arita, M.; Inoue, M. *Org. Lett.* **2009**, *11*, 3602.

⁸³Guindon, Y.; Delorme, D.; Lau, C. K.; Zamboni, R. *J. Org. Chem.* **1988**, *53*, 267.

acetyl and Grignard reagent⁸⁴ catalyzed by Cu salts, we attempted to employ this method for the preparation of the precursor to fragment **18**. The results are summarized in Table 3.1. No desired product was detected, with only the recovery of starting material, even though one equivalent of catalyst was added, and the reaction system was allowed to warm to room temperature.

Table 3.1 Coupling reaction between acetyl and Grignard reagent

Entry	catalyst	T (°C)	Product
1	CuI	−20→rt	Nil
2	Li ₂ CuCl ₄	−20→rt	Nil.
3	CuCN	−20→rt	Nil.
4	CuBr	−20→rt	Nil.

3.5 Conclusion

The C13–C21 fragment (**51**) of Palmerolide A has been successfully synthesized using our self-developed direct 1,3-diene construction methodology in high yield and

⁸⁴(a) Backvall, J. E.; Sellen, M. *J. Chem. Soc., Chem. Commun.*, **1987**, 827. (b) Backvall, J. E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615. (c) Tønder, J. E.; Hosseini, M.; Ahrenst, A. B.; Tanner, D. *Org. Biomol. Chem.*, **2004**, *2*, 1447. (d) Lu, X. Q.; Bittman, R. *Tetrahedron Lett.* **2005**, *46*, 1873. (e) Umezawa, T.; Shibata, M.; Kaneko, K.; Okino, T.; Matsuda, F. *Org. Lett.* **2011**, *13*, 904.

moderate diastereoselectivity. In addition, the C1–C9 fragment of the molecule was also synthesized, awaiting further transformation. Having successfully obtained the diene allylic alcohol **51**, further investigation into the synthesis of **25** is currently underway in our laboratory, as outlined in Scheme 3.11, involving introduction of a better leaving group like triflate instead of acetate, followed by boron-based crotylation, Yamaguchi esterification, ring-closing metathesis, Wittig reaction, Takai olefination, and finally enamide coupling to furnish the target molecule.

Scheme 3.11

3.6 Experimental Section

5-((tert-butyldimethylsilyl)oxy)pentan-1-ol (32)

To a suspension of NaH (60% in oil, 2.64 g, 66.0 mmol) in THF (80 mL) was added a solution of 1,5-pentanediol (6.29 mL, 60.0 mmol) in THF (20 mL) dropwise over 30 min at 0 °C. The reaction mixture was stirred for an additional 30 min and added a solution of TBSCl (10.9 g, 72.0 mmol) in THF (20 mL) dropwise over 40 min. Stirring was continued for 30 min and the reaction mixture was poured into crushed ice and extracted with Et₂O. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. Silica gel flash column chromatography (hexane/EtOAc, 20:1) afforded **32** (8.52 g, 65%) as a colorless oil. *R*_f = 0.22 (hexane/EtOAc, 5:1).

¹H NMR (400 MHz, CDCl₃) δ 3.58 (t, *J* = 6.5 Hz, 4H), 2.31 (s, 1H), 1.64 – 1.49 (m, 4H), 1.43 – 1.30 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 63.09, 62.55, 32.40, 32.34, 25.88, 21.94, 18.27, -5.38.

7-((tert-butyldimethylsilyl)oxy)hept-1-en-3-ol (34)

To a solution contained 4 Å MS (10.0 g), silica gel (10.0 g) and PCC (7.28 g, 33.8 mmol) in CH_2Cl_2 (60 mL) was added alcohol **32** (3.70 g, 16.9 mmol) at 0 °C, the solution was stirred at room temperature for 30 min, then diethyl ether (60 mL) was added, the reaction mixture was filter through a pad of silica gel and was washed with diethyl ether (200 mL). The combined organic extracts were concentrated *in vacuo*, The crude aldehyde **33** (2.67 g, 73%) was used without purification.

To another 100 mL round-bottom flask with a magnetic stirring bar was added the crude aldehyde **33** (2.67 g, 12.3 mmol) and anhydrous THF (20 mL). The solution was cooled to -78 °C prior to dropwise addition of vinylmagnesium bromide (14.8 mL, 1M in THF, 14.8 mmol). The reaction mixture was stirred at -78 °C for 2 h and quenched with aq NH_4Cl (20 mL), the mixture was extracted with ether (3 × 20 mL). The extracts were combined, washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure, and the residue was flash chromatographed (hexane/EtOAc = 15:1) to give allylic alcohol **34** (2.10 g, 70%) as a colorless oil. R_f = 0.45 (hexane/EtOAc, 5:1).

^1H NMR (400 MHz, CDCl_3) δ 5.84 (ddd, J = 16.9, 10.4, 6.2 Hz, 1H), 5.20 (d, J = 17.2 Hz, 1H), 5.08 (d, J = 10.4 Hz, 1H), 4.16 – 4.02 (m, 1H), 3.60 (t, J = 6.4 Hz, 2H), 1.81 (s, 1H), 1.60 – 1.47 (m, 4H), 1.44 – 1.34 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.20, 114.54, 73.12, 63.05, 36.66, 32.58, 25.93, 21.60, 18.32, -5.32.

(S)-7-((tert-butyldimethylsilyl)oxy)hept-1-en-3-ol (35)

To a solution of activated 4 Å MS (2 g) and CaH₂ (51.0 mg, 1.21 mmol) in 20 mL CH₂Cl₂ were added D-(-)-diisopropyl tartarate (0.370 mL, 1.74 mmol), Ti(OⁱPr)₄ (0.550 mL, 1.86 mmol) and ^tBuOOH (0.980 mL, 4.88 mmol) sequentially at -22 °C, the reaction mixture was stirred for 1h, followed by addition of the racemic allylic alcohol **34** (1.42 g, 5.81 mmol). The reaction mixture was stirred for 48 h at -22 °C and further it was kept in the freezer at -22 °C without stirring for 4 days. The reaction mixture was poured into a freshly prepared FeSO₄ (2.25 g, 8.08 mmol)/citric acid (0.859 g, 4.47 mmol) solution (15 mL H₂O) at 0 °C and stirred vigorously for 10 min. The molecular sieves were removed from the reaction mixture filtration. The organic layer was separated and the aqueous layer was extracted CH₂Cl₂ (3 x 20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. Purification by silica gel flash chromatography (hexane/EtOAc = 15:1) gave allylic alcohol **35** (0.570 g, 40%) as a colorless oil. R_f = 0.45 (hexane/EtOAc, 5:1).

[α]_D²⁵ = +5.4 (*c* 2.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 5.84 (ddd, *J* = 17.0, 10.4, 6.2 Hz, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.4 Hz, 1H), 4.13 – 4.01 (m, 1H), 3.60 (t, *J* = 6.4 Hz, 2H), 1.82 (s, 1H), 1.58 – 1.50 (m, 4H), 1.46 – 1.34 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 141.21, 114.53, 73.12, 63.05, 36.67, 32.58, 25.93,

21.60, 18.31, -5.33.

FTIR (NaCl, cm^{-1}): 3446.79, 3053.32, 2929.87, 2856.58, 1423.47, 1388.75, 1265.30, 1097.50, 837.11, 748.38.

HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{28}\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 267.1756, found 267.1745.

(S)-11,11-diisopropyl-2,2,3,3,12-pentamethyl-9-vinyl-4,10-dioxo-3,11-disilatridecane (36)

A solution of the allylic alcohol **35** (489 mg, 2.00 mmol) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.840 mL, 7.20 mmol) and TIPSOTf (0.810 mL, 3.00 mmol) at 0 °C. After stirring at 0 °C for 2 h, aq. NaHCO_3 was added followed by an extraction with ether. The combined organic extracts were washed with brine, dried and concentrated. The crude was purified by flash chromatography (hexanes/EtOAc 20:1) to give the target product **36** as a colorless oil (713 mg, 89%). R_f = 0.74 (hexane/EtOAc, 10:1).

$[\alpha]_D^{25} = +8.65$ (c 1.9, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 5.79 (ddd, J = 17.1, 10.3, 6.6 Hz, 1H), 5.14 – 5.09 (m, 1H), 5.02 (ddd, J = 10.4, 1.7, 1.0 Hz, 1H), 4.20 (dd, J = 12.0, 6.5 Hz, 1H), 3.59 (t, J = 6.5 Hz, 2H), 1.60 – 1.44 (m, 4H), 1.41 – 1.25 (m, 2H), 1.11 – 0.99 (m, 21H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.80, 113.72, 74.11, 63.19, 38.11, 32.97, 25.95, 20.94, 18.11, 17.69, 12.39, 12.28, -5.31.

FTIR (NaCl, cm^{-1}): 2941.44, 2864.29, 1463.97, 1386.82, 1265.30, 1095.57, 995.27, 837.11.

HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{49}\text{O}_2\text{Si}_2$ $[\text{M}+\text{H}]^+$: 401.3271, found 401.3271.

(S)-5-(((triisopropylsilyl)oxy)hept-6-en-1-ol (37)

To a solution of **36** (762 mg, 1.90 mmol) in THF/H₂O (20:1, 21 mL) was added PPTS (191 mg, 0.760 mmol) and *p*-toluenesulfonic acid monohydrate (36.0 mg, 0.190 mmol). After stirred the reaction mixture at room temperature for 10 h, aq NaHCO₃ (20 mL) was added, the reaction solution was extracted with ethyl acetate (3 x 20 mL), the combined extracts were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 10:1) to give the target product **37** as a colorless oil (392 mg, 72%). R_f = 0.25 (hexane/EtOAc, 5:1).

$[\alpha]_D^{25} = +16.01$ (c 1.4, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 5.77 (ddd, J = 17.1, 10.4, 6.6 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 5.01 (d, J = 10.4 Hz, 1H), 4.19 (dd, J = 12.0, 6.4 Hz, 1H), 3.58 (t, J = 6.7 Hz, 2H), 2.11 (s, 1H), 1.63 – 1.46 (m, 4H), 1.42 – 1.27 (m, 2H), 1.03 – 1.02 (m, 21H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.59, 113.83, 73.96, 62.68, 37.96, 32.75, 20.70,

18.02, 18.01, 12.33.

FTIR (NaCl, cm^{-1}): 3450.65, 3053.32, 2941.44, 2866.22, 1463.97, 1421.54, 1265.30, 1093.64, 995.27, 923.90, 883.40, 736.81.

HRMS (ESI) m/z calculated for $\text{C}_{16}\text{H}_{35}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 287.2406, found 287.2412.

(*S,E*)-methyl 7-((triisopropylsilyl)oxy)nona-2,8-dienoate (38**)**

To a mixture of Dess-Martin periodinane (521mg, 1.23 mmol), NaHCO_3 (516 mg, 6.14 mmol) in CH_2Cl_2 (10 mL) was added a solution of alcohol **37** (176 mg, 0.610 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The ultimate suspension was stirred at 0 °C for 1 h and was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) solution. The organic layer was separated and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts was washed with aq NaHCO_3 , brine, dried over anhydrous MgSO_4 , filtered and concentrated in *vacuo*. The crude aldehyde was used without purification for the next step reaction.

To another 25 mL round-bottom flask with a magnetic stirring bar was added CH_2Cl_2 (10 mL) and the above prepared crude aldehyde (174 mg, 0.610 mmol), followed by addition of methyl 2-(triphenylphosphoranylidene)acetate (410 mg, 1.23 mmol). The reaction mixture was stirred at room temperature for 16 h. Then water (10 mL) was added to the reaction solution, the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated under

reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc = 15:1) to give **38** (158 mg, 76%, *E/Z* = 91:9) as a colorless oil. R_f = 0.45 (hexane/EtOAc, 10:1).

^1H NMR (500 MHz, CDCl_3) δ 6.94 (dt, J = 15.6, 6.9 Hz, 1H), 5.82 – 5.70 (m, 2H), 5.15 – 5.06 (m, 1H), 5.06 – 4.98 (m, 1H), 4.21 (dd, J = 11.4, 6.1 Hz, 1H), 3.68 (s, 3H), 2.22 – 2.16 (m, 2H), 1.61 – 1.41 (m, 4H), 1.08 – 0.97 (m, 21H).

^{13}C NMR (125 MHz, CDCl_3) δ 167.04, 149.38, 141.44, 120.94, 114.01, 73.68, 51.29, 37.58, 32.22, 22.93, 18.05, 18.03, 12.34.

FTIR (NaCl, cm^{-1}): 2943.37, 2866.22, 1728.22, 1658.78, 1462.04, 1435.04, 1269.16, 1199.72, 1170.79, 1093.64, 920.05, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{19}\text{H}_{36}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 363.2331, found 363.2329.

(4*S*,5*S*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (40**)**

To a solution of dimethyl D-tartrate (20.0 g, 112 mmol) in anhydrous CH_2Cl_2 (100 mL), was added *p*TSA (2.13 g, 11.2 mmol) and 2,2-dimethoxypropane (34.4 mL, 280 mmol), the reaction mixture was heated to reflux for 10 h and was quenched with water (50 mL), the mixture was extracted with CH_2Cl_2 (3 $\times$ 50 mL). The combined extracts were washed with aq NaHCO_3 , brine, dried over Na_2SO_4 and evaporated

under reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc = 15:1) to give **40** (22.0 g, 90%) as a colorless oil. R_f = 0.32 (hexane/EtOAc, 10:1).

^1H NMR (400 MHz, CDCl_3) δ 4.72 (s, 2H), 3.73 (s, 6H), 1.40 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 169.86, 113.61, 76.78, 52.56, 26.09.

(4*S*,5*R*)-methyl 5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (41**)**

To a solution of **40** (1.60 g, 7.33 mmol) in methanol (30 mL) was cooled to $0\text{ }^\circ\text{C}$, sodium borohydride (166 mg, 4.39 mmol) was added in four portions over 1 h. The reaction mixture was stirred at the same temperature for 30 min and quenched with water (10 mL), the methanol was removed by evaporation under reduced pressure, and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with brine, dried over Na_2SO_4 , evaporated under reduced pressure, the residue was purified by flash chromatography (hexane/EtOAc = 2:1) to give **41** (0.420 g, 30%) as a colorless oil. R_f = 0.24 (hexane/EtOAc, 1:1).

^1H NMR (300 MHz, CDCl_3) δ 4.46 (dd, J = 7.7, 1.6 Hz, 1H), 4.24 (ddd, J = 8.1, 4.1, 1.4 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.79 (s, 3H), 3.73 (dd, J = 8.5, 3.7 Hz, 1H), 2.15 – 2.01 (m, 1H), 1.48 (s, 3H), 1.44 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ 171.19, 111.36, 79.08, 74.84, 61.75, 52.46, 26.73, 25.58.

(4*S*,5*S*)-methyl 5-(iodomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (42**)**

To a solution of the primary alcohol **41** (0.38 g, 2.0 mmol) in toluene (20 mL) was added triphenylphosphine (0.63 g, 2.4 mmol), imidazole (0.41 g, 6.0 mmol) and iodine (0.66 g, 2.6 mmol). Then the reaction mixture was stirred and heated to reflux for 1 h. After cooled to room temperature, the organic phase was washed with a saturated aq Na₂S₂O₃ (3 × 15 mL), the aqueous layer was extracted with diethyl ether (2 × 50 mL), and the combined organic extracts were washed with brine, dried over Na₂SO₄, evaporated under reduced pressure, the residue was purified by flash chromatography (hexane/CH₂Cl₂ = 1:3) to give **42** (0.44 g, 73%) as a colorless oil. *R*_f = 0.37 (hexane/CH₂Cl₂ = 1:2).

¹H NMR (500 MHz, CDCl₃) δ 4.25 (dd, *J* = 9.4, 3.9 Hz, 1H), 4.05 (dd, *J* = 7.3, 3.2 Hz, 1H), 3.77 (s, 3H), 3.49 – 3.43 (m, 1H), 3.39 – 3.32 (m, 1H), 1.49 (s, 3H), 1.40 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 170.37, 111.89, 79.24, 77.40, 52.52, 27.08, 26.04, 6.59.

(4*S*,5*S*)-methyl 2,2-dimethyl-5-((phenylsulfonyl)methyl)-1,3-dioxolane-4-carboxylate (24**)**

To a solution of **40** (3.20 g, 10.7 mmol) in DMF (40 mL) was added PhSO₂Na (3.51 g, 21.4 mmol), the reaction mixture was heated to 80 °C for 24 h, after cooled to room temperature, water (40 mL) was added to quench the reaction, the aqueous layer was extracted with diethyl ether (3 × 80 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/EtOAc = 10:1) gave **24** (2.86 g, 85%) as a viscous pale yellow oil; R_f = 0.37 (hexane/EtOAc = 5:1).

[α]_D²⁵ = +8.2 (*c* 2.7, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 7.7 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 4.54 (td, *J* = 7.2, 4.4 Hz, 1H), 4.29 (d, *J* = 7.0 Hz, 1H), 3.72 (s, 3H), 3.48 (qd, *J* = 14.5, 5.9 Hz, 2H), 1.30 (s, 3H), 1.24 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 169.55, 139.22, 133.79, 128.93, 128.18, 111.95, 77.82, 72.83, 58.98, 52.50, 26.68, 25.57.

FTIR (NaCl, cm⁻¹): 3057.17, 2991.59, 1762.94, 1739.79, 1438.90, 1384.89, 1319.31, 1265.30, 1213.23, 1145.72, 1101.35, 1083.99, 893.04, 835.18, 738.74.

HRMS (ESI) *m/z* calculated for C₁₃H₁₇O₆S [M+H]⁺: 301.0746, found 301.0757.

3-(4-methoxy-benzyloxy)-2(*R*)-methyl-propionaldehyde (**44**)⁷³

To a mixture of Dess-Martin periodinane (6.37 g, 15.0 mmol), NaHCO₃ (6.72 g, 80.0

mmol) in CH₂Cl₂ (15 mL) was added a solution of (*S*)-(-)-3-(4'-methoxybenzyloxy)-2-methylpropan-1-ol⁸⁵ (2.10 g, 10.0 mmol) in CH₂Cl₂ (20 mL) at 0 °C. The ultimate suspension was stirred at 0 °C for 1 h and quenching with saturated Na₂S₂O₃ (30 mL) solution. The organic layer was separated and the mixture was extracted with Et₂O (120 mL). The combined organic extracts was washed with brine, dried over anhydrous MgSO₄, filtered and concentrated in *vacuo* and purified by flash column chromatography (hexane/ethyl acetate = 6:1) provided **44** as a colorless oil (1.98 g, 95%). R_f = 0.37 (hexane/EtOAc, 4:1).

¹H NMR (300 MHz, CDCl₃) δ 9.69 (d, *J* = 1.5 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.44 (s, 2H), 3.78 (s, 3H), 3.67-3.58 (m, 2H), 2.80 – 2.50 (m, 1H), 1.10 (d, *J* = 7.1 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 203.81, 159.17, 129.88, 129.13, 113.70, 72.82, 69.67, 55.12, 46.66, 10.60.

(2*R*,3*R*)-1-((4-methoxybenzyl)oxy)-2,5-dimethylhex-5-en-3-ol (46)

To a solution of 3-(4-methoxy-benzyloxy)-2(*R*)-methyl-propionaldehyde (0.10 g, 0.50 mmol) and 4 Å MS (0.40 g) in CH₂Cl₂ (10 mL) at -78 °C was added SnCl₄ (0.60 mL, 1

⁸⁵Heckrodt, T. J.; Mulzer, J. *Synthesis* **2002**, 1857.

M in CH₂Cl₂, 0.60 mmol) dropwise via syringe pump over 10 min, and the reaction was stirred for a further 10 min, methyltrimethylsilane (80 mg, 0.60 mmol) was added to the reaction mixture dropwise, after addition, the reaction was stirred at -78 °C for 1 h. Then the reaction was quenched by aq. NaHCO₃ (15 mL), filtered a short pad of celite, the aqueous was extracted by CH₂Cl₂, the combined extracts were washed with brine, dried over Na₂SO₄, and concentrated in *vacuo* and purified by flash column chromatography (hexane/ethyl acetate = 5:1) provided **46** as a colorless oil (86 mg, 65%). R_f = 0.31(hexane/EtOAc, 4:1).

¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 4.84 (s, 1H), 4.78 (s, 1H), 4.43 (s, 2H), 3.78 (s, 3H), 3.73 – 3.61 (m, 1H), 3.51 (ddd, *J* = 15.7, 9.2, 5.7 Hz, 2H), 2.98 (s, 1H), 2.29 – 2.05 (m, 2H), 1.88-1.84 (m, 1H), 1.76 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 159.10, 143.05, 129.99, 129.15, 113.66, 112.84, 73.57, 72.87, 72.39, 55.09, 43.29, 38.33, 22.28, 13.89.

FTIR (NaCl, cm⁻¹): 3471.87, 2960.73, 2931.80, 2856.58, 1612.49, 1514.12, 1454.33, 1301.95, 1247.94, 1172.72, 1089.78, 1053.77, 889.18, 819.75.

HRMS (ESI) *m/z* calculated for C₁₆H₂₅O₃ [M+H]⁺: 265.1804, found 265.1812.

Triisopropyl(((2*R*,3*R*)-1-((4-methoxybenzyl)oxy)-2,5-dimethylhex-5-en-3-yl)oxy)silane (47**)**

A solution of the homoallylic alcohol **46** (264 mg, 1.00 mmol) in CH₂Cl₂ (6 mL) was added 2,6-lutidine (0.420 mL, 3.60 mmol) and TIPSOTf (0.400 mL, 1.50 mmol) at 0 °C. After stirring at 0 °C for 2 h, aq. NaHCO₃ was added followed by an extraction with ether. The combined organic extracts were washed with 1 M HCl and brine, dried and concentrated. The crude was purified by flash column chromatography (silica gel, hexanes/EtOAc 20:1) to give the target product **47** as a colorless oil (395 mg, 94%). R_f = 0.58 (hexane/EtOAc, 10:1).

¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.75 (s, 1H), 4.72 (s, 1H), 4.40 (s, 1H), 4.15 – 4.07 (m, 1H), 3.79 (s, 3H), 3.51 (dd, *J* = 9.4, 6.4 Hz, 1H), 3.28 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.26 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.16 (dd, *J* = 13.7, 6.0 Hz, 1H), 2.07 (ddd, *J* = 15.7, 7.9, 3.6 Hz, 1H), 1.71 (s, 3H), 1.07-1.04 (m, 21H), 0.98 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 158.98, 142.89, 130.92, 129.01, 113.63, 112.94, 72.58, 72.55, 71.81, 55.22, 42.46, 38.32, 22.80, 18.24, 12.89.

FTIR (NaCl, cm⁻¹): 2958.80, 2943.37, 2891.30, 2866.22, 1612.49, 1514.12, 1463.97, 1247.94, 1085.92, 1039.63, 883.40, 740.67, 678.94.

HRMS (ESI) *m/z* calculated for C₂₅H₄₅O₃Si [M+H]⁺: 421.3138, found 421.3140.

(2*R*,3*R*)-2,5-dimethyl-3-((triisopropylsilyl)oxy)hex-5-en-1-yl acetate (48)

To a solution of **47** (294 mg, 0.700 mmol) in CH₂Cl₂/H₂O (18:1, 8 mL) was added DDQ (191 mg, 0.840 mmol) slowly by spatula at 0 °C. The dark red solution was stirred at 0 °C for 50 min and at room temperature for 30 min. The ultimate reaction mixture was extracted with ethyl acetate (40 mL), washed with saturated NaHCO₃ solution, brine, dried over anhydrous Na₂SO₄. After removal of solvent, the crude product was dissolved in dichloromethane (10 mL) and was treated with pyridine (0.170 mL, 2.10 mmol) and acetic anhydride (0.200 mL, 2.10 mmol) and 4-DMAP (4.30 mg, 35.0 μmol). The resulting solution was stirred at room temperature for 6 h. The solvent was concentrated to dryness to give a crude product, which was subjected to column chromatography giving the acetate of **48** as a colorless oil (189 mg, 79% for two steps). R_f = 0.45 (hexane/EtOAc, 10:1).

¹H NMR (400 MHz, CDCl₃) δ 4.79 (s, 1H), 4.76 (s, 1H), 4.16 (dd, *J* = 11.0, 6.5 Hz, 1H), 4.07 (td, *J* = 5.7, 2.9 Hz, 1H), 3.93 (dd, *J* = 11.0, 7.4 Hz, 1H), 2.31 (dd, *J* = 13.9, 8.0 Hz, 1H), 2.22 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.04 (s, 3H), 1.73 (s, 3H), 1.04-1.08 (m, 21H), 1.01 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 171.07, 142.36, 113.29, 72.51, 65.92, 42.76, 37.14, 22.75, 20.98, 18.21, 13.82, 12.85.

FTIR (NaCl, cm⁻¹): 3053.32, 3020.53, 2964.59, 2943.37, 2893.22, 2866.22, 1732.08, 1647.21, 1463.79, 1421.54, 1367.53, 1263.37, 1217.80, 1118.71, 1039.63, 883.40, 759.95, 740.67, 705.95, 680.87.

HRMS (ESI) *m/z* calculated for C₁₉H₃₉O₃Si [M+H]⁺: 343.2668, found 343.2685.

(2*E*,4*E*,7*R*,8*R*)-butyl 9-acetoxy-5,8-dimethyl-7-((triisopropylsilyl)oxy)nona-2,4-

dienoate (20) (*E/Z* = 80:20)

A 10 mL round bottomed flask equipped with a magnetic stirring bar was added with **48** (206 mg, 0.600 mmol), Pd(OAc)₂ (13.5 mg, 60.0 μmol), Cu(OAc)₂ (218 mg, 1.20 mmol), 1,10-phenanthroline (13.0 mg, 72.0 μmol), AgSbF₆ (24.7 mg, 72.0 μmol), n-butyl acrylate (0.170 mL, 1.20 mmol) in 1.2 mL NMP/PivOH (v/v = 1:1). The flask was stirred at 120 °C for 48 h. The reaction mixture was cooled to room temperature, followed by the addition of saturated NaHCO₃ and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtrated and concentrated *in vacuo*, the residue was purified through column chromatography on silica gel to give the desired product **20** as a colorless oil (194 mg, 69%). R_f = 0.33 (hexane/EtOAc, 10:1).

¹H NMR (400 MHz, CDCl₃) δ 7.51 (dd, *J* = 15.1, 11.6 Hz, 1H), 6.03 (d, *J* = 11.7 Hz, 1H), 5.77 (d, *J* = 15.2 Hz, 1H), 4.16 – 4.04 (m, 4H), 4.00 – 3.89 (m, 1H), 2.46 – 2.28 (m, 2H), 2.02 (s, 3H), 1.88 (s, 3H), 1.68 – 1.58 (m, 2H), 1.42-1.34 (m, 2H), 1.06 - 0.85 (m, 21H), 0.98 – 0.89 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 170.84, 167.61, 145.81, 140.27, 126.16, 119.52, 72.11, 65.79, 64.04, 44.41, 37.85, 30.73, 20.87, 19.12, 18.10, 17.71, 12.89, 12.85, 12.80.

FTIR (NaCl, cm^{-1}): 3053.32, 3018.60, 2960.73, 2943.37, 2893.22, 2866.22, 1743.51, 1701.22, 1635.64, 1610.56, 1458.18, 1388.75, 1367.53, 1307.74, 1265.30, 1035.77, 883.40, 738.74, 704.02.

HRMS (ESI) m/z calculated for $\text{C}_{26}\text{H}_{49}\text{O}_5\text{Si}$ $[\text{M}+\text{H}]^+$: 469.3349, found 469.3338.

(2*E*,4*E*,7*R*,8*R*)-methyl 9-hydroxy-5,8-dimethyl-7-((triisopropylsilyl)oxy)nona-2,4-dienoate (49)

To a solution of **20** (145 mg, 0.310 mmol) in methanol (10 mL) was added K_2CO_3 (64.3 mg, 0.470 mmol) at room temperature. The reaction mixture was stirred at room temperature for 6h. The ultimate reaction mixture was quenched with water (5 mL), after remove the methanol by evaporation, the residue was extracted with ethyl acetate (3×5 mL), washed with birne, dried over anhydrous Na_2SO_4 . After removal of solvent, the crude product was subjected to column chromatography giving the primary alcohol **49** as a colorless oil (117 mg, 98%). R_f = 0.30 (hexane/EtOAc, 5:1).

^1H NMR (400 MHz, CDCl_3) δ 7.53 (dd, J = 15.1, 11.6 Hz, 1H), 6.03 (d, J = 11.6 Hz, 1H), 5.79 (d, J = 15.2 Hz, 1H), 4.22 – 4.13 (m, 1H), 3.84 (dd, J = 11.0, 4.1 Hz, 1H), 3.73 (s, 3H), 3.54 (d, J = 2.4 Hz, 1H), 2.59 – 2.36 (m, 3H), 1.88 (s, 3H), 1.80 – 1.67 (m, 1H), 1.16 – 0.96 (m, 24H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.89, 145.80, 140.40, 126.05, 119.29, 75.00, 64.39, 51.43, 45.74, 38.17, 18.16, 18.14, 17.61, 12.81, 12.75.

FTIR (NaCl, cm^{-1}): 3489.23, 3475.73, 2945.30, 2866.22, 1712.79, 1635.64, 1462.04, 1435.04, 1131.59, 1265.30, 1159.22, 1141.86, 910.40, 883.40.

HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{41}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 385.2774, found 385.2771.

(2*E*,4*E*,7*R*,8*R*)-methyl 9-((tert-butyldiphenylsilyl)oxy)-5,8-dimethyl-7-((triisopropylsilyl)oxy)nona-2,4-dienoate (50)

To a solution of **14** (805 mg, 2.09 mmol) in CH_2Cl_2 (20 mL) was added imidazole (313 mg, 4.60 mmol). The mixture was then cooled to 0 ° C, followed by addition of TBDPSCl (0.650 mL, 2.51 mmol) dropwise. The mixture was then stirred from 0 ° C to room temperature for 5 h. The reaction was quenched with water and extracted with ethyl acetate (3×5 mL), the organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Pure **50** (1.24 g, 95%) was obtained after flash column chromatography (*n*-hexane/ethyl acetate = 20:1) as a colorless oil. R_f = 0.67 (hexane/EtOAc, 10:1).

^1H NMR (400 MHz, CDCl_3) ^1H NMR (400 MHz, CDCl_3) δ 7.69 – 7.67 (m, 4H), 7.59 (dd, J = 15.1, 11.6 Hz, 1H), 7.48 – 7.34 (m, 6H), 6.05 (d, J = 11.7 Hz, 1H), 5.77 (dd, J = 15.1, 2.8 Hz, 1H), 4.46 – 4.39 (m, 1H), 3.77 (s, 3H), 3.55 (d, J = 7.3 Hz, 2H), 2.35 – 2.11 (m, 3H), 1.94 (s, 3H), 1.15 – 0.99 (m, 30H), 0.88 (d, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 168.07, 147.57, 135.53, 135.51, 127.63, 127.61, 125.84, 118.46, 71.38, 66.01, 51.34, 43.21, 41.76, 26.80, 19.12, 18.20, 18.18, 12.92, 12.86.

FTIR (NaCl, cm^{-1}): 2945.30, 2864.29, 1714.72, 1635.64, 1462.04, 1429.25, 1386.82, 1361.74, 1309.67, 1265.30, 883.40, 823.60.

HRMS (ESI) m/z calculated for $\text{C}_{37}\text{H}_{59}\text{O}_4\text{Si}_2$ $[\text{M}+\text{H}]^+$: 623.3952, found 623.3941.

(2*E*,4*E*,7*R*,8*R*)-9-((tert-butyldiphenylsilyl)oxy)-5,8-dimethyl-7-((triisopropylsilyl)oxy)nona-2,4-dien-1-ol (51)

To a solution of **50** (3.30 g, 5.31 mmol) in CH_2Cl_2 (30 mL) was added DIBAL-H (1M in *n*-heptane, 21.2 mmol, 21.2 mL) dropwise at -78°C . The mixture was stirred at that temperature for 2 h, then quenched with MeOH (5 mL) and saturated aqueous potassium sodium tartrate (30 mL). The resultant mixture was stirred vigorously until two clear layers were obtained (about 30 min). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers was washed with brine, dried over Na_2SO_4 , filtered, and concentrated in *vacuo*. Flash column chromatography (hexane/EtOAc, 80:1) afforded **51** (*syn* isomer) and **51'** (*anti* isomer) (2.84 g, 90%, **51**:**51'** = 91:9) as a colorless oil. **51** (*syn* isomer): R_f = 0.13

(hexane/EtOAc, 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.69 (dd, $J = 7.8, 1.5$ Hz, 4H), 7.48 – 7.35 (m, 6H), 6.46 (dd, $J = 15.1, 11.0$ Hz, 1H), 5.91 (d, $J = 10.9$ Hz, 1H), 5.75 – 5.67 (m, 1H), 4.35 – 4.31 (m, 1H), 4.21 (d, $J = 5.7$ Hz, 2H), 3.62 (dd, $J = 10.2, 8.3$ Hz, 1H), 3.53 (dd, $J = 10.3, 6.5$ Hz, 1H), 2.26 (dd, $J = 13.4, 5.3$ Hz, 1H), 2.16 (dd, $J = 13.6, 7.4$ Hz, 2H), 1.82 (s, 3H), 1.55 (s, 1H), 1.08-1.07 (m, 30H), 0.91 (d, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 136.97, 135.55, 135.53, 133.75, 129.50, 128.12, 127.58, 126.62, 71.59, 65.90, 63.77, 43.18, 41.52, 26.81, 19.14, 18.23, 17.26, 12.84, 11.56.

FTIR (NaCl, cm^{-1}): 3404.36, 3332.99, 2958.80, 2864.29, 1463.97, 1427.32, 1386.82, 1265.30, 1111.00, 1078.21, 883.40, 823.60.

HRMS (ESI) m/z calculated for $\text{C}_{36}\text{H}_{58}\text{O}_3\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 617.3822, found 617.3800.

51' (*anti* isomer): $R_f = 0.15$ (hexane/EtOAc, 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.66 (d, $J = 7.4$ Hz, 4H), 7.45 – 7.35 (m, 6H), 6.46 (dd, $J = 15.0, 11.0$ Hz, 1H), 5.88 (d, $J = 11.0$ Hz, 1H), 5.71 – 5.64 (m, 1H), 4.40 – 4.30 (m, 1H), 4.07 (d, $J = 5.3$ Hz, 2H), 3.60 – 3.49 (m, 2H), 2.35 (dd, $J = 13.5, 8.0$ Hz, 1H), 2.20 (dd, $J = 13.5, 4.9$ Hz, 1H), 2.10 (dd, $J = 13.2, 8.2$ Hz, 1H), 1.82 (s, 3H), 1.57 (s, 1H), 1.05-1.04 (m, 30H), 0.90 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 137.42, 135.57, 135.55, 133.81, 129.57, 128.84, 127.61, 126.86, 71.47, 66.14, 63.90, 41.89, 35.27, 26.85, 19.21, 18.29, 18.21, 12.95, 11.15.

FTIR (NaCl, cm^{-1}): 3689.83, 3606.89, 2929.87, 2864.29, 1463.97, 1427.32, 1265.30, 1111.00, 1064.71, 968.27.

HRMS (ESI) m/z calculated for $\text{C}_{36}\text{H}_{58}\text{O}_3\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 617.3822, found 617.3818.

**(2*E*,4*E*,7*R*,8*R*)-9-((*tert*-butyldiphenylsilyl)oxy)-5,8-dimethyl-7-
((triisopropylsilyl)oxy)nona-2,4-dien-1-yl acetate (**52**)**

The allylic alcohol **51** (239 mg, 400 μmol) was dissolved in dichloromethane (5 mL) and was treated with pyridine (75.0 μL , 0.800 mmol) and acetic anhydride (64.0 μL , 0.8 mmol) and followed by a catalytic 4-DMAP (2.40 mg, 20.0 μmol). The resulting solution was stirred at room temperature for 6 h. Then added aq NaHCO_3 , the reaction mixture was extracted with CH_2Cl_2 three times, washed with aq NaHCO_3 , brine, and dried over Na_2SO_4 , filtered, and concentrated in *vacuo*. Flash column chromatography (hexane/EtOAc, 20:1) afforded **52** (229 mg, 90%) as a colorless oil. R_f = 0.55 (hexane/EtOAc, 10:1).

^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.62 (m, 4H), 7.46 – 7.33 (m, 6H), 6.49 (dd, J = 15.1, 11.0 Hz, 1H), 5.88 (d, J = 11.0 Hz, 1H), 5.67 – 5.52 (m, 1H), 4.70 – 4.55 (m, 2H), 4.33 – 4.29 (m, 1H), 3.60 (dd, J = 10.2, 8.3 Hz, 1H), 3.51 (dd, J = 10.3, 6.5 Hz, 1H), 2.24 (dd, J = 13.4, 5.4 Hz, 1H), 2.18 – 2.10 (m, 2H), 2.08 (s, 3H), 1.80 (s, 3H), 1.09 – 1.02 (m, 30H), 0.89 (d, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 170.83, 138.25, 135.56, 135.54, 131.24, 129.54,

127.59, 126.35, 123.96, 71.60, 65.90, 65.32, 43.23, 41.52, 26.82, 21.03, 19.15, 18.22,
17.34, 12.86, 11.58.

FTIR (NaCl, cm^{-1}): 2943.37, 2864.29, 1735.93, 1462.04, 1427.32, 1111.00, 1064.71,
883.40, 734.88.

HRMS (ESI) m/z calculated for $\text{C}_{38}\text{H}_{61}\text{O}_4\text{Si}_2$ $[\text{M}+\text{H}]^+$: 637.4108, found 637.4111.

List of Publications

1. Wen Zhen-Kang, Xu Yun-He, Loh Teck-Peng. Palladium-Catalyzed Cross-Coupling of Unactivated Alkenes with Acrylates: Application to the Synthesis of C13–C21 Fragment of Palmerolide A. *Chem. Eur. J.* **2012**, *18*, 13284.
2. Xu Yun-He, Wang Wee-Jian, **Wen Zhen-Kang**, Hartley Joshua Johnathan and Loh Teck-Peng. Palladium catalyzed direct cross-coupling reaction between olefins *Tetrahedron Lett.* **2010**, *51*, 3504.

Conferences

Wen Zhen-Kang, Loh Teck-Peng. New Strategy for Diene Synthesis: Application in Total Synthesis of Palmerolide A. *6th Asian-European Symposium on Metal Mediated Efficient Reactions*, June 7–9, **2010**, Singapore.