Transformations of Alkenylmetalloids:

Hydroxyl-directed Hydroboration of Alkynes

&

Oxidative Methoxy Carbonylation, Oxidation and Fluorination of Alkenylstannanes

&

Formal Synthesis of Tubelactomicin A and Diverted Total Synthesis of 5,6-Dihydrocineromycin B

Dissertation

zur Erlangung des akademischen Grades eines

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der Technischen Universität Dortmund

vorgelegt von

Heiko Sommer

geboren am 21.02.1986

in Hannover

Mülheim an der Ruhr, 2016

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Die vorliegende Arbeit entstand unter Anleitung von Prof. Dr. Alois Fürstner in der Zeit von Oktober 2013 bis September 2016 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. Teile dieser Arbeit wurden bereits in folgenden Beiträgen veröffentlicht:

'Selective Formation of a Trisubstituted Alkene Motif by *trans*-Hydrostannation/Stille Coupling: Application to the Total Synthesis and Late-Stage Modification of 5,6-Dihydrocineromycin B'

S. M. Rummelt, J. Preindl, H. Sommer, A. Fürstner, *Angew. Chem., Int. Ed.* **2015**, *54*, 6241–6245; *Angew. Chem.* **2015**, *127*, 6339–6343.

'Hydroxyl-Assisted Carbonylation of Alkenyltin Derivatives: Development and Application to a Formal Synthesis of Tubelactomicin A'

H. Sommer, A. Fürstner, *Org. Lett.* **2016**, *18*, 3210–3213.

Teile dieser Arbeit entstanden in enger Zusammenarbeit mit Stephan M. Rummelt und Johannes Preindl (Kapital 6) und sind als solche gekennzeichnet. Um eine vollständige Diskussion zu ermöglichen, wurden diese Ergebnisse in die Besprechung mit aufgenommen.

1. Berichterstatter: Herr Prof. Dr. Alois Fürstner

2. Berichterstatter: Herr Prof. Dr. Norbert Krause

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Daher widme ich ihnen diese Arbeit.

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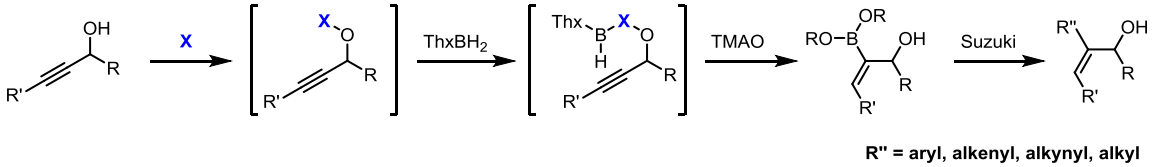
"Entscheidend ist, was hinten rauskommt."

– Helmut Kohl

Table of Contents

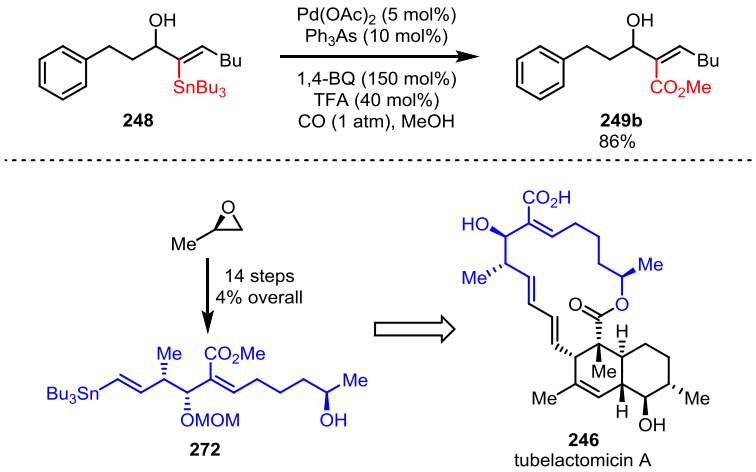
Abstract

A hydroxyl-directed *syn*-hydroboration of propargyl alcohols was developed (Scheme 1). This protocol allows for the one-pot transformations of propargyl alcohols into trisubstituted allyl alcohols. A transient linker was employed to extend the 'reach' of the propargyl alcohol to direct the hydroborating agent. Subsequent *in situ* oxidation of the borane and transition-metal catalyzed cross-couplings with alkynyl-, alkenyl-, aryl- and alkylhalides were demonstrated.



Scheme 1. Hydroxyl-directed hydroboration/Suzuki cross-coupling sequence.

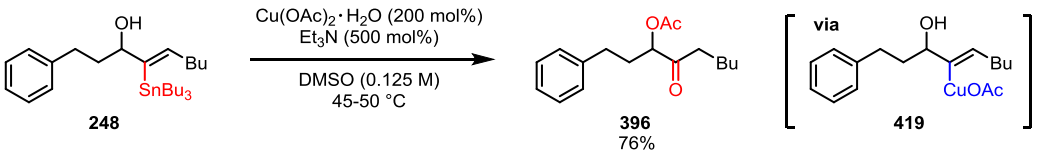
With reliable access to highly functionalized and stereodefined alkenylstannanes from previous works in our group, we sought to utilize this motif in complex molecule synthesis. Tubelactomicin A (**246**) was selected as an ideal target, containing an intriguing (hydroxymethyl)acrylic acid motif in the southern domain (Scheme 2). To realize our goal, a palladium catalyzed oxidative methoxy carbonylation of alkenylstannanes was developed, which provides direct access to α,β-unsaturated ester motifs in a single step. This in turn enabled a significant improvement in the route to fragment **272**.



Scheme 2. Palladium-catalyzed oxidative methoxy carbonylation and formal synthesis of tubelactomicin A.

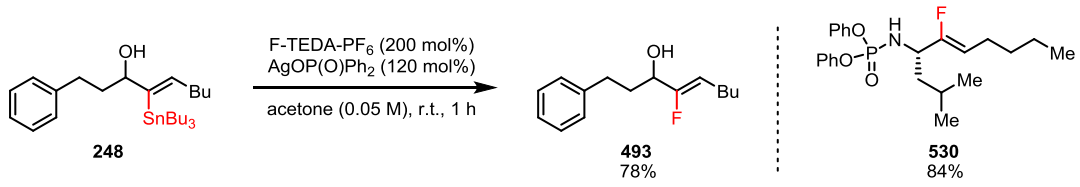
Next, we developed a methodology to convert alkenylstannanes to ketones, as this type of transformation had been previously limited to alkenylsilanes and alkenylboranes. Inspired by the well-known Chan-Lam coupling, we discovered that hydroxyl flanked alkenylstannanes could be transformed into α-acetoxy ketones in a copper-mediated process (Scheme 3). The reaction is proposed to proceed via copper species **419**. Furthermore, we found that stannanes

lacking an assisting hydroxyl group could be converted into the corresponding ketones utilizing copper(II) trifluoroacetate.



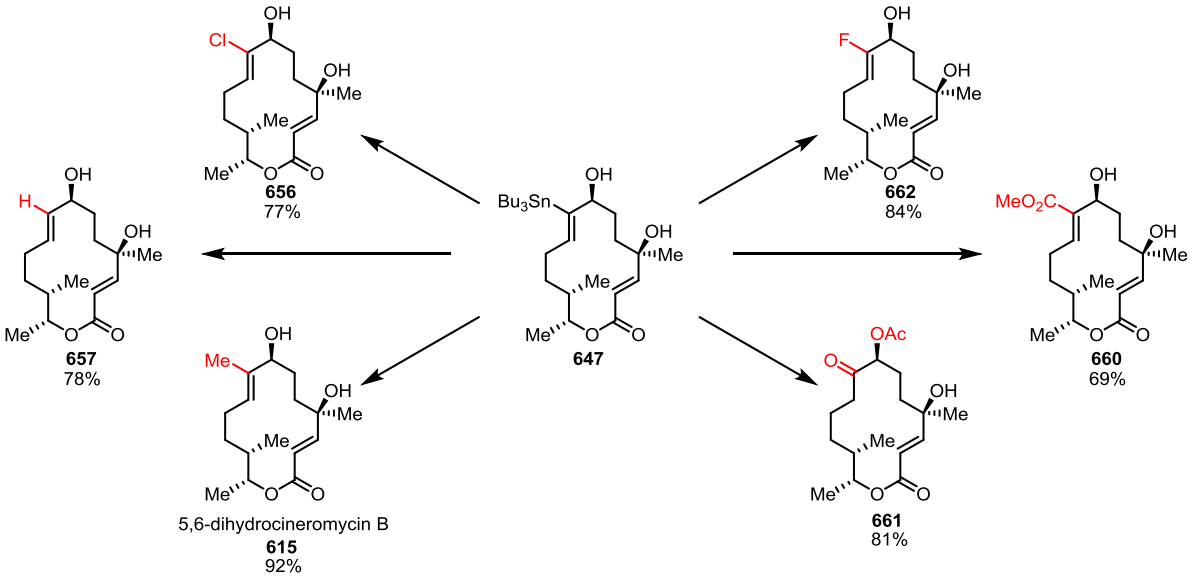
Scheme 3. Copper-mediated synthesis of α-acetoxy ketones from alkenyl stannanes.

Additionally, a reliable and broadly applicable method for the fluorination of alkenylstannanes was developed (Scheme 4). A mild protocol employing silver diphenylphosphinate and F-TEDA-PF_6 allowed access to various alkenyl fluorides. This method was then applied to the synthesis of biologically interesting peptide isosters such as **530**.



Scheme 4. Silver-mediated fluorination of alkenylstannanes.

Lastly, we achieved a highly convergent and efficient synthesis of 5,6-dihydrocineromycin B (**615**) utilizing multiple catalytic methods developed in our laboratory, namely ring-closing alkyne metathesis (RCAM), *trans*-selective hydrostannation, and methyl-Stille cross-coupling (Scheme 5). Furthermore, the late-stage functionalization of alkenylstannane **647** enabled divergent preparation of five additional non-natural analogs for biological evaluation.



Scheme 5. Synthesis of 5,6-dihydrocineromycin B and congeners.

Überblick

Eine neue hydroxyl-dirigierte *syn*-Hydroborierung von Propargylalkoholen wurde in der frühen Phase dieser Arbeit entwickelt (Abbildung 1).

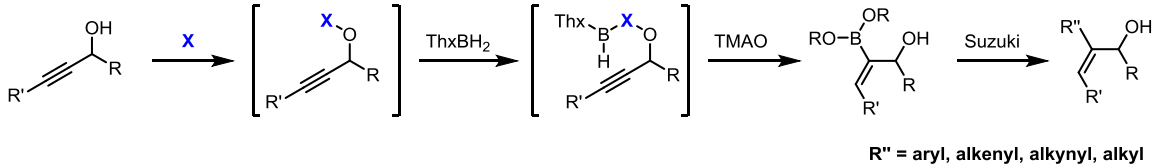


Abbildung 1. Hydroxyl-dirigierte Hydroborierung/Suzuki Kreuzkupplung Sequenz.

Diese bis dahin unbekannte Methode erlaubt die Eintopftransformation von Propargylalkoholen in dreifach substituierte Olefine. Dazu wurde die intermediäre Bildung eines Halbacetals genutzt um die ‚Reichweite' des Propargylalkohols zu erhöhen und das Hydroborierungsreagenz zu dirigieren. Anschließende *in situ* Oxidation und Kreuzkuppung mit Alkinyl-, Alkenyl-, Aryl- und Alkylhalogeniden sowie die Anwendung in der Totalsynthese wurde demonstriert.

Um das volle Potential der aus der ruthenium-katalysierten *trans*-Hydrostannierung von Alkinen hervorgehenden hochfunktionalisierten Alkenylstannane auszuschöpfen, wurde eine Formalsynthese vom Tubelactomicin A (**246**) initiiert (Abbildung 2).

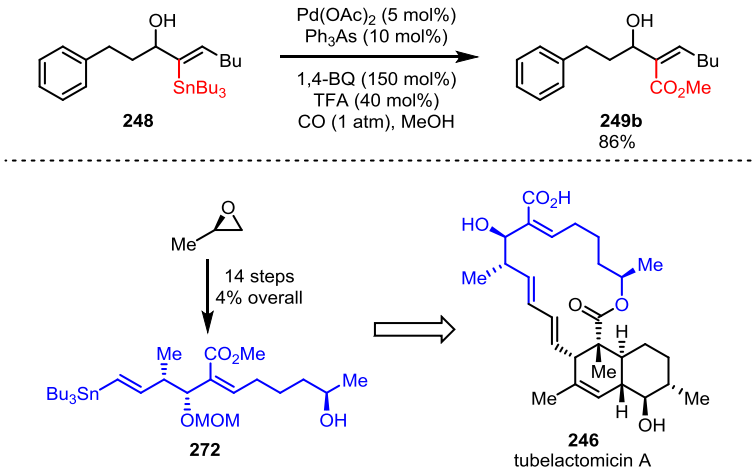


Abbildung 2. Palladium-katalysierte oxidative Methoxycarbonylierung und formale Synthese von Tubelactomicin A.

Dieser komplexe Naturstoff weist neben einer Reihe anderer Funktionalitäten ein interessantes Hydroxymethylacrylsäuremotiv auf. In der Literatur wurde Fragment **272** in einer 25-stufigen, linearen Sequenz synthetisiert. Ein hoch effizienter Zugang zu Hydroxymethylacrylsäuremotiven wurde daraufhin entwickelt, der auf einer neuen palladiumkatalysierten, oxidativen Methoxycarbonylierung basiert. Eine Vielzahl von α,β-

ungesättigten Estern konnte erhalten sowie die Anwendung der neuen Methodik in einer effizienten Formalsynthese von Tubelactomicin A demonstriert werden.

Die Umsetzung von Alkenylmetalloiden in die entsprechenden Carbonylverbindungen ist in der Literatur auf den Einsatz von Alkenylsilanen und Alkenylboranen beschränkt. Um diese Lücke zu schließen, entwickelten wir eine kupfermediierte Oxidation von Alkenylstannanen (Abbildung 3). Es konnte gezeigt werden, das hydroxysubstituierte Alkenylstannane in der Gegenwart von Kupfer(II)acetat in die entsprechenden α-Acetoxyketone umgesetzt werden können. Die Umwandlung läuft wahrscheinlich über eine Transmetallierung unter Bildung einer Alkenylkupferspezies **419** ab. Weiterhin ist die Synthese von Ketonen ohne benachbarte Hydroxygruppe mit Hilfe von Kupfer(II) trifluoracetat möglich.

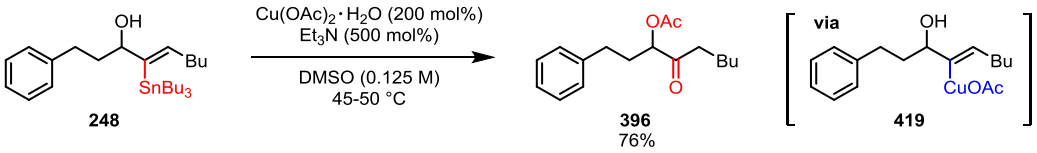


Abbildung 3. Kupfer(II)acetat vermittelte formale Oxidation von Alkenylstannanen.

Ein hochaktuelles Thema ist seit langem die Fluorierung organischer Verbindungen. Obwohl frühe Arbeiten zur Umsetzung von Alkenylstannanen in die entsprechenden Fluoride existieren, wurden die Limitierungen dieser Arbeiten bis heute nicht behoben. Wir konnten mit Hilfe eines zwar bekannten aber kaum untersuchten Silbersalzes in Gegenwart von einem Selectfluorderivat einen effizienten Zugang zu Alkenylfluoriden entwickeln (Abbildung 4). Die milden Reaktionsbedingungen erlaubten uns weiterhin, biologisch interessante Peptidisostere wie zum Beispiel Verbindung **530** zu synthetisieren.

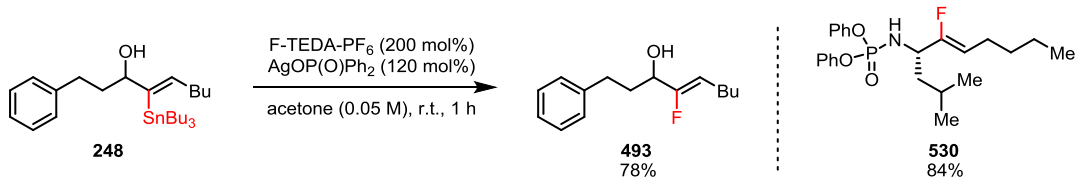


Abbildung 4. Silber-vermittelte Fluorierung von Alkenylstannanen.

Abschließend konnte ein hochkonvergenter Zugang zu 5,6-Dihydrocineromycin B erarbeitet werden, der zum großen Teil auf in dieser Arbeitsgruppe entwickelten, katalytischen Transformationen beruht. Schlüsselschritte der Synthese stellen eine ring-schließend Alkinmetathese (RCAM), die erwähnte Hydrostannierung und eine Methyl-Stille-Kreuzkupplung dar. Außerdem konnte das intermediär erhaltene Alkenylstannan im Kontext einer divergierenden Totalsynthese zur Darstellung von fünf nicht-natürlichen Analoga genutzt werden.

1. Introduction

1.1. Developing Ideal Chemistry

The complexity of organic molecules has inspired the imagination of synthetic chemists for more than a century. Tools for the construction of nearly every conceivable structural motif have been developed and the field matured considerably over more challenging molecules being synthesized. Nowadays, as chemists continue to innovate and develop elegant methodologies, they must not only consider the feasibility of a process but also its economic impact. Concepts like atom economy[1] or step economy[2] have evolved to allow the practitioner to quantify the efficiency of their designed approach.[3] When faced with a synthetic problem, e.g. the synthesis of a natural product, chemists have to foresee potential pitfalls and develop their strategy accordingly. An ideal synthesis plan should rapidly build up complexity in the minimum number of steps possible (Figure 1). A practical synthesis design balances the demands of practicality and ideality.

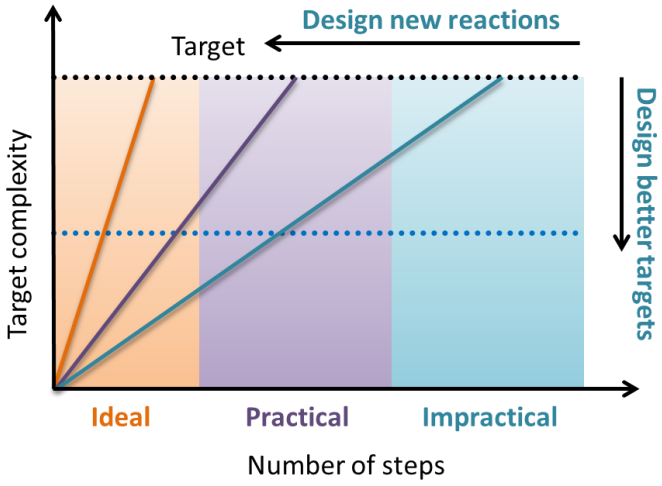


Figure 1. Developing ideal syntheses by Wender and Miller.[2b]

In pursuit of such 'ideal' synthesis, new tools are constantly being developed and refined. Carbon-carbon multiple bonds are extremely versatile scaffolds for functionalization and rapid generation of molecular complexity. For example, alkynes can be transformed into regio- and stereodefined olefins which may then be converted into a highly decorated alkane motif.

This thesis is concerned with the development of novel, step-economical protocols for the derivatization of alkynes with particular focus on transformations of resulting alkenylmetalloids in the context of complex molecule synthesis.

1.2. Hydrometalations of Internal Alkynes

The stereospecific hydrometalation of an internal alkyne presents an important transformation in organic chemistry (Figure 2). The resulting alkenylmetalloids are valuable substrates for a range of powerful cross-coupling methodologies, allowing access to stereodefined, trisubstituted olefins. Consequently, hydroborations, hydrostannylations and hydrosilylations constitute the most notable members in this field and have found numerous applications.[4] Classically, hydroelementation reactions occur in a *syn*-fashion. The ability of chemists to control the regio- and stereoselectivity of these reactions is vital for synthetic utility. Major advances in the last two decades yielded a number of valuable protocols for the highly selective synthesis of alkenylmetalloids.

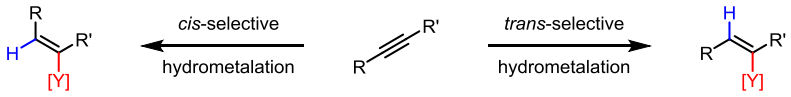


Figure 2. Stereodivergent hydrometalation of internal alkynes.

1.2.1. Mechanism of Metal-catalyzed *syn*-Selective Hydrometalations of Internal Alkynes

Most metal catalyzed hydrometalations of alkynes operate by one of the two mechanistic pathways which in analogy to hydrogenations, are termed 'dihydride' or 'monohydride' (Figure 3).

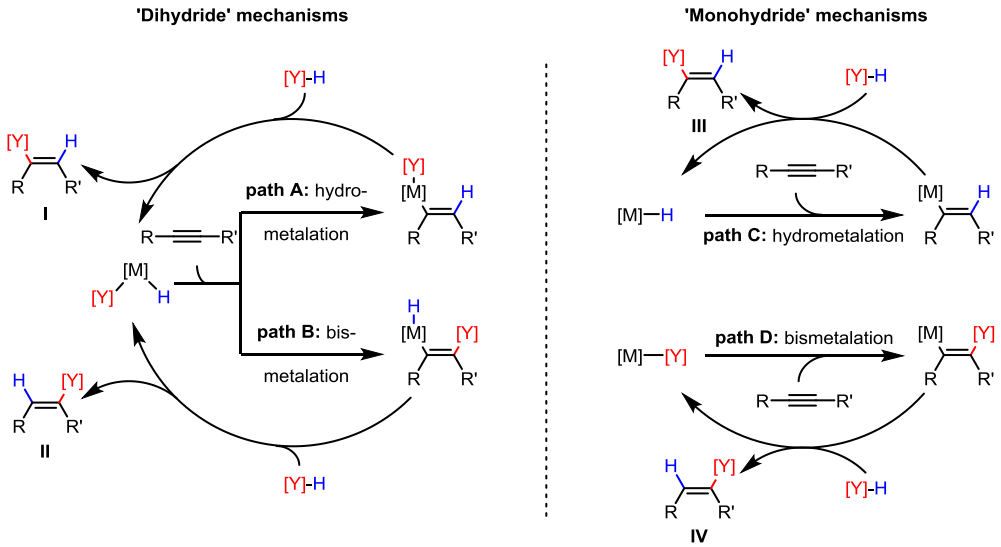


Figure 3. Typical hydrometalation pathways.

In the dihydride mechanisms, activation of the metalloid hydride ([Y]–H) by oxidative addition to the metal catalyst precedes hydrometalation (A) or bismetalation (B), providing regioisomeric products **I** and **II** after reductive elimination, depending on whether insertion of the alkyne occurs at the [M]–H (A) or [M]–Y (B) bond. These 'dihydride' mechanisms are generally referred to as Chalk-Harrod (A) and modified-Chalk-Harrod mechanisms (B), respectively.[5]

In the 'monohydride' mechanisms, a series of σ-bond metathesis steps leads to **III**/**IV** with only hydride (C) or metalloid (D) ever being bonded to the metal center. As pathways (A) and (C) and pathways (B) and (D) give rise to the same regioisomeric products, identification of the operating mechanism can be difficult.

1.2.2. Mechanism of Metal-catalyzed *trans*-Selective Hydrometalations of Internal Alkynes

In 2001, Trost and Ball demonstrated that the *trans*-selective hydrosilylation of terminal and internal alkynes is possible under ruthenium catalysis.[6] Recently, our group presented a ruthenium catalyzed system which effects regioselective *trans*-selective addition of silanes, boranes, stannanes and even dihydrogen to alkynes.[7] The versatility and mild conditions of the *trans*-selective hydrosilylation and hydrostannation have been documented in numerous total syntheses.[4d]

Subsequent mechanistic investigations provided evidence for a pathway which differs significantly from the mechanisms illustrated in Figure 3. In the initiating step, activation of the metalloid hydride occurs to give ruthenacyclopropene **V** with concomitant hydrometalation of the alkyne (Figure 4) (for the sake of clarity, Cp is drawn interchangeably for Cp*). Complex **V** may equilibrate via transient cation **VI** with isomeric metallacyclopropene **VII** before addition of [Y]. *trans*-Selectivity is thus explained by the reduced steric clash of H and Cp*-ligand compared to R' and Cp*-ligand. Reductive elimination closes the catalytic cycle (**VIII**) and reforms cationic ruthenium species **IX** after complexation.

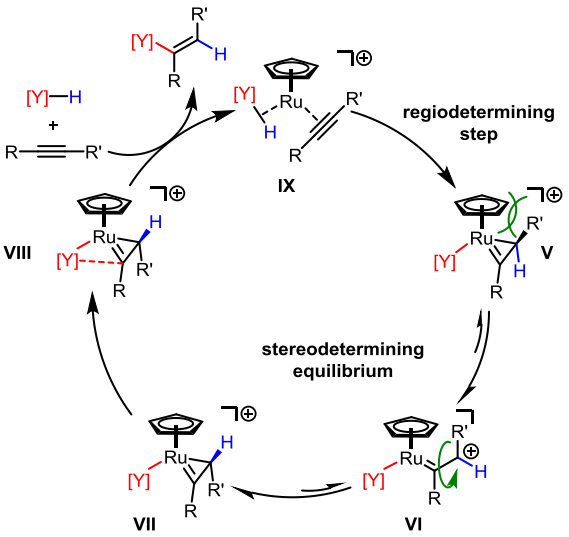
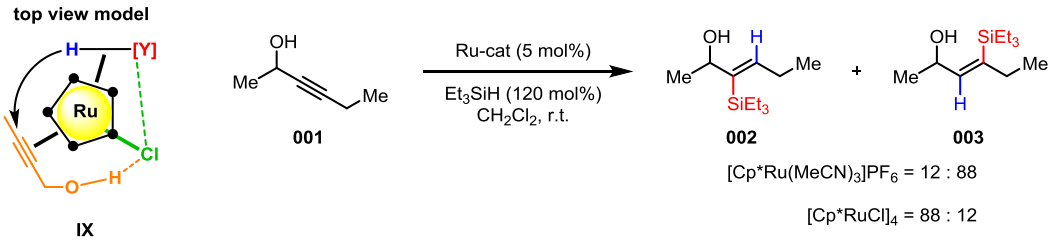


Figure 4. Mechanistic proposal for the ruthenium catalyzed *trans*-selective hydrometalation.

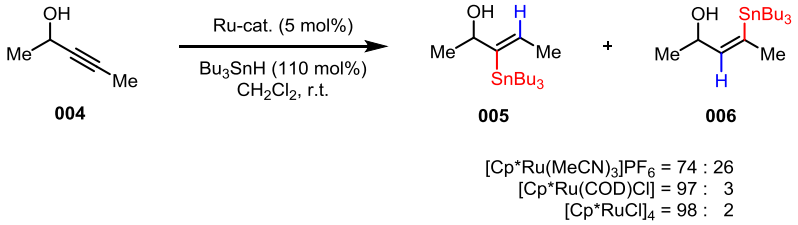
Although being still a matter of debate, this model accounts well for the observed *trans*-selectivity.[8] During their studies on the *trans*-selective hydrosilylation, Trost and Ball focused on the utilization of cationic $[CpRu(MeCN)_3]PF_6$ and $[Cp^*Ru(MeCN)_3]PF_6$ as precatalysts. High *E*/*Z*-selectivities were generally obtained, however, strong electronic or steric biases were necessary to achieve appreciable regiocontrol. In 2014, it was found that flanking protic groups, e.g. alcohols or amides, dictate the regioselectivity of this transformation when the neutral complex $[Cp^*RuCl]_4$ or its precursor $[Cp^*RuCl_2]_n$ are used as precatalysts in the *trans*-selective hydrostannation, hydrosilylation, and hydrogermylation.[7b, 7e] A model, supported by single-crystal X-ray analysis and computational studies, was elaborated that accounts for the observed regioselectivity (Scheme 1). Hydrosilylation in the presence of $[Cp^*Ru(MeCN)_3]PF_6$ preferentially delivers the silicon distal (**003**) to the alcohol, whereas neutral $[Cp^*RuCl]_4$ shows a propensity for proximal silylation (**002**). A similar trend was observed in the *trans*-selective hydrogermylation of propargyl alcohols.



Scheme 1. Typical example for the regiodivergent hydrosilylation of propargyl alcohols; • = CMe.

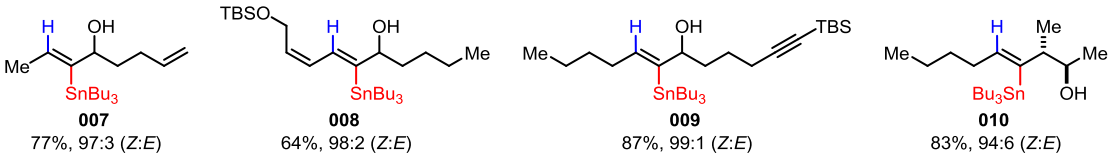
This result can be rationalized, by considering the top view model **IX**. Hydrogen bonding of the chloride ligand to both the π-coordinated propargyl alcohol and to the incoming metalloid hydride results in the formation of a rigid network. Consequently, hydride delivery occurs preferentially at the position which is distal to the alcohol.

The utilization of neutral ruthenium catalysts also led to the exclusive formation of the proximal product in the *trans*-selective hydrostannation (Scheme 2). The cationic ruthenium complex also showed an inherent preference for proximal selectivity but gave a less favorable isomer ratio.



Scheme 2. Hydroxyl-assisted *trans*-selective hydrostannation.

Subsequent studies broadened the scope of this reaction even further, allowing for its application in natural product synthesis (Scheme 3). Terminal (**007**) and internal olefins, as well as silyl protecting groups (**008**) or protected alkynes (**009**) are well tolerated. It was also shown that shifting the directing group by one (**010**) or two carbon atoms engenders no detrimental effect on regio- or stereoselectivity.

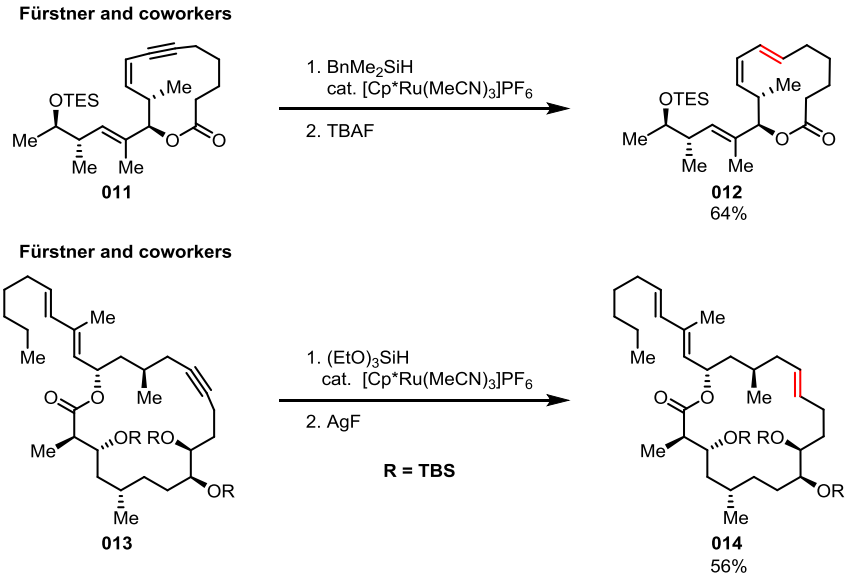


Scheme 3. Representative examples for the directed *trans*-selective hydrostannation.

1.2.3. Applications of *trans*-Selective Hydrosilylations in Total Synthesis

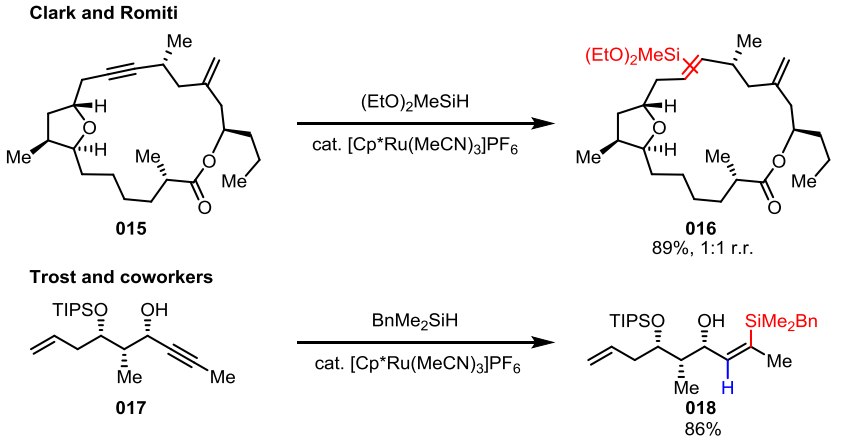
The majority of *trans*-selective hydro-metalations reported in the literature relate to the hydrosilylation of alkynes due to its long and successful history. The mild reaction conditions and excellent functional group tolerance render this methodology highly attractive for total synthesis. In most instances, the resulting alkenylsilanes are protodesilylated to provide net *trans*-reduction of the alkyne as illustrated in Scheme 4.

In the total syntheses of lactimidomycin[9] and tulearin C[10], Fürstner and coworkers employed the ruthenium catalyzed hydrosilylation for the overall *trans*-reduction of an internal alkyne (**011** and **013**) which was obtained via ring-closing alkyne metathesis (RCAM) (Scheme 4). This powerful combination enabled the late-stage introduction of an *E*-olefin with high stereoselectivity under mild conditions in the presence of sensitive functional groups (**012** and **014**).



Scheme 4. *trans*-selective hydrosilylation for net reduction of alknyes.

Clark and Romiti[11] prepared alkenyl silanes **016** which were subsequently utilized in a Fleming-Tamao oxidation to access amphidinolides T1, T3 and T4 from common precursor **015** (Scheme 5). In the synthesis of lasanolide A, Trost and coworkers engaged alkenyl silane **018** in an ensuing Hiyama-Denmark cross coupling.[12]



Scheme 5. Ruthenium catalyzed *trans*-hydrosilylation as prelude for follow-up chemistry.

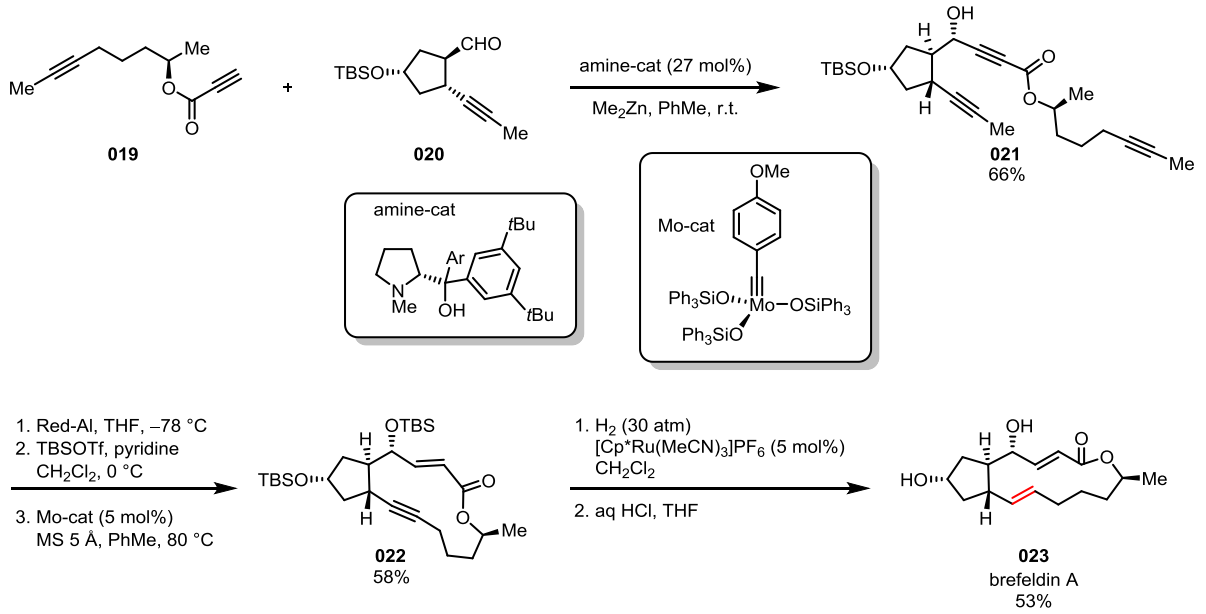
Synthetic applications have demonstrated the versatility of alkenylsilanes in complex molecule synthesis although examples are limited.

1.2.4. Application of *trans*-Selective Hydrogenation in Total Synthesis

In 2013, Fürstner and coworkers reported the first ruthenium catalyzed *trans*-selective hydrogenation of internal alkynes.[13] A mechanistic proposal that accounts for the observed selectivity, as well as the formation of over-reduction and isomerization products was supported by NMR studies and single-crystal X-ray analysis.[14] In the same year, the first application of this

novel transformation for the late-stage installation of an *E*-olefin was impressively demonstrated in the large scale synthesis of brefeldin A (**023**) (Scheme 6).[7c]

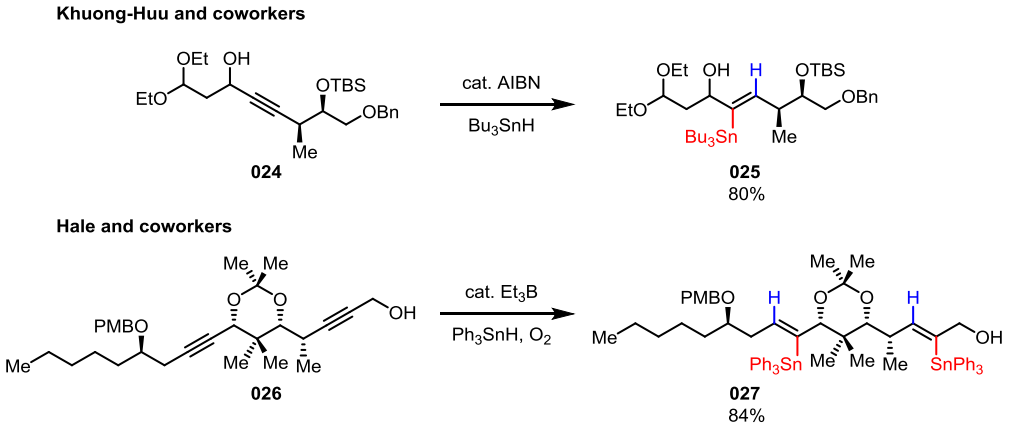
Fragments **019** and **020** were joined by an enantioselective alkynylation to yield triyne **021**. Routine functional group manipulations set the stage for the RCAM providing access to enyne **022**. Ruthenium catalyzed *trans*-selective hydrogenation and global deprotection delivered brefeldin A (**023**) in good overall yield. Notably, this single approach generated more material than all previous attempts combined. The cooperation of RCAM and *trans*-selective hydrogenation allows expeditious access to stereodefined double bonds in a highly atom economical way.



Scheme 6. Endgame in total synthesis of brefeldin A (**023**).

1.2.5. Applications of *trans*-Selective Hydrostannations in Total Synthesis

At the outset of this project, no application of the ruthenium catalyzed *trans*-selective hydrostannation, in the context of natural product synthesis, had been reported. However, *trans*-alkenylstannanes had previously been obtained via radical hydrostannations of alkynes with appreciable regio- and stereoselectivities. Notable examples are presented in Scheme 7. In a study towards the synthesis of maytansine, Khuong-Huu and coworkers employed a radical hydrostannation of propargyl alcohol **024** to access fragment **025**.[15] Hale and coworkers exploited a doubly O-directed, regio- and stereoselective radical hydrostannation with triphenylstannane in the presence of triethylborane as an initiator to obtain fragment **027**.[16]



Scheme 7. Radical *trans*-selective hydrostannation of alkynes.

Given the diversity of Stille cross-coupling protocols, the synthesis of stereodefined alkenylstannanes is of much greater interest to the synthetic community than their corresponding silyl counterparts.[17] At the same time, due to the potential toxicity of alkenylstannanes, methods to introduce and convert other alkenylmetalloids remain highly desirable.

1.3. Concluding Remarks

trans-Hydrometalation methodologies represent a powerful complement to their established *syn*-selective counterparts. The synthetic utility of the resulting alkenylmetalloids and the possibility to conduct these transformations at the late stages of complex molecule syntheses, render this an exciting area of research. This thesis will expand the scope of directed hydrometalations (chapter 2), as well as develop novel transformations of the resulting alkenylmetalloids (chapters 3-5). Finally, the applicability of the methodologies disclosed herein is demonstrated in the context of a diverted total synthesis (chapter 6).

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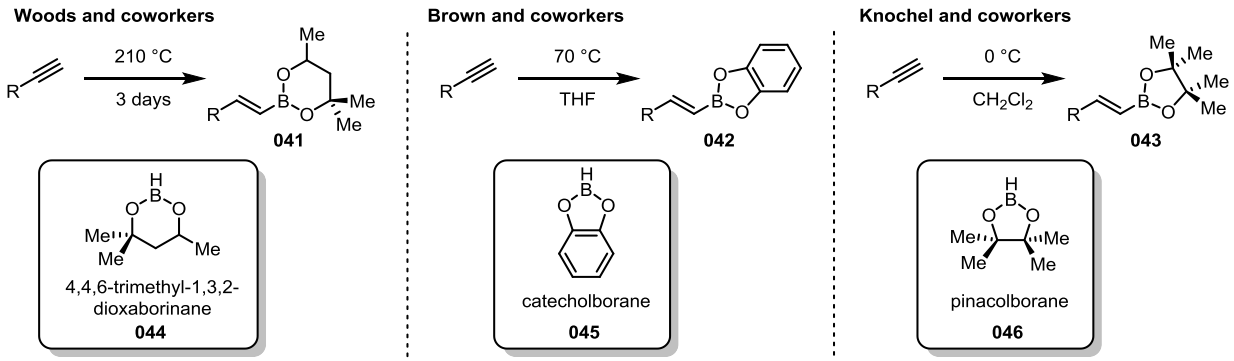
2. Directed Hydroboration of Propargyl Alcohols and Suzuki Cross-coupling for the Selective Synthesis of Trisubstituted Olefins

2.1. Introduction

2.1.1. Historic Background on Hydroboration

The first hydroboration of a carbon-carbon multiple bond was described in 1948 by Hurd.[1] He observed the hydroboration of ethylene at 100°C in the gas phase with diborane to yield triethylborane. This result was later mechanistically investigated by Wheatly and Pease[2] and refined by Brown and coworkers.[3] In a landmark discovery, Brown and coworkers found that the addition of ethereal solvents promotes the hydroboration of alkenes with diborane, allowing the conversion of terminal olefins to alkyl boranes to proceed at room temperature.[4] The first hydroboration of an alkyne was reported in 1966. In a seminal publication, Woods and coworkers utilized borane **044** at high temperatures to access alkenylboronates **041** (Scheme 1)[5]. By using the less hindered and therefore more reactive catecholborane **045** in ethereal solvents, Brown and coworkers were able to access a variety of catecholboronates **042**.[6] In 1992, Knochel reported the synthesis of pinacolborane **046**, one of the most widely used boranes to date.[7] It was found that **046** readily reacts with terminal alkynes at temperatures as low as 0°C in non-ethereal solvents.[8]



Scheme 1. Evolution of alkyne hydroborations.

2.1.2. Mechanistic Considerations

The mechanism of alkene hydroboration has been studied in detail by Brown and Pasto. Two possible pathways have been proposed. A dissociative pathway was mainly advocated by Brown on the basis of numerous kinetic studies.[9] An associative pathway is favored according to Pasto[10] and Schleyer[11]. Furthermore, some mechanistic insight has been gained by computational methods.[12]

From kinetic studies, Brown deduced that prior to association of the alkene, the Lewis base dissociates from the boron center (**049**). He found that excess Lewis-base present in the reaction medium effectively suppresses hydroboration. Upon coordination of the alkene, the crucial hydroboration takes place and the product alkane **050** is again complexed by the Lewis base (**051**).

An alternative pathway has been put forward by Pasto and Schleyer who proposed an associative pathway in which the Lewis base is replaced in a S_N2-like mode by the alkene (**052**). They argue that according to the Hammond postulate, the hydroboration proceeds through a very early transition state as the activation barrier is extremely low, involving very little rehybridization of the olefin carbons. In BH_3·THF, the boron atom is sp^3 hybridized which results in S_N2-like displacement of THF over the course of the reaction by an overlap between the π-electron system of the olefin and the σ*-orbital on boron. As the reaction proceeds through a very early transition state, the displacement of THF would not have significant effect on the entropy of activation of the reaction.

In contrast, very little is known about the mechanism of hydroboration of alkynes although analogous reactivity to alkenes has been proposed.

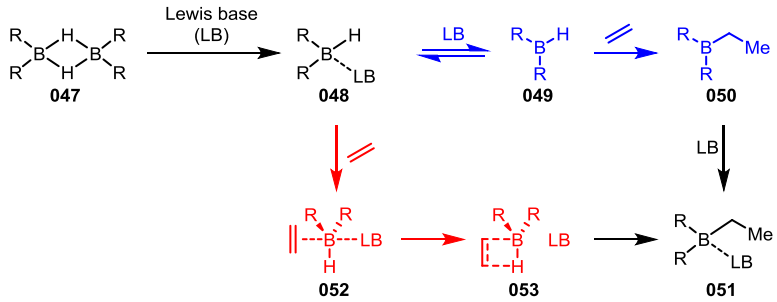


Figure 1. Brown's dissociative pathway (blue) and Pasto's associative pasthway (red).

2.1.3. State of the Art in Directed Hydroborations

As the hydroboration of an unsymmetrical alkyne can give rise to two regioisomers, a plethora of studies has been conducted attempting to access both regioisomers in a highly selective fashion. The regiochemical outcome is predominantly influenced by the steric properties of the alkyne and the hydroborating agent, though electronic factors have also shown to influence regiochemistry. Such substrate control can be overridden by intramolecular delivery of the borane or by organometallic catalysis. The most commonly employed hydroborating agents are depicted in Figure 2.

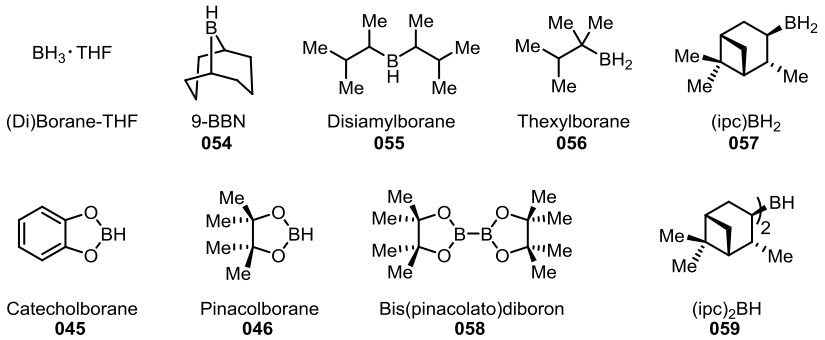


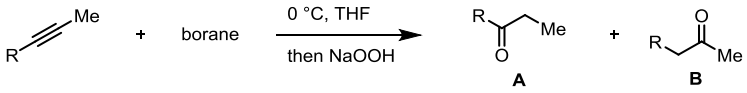
Figure 2. Commonly employed borane sources.

A selection of the most relevant examples of regioselective hydroboration is presented below to summarize the current state of the art.

2.1.3.1. Uncatalyzed Regioselective Hydroboration of Alkynes and Alkenes

Systematic studies have been conducted by Zweifel[13] and Brown[14] who treated a variety of methyl-capped alkynes with thexylborane (**056**) or 9-BBN (**054**), respectively, followed by an oxidative work-up (Table 1). A correlation between increased steric demand of the **R**-substituent and enhanced selectivity towards the methyl ketone **B** was observed. For example, treating 2-hexyne (R=Pr) with $ThxBH_2$ or 9-BBN results in low regioselectivity in both cases. Employing the same reagents for the hydroboration of bulkier *neo*-heptyne (R=*t*Bu), the product is obtained with much enhanced regioselectivity.

Table 1. Regioselective hydroboration of methyl-capped alkynes.

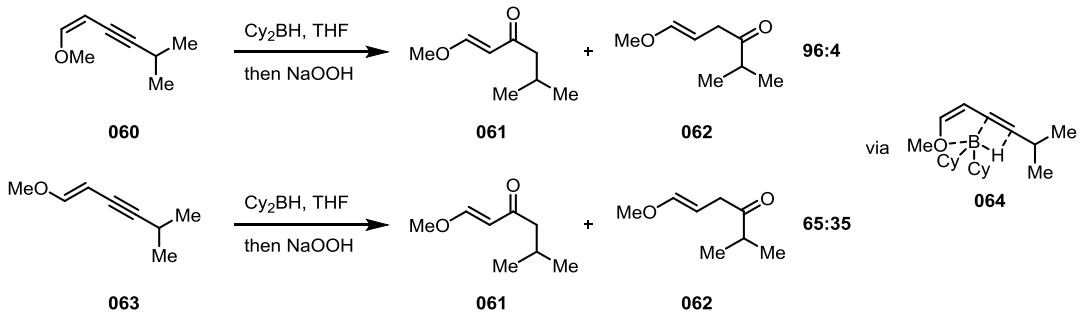


R	$ThxBH_2$ A : B	9-BBN A : B	ThxBHO*i*Pr A : B	$ThxBHCl{\cdot}SMe_2$ A : B
Pr	39 : 61	22 : 78	39 : 61	2 : 98
***i*Pr**	19 : 81	4 : 96	n.d.	n.d.
Cy	22 : 78	4 : 96	n.d.	n.d.
***t*Bu**	3 : 97	1 : 99	n.d.	n.d.
Ph	43 : 57	65 : 35	17 : 83	3 : 97

Not only the steric bias of the alkyne has a tremendous impact on the regiochemical outcome, also the steric bulk of the hydroborating agent is of critical importance. Cha and coworkers reported that an alkoxyl alkylborane, formed on treatment of thexylborane (**056**) with one equivalent of an alcohol, delivers the methyl ketone in a far more selective fashion.[15] It

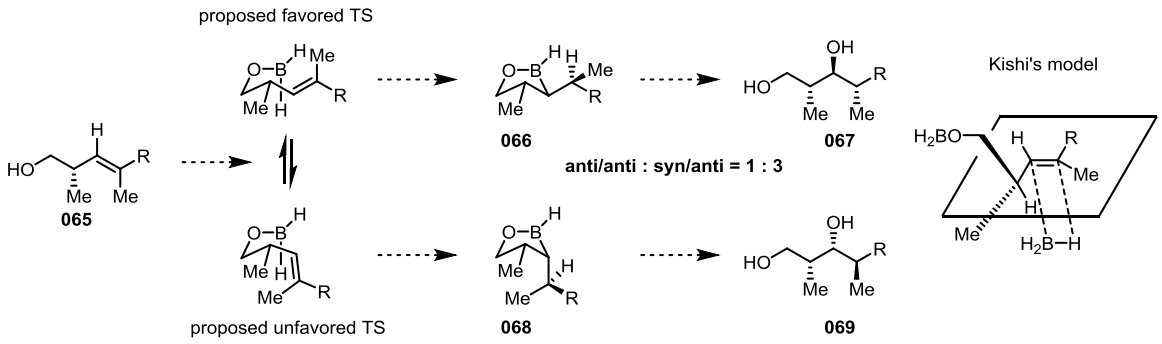
was found that by increasing the size of the alkoxide on the borane, the regioselectivity could be improved. Interestingly, despite its lower steric bulk, chloro thexylborane delivered the same product in an even more selective fashion which might be due to an increased electrophilicity of the boron center.[16]

Intramolecular delivery of the hydroborating agent was first proposed by Zweifel and coworkers.[17] They found that by treating methoxy enynes **060** and **063** with dicyclohexylborane, the observed regioselectivity strongly depended on the olefin geometry (Scheme 2). Based on these results, coordination of the borane to the vinyl ether prior to hydroboration was proposed (**064**). It should be noted at this point that the double bond geometry of vinyl ethers **061** and **062** equilibrates under the basic oxidative work-up conditions.



Scheme 2. Regioselective hydroboration of enynes by Zweifel and coworkers.

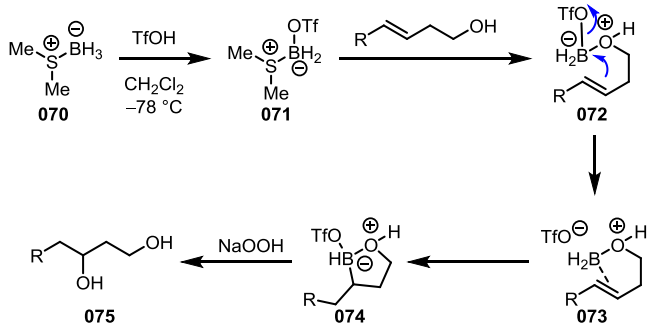
This explanation has been questioned as similar models for alkene hydroboration failed to predict the observed regio- or stereochemical outcome. For example, Heathcock reported a diastereoselective hydroboration/oxidation sequence as part of a total synthesis (Scheme 3).[18] Although it seems tempting to deem an intramolecular borane delivery responsible for the observed outcome, the result can also be explained by considering Kishi's model.[19] Furthermore, it was found that a minimum of two equivalents of borane was necessary to reach full conversion. An intermolecular hydroboration invoking a transition state in accordance to Kishi's model correctly predicts the observed regio- and stereochemical outcome.



Scheme 3. Intramolecular vs. intermolecular hydroboration.

Additional examples have been reported in the literature but no general model has been put forward. Furthermore, no reports on the intramolecular hydroboration of internal alkynes have been disclosed to date.

Some examples of intramolecular hydroboration of alkenes can be found in recent work from the Vedejs group (Scheme 4).[20] After activation of $BH_3{\cdot}SMe_2$ (**070**) with TfOH, a highly reactive hydroborating agent (**071**) is formed. Upon treatment of a variety of homoallyl alcohols with **071**, the corresponding 1,3-diols **075** were obtained after oxidative work-up with near perfect regioselectivity, albeit in modest yields.

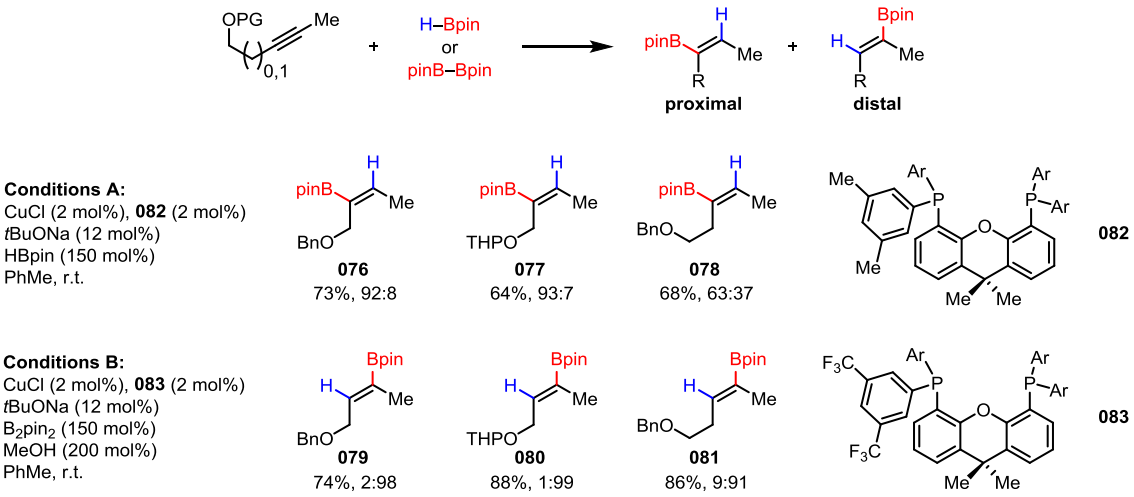


Scheme 4. Intramolecular hydroboration of homoallyl alcohols.

The intramolecular delivery was confirmed by conducting the reaction in the presence of five equivalents of cyclohexene. After oxidative work-up, no cyclohexanol was detected and the isolated yields were comparable to those obtained in the absence of cyclohexene. Besides homoallyl alcohols, homoallyl amines and phosphines can also serve as substrates in this transformation. Surprisingly though, no attempts were made to extend the scope towards the alkynyl counterparts.[21]

2.1.3.2. Catalytic Regioselective Hydroboration of Alkynes and Alkenes

The field of metal-catalyzed hydroboration of alkynes has received considerably more attention than its uncatalyzed ancestors. The results of these endeavors have been recently reviewed and a selection of the most illustrative examples will be given below.[8b, 8c, 22] One of the most prominent examples stems from the recent work of Tsuji and coworkers (Scheme 5).[23] They found that by treating protected propargyl and homopropargyl alcohols under copper catalysis in the presence of modified XantPhos ligands **082** and **083**, a regiodiverse formal hydroboration can be accomplished.



Scheme 5. Regiodivergent formal hydroboration of alkynes by Tsuji and coworkers.

The differences in regioselectivity of the two protocols can be attributed to the different copper species obtained during the catalytic cycle (Figure 3). When pinacol borane is employed, a copper hydride forms which undergoes a regioselective hydrocupration of the alkyne followed by a σ-bond metathesis to furnish α-hydroborated products. If bis(pinacolato)diboron is utilized, a boryl copper species forms that undergoes borylcupration. In the presence of methanol, the resulting alkenyl copper species is protonated and the copper alkoxide re-enters the catalytic cycle.

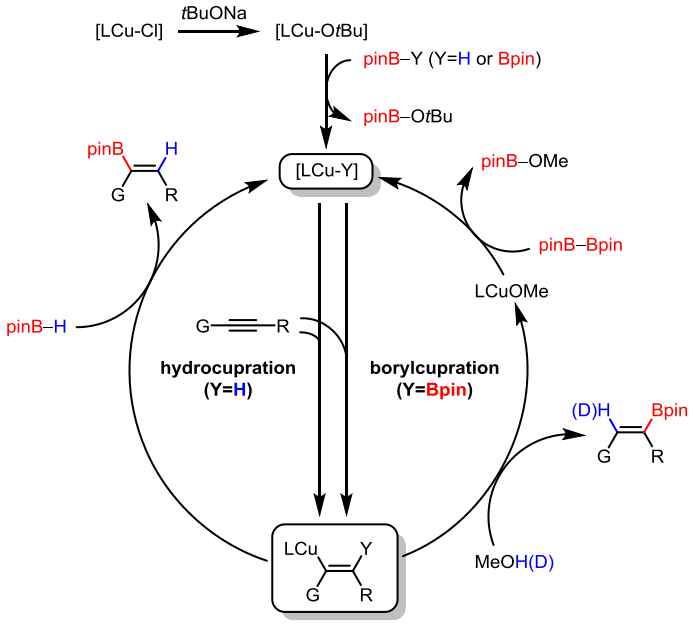
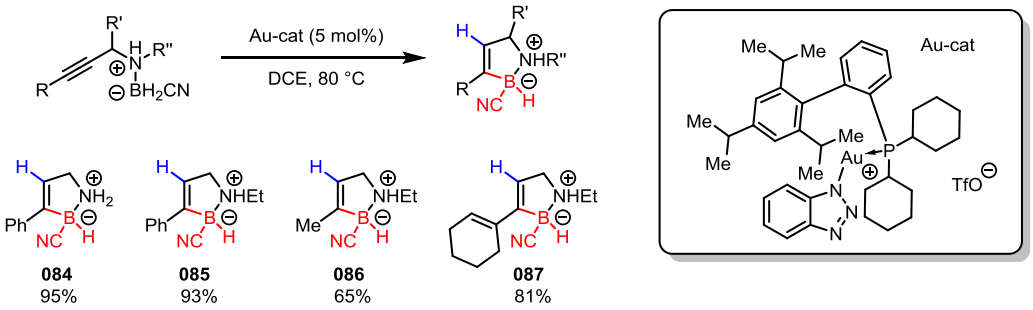


Figure 3. Proposed catalytic cycle of the copper-mediated regiodivergent hydroboration by Tsuji and coworkers.

This has been confirmed by adding MeOD instead of MeOH to quench the alkenyl copper species. The observation that the copper resides after hydro- or borylcupration next to the alcohol functionality was not rationalized. It can only be speculated at this point if electronic or steric factors are accountable for the high regioselectivity.

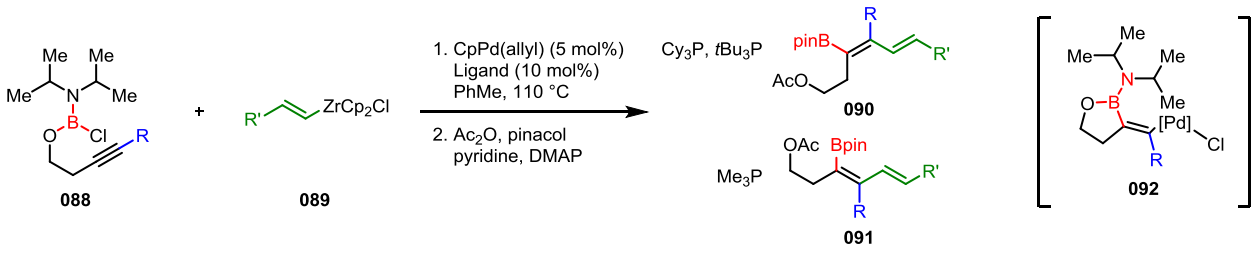
Another very similar protocol has been disclosed by McQuade and coworkers who applied a copper-NHC complex to achieve good selectivity with protected propargyl alcohols.[24] The major drawback of that procedure lies in the necessity of using a *p*-nitrobenzene protecting group that can only be cleaved in two steps.

An alternative approach has been reported by Shi and coworkers (Scheme 6).[25] By reacting sodium cyanoborohydride with propargyl amines, ammonium borohydrides were obtained. In the presence of a gold catalyst, these reagents underwent a highly *endo*-selective hydroboration to give aminoboranes **084 - 087** in good to excellent yield. Additionally, the group demonstrated the cleavage of the cyano group by treatment with lithium aluminumhydride or replacement with phenylmagnesium bromide.



Scheme 6. Gold catalyzed endo-selective hydroboration by Shi and coworkers.

Over the past decades, Suginome and coworkers disclosed significant contributions to the field of carboboration.[26] The underlying concept of tethering a reactive borane source to a (homo)propargyl alcohol is directly relevant to the development of our own methodology. An illustrative example is shown in Scheme 7.[27] Depending on the ligand employed, the group was able to obtain either the (*E*)- or (*Z*)-carboborated products, **090** or **091**, respectively. The use of sterically demanding tricyclohexyl- or tris(*t*-butyl)phosphine favors the (*E*)-configured product while the less bulky trimethylphosphine favors the (*Z*)-carboborated product after cross-coupling of the *in situ* formed alkenyl palladium **092** with vinyl zirconium species **089**.

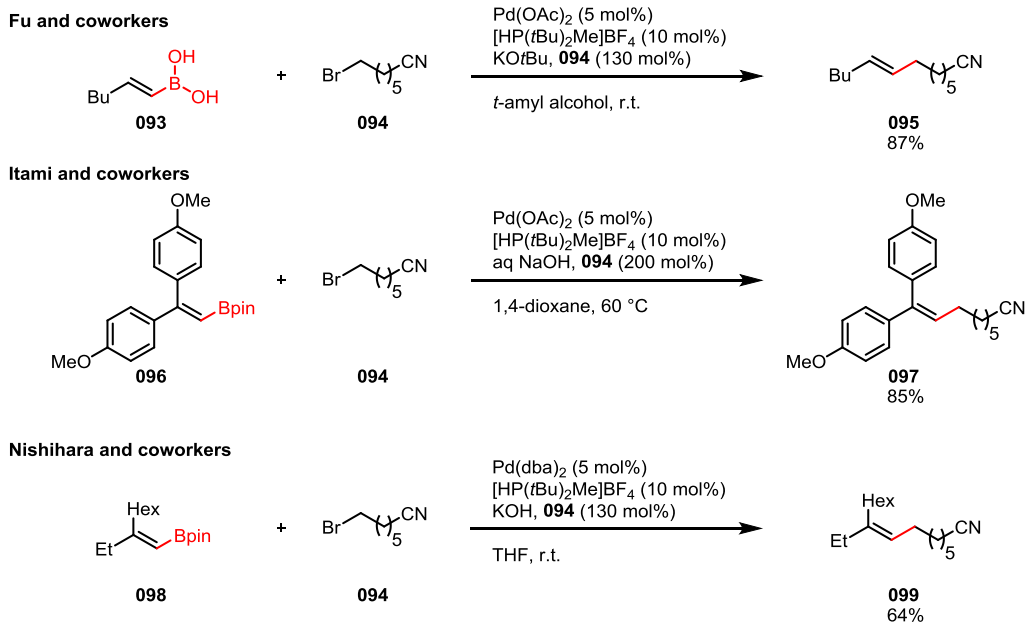


Scheme 7. Stereodivergent carboboration of alkynes by Suginome and coworkers.

This outcome can be rationalized by steric repulsion between the bulky phosphine ligand on the palladium and the di-*iso*-propylamine substituent on the borane. The structure of the intermediate palladium species was confirmed by X-ray crystallography.

2.1.4. (Alkyl)-Suzuki Miyaura Cross-coupling

The Suzuki cross-coupling is unquestionably one of the most powerful transformations in organic chemistry and has been reviewed numerous times in both articles[28] and monographs[29]. Despite having been studied for more than a decade[30], the alkyl Suzuki cross-coupling remains highly challenging. Only a limited number of protocols have been disclosed that employ alkyl halides as coupling partners. These include palladium[31], nickel[32], copper[33] and iron[34] catalyzed processes. As part of this project we were interested in developing a robust cross-coupling protocol that would allow us to combine any alkyl halide with an *in situ* formed alkenyl boronic acid. From the above mentioned protocols, only three seem to be applicable to our system as these employ alkenyl boronic acid derivatives (Scheme 8).



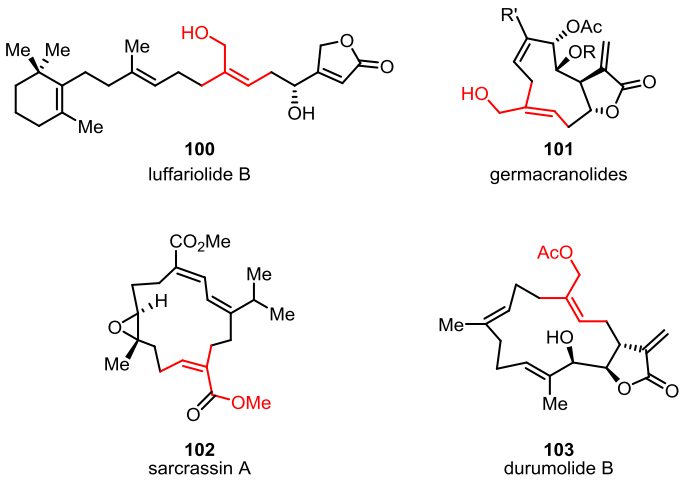
Scheme 8. Palladium catalyzed alkyl Suzuki cross-coupling protocols.

Especially challenging in this specific transformation is the suppression of β-hydride elimination from the intermediate alkyl-palladium species. In their landmark publication, Fu and coworkers found that the sterically demanding di(*t*-butyl)methyl phosphine ligand performed exceptionally well.[31d] The barrier for β-hydride elimination was even high enough to obtain a single-crystal X-ray structure of the intermediate alkyl-palladium species. It is believed, that the unparalleled mild reaction conditions i.e. anhydrous base and low temperatures in combination with an extremely fast oxidative addition, effectively suppress β-hydride elimination. Only upon warming to >50°C does β-hydride elimination become a major issue. Ensuing studies could not

improve upon the seminal conditions; however, it was found that aqueous bases and aprotic solvents can also be employed as demonstrated Itami[31a] and Nishihara.[31c]

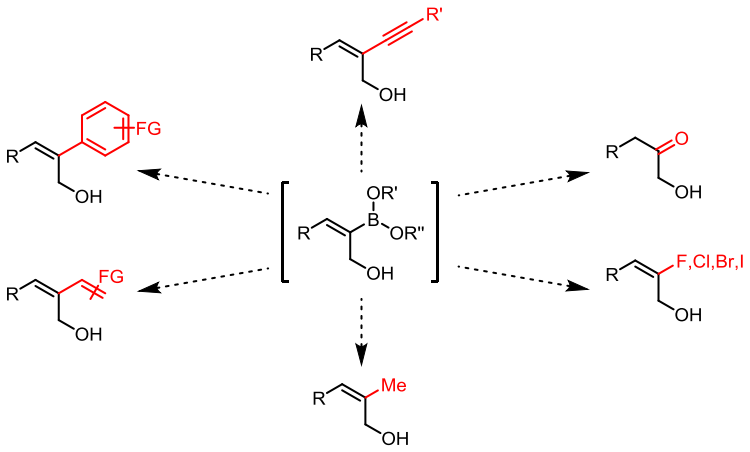
2.1.5. Motivation

With the disclosure of the *trans*-selective ruthenium catalyzed hydroboration of alkynes, our group has reported a highly valuable tool for the stereoselective synthesis of trisubstituted olefins.[35] This transformation shows a broad functional group tolerance and delivers valuable building blocks for potential late-stage diversification in natural product synthesis. The major drawback though lies in the lack of regioselectivity. So far no protocol could be developed that overrides substrate control. To overcome this obstacle we sought to develop a method that exploits the possible directing effects of propargyl alcohols. The resulting alkenylboronates would then be amenable to the aforementioned alkyl Suzuki cross-coupling to give rise to trisubstituted allyl alcohols. As the resulting (*Z*)-but-2-en-1-ols constitute important motifs in natural products, this would enable us to access a plethora of biologically relevant products. A selection of possible targets is shown in Scheme 9 wherein the critical (*Z*)-but-2-en-1-ol motif is highlighted in red.[36]



Scheme 9. Possible applications for directed hydroboration/Suzuki cross-coupling.

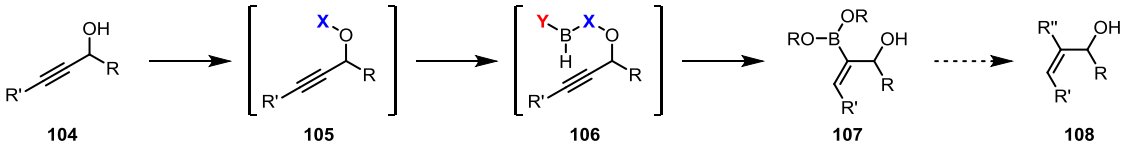
Besides their application in total synthesis, the alkenylboronates may also be useful synthons for the introduction of various functional groups as illustrated in Scheme 10.



Scheme 10. Possible transformations of the resulting alkenylboronates.

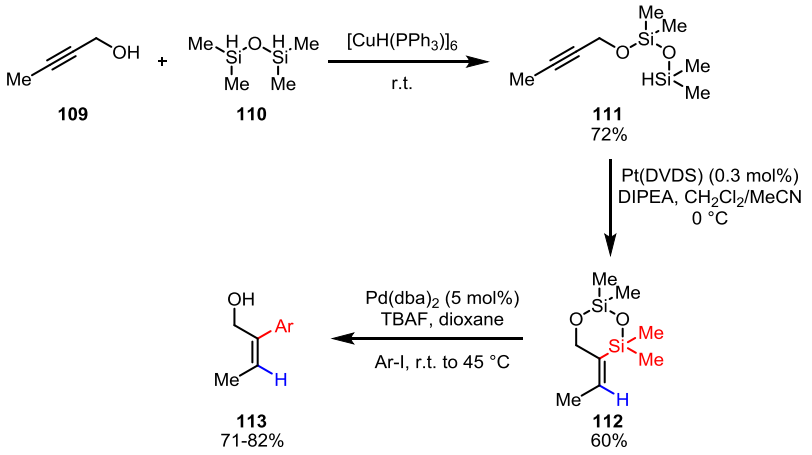
2.1.6. General Considerations and Rationale

As emphasized in the previous discussion, the most promising way to affect regioselective hydroboration appears to tether a suitable borane source to the propargyl alcohol. For geometric reasons, the borane cannot be directly attached to the alcohol functionality as a four-membered intermediate would have to form for intramolecular borane delivery. To increase the 'reach' of the propargyl alcohol, an extending linker has to be attached first. This idea can either be realized by a transient hemilabile or covalently attached linker. The general concept is presented in Scheme 11.



Scheme 11. General concept of hemilabile linker assisted hydroboration.

Some inspiration has been taken from a report by Denmark and coworkers (Scheme 12).[37] By tethering disiloxane **110** to propargyl alcohol **109**, followed by hydrosilylation and cross-coupling, a 'library' of (*E*)- or (*Z*)-but-2-en-1-ols was accessed depending on the catalyst employed in the hydrosilylation.



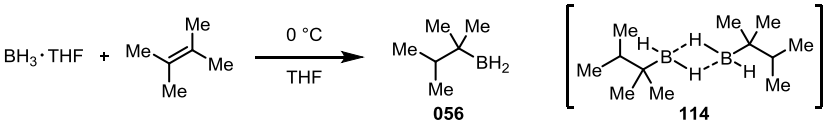
Scheme 12. Three step sequence for the functionalization of propargyl alcohols by Denmark *et al.*.

As the siloxane in **112** is cleaved under the cross-coupling conditions, no additional deprotection step is required. The major drawback though lies in the utilization of the rather limited Hiyama-Denmark coupling that predominantly employs activated electrophiles.[38] In our investigation, we also sought to employ a hemilabile linker which can be installed and cleaved during the hydroboration/cross-coupling event. With that requirement in mind, we were mainly interested in reactive carbonyl derivatives that can form hemiacetals, imides or carbonates *in situ*. It was expected that under the strongly basic conditions of the ensuing Suzuki cross-coupling, this hemilabile linker can effectively be cleaved such that no additional steps are added to the hydroboration/Suzuki cross-coupling sequence.

2.2. Results and Discussion

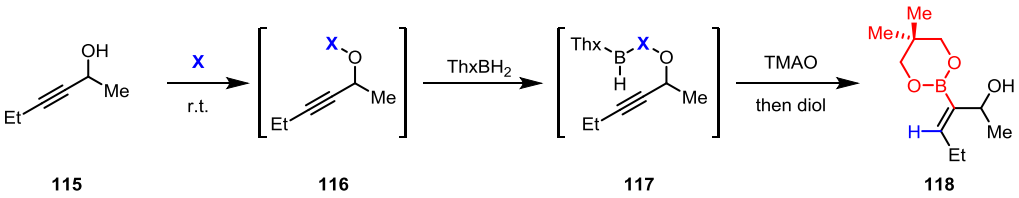
2.2.1. Reaction Development

At the outset of this endeavor, a suitable linker and borane source had to be identified. As one of the hydrides on the borane has to react with the linker and the other one with the alkyne, we had to focus on monoalkyl boranes. Furthermore, it was expected from the works of Cha and coworkers[15] that thexyl alkoxyboranes are suitable hydroborating agents for alkynes. Therefore, we initiated the study with thexylborane as the hydroborating agent. Thexylborane (**056**) can conveniently be prepared as a stock solution in THF by mixing BH_3·THF and 2,3-dimethylbutene (Scheme 13).[39] The resulting solution can be stored for prolonged periods in the fridge under an argon atmosphere without noticeable loss of activity.



Scheme 13. Preparation of thexylborane.

In solution, **056** exists as a mixture of its dimer **114** and THF-stabilized monomer. Because of the steric bulk, only the monoalkyborane is formed. The concentration of the obtained stock solution was determined by titration of an aliquot with EtOH/H_2O with a gas burette under ice cooling. Other boranes were also tested during the development of this protocol and prepared in a similar way. The choice of the linker proved to be more difficult. A screening was initiated in which the resulting alkenyl borane was first oxidized with trimethylamine-*N*-oxide (TMAO)[40] and the resulting borinate trapped as the neopentyl boronate as exemplified in Scheme 14.



Scheme 14. Development of a directed hydroboration protocol.

Prior to addition of **056**, the free propargyl alcohol was allowed to react with trichloroacetonitrile[41], *p*-toluenesulfonyl isocyanate[42], *p*-nitrobenzaldehyde or methyl trifluoropyruvate[43] to yield the corresponding linkages *in situ*. Thexylborane (**056**) was then added at −78 °C. After warming to room temperature, oxidative work-up, and trapping, alkenylboronate **118** was obtained. The results are presented in Table 2 and the linkers employed are given in Figure 4.

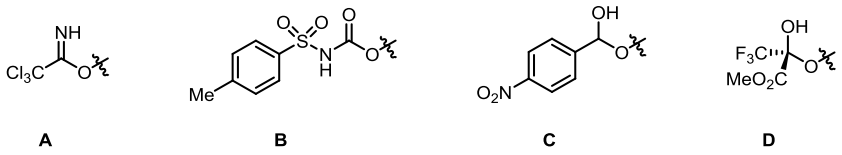
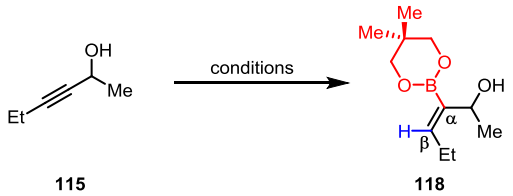


Figure 4. Linkers employed in the directed hydroboration with $ThxBH_2$.

Table 2. Optimization of directed hydroboration of propargyl alcohols with ThxBH$_2$.



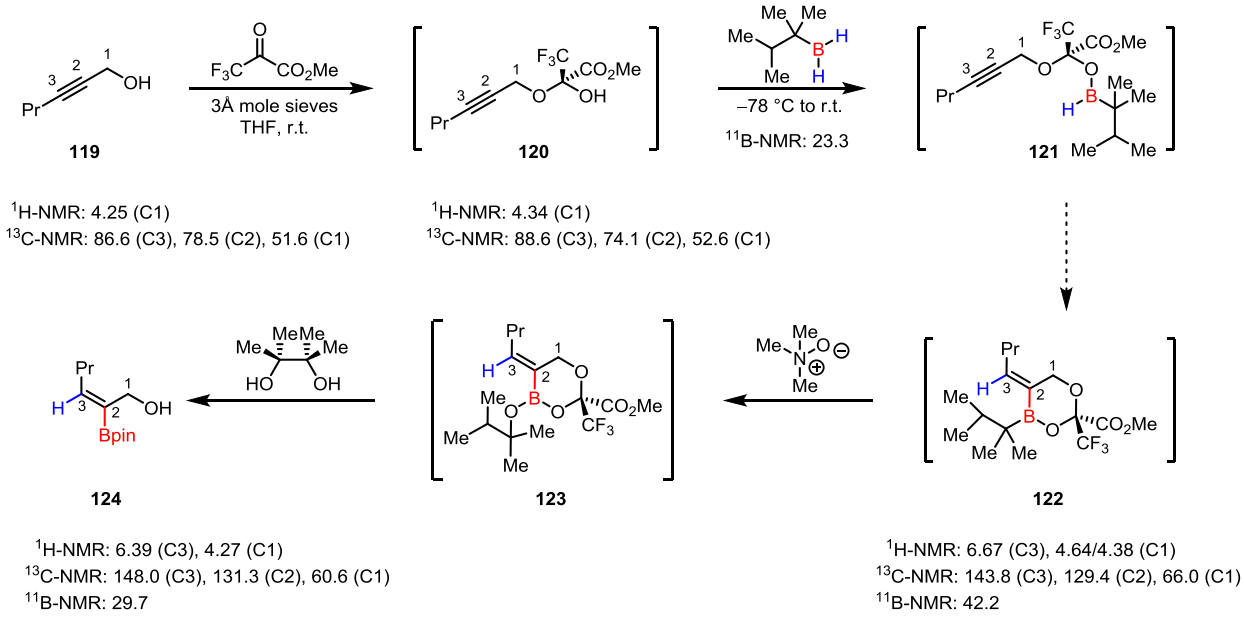
115 118

Entry	Linker	Temp.	Additive	Conc.[a]	α : β[b]	comment
1	**-**	–78 °C to r.t.	**-**	0.5 M	1.5 : 1	full conversion
2	**A**	–78 °C to r.t.	**-**	0.5 M	**-**	no vinyl species
3	**B**	–78 °C to r.t.	**-**	0.5 M	**-**	no vinyl species
4	**C**	r.t.	**-**	0.5 M	**-**	no hemiacetal formation
5	**D**	–78 °C to r.t	**-**	0.5 M/0.1 M	4.0 : 1	full conversion
6	**D**	–25 °C to r.t	**-**	0.5 M/0.1 M	3.5 : 1	full conversion
7	**D**	r.t.	**-**	0.1 M	2.5 : 1	full conversion
8	**D**	–25 °C to r.t	Pentane	0.1 M	3.5 : 1	full conversion
9	**D**	–25 °C to r.t	CH_2Cl_2	0.1 M	3.5 : 1	full conversion
10	**D**	–25 °C to r.t	PhMe	0.1 M	3.5 : 1	full conversion
11	**D**	–78 °C to r.t	1 eq. Me_2S	0.1 M	2.0 : 1	full conversion
12	**D**	–78 °C to r.t	1 eq. Ph_3P	0.1 M	1.5 : 1	full conversion
13	**D**	–78 °C to r.t	1 eq. Et_3N	0.1 M	1.0 : 2	low conversion

[a]in THF; [b]determined by crude NMR

The results in Table 2 demonstrate the low inherent selectivity for the site of hydroboration of the propargyl alcohol (entry 1). Interestingly, linkers **A**, **B** and **C** failed to deliver any product at all (entries 2-4). Only hemiacetal **D** (entry 5) provided the product and, as anticipated, gave an improved α/β-ratio compared to the parent propargyl alcohol. Unfortunately though, attempts to improve regioselectivity by changing temperature, solvent or concentration were all met with failure (entries 6-10). Adding common Lewis bases like Me_2S, PPh_3 or Et_3N only led to a deterioration or even reversal of regioselectivity (entries 11-13).

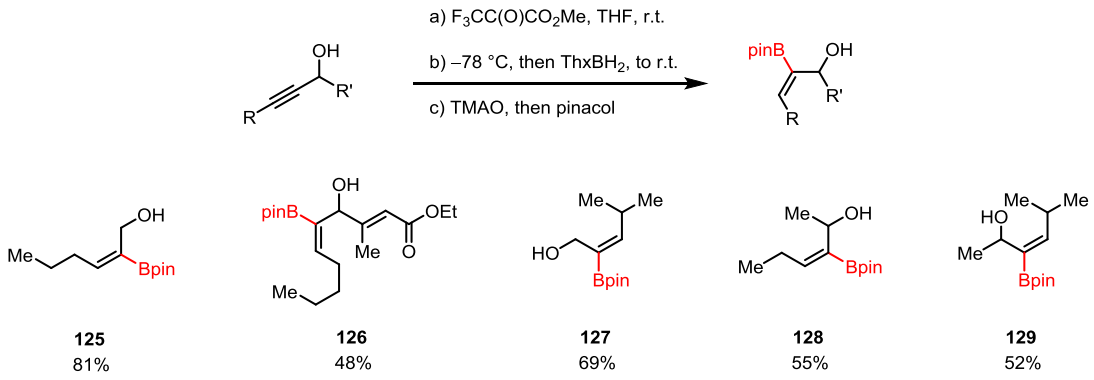
To test our hypothesis that a cyclic boroxinane is formed as an intermediate, the different stages of this transformation were followed by NMR (Scheme 15). As expected, the electronic nature of the alkyne changes significantly upon hemiacetal formation: the α-carbon experiences a downfield shift of 2.0 ppm while the β-carbon is shifted upfield by 4.4 ppm (**120**). This can be attributed to the strong negative inductive effect of the hemiacetal. After $ThxBH_2$ addition, a new boron species is observed as is evident from the boron downfield shift from 23.3 ppm (thexylborane) to 42.2 ppm. This signal corresponds to a RR'BOR'' species which is in good accordance with our proposed dioxaborinane intermediate **122**.[44] Furthermore, a splitting of the two protons at C1 of the allylic alcohol is observed which advocates the formation of cyclic intermediate. Additionally, one of these protons experiences a downfield shift of 0.3 ppm. After oxidative work-up and trapping with pinacol, a new alkenylboron species (**124**) is formed that is well precedented in the literature.[45] Based on this study we felt confident that a boroxinane is formed during the course of the reaction, and that the intermediate hemiacetal should play a major role in dictating the regiochemical outcome.



Scheme 15. NMR study of pyruvate directed hydroboration.

2.2.2. Initial Substrate Scope

With the optimized conditions in hand, we sought to determine the scope of the reaction. In some cases the corresponding pinacol boronates were isolated as shown in Scheme 16. The isolated yields correspond to pure products. In general it was possible to separate both regioisomers on silica.

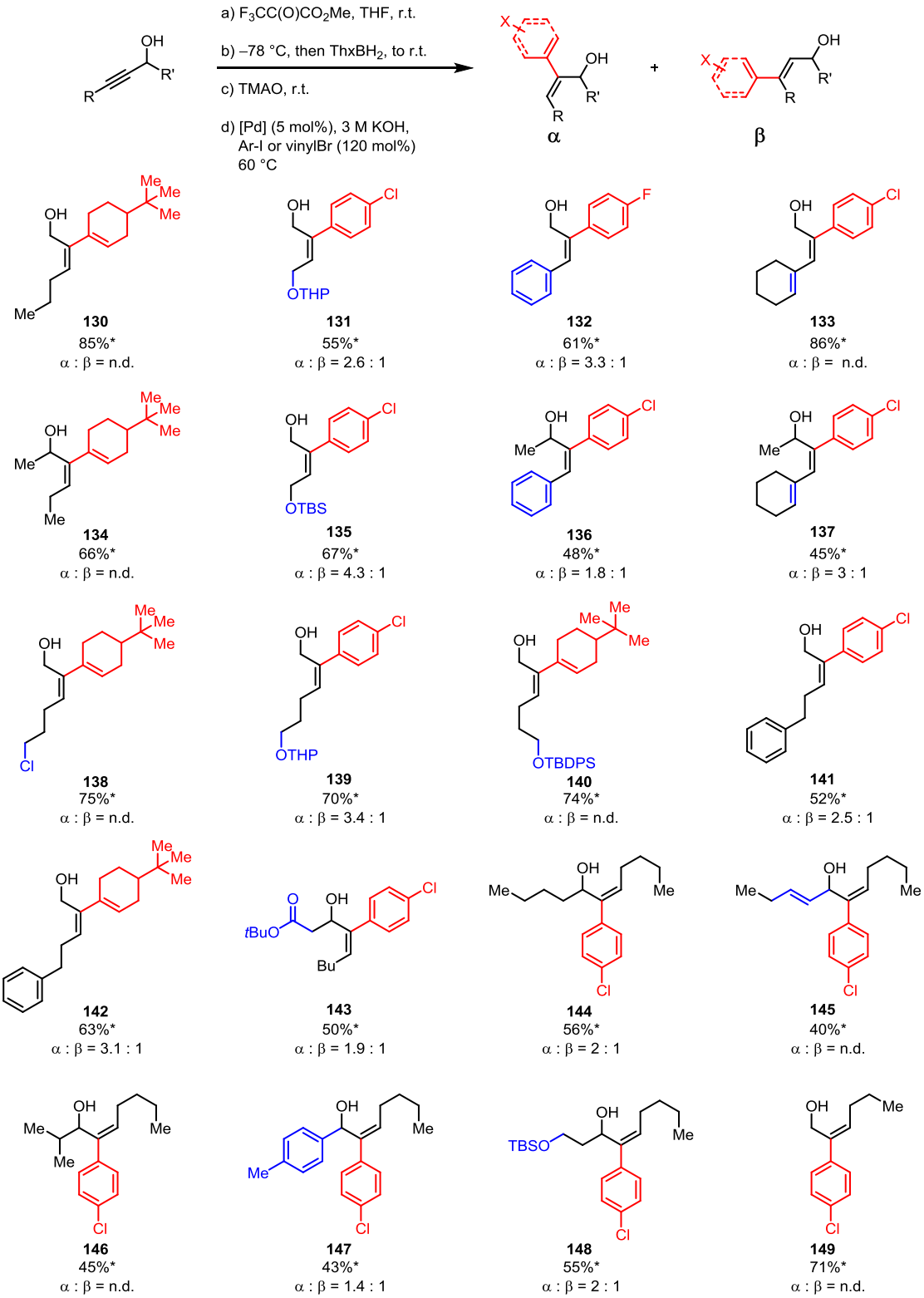


Scheme 16. Directed hydroboration and pinacol boronate formation.

The *in situ* formed alkenyl boronic acids were also coupled under standard Suzuki conditions with either aryl or vinyl halides. After a brief screening, (dppf)$PdCl_2$ in the presence of aqueous 3 M KOH proved optimal and provided the desired product in reliably moderate to good yield. Generally, the Suzuki cross-coupling showed full conversion in less than 1 h at 60 °C. The results are presented in Scheme 17. The crude regiochemical outcome was determined by NMR analysis but the yields shown correspond to pure isolated α-products.

As is evident from Scheme 17, primary alcohols furnish the corresponding products in much higher yield compared to their secondary counterparts (compare **130** to **134**). A variety of functional groups is tolerated including acetals (**139**), halides (**138**), silyl ethers (**135**), esters (**143**) and internal olefins (**145**). Aryl iodides and vinyl bromides couple equally well, e.g. **130** and **149**.

Besides demonstrating an impressive substrate scope, these results raise an important question: *why do primary alcohols provide higher yields and regioselectivities than secondary ones?* This seems counter-intuitive to our initial hypothesis since one would expect that an increasing Thorpe-Ingold effect in secondary alcohols should lead to an increase in regioselectivity.



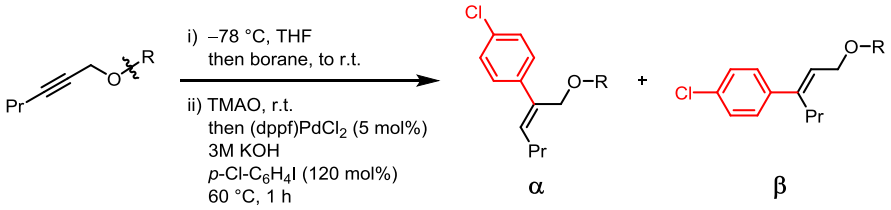
Scheme 17. Substrate scope of the directed hydroboration/Suzuki cross-coupling sequence (*yields refer to pure α).

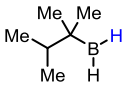
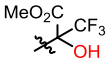
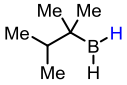
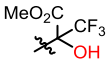
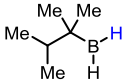
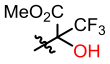
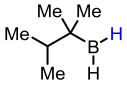
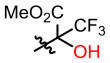
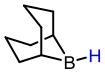
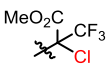
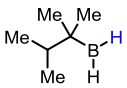
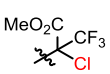
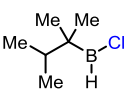
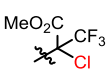
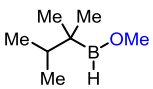
2.2.3. Mechanistic investigation

Although it seems reasonable to propose a reaction of the borane with the hemiacetal prior to hydroboration, the experiments conducted to this point do not provide sufficient evidence to support or refute this hypothesis. Our mechanistic investigation thus sought to answer three major questions: 1) what is the order of events? 2) what determines the regiochemical outcome? 3) how is the other regioisomer formed?

At first, a study was conducted aiming at answering the question how the hemiacetal linker influences the regioselectivity of the hydroboration (Table 3). Therefore, derivatives of both the linker and the borane were prepared and exposed to the reaction conditions to gain insight into the actual mechanism.

Table 3. Determination of reaction pathway: intramolecular vs. intermolecular.



Entry	R	Borane	conditions	NMR ratio α : β	HPLC ratio α : β	comment
1			–78 °C to r.t.	2.3 : 1	2.0 : 1	-
2			–78 °C to r.t.	4.5 : 1	4.0 : 1	-
3			–60 °C, 18 h	4.3 : 1	3.7 : 1	-
4			–40 °C, 18 h	4.4 : 1	4.5 : 1	70% yield
5			–78 °C to r.t.	no hydroboration	no hydroboration	-
6			–78 °C to r.t.	-	2.2 : 1	34% conversion after 18 h
7			–78 °C to r.t.	-	-	very low conversion
8			–78 °C to r.t.	-	-	very low conversion

The first two entries are added for clarity and reflect the standard conditions with and without the pyruvate linker. Entries 3 and 4 show that the regioselectivity is independent of the

reaction temperature and indicate that the regioselectivity is possibly dictated by the inherent reactivity of the propargyl alcohol. When 9-BBN is used instead of thexylborane, no hydroboration takes places (entry 5). As the reactivity of 9-BBN is similar to that of thexylborane, this result indicates that the reaction of the borane source with the hemiacetal is faster than with the alkyne. If the hydroxy group on the hemiacetal is replaced by a chloride to prevent tethering (entry 6) very low conversion is observed with low regioselectivity. This indicates that it is almost certainly not thexylborane itself that reacts intermolecularly with the alkyne moiety, as the observed selectivity is identical to the outcome of the control experiment (entry 1). Interestingly, when chloro thexylborane or methoxy thexylborane are employed, no conversion is observed. As these two boranes resemble the electronic nature of the presumably *in situ* formed tethered alkoxy thexylborane, it seems likely that the actual hydroborating agent is a tethered alkoxyborane. To probe the influence of the electronic nature of the alkyne, 1-hexynol was compared to trifluorobutynol both with and without the pyruvate linker by NMR spectroscopy (Figure 5).

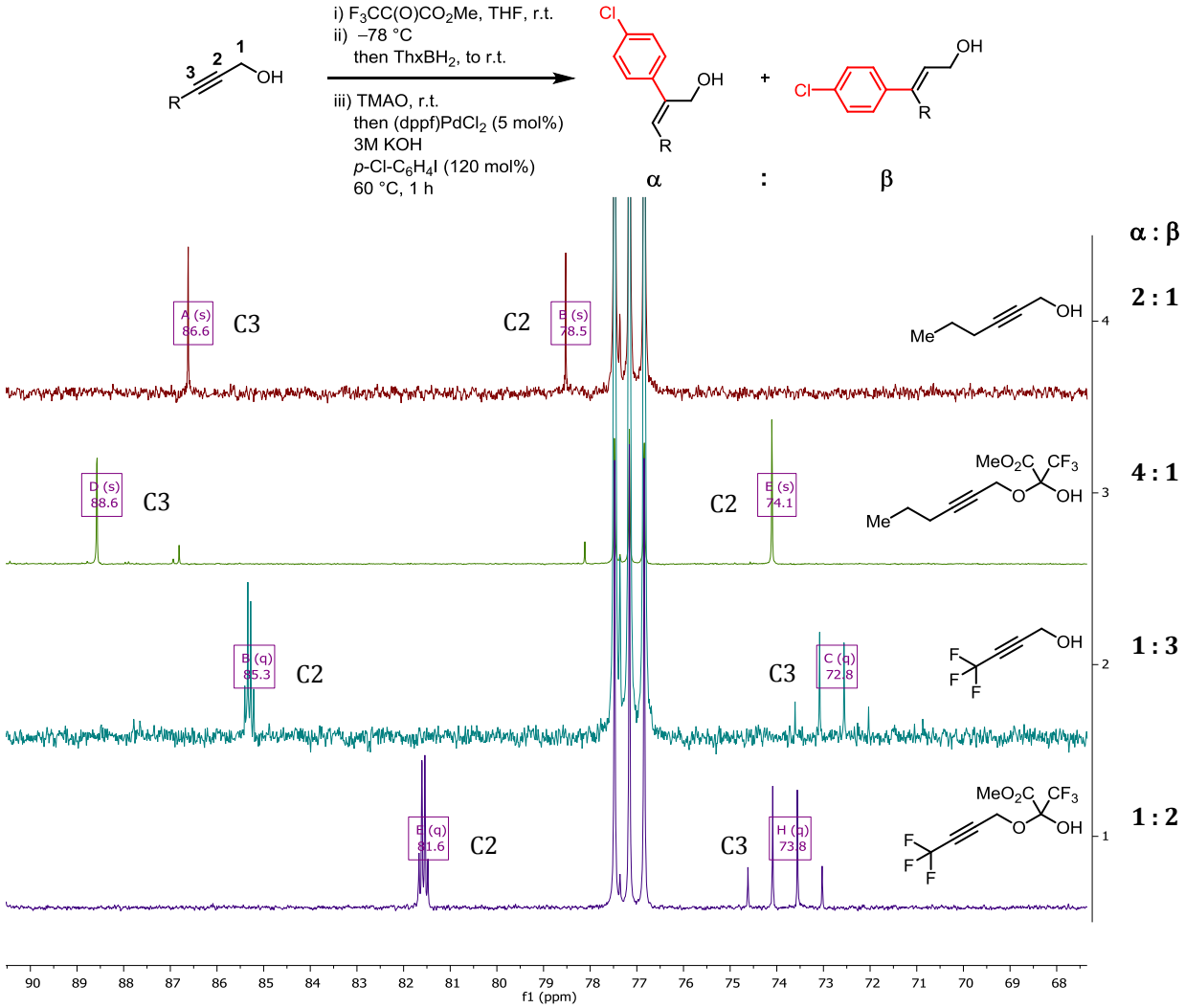


Figure 5. NMR spectra of 1-hexynol and trifluorobutynol with and without pyruvate linker ($^{13}C\{^{1}H\}$ in $CDCl_3$@298K).

By comparing the first two spectra it is evident that attaching the linker to the propargyl alcohol results in an increased electron density on C2 and a decrease on C3 due to their up- and downfield shifts, respectively. This is reflected by an increased Δδ(C2-C3) from 8.1 ppm to 14.5 ppm. In the case of trifluorobutynol this trend is reversed, as C3 is more deshielded than C2. By attaching the pyruvate linker, Δδ(C3-C2) decreases from 12.5 ppm to 7.8 ppm reflecting a shift of electron density towards the alcohol carbon. A schematic representation is given in Figure 6. The charges qualitatively represent the relative electron density at each carbon atom.

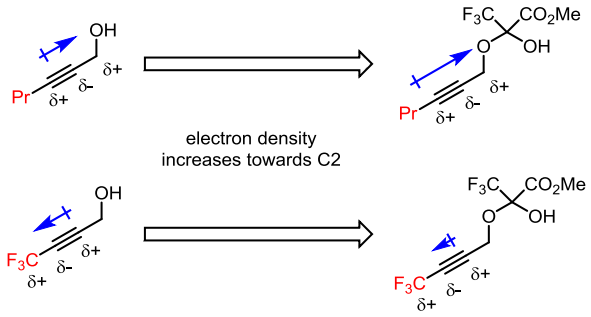


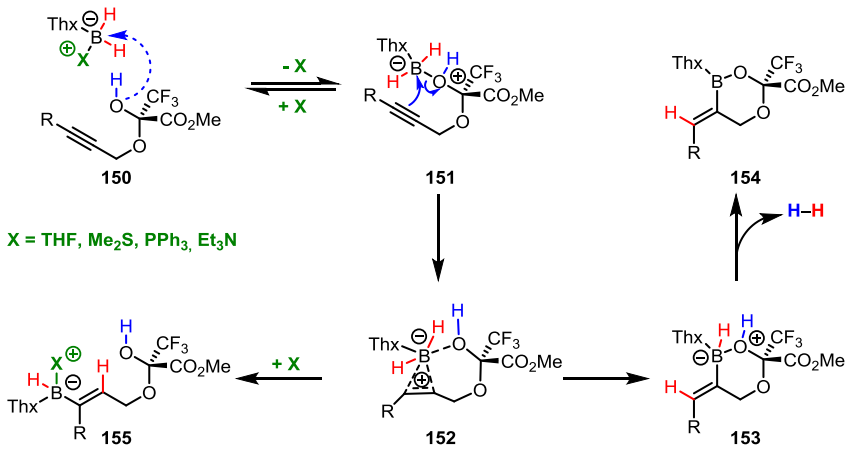
Figure 6. Effect of pyruvate linker to electronic structure of alkyne.

Based on the results of this study, it seems reasonable to propose that *the borane adds across the alkyne such that the boron preferentially ends up at the carbon atom of highest electron density*. In the first case the electron density is increased at C2 by linking an electron withdrawing substituent to the alcohol. Therefore, the regioselectivity increases from 2:1 to 4:1. In trifluorobutynol, the inherent polarity of the alkyne is reversed compared to hexynol. Here C3 is the most electron-rich carbon. By attaching the pyruvate linker to the alcohol, the polarity is reduced and as a result the observed regioselectivity decreases from 1:3 to 1:2.

These results are counterintuitive as one would expect that the hydroboration would simply follow Markovnikov rules. During this process a formal positive charge *next* to the borane is generated which is best stabilized at the position of highest electron density. This would result in the opposite regiochemical outcome. Based on these observations, a possible mechanism is proposed.

In the first step, hemiacetal **150** attacks the Lewis base adduct of thexylborane and displaces the Lewis base, in most cases THF. The newly formed adduct **151** then directs the borane across the alkyne to form transient intermediate **152**. This can be understood as a 3c-2e system. According to the observations made by the NMR experiments, the triangular complex is distorted towards the α-carbon as this carries the higher electron density. From this adduct, two possible pathways are conceivable. If the borane transfers one of its hydrides to the α-position then the unwanted regioisomer **155** is formed. If the hydride is transferred to the β-position, then the resulting borane can react with the hemiacetal to extrude hydrogen via σ-bond

metathesis to give adduct **153**. This would finally yield boroxinane **154** as the predominant product.



Scheme 18. Proposed mechanistic rational for the directed intramolecular hydroboration of alkynes.

This proposal is in good agreement with the observations made in the NMR and regioselectivity studies:

1) Extraneous Lewis bases slow down and decrease the selectivity of the reaction (Table 2) as they compete with the hemiacetal for binding the borane in the pre-equilibrium.

2) If this reaction would yield a thermodynamic and a kinetic product, then a temperature dependence of the regioselectivity would be expected. As the regioselectivity is independent of the temperature (Table 3 entries 2-4), the outcome is solely dictated by the inherent selectivity of the substrate. This control can be conclusively explained considering an intramolecular pathway.

3) The complexation of the borane precedes the actual hydroboration event as for geometric reasons (Baldwin rules and ring-strain) the unwanted β-isomer can only be formed before boron-oxygen bond formation (Table 3, entries 5-8).

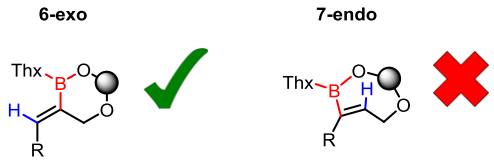
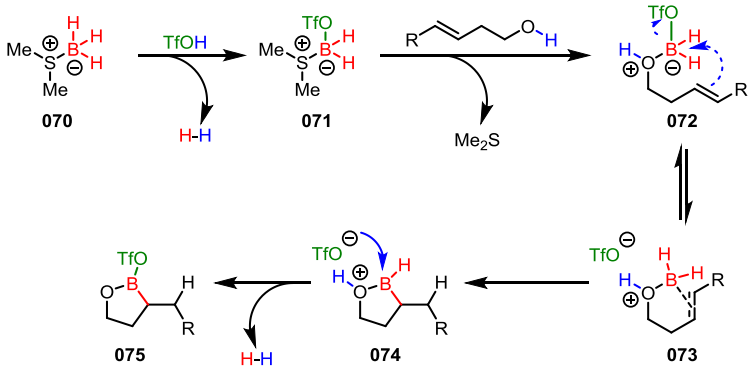


Figure 7. 6-exo-hydroboration vs. 7-endo-hydroboration.

4) The regioselectivity is determined by the electronic and steric environment of the propargyl hemiacetal (Scheme 17, Figure 5). This explains why secondary propargyl alcohols provide products with lower regioselectivity, as the electronic bias is overridden by steric repulsion of the bulky borane and the alcohol substituent.

Our mechanistic proposal closely resembles the hypothesis of Vedejs and coworkers for the intramolecular hydroboration of alkenes. Their general concept is again shown in Scheme 19. It is proposed that the activated borane species **071** first forms a Lewis pair adduct **072** with the homoallyl alcohol on displacement of Me_2S. In the next step the alkene extrudes a leaving group on the borane to give adduct **073**. This complex can then undergo the crucial hydroboration furnishing borane **074**. Upon reaction with the previously displaced leaving group, the resulting oxaborolane expels hydrogen and forms borinane **075**.

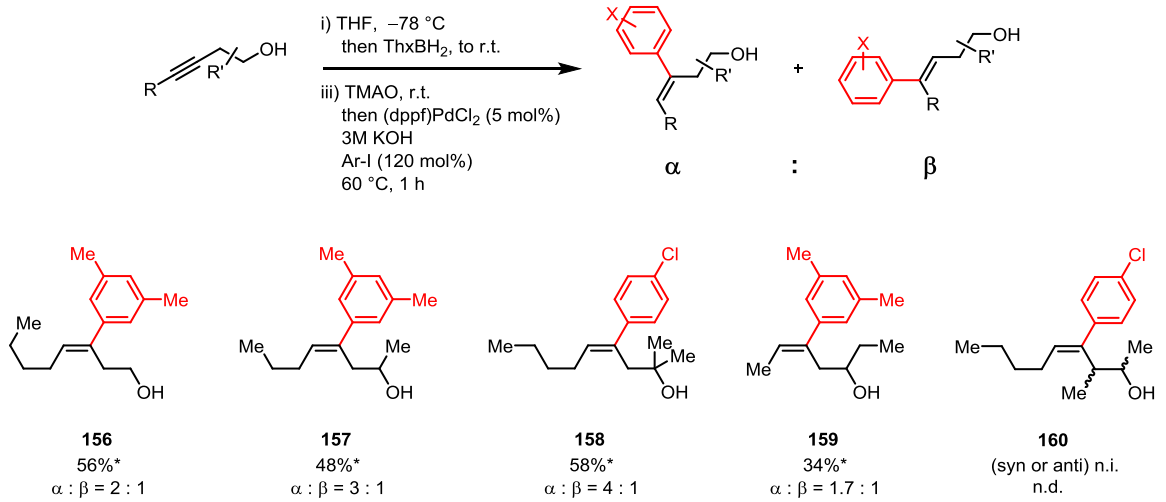


Scheme 19. Directed intramolecular hydroboration of alkenes according to Vedejs[20c].

Having established a protocol for the directed hydroboration/Suzuki cross-coupling and conducted a mechanistic investigation, we pursued to extend the substrate scope further.

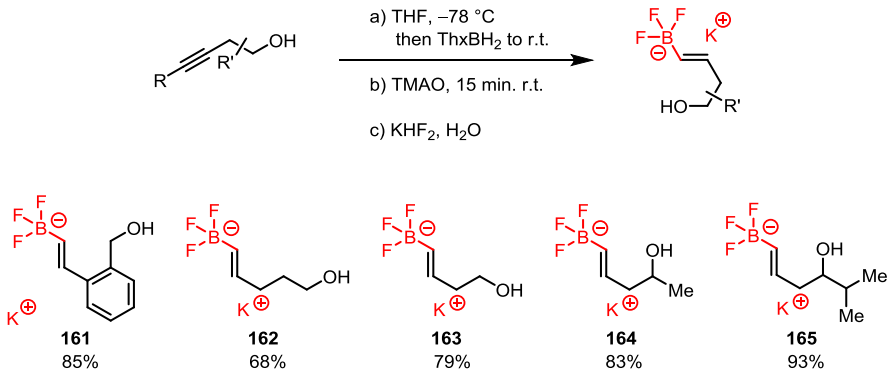
2.2.4. Extended Substrate Scope and Development of an Alkyl Suzuki Coupling Protocol

As proposed in Section 2.2.3, the hemiacetal linker only serves as an anchor for thexylborane to direct the borane towards the alkyne. In principle, other alkynols could also serve as good substrates for the directed intramolecular hydroboration. Indeed, since homopropargyl alcohols may be able to form 5-membered boroxinane intermediates, the hemiacetal linker may even be unnecessary for these substrates. As can be seen from Scheme 20, the results are disappointing, giving low regioselectivities and moderate isolated yields. Interestingly though, a trend can be deduced whereby an increase in the Thorpe-Ingold effect results in an increase in regioselectivity (**156** to **158**).



Scheme 20. Substrate scope of the directed hydroboration/Suzuki cross-coupling sequence (*yields refer to pure α).

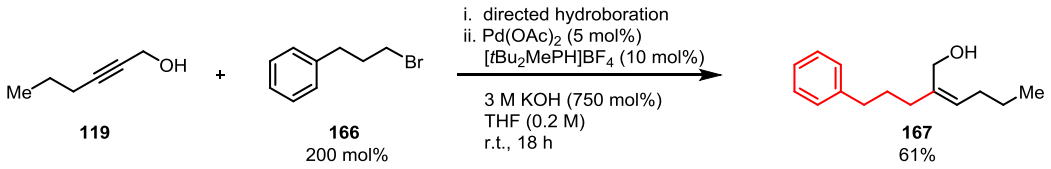
Employing terminal alkynols and trapping the resulting hydroboration products as their respective trifluoroborate salt to assist their purification, a variety of alkenyl borates was obtained (Scheme 21).



Scheme 21. Trifluoroborate salts obtained after hydroboration/oxidation.

The hydroboration showed perfect selectivity for the terminal alkenyl borate irrespective of the length of the tether. Furthermore, the reaction can be conducted with equimolar amounts of alkynol and thexylborane and provides in one-pot the trifluoroborate from the alkynol. Other protocols found in the literature employ more than two equivalents of a borane and require a chromatographic work-up before trifluoroborate formation.[46] The present protocol is therefore a major advance for the synthesis of these versatile building blocks.

As mentioned in the introduction, for complex molecule synthesis an alkyl Suzuki cross-coupling protocol is of great interest as the resulting (*Z*)-but-2-en-1-ol motif is prominently featured in natural products. To this end an efficient cross-coupling protocol was developed (Scheme 22).

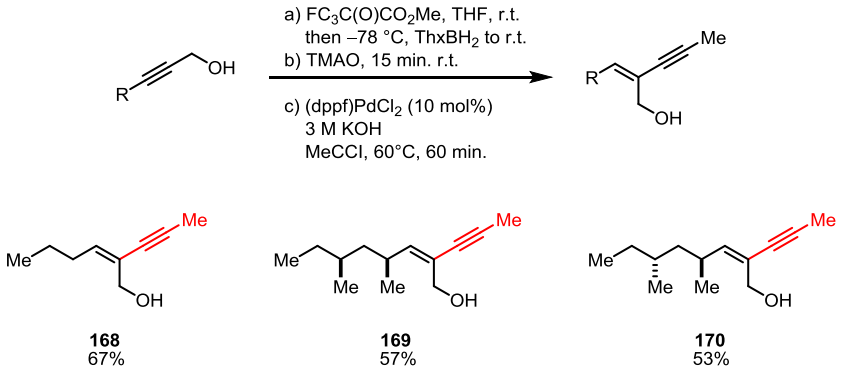


Pd-source (5 - 10 mol%)	**ligand (10 - 20 mol%)**	**base (300 - 750 mol%)**
$Pd(dba)_2$, $Pd_2(dba)_3$ $Pd(OAc)_2$	[*t*-Bu_2MePH]BF_4, PCy_3 [*t*-$BuCy_2$PH]BF_4	3 M KOH, 2 M Na_2CO_3 2 M K_3PO_4, KOH, KO*t*-Bu
solvent (0.1 M - 0.2 M)	**ratio (alkyne : bromide)**	**temperature**
THF, 1,4-dioxane, *t*-amyl-OH	1.3:1 to 1:2	r.t., 40 °C, 60 °C

Scheme 22. Optimization of alkyl Suzuki cross-coupling.

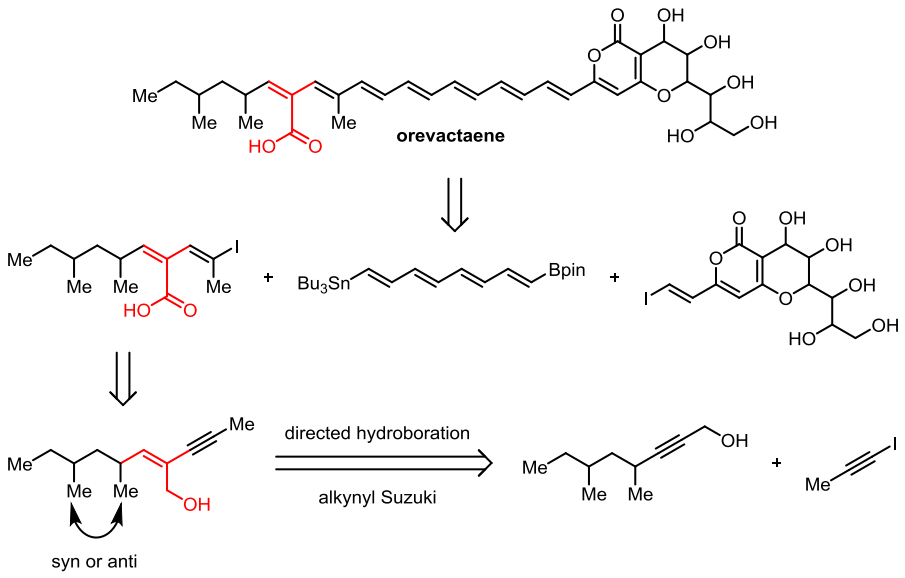
After considerable optimization, we were able to identify conditions that allowed us to accomplish the synthesis of trialkylsubstituted olefin **167** in 61% yield in a single transformation. No intermediate purification was necessary and the (precious) alkynol could be utilized as the limiting reaction partner. As reported by Fu and coworkers, (tBu)$_2$MeP proved to be the ligand of choice. Palladium acetate was identified as the optimal pre-catalyst in conjunction with aqueous potassium hydroxide as base. Furthermore, high concentrations are essential to obtain appreciable conversion.

Finally, the hydroboration/Suzuki cross-coupling protocol was extended to alkynyl Suzuki coupling with iodopropyne (Scheme 23).



Scheme 23. Enyne formation via directed hydroboration/alkynyl Suzuki cross-coupling (*J. Preindl*).

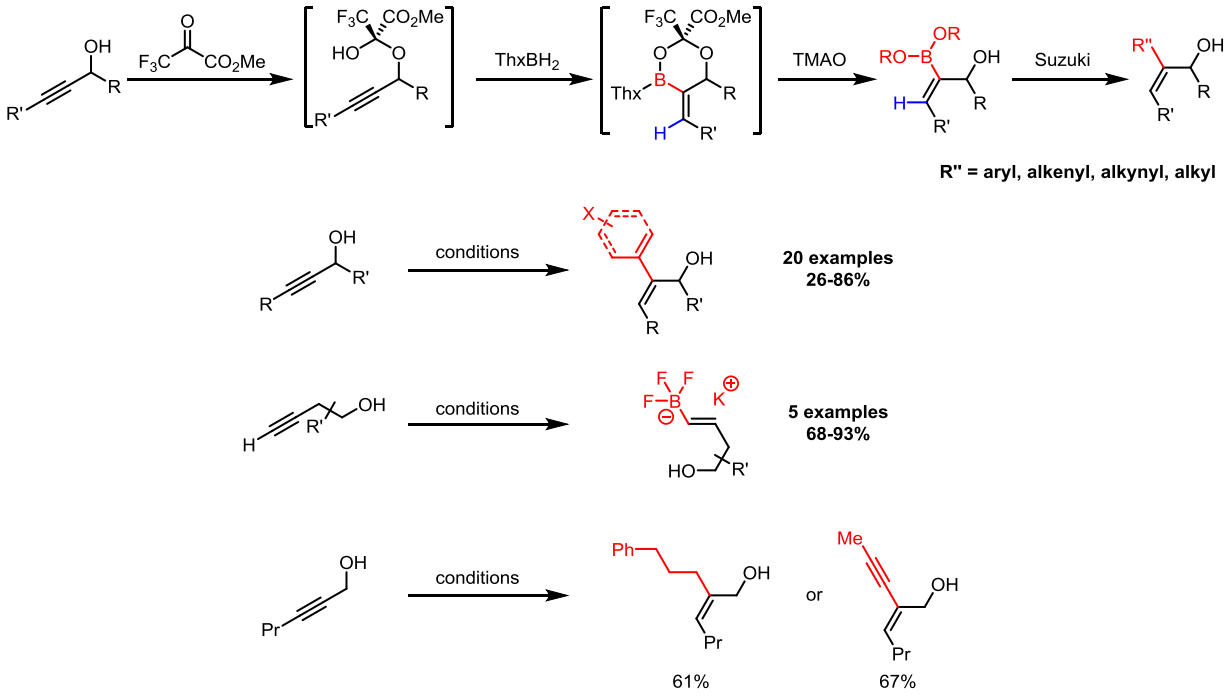
In the model system with 1-hexyne, enyne (**168**) was obtained in 67% yield, whereas more elaborate fragments could be synthesized in 57% (*syn*-**169**) and 53% (*anti*-**170**), respectively. To demonstrate the feasibility of this new directed hydroboration/Suzuki cross-coupling protocol, this transformation was implemented into a total synthesis project directed towards the synthesis of putative orevactaene (Scheme 24).[47] The crucial (*Z*)-but-2-en-1-ol motif is again highlighted in red. This application constitutes also one of the rare examples of an alkynyl Suzuki cross-coupling employing alkenylboronates as the coupling partners.[48]



Scheme 24. Retrosynthetic analysis of orevactaene *(J. Preindl)*.

2.3. Conclusion and Outlook

In summary, we have developed a useful protocol for the transformation of (homo)propargyl alcohols to trisubstituted olefins via a directed hydroboration/Suzuki cross-coupling sequence. The directing effect of the pyruvate linker was studied in detail and determined to be primarily electronic in nature. Additionally, a practical alkyl Suzuki cross-coupling protocol was established which is highly relevant for natural product synthesis. Furthermore, we were able to access a variety of terminal vinyl trifluoroborates in a one-pot sequence which tolerates the presence of protic functional groups. Finally, an alkynyl Suzuki cross-coupling served as one of the cornerstones in the total synthesis of putative orevactaene. The results presented in this chapter are summarized in Scheme 25.



Scheme 25. Summary of products obtained via directed hydroboration.

2.4. Literature

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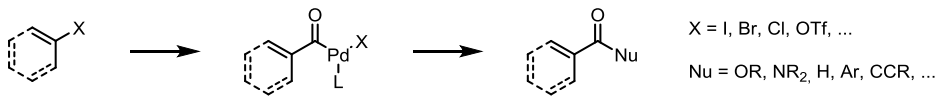
3. Hydroxyl-Assisted Carbonylation of Alkenyltin Derivatives: Development and Application to a Formal Synthesis of Tubelactomicin A

3.1. Introduction

3.1.1. Palladium Catalyzed Carbonylation Reactions of Aryl and Vinyl Halides

The conversion of aryl or vinyl (pseudo)halides to carbonyl derivatives in the presence of carbon monoxide represents an important transformation in organic synthesis.[1] In 1974, Heck and coworkers described the palladium catalyzed conversion of aryl and vinyl halides to the corresponding esters under atmospheric pressure of carbon monoxide.[2] Since this landmark discovery, reaction optimization has led to the development of protocols utilizing essentially stoichiometric amounts of carbon monoxide at moderate temperatures.[3] Furthermore, the intermediate acyl palladium species can be trapped with a variety of different reaction partners including alcohols, amines, silanes or carbon nucleophiles (Scheme 1).[4]



Scheme 1. General carbonylative coupling of organic halides.

In their initial disclosure, Heck and coworkers proposed a mechanistic rationale that has not been significantly altered over the past decades (Figure 1). The first step comprises the oxidative insertion of palladium(0) into the carbon (pseudo)halide bond of **190** (step I). In the presence of carbon monoxide a migratory insertion takes place forming acyl palladium species **192** (step II). Transmetalation (step III) with the nucleophile occurs with extrusion of M-X, wherein M can be hydrogen or a metalloid. Adduct **193** undergoes reductive elimination (step IV) furnishing product **194** while reforming the catalyst to close the catalytic cycle.

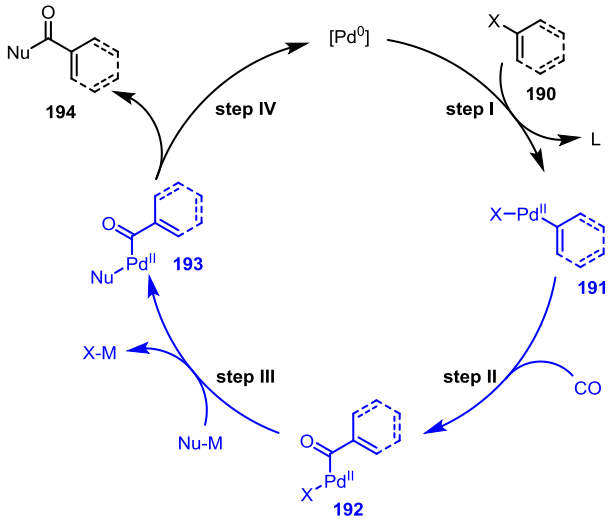
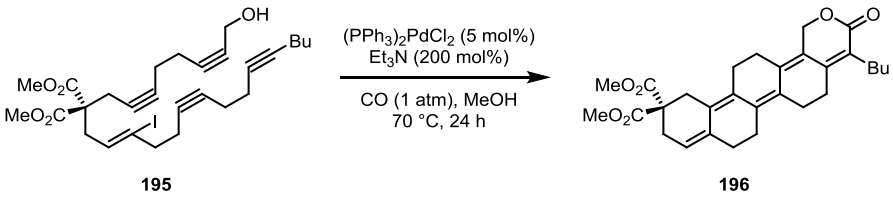


Figure 1. Catalytic cycle of the palladium catalyzed carbonylation of organic halides.

Key to success of this chemistry is the orchestration of the order of events, as migratory insertion of carbon monoxide has to precede transmetalation. Fascinating extensions of this chemistry have been reported over the past years. Carbonylative Heck cyclizations undoubtedly constitute a highlight. This chemistry has been reviewed by Negishi and coworkers and systematically ordered by the type of events taking place.[5] One of the most striking examples is the cyclization of pentayne **195** with formation of a lactone (**196**) in the terminating event (Scheme 2).[6]



Scheme 2. Heck cyclization/carbonylation cascade by Negishi and coworkers.

The synthesis of the required alkenyl halides can be cumbersome, although being for most purposes an attractive solution.[7] As most alkenyl halides are formed by metal-halide exchange, an oxidative coupling of the corresponding metal species offers a striking shortcut.

3.1.2. Palladium Catalyzed Oxidative Cross-Coupling

The field of oxidative cross-coupling has received substantial attention over the past years. Despite this fact, it can still be considered of being in its infancy as most of the protocols suffer from severe selectivity issues.[8] In this transformation, two nucleophilic reaction partners undergo cross-coupling in the presence of an extraneous oxidant (X–Y) (Figure 2).

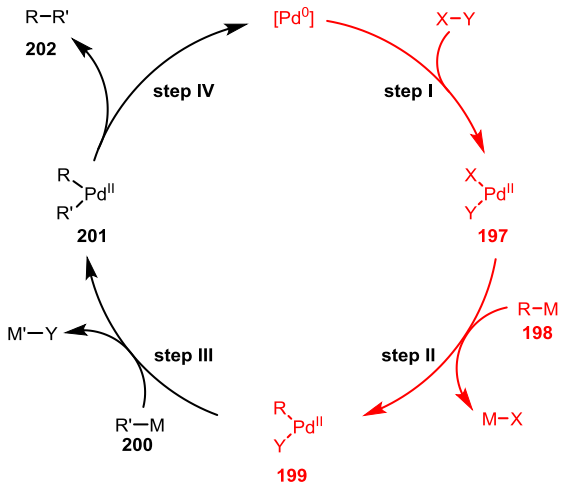
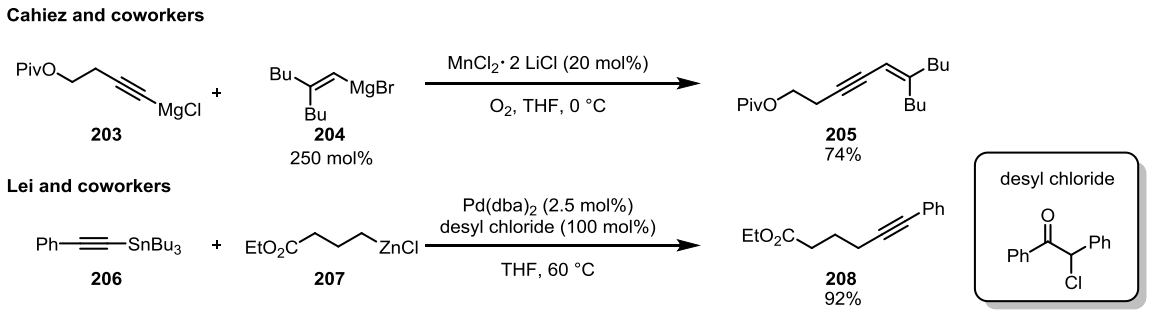


Figure 2. Catalytic cycle in the palladium catalyzed oxidative cross-coupling.

At the outset of the reaction, and similar to the traditional cross-couplings, an oxidative addition takes place to yield **197** (step I). In contrast though, X–Y does not represent a coupling partner and therefore both of the residues are not transferred over the course of the reaction. The obtained palladium(II) species **197** undergoes transmetalation with the first nucleophile **198** to give **199** (step II). A second transmetalation event (step III) with **200** follows to furnish **201**. The palladium(0) precatalyst is restored after product formation (**202**) via reductive elimination (step IV).

As mentioned earlier, homocoupling constitutes the central issue and some strategies have been developed to overcome this obstacle. The easiest solution lies in the utilization of an excess of the less reactive coupling partner thereby facilitating the quench of intermediate **199**.

This approach has been exploited for example in the cross-coupling between two Grignard reagents (Scheme 3).[9] Alternatively, by fine-tuning the coupling partners and the catalytic system, selective cross-couplings are also possible as demonstrated by Lei and coworkers.[10] By employing alkynyl stannanes and alkyl zinc reagents in the presence of desyl chloride as the oxidant, a highly chemoselective coupling was achieved.

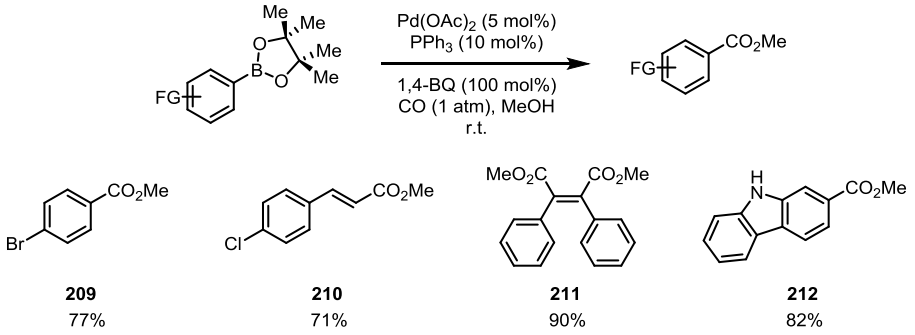


Scheme 3. Representative examples of oxidative cross-couplings.

Recent solutions also include the *in situ* formation of one of the reaction partners by C-H activation. Ensuing cross-coupling with boronic acids provides access to a variety of interesting motifs.[11] Boronic acid derivatives appear to be predestined reaction partners as they are less susceptible towards homocoupling and fairly stable under the usually harsh reaction conditions of C-H activation.

3.1.3. Palladium Catalyzed Oxidative Carbonylation of Boronic Acid Derivatives

In a recent report, Yamamoto described the oxidative alkoxy carbonylation of aryl and alkenyl boronic acids under palladium catalysis (Scheme 4).[12] Although the concept had already previously been disclosed by Uemura[13] and Suzuki[14], no general method had evolved.



Scheme 4. Substrate scope of the oxidative methoxy carbonylation of pinacol boronates by Yamamoto.

It was found, that the method tolerates a variety of functional groups and substitution patterns on the pinacol boronate. Most strikingly, alkenyl boronates proved to be suitable reaction partners, although minor amounts of homocoupling by-products were observed.

A catalytic cycle (Figure 3) was proposed based on a combination of the carbonylation process (Figure 1) and the oxidative cross-coupling (Figure 2).

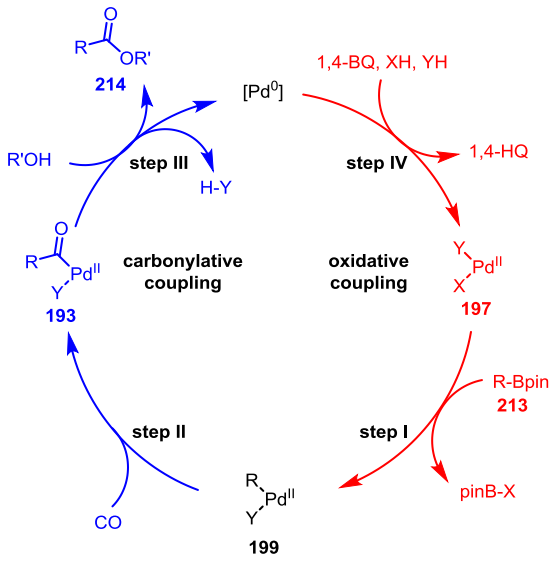
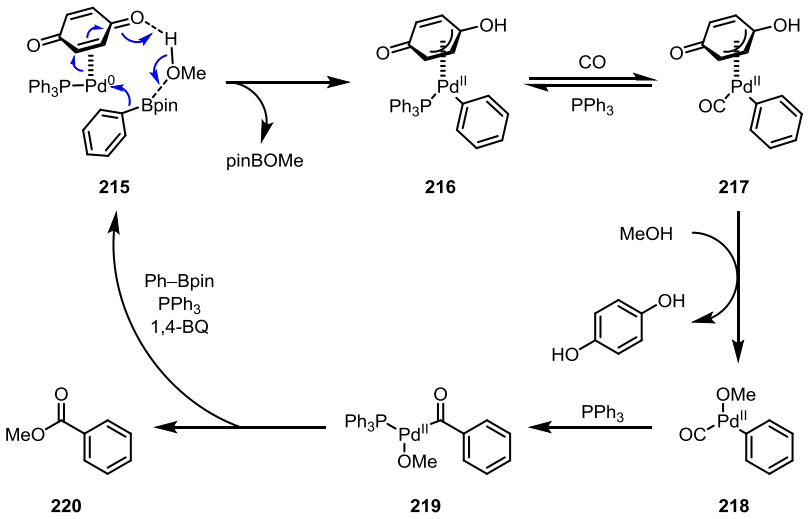


Figure 3. Catalytic cycle for the oxidative alkoxy carbonylation of pinacol boronates.

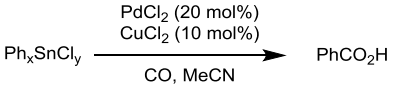
Specifically, and in contrast to traditional carbonylative cross-coupling, a transmetalation (step I) precedes the migratory insertion of carbon monoxide (step II). After ligand exchange and reductive elimination (step III), the resulting palladium(0) is oxidized and reenters the catalytic cycle (step IV). Interestingly, it was found that the reaction did not proceed with potassium trifluoroborates as coupling partners, although other boronic acid derivatives delivered the products in moderate to good yields. Furthermore, the addition of bases inhibited the reaction. A transition state model was developed based on these observations as well as on computational studies (Scheme 5).



Scheme 5. Mechanistic rational for the oxidative alkoxy carbonylation of boronates.

It was found that MeOH plays a key role in activating the Pd-1,4-benzoquinone (BQ) complex by protonation. As a result, a hydrogen-bond network was proposed (**215**). In this model, MeOH is coordinated by the boronate, which has two major consequences. Initially, it increases the acidity of the MeOH proton and thereby the electrophilicity of 1,4-BQ. Secondly, it activates the boronate towards transmetalation. This process can be understood as a proton-coupled electron transfer reaction from palladium to 1,4-BQ. The resulting palladium(II) species **216** is in equilibrium with the corresponding CO-complex **217**. Replacement of 1,4-hydroquinone by MeOH (**218**) and ligand-induced migratory insertion of carbon monoxide provides the acyl palladium complex **219** which undergoes reductive elimination to give benzoate **220**. Intermediate Pd(0) is captured by 1,4-BQ and PPh_3 to reform **215**.

To the best of our knowledge there is only one report in the literature in which stannanes are employed under oxidative carbonylation reactions (Scheme 6).[15]

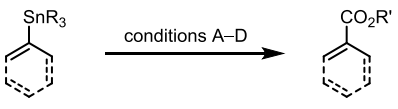


Scheme 6. Oxidative palladium catalyzed carbonylation of aryl chlorostannanes by Uemura and coworkers.

Under the reported conditions variable amounts of the corresponding benzoic acids and ketones were obtained depending on the Ph-to-Cl-ratio on the stannane. As the usage of $CuCl_2$ as a (stoichiometric) oxidant in the presence of alkenylstannanes leads to the formation of alkenyl chlorides, this methodology cannot be applied to the synthesis α,β-unsaturated esters.[16]

3.1.4. State of the Art the Synthesis of Acrylates from Alkenyltin Derivatives

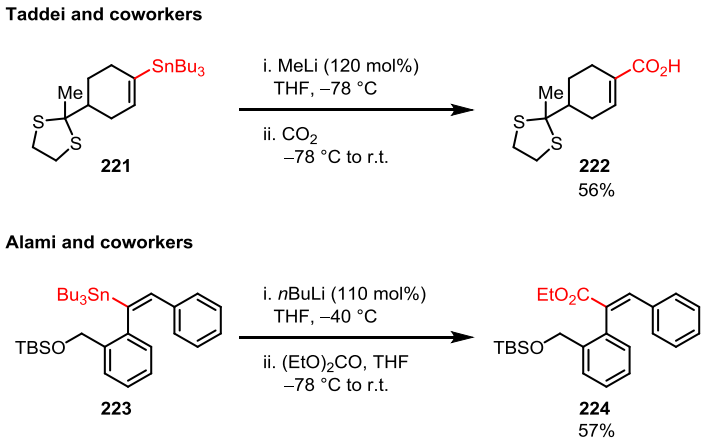
The ready accessibility of stereodefined alkenylstannanes by ruthenium-catalyzed *trans*-selective hydrostannation of alkynes prompted us to develop an efficient method to access α,β-unsaturated ester motifs. Prior to our own contribution, four concepts have been disclosed to convert stannanes to acid derivatives (Scheme 7). Tin-lithium exchange and subsequent trapping with electrophiles (examples 1-2), tin-halide exchange preceding alkoxy carbonylation (example 3) or cross-coupling with chloroformates (example 4).



Scheme 7. Commonly employed methods for the R-Sn to R-CO_2R' conversion.

3.1.4.1. Activation and Subsequent Carboxylation with CO_2 or Equivalent Reagent

A very robust way to access α,β-unsaturated esters from alkenyltin derivatives is the activation of the carbon-tin bond by addition of an alkyllithium reagent. The intermdiate alkenyllithium formed via tin lithium exchange is trapped with either CO_2[17] or equivalent reagents like carbonates[18] (Scheme 8).



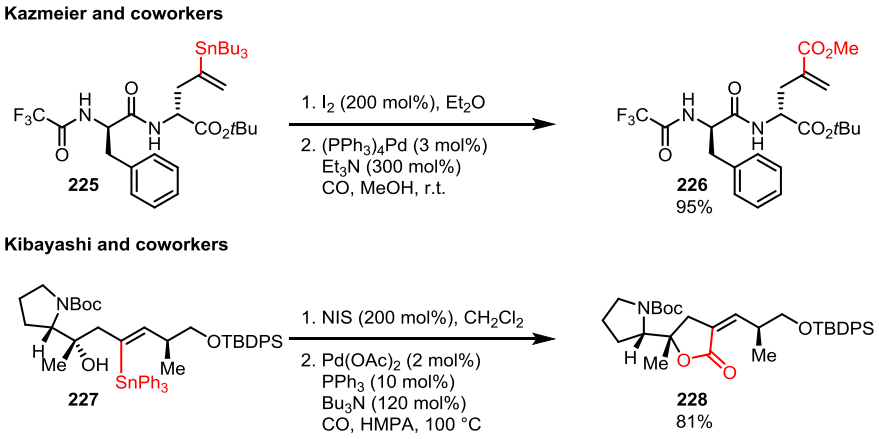
Scheme 8. Representative examples of alkenyltin to carboxylic acid derivative by tin-lithium exchange.

Although an operationally simple protocol, the use of strongly nucleophilic organolithium reagents to activate the stannane renders this method incompatible with a variety of electrophilic functional groups. Additionally, the overall moderate yield of the process has prevented its use as a convenient method for the synthesis of α,β-unsaturated esters.

3.1.4.2. Tin-Halide Exchange and Subsequent Palladium Catalyzed Carbonylation

One of the most prominent ways to transform alkenyltin derivatives into the corresponding α,β-unsaturated esters is based on tin halide exchange followed by traditional palladium catalyzed carbonylation (Scheme 9). In the first step, highly functionalized alkenylstannanes are transformed by treatment with I_2 or Br_2 or the respective succinimides (NIS, NBS) into the corresponding halides. In the second step, a traditional palladium catalyzed alkoxy carbonylation provides the targeted material **226** and **228**.

Kazmeier and coworkers[19] utilized this methodology to access a variety of modified peptides **226** while Kibayashi and coworkers[20] trapped the acyl palladium species to form a lactone in their approach to pumiliotoxin alkaloids (**228**).

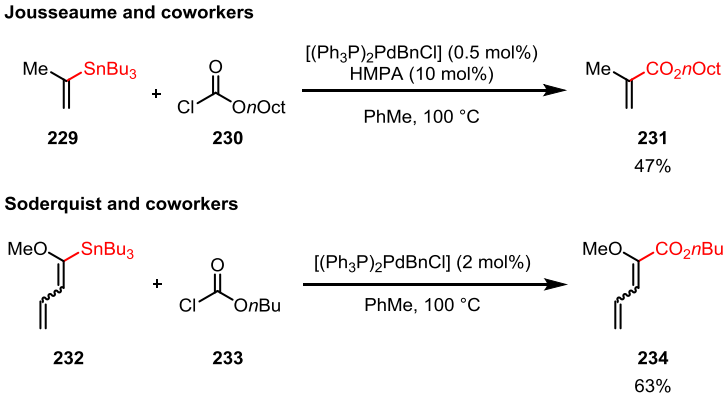


Scheme 9. Representative examples for tin halide exchange followed by carbonylation.

Although offering an attractive solution to this long-standing problem, the indirect transformation of the alkenylstananne via the corresponding halide entails some difficulties. The use of electrophilic halogenating agents like iodine or NIS can lead to undesired side-reactions like isomerizations or halogenations of olefins or electron-rich arenes. Furthermore, this protocol requires the isolation of the intermediate alkenylhalide. Lastly, this method does not tolerate other (pseudo)halides as these are potential reaction partners in their own right.

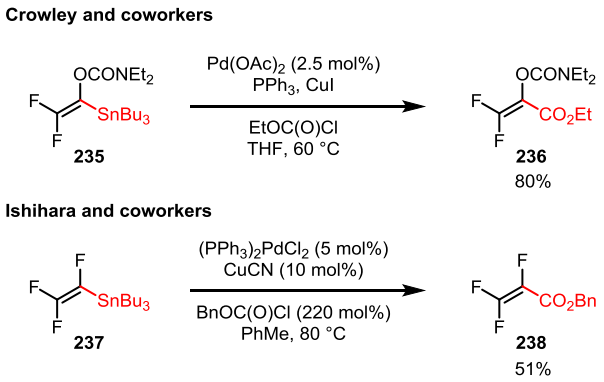
3.1.4.3. Palladium Catalyzed Cross-coupling with Chloroformates

The cross-coupling between chloroformates and alkenylstannanes was described by Jousseaume and coworkers in 1991 to access a variety of α,β-unsaturated esters and amides. The use of catalytic [$(Ph_3P)_2PdBnCl$] and HMPA as cosolvent proved to be optimal (Scheme 10).[21] A similar result was reported in the same year by Kang and coworkers.[22] The moderate yields were attributed to pronounced decomposition of the chloroformate at high temperatures. Interestingly, similar conditions were reported by Soderquist and coworkers who extended the scope of the reaction to more demanding substrates.[23] Very recently, Yamada and coworkers used this methodology to access a set of unsymmetric vinyl malonate structures.[24]



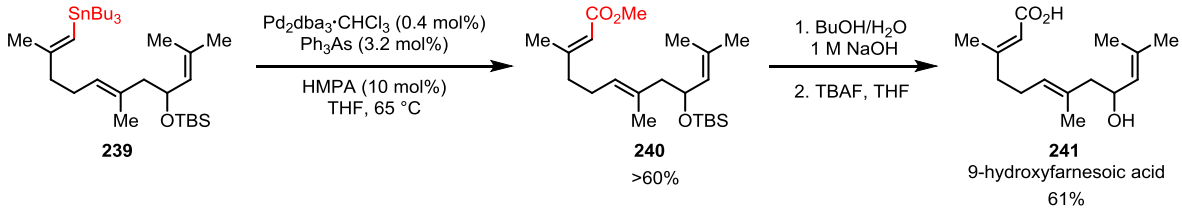
Scheme 10. Palladium catalyzed cross-coupling of alkenylstannanes with chloroformates.

An important improvement was reported by Crowley and Stansfield by adding catalytic copper iodide[25] to the reaction mixture(Scheme 11).[26] Ishihara and coworkers found that catalytic CuCN exhibited a similar effect.[27]



Scheme 11. Palladium and copper cocatalyzed chloroformate cross-coupling.

The most elaborate example has been described by Whitby and coworkers in their total synthesis of 9-hydroxyfarnesoic acid (**241**) (Scheme 12).[28]



Scheme 12. Endgame in the total synthesis of 9-hydroxyfarnesoic acid (**241**) by Whitby and coworkers.

Crucial to success was the addition of methyl chloroformate over 1 h by syringe pump to the reaction mixture to prevent decomposition of **239**. Furthermore, by decreasing the catalyst loading the yield could be increased to >60%. It has been reported that chloroformates disproportionate under palladium catalysis to give the corresponding symmetric carbonates and phosgene, leading to the formation of symmetric ketones and catalyst deactivation.[29]

3.1.5. Motivation

At the outset of this project, we wanted to establish a new protocol that would allow us to directly transform alkenylstannanes into α,β-unsaturated esters without the need for protecting groups. As we were aiming for applying this new method in the context of total synthesis, we also had to ensure that the new transformation is sufficiently mild to tolerate a variety of functionalities. We did not want to abandon chloroformates outright as they offer a well precedented approach. With a solution to this problem in hand, a plethora of potential target molecules come into reach (Figure 4). The crucial (*E*)-hydroxymethyl acrylic acid motif is highlighted in red.

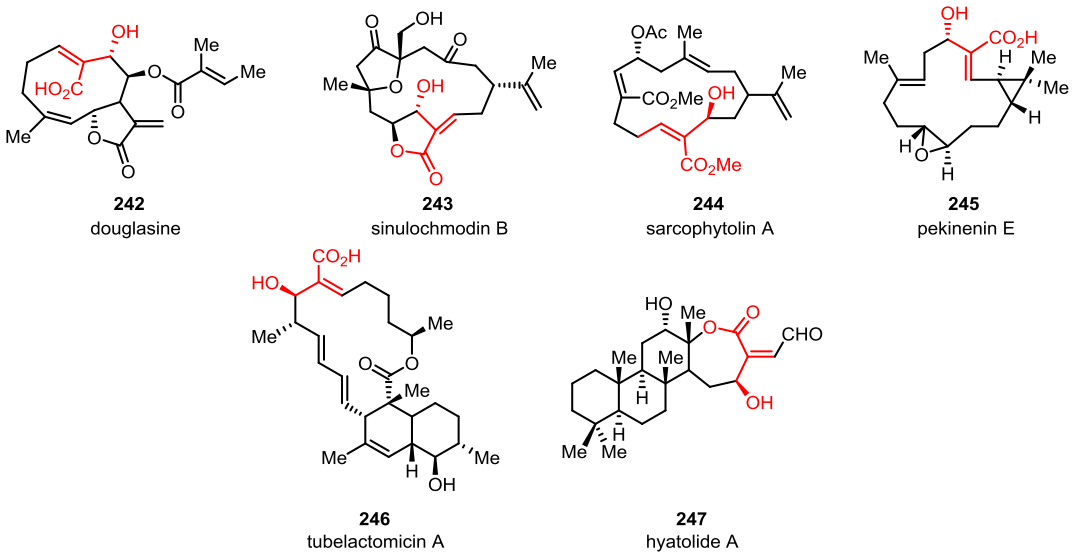


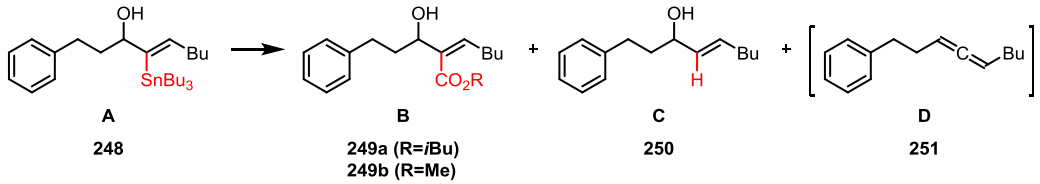
Figure 4. Possible target molecules for the carbonylative Stille coupling: **242**[30], **243**[31], **244**[32], **245**[33], **246**[34], **247**[35].

3.2. Results and Discussion

3.2.1. Development of an Oxidative Palladium Catalyzed Carbonylation

Our initial goal was to evaluate the feasibility of the direct cross-coupling of chloroformates or their derivatives with a suitable alkenylstannane. As the required starting materials stem from the directed *trans*-hydrostannation of (homo)propargyl alcohol derivatives, the development was purposely initiated without protecting groups. The reaction shown in Table 1 was chosen as our model system. Incompatibility of the free alcohol in **248** with the reaction conditions was expected and an evaluation of existing protocols quickly affirmed our anticipations. Besides targeted product **249**, mainly proto-destannation (**250**) and allene formation (**251**) was observed.

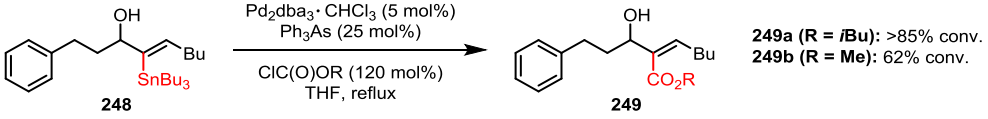
Table 1. Optimization of conditions for cross-coupling with isobutyl chloroformate.



Entry	XCO_2iBu (eq)	[Pd] (mol%)	Ligand (mol%)	Additive (eq)	Solvent (conc.)	T [°C] t [h]	Ratio (A : B : C)[a]
1	$ClCO_2iBu$ (1.5)	$(PPh_3)_2PdBnCl$ (5)	-	-	PhMe (0.125 M)	60, 12	1 : 0 : 0
2	$ClCO_2iBu$ (1.5)	$Pd_2dba_3{\cdot}CHCl_3$ (2.5)	PPh_3 (12.5)	-	DME (0.125 M)	60, 12	1 : 0 : 2
3	$ClCO_2iBu$ (1.5)	$(PPh_3)_2PdBnCl$ (5)	-	CuI (0.05)	THF (0.125 M)	50, 0.5	0 : 0 : 1
4	$ClCO_2iBu$ (1.5)	$(PPh_3)_4Pd$ (5)	-	TBADPP (1.1) CuTC (1.05)	DMF (0.2 M)	r.t., 5 min	0 : 0 : 1
5	$ClCO_2iBu$ (1.5)	-	-	CuTC (1.05)	DMF (0.2 M)	r.t., 5 min	0 : 0 : 1
6	$tolSCO_2iBu$ (1.1)	$(PPh_3)_4Pd$ (5)	-	CuTC (1.2)	THF/Hex (0.063 M)	50, 12	0 : 1 : 1.3
7	$tolSCO_2iBu$ (1.1)	$Pd_2dba_3{\cdot}CHCl_3$ (2.5)	$AsPh_3$ (12.5)	CuDPP (1.2)	THF/Hex (0.125 M)	r.t., 12	0 : 1 : 2
8	$tolSCO_2iBu$ (1.1)	$Pd_2dba_3{\cdot}CHCl_3$ (2.5)	$(furyl)_3P$ (20)	CuDPP (1.2)	THF/Hex (0.125 M)	r.t., 12	0 : 1 : 1
9	$ClCO_2iBu$ (1.1)	$Pd_2dba_3{\cdot}CHCl_3$ (2.5)	$AsPh_3$ (10)	-	THF (0.25 M)	60, 12	1 : 2.1 : 0
10	$ClCO_2iBu$ (2.0)	$Pd_2dba_3{\cdot}CHCl_3$ (2.5)	$AsPh_3$ (10)	-	THF (0.25 M)	60, 12	1 : 1.7 : 0
11	$ClCO_2iBu$ (2.0)	$Pd_2dba_3{\cdot}CHCl_3$ (2.5)	$AsPh_3$ (10)	-	THF (0.5 M)	60, 12	1 : 0.6 : 0
12	$ClCO_2iBu$ (1.5)	$Pd_2dba_3{\cdot}CHCl_3$ (2.5)	$AsPh_3$ (12.5)	-	THF (0.125 M)	60, 12	1 : 1.4 : 0[b]
13	$ClCO_2iBu$ (1.2)	$Pd_2dba_3{\cdot}CHCl_3$ (2.5)	$AsPh_3$ (12.5)	-	THF (0.125 M)	60, 12	1 : 3.1 : 0[c]
14	$ClCO_2iBu$ (1.2)	$Pd_2dba_3{\cdot}CHCl_3$ (5.0)	$AsPh_3$ (25.0)	-	THF (0.125 M)	60, 12	1 : 5.6 : 0[c]

[a]determined by crude NMR analysis; [b]slow add'n of substrates over 2 h; [c]slow add'n of catalyst over 2 h.

The standard conditions reported in the literature failed to provide appreciable conversions or product-to-protodestannation ratios (entries 1-3).[17, 21, 23] Palladium-black formation in all cases indicated the lability of the *in situ* formed catalyst. Addition of CuTC or CuI did only result in rapid protodestannation (entries 4-5).[36] Employing the corresponding thiocarbonate under Liebeskind-Srogl conditions led for the first time to the formation of significant amounts of product along with protodestannation (entries 6-8).[37] Although being ultimately unsuccessful in this case, thiocarbonates have not been used in a Liebeskind-Srogl cross-coupling before. Unfortunately proto-destannation could not be suppressed. Finally, changing the ligand from Ph_3P to Ph_3As in the absence of copper salts led to the formation of product with suppression of proto-destannation (entry 9-11). The outstanding performance of Ph_3As in Stille cross-couplings has been reported by Farina and coworkers, showing a significant rate acceleration compared to Ph_3P.[38] Palladium-black formation was still observed, though at a lower rate compared to phosphine ligands. It was surmised, that the conversion could be boosted by reducing the contact time between the reagents and the catalyst to a minimum. After considerable screening, it was found that slow addition of a preformed catalyst solution over 2 h to a refluxing mixture of the reaction partners reliably provided >85% conversion without substantial amounts of protodestannation (entries 12-14). With these optimized conditions we felt confident to employ other chloroformates as well. Unfortunately, after switching from *iso*-butyl chloroformate to methyl chloroformate, the conversion significantly dropped to 62% under otherwise identical conditions (Scheme 13).



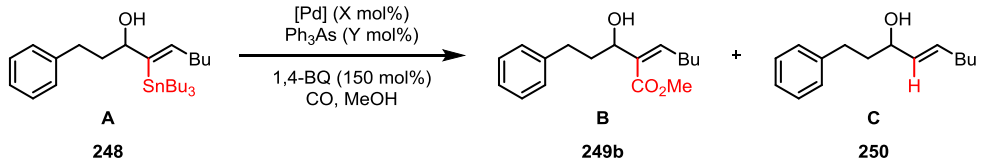
Scheme 13. Optimized conditions for the coupling with chloroformates

Therefore, we decided to investigate the viability of an oxidative palladium catalyzed carbonylation as an alternative. We began our studies with a screening of suitable palladium and ligand combinations (Table 2).

The originally reported conditions (entry 1) failed to provide any product;[12] rapid palladium-black formation was observed instead. Changing to other phosphine ligands did not result in much improvement and starting material was mainly recovered (entries 2-7). From the previous attempts with chloroformates we learned that Ph_3As performed remarkably well. Changing the ligand to Ph_3As resulted in substantial improvement (entry 8). With the optimal ligand in hand, we continued to examine the influence of the palladium source (entries 9-12). It was found that cationic palladium salts proved significantly more effective than $Pd(OAc)_2$. The

increased rate was attributed to the *in situ* formation of the corresponding acids in the presence of MeOH.

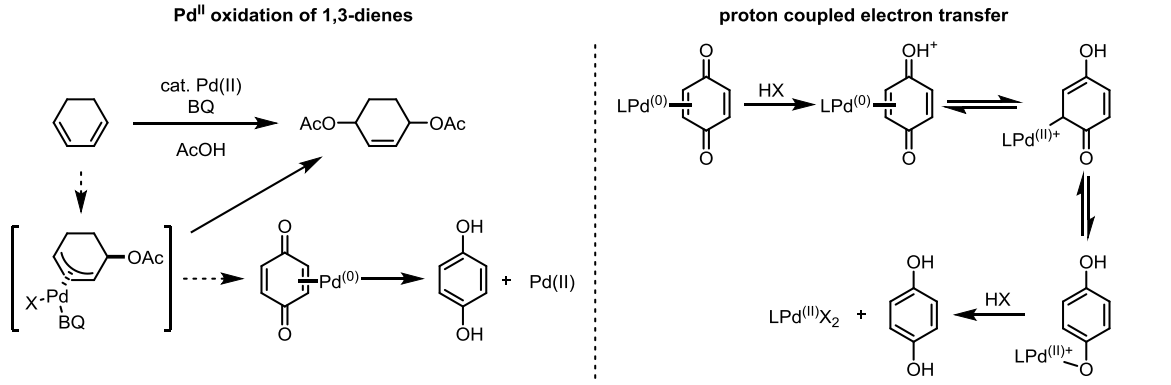
Table 2. Palladium source and ligand optimization in the oxidative carbonylation.



Entry	[Pd] (mol%)	Ligand (mol%)	Additive (eq)	Solvent (conc.)	T [°C] t [h]	ratio (A : B : C)[a]
1	$Pd(OAc)_2$ (5.0)	PPh_3 (12.5)	1,4-BQ (1.0)	MeOH (0.1 M)	70 , 12	n.r.
2	$Pd(OAc)_2$ (10)	JohnPhos (20)	1,4-BQ (1.5)	MeOH (0.5 M)	r.t. , 12	n.r.
3	$Pd(OAc)_2$ (10)	BiphenylCy_2P (20)	1,4-BQ (1.5)	MeOH (0.5 M)	r.t., 12	1 : 0.10 : 0
4	$Pd(OAc)_2$ (10)	PCy_3 (20)	1,4-BQ (1.5)	MeOH (0.5 M)	70 , 12	1 : 0.50 : 0
5	$Pd(OAc)_2$ (10)	$PhPCy_2$ (20)	1,4-BQ (1.5)	MeOH (0.5 M)	70 , 12	1 : 0.23 : 0
6	$Pd(OAc)_2$ (10)	Cy_2*t*BuP (20)	1,4-BQ (1.5)	MeOH (0.5 M)	70 , 12	1 : 0.68 : 0
7	$Pd(OAc)_2$ (10)	*t*Bu_2MeP (20)	1,4-BQ (1.5)	MeOH (0.5 M)	70 , 12	1 : 0.70 : 0
8	$Pd(OAc)_2$ (10)	$AsPh_3$ (20)	1,4-BQ (1.5)	MeOH (0.5 M)	70 , 12	1 : 2.70 : 0
9	$PdCl_2$ (10)	$AsPh_3$ (20)	1,4-BQ (1.5)	MeOH (0.5 M)	70 , 12	1 : 0.83 : 0
10	$(PhCN)_2PdCl_2$ (10)	$AsPh_3$ (20)	1,4-BQ (1.5)	MeOH (0.5 M)	70 , 12	1 : 4.22 : 0
11	$Pd(TFA)_2$ (10)	$AsPh_3$ (20)	1,4-BQ (1.5)	MeOH (0.5 M)	r.t., 12	1 : 2.00 : 0
12	$(MeCN)_4Pd(BF_4)_2$ (10)	$AsPh_3$ (20)	1,4-BQ (1.5)	MeOH (0.5 M)	r.t., 12	1 : 7.48 : 0

[a]determined by crude NMR analysis.

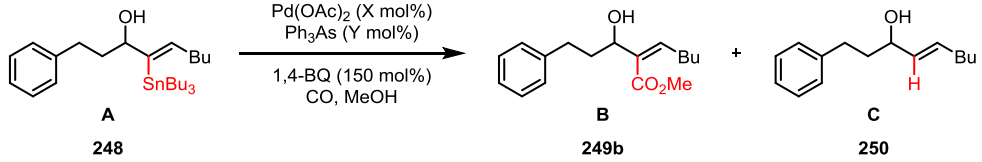
A related observation had been made by Bäckvall and coworkers when they studied the oxidation of 1,3-dienes with $Pd(OAc)_2$ and 1,4-BQ as the stoichiometric oxidant (Scheme 14).[39] By increasing the acidity of the reaction medium, a significant rate acceleration was observed. The electron transfer from the ligated palladium to the 1,4-BQ ligand was found to be the rate determining step. Obviously, protonation of the 1,4-BQ results in an increased electrophilicity and thereby an increased oxidation potential. To gain insight into this transformation, Bäckvall and coworkers treated isolated (COD)Pd(BQ) with AcOH, TFA and MsOH and the respective NMR spectra were recorded. It was found that only TFA and MsOH promoted a two-electron oxidation of palladium. As TFA can be handled more conveniently and is milder than MsOH, it was chosen for further refinement of the methodology (Table 3).



Scheme 14. Proton coupled electron transfer in Pd/1,4-BQ mediated oxidation of dienes.

The addition of 50 mol% of TFA to the reaction had a significant impact (Table 3, entries 1 and 2). Essentially full conversion was achieved at ambient temperature. Over the course of the optimization it was noted that the lipophilic stannane was insufficiently soluble in MeOH. Decreasing the concentration from 0.5 M to 0.25 M led to exclusive product formation without competing protodestannation (entry 3). Efficacy was substantially reduced when the catalyst or TFA loadings were decreased (entries 4-6). With the optimized conditions in hand the substrate scope of this novel transformation was investigated (Figure 5).

Table 3. Optimization of reaction conditions for oxidative methoxy carbonylation.



Entry	[Pd] (mol%)	Ligand (mol%)	Additive (eq)	Solvent (conc.)	T [°C] t [h]	ratio (A : B : C)[a]
1	$Pd(OAc)_2$ (10)	$AsPh_3$ (20)	1,4-BQ (1.5)	MeOH (0.5 M)	70 , 12	1 : 2.70 : 0
2	$Pd(OAc)_2$ (10)	$AsPh_3$ (20)	1,4-BQ (1.5) TFA (0.50)	MeOH (0.5 M)	r.t., 12	1 : 4.18 : 0
3	$Pd(OAc)_2$ (5)	$AsPh_3$ (10)	1,4-BQ (1.5) TFA (0.40)	MeOH (0.25 M)	r.t., 12	0 : 1.00 : 0 (78%)[b]
4	$Pd(OAc)_2$ (5)	$AsPh_3$ (10)	1,4-BQ (1.5) TFA (0.20)	MeOH (0.25 M)	r.t., 12	1 : 1.00 : 0
5	$Pd(OAc)_2$ (2.5)	$AsPh_3$ (5)	1,4-BQ (1.5) TFA (0.40)	MeOH (0.25 M)	r.t., 12	1 : 6.38 : 0
6	$Pd(OAc)_2$ (2.5)	$AsPh_3$ (5)	1,4-BQ (1.5) TFA (0.20)	MeOH (0.25 M)	r.t., 12	1 : 1.51 : 0

[a]determined by crude NMR analysis; [b]isolated yield.

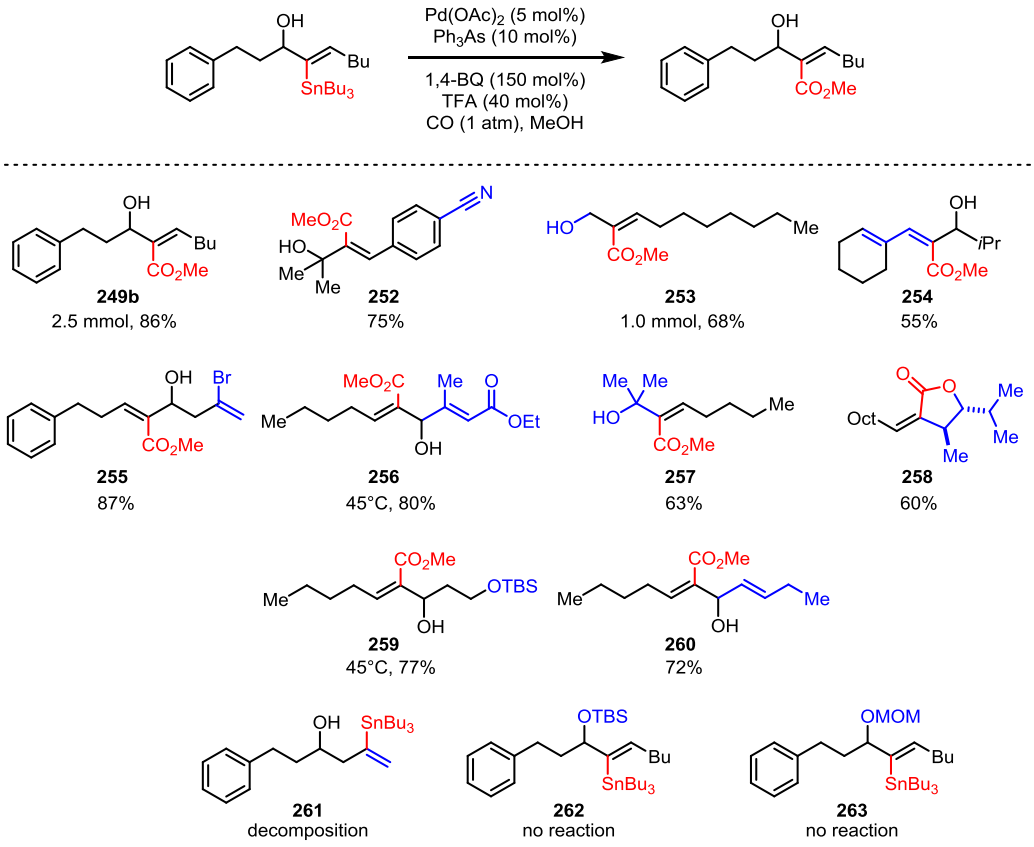


Figure 5. Substrate scope of the oxidative palladium-catalyzed methoxy carbonylation.

It was found that the palladium-catalyzed oxidative methoxy carbonylation is compatible with a variety of functional groups and also amenable to large-scale synthesis (**249b**). Primary, secondary and tertiary alcohols are well tolerated, as are nitriles (**252**), silyl ethers (**259**), acid sensitive allyl alcohols (**260**), esters (**256**) and alkenyl bromides (**255**). The latter is of particular interest as alkenyl bromides serve as common substrates in traditional palladium catalyzed carbonylation reactions. This example underlines the mechanistic proposal that no palladium(0) exits the catalytic cycle as it is rapidly oxidized by 1,4-BQ. Interestingly though, TBS or MOM protected propargyl alcohols (**262** and **263**) do not participate in this transformation which highlights the importance of the flanking hydroxyl group. Additionally, terminal olefin **261** decomposed under the reaction conditions. A mechanistic proposal based on the work of Yamamoto is formulated in Figure 6.

For every transition state, two possible structures have to be considered as the exact role of TFA is unknown. In the first step, transmetalation from tin to palladium leads to intermediate **264**. TFA acts as a promoter by pre-organizing the reaction partners in a hydrogen bonding network. A direct hydrogen-bonding between the ligated 1,4-BQ and the allyl alcohol could be a viable alternative (**265**).

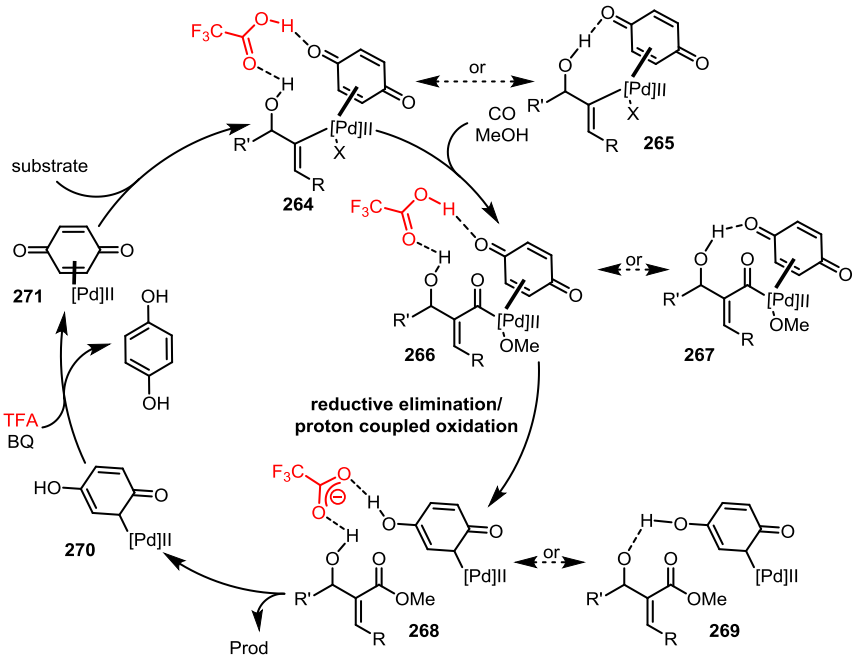


Figure 6. Catalytic cycle of the oxidative palladium catalyzed methoxy carbonylation.

After ligand exchange and migratory insertion of carbon monoxide, acyl palladium species **266** or **267** are obtained. The following reductive elimination/proton coupled electron transfer step is accelerated by TFA via protonation of 1,4-BQ, leading to an increased oxidation potential. Next, the resulting palladium enolate **270** is protonated to extrude 1,4-hydroquinone. The unconfined palladium(II), which is stabilized by the Ph_3As ligand, is immediately ligated by

another equivalent of 1,4-BQ to reenter the catalytic cycle. The predominant reason for the failure of phosphine ligands is their increased reduction potential for palladium(II) compared to Ph_3As.

An alternative pathway similar to the one proposed by Yamamoto[12] in which palladium(0) plays a major role was deemed unlikely for two reasons: 1) It was found that in a stoichiometric experiment with $Pd(TFA)_2$ but without 1,4-BQ oxidant, full conversion was observed yielding a 1:2 mixture of product to protodestannation. 2) As an alkenyl bromide endures the reaction, no intermediate palladium(0) can be formed as this would lead to rapid decomposition.

With these results in hand, we set out to apply this new methodology to the synthesis of a natural product.

3.2.2. Formal Synthesis of Tubelactomicin A

3.2.2.1. Motivation

As presented in Figure 4, the (hydroxylmethyl)acrylic acid motif is a recurring feature in many natural products. The most attractive of the possible targets shown is tubelactomicin A (**246**). Two total syntheses have been disclosed to date by Tadano[40] and Tatsuta[41], and one study towards the total synthesis was reported by Ryu[42]. Key fragment **272** in the synthesis of Tadano and coworkers has previously been accessed in 25 steps in a highly linear manner and was selected as our target molecule. The retrosynthetic analysis is shown in Figure 7. The group utilized a Stille cross-coupling between iodide **273** and stannane **272** followed by desilylation and macrolactonization to access the carbon skeleton of tubelactomicin A (**246**). Furthermore, as other members of the same family can potentially be addressed via the same key intermediate, our contribution would allow us to prepare a variety of natural and unnatural analogs.[43]

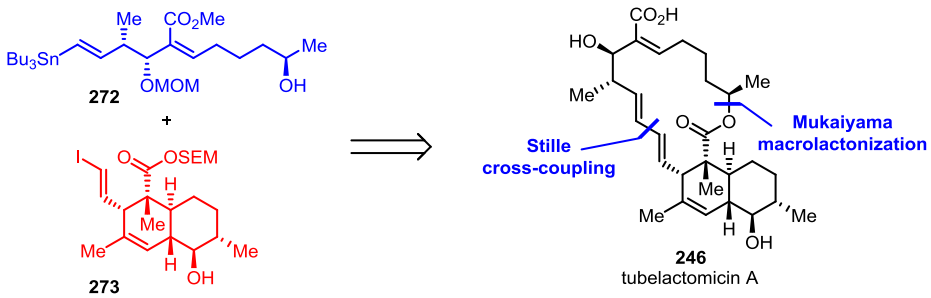


Figure 7. Retrosynthetic analysis of to Tadanao and coworkers.

3.2.2.2. The Tubelactomicin Family of Natural Products

Tubelactomicin A (**246**) was isolated by Igarashi *et al.* from the strain MK703-102F1 found in a soil sample in Suwashi, Japan in 2000.[34, 44] In 2001, the same group disclosed the isolation of tubelactomicins B (**274**), D (**275**) and E (**276**).[45] No structure of tubelactomicin C was reported.

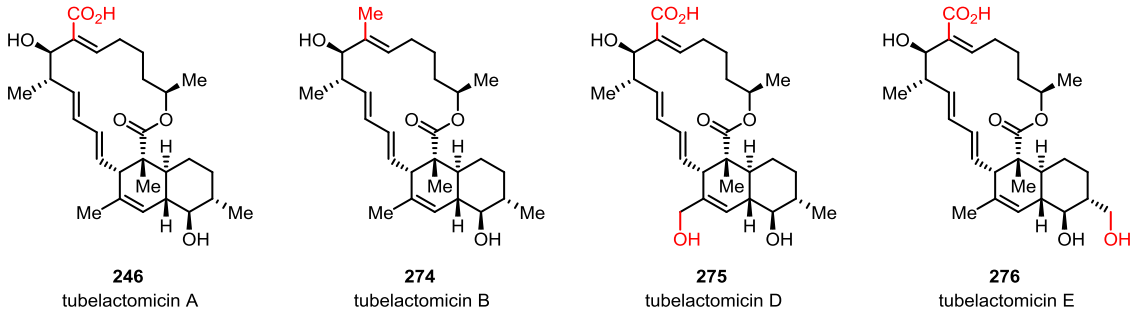


Figure 8. Structures of tubelactomicins A, B, D, E.

Tubelactomicin A (**246**) shows strong and specific antimicrobial activities against *Mycobacterium* including some drug-resistant strains. Furthermore, **246** exhibits no acute toxicity in mice at a dose of 100 mg/kg (intravascular).[34] The structure of **246** was elucidated by NMR, HRMS, IR and UV analyses, and the absolute stereochemistry was established by crystallization of a carboxamide derivative.[44] With the completed total synthesis of Tadano and coworkers the proposed structure was confirmed.

246 comprises a 16-membered lactone ring (blue) and a *trans*-decalin backbone (red) as illustrated in Figure 9. It comprises 9 stereogenic centers (colored circles) of which 6 are located in the southern domain and one of them being quaternary (green circle). Furthermore, a (*E,E*)-diene is part of the lactone ring (orange). The crucial (hydroxylmethyl)acrylic acid motif is highlighted in blue in the right hand structure.

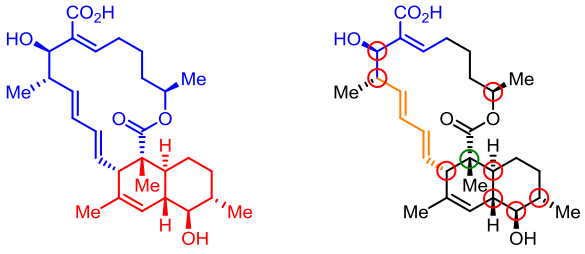
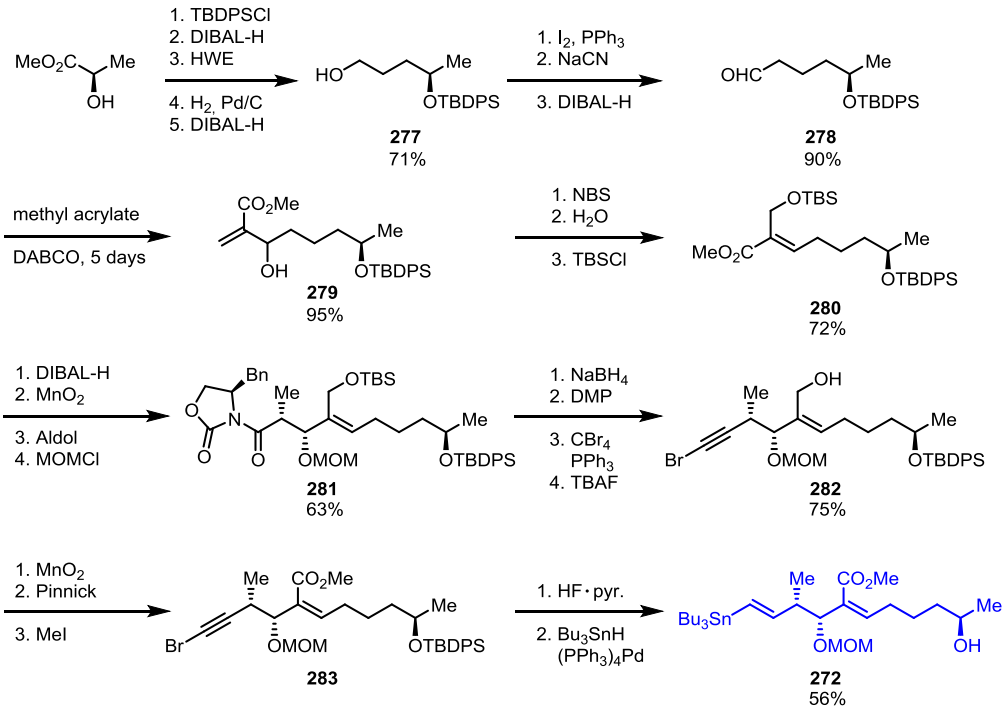


Figure 9. Key features of tubelactomicin A (**246**).

3.2.2.3. Previous Syntheses of Tubelactomicin A

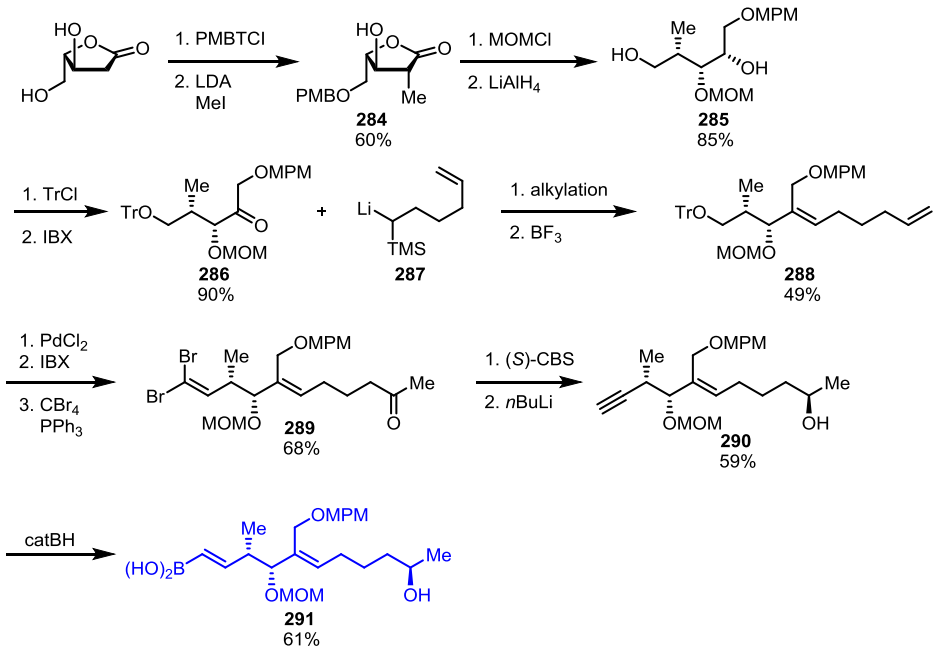
As the major goal of this project was to establish a new route to key fragment **272** which represents a formal synthesis of tubelactomicin A, only synthetic approaches towards the northern fragment are discussed. The key steps in the synthesis of Tadano and coworkers are illustrated in Scheme 15.[40c]



Scheme 15. Synthesis of the northern fragment by Tadano and coworkers.

The carbon chain was evolved stepwise, starting from methyl (*R*)-lactate to give the required northern fragment in an impressive overall yield of 12% after 25 steps. Key steps include a Baylis-Hillman reaction, a *syn*-selective Evans-aldol reaction, a Corey-Fuchs alkynylation and finally a Pattenden hydrostannylation.

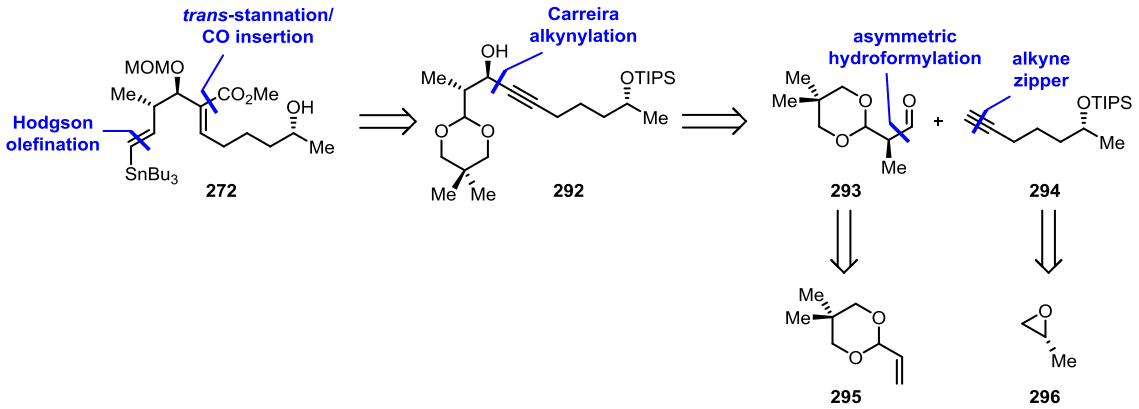
In the synthesis of Tatsuta and coworkers, a slightly different intermediate was targeted as the crucial cross-coupling event was projected to be a Suzuki cross-coupling (Scheme 16).[41] This choice prohibited the prior installation of the ester moiety as its hydrolysis was assumed. Downstream introduction of the carboxylic acid was realized via a NiO_2 catalyzed oxidation.[46] Two of the three required stereocenters stem again from a 'chiral pool' building block, in this case 2-deoxy-*L*-ribonolactone. The cornerstones of this approach are a highly selective Peterson olefination, a Wacker oxidation, a Corey-Fuchs alkynylation and a Corey-Bakshi-Shibata reduction. The final fragment was accessed in 14 steps with an overall yield of 6%.



Scheme 16. Synthesis of the northern fragment by Tatsuda and coworkers.

3.2.2.4. Retrosynthetic Analysis and Forward Formal Synthesis of Tubelactomicin A – Part I

As the crucial alkenylstannane necessary for the Stille cross-coupling has to be introduced at the end of the synthesis, we decided to access this motif utilizing the Hodgson olefination (Scheme 17).[47]



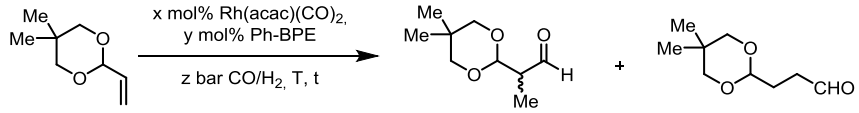
Scheme 17. First retrosynthetic analysis for the formal synthesis of tubelactomicin A.

This traced us back to propargyl alcohol **292** which in turn could result from asymmetric Carreira addition of aldehyde **293** and alkyne **294**.[48] Aldehyde **293** was thought to derive from an asymmetric hydroformylation of acrolein acetal **295** following a recently disclosed procedure from Morken and coworkers.[49] Alkyne **294** could originate from opening of (*R*)-propylene oxide with butynyllithium and a subsequent alkyne zipper reaction.[50]

We began our journey with the hydroformylation of **295** according to Morken and coworkers.[49] In their contribution, a variety of allyl alcohol derivatives were exposed to

asymmetric hydroformylation conditions to yield different Roche-type aldehydes. We were particularly interested in the hydroformylation of the acrolein acetal **295** as this would enable us to pursue the synthesis with minimal redox manipulations. Attempts to reproduce the literature example were initially met with failure (Table 4). Neither the isomeric ratio nor the enantiomeric excess could be replicated. After considerable optimization it was found that optimal results were ensured when a stock solution of the rhodium salt was added to a freshly prepared ligand/substrate mixture. Upon completion, the crude aldehyde obtained had to be used immediately as prolonged exposure to air or silica led to significant deterioration of the enantiomeric excess.

Table 4. Optimization of enantioselective hydroformylation by Morken and coworkers.



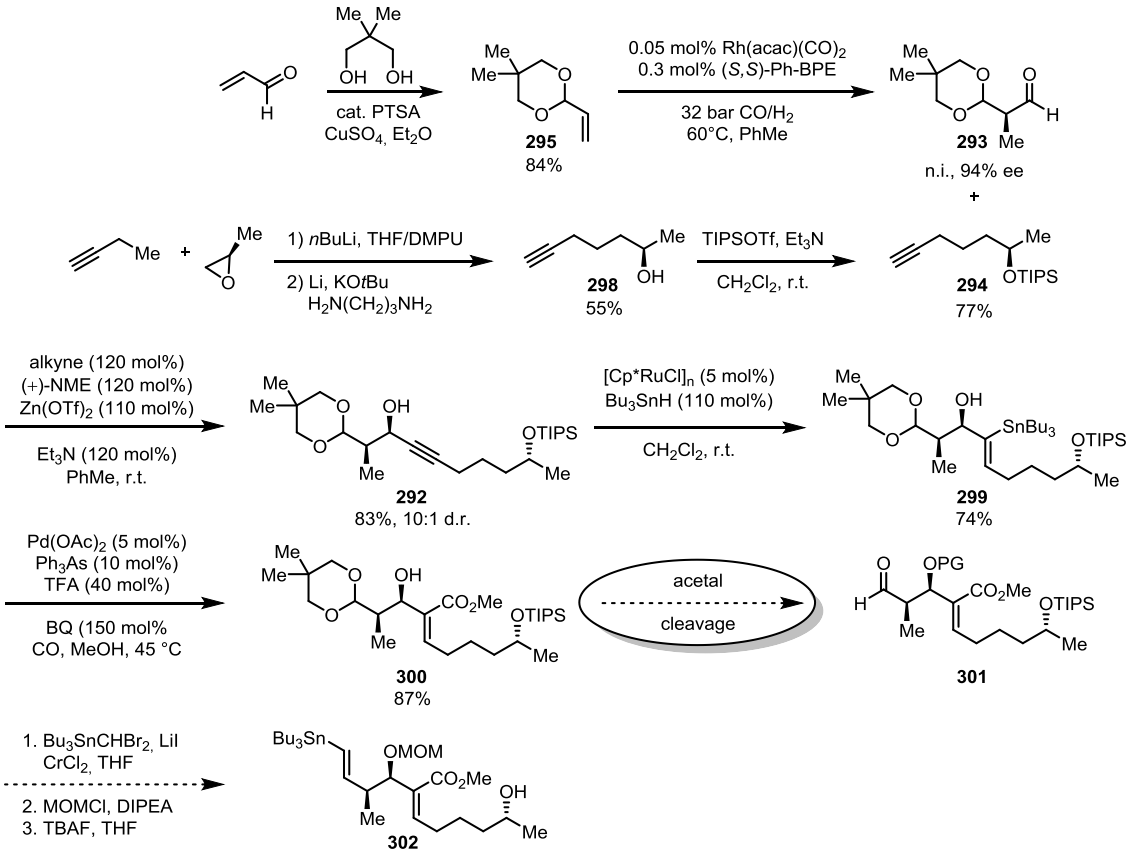
295 **A** **293** **B** **297**

Entry	$Rh(CO)_2(acac)$ (mol%)	Ligand (mol%)	conc. [mol/L]	H_2/CO [bar]	T [°C]	T [h]	ratio[a] (A : B)	ee[b] (%)
1	0.20*	0.22*	1.43	15	80	12	n.d.	80 [R]
2	0.20*	0.22*	1.43	15	60	12	4.3 : 1	84 [R]
3	0.20*	0.22*	2.5	15	40-60	12+12	1.2 : 1	7.3 [R]
4	0.29	0.35	2.5	12	80	12	1.7 : 1	71 [S]
5	0.36	0.59	1.25	12	80	12	1.6 : 1	70 [S]
6	0.23	0.52	2.5	12	60	12	1.7 : 1	74 [S]
7	0.20*	0.22*	1.7	32	60	4	2.3 : 1	72 [S]
8	0.20*	0.22*	1.7	32	40	12	1.8 : 1	72 [S]
9	0.16	0.32	2.5	32	60	12	3.0 : 1	84 [R]
10	0.18	0.36	10	32	60	12	3.5 : 1	33 [R]
11	0.05*	0.20	2.5	32	60	12	14 : 1	78 [R]
12	0.10*	0.20	2.5	32	60	4	3.6 : 1	88 [R]‡
13	0.05*	0.32	2.5	32	60	4	13 : 1	94 [R]‡

[a]determined by GCMS of crude mixture; [b]determined by chiral GCMS; *indicates stock solution in PhMe; ‡ ee determined of crude reaction mixture without prior purification.

With the required aldehyde **293** in hand, we were able to quickly assemble the main fragments employing routine chemistry (Scheme 18). Opening of (*R*)-propylene oxide with butynyllithium[51] proved to be straightforward in the presence of DMPU as cosolvent.[52] An alkyne zipper reaction with KO*t*Bu/lithio diaminopropane[50] and subsequent TIPS protection furnished alkyne **294**. Carreira addition worked uneventfully to provide propargyl alcohol **292** in good yield and excellent diastereoselectivity.[48a] Subsequent *trans*-selective hydrostannation

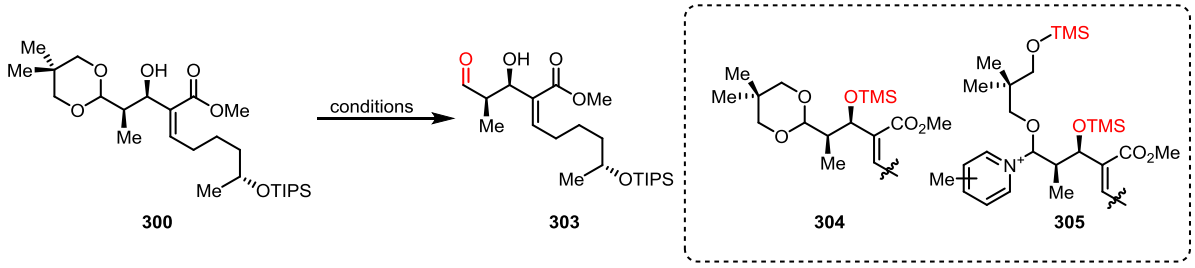
followed by a palladium catalyzed oxidative methoxy carbonylation according to the new procedure disclosed herein gave rise to α,β-unsaturated ester **300.**



Scheme 18. First attempt for the formal synthesis of tubelactomicin A.

As it was anticipated that deprotection of the cyclic acetal in the presence of a MOM protecting group would be problematic, it was decided to install the MOM ether at a later stage of the synthesis. The formation of an intermediate oxonium ion during the deprotection step had to be suppressed as these are known to cause epimerization of α-chiral aldehydes. Literature precedents are scarce but in a recent disclosure, Leighton and coworkers were able to deprotect an α-chiral dioxolane[53] by employing the method of Fujioka and Kita.[54] By treating acetals with TESOTf or TMSOTf in the presence of pyridine bases, the group was able to show that epimerizable aldehydes can be deprotected without intermediate formation of an oxonium ion. Key to success is the formation of stable pyridinium adducts (**305**) that are hydrolyzed upon work-up (Table 5). Furthermore, free alcohols are silyl protected *in situ* which rendered this methodology especially attractive for our synthesis (**304**).

Table 5. Optimization of deprotection conditions for cyclic acetal.



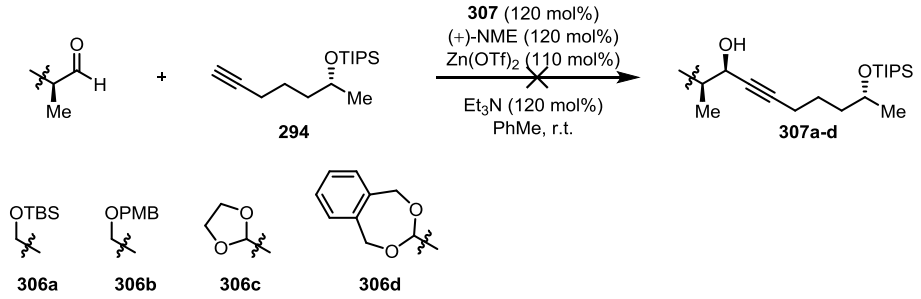
Entry	Conditions	Result[a]
1	aq. TFA CH_2Cl_2 (0.01 M), r.t.	multiple aldehydes formed
2	cat. TsOH acetone (0.1 M), r.t.	no reaction (after 18h)
3	aq. HCl (10 equiv.) THF (0.07 M), r.t.	no reaction (after 18h)
4	TMSOTf (5 equiv.), 2,6-lutidine (10 equiv.) CH_2Cl_2 (0.04 M), –78 °C to 0 °C	20% conversion, 4% product, 15% byproduct
5	BBr_3(5 equiv.), 2,6-lutidine (10 equiv.) CH_2Cl_2 (0.04 M), –78 °C to 0 °C	Decomposition
6	BCl_3(5 equiv.), 2,6-lutidine (10 equiv.) CH_2Cl_2 (0.04 M), –78 °C to 0 °C	Decomposition
7	TMSOTf (5 equiv.), 2,6-lutidine (10 equiv.) CH_2Cl_2 (0.04 M), –78 °C to r.t.	~ 50% conversion
8	TMSOTf (5 equiv.), 2,6-lutidine (10 equiv.) CH_2Cl_2 (0.2 M), –78 °C to r.t.	70% conversion, 3 species
9	TMSOTf (5 equiv.), 2,4,6-collidine (20 equiv.), CH_2Cl_2 (0.2M), 0 °C	40% conversion, 3 species
10	TMSOTf (10 equiv.), 2,4,6-collidine (20 equiv.), CH_2Cl_2 (0.2 M), 0 °C	20% conversion, 3 species
11	TMSOTf (10 equiv.), 2,6-lutidine (10 equiv.) CH_2Cl_2 (0.4 M), 0 °C	60% conversion, 3 species
12	TMSOTf (10 equiv.), 2,6-lutidine (10 equiv.) CH_2Cl_2 (0.4 M), –10 °C	10% conversion, n.d.
13	TMSOTf (10 equiv.), 2,6-lutidine (10 equiv.) CH_2Cl_2 (0.4 M), –10 °C to r.t.	50% conversion, mainly desired
14	1,3-propanedithiol (1.5 equiv.), BF_3Et_2O (10 mol%), CH_2Cl_2 (0.2 M), r.t.	decomp.

[a]determined by crude NMR analysis

A variety of conventional methods for acetal cleavage failed or led to decomposition (entries 1-3). TMSOTf provided some conversion (entry 4) whereas BCl_3 or BBr_3 (entries 5-6) only

decomposed the starting material. This result can be ascribed to interference of the free alcohol and formation of HX *in situ*. After some optimization, it was found that multiple aldehydes were formed in cases where some conversion was observed (entry 7-13); this was attributed to significant epimerization. Finally, transacetalization to a dithiane was probed. The corresponding thioacetals are known to be deprotected under much milder conditions.[55] Unfortunately this attempt was also met with failure.

At this stage we had to abandon our original strategy and turn our attention towards the synthesis of more conveniently handled building blocks. As the cyclic acetal proved to be the major pitfall, we decided to replace it by a different protecting group or by a protected alcohol. This traced us back to a range of different Roche aldehydes. These were accessed by the same hydroformylation reaction employed earlier with comparable results and tested in the previously successful Carreira alkynylation (Scheme 19). We quickly found, that no conversion was observed no matter which protecting group was tested. Neither TBS or PMB protected allyl alcohols **306a** and **306b** nor acetals **306c** or **306d** provided any product (**307**).



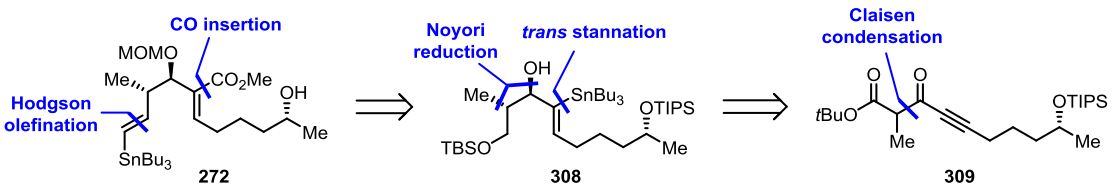
Scheme 19. Attempted Carreira alkynylation of different Roche aldehydes.

The Carreira alkynylation has been proven in the past to be problematic in mismatched cases especially with bulky neighboring groups on the aldehyde. Striking examples can be found in the literature.[56] A possible explanation why acrolein acetal **293** behaved so differently than all other Roche aldehydes, might be its reduced steric demand. The strong Thorpe-Ingold effect of the *gem*-dimethyl group in the backbone results in compression of the dioxane ring and thereby in a reduction of steric bulk. At this point we devised a new route which is detailed in the next section.

3.2.2.5. Retrosynthetic Analysis and Forward Formal Synthesis of Tubelactomicin A – Part II

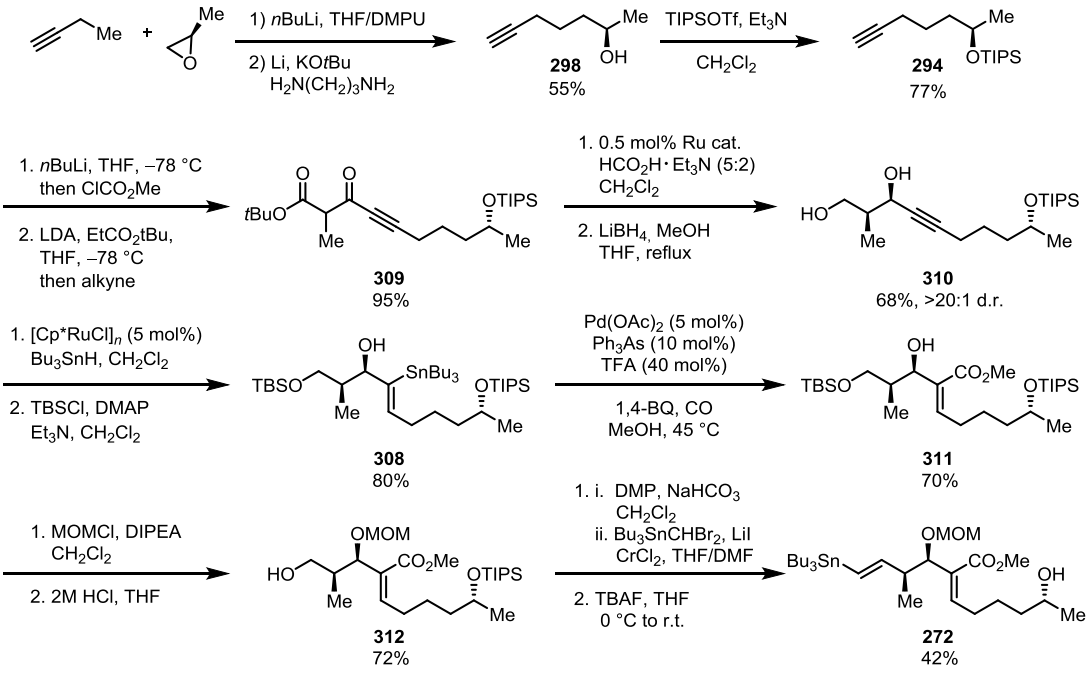
We learned from the previous attempt that we had to access an intermediate bearing a protected alcohol that could later be transformed into the required aldehyde for the Hodgson olefination. As the synthesis of the alkyne part was already established, we planned to introduce the *syn*-aldol motif by an asymmetric Noyori reduction.[57] This would allow us to quickly

assemble the carbon backbone and set the stereocenters with high enantiomeric excess and diastereoselectivity.



Scheme 20. Second retrosynthetic analysis for the formal synthesis of tubelactomicin A.

To this end, the synthesis illustrated in Scheme 21 was executed. Alkyne **294** from the previous attempt was first acylated with methyl chloroformate. The resulting propionic ester then undergoes Claisen condensation with *tert*-butyl propiolate to give β-keto ester **309**.[58] Noyori reduction under transfer hydrogenation conditions furnished *syn*-propargyl alcohol in excellent enantiomeric excess and diastereoselectivity employing a modified catalyst.[57] $LiBH_4$ reduction in the presence of MeOH in refluxing THF cleanly provided diol **310**.[59] *trans*-Selective hydrostannation[60] worked uneventfully giving the product as a single regioisomer, and was followed by selective TBS protection of the primary alcohol. The critical oxidative palladium-catalyzed methoxy carbonylation delivered α,β-unsaturated ester **311** in good yield. MOM protection and TBS deprotection set the stage for the crucial Hodgson olefination. Dess-Martin periodinane oxidation delivered the critical aldehyde which was used without further purification in the olefination reaction.[61] TIPS removal with TBAF completed the formal synthesis of tubelactomicin A (**272**).

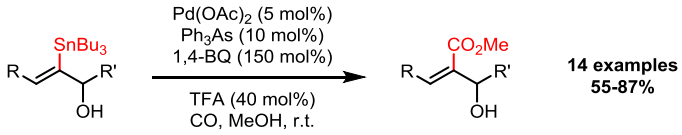


Scheme 21. Formal synthesis of tubelactomicin A.

The synthesis comprised 14 steps and gave an overall yield of 4%, cutting the step count of the previous synthesis almost in half. Key transformations include a highly enantio- and diastereoselective Noyori transfer reduction, a directed *trans*-hydrostannation, a novel oxidative palladium-catalyzed methoxy carbonylation and a Hodgson olefination. With significant amounts of key fragment **272** in hand, future studies will aim to complete the total synthesis of tubelactomicin A (**246**).

3.3. Conclusion and Outlook

With the new condition presented herein, we have developed a powerful tool for the direct conversion of alkenylstannanes into α,β-unsaturated esters. Under these mild reaction conditions, a variety of highly functionalized esters could be accessed (Scheme 22). By combining the knowledge gained from studies on Stille cross-coupling[38], allylic oxidation[39] and aryl boronic acid oxidative carbonylation[12], a new protocol has been implemented. Furthermore, the viability of this methodology was successfully proven in the context of a formal synthesis of tubelactomicin A. Future studies will focus on the total synthesis of tubelactomicin A and congeners.



Scheme 22. Palladium catalyzed oxidative methoxy carbonylation.

Oxidative cross-coupling reactions of alkenylstannanes, e.g. Heck-reactions or cross-couplings with other organometalloids, could yield additional highly valuable protocols and hold some promise for future development.

3.4. Literature

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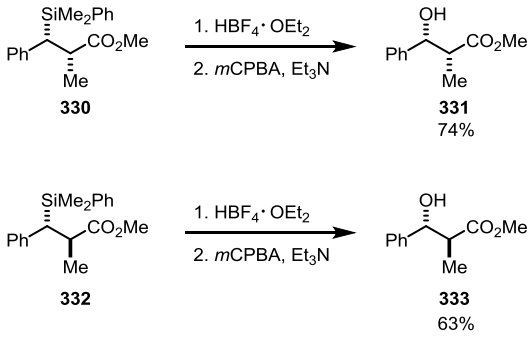
4. Oxidation of Alkenylstannanes to (Hydroxy)ketones

4.1. Introduction

4.1.1. Conversion of C-M to C-O bonds – State of the Art

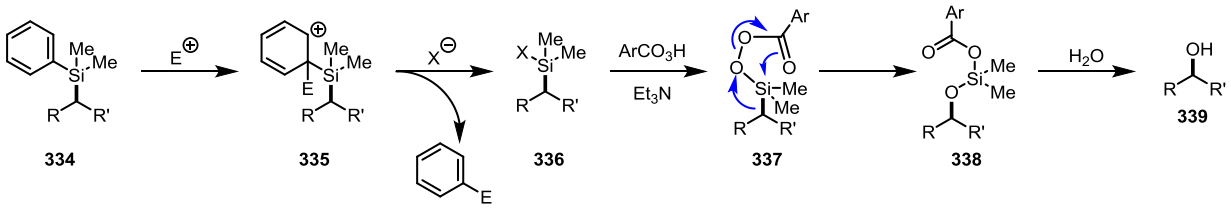
4.1.1.1. Fleming-Tamao Oxidation of Silanes

The late stage introduction of carbon-oxygen bonds is an important task in natural product synthesis. An important solution to this problem is the Fleming-Tamao oxidation of organic silanes wherein a C-Si bond is converted into a C-O bond and occurs with retention of configuration as exemplified in Scheme 1.[1]



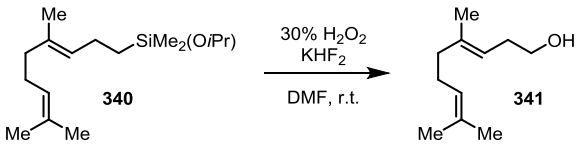
Scheme 1. Fleming oxidation under retention of configuration.

Under Fleming conditions, the phenyl group of silane **334,** upon activation with a strong electrophile, undergoes *ipso*-displacement by a counterion X to give **336** (Scheme 2). After addition of an oxidant such as a peracid, ligand exchange takes place (**337**). Ensuing 1,2-migration from silicon to oxygen via **337** affords alcohol **339** after hydrolysis.



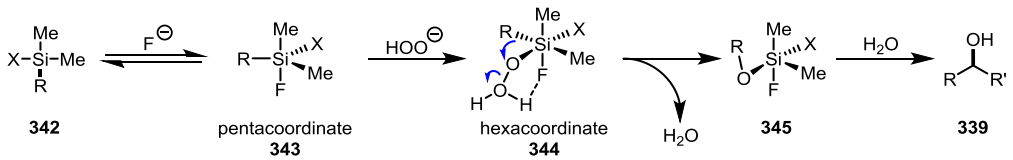
Scheme 2: Mechanism of the Fleming oxidation.

Under oxidative, basic conditions, Tamao and Kumada used monoalkoxysilanes for a similar transformation in the presence of a fluoride source (Scheme 3).



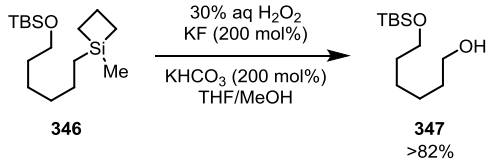
Scheme 3. Tamao-Kumada oxidation.

As illustrated in Scheme 3, the silane bears at least one heteroatom, and therefore preactivation as in the Fleming oxidation is unnecessary. Although exact mechanisms are still unknown, Tamao has developed a mechanistic proposal based on observations with H_2O_2 as the oxidant (Scheme 4).[2] Silane **342** is activated by an extraneous fluoride source to yield a pentacoordinated silane **343**. As this opens up a second coordination site on silicon and thereby rendering the silane more electrophilic, the silicon center can in turn be attacked by peroxide to give hexacoordinated **344**. Subsequent 1,2-migration and hydrolysis generates the target alcohol **339**.



Scheme 4. Mechanism of the Tamao-Kumada oxidation.

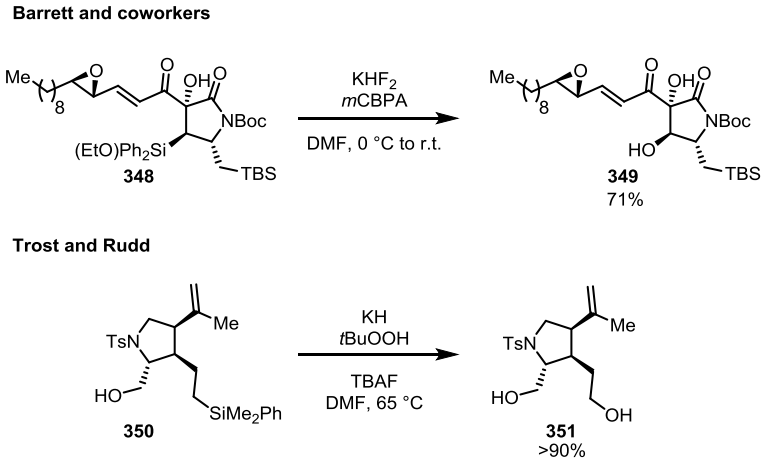
In the past decades, this useful transformation has experienced a number of advancements, especially concerning the nature of the silane employed. For example, strained siletanes undergo Fleming-Tamao oxidation without prior activation (Scheme 5).[1c]



Scheme 5. Fleming-Tamao oxidation of strained silanes by Dudley and coworkers.

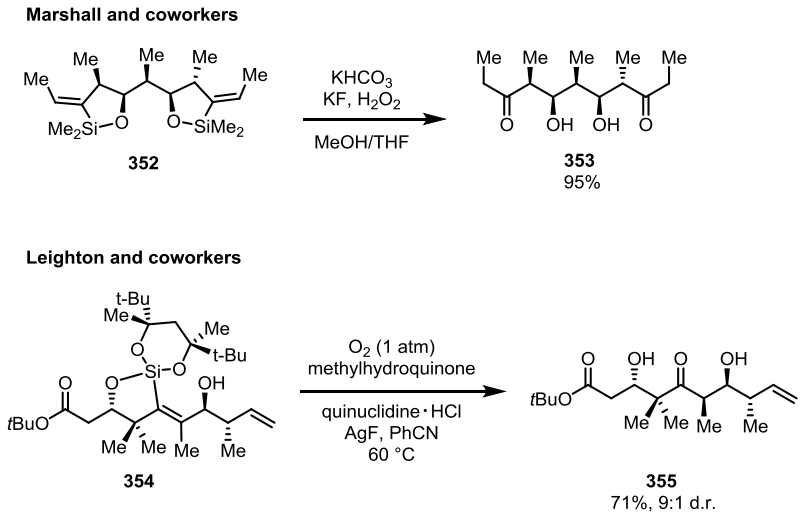
With the rise of transition-metal catalyzed hydrosilylations[3], the importance of the Fleming-Tamao oxidation as a tool for organic synthesis has increased dramatically.[4] Silanes can easily be introduced in an asymmetric fashion and serve as masked hydroxy groups. This strategy has found many applications in the past years.[5]

Barett and coworkers utilized a late-stage Fleming-Tamao oxidation in their endeavor towards an enantioselective synthesis of (+)-pranamicin (Scheme 6).[6] It should be noted that an alkyl TBS group did not participate in this transformation. Trost and Rudd reported a modified Fleming oxidation under strongly nucleophilic conditions towards the total synthesis of (+)-α-kainic acid.[7]



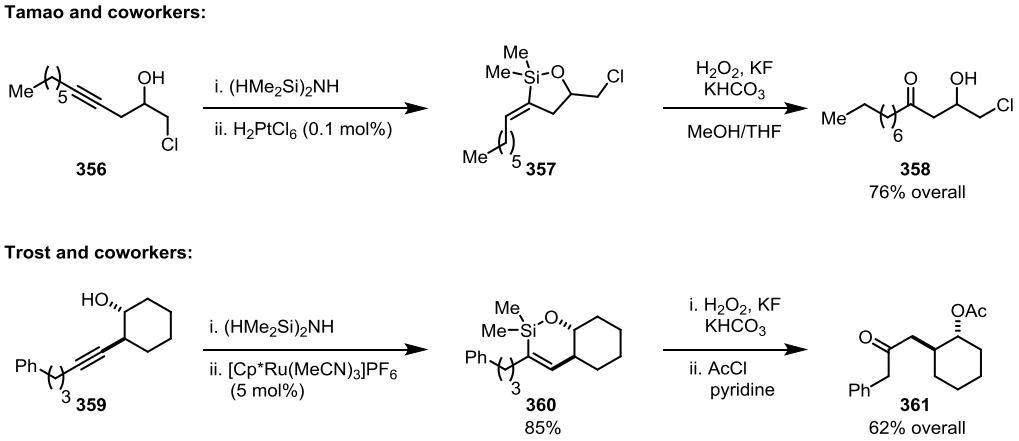
Scheme 6. Recent examples of Fleming-Tamao oxidation in total synthesis.

Besides alkyl silanes, alkenyl silanes can also be subjected to Fleming-Tamao conditions to yield the corresponding carbonyls. This process has become of special interest with the disclosure of the *trans*-selective hydrosilylation by Trost and coworkers.[5b, 8] The late-stage introduction of carbonyls has also found numerous applications in total synthesis and two recent examples from the groups of Marshall[9] and Leighton[10] are presented in Scheme 7.



Scheme 7. Fleming-Tamao oxidation of alkenyl silanes as key steps.

The intramolecular hydrosilylation/oxidation sequence of internal alkynes has been developed as a tool to install a carbonyl group at discrete positions. Employing a platinum catalyst the 5-*exo*-dig cyclization product **357** is obtained[11], whereas the application of a cationic ruthenium catalyst on similar alcohol substrate **359**, selectively furnishes the 6-*endo*-dig cyclization product **360**.[8h] Oxidation under Tamao-conditions delivers the corresponding (homo)aldol products **358** and **361**, respectively.

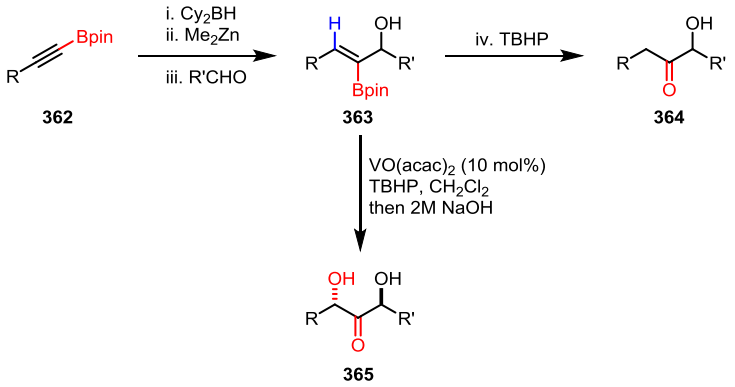


Scheme 8. Regiodivergent hydrosilylation of alkynes.

This strategy still suffers from the requirement of an additional transformation to install the silane which might lead to interferences with other protic groups in the same molecule. Furthermore, it was found that unreacted silane leads to rapid catalyst deactivation which necessitates a tedious purification step after alkoxysilane formation.[12] Generally, the orthogonality with silyl protecting groups can be a major concern in total synthesis.

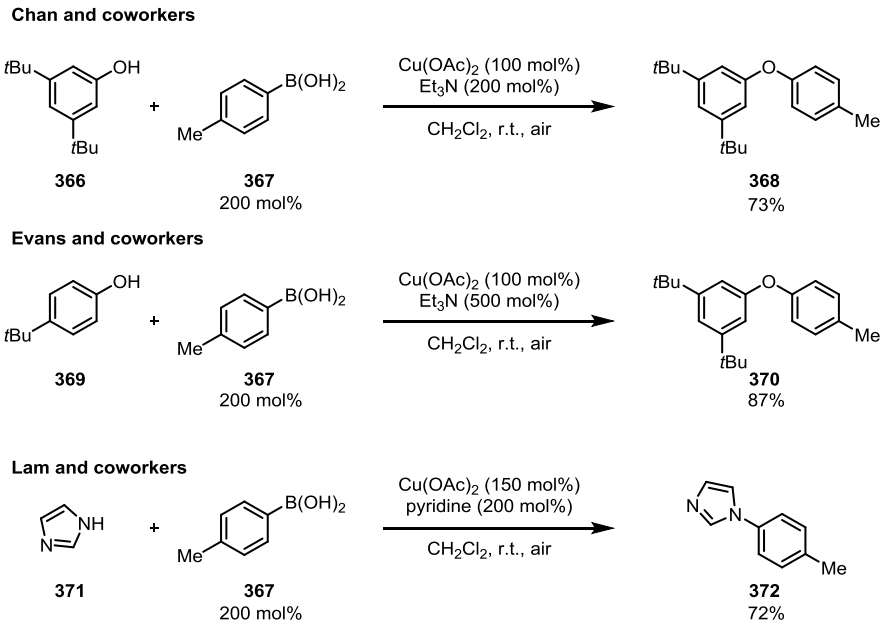
4.1.1.2. Oxidation of Boranes

Another well-established approach for the transformation of C-M to C-O bonds is the oxidation of the carbon-boron bond with basic peroxide to access alcohols or carbonyls.[13] With a plethora of methodologies available for the selective hydroboration of alkenes[14], the late-stage introduction of alcohols via the corresponding boranes proved to be the method of choice.[15] This strategy has only rarely been used for the introduction of carbonyls which might be attributed to the lack of methodology available to selectively obtain the corresponding alkenyl boranes by hydroboration. Two elegant protocols employing the prior installation of alkenyl boranes have been developed by Walsh and coworkers (Scheme 9).[15b, 16] Although being a useful approach, the borane can only be installed in discrete positions at the outset of the synthesis. Furthermore, the use of strong oxidizing agents like TBHP prohibits the presence of other sensitive functional groups in the molecule.



Scheme 9. Multicomponent approach for the synthesis of hydroxyketones by Walsh and coworkers.

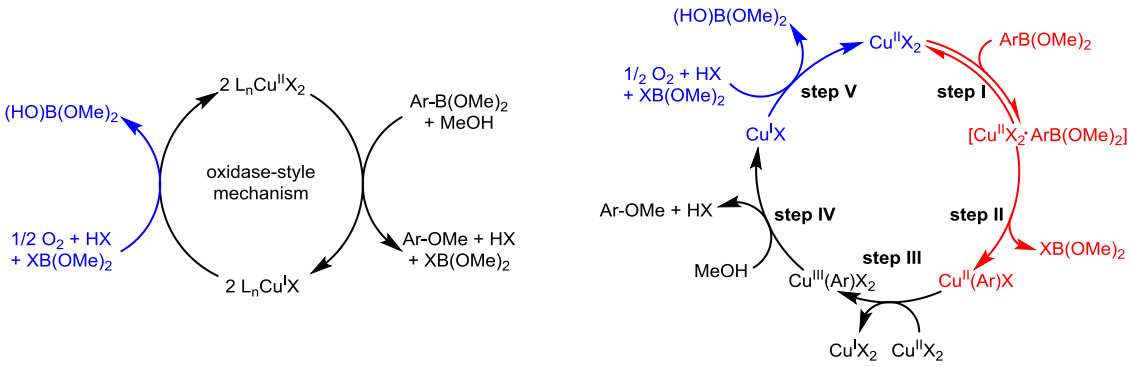
An alternative way to transform the C-B bond to a C-O bond has independently been reported by the groups of Chan, Evans and Lam.[17] They showed that aryl boronic acids undergo copper mediated cross coupling reactions with alcohols or amines to give the corresponding arylated products (Scheme 10). Generally, excess copper(II) acetate and boronic acid in the presence of amine base was employed and the reaction run under aerobic conditions to ensure full conversion.



Scheme 10. Chan-Evans-Lam coupling of boronic acids.

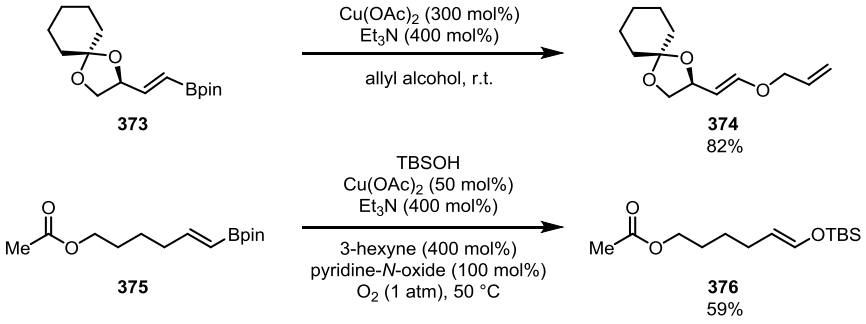
In 2009, Stahl and coworkers disclosed the mechanism of the reaction based on evidence for the existence of Cu^{I}, Cu^{II} and Cu^{III} species in the catalytic cycle (Scheme 11).[18] First, a copper(II)-boronic acid adduct is formed (step I). This adduct then undergoes transmetalation from boron to copper (step II). The resulting copper species is oxidized by another equivalent of copper(II) to give an aryl-copper(III) adduct (step III) that rapidly undergoes reductive elimination. In the presence of MeOH, the corresponding anisol derivate and a copper(I) species (steps IV) are obtained. Under an oxygen atmosphere, the resulting copper(I) species are

reoxidized and reenter the catalytic cycle. This mechanism (left hand picture) can be understood as the synthetic equivalents of nature's oxygenases.



Scheme 11. Catalytic mechanism of the Chan-Evans-Lam coupling.

More recently, the cross-coupling between alkenyl boronic acids and alcohols has received much attention as the resulting vinyl ethers are useful intermediates in organic synthesis.[19] Merlic and coworkers showed that the coupling of terminal alkenyl boronic acids in neat alcohol provides ready access to a variety of vinyl ethers (Scheme 12).

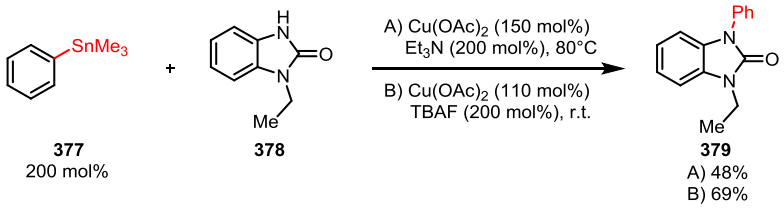


Scheme 12. Synthesis of vinyl ether by Merlic and coworkers.[19c, 19k]

Other research groups have shown that trifluoroborates[19i] or carboxylates[19j] can be valuable coupling partners in this reaction. Although being a very successful transformation for boronic acid derivatives, the potential of other aryl- or alkenylmetal species still demands further investigation.

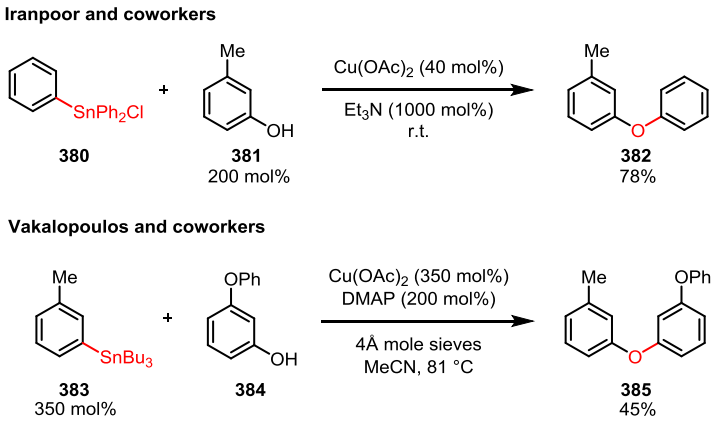
4.1.1.3. Chan-Evans-Lam Coupling of Stannanes

In 2000, Lam and coworkers reported the use of aryl stannanes as coupling partners in the Chan-Evans-Lam coupling, although with limited success.[20] Under the optimized conditions only half of the yield compared to the corresponding boronic acid was obtained. Furthermore, long reaction times and the use of the trimethyltin derivative were required to obtain appreciable results. Two years later, an optimized protocol was disclosed employing TBAF as the base (Scheme 13).[21]



Scheme 13. Chan-Evans-Lam coupling with aryl stannanes by Lam and coworkers.

Since the seminal work by Lam and coworkers was disclosed, only two examples utilize aryl stannanes under Chan-Evans-Lam conditions for the synthesis of aryl ethers (Scheme 14).

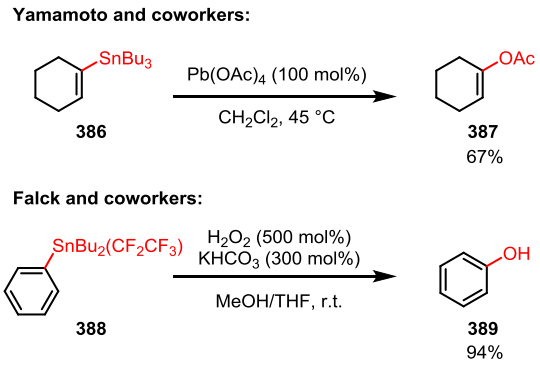


Scheme 14. Chan-Evans-Lam coupling with aryl stannanes.

Iranpoor and coworkers employed triphenylchloro stannane as the coupling partner and triethylamine as the solvent.[22] However, exclusively phenylether and aniline formation was reported. Additionally, Vakalopoulos and coworkers disclosed a coupling reaction that required 3.5 equivalents of the stannane to obtain the biaryl ether in moderate yield.[23] Both procedures suffer from severe limitations e.g. the utilization of chloro triphenylstannane or low yields. Nevertheless, it was shown that the transformation of the C-Sn bond to a C-O bond is *a priori* feasible under copper catalysis.

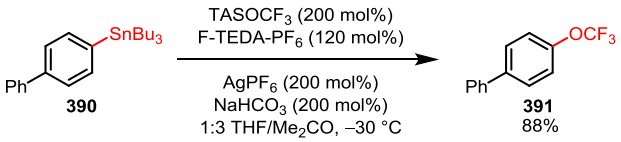
4.1.1.4. Miscellaneous Protocols for the C-Sn to C-O Transformation

The first example of the oxidation of a C-Sn bond was disclosed by Shibasaki and coworkers yielding a mixture of oxygenated products in low yields.[24] In 1988, Yamamoto and coworkers found that alkenyl stannanes can be transformed into the corresponding vinyl ethers by treatment with $Pb(OAc)_4$ (Scheme 15).[25] In 1999, Falck and coworkers disclosed an oxidation of aryl stannanes under conditions similar to those used in the Fleming-Tamao oxidation of silanes.[26] It is imperative to introduce a perfluoroethyl group on the stannane, to render the metal center sufficiently electrophilic for oxidation by basic peroxide.



Scheme 15. Oxidation of alkenylstannanes.

Recently, Ritter and coworkers developed a protocol to access trifluoromethyl ethers (Scheme 16). Under strongly oxidative conditions, aryl stannane **390** was treated with superstoichiometric amounts of $AgPF_6$ to afford trifluoromethyl aryl ether **391** in high yield.

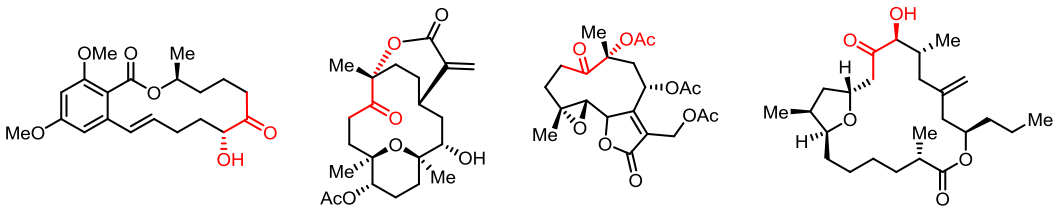


Scheme 16. Ether formation by Ritter and coworkers.

Despite the fact that some methods have been established in the literature, the utility of alkenyl stannanes as masked hydroxyl- or carbonyl groups is still massively underdeveloped. Furthermore, all procedures presented herein pose strong limitations.

4.1.2. Motivation

As the directed *trans*-hydrostannation of (homo)propargyl alcohols reliably delivers stannylated (homo)allyl alcohols, we sought of a way to exploit this motif to access hydroxyketones. An alternative protocol to the commonly employed Fleming-Tamao oxidation is of great interest considering orthogonality with other protecting groups. Furthermore, as we are interested in applying the new methodology in the context of natural product synthesis, mild procedures that tolerate a variety of functional groups are preferred. Some potential targets that might come into reach of total synthesis are given in Figure 1. The crucial hydroxyketone motif is highlighted in red.



392 5'-hydroxyzearalenone

393 querciformolides A

394 glaucolide B

395 amphidinolide T

Figure 1. Possible natural products accessible by oxidation of alkenylstannanes; **392**[27], **393**[28], **394**[29], **395**[30].

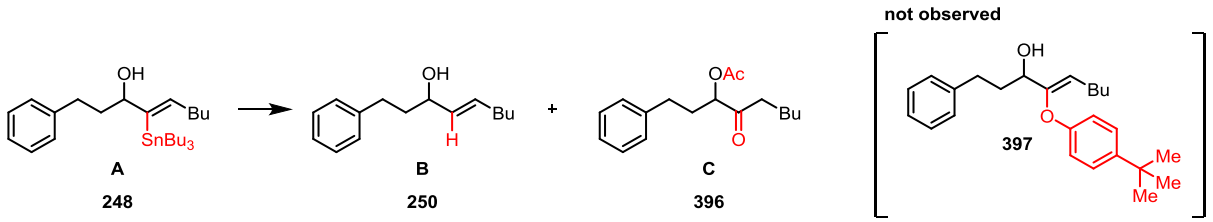
4.2. Results and Discussion

4.2.1. Reaction Development and Substrate Scope

We decided to investigate the possibility to achieve an oxidation of alkenylstannanes by employing the marginally effective Chan-Evans-Lam-type conditions to form the corresponding vinyl ether (Table 1).

The original conditions according to the Chan-Evans-Lam coupling protocol failed to deliver any coupling products. Instead, the α-acetoxy ketone **397** was isolated in 17% yield (entry 1). We quickly found that increasing the equivalents of copper acetate led to an increased conversion of starting material (entry 3), but addition of pyridine (entry 2) or fewer equivalents of base (entry 4) resulted in diminished efficacy. Interestingly, running the reaction under an oxygen atmosphere inhibited the conversion completely (entry 5). Screening of different solvents revealed that polar, aprotic solvents like DMF or DMSO effectively promote the reaction (entries 11-12). Apolar or less polar solvents like toluene, pentane, acetonitrile, THF or acetone all failed to furnish appreciable amounts of the product (entries 6-10). As DMSO is less toxic than DMF and more conveniently handled, it was selected as the solvent of choice for further optimization (Table 2).

Table 1. Initial reaction development of copper mediated formal oxidation.

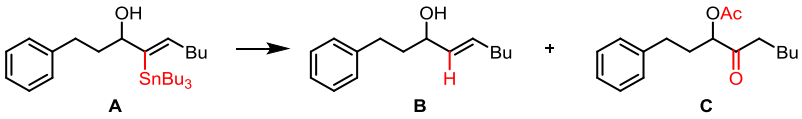


Entry	Reagent (mol%)	Modification	Base (eq)	Solvent	T [°C] t [h]	Ratio[a] (A : B : C)
1	$Cu(OAc)_2$ (100)	*p*-*t*BuC_6H_4OH (2)	Et_3N (5)	CH_2Cl_2 (0.125 M)	r.t., 12	1 : 2.1 : 1.5
2	$Cu(OAc)_2$ (100)	*p*-*t*BuC_6H_4OH (2)	C_5H_5N (5)	CH_2Cl_2 (0.125 M)	r.t., 12	1 : 0.33 : 0.16
3	$Cu(OAc)_2$ (200)	-	Et_3N (5)	CH_2Cl_2 (0.125 M)	r.t., 12	1 : 9.5 : 11
4	$Cu(OAc)_2$ (200)	-	Et_3N (1.5)	CH_2Cl_2 (0.125 M)	r.t., 12	1 : 0.28 : 0.69
5	$Cu(OAc)_2$ (200)	O_2 balloon	Et_3N (5)	CH_2Cl_2 (0.125 M)	r.t., 12	1 : 0 : 0
6	$Cu(OAc)_2$ (200)	-	Et_3N (5)	PhMe (0.125 M)	r.t., 12	1 : 0.02 : 0.01
7	$Cu(OAc)_2$ (200)	-	Et_3N (5)	MeCN (0.125 M)	r.t., 12	0 : 1.0 : 2.1
8	$Cu(OAc)_2$ (200)	-	Et_3N (5)	pentane (0.125 M)	r.t., 12	1 : 0.04 : 0.01
9	$Cu(OAc)_2$ (200)	-	Et_3N (5)	Me_2CO (0.125 M)	r.t., 12	1 : 0.15 : 0.21
10	$Cu(OAc)_2$ (200)	-	Et_3N (5)	THF (0.125 M)	r.t., 12	1 : 0.43 : 0.07
11	$Cu(OAc)_2$ (200)	-	Et_3N (5)	DMSO (0.125 M)	r.t., 12	0.13 : 1 : 2.72
12	$Cu(OAc)_2$ (200)	-	Et_3N (5)	DMF (0.125 M)	r.t., 12	0 : 1 : 3.3

[a]determined by crude NMR analysis.

To suppress protodestannation, the reaction was run under strictly anhydrous conditions which resulted in a significant drop of selectivity (entry 1). With copper acetate hydrate (entry 2) or reagent grade solvent (entry 3), virtually no conversion was observed. Gratifyingly, by heating the mixture to 45°C, full conversion of starting material and excellent selectivity was obtained (entry 4). In order to decrease the amount of protodestannation, other organic and inorganic bases were tested, albeit no improvement was achieved (entries 5-11). It should be noted that in the presence of potassium carbonate rapid conversion but slightly diminished selectivity was observed (entry 8). Changing the equivalents of base and copper salt led only to a minor improvement in the product ratio; therefore we decided to preserve the initial stoichiometries (entries 12-14). To evaluate the influence of an extraneous oxidant, the reaction was run in degassed solvent (entry 15) or under air (entry 16), which had no significant impact. When the reaction was finally run under an atmosphere of oxygen, only protodestannation was observed (entry 17).

Table 2. Optimization of copper mediated formal oxidation of alkenylstannanes.



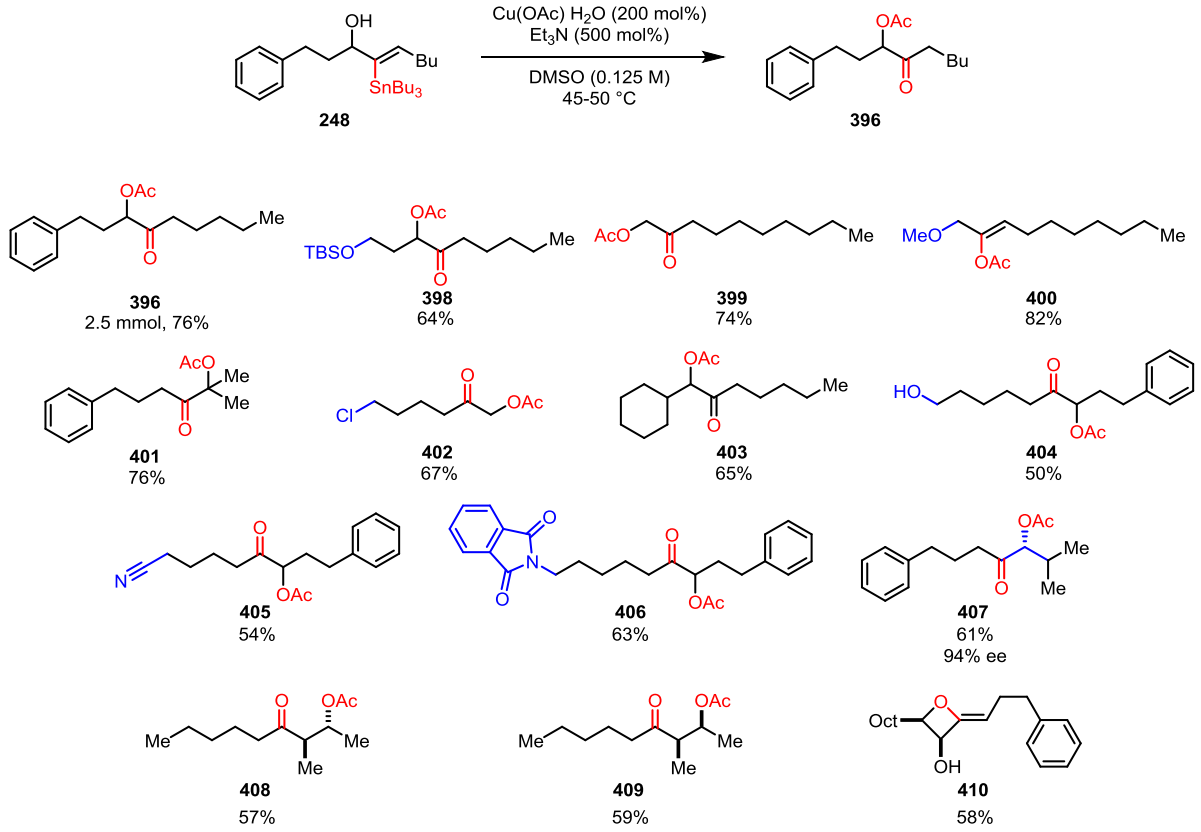
Entry	Reagent (mol%)	Modification	Base (eq)	Solvent	T [°C] t [h]	Ratio[a] (A : B : C)
1	$Cu(OAc)_2$ (200)	3Å mole sieves	Et_3N (5)	DMSO (0.125 M)	r.t., 12	0 : 1 : 1.00
2	$Cu(OAc)_2$* (200)	-	Et_3N (5)	DMSO (0.125 M)	r.t., 12	1 : 0 : 0.03
3	$Cu(OAc)_2$* (200)	-	Et_3N* (5)	DMSO‡ (0.125 M)	r.t., 12	1 : 0 : 0.00
4	$Cu(OAc)_2$* (200)	-	Et_3N* (5)	DMSO‡ (0.125 M)	45, 12	0 : 1 : 7.64
5	$Cu(OAc)_2$* (200)	-	Cy_2NMe (5)	DMSO‡ (0.125 M)	45, 12	0 : 1 : 4.58
6	$Cu(OAc)_2$* (200)	-	iPr_2Net (5)	DMSO‡ (0.125 M)	45, 12	0 : 1 : 7.50
7	$Cu(OAc)_2$* (200)	-	DBU (5)	DMSO‡ (0.125 M)	45, 12	0 : 1 : 0.12
8	$Cu(OAc)_2$* (200)	-	K_2CO_3 (5)	DMSO‡ (0.125 M)	45, 2	0 : 1 : 6.10
9	$Cu(OAc)_2$* (200)	-	K_3PO_4 (3)	DMSO‡ (0.125 M)	45, 12	0 : 1 : 2.06

Entry	Reagent (mol%)	Modification	Base (eq)	Solvent	T [°C] t [h]	Ratio[a] (A : B : C)
10	$Cu(OAc)_2$* (200)	-	$NaHCO_3$ (5)	DMSO‡ (0.125 M)	45, 6	0 : 1 : 1.65
11	$Cu(OAc)_2$* (200)	-	NaOAc (5)	DMSO‡ (0.125 M)	45, 2	0 : 1 : 1.17
12	$Cu(OAc)_2$* (200)	-	Et_3N* (10)	DMSO‡ (0.125 M)	45, 12	0 : 1 : 6.87
13	$Cu(OAc)_2$* (200)	-	Et_3N* (5)	DMSO‡ (0.125 M)	45, 12	0 : 1 : 9.79
14	$Cu(OAc)_2$* (300)	-	Et_3N* (10)	DMSO‡ (0.125 M)	45, 12	0 : 1 : 11.73
15	$Cu(OAc)_2$* (200)	open to air	Et_3N (5)*	DMSO‡ (0.125 M)	45, 12	0 : 1 : 5.46
16	$Cu(OAc)_2$* (200)	degassed DMSO	Et_3N (5)	DMSO‡ (0.125 M)	45, 12	0 : 1 : 6.00
17	$Cu(OAc)_2$* (200)	O_2 balloon	Et_3N* (5)	DMSO‡ (0.125 M)	45, 12	1 : 0.30 : 0

[a]determined by crude NMR analysis; *reagent grade quality; ‡reagent grade, 212 ppm H_2O.

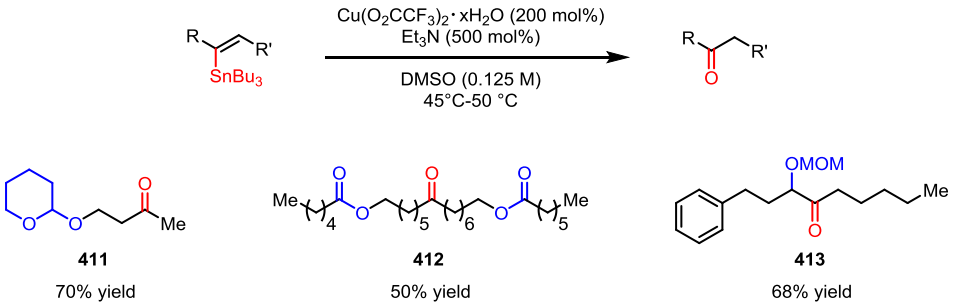
With this new protocol in hand, we set out to evaluate the synthetic potential of this novel transformation. An array of different stannanes was subjected to the optimized reaction conditions and the results are shown in Scheme 17. Primary (**399**), secondary (**403**), and tertiary alcohols (**401**) participate equally well. An experiment with 2.5 mmol of substrate proved the scalability of the reaction without loss of efficiency (**396**). Furthermore, silyl ether **398** is tolerated which would be inconceivable under standard Fleming-Tamao conditions. Halides (**402**), other free alcohols (**404**), nitriles (**405**), and phthalimides (**406**) do not affect the reaction. Importantly, enantiopure alcohol (**407**) can be transformed into the corresponding acetoxy ketones without loss of stereochemical information. When protected alcohol **400** was employed as a substrate, the respective alkenyl acetate was isolated. Homoallylstannanes serve as productive substrates as well, furnishing aldol products **408** and **409**, respectively. Interestingly, if a second alcohol is present in the homoallylic position, a rarely described oxetane ring is formed (**410**).[31] Attempts to expand the scope to simple homoallylstannanes failed, as purification of the oxetanes proved difficult as well as their hydrolysis with aqueous acids. Nevertheless, considering their unexplored nature this transformation might hold some promise for future developments.

Substrates bearing additional degrees of unsaturation in conjugation with the alkenylstannanes, a free acid or the corresponding amides result in exclusive protodestannation.



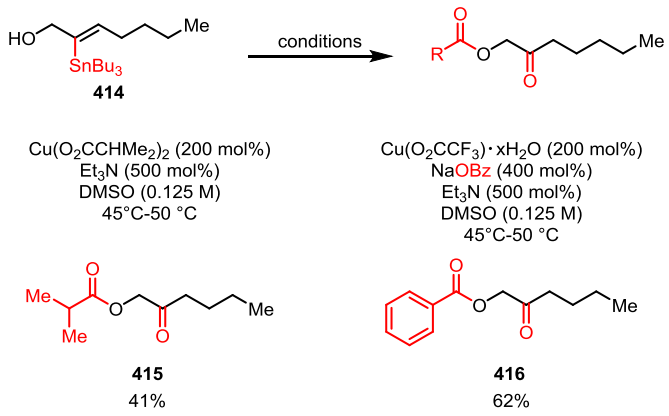
Scheme 17. Substrate scope of the copper acetate mediated oxidation.

With these encouraging results in hand, we sought to extend the scope of this transformation to the synthesis of ketones with no flanking free alcohol. To this end, we quickly encountered that the conversion of alkenylstannes into the corresponding ketones was straightforward in the presence of $Cu(O_2CCF_3)_2$ (Scheme 18). In contrast to the formation of **400** in the presence of copper(II) acetate, formation of the respective vinyl trifluoroacetate was not observed.



Scheme 18. Substrate scope of the copper trifluoroacetate mediated oxidation.

Finally, it was found that other copper carboxylates lead to the formation of different carboxy ketones (Scheme 19). When copper isobutyrate was used in the place of copper(II) acetate, the corresponding isobutyric ester was isolated. Copper trifluoroacetate in the presence of sodium benzoates yields the respective benzoate, presumably via *in situ* formation of copper(II) benzoate.



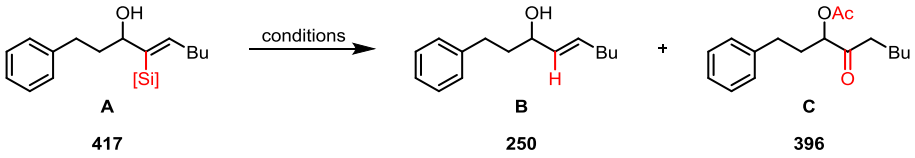
Scheme 19. Copper mediated keto carboxylate formation.

4.2.2. Preliminary Results for the Oxidation of Alkenylsilanes

With the optimal conditions in hand, we examined the possibility to extend this transformation to the conversion of alkenylsilanes into the corresponding ketones (Table 3). This could be a useful alternative to the ubiquitously applied Fleming-Tamao oxidation. Triethoxysilane derivative **417** was chosen as a model substrate and exposed to the established reaction conditions.

Under the standard conditions, only protodesilylation was obtained (entry 1). Using dry solvents and reagents (entries 2) or potassium carbonate as a base (entry 3) had no impact on the reaction outcome. In the presence of water, product formation was observed as well as protodesilylation (entry 4). As fluoride additives are common activators for silanes, different fluoride sources were subsequently screened. At room temperature potassium fluoride provided superior results (entry 7) compared to cesium fluoride (entries 5-6) or sodium fluoride (entry 8). Gratifyingly, upon heating rapid conversion of the starting material was observed (entry 9). Interestingly, the analogous dimethylbenzyl silane derivative was inert under these conditions (entry 10). All efforts to improve the selectivity by changing fluoride sources and stoichiometries of copper(II) acetate were unsuccessful (entries 11-14). Nevertheless, it seems reasonable to assume that this methodology offers the possibility to develop an alternative protocol to the Fleming-Tamao oxidation of silanes.

Table 3. Optimization of copper mediated oxidation of alkenylsilanes.

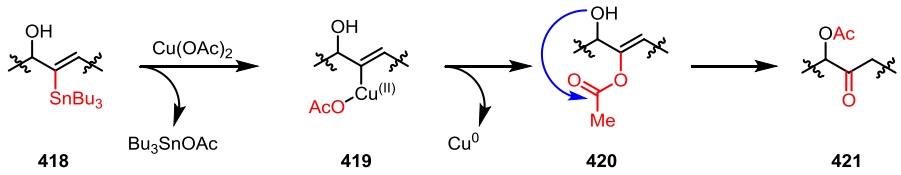


Entry	Reagent (mol%)	[Si]	Base (eq)	Solvent	T [°C] t [h]	Ratio[a] (A : B : C)
1	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	Et_3N (5)*	DMSO‡ (0.125 M)	45, 12	0 : 1 : 0
2	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	Et_3N (5)	DMSO (0.125 M)	45, 12	0 : 1 : 0.06
3	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	K_2CO_3 (5)	DMSO‡ (0.125 M)	45, 12	1 : 0.92 : 0.05
4	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	Et_3N (5)*	DMSO/H_2O, 9:1 (0.125 M)	45, 12	0 : 1 : 1.25
5	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	CsF (1)	DMSO‡ (0.125 M)	r.t., 12	0 : 1 : 0.73
6	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	CsF (2)	DMSO‡ (0.125 M)	r.t., 12	0 : 1 : 1.28
7	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	KF · 2 H_2O (2)	DMSO‡ (0.125 M)	r.t., 12	0 : 1 : 1.39
8	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	NaF (2)	DMSO‡ (0.125 M)	r.t., 12	0 : 1 : 0.25
9	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	KF · 2 H_2O (3)	DMSO‡ (0.125 M)	50, 2	0 : 1 : 2.96
10	$Cu(OAc)_2$* (200)	$SiBnMe_2$	KF · 2 H_2O (2)	DMSO‡ (0.125 M)	50, 12	1 : 0 : 0
11	$Cu(OAc)_2$* (300)	$Si(OEt)_3$	KF · 2 H_2O (3)	DMSO‡ (0.125 M)	50, 2	0 : 1 : 2.77
12	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	TBAF · 3 H_2O (3)	DMSO‡ (0.125 M)	50, 2	0 : 1 : 0.38
13	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	TMAF (3)	DMSO‡ (0.125 M)	50, 2	0 : 1 : 1.85
14	$Cu(OAc)_2$* (200)	$Si(OEt)_3$	KF · 2 H_2O (3), Et_3N (5)	DMSO‡ (0.125 M)	50, 1	0 : 1 : 1.23

[a]determined by crude NMR analysis; *reagent grade quality; ‡reagent grade, 212 ppm H_2O

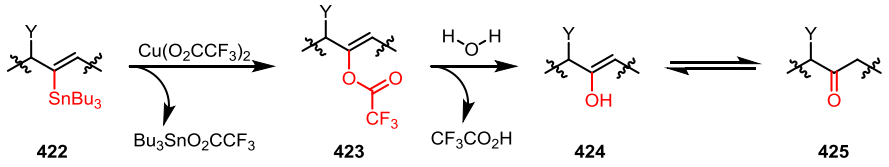
4.2.3. Mechanistic Proposal

Based on the observations made during the investigation of the substrate scope, a mechanistic rationale can be proposed (Scheme 20).



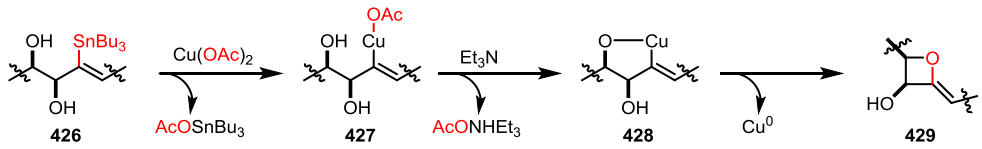
Scheme 20. Mechanistic proposal for the formation of acetoxy ketones.

In accordance to the work of Stahl and coworkers,[18] in the first step a transmetalation from tin to copper occurs with extrusion of tributyltin acetate to give **419**. This transformation could be a radical process as under an oxygen atmosphere no conversion was observed and oxygen has been reported to be a good radical inhibitor.[32] The resulting alkenylcopper species then undergoes reductive elimination to afford vinyl acetate **420**, giving off copper(0). This proposal was confirmed as vinyl acetate **400** was isolated when a methylated allyl alcohol was employed. It was noticed in all examples that large amounts of a brown precipitate, presumably copper(0), formed after full conversion. Furthermore, when the reaction was run under air no such precipitate was observed, although full conversion was obtained. This advocates that the copper(0) formed is reoxidized under air. Finally, the neighboring alcohol captures intermediate acetate **420** and tautomerization gives acetoxy ketone **421**. In the presence of copper trifluoroacetate, the corresponding vinyl acetates are supposedly hydrolyzed under the reaction conditions as these are highly reactive acyl transfer reagents (Scheme 21).



Scheme 21. Mechanism of the copper trifluoroacetate mediated ketone formation.

The formation of oxetane **429** provides further evidence for the intermediacy of an alkenyl copper species and can be rationalized as follows (Scheme 22). Stannane **426** undergoes transmetalation to yield alkenyl copper **427**. Subsequently, the neighboring homoallylic alcohol forms a 5-membered ring by replacing the remaining acetate on the copper species, giving intermediate **428**. Reductive elimination then furnishes oxetane **429** with the extrusion of copper(0).

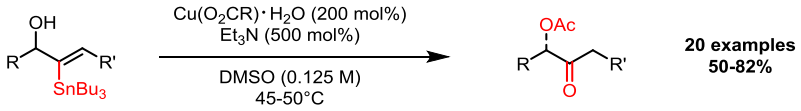


Scheme 22. Copper mediated oxetane formation.

4.3. Conclusion and Outlook

By drawing inspiration from the important contributions of Chan, Evans and Lam, a new protocol for the formal oxidation of alkenylstannanes was developed. Under optimized conditions, it is now possible to transform alkenylstannanes into functionalized ketones. The respective acetoxyketones could be isolated in moderate to good yields without epimerization of neighboring stereocenters. Furthermore, the synthesis of plain ketones is possible by changing copper(II) acetate to copper(II) trifluoroacetate. When other copper carboxylates are employed, the corresponding α-carboxy ketones are obtained. Finally, a reasonable reaction mechanism of the reaction was proposed.

The syntheses of vinyl ethers, amides or enamines would constitute important objectives for future developments. Especially the synthesis of stereodefined enamines is of great interest as these are important intermediates in C-C bond forming processes.[33] With this exceptionally mild protocol the natural products shown in Figure 1 might be accessible by means of RCAM/hydrostannation/late-stage oxygenation.



Scheme 23. Copper mediated formal oxidation of alkenylstannanes.

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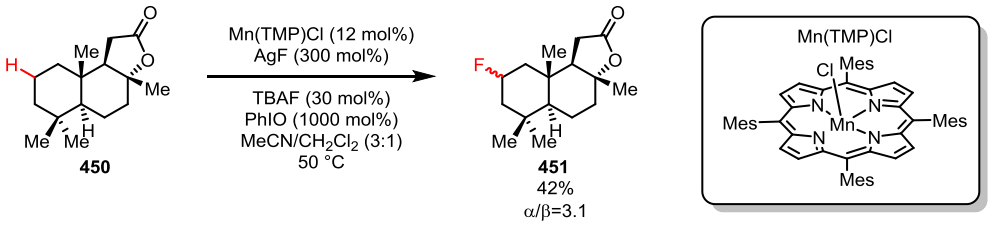
5. Fluorination of Alkenylstannanes and Synthesis of Peptide Bioisosters

5.1. Introduction

5.1.1. Fluorination in Organic Chemistry

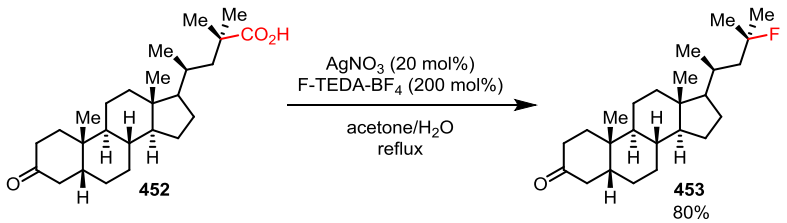
5.1.1.1. Late-stage Introduction of Fluorine

The role of fluorine in synthetic and medicinal chemistry receives an ever increasing attention and over the past decades numerous review articles[1] and monographs[2] covered this topic. Fluorine plays a unique role in influencing the conformation, solubility, potency, permeability or degradability of small molecules. The late-stage introduction of fluorine is of great interest as it allows the modification of complex molecules without changing the synthetic route. Furthermore, small molecules from natural sources can be employed. An impressive example stems from the work of Groves and coworkers, who employed a manganese porphyrine catalyst in combination with iodosobenzene and silver fluoride to activate C-H bonds in a highly selective manner (Scheme 1).[3]



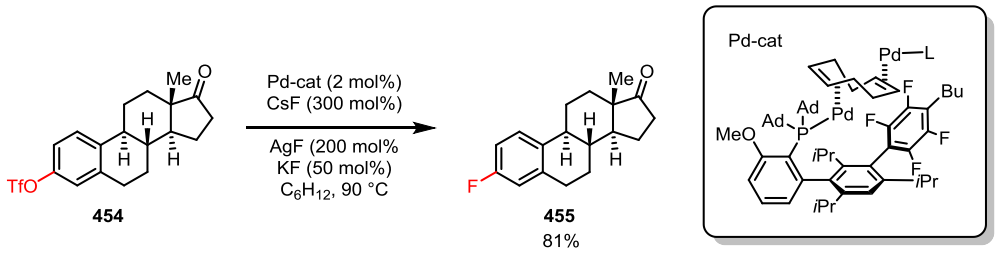
Scheme 1. Selective fluorination of sclareolide by Groves and coworkers.

Instead of relying on catalyst selectivity, a common strategy to introduce fluorine is the conversion of existing functionalities. In a recent disclosure, Li and coworkers showed that aliphatic carboxylic acids undergo silver catalyzed decarboxylative fluorination (Scheme 2).[4]



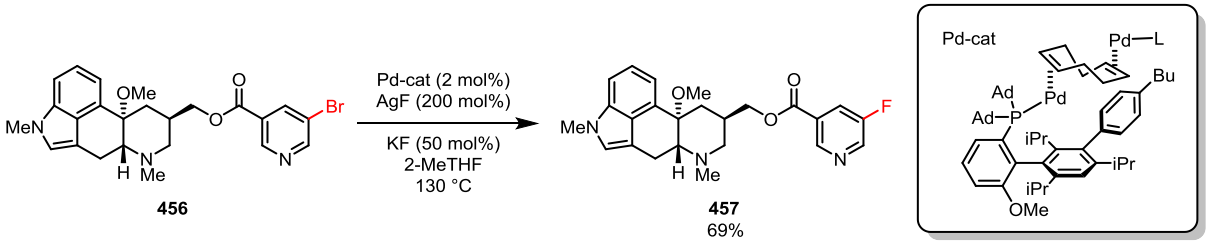
Scheme 2. Silver catalyzed decarboxylative fluorination by Li and coworkers.

Another strategy involves the selective activation of the substrate prior to the fluorination event by triflation. The resulting aryl triflates have recently been demonstrated to undergo fluorination with nucleophilic fluorinating agents. Important contributions have been made by the Buchwald group and a representative example with estrone triflate is shown in Scheme 3.[5]



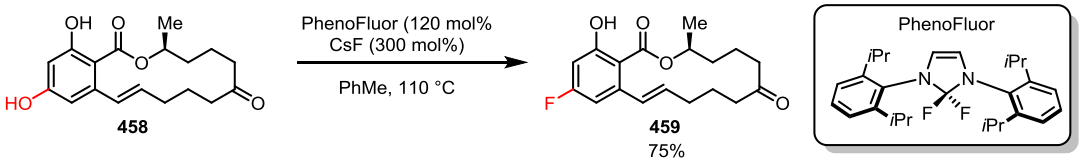
Scheme 3. Palladium catalyzed fluorination of aryl triflates by Buchwald and coworkers.

A related catalytic system was used to convert aryl bromides into the corresponding fluorides, exemplified by the fluorination of the vascular disorder drug Nicergoline (**456**) (Scheme 4).[6]



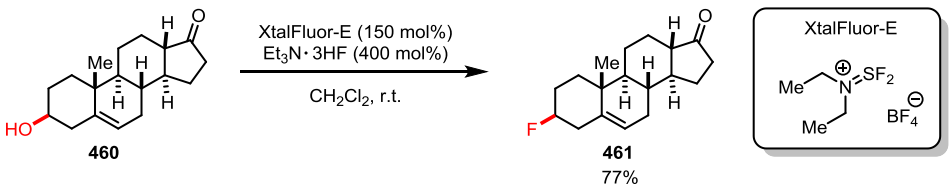
Scheme 4. Palladium catalyzed fluorination of aryl bromides by Buchwald and coworkers.

In 2011, Ritter and coworkers showed that phenols are converted into the corresponding fluorides utilizing Phenofluor[7] (Scheme 5).[8] In this elegant approach, no prior activation of the phenol is necessary as exemplified by the conversion of zearalenone into the corresponding fluorinated analog. Furthermore, the PhenoFluor reagent is a benchstable, easy-to-handle solid.



Scheme 5. Deoxyfluorination of phenols by Ritter and coworkers.

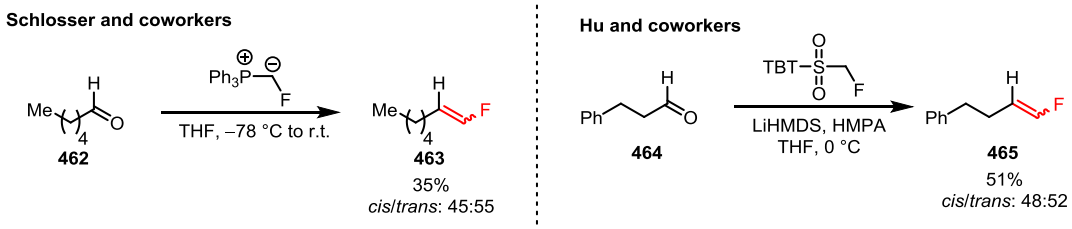
Other groups have used similar strategies employing aminodifluorosulfinium salts as deoxyfluorinating agents (Scheme 6). [9] XtalFluor-E was utilized for the direct transformation of androstenolone into the corresponding fluoride without the need of preceding activation of the hydroxyl group.



Scheme 6. Deoxyfluorination of alcohols with XtalFluor-E by L'Heureux *et al*..

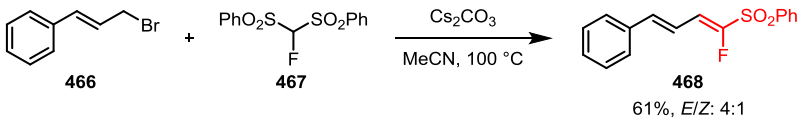
5.1.1.2. Synthesis of Fluoroalkenes – State of the Art

The synthesis of fluoroalkenes has received less attention and only few general protocols have been developed. A common way to install a fluorine atom is the application of existing olefination protocols utilizing a fluorine bearing reagent. In this vein, Wittig-[10] or Julia-Kocienski-olefinations[11] have been developed, though with limited success (Scheme 7).



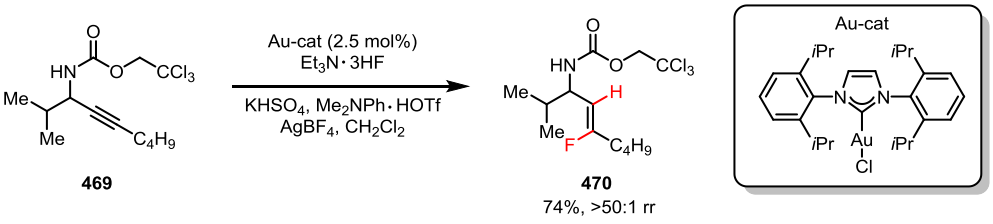
Scheme 7. Olefination with methylenefluoride building blocks.

A related approach was devised by Olah and coworkers exploiting an alkylation/elimination sequence to access different alkenyl fluorides (Scheme 8).[12]



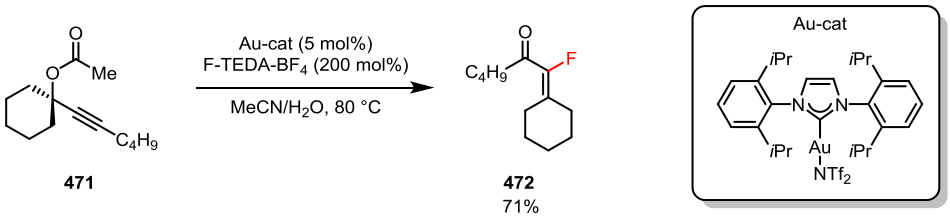
Scheme 8. Synthesis of fluorovinyl sulfones by Olah and coworkers.

The major drawback of these approaches lies in the low E/Z selectivity along with a limited substrate scope. To circumvent these issues, different strategies have evolved. One elegant approach is the directed, gold catalyzed hydrofluorination of alkynes disclosed by Miller and coworkers (Scheme 9).[13] To control regioselectivity, propargyl alcohol and amine derivatives were employed that were able to coordinate to the cationic gold complex.



Scheme 9. Gold catalyzed hydrofluorination by Miller and coworkers.

Finally, Nevado and de Haro reported a gold mediated [1,3]-sigmatropic rearrangement of propargyl acetates to install the alkenyl fluoride (Scheme 10).[14]

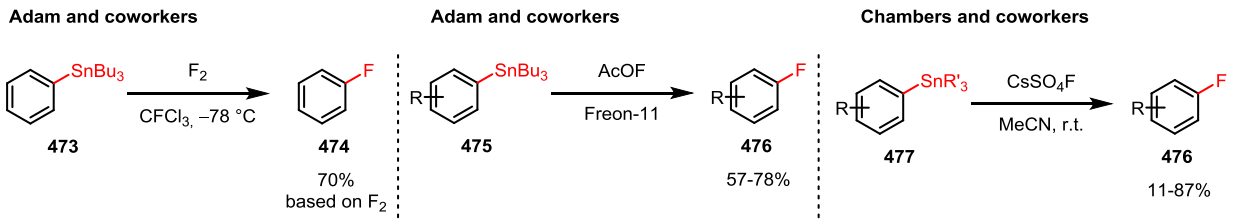


Scheme 10. Gold catalyzed fluorination by Nevado and de Haro.

Another very attractive way to install fluorine at a distinct position in an organic compound is the fluorination of an organometallic intermediate. Predominantly, boronic acid derivatives[15], silanes[15j, 16], and stannanes are employed. As we are mainly interested in the conversion of alkenylstannanes into the corresponding fluorides, the following chapter will cover that particular transformation.

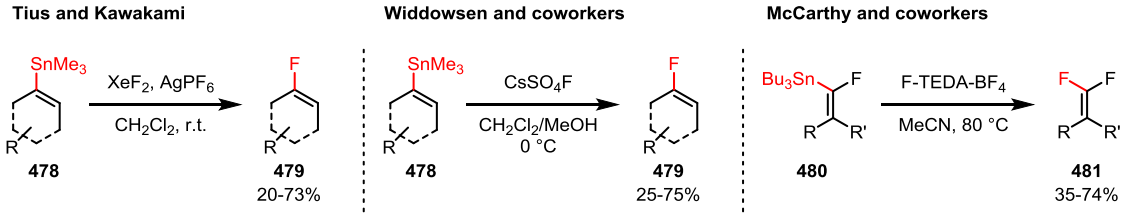
5.1.1.3. Synthesis of Csp²-F by Tin-Fluoride Exchange – State of the Art

The first report of a tin-fluoride exchange on sp²-carbons was disclosed in 1981 by Adam and coworkers (Scheme 11).[17] By exposing phenyl tributylstannane (**473**) to fluorine gas at cryogenic temperature, the formation of fluorobenzene was observed. This initial discovery led to further developments by the same group employing acetyl hypofluorite.[18] Later, Chambers and coworkers demonstrated the utility of cesium fluoroxysulfate.[19]



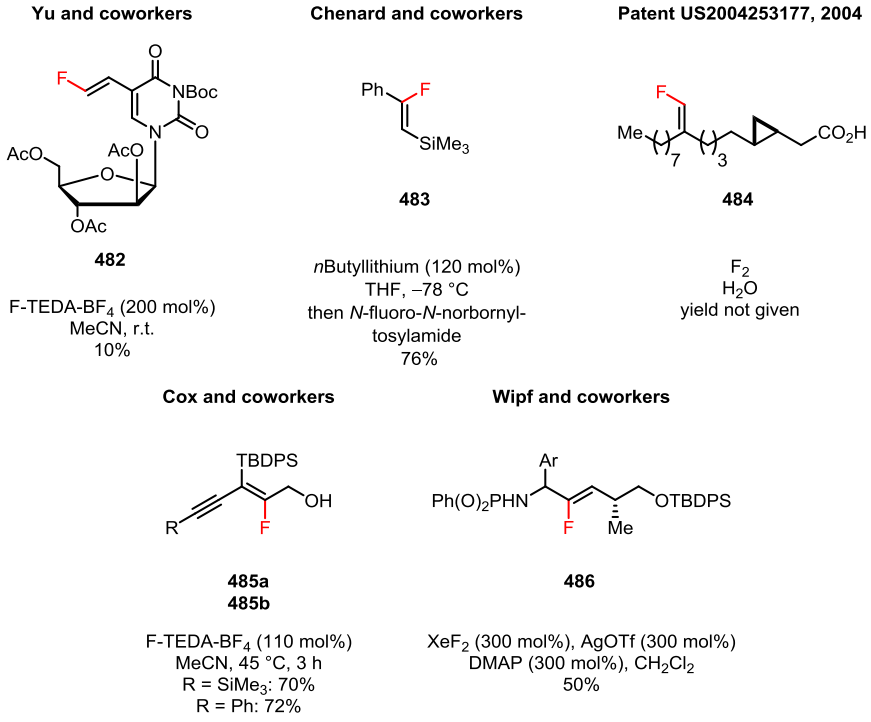
Scheme 11. Fluorination of aryl stannanes.

Since these early reports, numerous advancements have been reported in the literature as fluorine gas or acetyl fluoride are difficult to handle, hazardous reagents. The most significant contributions were made by Tius and Kawakami in the early 90's.[20] They found that alkenylstannanes (**478**) can be effectively fluorinated with xenon difluoride in the presence of a silver salt (Scheme 12). At the same time, Widdowsen and coworkers showed that cesium fluoroxysulfate is also capable of delivering the corresponding fluorides from alkenylstannanes (**478**).[21] McCarthy and coworkers utilized F-TEDA-BF_4 (Selectfluor®)[22] for the synthesis of *gem*-vinyl fluorides **481**.[23]



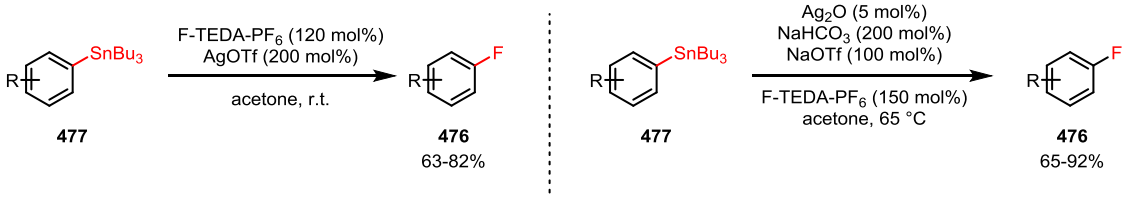
Scheme 12. Advancements in the synthesis of alkenyl fluorides from stannanes.

This methodology has found applications in the synthesis of building blocks and pharmaceutically interestingly compounds (Scheme 13).[24]



Scheme 13. Recent examples of alkenylfluoride synthesis via tin-fluoride exchange.

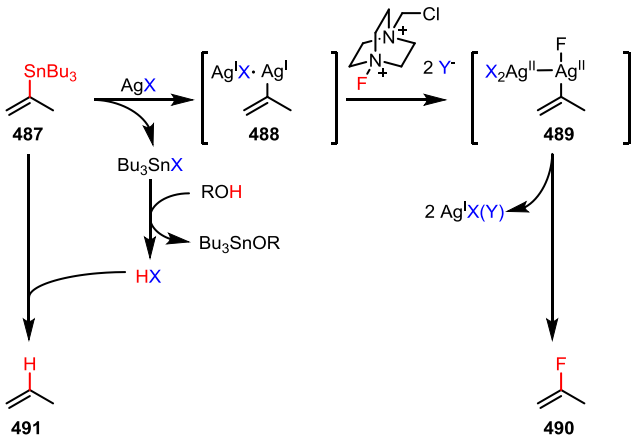
In 2009, Ritter and coworkers found that an amalgamation of the conditions reported by Tius and McCarthy yields a highly effective protocol for the fluorination of aryl stannanes (Scheme 14).[25] One year later the same group reported a catalytic-in-silver protocol with an extended substrate scope and elucidated the role of the silver salt.[26]



Scheme 14. Fluorination of aryl stannanes by Ritter and coworkers.

5.1.2. Mechanistic Proposal for the Silver-mediated Fluorination of Stannanes

In the first step, stannane **487** reacts with the silver salt to give the dinuclear silver-cluster **488** (Scheme 15). Upon fluorination of the alkenylsilver, a formal two-electron oxidation with formation of a silver-silver bond gives complex **489**. Reductive elimination furnishes **490** and recovers silver(I). During this process, the counterion of the silver salt captures the tributyltin cation. The resulting tin species can undergo hydrolysis or alcoholysis with the free alcohol to deliver HX. This potentially acidic species, e.g. TfOH or TsOH, can lead to rapid protodestannation of the starting material. Therefore, if the counterion X on silver has a weak corresponding acid, then protodestannation can be avoided.



Scheme 15. Mechanistic proposal of the silver mediated tin-fluoride exchange.

5.1.3. Motivation

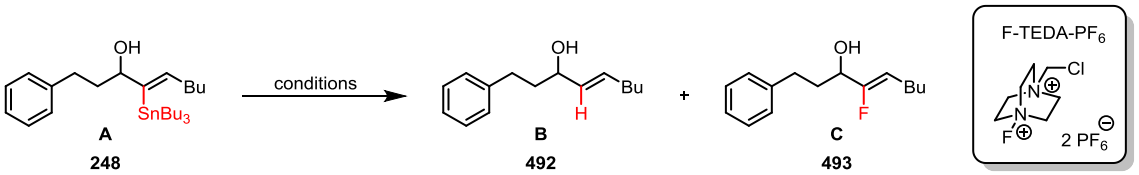
As is apparent from the examples outlined above, a general procedure for the transformation of alkenylstannanes into the corresponding fluorides is still lacking. Although major advancements have been disclosed for the conversion of aryl stannanes, these have not been extended to alkenyl derivatives. For example, Ritter and coworkers applied the catalytic protocol to the conversion of a terminal alkenylstannane which gave an isolated yield of 35%.[26] They attributed the low yield to the volatility of the product but no attempts were made to develop an optimized procedure. With the possibility to selectively access stereodefined alkenylstannanes, we sought of a way to explore the possibilities to synthesize the corresponding fluorides. Furthermore, as vinyl chlorides and bromides are abundant in nature, the corresponding fluoride analogs constitute interesting synthetic and biological targets. Lastly, fluoride isosters of amides can ultimately be addressed in an efficient manner.

5.2. Results and Discussion

5.2.1. Initial Screening Results for the Tin-Fluoride Exchange

We began our studies with standard substrate **248** (Table 1). At the outset, the most relevant conditions reported in the literature were tested to evaluate their potential in the synthesis of alkenylfluorides. Furthermore, as copper(II) salts are capable of forming the corresponding alkenylcopper species, copper(II) fluoride was also examined as a potential fluorinating agent.

Table 1. Initial screening for the tin-fluoride exchange.



Entry	Ag-salt (mol%)	F⁺-source (eq)	Additive (eq)	Solvent	T [°C] t [h]	Ratio[a] (A : B : C)
1	-	CuF_2 (2)	Et_3N (5) O_2	DMSO (0.125 M)	r.t., 18	1 : 0 : 0
2	-	CuF_2 (2)	Et_3N (5) 3Å MS	DMSO (0.125 M)	r.t., 18	1 : 6.4 : 0
3	-	CuF_2 (2)	Et_3N (5)	DMSO (0.125 M)	r.t., 18	1 : 0.9 : 0
4	-	CuF_2 (2)	Et_3N (5)	DMSO (0.125 M)	50°C, 18	1 : 2.2 : 0
5	AgOTf (10)	F-TEDA-PF_6 (1.5)	$NaHCO_3$ (2)	Acetone (0.05 M)	r.t., 18	0 : 1 : 0.9
6	Ag_2O (5)	F-TEDA-PF_6 (1.5)	NaOTf (1) $NaHCO_3$ (2)	Acetone (0.05 M)	r.t., 18	7.6 : 1 : 6.0
7	AgOTf (20)	F-TEDA-BF_4 (1.2)	$Bu_4NOP(O)Ph_2$ (2.0)	Acetone (0.05 M)	r.t., n.a.	0 : 1 : 0.8
8	AgOTf (20)	F-TEDA-PF_6 (1.2)	$Bu_4NOP(O)Ph_2$ (2.0)	Acetone (0.05 M)	r.t., n.a.	0 : 1 : 0.7
9	AgOTf (20)	F-TEDA-PF_6 (1.2)	$Bu_4NOP(O)Ph_2$ (2.0) DTBMP (0.2)	Acetone (0.05 M)	r.t., n.a.	0 : 1 : 0.5
10	AgOTf (40)	F-TEDA-BF_4 (1.2)	$Bu_4NOP(O)Ph_2$ (3.0)	H_2O/PhF (0.05 M)	r.t., n.a.	0 : 1 : 0.0
11	AgOTf (200)	F-TEDA-BF_4 (1.2)	-	Acetone (0.05 M)	r.t., 0.25	0 : 1 : 1.1
12	AgOTf (200)	F-TEDA-PF_6 (1.2)	-	Acetone (0.05 M)	r.t., 0.25	0 : 1 : 1.9

[a]determined by crude NMR analysis.

We found that copper(II) fluoride exclusively led to protodestannation of the starting material (entries 1-4). Under the reported catalytic-in-silver conditions of Ritter and coworkers[26], unsatisfying conversion was observed (entries 5-6). The low selectivity (entry 5) and low conversion (entry 6) led us to examine the role of a suitable tin scavenger. According to the mechanistic proposal from Ritter and coworkers, *in situ* formation of HX promotes protodestannation.

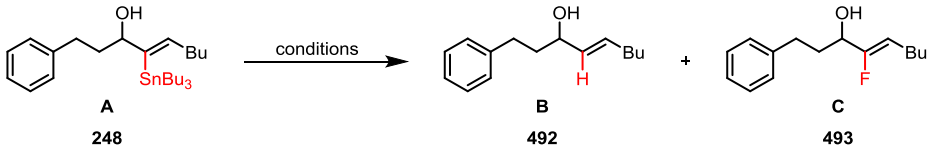
Fürstner and others have previously reported that the addition of tetrabutylammonium diphenylphosphinate (TBDPP) to Stille cross-coupling reactions exhibited a promoting effect by quenching tributyltin halides.[27] Unfortunately, the addition of TBDPP alone or in conjunction with di-*tert*-butylmethyl pyridine (DTBMP)[20a] did not lead to any improvement (entries 7-10). With these results in hand, we found that the previously reported stoichiometric protocol might offer a possible solution (entries 11-12)[25]. In accordance to Ritter and coworkers, employing F-TEDA-PF_6 instead of Selectfluor® (F-TEDA-BF_4) a significant improvement in selectivity was observed.

5.2.2. Optimization of Reaction Conditions for the Tin-Fluoride Exchange

With the optimal fluorinating agent identified, we examined the role of other parameters on the reaction outcome (Table 2). As the employed silver salt exhibits a major impact on the reaction outcome, different silver salts were tested. Although we found no beneficial effect of TBDPP in the catalytic version of the fluorination, we decided to exam silver diphenylphosphinate (AgDPP) in a stoichiometric protocol.

The synthesis of AgDPP is straightforward and was disclosed by Wiberg and coworkers in 1981.[28] Reaction of silver nitrate with *in situ* formed sodium diphenylphosphinate in water provides AgDPP as a non-hygroscopic, bench-stable solid in quantitative yield. We were pleased to discover that this reagent performed much better than all other silver sources (e.g. AgOTf or AgOTs) (entries 1-3), emphasizing the importance of the silver counterion. Again, a marked difference in selectivity between F-TEDA-BF_4 and F-TEDA-PF_6 was observed (entry 4). Different solvents or solvent combinations did not result in any improvement of selectivity (entries 5-12).

Table 2. Further screening of reaction parameters for tin-fluoride exchange.



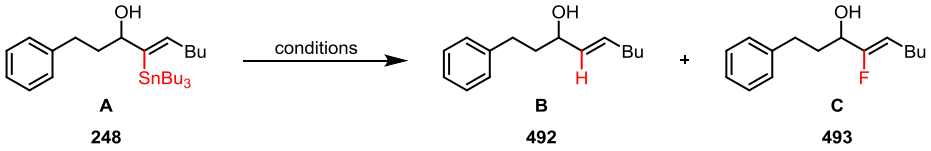
Entry	Ag-salt (mol%)	F⁺-source (eq)	Additive	Solvent	T [°C] t [h]	Ratio[a] (A : B : C)
1	AgOTf (200)	F-TEDA-PF_6 (1.2)	-	Acetone (0.05 M)	r.t., 0.25	0 : 1 : 1.9
2	AgOTs (200)	F-TEDA-PF_6 (1.2)	-	Acetone (0.05 M)	r.t., 0.25	0 : 1 : 0.4
3	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (1.2)	-	Acetone (0.05 M)	r.t., 0.25	0 : 1 : 2.4
4	$AgOP(O)Ph_2$ (200)	F-TEDA-BF_4 (1.2)	-	Acetone (0.05 M)	r.t., 0.25	0 : 1 : 0.5
5	$AgOP(O)Ph_2$ (200)	F-TEDA-BF_4 (1.2)	3 Å MS	Acetone (0.05 M)	50°C, 48	0.8 : 1 : 2.7
6	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (1.2)	3 Å MS	Acetone (0.05 M)	50°C, 48	0.7 : 1 : 1.1
7	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (1.2)	-	DMF (0.05 M)	r.t., 0.25	0 : 1 : 2.1
8	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (1.2)	-	DMSO (0.05 M)	r.t., 0.25	0 : 1 : 0.0
9	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (1.2)	-	THF (0.05 M)	r.t., 0.25	0 : 1 : 0.0
10	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (1.2)	-	MeCN (0.05 M)	r.t., 0.25	0 : 1 : 2.1
11	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (1.2)	-	Acetone/DMF (0.05 M)	r.t., 0.25	0 : 1 : 2.4
12	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (1.2)	-	Acetone* (0.05 M)	r.t., 0.25	0 : 1 : 1.7

[a]determined by crude NMR analysis.

The first improvement was made by increasing the amount of F-TEDA-PF_6 from 150 mol% (entry 1) to 200 mol% (entry 2) (Table 3). Performing the reaction under ice cooling had only a minor impact on the selectivity (entry 3). This approach was not pursued further as the reaction time increased dramatically. In their disclosure[20a], Tius and Kawakami noted that increased reaction times led to an increase in protodestannation. This was attributed to insufficient quenching of the intermediate silver species. This proposal was quickly confirmed, as slow addition of the fluorinating agent resulted in a decrease in selectivity (entry 4) whereas slow addition of the stannane afforded increased selectivity (entry 5). Extending the addition time

from 30 minutes to 1 h and finally reducing the amount of silver salt, provided the product in excellent selectivity with only minor amounts of protodestannation (entries 6-11). AgDPP in the absence of F-TEDA-PF_6 furnished exclusively protodestannation product **492** (entry 12). F-TEDA-PF_6 in absence of AgDPP in turn yields an undefined mixture of products (entry 13).

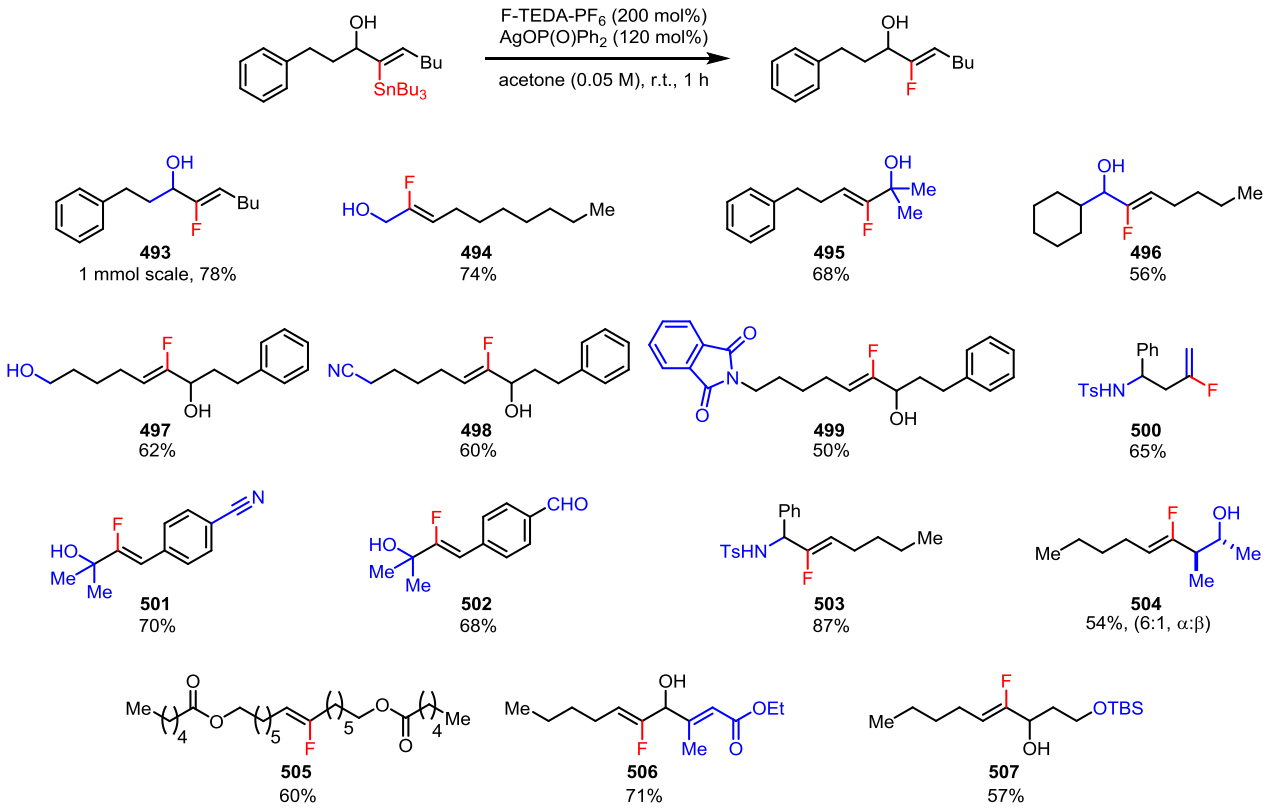
Table 3. Final adjustments of reaction conditions.



Entry	Ag-salt (mol%)	F⁺-source (eq)	Additive (eq)/comment	Solvent	T [°C] t [h]	Ratio[a] (A : B : C)
1	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (1.5)	-	Acetone (0.05 M)	r.t., 0.25	0 : 1 : 2.6
2	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (2.0)	-	Acetone (0.05 M)	r.t., 0.25	0 : 1 : 3.1
3	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (2.0)	-	Acetone (0.05 M)	0°C, 18	0 : 1 : 4.1
4	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (2.0)	dropwise addition of F-TEDA-PF_6	Acetone (0.05 M)	r.t., 0.25	0 : 1 : 2.6
5	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (2.0)	syringe pump addition of stannane	Acetone (0.05 M)	r.t., 0.5	0 : 1 : 4.4
6	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (2.0)	syringe pump addition of stannane	Acetone (0.05 M)	r.t., 1.0	0 : 1 : 5.8
7	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (2.0)	syringe pump addition of stannane	Acetone (0.04 M)	r.t., 1.0	0 : 1 : 2.7
8	$AgOP(O)Ph_2$ (120)	F-TEDA-PF_6 (2.0)	syringe pump addition of stannane	Acetone (0.05 M)	r.t., 1.0	0 : 1 : 11
9	$AgOP(O)Ph_2$ (120)	F-TEDA-PF_6 (1.2)	syringe pump addition of stannane	Acetone (0.05 M)	r.t., 1.0	0 : 1 : 3.4
10	$AgOP(O)Ph_2$ (200)	F-TEDA-PF_6 (2.0)	syringe pump addition of stannane	Acetone (0.05 M)	r.t., 0.5	0 : 1 : 4.4
11	$AgOP(O)Ph_2$ (120)	F-TEDA-PF_6 (2.0)	syringe pump 1.0 mmol	Acetone (0.05 M)	r.t., 1.0	0 : 1 : 13
12	$AgOP(O)Ph_2$ (120)	-	-	Acetone (0.05 M)	r.t., 1.0	0 : 1 : 0
13	-	F-TEDA-PF_6 (2.0)	-	Acetone (0.05 M)	r.t., 18	mixture of prod.

[a]determined by crude NMR analysis.

Having established a protocol for the tin-fluoride exchange of alkenylstannes, the scope of this reaction was probed on a variety of different substrates (Scheme 16).



Scheme 16. Substrate scope of the silver-mediated tin-fluoride exchange.

A range of different functional groups was evaluated. Neighboring primary (**494**), secondary (**496**) and tertiary alcohols (**495**) do not affect the reactivity. Free alcohols (**497**), nitriles (**498**), aldehydes (**502**), silyl protecting groups (**507**), esters (**506**) or pthalimides (**499**) are well tolerated. Furthermore, the neighboring alcohol is not essential for reactivity (**505**). Tosylamides **500** and **503**, and homoallylic alcohols (**504**) also serve as fruitful substrates. To confirm the retentive nature of this transformation, single-crystal X-ray analysis of amide **503** provided conclusive evidence. Additionally, X-ray analysis of the corresponding stannane **508** was obtained. Both structures are shown in Figure 1. Evidently, the *trans*-arrangement of the double-bond is conserved during the process. Another noticeable feature in fluorinated tosylamide **503** is the orientation of the amide hydrogen towards the alkenyl fluoride. It has been proposed in the literature that this hydrogen bonding is essential to stabilize a preferred conformation.

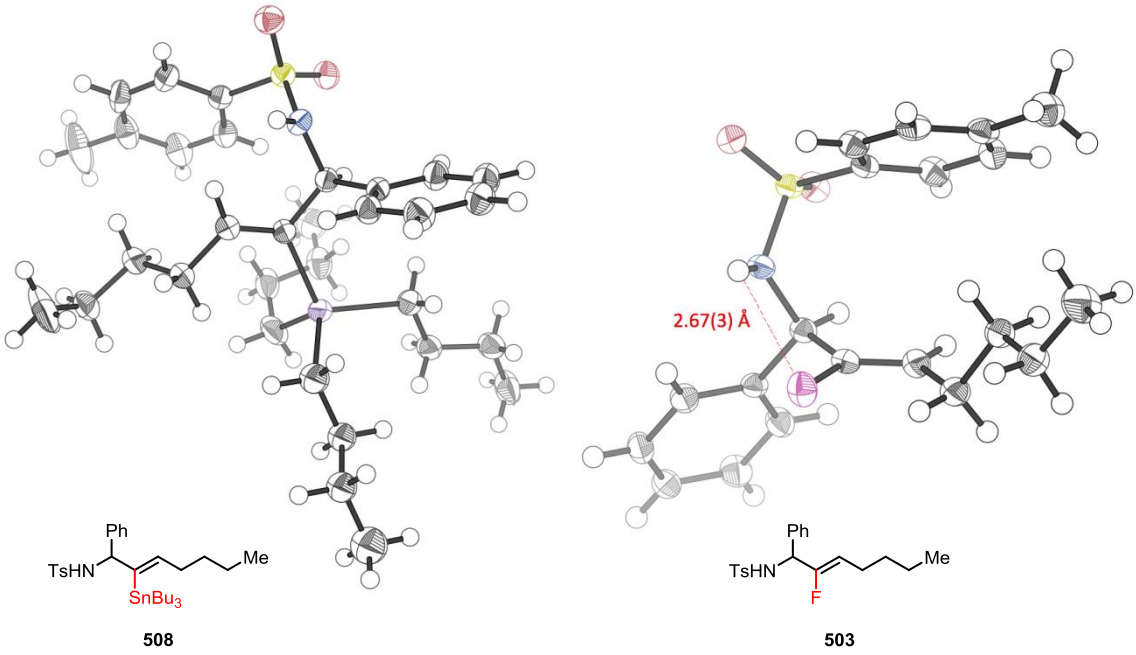


Figure 1. X-ray crystal structures of alkenylstannane **508** and corresponding fluoride **503**.

5.2.3. Aminofluoroolefins as Peptide Bioisosters

5.2.3.1. Background and Application of Aminofluoroolefins

Peptides play an important role in biology and medicine as they function as hormones, enzyme substrates or neurotransmitters in the human body. Although being potentially very potent compounds for drug-use, their lack of bioavailability and stability is a major concern. These drawbacks stem from the lability of the amide bond to hydrolysis during metabolism. To circumvent this pitfall, strategies have evolved to replace sensitive positions in peptides by mimetic motifs to improve the biological profile.[29] One of these approaches involves the replacement of the amide carbonyl by an alkenylfluoride (Figure 2). These aminofluoroolefins have been shown to mimic the steric and electronic nature of an amide but lack their hydrolytic lability.

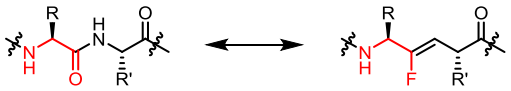


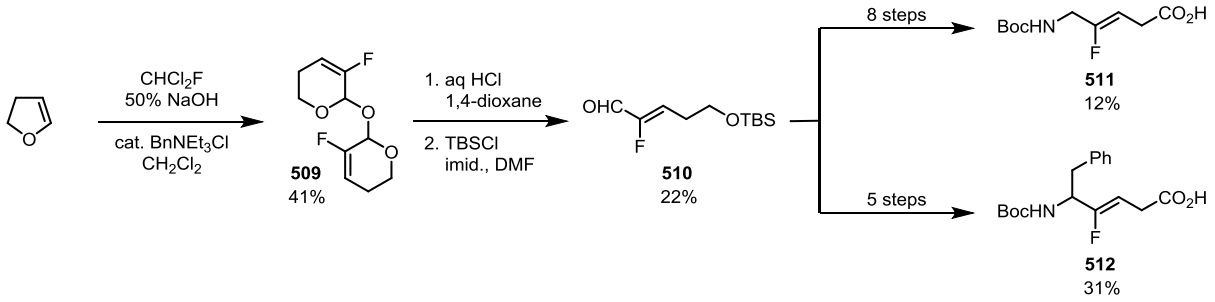
Figure 2. Amide vs. aminofluoroolefin.

Peptidomimetics with this structural motif were evaluated as peptidase IV(CD26)[30] and IV(DPP IV)[31] inhibitors, GPR54-agonists[32], hepatitis C virus NS5A inhibitors[33], small alpha-helical anti-HIV analogs[34], transporter probes (PEPT1)[35] or CXCR4 antagonists[36]. Peptidomimetic analogs of established drugs, e.g. KRN7000[37] or Enalapril[38] demonstrate improved metabolic stability. Consequently, a variety of methods have been developed to access this important motif.

5.2.3.2. State of the Art in the Preparation of Aminofluoroolefins

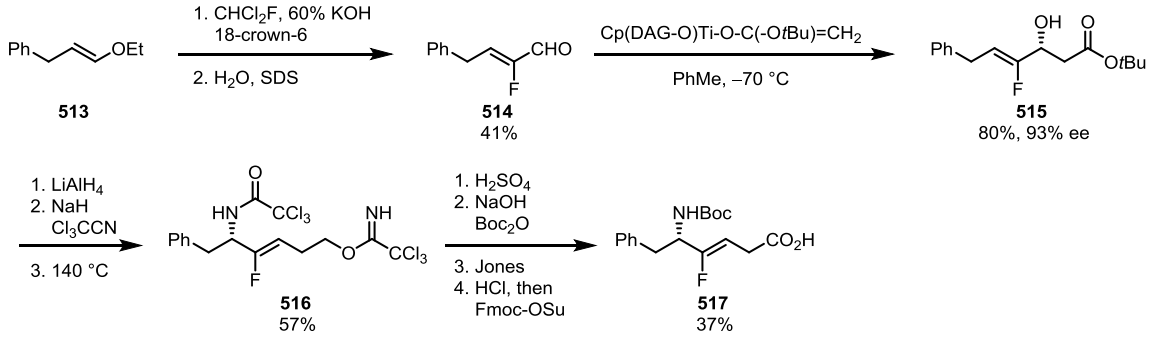
The first reports on the synthesis and biological properties of aminofluoroolefins were unveiled by Allmendinger and coworkers in 1990 (Scheme 17).[39] In these landmark communications, syntheses of (*E*)- and (*Z*)-isomeric aminofluoroolefins were disclosed.

A Reimer-Tiemann-type reaction of 2,3-dihydrofuran under phase-transfer conditions delivered key fluorinated building block **509**. Hydrolysis and protection provided access to aldehyde **510**. With this intermediate in hand, either the primary amine **511** or the secondary amine **512** was accessed in 8 or 5 steps, respectively.



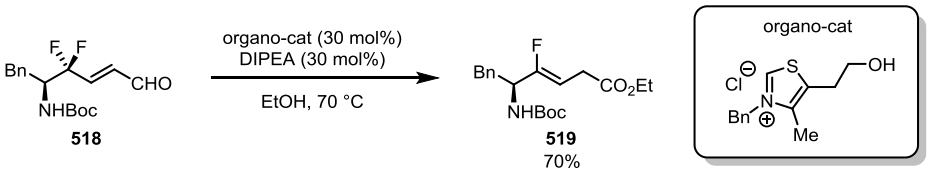
Scheme 17. Synthesis of aminofluoroolefins by Allmendinger and coworkers.

An enantioselective variant employing a different strategy was also reported starting from vinyl ether **513** (Scheme 18)**.** Cyclopropanation and ring opening delivered aldehyde **514** which underwent a Duthaler-Hafner-type aldol reaction[40]. The corresponding allyl amine was accessed via an Overman rearrangement to give amide **516**. Functional group manipulations finally furnished aminofluoroolefin **517** in good yield and high enantiomeric excess.



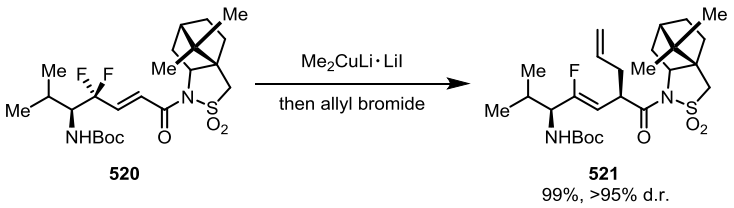
Scheme 18. Enantioselective synthesis of aminofluoroolefins.

Other methods involving metal catalyzed or organocatalytic defluorinations of *gem*-difluoroolefins have been developed. The group of Otaka disclosed a number of different strategies in the past years (Scheme 19). Aldehyde **518** is treated under Stetter-type conditions to yield aminofluoroolefin ester **519** via redox defluorination of the *gem*-difluoroolefin.[41]



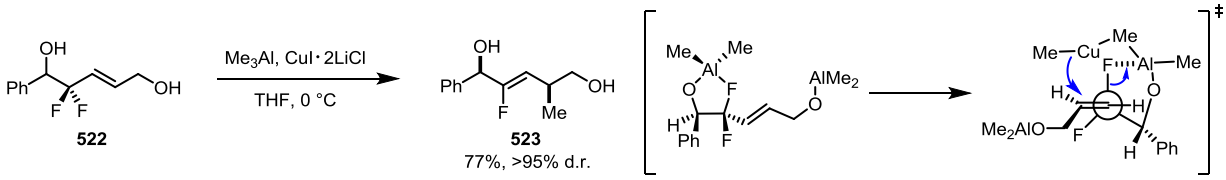
Scheme 19. Redox defluorination by Otaka and coworkers.

Similar strategies involve the reduction of *gem*-difluoroolefins with stoichiometric samarium diiodide[42] or chromium dichloride[43], catalytic palladium(0)[44] or under classic Stetter conditions with potassium cyanide.[45] An interesting modification of these procedures is the reduction of **520** with a cuprate and subsequent treatment with an electrophile, e.g. allyl bromide as reported by Fujii and coworkers (Scheme 20).[35, 46]



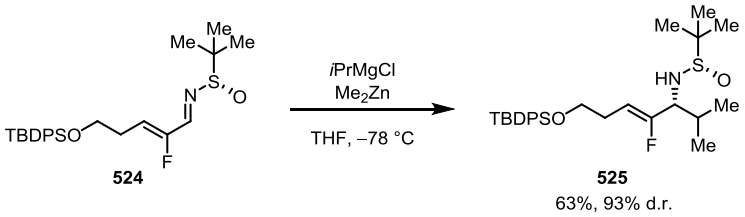
Scheme 20. Copper mediated defluorination/alkylation by Fujii and coworkers.

A different approach to convert *gem*-difluoroolefins into the corresponding fluoroolefins, exploits a S_N2'-displacement of one of the fluorides by an organometallic reagent. The group of Taguchi found that this displacement could be realized by the addition of copper reagents in the presence of trimethylaluminum (Scheme 21)[47]. The high *syn*-selectivity was attributed to an activation of one of fluorides by the Lewis acid.



Scheme 21. Aluminum and copper mediated allylic displacement by Taguchi and coworkers.

Similar protocols have been disclosed by the same group to extend the scope of this reaction.[48] Another approach was followed by Pannecoucke and coworkers by asymmetric addition of organometallic reagents to Ellman's sulfoximines (Scheme 22).[49] These substrates have been proven to undergo highly diastereoselective 1,2-additions with a variety of carbon nucleophiles to furnish the corresponding amines.[50]

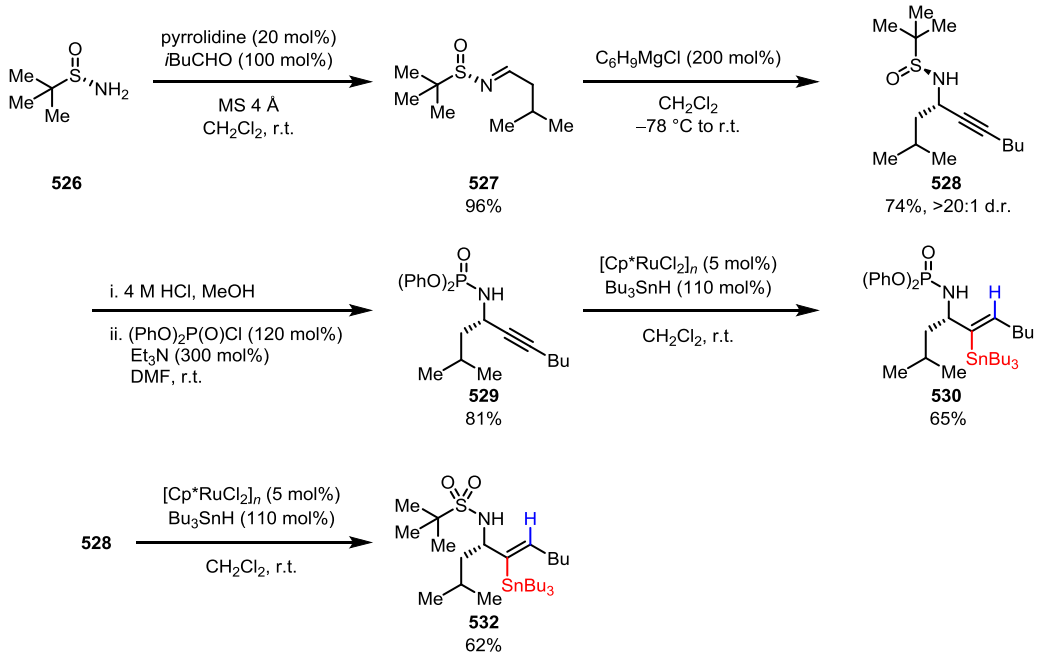


Scheme 22. Diastereoselective adddition of Grignard reagents to sulfoximines by Pannecoucke and coworkers.

Recently the diastereoselective reduction of the respective ketimines has also been reported.[51] Alternative methods include the organocatalytic monofluorovinylation of imines[52] or the stereoselective opening of *gem*-difluorocyclopropanes.[53]

5.2.3.3. Synthesis of Aminofluoroolefins by Tin-Fluoride Exchange

We developed a route to access aminofluoroolefins by late-stage fluorination of the corresponding alkenylstannane. In contrast to the presented approaches, our strategy allows us to assemble the carbon backbone independent of available fluorinated building blocks (Scheme 23).

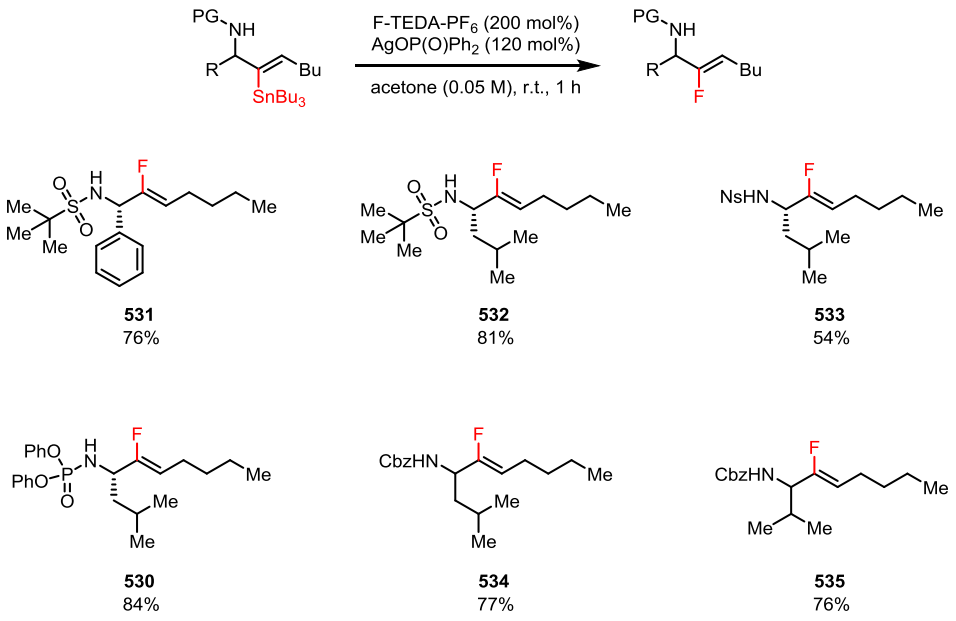


Scheme 23. Synthesis alkenylstannane precursor for aminofluoroolefin synthesis.

First, a pyrrolidine catalyzed condensation of *iso*-valeraldehyde with chiral amine **526** furnished sulfoximine **527**. Diastereoselective addition of hexynylmagnesium chloride delivered protected propargyl amine **528** with good yield and excellent diastereoselectivity. Acid-mediated hydrolysis and protection with diphenylphosphonyl chloride provided access to **529** which smoothly underwent ruthenium-catalyzed hydrostannation, yielding alkenylstannane

530 in a concise way. Notably, all residues of the propargyl amine can be altered, simply by employing different aldehydes, alkynes and protecting groups, respectively.

The fluorination under optimized reaction conditions worked uneventfully and in generally good yield (Scheme 24).



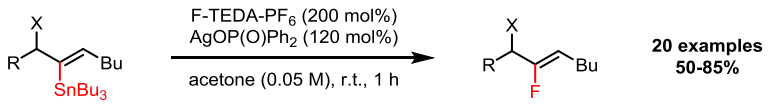
Scheme 24. Fluoropeptidomimetics obtained by tin-fluoride exchange.

As evident from this library, different protecting groups on the nitrogen are tolerated, exemplified by the Bus- [54], Nosyl- or Cbz-groups. Furthermore, a diphenylphosphinamide is compatible as well. This approach potentially allows access to variety of new peptidomimetics that could not be easily prepared by any previous method.

5.3. Conclusion and Outlook

A protocol for the conversion of alkenyltin derivatives into the corresponding fluorides was developed. By employing AgDPP as a mediator and F-TEDA-PF_6 as the fluorinating agent, a library of new alkenylfluorides was successfully synthesized (Scheme 25). This new procedure tolerates a variety of functional groups and the required reagents are bench-stable and easy-to-handle solids. Furthermore, the same protocol provided access to interesting peptidomimetics comprising an aminofluoroolefin substructure.

The utility of this method will be tested in the context of late-stage diversification to permit the synthesis of non-natural analogs.



Scheme 25. Silver mediated fluorination of alkenylstannanes.

5.4. Literature

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6. Diverted Total Synthesis of 5,6-Dihydrocineromycin B

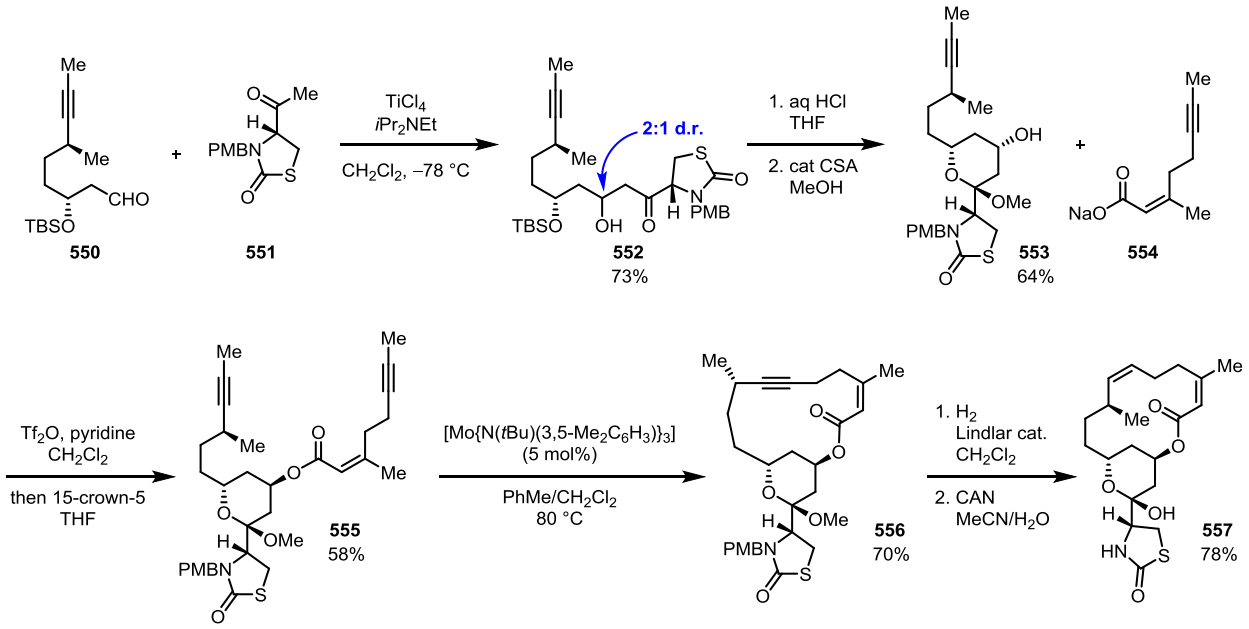
6.1. Introduction

6.1.1. Diverted Total Synthesis

In 2006, Danishefsky introduced the term 'diverted total synthesis' (DTS).[1] The idea behind this concept is the proposition that natural products are not optimized for the biological activity that mankind desires. Structural modifications are therefore often necessary to improve their biological profile. This strategy has found numerous applications in total synthesis and medicinal chemistry and a selection will be presented in the following section.[2]

6.1.1.1. Diverted Total Synthesis of Latrunculin B

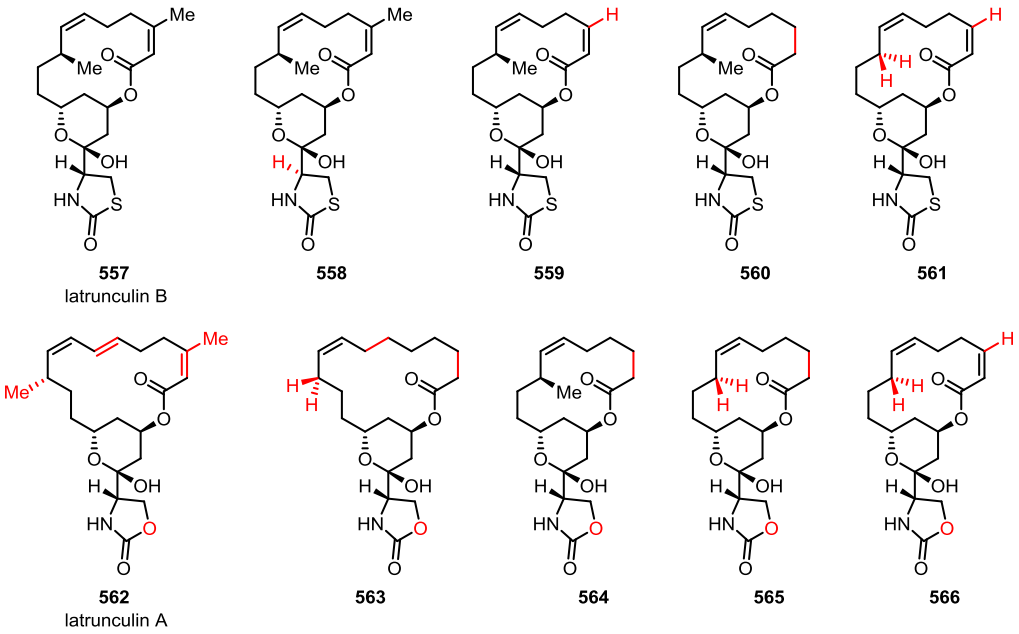
In 2003, Fürstner and coworkers disclosed a concise total synthesis of latrunculin B (**557**) (Scheme 1).[3] The three main fragments **550**, **551** and **554** were joined together by an aldol reaction, an acylation followed by a ring-closing-alkyne metathesis (RCAM). Subsequent Lindlar reduction and deprotection of **556** furnished latrunculin B (**557**).



Scheme 1. Total synthesis of latrunculin B by Fürstner and coworkers.

This highly modular synthetic strategy was then used to create a library of unnatural analogs that were tested for their microfilament disrupting activity (Scheme 2).[2l] Variations in ring sizes or degrees of unsaturation could easily be introduced by modification of carboxylate fragment **554** or aldehyde **550**. Additionally, the thiazolidinone moiety in fragment **551** could be replaced by an analogous oxazolidinone. Interestingly, it was found that bis-desmethyl-oxo-analog **566** exhibited higher activity than latrunculin B and proved to be as potent as latrunculin

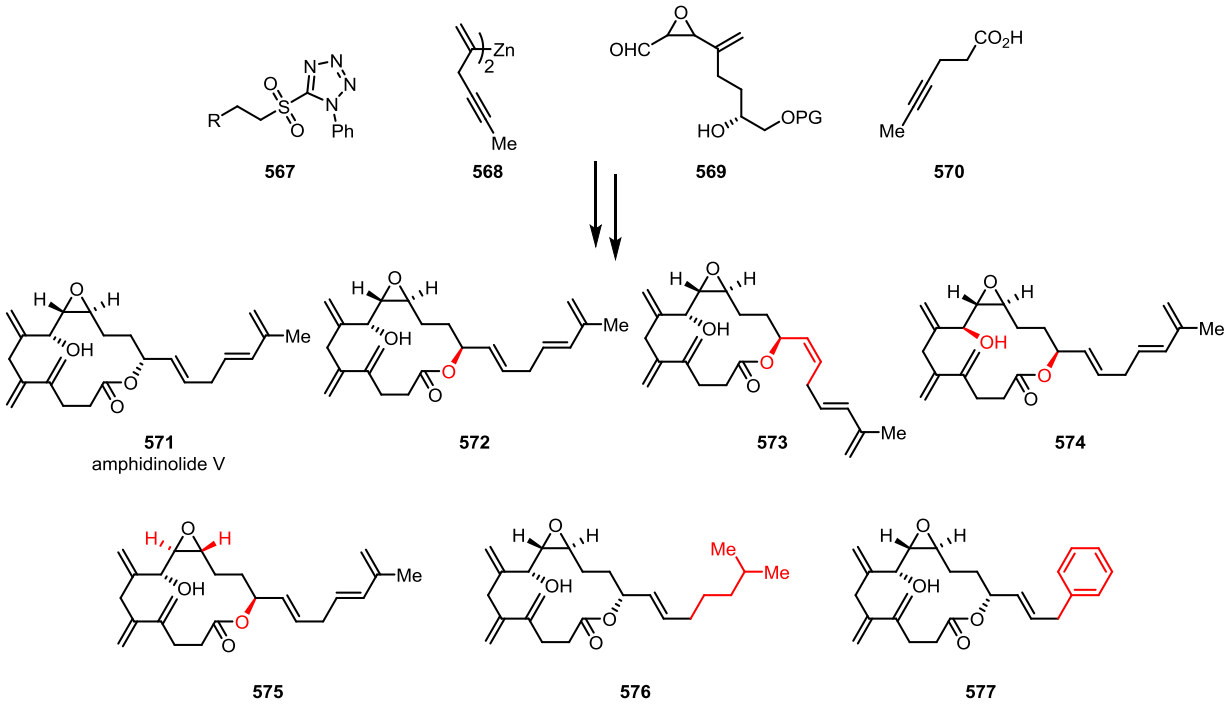
A (**562**), the most active member in this natural product family. Furthermore, the scalable route to **566** was significantly shorter than that to latrunculin B (**557**).



Scheme 2. Natural latrunculin B analogs and latrunculin A by Fürstner and coworkers.

6.1.1.2. Diverted Total Synthesis of Amphidinolide V

In 2007, the same group reported a total synthesis of amphidinolide V **571** (Scheme 3).[4] At the outset of this synthetic endeavor the absolute configuration of the target was unknown. Therefore, a small library of compounds was prepared to ultimately unravel the absolute configuration.[5] The highly modular approach allowed the group to rapidly access various stereoisomers. Additional modification of the side-chain was achieved to determine its role in biological activity.

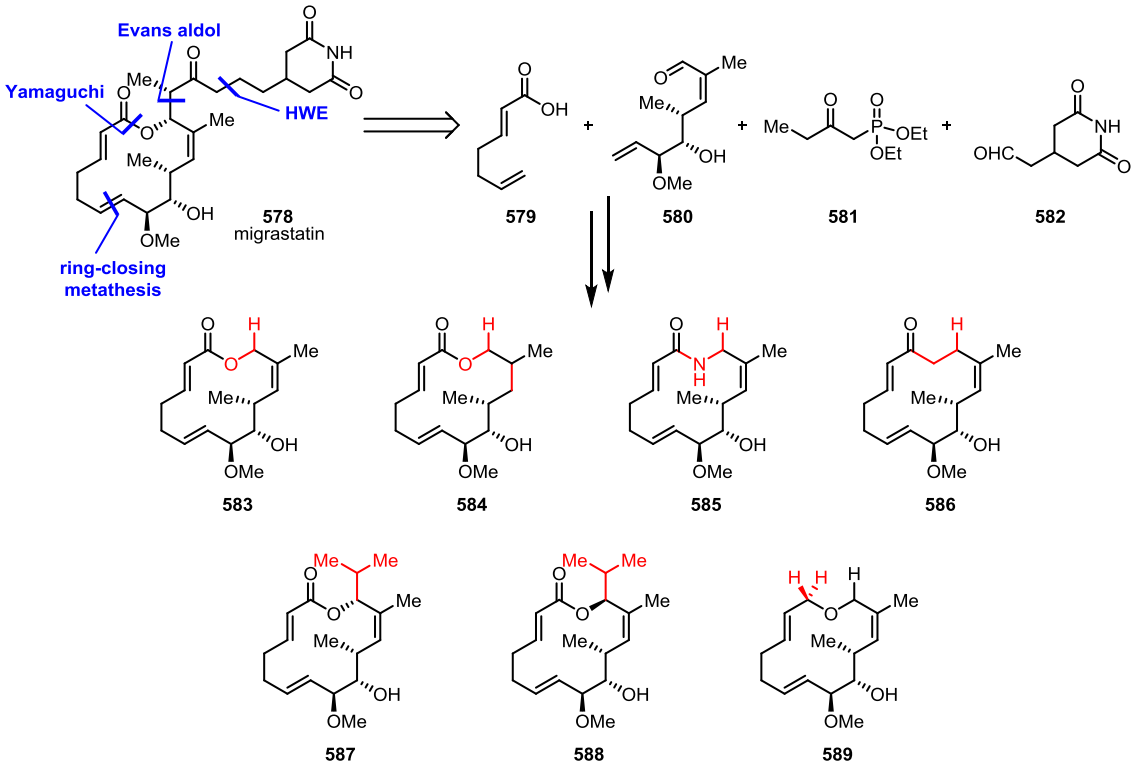


Scheme 3. Synthesis and structure of amphidinolide V and its analogs by Fürstner and coworkers.

Cytotoxicity assays of the analogs against P388 murine lymphoma cells revealed that inversion of any stereoconfiguration or the alkene geometry led to complete loss of biological activity. In addition, only small changes on the side-chain were tolerated. In summary, biologically active synthetic analogs can be obtained, provided that the core structure of amphidinolide V is retained.

6.1.1.3. Diverted Total Synthesis of Migrastatin

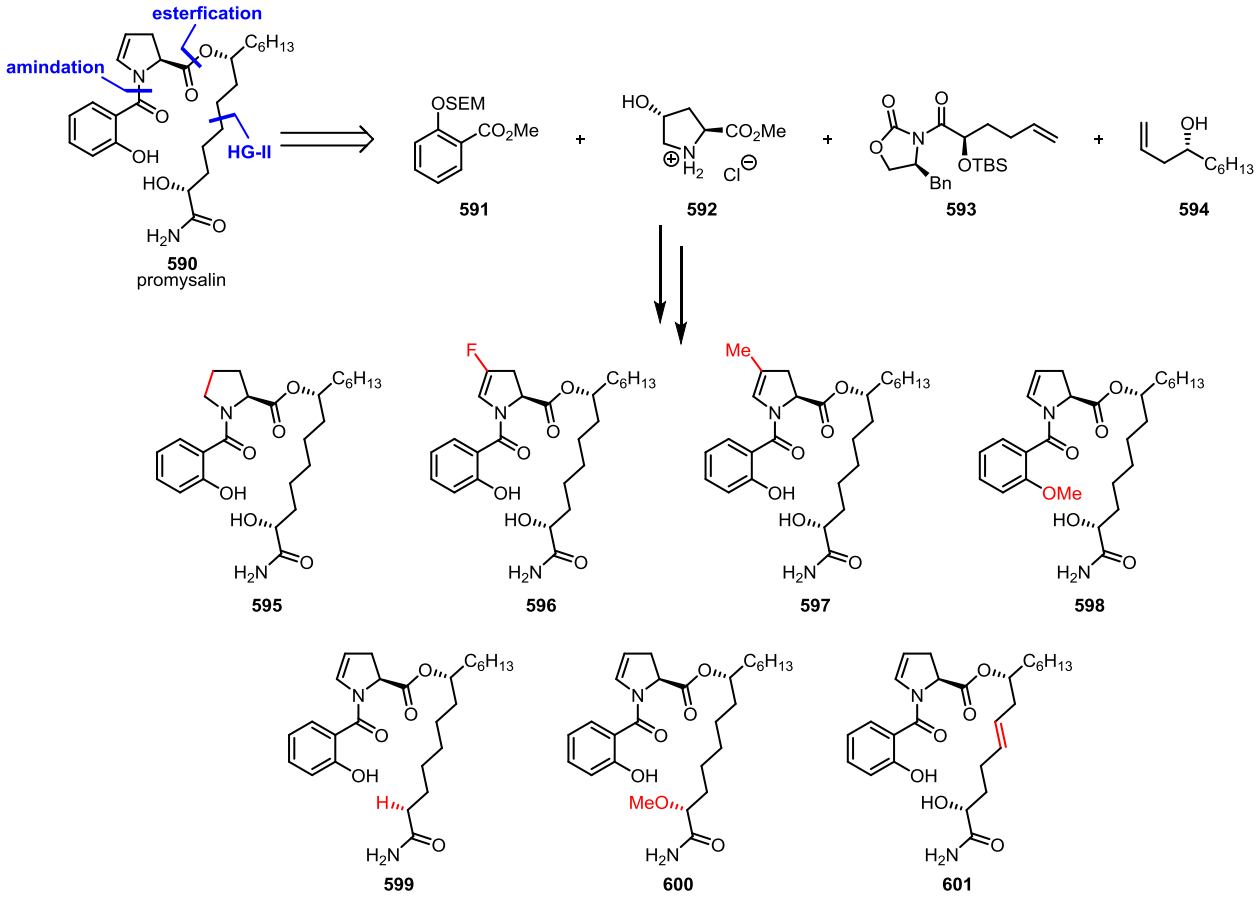
In 2003, Danishefsky and coworkers accomplished a total synthesis of migrastatin (**578**) (Scheme 4).[6] Subsequent biological evaluation of its analogs revealed that the glutaramide side-chain was nonessential for bioactivity.[2f, 7] With ether analog **589** the most potent member was finally encountered.[2g, 8] Analog **589** is an effective inhibitor of transwell cancer cell migration of human breast cancer cell lines. The highly convergent synthesis plan enabled efficient and selective modifications of the desired positions in the molecule, ultimately leading **589** that was more potent than the natural product itself.



Scheme 4. Diverted total synthesis of migrastatin (**578**) and its analogs by Danishefsky and coworkers.

6.1.1.4. Diverted Total Synthesis of Promysalin

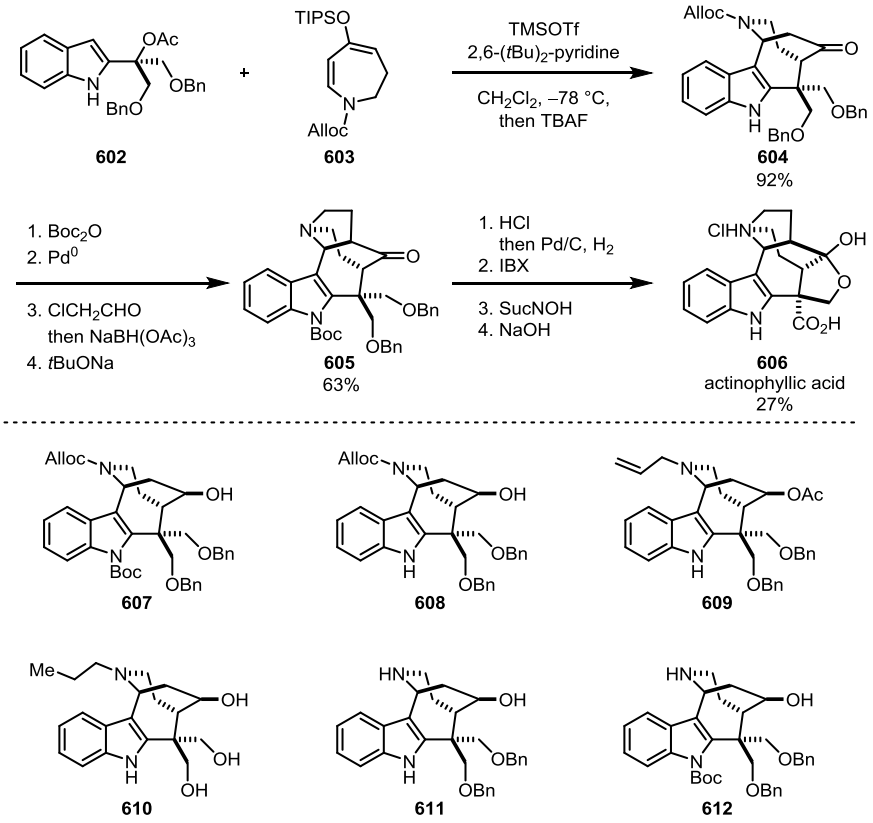
Determination of the biological mode of action of a natural product can be aided by diverted total synthesis. A total synthesis of promysalin (**590**) was recently disclosed by Wuest and coworkers and its biological profile was evaluated (Scheme 5).[9] During these studies, it was found that promysalin (**590**) effectively inhibits the growth of *Pseudomonas aeruginosa* at nanomolar concentrations. It was hypothesized that promysalin acts as a chelating agent for intracellular Fe^{3+} through a hydrogen-bonding network. This proposal could be validated by synthesizing a small library of compounds.[2e] Biological evaluation of the analogs quickly revealed that only minor perturbations of the parent structure were tolerated and that the methylated analogs **598** and **600** were essentially inactive. Only the fluoro-derivative **596**, desoxy-derivate **599** and olefin-derivative **601** exhibited biological activity comparable to the parent compound.



Scheme 5. Diverted total synthesis of promysalin and its analogs by Wuest and coworkers.

6.1.1.5. Diverted Total Synthesis of Actinophyllic Acid

Total synthesis of actinophyllic acid (**606**) was recently achieved by Martin and coworkers (Scheme 6).[2j, 10] The key step involving a Lewis acid mediated carbocation/π-nucleophile cascade allows rapid access to intermediate **604**. After routine manipulations, **606** was obtained in good overall yield. In addition, the analogs highlighted and the natural product itself were screened for their ability to induce cell death in Hs578t human breast cancer cell lines. Although actinophyllic acid (**606**) was completely inactive, analog **612** exhibited appreciable potency and was additionally tested against other cell lines (human lymphoma U937, human lung cancer A549 and human glioblastoma U87) having IC_{50} values of ~5-8 μM, respectively.



Scheme 6. Total synthesis of actinophyllic acid and analogs by Martin and coworkers.

In summary, diverted total synthesis proved to be an important tool for the development of new pharmaceutical lead structures and provides insight into the mode of action of these compounds. Furthermore, new pharmacophores made available by the assembly line can be tested for their biological activity and might in turn serve as new lead structures, c.f. migrastatin analog **589**.

6.1.2. Isolation and Biological Activity of 5,6-Dihydrocineromycin B

Cineromycin B (**613**) was isolated in 1966 by Miyairi *et al.*[11] (Figure 1). Thirty years later, Zeeck and coworkers reported the isolation of additional members of the cineromycin family from *Streptomyces Sp.* Gö 40/10 and *Streptomyces griseoviridis* (FH-S 1832) in 1996[12] and 1999[13], respectively. The characteristic feature of this class of natural products is the 14-membered macrolactone with an (*S*)-configured tertiary alcohol at positions 4. Position 7 bears an additional oxygen functionality, generally in the alcohol oxidation state. Different degrees of unsaturation, inverted stereochemistry (**619**), methylation (**617**), or oxidation state (**618**) distinguish the group members. In a preliminary biological evaluation, 5,6-dihydrocineromycin B (**615**) and other cineromycin metabolites showed weak activity against *Staphylococcus aureus*. This result is in stark contrast to the reported significant antibacterial activity of albocycline (**617**) against methicillin-resistant *Staphylococcus aureus* (MRSA).[14]

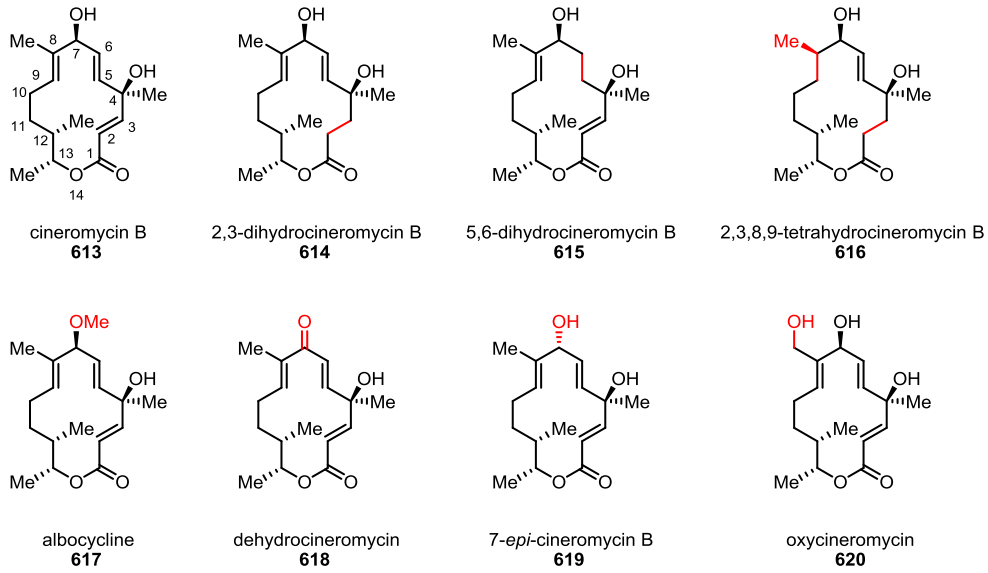


Figure 1. Structures of isolated members of the cineromycin family.

6.1.3. Previous Syntheses of 5,6-Dihydrocineromycin B

Due to its relatively 'simple' structure but promising biological profile, 5,6-dihydrocineromycin B (**615**) has received much attention from the synthetic community. Two total syntheses and one formal synthesis have been disclosed to date and will be discussed in this scetion.

6.1.3.1. Total Synthesis of 5,6-Dihydrocineromycin B by Tietze and Völkel

In 2001, Tietze and Völkel reported the first total synthesis of 5,6-dihydrocineromycin B (**615**).[15] Their retrosynthetic route is illustrated in Figure 2. It consists of an unselective addition of alkyllithium **624**, derived from the corresponding iodide, into aldehyde **621**. Macrolactonization and functional group manipulations finalize the synthesis of **615**. The required acid was obtained via hydroboration/oxidation of terminal olefin **624**. Aldehyde **621** was obtained by hydroboration/Suzuki cross-coupling of **622** with iodide **623**. The chiral homoallyl alcohol **624** was synthesized from asymmetric allylation of ketone **625**.

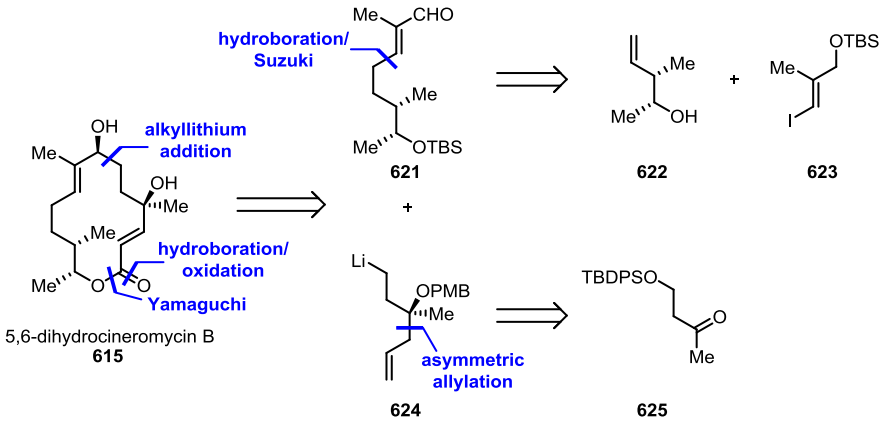
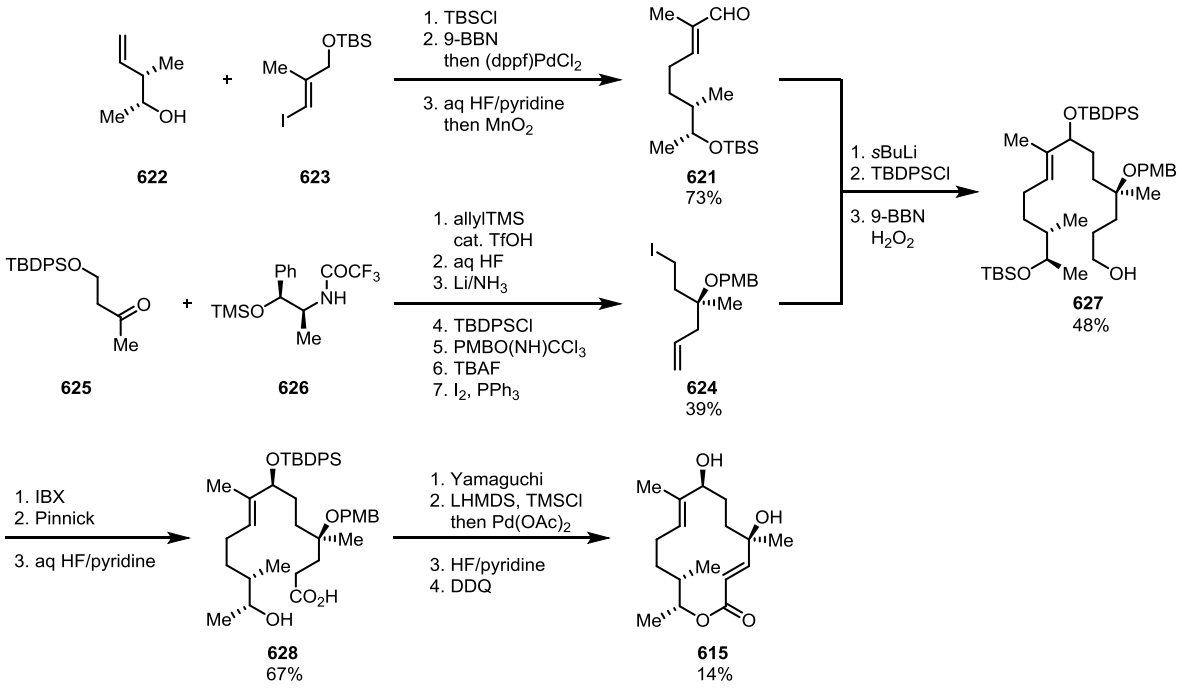


Figure 2. Retrosynthetic analysis of 5,6-dihydrocineromycin B by Tietze and Völkel.

In the forward sense, alcohol **622** was protected and subjected to hydroboration/Suzuki cross-coupling with **623**, followed by selective deprotection and oxidation to give aldehyde **621** (Scheme 7). Iodide **624** was prepared in 7 steps starting from ketone **625**.[16] The two fragments were joined via alkyllithium addition to give after silylation and hydroboration/oxidation alcohol **627.** *seco*-Acid **628** was obtained in 3 additional steps. Macrolactonization, Saegusa oxidation, and deprotection of TBDPS and PMB protecting groups furnished **615** as a single diastereomer in 19 steps from ketone **625** with an overall yield of 1%.



Scheme 7. Total synthesis of 5,6-dihydrocineromycin B by Tietze and Völkel.

The major drawback in this synthesis is the non-stereoselective 1,2-addition of the alkyllithium species derived from iodide **624** to aldehyde **621**, even though the undesired diastereomer could be recycled by oxidation and Noyori reduction with only modest diastereoselectivity.

6.1.3.2. Total synthesis of 5,6-dihydrocineromycin B by Zhai and coworkers

Another total synthesis of 5,6-dihydrocineromycin B (**615**) was reported by Zhai and coworkers in 2009 following an alternative strategy.[17] The key retrosynthetic analysis is illustrated in Figure 3 and consists of ring-closing Horner-Wadsworth-Emmons (HWE) olefination and Steglich esterification. The crucial fragments **630** and **632** were derived from the 'chiral pool' building blocks geraniol (**631**) and (–)-linalool (**633**), respectively.

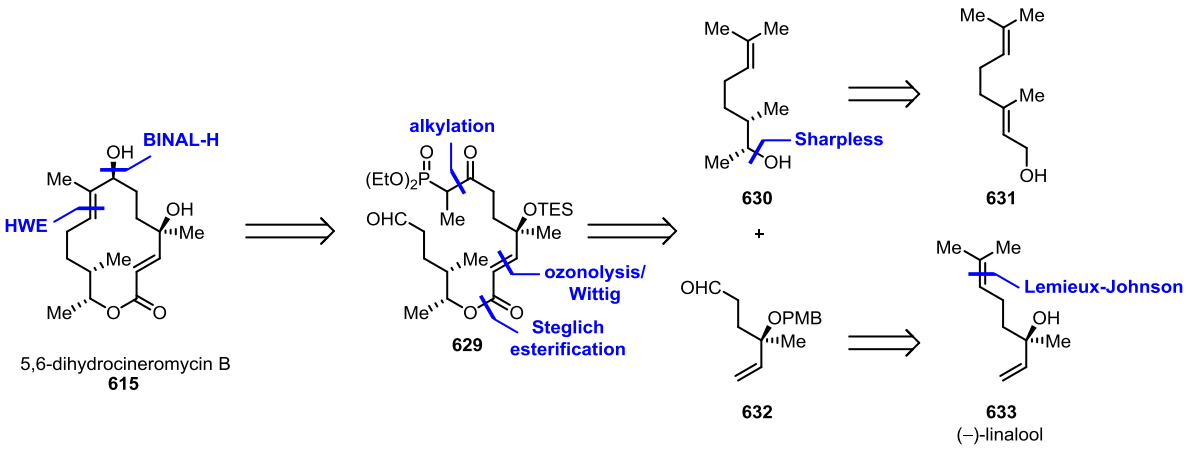
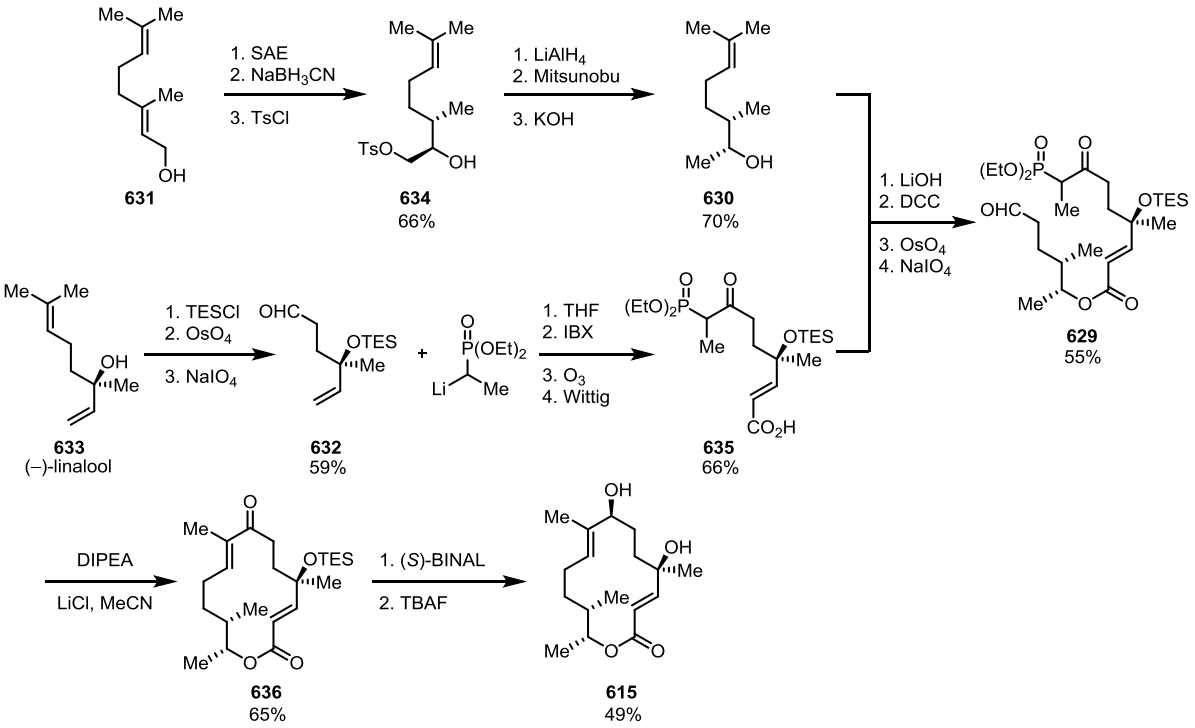


Figure 3. Retrosynthetic analysis of 5,6-dihydrocineromycin B by Zhai and coworkers.

The forward synthesis commenced with conversion of geraniol (**631**) into tosylate **634** in 3 steps by Sharpless epoxidation, reductive epoxide opening and tosylation (Scheme 8). Reductive detosylation and Mitsunobu inversion furnished alcohol **630**. The second fragment was made from (–)-linalool via TES protection, selective oxidative cleavage followed by alkylation and oxidation to give aldehyde **632**. Wittig olefination and saponification yielded acid **635**. Steglich esterification and subsequent oxidative cleavage of alkene **629**, and crucial HWE olefination delivered macrocycle **636**. As reported previously by Tietze and Völkel, the ensuing Noyori reduction furnished the alcohol in **615** with modest diastereoselectivity of 2.5:1. Desilylation completed the total synthesis of 5,6-dihydrocineromycin B in 12 steps in the longest linear sequence with an overall yield of 7%. The major drawback of this synthesis is again the poor enantioselectivity in the formation of the alcohol at position 7.



Scheme 8. Total synthesis of of 5,6-dihydrocineromycin B by Zhai and coworkers.

6.1.3.3. Formal synthesis of 5,6-dihydrocineromycin B by Rao and coworkers

A synthesis of TES-protected 5,6-dihydrocineromycin B was accomplished by Rao and coworkers in 2012.[18] Key disconnections are shown in Figure 4. A ring-closing alkene metathesis and Yamaguchi esterification were employed to join fragments **638** and **640**. Alcohol **638** was derived from 4-pentenol (**639**) whereas α-β-unsaturated acid **640** originated from diol **641**.

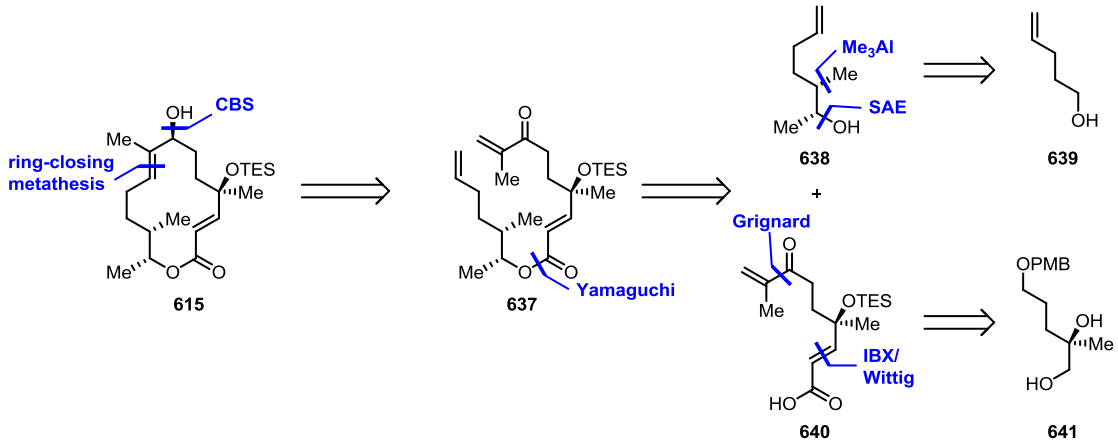
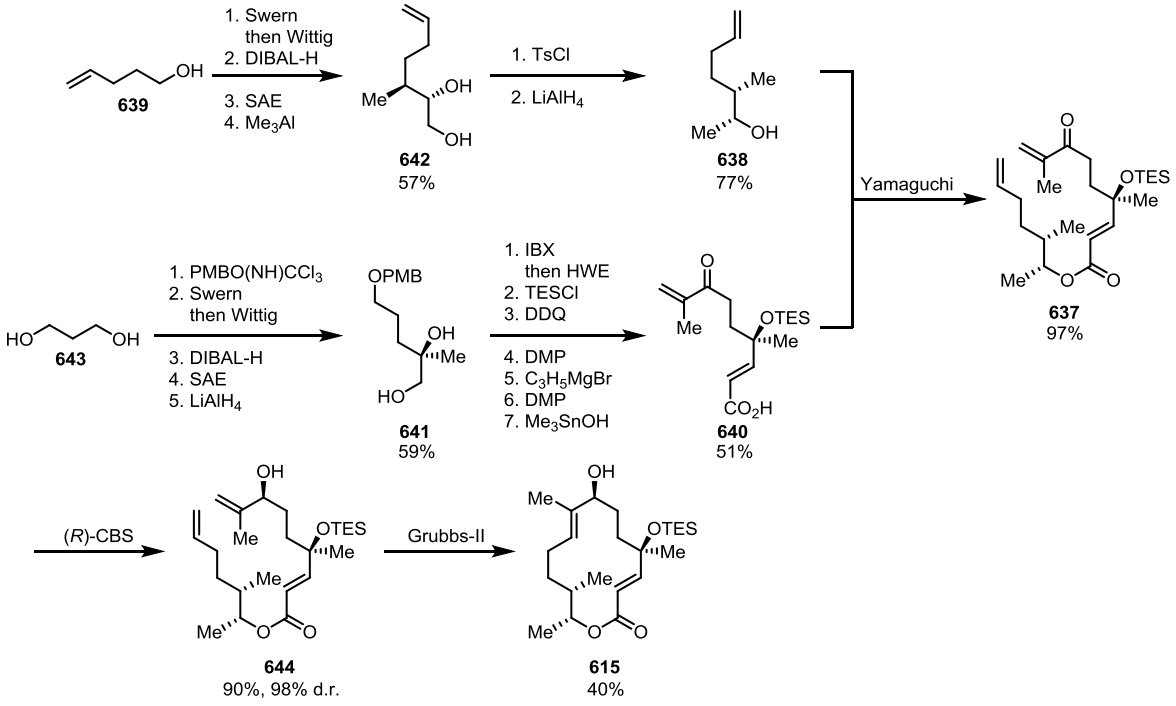


Figure 4. Retrosynthetic analysis of 5,6-dihydrocineromycin B by Rao and coworkers.

The forward synthesis is presented in Scheme 9. 4-Pentenol (**639**) was elaborated in 4 steps to diol **642** including oxidation/Wittig reaction, DIBAL–H reduction, Sharpless epoxidation, and epoxide opening. Subsequent tosylation and reductive detosylation furnished alcohol **638**. Acid

640 was synthesized starting from propanediol (**643**). Selective protection, oxidation/Wittig reaction of **643** were followed by DIBAL–H reduction, Sharpless epoxidation, and reductive epoxide opening to give diol **641**. Oxidation/HWE reaction and TES protection set the stage for PMB deprotection, another oxidation/alkylation/oxidation sequence, and final ester hydrolysis to furnish acid **640**. Yamaguchi esterification, CBS reduction, and ring-closing alkene metathesis completed the formal synthesis of 5,6-dihydrocineromycin B (**615**) in 14 steps in the longest linear sequence with an overall yield of 11%. Although excellent stereocontrol was achieved at the previously problematic tertiary hydroxyl group at position 7, the crucial ring closing alkene metathesis gave only 40% yield.



Scheme 9. Formal synthesis of 5,6-dihydrocineromycin B by Rao and coworkers.

All approaches disclosed to date have major shortcomings. The syntheses of Tietze *et al.* and Zhai *et al.* were unable to provide a reliable access to only one diastereomer of the natural product, whereas the formal synthesis of Rao failed to deliver good yields in the key ring-closing event. Furthermore, all approaches hardly allow the concept of diverted total synthesis to be pursued as no intermediate amenable to late-stage diversification is passed through.

6.1.4. Motivation

Our goal was to design a route that exploits the possibility granted by the directed *trans*-selective hydrostannation of propargyl alcohols.[19] In addition, late-stage installation of an alkenylstannane would enable us to introduce a variety of different functionalities and demonstrate the flexibility of this new tool (Figure 5). Having established new synthetic

transformations of alkenylstannanes in prior projects disclosed herein, stannane **645** served as the key intermediate.

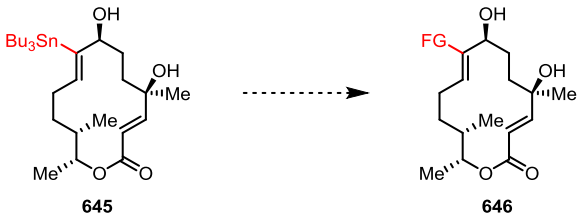


Figure 5. Concept for late-stage transformation of alkenylstannanes.

6.2. Results and Discussion

The following synthesis project was executed in close cooperation with Johannes Preindl[20] and Stephan M. Rummelt[21], their contributions are highlighted.

6.2.1. Retrosynthetic Analysis

As mentioned above, the key intermediate **647** obtained by directed *trans*-selective hydrostannation of a propargyl alcohol, would serve to access either 5,6-dihydrocineromycin B (**615**) or its analogs **646** (Figure 6). The crucial propargyl alcohol would in turn be derived from esterification and ring-closing alkyne metathesis (RCAM) of fragments **648** and **650** which can be traced back to (+)-citronellene and (–)-linalool, respectively.

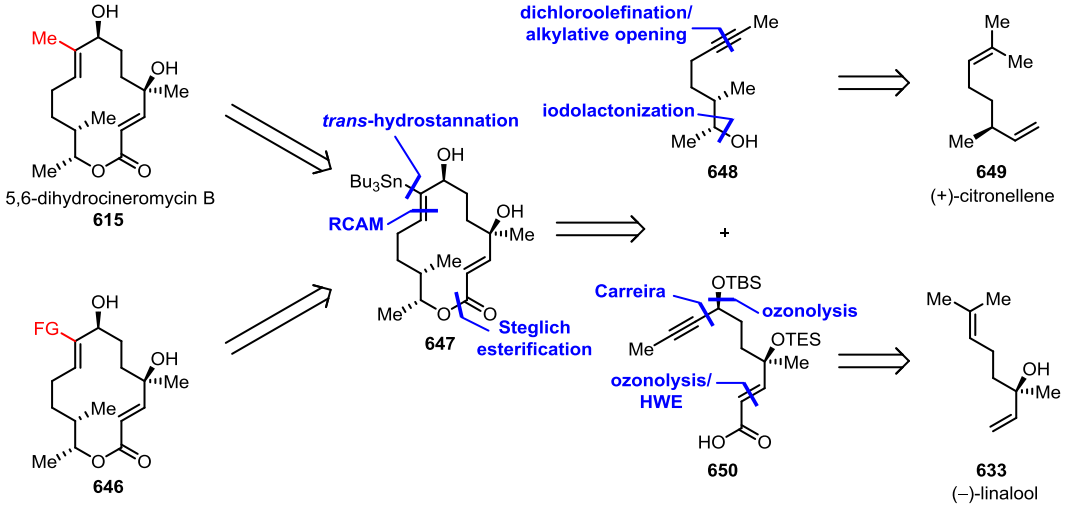
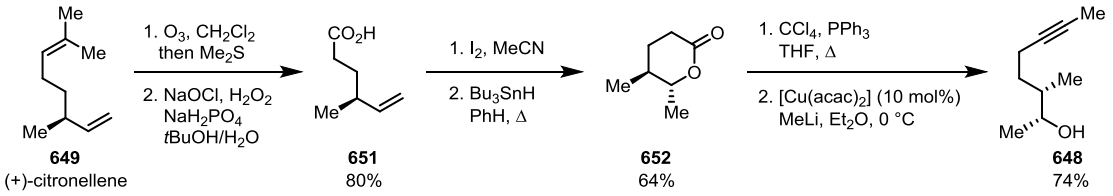


Figure 6. Retrosynthetic analysis of 5,6-dihydrocineromycin B (**615**).

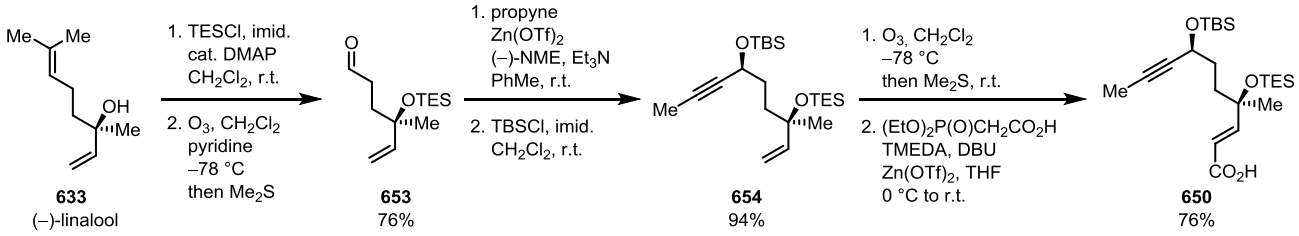
6.2.2. Total Synthesis and DTS of 5,6-dihydrocineromycin B

Our synthesis commenced with chemoselective ozonolysis of (+)-citronellene (**649**) followed by oxidation of the resulting aldehyde to give acid **651** (Scheme 10). Subsequent iodolactonization and dehalogenation with tributyltin hydride furnished lactone **652**.[22] Finally, dichloroolefination and copper-catalyzed lactone opening/methylation delivered alkynol **648** in good overall yield.[23]



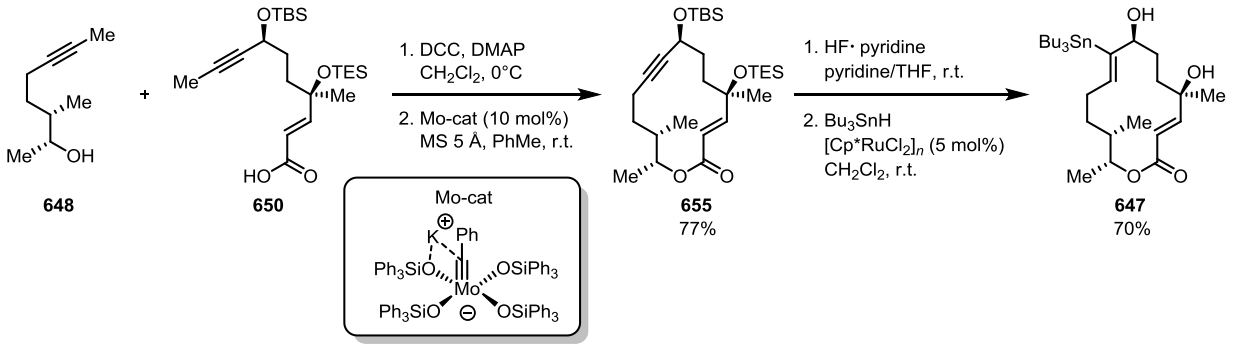
Scheme 10. Synthesis of alcohol **648** *(J. Preindl).*

In order to prepare acid **650**, (–)-linalool (**633**) was subjected to TES protection and ozonolysis of the more electron-rich olefin[24] to give aldehyde **653**, which then underwent Carreira alkynylation[25] and TBS protection to provide propargyl alcohol **654** (Scheme 11). Selective ozonolysis of the olefin in the presence of the alkyne followed by HWE olefination[26] furnished fragment **650** in high overall yield.



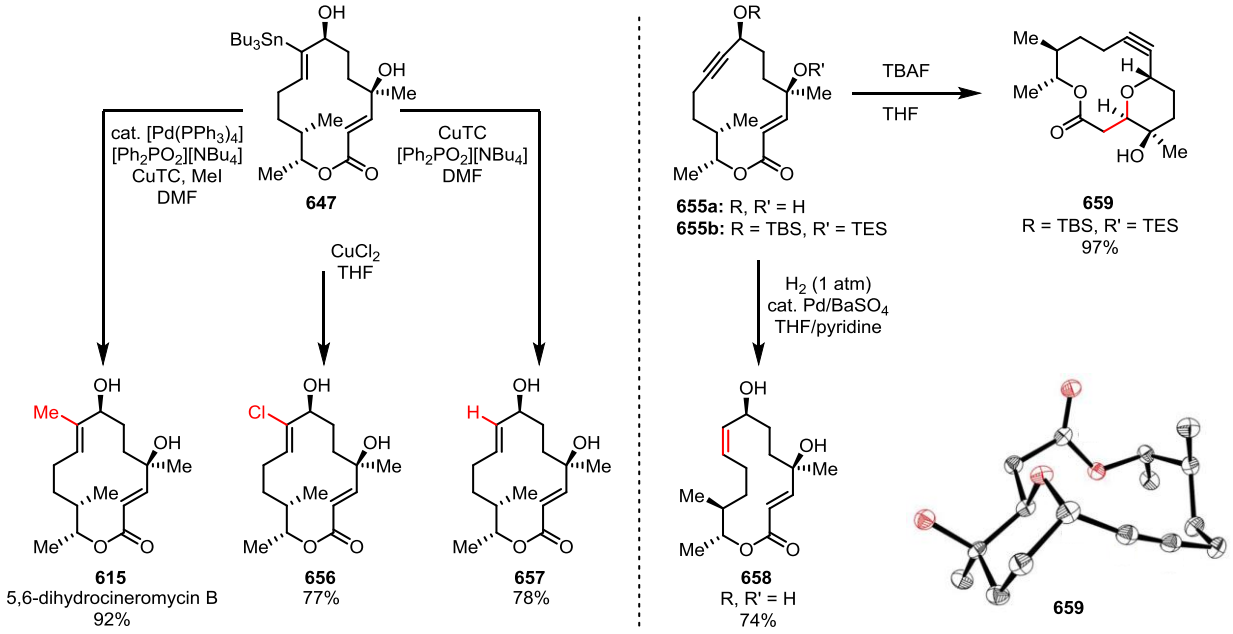
Scheme 11. Synthesis of acrylic acid **650** *(S. M. Rummelt).*

The two fragments were then joined by a Steglich esterification, and the resulting diyne was exposed to standard RCAM conditions to furnish alkyne **655** in good yield.[27] Double desilylation was accomplished with HF·pyridine, and the crucial *trans*-selective hydrostannation gave stannane **647** in high overall yield and >20:1 regioselectivity.



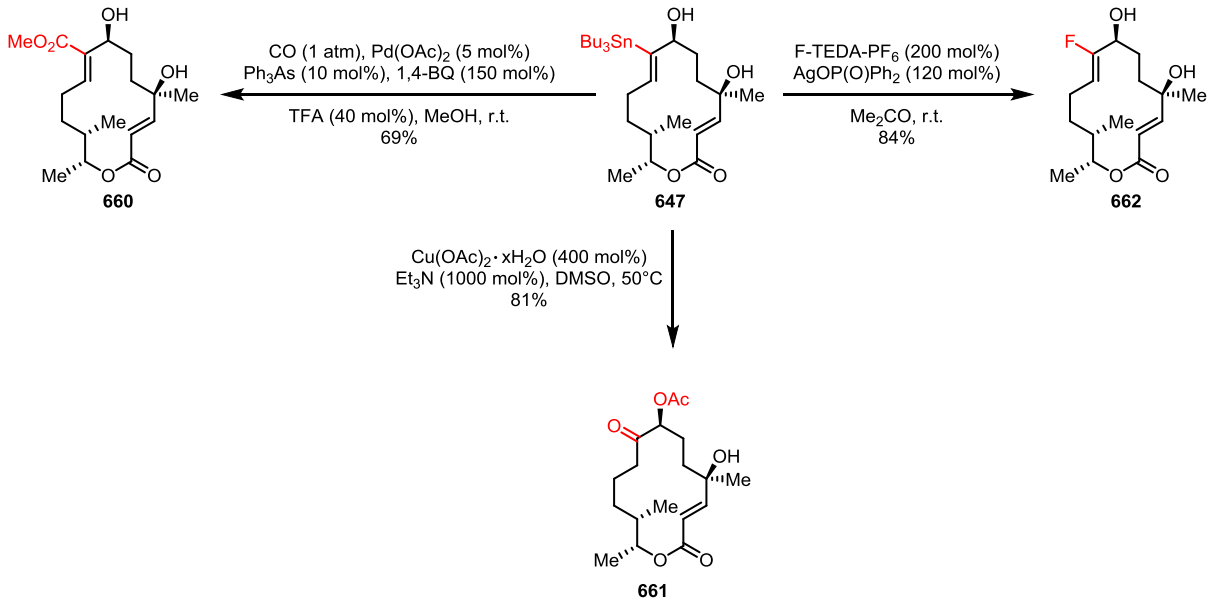
Scheme 12. Synthesis of key stannane **647** *(H. Sommer, S. M. Rummelt).*

After some optimization, the crucial methyl Stille cross-coupling reaction[28] successfully completed the total synthesis of 5,6-dihydrocineromycin B (**615**). Notably >100 mg of the natural product were obtained in a single-batch in 10 longest linear steps (16 steps total) with an overall yield of 32% (Scheme 13). With stannane **647** in hand, we were able to prepare alkenyl chloride **656** and protodestannation product **657** in good yield. Furthermore, Lindlar reduction of the deprotected alkyne **655** gave the corresponding *cis*-olefin isomer **658**. Finally, deprotection of alkyne **655** with TBAF unexpectedly yielded oxa-Michael adduct **659** in excellent yield. Its structure was confirmed by single-crystal X-ray crystallography.



Scheme 13. Completion of DTS of 5,6-dihydrocineromycin B *(J. Preindl, S. M. Rummelt, H. Sommer).*

With a substantial amount of stannane **647** in hand, the applicability of the protocols developed herein was probed. Stannane **647** smoothly underwent the oxidative palladium-catalyzed methoxy carbonylation to give unsaturated ester **660** (Scheme 14). Copper-mediated oxidation furnished α-acetoxy ketone **661**. Finally, silver-mediated fluorination delivered alkenyl fluoride **662**.



Scheme 14. Application of new methodologies in DTS of 5,6-dihydrocineromycin B.

As shown in Scheme 13 and Scheme 14 the natural product and a total of seven analogs were obtained either from stannane **647** or its precursor alkyne **655**.

6.3. Conclusion and Outlook

A highly convergent and efficient total synthesis of 5,6-dihydrocineromycin B has been described. Key transformations of this endeavor comprise a RCAM, a directed *trans*-selective hydrostannation, and an unprecedented methyl Stille cross-coupling. Furthermore, by exploiting the concept of diverted total synthesis, a variety of non-natural analogs was obtained. The key alkenylstannane **647** was utilized as a platform to showcase the newly developed reactions described in the previous chapters. Additional novel methodologies could be tested on stannane **647** to demonstrate their feasibility in future natural product synthesis efforts.

6.4. Literature

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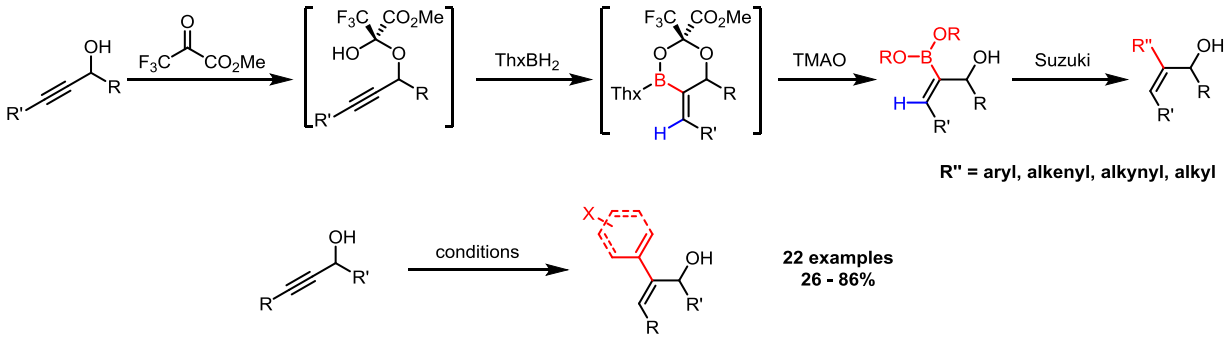
[28] A. Furstner, J.-A. Funel, M. Tremblay, L. C. Bouchez, C. Nevado, M. Waser, J. Ackerstaff, C. C. Stimson, *Chem. Comm.* **2008**, 2873-2875.

7. Summary

The work presented herein describes new methodologies for the selective synthesis of trisubstituted olefins and their applications. Five different topics which have been covered, are summarized in the following sections.

7.1. Directed Hydroboration of Propargyl Alcohols and Suzuki Cross-Coupling for Selective Synthesis of Trisubstituted Olefins

Hydroxyl-directed hydroboration/Suzuki cross-coupling of propargyl alcohols to yield stereodefined trisubstituted olefins was developed. It was found that an *in situ* generated hemiacetal enhanced the directing effect of the propargyl alcohol. Experimental data suggested that electronic and steric factors determine the regioselectivity of the reaction rather than covalent directing effects. The alkenylboronates formed *in situ* were directly transformed via Suzuki cross-coupling into various trisubstituted olefins. Numerous aryl-, alkenyl-, alkyl- and alkynyl-halides successfully underwent the cross-coupling (Scheme 1). This methodology has found a first application in the synthesis of putative orevactaene.

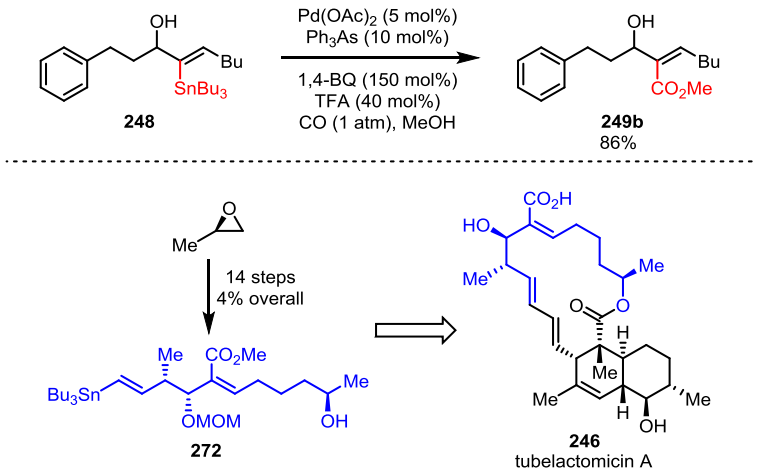


Scheme 1. Hydroxyl-directed hydroboration/Suzuki cross coupling.

7.2. Hydroxyl-Assisted Carbonylation of Alkenyltin Derivatives: Development and Application to a Formal Synthesis of Tubelactomicin A

The recently disclosed ruthenium-catalyzed directed *trans*-selective hydrostannation of alkynes prompted us to develop robust and synthetically useful transformations of alkenylstannanes. To this end, hydroxyl-assisted palladium catalyzed oxidative methoxy carbonylation of alkenyltin derivatives was developed and then applied to the synthesis of (hydroxymethyl)acrylic acid motifs (Scheme 2). Previously reported conditions for the analogous transformation of boranes failed completely. After much experimentation, we discovered that the use of triphenylarsine as the ligand and an acidic reaction medium were crucial for the successful reaction outcome. Using this method, a series of highly functionalized α,β-unsaturated esters was synthesized including key intermediate **272** in the total synthesis of

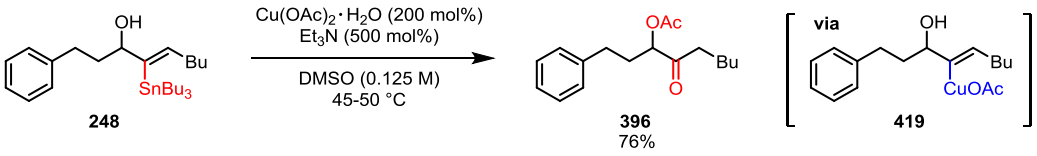
tubelactomicin A. Our concise route allowed us to significantly reduce the step-count compared with a previously reported approach.



Scheme 2. Palladium catalyzed oxidative methoxy carbonylation and formal synthesis of tubelactomicin A.

7.3. Oxidation of Alkenylstannanes to (Hydroxy)ketones

Numerous alkenylmetalloids have been shown to undergo oxidations to the corresponding ketones. However, stannane variants of this transformation have not been reported yet. Inspired by the seminal studies towards well-known Chan-Lam coupling, alkenylstannanes flanked by a hydroxyl group were exposed to stoichiometric copper(II)acetate in the presence of an amine base to give the corresponding functionalized α-acetoxy ketones (Scheme 3). Furthermore, transformation of alkenylstannanes lacking an assisting hydroxyl group into the corresponding ketones were accomplished utilizing copper(II) trifluoroacetate. Initial mechanistic studies indicate the intermediacy of an alkenylcopper species.

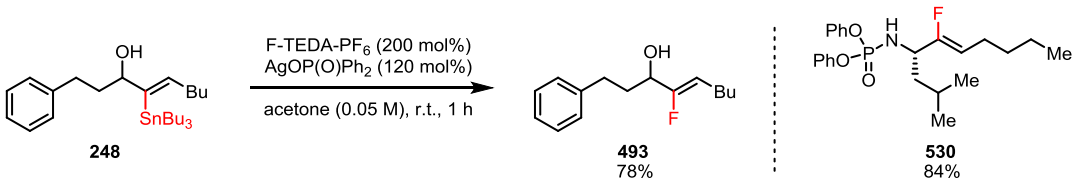


Scheme 3. Copper mediated oxidation of alkenylstannanes.

7.4. Fluorination of Alkenylstannanes and Synthesis of Peptide Bioisosters

Although alkenylfluorides constitute an important class of compounds in medicinal, agricultural and material chemistry, no general method has been reported to obtain this structural motif from the corresponding tin derivatives. A silver-mediated fluorination was developed utilizing a Selecfluor® derivative as fluorinating agent (Scheme 4). It was found that silver diphenylphosphinate effectively suppressed protodestannation while ensuring high isolated yields. Further refinement of the methodology enabled us to develop a general protocol

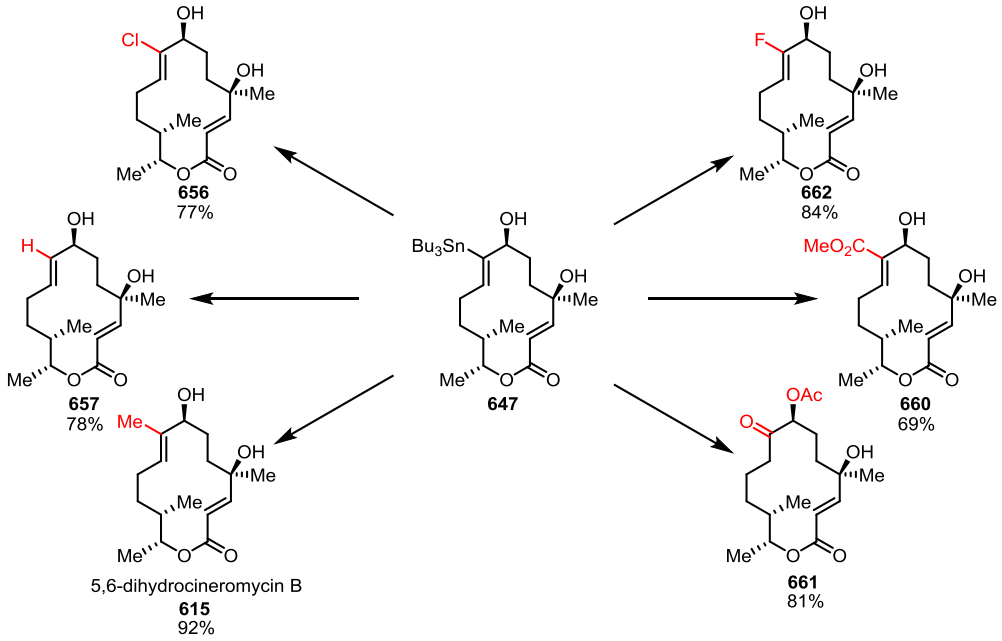
for the conversion of alkenylstannanes to the corresponding fluorides. In addition, this mild and functional group tolerant method allowed us to synthesize a library of peptide bioisosters exemplified by **530**.



Scheme 4. Fluorination of alkenylstannanes and synthesis of bioisosters.

7.5. Diverted Total Synthesis of 5,6-Dihydrocineromycin B

Finally, the utility of the directed *trans*-selective hydrostannation and subsequent catalytic reactions was demonstrated in the total synthesis of 5,6-dihydrocineromycin B. In a highly catalysis-based approach, the natural product itself along with five non-natural analogs was synthesized via late-stage diversification. To complete the synthesis of **615**, a methyl-Stille cross-coupling was implemented to access the target in 10 longest linear steps (16 steps total) with high overall yield. The methodologies described herein were probed on stannane **647** giving rise to fluoride **662**, ester **660** and ketone **661**, respectively.



Scheme 5. Synthesis of 5,6-dihydrocineromycin B and congeners.

8. Experimental Procedures

8.1. General Experimental Details

If not indicated otherwise, all reactions were carried out under Ar in flame-dried glassware.

Solvents

The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2, MeCN (CaH_2), toluene, benzene (Na/K), MeOH (Mg). DMF and Et_3N were dried by an absorption solvent purification system based on molecular sieves. Pyridine was purified by distillation over CaH_2 and transferred under Ar. Technical grade solvents were used for flash chromatography and routine extractions. Mol sieves (3 Å, 4 Å and 5 Å) were dried under high vacuum at >120 °C for 24 h.

Chromatography

For flash chromatography, Merck silica gel 60 (40–63 µm) was used. For thin layer chromatography (TLC), Macherey-Nagel (40x80 mm, Polygram® SIL >G/UV_{254} or Polygram® ALOX N/UV_{254}) were used. Detection was accomplished under UV light (254 nm) or by staining with *p*-anisaldehyde, $KMnO_4$, I_2 or phosphomolybdic acid.

NMR spectroscopy

Spectra were recorded on a Bruker AV 400 spectrometer or a Bruker AV VIII 300 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δC ≡ 77.16 ppm; residual $CHCl_3$ in $CDCl_3$: δH ≡ 7.26 ppm). ^{119}Sn NMR spectra were using Me_4Sn as external standard. Multiplets are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet; hept: heptet, m: multiplet. The abbreviation "br" indicates a broad signal. ^{13}C NMR spectra were recorded [1H]-decoupled and the values of chemical shifts are rounded to one position after the decimal point.

Infrared spectroscopy

Spectra were recorded on an Alpha Platinum ATR spectrometer (Bruker) at room temperature, wavenumbers ($\tilde{\nu}$) in cm^{-1}.

Mass spectrometry

Finnigan MAT 8200 (70 eV), ESIMS: ESQ 3000 (Bruker). Accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or MAT 95 (Finnigan).

Optical rotation

Optical rotations were measured on a 343 Plus (Perkin Elmer) or P8000-T (A. Krüss Optronic).

Reagents

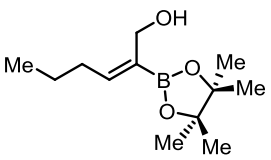
Unless stated otherwise, all commercially available compounds (ABCR, Acros, Aldrich, Strem, Apollo Scientific, TCI, Fluorochem) were used as received. Thexylborane solution was prepared according to literature procedure and stored under argon at 4°C.[1] Thexylalkoxyboranes were prepared by reacting thexylborane *in situ* with the corresponding alcohols.[2] Thexylchloroborane was prepared by treatment of thexylborane *in situ* with 4 M HCl in dioxane.[3] $[Cp^*RuCl_2]_n$[4] and $[Cp^*RuCl]_4$[5] were prepared according to literature procedures and stored under Argon. Commercial Bu_3SnH is stabilized with 0.05% of 3,5-di-tert-butyl-4-hydroxytoluene, which was not removed in the reactions described herein. The following compounds were prepared according to literature procedures: *tert*-butyl 3-hydroxydec-4-ynoate[6], 4-methylpent-2-yn-1-ol[7], 3-phenylprop-2-yn-1-ol[8], 3-(cyclohex-1-en-1-yl)prop-2-yn-1-ol[9], 4-(cyclohex-1-en-1-yl)but-3-yn-2-ol[10], 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol[11], *tert*-butyl(pent-4-yn-1-yloxy)diphenylsilane[12], 2-methylnon-4-yn-3-ol[13], undec-6-yn-5-ol[14], 1-phenylnon-4-yn-3-ol[15], 1-(cyclohex-1-en-1-yl)-4-methylpent-1-yn-3-ol[16], 5-phenylpent-2-ynal[17], dodec-3-yn-2-ol[18], tributyl(dibromomethyl)stannane[19].

8.2. Directed Hydroboration of Propargyl Alcohols and Suzuki Cross Coupling for the Selective Synthesis of Trisubstituted Olefins

8.2.1. Representative procedure 1: Synthesis of Alkenylboronate Esters from Propargyl Alcohols

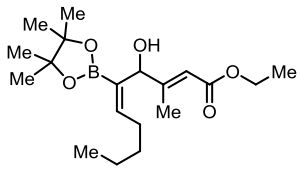
2-Hexyn-1-ol (110 µL, 1.0 mmol, 1.0 equiv.) was dissolved in dry THF (1 mL) and the solution stirred at room temperature in a flame-dried Schlenk flask in the presence of 3 Å mol sieves (200 mg per mmol alkynol). Stirring was continued for 15 minutes before the mixture was cooled with an ice bath. Neat trifluoromethylpyruvic acid methylester (122 µL, 1.2 mmol, 1.2 equiv.) was added and the mixture stirred until disappearance of starting material was judged by TLC (hexanes/ethyl acetate, 4:1, generally after 15 minutes of stirring for primary and about 30 minutes for secondary alcohols). Dry THF (10 mL) was added and the mixture cooled to −78 °C. $ThxBH_2$ solution (1.14 mL, 1.05 M in THF, 1.2 mmol, 1.2 equiv.) was slowly added over 1 minute. The mixture was stirred for 1 minute at the same temperature and was then allowed to warm to room temperature by removing the cooling bath. Upon warming vigorous bubbling is generally observed. The mixture was stirred for 15 minutes at room temperature before neat trimethylamine-*N*-oxide (90 mg, 1.2 mmol, 1.2 equiv.) was introduced followed by pinacol (354 mg, 3.0 mmol, 3.0 equiv.). After 10 minutes, most of the insoluble TMAO disappears while the mixture warmed up. When disappearance of starting material was judged by TLC (hexanes/ethyl acetate, 4:1) the volatile materials were removed under reduced pressure and the crude residue was purified by flash chromatography (SiO_2, hexanes/ethyl acetate) to yield the products as oils.

(*Z*)-2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hex-2-en-1-ol - (125)



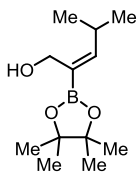
82% yield, (185 mg, 0.82 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.39 (tt, J = 7.3, 1.4 Hz, 1H), 4.27 (d, J = 1.4 Hz, 2H), 2.13 (q, J = 7.4 Hz, 2H), 1.43 (h, J = 7.4 Hz, 2H), 1.27 (s, 12H), 0.91 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 148.0, 83.7, 77.4, 60.6, 30.9, 24.9, 22.3, 14.1 ppm. **IR (film, $CHCl_3$)** 3457, 2977, 2873, 1757, 1631, 1372, 1300, 1139, 1005, 860 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{23}O_3BNa$ [M+Na$^+$]: 249.16309, found 249.16324.

Ethyl (2E,5Z)-4-hydroxy-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)deca-2,5-dienoate - (126)



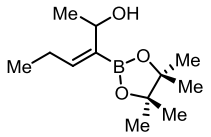
48% yield (336 mg, 0.95 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.41**. ^{1}H NMR (400 MHz, Chloroform-d) δ** 6.43 (ddd, J = 7.8, 6.4, 1.2 Hz, 1H), 5.98 – 5.91 (m, 1H), 4.87 (d, J = 4.7 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.57 – 3.45 (m, 1H), 2.26 (dq, J = 15.3, 7.6 Hz, 1H), 2.17 – 2.08 (m, 1H), 2.06 (d, J = 1.3 Hz, 3H), 1.46 – 1.27 (m, 5H), 1.24 (s, 8H), 1.21 (s, 6H), 0.88 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.2, 160.0, 149.3, 131.2, 114.5, 84.0, 74.6, 59.7, 31.1, 29.2, 25.1, 24.3, 22.6, 15.5, 14.4, 14.0 ppm. **IR (film, $CHCl_3$)** 2978, 2931, 1715, 1651, 1372, 1308, 1207, 1136, 1042, 854, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{19}H_{33}O_5BNa$ [M+Na$^+$]: 375.23126, found 375.23132.

(*Z*)-4-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-en-1-ol - (127)



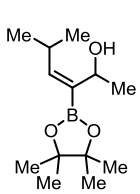
69% yield (313 mg, 1.38 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.40. **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.17 (dt, J = 9.6, 1.3 Hz, 1H), 4.25 (d, J = 1.3 Hz, 2H), 2.69 (dhept, J = 9.5, 6.6 Hz, 1H), 2.43 (s, 1H), 1.25 (s, 12H), 0.95 (d, J = 6.7 Hz, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 154.8, 128.5, 83.6, 60.5, 27.8, 24.9, 22.7 ppm. **^{11}B NMR (128 MHz, $CDCl_3$) δ** 27.9 ppm. **IR (film, $CHCl_3$)** 3467, 2963, 1632, 1371, 1300, 1141, 1008, 964, 862, 674 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{23}O_3BNa$ [M+Na$^+$]: 249.16324, found 249.16324.

(*Z*)-3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hex-3-en-2-ol - (128)



55% yield (250 mg, 1.1 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.47. **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.21 (td, J = 7.2, 1.2 Hz, 1H), 4.68 – 4.55 (m, 1H), 3.01 – 2.81 (m, 1H), 2.24 – 2.12 (m, 1H), 2.12 – 1.99 (m, 1H), 1.29 – 1.22 (m, 23H), 0.98 (t, J = 7.6 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.0 135.2, 83.6, 67.0, 25.0, 25.0, 24.6, 21.8, 13.7 ppm. **^{11}B NMR (128 MHz, $CDCl_3$) δ** 27.82 ppm. **IR (film, $CHCl_3$)** 3559, 2971, 1629, 1371, 1305, 1257, 1140, 1048, 975, 854, 696 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{23}O_3BNa$ [M+Na$^+$]: 249.16321, found 249.16324.

(*Z*)-5-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-3-en-2-ol - (129)

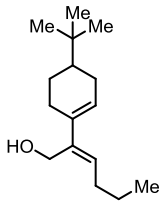


52% yield (252 mg, 1.05 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.60. **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.04 (dd, J = 9.8, 1.1 Hz, 1H), 4.63 (qd, J = 6.5, 1.1 Hz, 1H), 2.68 (ddq, J = 13.2, 9.8, 6.6 Hz, 2H), 1.30 – 1.24 (m, 15H), 0.99 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 152.2, 133.1, 83.6, 67.1, 27.7, 25.5, 25.07, 24.7, 22.7 ppm. **^{11}B NMR (128 MHz, $CDCl_3$) δ** 28.5 ppm. **IR (film, $CHCl_3$)** 2865, 1630, 1371, 1304, 1257, 1142, 1051, 975, 859, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{13}H_{25}O_3BNa$ [M+Na^+]: 263.17887, found 263.17889.

8.2.2. Representative procedure 2: Suzuki Cross-Coupling of *in situ* Generated Alkenylboronic Acids from Propargyl Alcohols

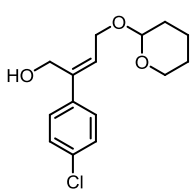
2-Hexyn-1-ol (220 µL, 2.0 mmol, 1.0 equiv.) was dissolved in dry THF (1.0 mL) equipped with 3 Å mol sieves (200 mg per mmol alkynol) and the suspension stirred in an oven-dried Schlenk flask under an argon atmosphere. Methyl trifluoropyruvate (343 µL, 2.2 mmol, 1.1 equiv.) was added and stirring continued at room temperature until disappearance of starting material was judged by TLC (hexanes/ethyl acetate, 4:1). Then the mixture was diluted with THF (10 mL) and cooled to −78 °C before a solution of $ThxBH_2$ in THF (2.2 mL, 1.0 M in THF, 2.2 mmol, 1.1 equiv.) was slowly added. The mixture was allowed to warm to room temperature and stirred for 1 h. Then, neat TMAO (233 mg, 2.1 mmol, 1.05 equiv.) was added followed after 15 minutes by degassed KOH (5.0 mL, 15 mmol, 3 M in water, 7.5 equiv.), 1-bromo-4-(*tert*-butyl)cyclohex-1-ene (579 mg, 2.4 mmol, 1.2 equiv.) and [1,1'-bis-(diphenylphosphino)-ferrocene]-palladium(II)-chloride-methylenechloride-complex (82 mg, 0.1 mmol, 5.0 mol%). The mixture was heated with a preheated oil-bath to 60 °C for 1 h before the reaction was quenched with brine at room temperature. The mixture was extracted two times with ethyl acetate, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate) yielded pure products as a single regioisomer.

(Z)-2-(4-(*tert*-Butyl)cyclohex-1-en-1-yl)hex-2-en-1-ol - (130)



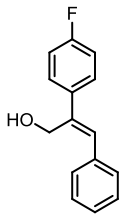
85% yield (401 mg, 1.70 mmol, 2.0 mmol scale). **^{1}H NMR (400 MHz, Chloroform-d) δ** 5.95 (dt, J = 5.1, 2.1 Hz, 1H), 5.58 (t, J = 7.5 Hz, 1H), 4.34 (s, 2H), 2.37 – 2.24 (m, 1H), 2.22 – 2.04 (m, 4H), 1.99 – 1.84 (m, 2H), 1.40 (dt, J = 14.7, 7.3 Hz, 3H), 1.31 – 1.09 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H), 0.87 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 139.0, 135.4, 128.5, 124.0, 57.9, 44.1, 32.3, 30.2, 27.7, 27.5, 27.3, 24.3, 23.3, 14.0 ppm. **IR (film, $CHCl_3$)** 3330, 2956, 2870, 1468, 1364 1393, 1248, 1007, 914, 805, 733, 663 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{28}ONa$ [M+Na^+]: 259.20323, found 259.20322.

(Z)-2-(4-Chlorophenyl)-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-en-1-ol - (131)



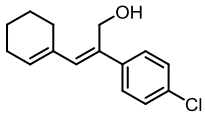
55% yield (310 mg, 1.1 mmol). **TLC** (hexanes/ethyl acetate, 1:1), Rf = 0.64**. ^{1}H NMR (400 MHz, Chloroform-d) δ** 7.46 – 7.41 (m, 2H), 7.33 – 7.27 (m, 2H), 6.02 (dd, J = 7.7, 6.4 Hz, 1H), 4.76 (t, J = 3.3 Hz, 1H), 4.53 (d, J = 12.4 Hz, 1H), 4.47 – 4.39 (m, 2H), 4.31 (dd, J = 12.7, 7.8 Hz, 1H), 3.87 (ddd, J = 11.3, 9.0, 3.2 Hz, 2H), 3.56 (dtd, J = 11.3, 4.2, 1.3 Hz, 1H), 2.76 (s, 1H), 1.88 – 1.68 (m, 2H), 1.66 – 1.48 (m, 4H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 142.9, 139.4, 133.5, 128.7, 127.7, 127.4, 97.3, 63.1, 62.1, 60.07, 30.5, 25.4, 19.1 ppm. . **IR (film, $CHCl_3$)** 3427, 2943, 2871, 1492, 1351, 1116, 1023, 814 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{19}ClO_3Na$ [M+Na^+]: 305.09150, found 305.09149.

(Z)-2-(4-Fluorophenyl)-3-phenylprop-2-en-1-ol - (132)



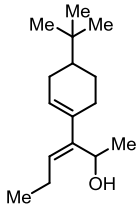
60% yield (138 mg, 0.605 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.71. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.61 – 7.54 (m, 2H), 7.43 – 7.37 (m, 4H), 7.31 (tdd, J = 5.2, 3.7, 2.8 Hz, 1H), 7.16 – 7.04 (m, 2H), 6.93 (s, 1H), 4.69 (s, 2H), 1.58 (s, 2H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 162.9, 160.5, 138.36, 136.0, 130.5, 128.2, 127.7, 127.6, 127.5, 126.7, 114.9, 114.7, 59.7 ppm. **IR (film, $CHCl_3$)** 3348, 3022, 2929, 1598, 1506, 1225, 1159, 1008, 838, 701 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{13}FONa$ [M+Na^+]: 251.08435, found 251.08426.

(Z)-2-(4-Chlorophenyl)-3-(cyclohex-1-en-1-yl)prop-2-en-1-ol - (133)



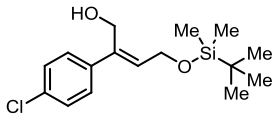
86% yield (426 mg, 1.72 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.19. **Mp:** 63-66°C. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.45 – 7.39 (m, 2H), 7.34 – 7.28 (m, 2H), 6.24 (d, J = 1.5 Hz, 1H), 5.80 (dq, J = 3.9, 1.8 Hz, 1H), 4.65 (s, 2H), 2.17 (qq, J = 3.8, 2.1 Hz, 4H), 1.73 – 1.58 (m, 3H), 1.48 – 1.40 (m, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 139.8, 136.6, 134.8, 133.1, 130.5, 129.0, 128.7, 127.9, 60.6, 29.1, 25.9, 22.9, 22.1 ppm. **IR (film, $CHCl_3$)** 3228, 2925, 1618, 1490, 1321, 1092, 1008, 843, 820, 717, 536 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{17}OClNa$ [M+Na$^+$]: 271.08602, found 271.08601.

(Z)-3-(4-(*tert*-Butyl)cyclohex-1-en-1-yl)hex-3-en-2-ol - (134)



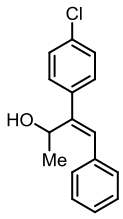
66% yield (311 mg, 1.3 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.47. **^{1}H NMR (400 MHz, Chloroform-d) δ** 5.71 (dt, J = 3.4, 2.0 Hz, 1H), 5.30 (td, J = 7.3, 4.3 Hz, 1H), 4.79 (q, J = 6.7 Hz, 1H), 2.28 – 2.04 (m, 4H), 1.84 (dddt, J = 14.8, 6.8, 4.6, 2.0 Hz, 2H), 1.68 (s, 1H), 1.32 (dd, J = 6.7, 3.0 Hz, 3H), 1.29 – 1.09 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H), 0.86 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 144.6, 144.4, 137.3, 137.3, 129.3, 129.2, 125.2, 125.0, 66.5, 66.3, 43.8, 32.3, 30.9, 30.8, 27.3, 24.5, 23.0, 22.9, 21.1, 21.0, 14.7, 14.7 ppm. **IR (film, $CHCl_3$)** 3381, 2961, 2871, 1468, 1364, 1248, 1107, 1061, 897 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{28}O$ [M$^+$]: 236.21383, found 236.21402.

(Z)-4-((*tert*-Butyldimethylsilyl)oxy)-2-(4-chlorophenyl)but-2-en-1-ol - (135)



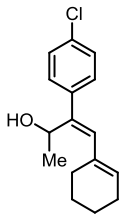
67% yield (419 mg, 1.34 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.71. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.42 – 7.35 (m, 2H), 7.35 – 7.27 (m, 2H), 6.01 (t, J = 6.3 Hz, 1H), 4.50 (s, 2H), 4.42 (d, J = 6.3 Hz, 2H), 2.32 (s, 1H), 0.93 (s, 9H), 0.12 (s, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.2, 139.4, 133.5, 130.7, 128.7, 127.8, 60.7, 59.9, 26.1, 18.5, -5.0 ppm. **IR (film, $CHCl_3$)** 3406, 2955, 2930, 2857, 1492, 1471, 1365, 1254, 1082, 1011, 834, 775 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{25}O_2ClSiNa$ [M+Na$^+$]: 335.12050, found 335.12046.

(Z)-3-(4-Chlorophenyl)-4-phenylbut-3-en-2-ol - (136)



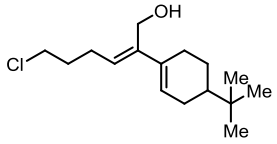
48% yield (249 mg, 0.96 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.56. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.55 – 7.49 (m, 2H), 7.43 – 7.37 (m, 2H), 7.37 – 7.28 (m, 5H), 6.66 (s, 1H), 5.15 (q, J = 6.5 Hz, 1H), 1.67 (s, 1H), 1.29 (d, J = 6.5 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 144.1, 138.9, 136.6, 133.4, 131.5, 130.2, 129.0, 128.5, 128.29, 127.4, 66.0, 22.4 ppm. **IR (film, $CHCl_3$)** 3365, 2974, 1489, 1444, 1371, 1090, 1014, 837, 699, 509 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{15}ClONa$ [M+Na^+]: 281.07056, found 281.07036.

(Z)-3-(4-Chlorophenyl)-4-(cyclohex-1-en-1-yl)but-3-en-2-ol - (137)



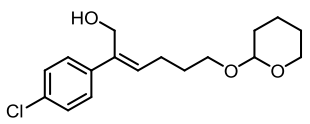
45% yield (238 mg, 0.906 mmol, 2.0 mmol scale). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.33 – 7.29 (m, 2H), 7.21 – 7.17 (m, 2H), 5.87 – 5.78 (m, 1H), 5.60 (td, J = 3.8, 1.8 Hz, 1H), 5.10 (q, J = 6.6 Hz, 1H), 2.12 – 1.96 (m, 4H), 1.71 (s, 1H), 1.65 – 1.47 (m, 4H), 1.16 (d, J = 6.6 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.8, 139.5, 134.6, 134.1, 132.9, 130.1, 128.1, 127.7, 66.3, 29.3, 25.7, 22.8, 22.7, 22.1 ppm. **IR (film, $CHCl_3$)** 3377, 2927, 2833, 1488, 1446, 1369, 1269, 1089, 1014 1043, 895 928, 826 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{19}OCl$ [M^+]: 262.11244, found 262.11253.

(Z)-2-(4-(*tert*-Butyl)cyclohex-1-en-1-yl)-6-chlorohex-2-en-1-ol - (138)



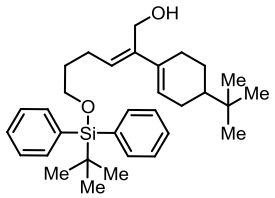
75% yield (408 mg, 1.51 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.62. **^{1}H NMR (400 MHz, Chloroform-d) δ** 5.98 (dt, J = 5.1, 2.2 Hz, 1H), 5.52 (t, J = 7.6 Hz, 1H), 4.35 (s, 2H), 3.54 (t, J = 6.4 Hz, 2H), 2.37 (q, J = 7.3 Hz, 2H), 2.33 – 2.23 (m, 1H), 2.21 – 2.03 (m, 2H), 2.00 – 1.82 (m, 4H), 1.57 (s, 1H), 1.31 – 1.10 (m, 2H), 0.87 (s, 9H).ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 140.4, 135.2, 126.0, 124.7, 57.7, 44.5, 44.0, 32.6, 32.2, 27.6, 27.5, 27.3, 25.2, 24.3 ppm. **IR (film, $CHCl_3$)** 3357, 2955, 2868, 1472, 1436, 1393, 1364, 1003, 914, 807, 738, 653 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{27}OClNa$ [M+Na^+]: 293.16438, found 293.16426.

(Z)-2-(4-Chlorophenyl)-6-((tetrahydro-2H-pyran-2-yl)oxy)hex-2-en-1-ol - (139)



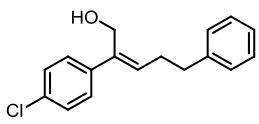
70% yield (434 mg, 1.40 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.44. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.45 – 7.40 (m, 2H), 7.32 – 7.27 (m, 2H), 5.82 (dd, J = 8.8, 7.1 Hz, 1H), 4.59 (d, J = 12.3 Hz, 1H), 4.52 (dd, J = 5.6, 2.6 Hz, 1H), 4.46 – 4.38 (m, 1H), 3.91 – 3.84 (m, 1H), 3.80 (ddd, J = 9.9, 8.7, 4.5 Hz, 1H), 3.53 – 3.44 (m, 2H), 2.76 (s, 1H), 2.51 (dtd, J = 14.6, 8.6, 6.0 Hz, 1H), 2.39 – 2.29 (m, 1H), 1.93 – 1.65 (m, 4H), 1.61 – 1.46 (m, 4H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 140.1, 139.3, 132.8, 131.6, 128.5, 127.7, 99.6, 65.9, 63.7, 59.5, 31.0, 28.9, 25.4, 24.8, 20.4 ppm. **IR (film, $CHCl_3$)** 3436, 2941, 2869, 1491, 1353, 1137, 1121, 1029, 824 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{23}O_3ClNa$ [M+Na$^+$]: 333.12274, found 333.12279.

(Z)-2-(4-(*tert*-Butyl)cyclohex-1-en-1-yl)-6-((tert-butyldiphenylsilyl)-oxy)hex-2-en-1-ol - (140)



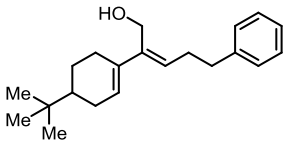
74% yield (835 mg, 1.70 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.71 – 7.63 (m, 4H), 7.50 – 7.32 (m, 6H), 5.98 (dt, J = 5.2, 2.3 Hz, 1H), 5.55 (t, J = 7.6 Hz, 1H), 4.36 (s, 2H), 3.69 (t, J = 6.1 Hz, 2H), 2.32 (q, J = 7.4 Hz, 2H), 2.27 – 2.03 (m, 2H), 2.00 – 1.85 (m, 1H), 1.66 (s, 1H), 1.64 – 1.55 (m, 2H), 1.33 – 1.10 (m, 2H), 1.06 (s, 10H), 0.89 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 139.8, 135.7, 135.4, 133.9, 129.74, 127.8, 127.7, 124.1, 63.1, 57.8, 44.1, 32.7, 32.3, 27.7, 27.6, 27.3, 27.0, 24.4, 24.3, 19.3 ppm. **IR (film, $CHCl_3$)** 2932, 2859, 1472, 1428, 1391, 1364, 1108, 1007, 823, 739, 701, 613, 504 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{32}H_{46}O_2SiNa$ [M+Na$^+$]: 513.31596, found 513.31593.

(Z)-2-(4-Chlorophenyl)-5-phenylpent-2-en-1-ol - (141)



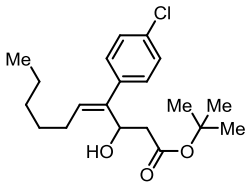
52% yield (285 mg, 1.05 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.44. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.39 – 7.27 (m, 6H), 7.22 m, 3H), 5.90 (t, J = 7.7 Hz, 1H), 4.35 – 4.30 (m, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.65 – 2.57 (m, 2H), 0.86 – 0.80 (m, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.4, 139.6, 138.7, 133.0, 131.5, 128.8, 128.6, 128.6, 127.7, 126.4, 59.6, 35.9, 30.6 ppm. **IR (film, $CHCl_3$)** 3360, 2927, 1491, 1453, 1092, 1012, 825, 750, 699 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{17}OClNa$ [M+Na$^+$]: 295.08605, found 295.08601.

(Z)-2-(4-(*tert*-Butyl)cyclohex-1-en-1-yl)-5-phenylpent-2-en-1-ol - (142)



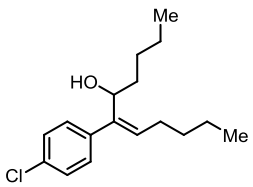
63% yield (375 mg, 1.26 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.53. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.34 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 5.95 (dt, J = 5.3, 2.2 Hz, 1H), 5.63 (t, J = 7.6 Hz, 1H), 4.23 (d, J = 2.8 Hz, 2H), 2.73 (t, J = 7.4 Hz, 2H), 2.57 – 2.49 (m, 2H), 2.34 – 2.24 (m, 1H), 2.23 – 2.05 (m, 2H), 2.00 – 1.87 (m, 2H), 1.33 – 1.13 (m, 2H), 1.01 (s, 1H), 0.89 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.7, 139.7, 135.3, 128.7, 128.5, 127.0, 126.1, 124.4, 57.8, 44.0, 36.3, 32.3, 30.3, 27.7, 27.5, 27.3, 24.3 ppm. **IR (film, $CHCl_3$)** 2957, 1453, 1364, 998, 908, 730, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{21}H_{30}ONa$ [M+Na$^+$]: 321.21897, found 321.21888.

***tert*-Butyl (Z)-4-(4-chlorophenyl)-3-hydroxydec-4-enoate - (143)**



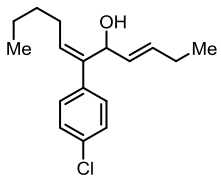
50% yield (350 mg, 0.99 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.26. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.37 – 7.31 (m, 2H), 7.25 (m, 2H), 5.60 (t, J = 7.4 Hz, 1H), 5.21 (dt, J = 10.1, 3.0 Hz, 1H), 3.17 (d, J = 2.9 Hz, 1H), 2.51 (dd, J = 16.6, 10.1 Hz, 1H), 2.38 – 2.18 (m, 3H), 1.43 (s, 11H), 1.37 – 1.28 (m, 4H), 0.98 – 0.83 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 172.3, 139.6, 139.4, 134.4, 132.9, 130.0, 128.1, 81.5, 66.9, 41.3, 31.6, 29.5, 28.2, 28.0, 22.7, 14.2 ppm. **IR (film, $CHCl_3$)** 3465, 2927, 1709, 1488, 1367, 1148, 1091, 1014, 831 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{20}H_{29}O_3ClNa$ [M+Na$^+$]: 375.16980, found 375.16974.

(Z)-6-(4-Chlorophenyl)undec-6-en-5-ol - (144)



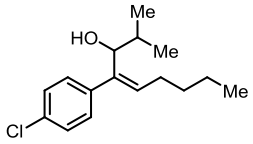
56% yield (1.5 equiv. halide, 313 mg, 1.12 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.53. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.37 – 7.31 (m, 2H), 7.29 – 7.23 (m, 2H), 5.58 (t, J = 7.5 Hz, 1H), 4.79 (t, J = 7.1 Hz, 1H), 2.34 – 2.17 (m, J = 7.2 Hz, 2H), 1.67 – 1.52 (m, 2H), 1.51 – 1.33 (m, 5H), 1.33 – 1.09 (m, 3H), 0.93 (t, J = 7.1 Hz, 4H), 0.84 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.4, 139.8, 133.7, 132.7, 130.0, 128.1, 70.2, 35.5, 32.2, 28.2, 27.7, 22.6, 14.1 ppm. **IR (film, $CHCl_3$)** 3364, 2956, 2928, 2859, 1488, 1465, 1092, 1014, 827 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{25}OClNa$ [M+Na$^+$]: 303.14869, found 303.14861.

(3E,6Z)-6-(4-Chlorophenyl)undeca-3,6-dien-5-ol - (145)



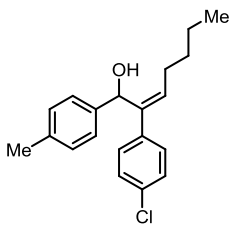
40% yield (225 mg, 0.81 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.33. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.26 – 7.22 (m, 2H), 7.19 – 7.15 (m, 2H), 5.67 (dtd, J = 15.4, 6.3, 1.4 Hz, 1H), 5.57 – 5.53 (m, 1H), 5.49 (ddt, J = 15.4, 5.8, 1.5 Hz, 1H), 5.21 (d, J = 6.1 Hz, 1H), 2.29 – 2.09 (m, J = 7.3 Hz, 2H), 1.97 (qdt, J = 7.5, 6.3, 1.3 Hz, 2H), 1.60 (s, 1H), 1.43 – 1.25 (m, 4H), 0.93 – 0.82 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 140.3, 139.4, 134.1, 133.1, 132.8, 129.9, 129.7, 128.1, 71.1, 32.0, 27.8, 25.4, 22.6, 14.1, 13.6 ppm. **IR (film, $CHCl_3$)** 3356, 2959, 2928, 1489, 1460, 1091, 1014, 965, 824 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{23}OCl$ [M^+]: 278.14389, found 278.14374.

(Z)-4-(4-Chlorophenyl)-2-methylnon-4-en-3-ol - (146)



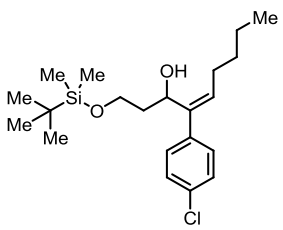
42% yield (226 mg, 0.85 mmol). **TLC** (hexanes/ethyl acetate, 20:1), Rf = 0.31.**^{1}H NMR (400 MHz, Chloroform-d) δ** 7.43 – 7.36 (m, 2H), 7.29 – 7.17 (m, 2H), 5.64 (t, J = 7.5 Hz, 1H), 4.33 (d, J = 9.8 Hz, 1H), 2.36 – 2.19 (m, J = 7.3 Hz, 2H), 1.69 (tdd, J = 11.5, 8.9, 5.8 Hz, 2H), 1.49 – 1.31 (m, 4H), 1.04 (d, J = 6.5 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H), 0.69 (d, J = 6.7 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 140.7, 140.3, 134.9, 132.7, 129.9, 128.1, 76.2, 32.2, 31.9, 27.8, 22.6, 19.6, 19.0, 14.2 ppm. **IR (film, $CHCl_3$)** 3444, 2965, 2926, 2871, 1488, 1466, 1380, 1092, 1013, 827 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{23}OClNa$ [$M+Na^+$]: 289.13300, found 289.13296.

(Z)-2-(4-Chlorophenyl)-1-(*p*-tolyl)hept-2-en-1-ol - (147)



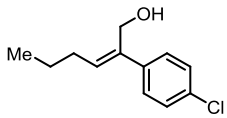
43% yield (273 mg, 0.87 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.43.**^{1}H NMR (400 MHz, Chloroform-d) δ** 7.28 – 7.23 (m, 2H), 7.18 – 7.08 (m, 6H), 5.98 (s, 1H), 5.81 (dd, J = 7.7, 7.0 Hz, 1H), 2.43 – 2.25 (m, 5H), 1.94 (s, 1H), 1.55 – 1.34 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 140.4, 139.4, 138.9, 136.9, 133.7, 132.9, 129.7, 129.2, 128.2, 125.8, 71.2, 32.0, 28.21, 22.7, 21.2, 14.1 ppm. **IR (film, $CHCl_3$)** 3395, 2956, 2925, 2871, 1489, 1174, 1092, 1015, 825, 757 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{20}H_{23}ClONa$ [$M+Na^+$]: 337.13343, found 337.13296.

(Z)-1-((*tert*-Butyldimethylsilyl)oxy)-4-(4-chlorophenyl)non-4-en-3-ol - (148)



55% yield (420 mg, 1.10 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.66. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.40 – 7.32 (m, 2H), 7.29 – 7.21 (m, 3H), 5.56 (t, J = 7.4 Hz, 1H), 5.05 (dd, J = 9.4, 3.4 Hz, 1H), 3.78 (tddd, J = 10.3, 8.1, 6.1, 4.5 Hz, 2H), 2.90 (s, 1H), 2.38 – 2.20 (m, 2H), 1.93 – 1.77 (m, 1H), 1.68 – 1.49 (m, 2H), 1.49 – 1.19 (m, 4H), 0.90 (s, 9H), 0.06 (d, J = 2.2 Hz, 7H).ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.3, 140.4, 133.3, 132.7, 130.0, 128.0, 69.6, 62.1, 38.2, 32.2, 27.7, 26.0, 22.6, 18.3, 14.1, -5.3 ppm. **IR (film, $CHCl_3$)** 3461, 2955, 2929, 2858, 1710, 1489, 1470, 1255, 1091, 834, 777 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{21}H_{35}O_2ClSiNa$ [M+Na$^+$]: 405.19901, found 405.19871.

(Z)-2-(4-Chlorophenyl)hex-2-en-1-ol - (149)



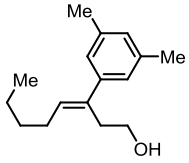
71% yield (297 mg, 1.41 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.29. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.41 – 7.36 (m, 2H), 7.33 – 7.27 (m, 2H), 5.89 (t, J = 7.5 Hz, 1H), 4.55 (d, J = 5.4 Hz, 2H), 2.26 (q, J = 7.4 Hz, 2H), 1.50 (h, J = 7.4 Hz, 2H), 1.32 (t, J = 5.5 Hz, 1H), 0.97 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 139.6, 137.9, 133.2, 132.9, 128.7, 127.7, 59.8, 30.5, 23.1, 14.0 ppm. **IR (film, $CHCl_3$)** 3339, 2958, 2871, 1491, 1378, 1093, 1011, 822 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{15}OClNa$ [M+Na$^+$]: 233.07042, found 233.07036.

8.2.3. Representative procedure 3: Suzuki cross-coupling of *in situ* generated alkenylboronic acids from homopropargyl alcohols

3-Octyn-1-ol (287 µL, 2.0 mmol, 1.0 equiv.) was dissolved in dry THF (10 mL) containing 3 Å mol sieves (200 mg per mmol substrate). The suspension was stirred at –78 °C. A solution of $ThxBH_2$ in THF (2.2 mL, 1.0 M in THF, 2.2 mmol, 1.1 equiv.) was slowly added. The mixture was allowed to warm to room temperature and stirred for 1 h. Then, neat TMAO (245 mg, 2.2 mmol, 1.1 equiv.) was added followed after 15 minutes by degassed KOH (5.0 mL, 3 M in water, 15 mmol, 7.5 equiv.), 5-iodo-*m*-xylene (377 µL, 2.6 mmol, 1.3 equiv.) and [1,1'-bis-(diphenylphosphino)-ferrocene]-palladium(II)-chloride-methylenechloride-complex (82 mg, 0.1 mmol, 5.0 mol%). The mixture was heated with a preheated oil-bath to 60 °C for 1 h before the reaction was quenched with brine at room temperature. The mixture was extracted two times with ethyl acetate, the combined organic layers were washed with brine, dried over

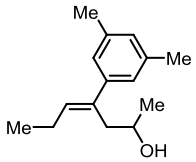
magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate) yielded pure products as a single regioisomer.

(E)-3-(3,5-Dimethylphenyl)oct-3-en-1-ol - (156)



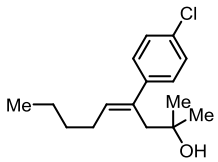
56% yield (259 mg, 1.12 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.57. **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.98 (s, 2H), 6.90 (s, 1H), 5.81 (t, J = 7.3 Hz, 1H), 3.63 (q, J = 6.7 Hz, 2H), 2.81 (t, J = 6.9 Hz, 2H), 2.33 (d, J = 0.8 Hz, 6H), 2.25 (q, J = 7.3 Hz, 2H), 1.59 – 1.51 (m, 1H), 1.51 – 1.33 (m, 4H), 0.95 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 142.8, 137.8, 136.0, 131.8, 128.6, 124.3, 61.5, 33.3, 32.2, 28.5, 22.6, 21.5, 14.2 ppm. **IR (film, $CHCl_3$)** 3318, 2955, 2921, 2871, 1599, 1463, 1039, 840, 705 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{24}ONa$ [M+Na$^+$]: 255.17184, found 255.17193.

(E)-4-(3,5-Dimethylphenyl)hept-4-en-2-ol - (157)



56% yield (243 mg, 1.11 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.29. **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.95 (s, 2H), 6.89 (s, 1H), 5.77 (dd, J = 7.7, 6.9 Hz, 1H), 3.77 (qd, J = 7.8, 6.7, 2.3 Hz, 1H), 2.71 (ddd, J = 13.8, 8.0, 0.6 Hz, 1H), 2.62 (ddd, J = 13.8, 5.2, 0.7 Hz, 1H), 2.31 (t, J = 0.7 Hz, 6H), 2.29 – 2.20 (m, 2H), 1.55 (d, J = 2.7 Hz, 1H), 1.18 (d, J = 6.2 Hz, 3H), 1.06 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 143.0, 137.9, 136.4, 133.8, 128.7, 124.5, 66.7, 39.7, 22.9, 22.2, 21.5, 14.5 ppm. **IR (film, $CHCl_3$)** 3346, 2965, 2930, 1599, 1457, 1373, 1116, 1076, 939, 847, 706 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{22}ONa$ [M+Na$^+$]: 241.15642, found 241.15628.

(E)-4-(4-Chlorophenyl)-2-methylnon-4-en-2-ol - (158)

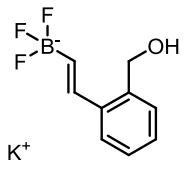


58% yield (310 mg, 1.16 mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.25. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.26 (s, 4H), 5.73 (t, J = 7.3 Hz, 1H), 2.74 (s, 2H), 2.22 (q, J = 7.2 Hz, 2H), 1.47 – 1.34 (m, 4H), 1.33 (s, 1H), 1.09 (s, 6H), 0.92 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 143.5, 135.8, 134.8, 132.5, 128.6, 128.1, 72.2, 42.9, 31.9, 30.0, 29.3, 22.6, 14.2 ppm. **IR (film, $CHCl_3$)** 3407, 2960, 2927, 2858, 1490, 1465, 1376, 1141, 1091, 1011, 900, 826 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{23}OClNa$ [M+Na$^+$]: 289.13320, found 289.13296.

8.2.4. Representative procedure 4: Synthesis of Potassium Trifluoroborates from Terminal Alkynols

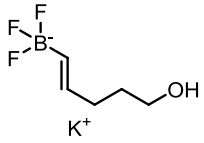
2-Methylbenzyl alcohol (264 mg, 2.0 mmol, 1.0 equiv.) was dissolved in dry THF (10 mL) and the solution stirred at −78 °C in a flame-dried Schlenk-flask under an argon atmosphere. $ThxBH_2$ solution (2.29 mL, 1.05 M in THF, 2.40 mmol, 1.2 equiv.) was slowly added and after 5 minutes the mixture was allowed to warm to room temperature. During the warm-up vigorous gas evolution was generally observed, at about −25 °C. The mixture was then allowed to stir for about 5 minutes at room temperature before solid trimethylamine-N-oxide (180 mg, 2.4 mmol, 1.2 equiv.) was added. After 10 minutes, most of the insoluble TMAO disappears while the mixture warmed up. Then water (4 mL) was added followed by solid KHF_2 (709 mg, 6.0 mmol, 3.0 equiv.) and stirring is continued at room temperature for 30 minutes before the volatile materials were removed under reduced pressure. The crude colorless solids were then extracted two times with boiling acetone/EtOH (25 mL, ~1:1) and once with acetone (25 mL), and the hot suspensions were filtered through a frit with suction. The combined extracts were dried again under reduced pressure and the solid material was recrystallized from acetone/MTBE. Organic by-products were successfully extracted with neat MTBE if necessary. By this means, analytically pure products were obtained generally as colorless, moisture and bench-stable solids.

Potassium trifluoro(1-(2-(hydroxymethyl)phenyl)vinyl)borate - (161)



85% yield (410 mg, 1.71 mmol). **^{1}H NMR (400 MHz, DMSO-d_6) δ** 7.37 (m, Ar-*H*, 2H), 7.13 (m, Ar-*H*, 2H), 6.69 (d, *J* = 18.0 Hz, CH_2, 1H), 6.07 (dq, *J* = 18.2, 3.5 Hz, CH_2, 1H), 5.04 (s, O*H*, 1H), 4.54 (s, 2H) ppm**. ^{13}C NMR (101 MHz, DMSO-d_6) δ** 141.2, 138.0, 129.4, 126.7, 126.6, 125.5, 124.4, 60.8, 58.4 ppm. **^{11}B NMR (96 MHz, DMSO-d_6) δ** 2.45 ppm. **IR (neat):** 3514, 3012, 2879, 1620, 1480, 1241, 1078, 941, 735, 550 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_9H_9OBF_3$ [M-K^+]: 201.07036, found 201.07041.

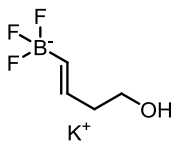
Potassium trifluoro(5-hydroxypent-1-en-2-yl)borate - (162)



68% yield (260 mg, 1.35 mmol). **^{1}H NMR (400 MHz, DMSO-d_6) δ** 5.53 – 5.36 (m, 1H), 5.28 – 5.12 (m, 1H), 4.30 (s, 1H), 3.35 (t, *J* = 6.7 Hz, 2H), 1.99 – 1.78 (m, 2H), 1.42 (dq, *J* = 8.7, 6.8 Hz, 2H) ppm**. ^{13}C NMR (101 MHz, DMSO-d_6) δ** 133.3, 133.3, 60.7, 59.1, 32.8, 31.8 ppm. **^{11}B NMR (96 MHz, DMSO-d_6) δ** 2.29

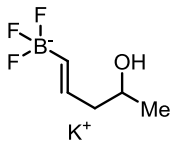
ppm. **IR (neat):** 3530, 2929, 1645, 1407, 1301, 1088, 998, 919, 750 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_5H_9OBF_3$ [M-K^+]: 153.07042, found 153.07041.

Potassium trifluoro(4-hydroxybut-1-en-2-yl)borate - (163)



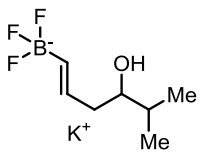
79% yield (280 mg, 1.57 mmol). **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 5.52 – 5.39 (m, 1H), 5.32 – 5.18 (m, 1H), 4.28 (s, 1H), 3.34 (t, *J* = 7.4 Hz, 2H), 2.13 – 1.98 (m, 2H) ppm**. ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** 130.2, 130.1, 61.5, 58.7 ppm. **^{11}B NMR (96 MHz, DMSO-*d*$_6$) δ** 2.09 ppm. **IR (neat):** 3517, 2945, 1651, 1401, 1243, 1089, 997, 940, 729, 592 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_4H_7OBF_3$ [M-K^+]: 139.05475, found 139.05476.

Potassium trifluoro(4-hydroxypent-1-en-2-yl)borate - (164)



83% yield (320 mg, 1.67 mmol). **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 5.52 – 5.41 (m, 1H), 5.28 – 5.18 (m, 1H), 4.29 (s, 1H), 3.52 (q, *J* = 6.3 Hz, 1H), 2.12 – 2.00 (m, 1H), 1.91 – 1.80 (m, 1H), 0.98 (d, *J* = 6.1 Hz, 3H) ppm**. ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** 130.8, 130.7, 66.6, 46.4, 23.1 ppm. **^{11}B NMR (96 MHz, DMSO-*d*$_6$) δ** 2.07 ppm. **IR (neat):** 3317, 2966, 1644, 1295, 1091, 970, 848, 737, 590 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_5H_9OBF_3$ [M-K^+]: 153.07041, found 153.07041.

Potassium trifluoro(4-hydroxy-5-methylhex-1-en-2-yl)borate - (165)

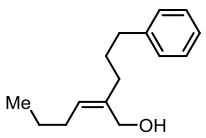


93% yield (410 mg, 1.86 mmol). **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 5.50 (dtd, *J* = 17.7, 6.5, 1.4 Hz, 1H), 5.30 – 5.15 (m, 1H), 4.01 (d, *J* = 5.2 Hz, 1H), 3.16 (tdd, *J* = 5.9, 5.1, 3.8 Hz, 1H), 1.96 (tdt, *J* = 6.9, 4.6, 1.4 Hz, 2H), 1.55 (pd, *J* = 6.8, 4.4 Hz, 1H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H) ppm**. ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** 131.0, 74.8, 41.3, 31.8, 19.5, 16.6 ppm. **^{11}B NMR (96 MHz, DMSO-*d*$_6$) δ** 2.05 ppm. **IR (neat):** 3548, 2959, 1645, 1468, 1289, 1091, 927, 738 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_7H_{13}OBF_3$ [M-K^+]: 181.10168, found 181.10171.

8.2.5. Representative procedure 5: Alkyl Suzuki Cross-Coupling of *in situ* Generated Alkenylboronic Acids from Propargyl Alcohols

2-Hexyn-1-ol (110 µL, 1.0 mmol, 1.0 equiv.) was dissolved in dry THF (1 mL) equipped with 3 Å mol sieves (200 mg per mmol substrate) and the suspension stirred in an oven-dried Schlenk flask under an argon atmosphere. Methyl trifluoropyruvate (167 µL, 1.25 mmol, 1.25 equiv.) was added and stirring continued at room temperature until disappearance of starting material was judged by TLC (hexanes/ethyl acetate, 4:1). Then the mixture was cooled to −78 °C before a solution of $ThxBH_2$ in THF (1.34 mL, 0.93 M in THF, 1.25 mmol, 1.25 equiv.) was slowly added. The mixture was allowed to warm to room temperature and stirred for 1 h. Then neat TMAO hydrate (117 mg, 1.05 mmol, 1.05 equiv.) was added followed after 15 minutes by degassed KOH (2.5 mL, 7.5 mmol, 3M in water, 7.5 equiv.), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5.0 mol%), di-*tert*-butyl-(methyl)-phosphonium-tetrafluoroborate (25 mg, 0.1 mmol, 10 mol%) and 1-bromo-3-phenylpropane (304 µL, 2.0 mmol, 2.0 equiv.). The mixture was stirred for 12 h at room temperature before the reaction was quenched with brine at room temperature. The mixture was extracted two times with ethyl acetate, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate) yielded pure product as a single regioisomer.

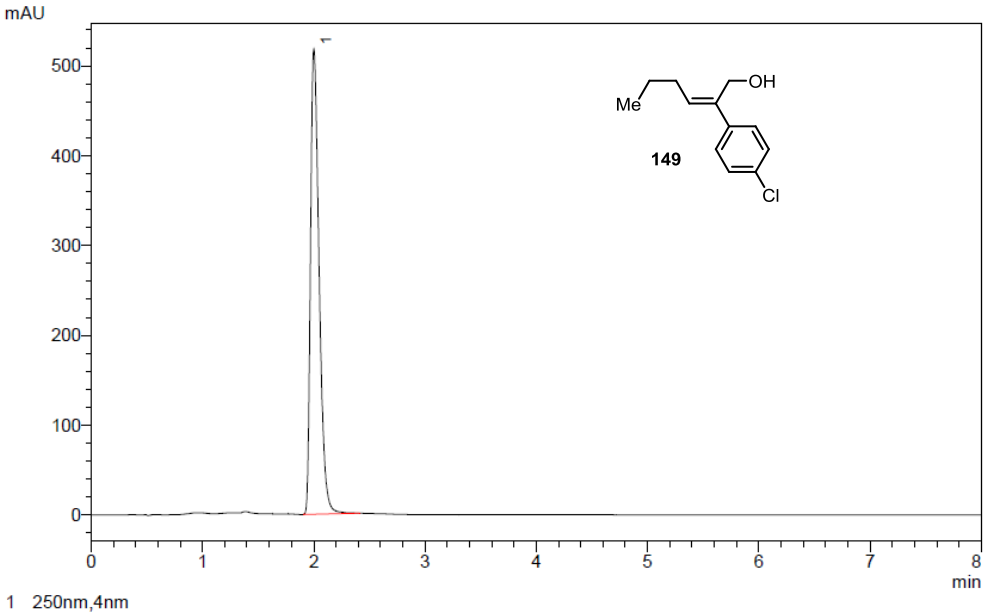
(Z)-2-(3-Phenylpropyl)hex-2-en-1-ol - (167)



61% yield (132mg, 0.61mmol). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.21. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.31 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 5.33 (t, J = 7.5 Hz, 1H), 4.15 (d, J = 3.3 Hz, 2H), 2.66 – 2.57 (m, 2H), 2.21 – 2.14 (m, 2H), 2.10 – 2.02 (m, 2H), 1.83 – 1.73 (m, 2H), 1.38 (h, J = 7.3 Hz, 2H), 1.08 (d, J = 4.8 Hz, 1H), 0.90 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 142.7, 138.3, 129.2, 128.6, 128.4, 125.8, 60.4, 35.8, 34.9, 30.3, 29.7, 23.3, 13.9 ppm. **IR (film, $CHCl_3$)** 3324, 2929, 2957, 2860, 1496, 1454, 1377, 1008, 898, 746, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{22}ONa$ [M+Na^+]: 241.15642, found 241.15628.

8.2.6. Studies on the Regioselectivity of Hydroxyl-directed Hydroboration

Pure product after flash chromatography

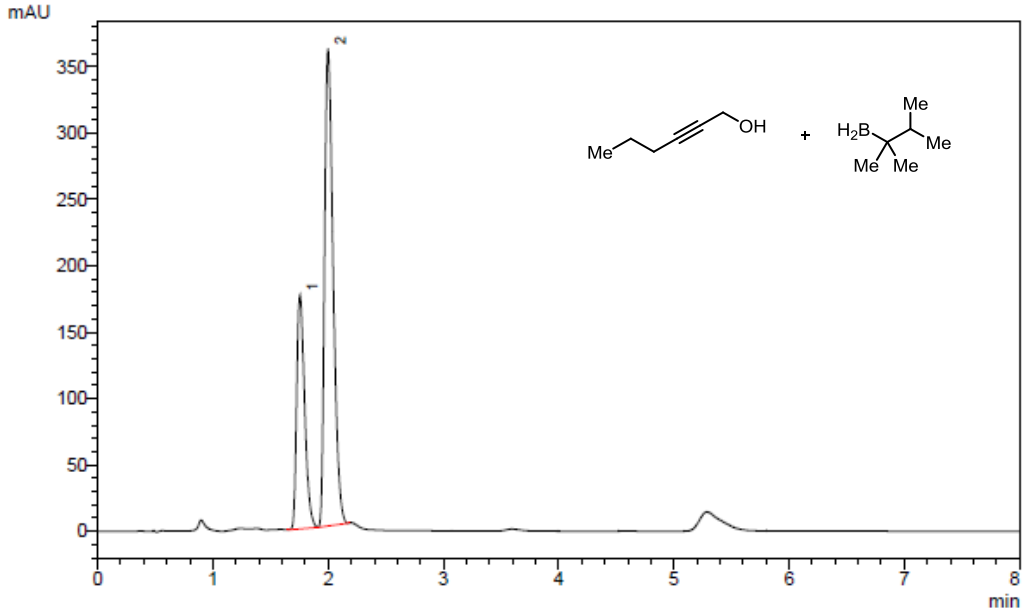


1 250nm,4nm

PDA Ch1 250nm

Peak #	Ret. Time	Area %
1	2,00	100,00
Total		100,00

Hydroboration with thexylborane in the absence of trifluoromethylpyruvate

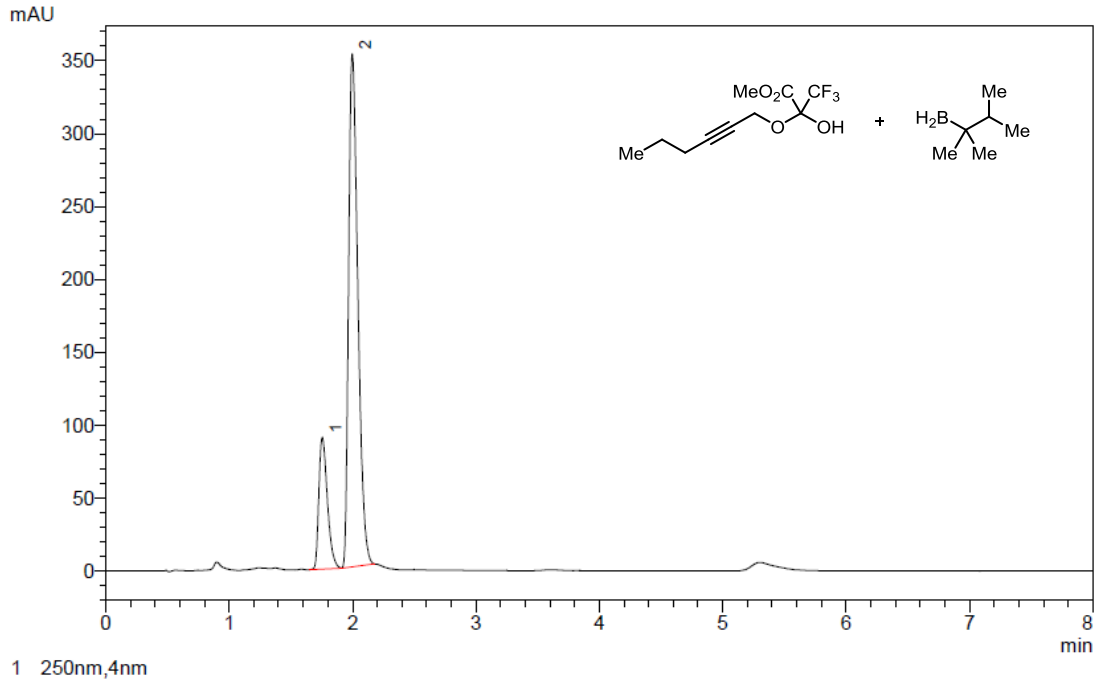


1 250nm,4nm

PDA Ch1 250nm

Peak #	Ret. Time	Area %
1	1,76	31,20
2	2,00	68,80
Total		100,00

Hydroboration with thexylborane under standard conditions

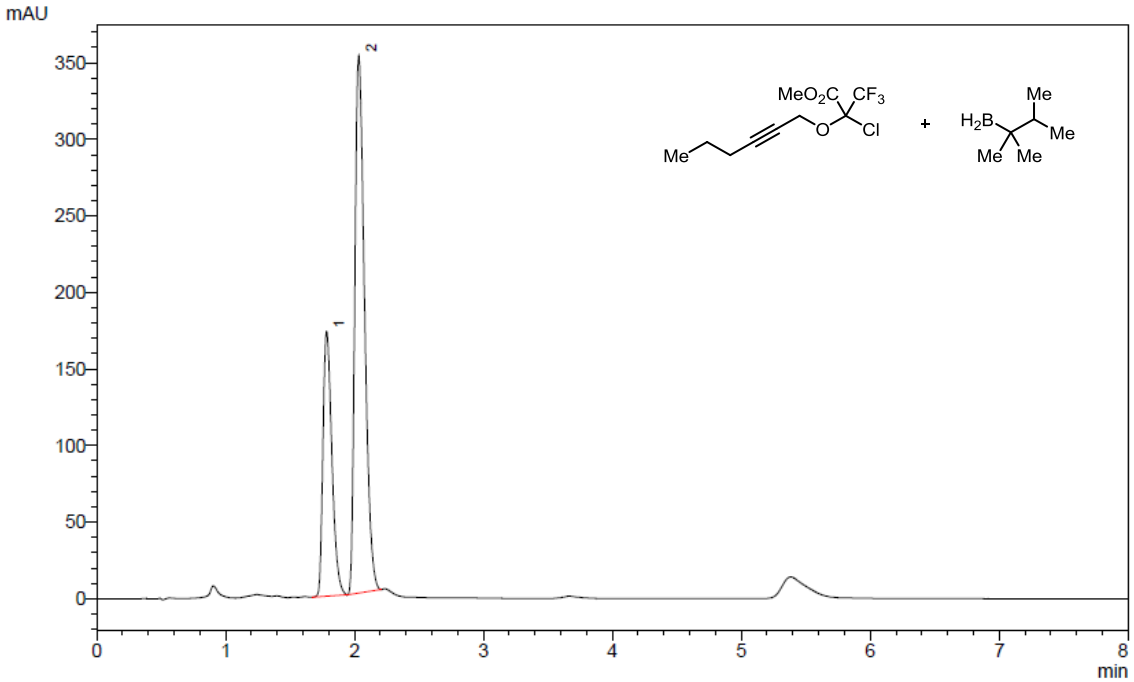


1 250nm,4nm

PDA Ch1 250nm

Peak #	Ret. Time	Area %
1	1,75	19,19
2	2,00	80,81
Total		100,00

Hydroboration with thexylborane of chlorohemiacetal



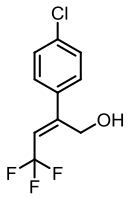
1 250nm,4nm

PDA Ch1 250nm

Peak #	Ret. Time	Area %
1	1,78	31,26
2	2,03	68,74
Total		100,00

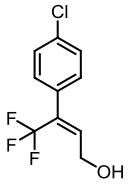
All compounds were prepared according to representative procedure 2.

(Z)-2-(4-Chlorophenyl)-4,4,4-trifluorobut-2-en-1-ol - (SI-1)



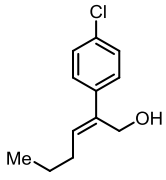
21% yield (100 mg, 0.42 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.74. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.37 – 7.30 (m, 2H), 7.29 – 7.22 (m, 2H), 6.19 (t, J = 5.6 Hz, 1H), 4.58 (dq, J = 5.8, 2.9 Hz, 2H), 2.30 (s, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.2 (q, J = 2.7 Hz), 134.8 (s), 133.7 (d, J = 1.7 Hz), 130.2 (q, J = 31.3 Hz), 129.4 (s), 128.8 (s), 123.5 (q, J = 275.5 Hz), 59.6 (q, J = 3.7 Hz) ppm. **IR (film, $CHCl_3$)** 3368, 1651, 1493, 1340, 1257, 1110, 1012, 815, 711 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{10}H_8OClF_3$ [M]: 236.02138, found 236.02158.

(Z)-3-(4-Chlorophenyl)-4,4,4-trifluorobut-2-en-1-ol - (SI-2)



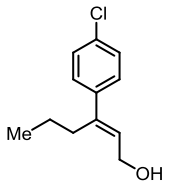
18% yield (85 mg, 0.36 mmol). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.48. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.37 – 7.30 (m, 2H), 7.29 – 7.22 (m, 2H), 6.19 (t, J = 5.6 Hz, 1H), 4.58 (dq, J = 5.8, 2.9 Hz, 2H), 2.30 (s, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.2 (q, J = 2.7 Hz), 134.8 (s), 133.7 (d, J = 1.7 Hz), 130.2 (q, J = 31.3 Hz), 129.4 (s), 128.8 (s), 123.5 (q, J = 275.5 Hz), 59.6 (q, J = 3.7 Hz) ppm. **IR (film, $CHCl_3$)** 3344, 2958, 2873, 1595, 1493, 1365, 1198, 1161, 1118, 1092, 1016, 908, 823, 624 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{10}H_8OClF_3$ [M]: 236.02138, found 236.02158.

(Z)-2-(4-Chlorophenyl)hex-2-en-1-ol - (SI-3)

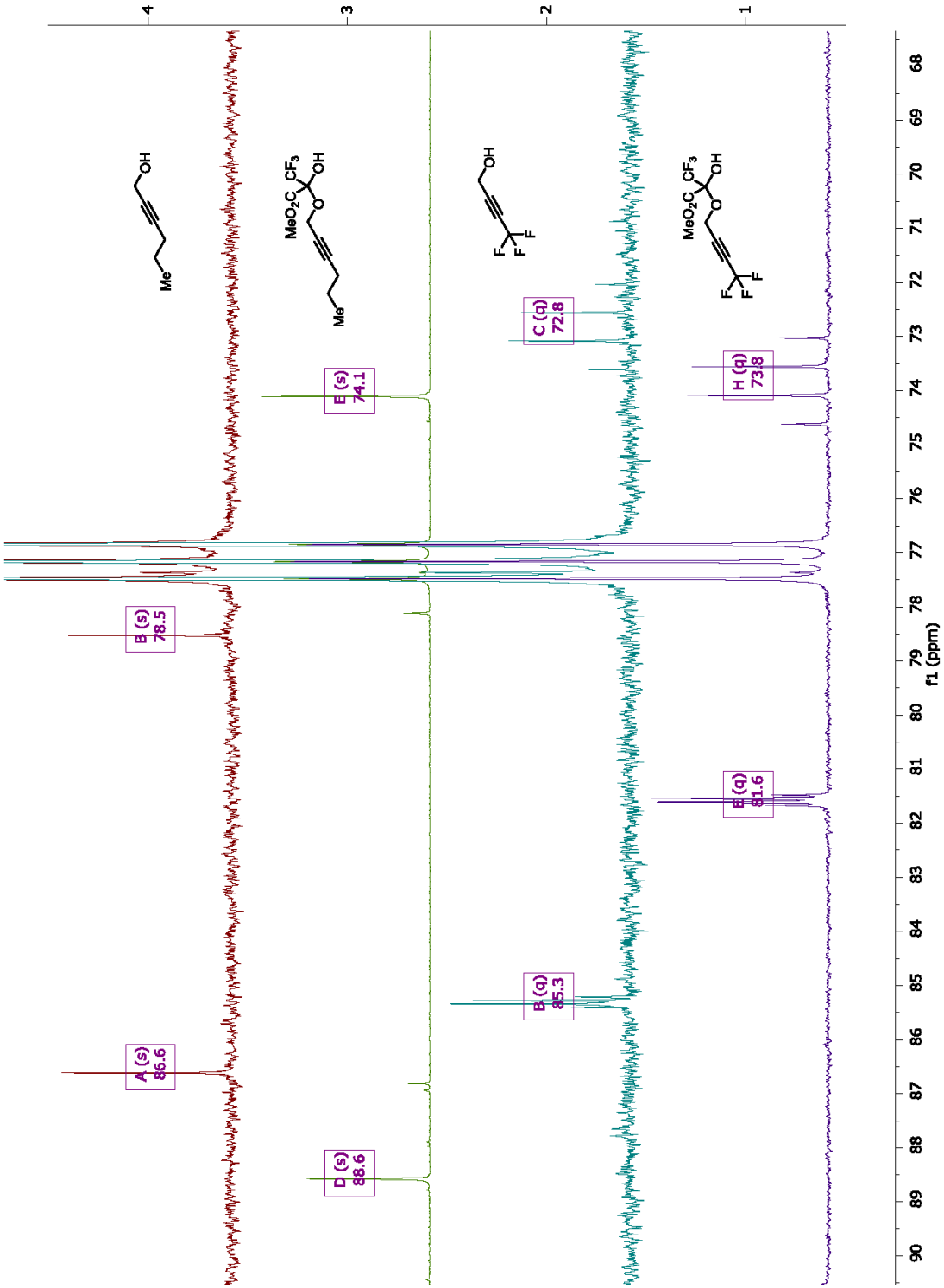


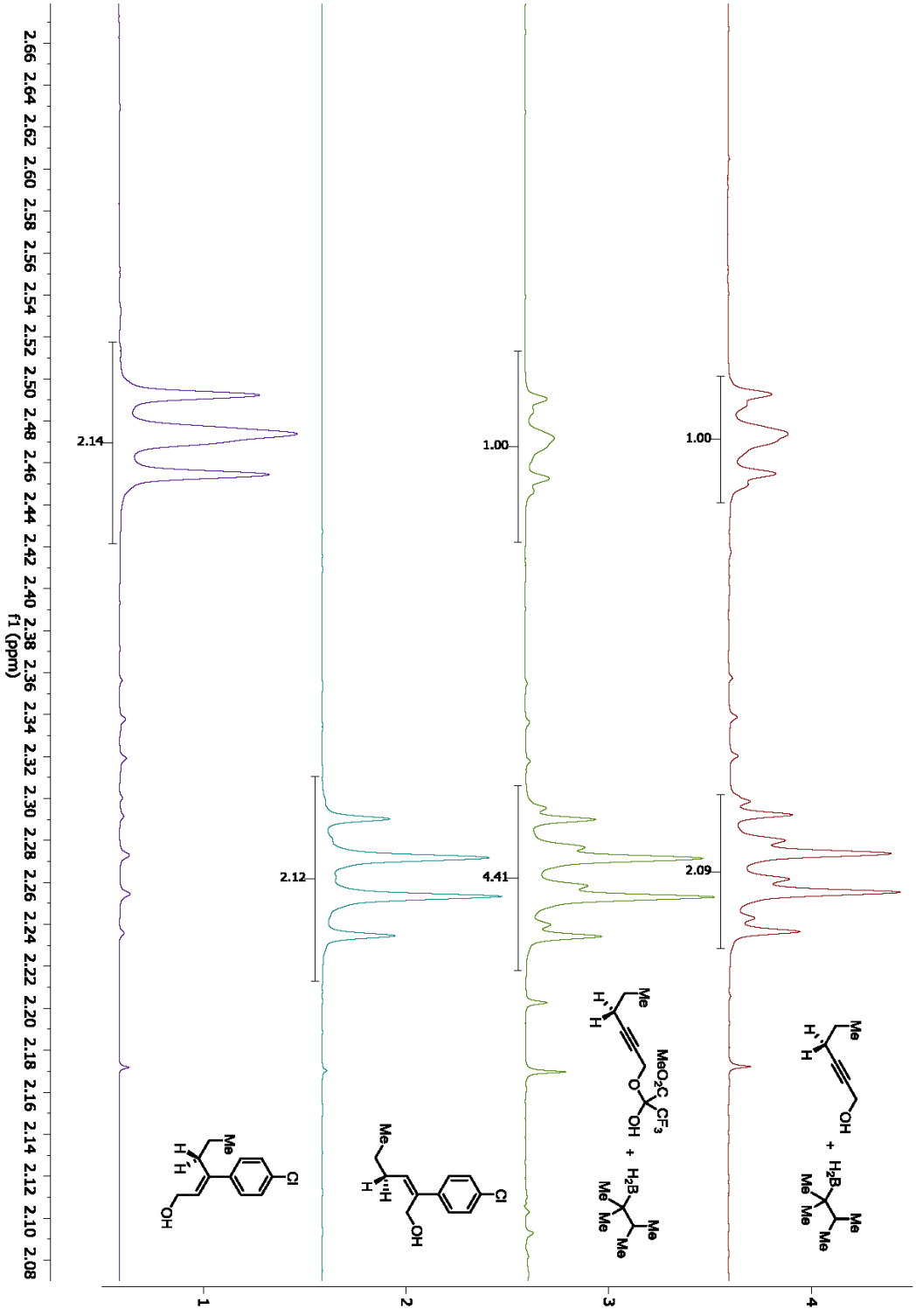
^{1}H NMR (400 MHz, Chloroform-d) δ 7.29 (s, 4H), 5.87 – 5.80 (m, 1H), 4.34 (dd, J = 7.0, 3.0 Hz, 2H), 2.51 – 2.43 (m, 2H), 1.41 – 1.29 (m, 3H), 0.87 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 142.2, 140.8, 133.1, 128.6, 127.9, 127.8, 59.8, 32.0, 22.0, 13.9 ppm. **IR (film, $CHCl_3$)** 3327, 2958, 2930, 2871, 1491, 1093, 1011, 821 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{15}OCl$ [M]: 210.08090, found 210.08114.

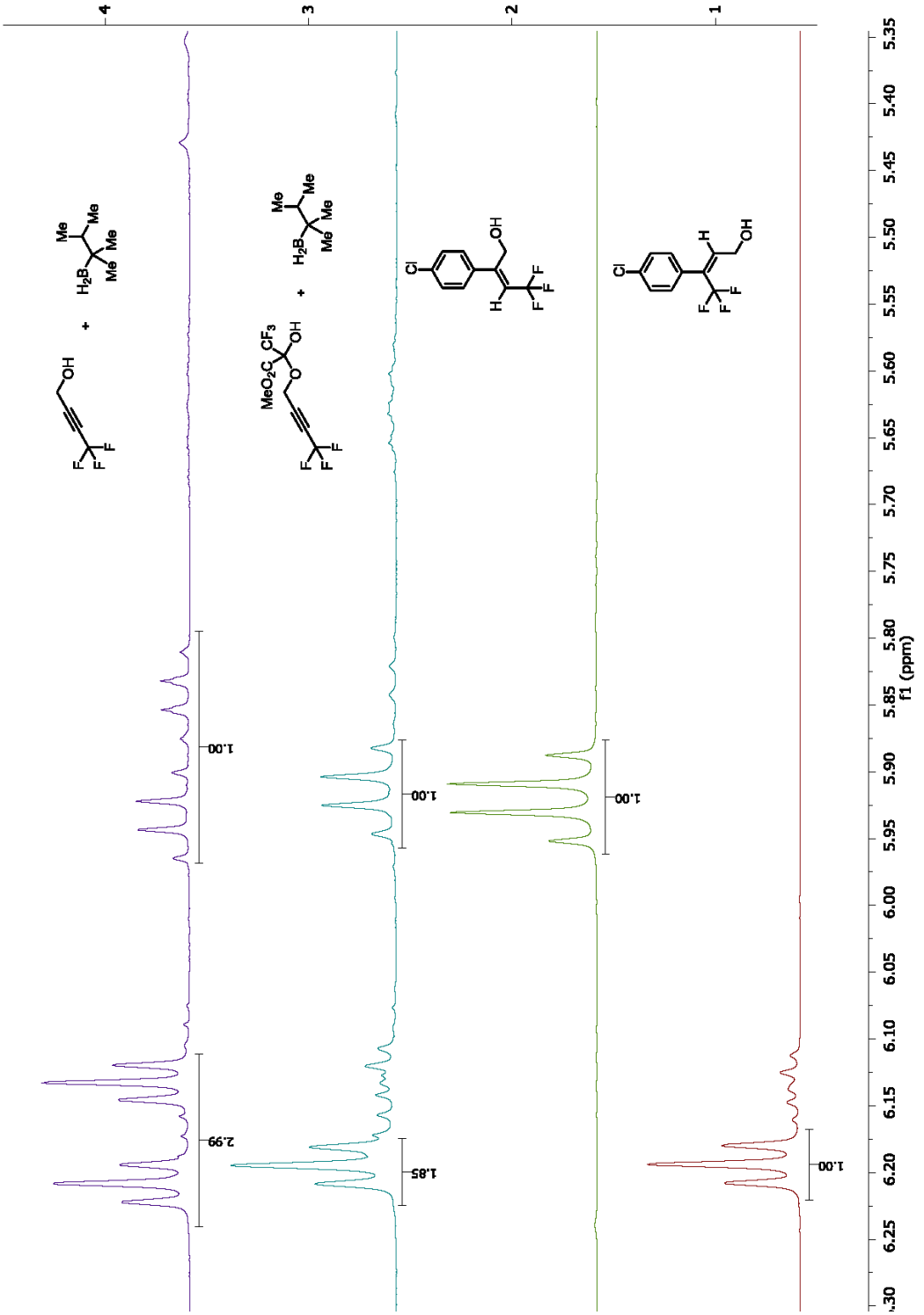
(E)-3-(4-Chlorophenyl)hex-2-en-1-ol - (SI-4)



^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.36 (m, 2H), 7.32 – 7.27 (m, 2H), 5.89 (t, J = 7.5 Hz, 1H), 4.55 (d, J = 4.8 Hz, 2H), 2.26 (q, J = 7.4 Hz, 2H), 1.50 (h, J = 7.4 Hz, 2H), 1.39 – 1.30 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 139.7, 138.0, 133.2, 132.9, 128.7, 127.7, 59.8, 30.5, 23.1, 14.0 ppm. **IR (film, $CHCl_3$)** 3327, 2959, 2931, 2871, 1491, 1091, 1012, 823 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{12}H_{15}OCl$ [M]: 210.08091, found 210.08114.


A (s) 86.6
B (s) 78.5
D (s) 88.6
E (s) 74.1
B (q) 85.3
C (q) 72.8
E (q) 81.6
H (q) 73.8
f1 (ppm)


2.66 2.64 2.62 2.60 2.58 2.56 2.54 2.52 2.50 2.48 2.46 2.44 2.42 2.40 2.38 2.36 2.34 2.32 2.30 2.28 2.26 2.24 2.22 2.20 2.18 2.16 2.14 2.12 2.10 2.08
f1 (ppm)
2.14
2.12
1.00
4.41
1.00
2.09
Me
H
H
OH
Cl
Me
H
H
OH
Cl
Me
H
H
O
OH
MeO2C
CF3
+
H2B
Me
Me
Me
Me
Me
H
H
OH
+
H2B
Me
Me
Me
Me
1
2
3
4

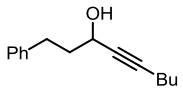

4
3
2
1
1.00
2.99
1.00
1.85
1.00
1.00
f1 (ppm)

Synthesis of starting materials

8.2.7. Representative procedure 6: Synthesis of Propargyl Alcohols from Aldehydes and Ketones

A flame-dried 250 mL two-necked flask was equipped with a dropping funnel and charged with dry THF (100 ml) and 1-hexyne (6.61 mL, 57.5 mmol, 1.2 equiv.), and cooled with a dry-ice bath. *n*-Butyllithium (34.4 mL, 1.6 M in hexanes, 55 mmol, 1.1 equiv.) was slowly added via the dropping funnel and stirring was continued for 1 h before neat hydrocinnamaldehyde (6.58 mL, 50 mmol, 1.0 equiv.) was added in one portion. After being stirred for 30 minutes, the dry-ice bath was removed and the mixture allowed to warm to room temperature. The reaction was quenched with saturated ammonium chloride solution, the mixture extracted two times with MTBE, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Pure products were obtained after flash chromatography (SiO_2, hexanes/ethyl acetate).

1-Phenylnon-4-yn-3-ol - (SI-5)



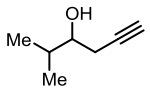
99% yield (10.7 g, 49.5 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.33 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 4.37 (tt, J = 6.4, 2.0 Hz, 1H), 2.80 (t, J = 7.9 Hz, 2H), 2.24 (td, J = 7.0, 2.0 Hz, 2H), 2.01 (tt, J = 7.8, 6.2 Hz, 2H), 1.62 – 1.48 (m, 2H), 1.48 – 1.35 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.6, 128.6, 128.5, 126.0, 86.1, 81.1, 62.2, 39.8, 31.6, 30.8, 22.1, 18.5, 13.7 ppm. **IR (film, $CHCl_3$)** 3338, 3027, 2955, 2931, 2861, 1603, 1496, 1454, 1379, 1328, 1134, 1030 1054, 914, 746, 699 cm^{-1}.
Analytical data in accordance with literature[15].

8.2.8. Representative procedure 7: Propargylation of Carbonyl Compounds with Propargyl Bromide[20]

Magnesium turnings (1.6 g, 66 mmol, 1.58 equiv.) and $HgCl_2$ (135 mg, 0.25 mmol, 1.0 mol%) were placed in an oven-dried two-necked flask equipped with a reflux condenser and stirred under an argon atmosphere. Diethyl ether (120 mL) was added followed by dropwise addition of propargyl bromide (6.68 mL, 80 wt% in toluene, 60 mmol, 1.2 equiv.). The mixture started to reflux and stirring was continued until almost all of the magnesium turnings were dissolved. Then *iso*-butyraldehyde (3.8 mL, 42 mmol, 1.0 equiv.) was added dropwise and stirring continued with the conversion monitored by TLC (hexanes/ethyl acetate, 4:1). After complete

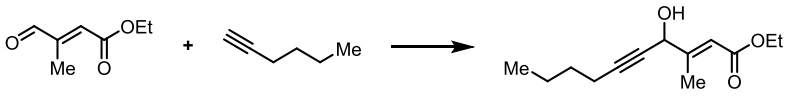
consumption of the carbonyl compound the reaction was carefully quenched with saturated ammonium chloride solution and the pH brought to 1 with 2 M HCl. The mixture was extracted three times with MTBE, the combined extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a crude oil.

2-Methylhex-5-yn-3-ol - (SI-6)



64% yield (3.0 g, 26.7 mmol). **B.p.** (0.1 mbar, 65-70 °C). **^{1}H NMR (400 MHz, Chloroform-d) δ** 3.45 (ddd, J = 7.4, 6.1, 4.5 Hz, 1H), 2.38 (ddd, J = 16.8, 4.5, 2.6 Hz, 1H), 2.29 (ddd, J = 16.7, 7.4, 2.7 Hz, 1H), 2.01 (t, J = 2.7 Hz, 1H), 1.75 (dq, J = 13.5, 6.8 Hz, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 81.4, 74.7, 70.6, 32.7, 24.7, 18.8, 17.6 ppm. **IR (film, $CHCl_3$)** 3411, 3306, 2962, 2875, 1674, 1469, 1386, 1253, 1126, 1046, 999, 858, 627 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_7H_{12}ONa$ [M+Na+]: 135.078120, found 135.078034.

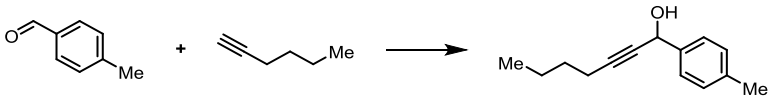
Ethyl (E)-4-hydroxy-3-methyldec-2-en-5-ynoate - (SI-7)



1-Hexyne (2.30 mL, 30 mmol, 1.0 equiv.) was dissolved in dry THF (40 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere at −78 °C. *n*-Butyllithium (13.8 mL, 1.6 M in hexanes, 22 mmol, 1.1 equiv.) was slowly added and stirring continued for 30 minutes at the same temperature before ethyl (E)-3-methyl-4-oxobut-2-enoate (3.0 mL, 22 mmol, 1.1 equiv.) was added in one portion under vigorous stirring which was continued for 10 minutes. The reaction was then quenched with saturated ammonium chloride solution. Aqueous HCl (2 M) was added until all solids were completely dissolved. The mixture was extracted two times with MTBE, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 9:1 to 6:1 to 4:1) yielded the product as a pale yellow oil (3.87 g, 17.3 mmol, 86% yield). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.58. **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.06 (p, J = 1.3 Hz, 1H), 4.77 (q, J = 1.8 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.26 – 2.15 (m, 5H), 1.56 – 1.42 (m, 2H), 1.42 – 1.30 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.9, 155.9, 116.0, 87.8, 78.1, 67.2, 60.1, 30.6, 22.1,

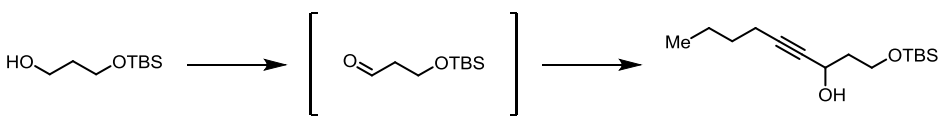
18.5, 15.2, 14.4, 13.7 ppm. **IR (film, $CHCl_3$)** 3434, 2959, 2934, 2873, 1717, 1699, 1657, 1432, 1368, 1295, 1210, 1146, 1040, 876 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{13}H_{18}O_3Na$ [M+Na^+]: 245.11484, found 245.11481.

1-(*p*-Tolyl)hept-2-yn-1-ol - (SI-8)



1-Hexyne (2.52 mL, 22 mmol, 1.1 equiv.) was dissolved in dry THF (40 mL) and the solution stirred in an oven-dried Schlenk flask at −78 °C under an argon atmosphere. *n*-Butyllithium (13.1 mL, 1.6 M in hexanes, 21 mmol, 1.05 equiv.) was slowly added and stirring continued for 30 minutes before 4-methylbenzaldehyde (2.37 mL, 20 mmol, 1.0 equiv.) was added. The conversion was monitored by TLC (hexanes/ethyl acetate, 4:1). After about 15 minutes, TLC showed complete consumption of starting material so the reaction was quenched with the addition of saturated ammonium chloride solution. Aqueous HCl (2 M) was slowly added until all solids had been dissolved. The mixture was extracted two times with MTBE, the combined organic layer were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 20:1 to 10:1) yielded the product as a colorless oil (1.13 g, 5.6 mmol, 28% yield). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.27. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.47 – 7.40 (m, 2H), 7.22 – 7.15 (m, 2H), 5.42 (dt, J = 5.8, 2.0 Hz, 1H), 2.36 (s, 3H), 2.28 (td, J = 7.1, 2.0 Hz, 2H), 2.11 (d, J = 5.6 Hz, 1H), 1.59 – 1.48 (m, 2H), 1.48 – 1.36 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 138.6, 138.1, 129.33, 126.7, 87.6, 80.1, 64.8, 30.8, 22.1, 21.3, 18.7, 13.7 ppm. **IR (film, $CHCl_3$)** 3366, 2957, 2931, 2871, 1512, 1457, 1378, 1178, 1133, 992, 819, 757 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{14}H_{18}ONa$ [M+Na^+]: 225.12498, found 225.12498.

1-((*tert*-Butyldimethylsilyl)oxy)non-4-yn-3-ol - (SI-9)

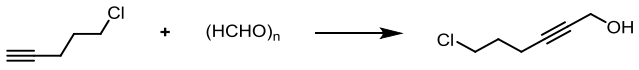


$(COCl)_2$ (1.99 mL, 23.2 mmol, 1.16 equiv.) was dissolved in CH_2Cl_2 (50 mL) and the solution stirred at −60 °C in a flame-dried Schlenk flask. DMSO (3.41 mL, 48 mmol, 2.4 equiv.) in CH_2Cl_2

(10 mL) was added to the reaction mixture. After 5 minutes, 3-(*tert*-butyl-dimethyl-silanyloxy)-propan-1-ol (3.81 g, 20 mmol, 1.0 equiv.) was added dropwise at −60 °C followed by dropwise addition of Et_3N (14.1 mL, 101 mmol, 5.1 equiv.). The mixture was allowed to warm to room temperature and the reaction was quenched with water (100 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, water and a second time with brine before being dried over magnesium sulfate. The solvents were removed under reduced pressure, the mixture was dissolved in diethyl ether, filtered over Celite® and the ether was removed under reduced pressure. The crude product was used without further purification for the next step.

1-Hexyne (1.38 mL, 12 mmol, 1.2 equiv.) was dissolved in dry THF (25 mL) and the solution stirred in an oven-dried Schlenk flask on a dry-ice bath under an argon atmosphere. *n*-Butyllithium (7.5 mL, 1.6 M in hexanes, 12 mmol, 1.2 equiv.) was added and stirring continued for 1 h at the same temperature before freshly prepared 3-((*tert*-butyldimethyl-silyl)oxy)propanal (1.88 g, 10 mmol, 1.0 equiv.) was introduced. After 1 h, the mixture was allowed to warm to room temperature and the reaction was quenched with the addition of saturated ammonium chloride solution. The mixture was extracted two times with ethyl acetate, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 10:1) yielded the product as a pale yellow oil (2.29 g, 8.5 mmol, 85% yield). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.26. **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.54 (tt, J = 4.3, 2.2 Hz, 1H), 3.97 (ddd, J = 10.2, 7.6, 4.2 Hz, 1H), 3.77 (ddd, J = 10.4, 6.2, 4.5 Hz, 1H), 3.37 (s, 1H), 2.17 (td, J = 7.0, 2.0 Hz, 2H), 1.91 (ddt, J = 14.1, 7.6, 4.5 Hz, 1H), 1.80 (dtd, J = 14.1, 6.3, 4.2 Hz, 1H), 1.53 – 1.29 (m, 4H), 0.89 – 0.83 (m, 12H), 0.04 (s, 3H), 0.04 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 85.4, 80.7, 61.9, 61.2, 39.2, 30.8, 25.9, 22.0, 18.5, 18.2, 13.7, -5.5 ppm. **IR (film, $CHCl_3$)** 2955, 2929, 2858, 1470, 1253, 1099, 1006, 939, 832, 775 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{30}O_2SiNa$ [M+Na^+]: 293.19070, found 293.19073.

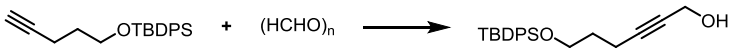
6-Chlorohex-2-yn-1-ol - (SI-10)



5-Chloro-1-pentyne (2.14 mL, 20 mmol, 1.0 equiv.) was dissolved in dry THF (20 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere at −78 °C. *n*-Butyllithium (12.5 mL, 1.6 M in hexanes, 20 mmol, 1.0 equiv.) was added dropwise and the

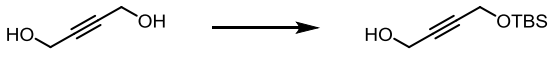
mixture placed on an ice bath for 15 minutes. Then, paraformaldehyde (1.62 g, 54 mmol, 2.7 equiv.) was added in one portion and the mixture was warmed to 45 °C for 2 h with an oil bath. After being cooled again to room temperature, saturated ammonium chloride solution was added. The mixture was extracted two times with MTBE, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/MTBE, 3:1) yielded the product as a colorless oil (2.15 g, 15.4 mmol, 77% yield). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.28. **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.25 (t, J = 2.2 Hz, 2H), 3.65 (t, J = 6.3 Hz, 2H), 2.42 (tt, J = 6.8, 2.2 Hz, 2H), 1.96 (p, J = 6.6 Hz, 2H), 1.83 – 1.74 (m, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 84.5, 79.5, 51.4, 43.8, 31.3, 16.3 ppm. **IR (film, $CHCl_3$)** 3340, 2918, 1433, 1290, 1131, 1010, 859, 726, 652 cm^{-1}. **HRMS (ESI):** *m/z* calculated for C_6H_9OClNa [M+Na^+]: 155.02346, found 155.02341.

6-((*tert*-Butyldiphenylsilyl)oxy)hex-2-yn-1-ol - (SI-11)



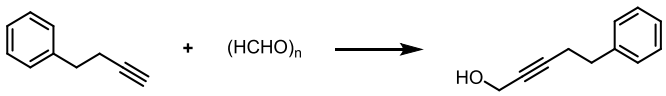
tert-Butyl(pent-4-yn-1-yloxy)diphenylsilane (3.23 g, 10 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. *n*-Butyllithium (6.56 mL, 1.6 M in hexanes, 10.5 mmol, 1.05 equiv.) was added dropwise and the mixture placed on an ice bath for 15 minutes. Then, paraformaldehyde (811 mg, 27 mmol, 2.7 equiv.) was added in one portion and the mixture was stirred for 18 h at room temperature. The reaction was then quenched with saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, pentane/ethyl acetate, 4:1) yielded the product as a colorless oil (1.72 g, 4.9 mmol, 49% yield). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.44. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.73 – 7.63 (m, 4H), 7.47 – 7.35 (m, 6H), 4.21 (t, J = 2.2 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 2.38 (tt, J = 7.1, 2.2 Hz, 2H), 1.76 (tt, J = 7.1, 5.9 Hz, 2H), 1.49 (s, 1H), 1.06 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 135.7, 133.9, 129.7, 127.8, 86.2, 78.6, 62.4, 51.5, 31.6, 27.0, 19.4, 15.4 ppm. **IR (film, $CHCl_3$)** 3343, 2930, 2857, 1472, 1427, 1104, 1007, 972, 822, 700, 613, 504 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{22}H_{28}O_2SiNa$ [M+Na^+]: 375.17508, found 375.17508.

4-((*tert*-Butyldimethylsilyl)oxy)but-2-yn-1-ol - (SI-12)



But-2-yne-1,4-diol (8.61 g, 100 mmol, 4.0 equiv.), 1H-imidazole (2.04 g, 30 mmol, 1.2 equiv.) and catalytic amounts of DMAP were dissolved in THF (45 mL) and the solution stirred in an oven-dried two-necked flask equipped with a dropping funnel at room temperature. *tert*-Butylchlorodimethylsilane (3.77 g, 25 mmol, 1.0 equiv.) dissolved in THF (20 mL) was added dropwise over 15 minutes and stirring continued for 5 h at room temperature before the reaction was quenched with the addition of water. The mixture was extracted two times with ethyl acetate, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 4:1) yielded the product as a yellowish oil (4.91 g, 24.5 mmol, 98% yield). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.27. **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.35 (t, J = 1.8 Hz, 2H), 4.30 (dt, J = 6.2, 1.8 Hz, 2H), 1.62 – 1.56 (m, 1H), 0.90 (d, J = 2.9 Hz, 9H), 0.12 (d, J = 2.9 Hz, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 84.6, 83.1, 51.9, 51.4, 26.0, 18.5, -5.0.ppm. **IR (film, $CHCl_3$)** 3358, 2954, 2929, 2858, 1472, 1362, 1254, 1130, 1079, 1008, 831, 775 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{10}H_{20}O_2SiNa$ [M+Na^+]: 223.11251, found 223.11248.

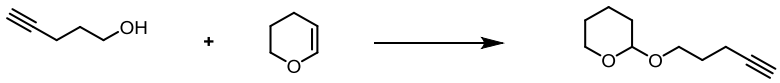
5-Phenylpent-2-yn-1-ol - (SI-13)



But-3-yn-1-ylbenzene (1.41 mL, 10 mmol, 1.0 equiv.) was dissolved in THF (25 mL) and stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. *n*-Butyllithium (6.88 mL, 1.6 M in hexanes, 11 mmol, 1.1 equiv.) was added dropwise and the mixture placed on an ice bath for 60 minutes. Then, paraformaldehyde (811 mg, 27 mmol, 2.7 equiv.) was added in one portion and the mixture was stirred for 18 h at room temperature. The reaction was then quenched with saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, pentane/ethyl acetate, 4:1) yielded the product as a colorless oil (1.35 g, 8.4 mmol, 84% yield). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.21. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.35 – 7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 4.23 (t, J = 2.2 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H), 2.52 (tt, J = 7.5, 2.1 Hz, 2H), 1.70 (s, 1H) ppm.

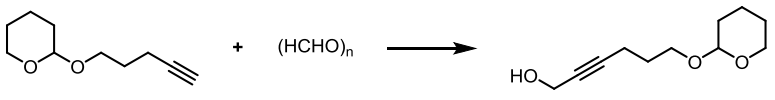
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 128.5, 128.5, 126.4, 85.8, 79.2, 51.4, 35.1, 21.0 ppm. **IR (film, $CHCl_3$)** 3335, 3027, 2927, 2863, 1496, 1453, 1132, 1008, 744, 697, 504 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{11}H_{12}ONa$ [M+Na^+]: 183.07807, found 183.07803.

2-(Pent-4-yn-1-yloxy)tetrahydro-2*H*-pyran - (SI-14)



Pent-4-yn-1-ol (1.86 mL, 20 mmol, 1.0 equiv.) and 3,4-dihydro-2H-pyran (2.01 mL, 22 mmol, 1.1 equiv.) were dissolved in dry CH_2Cl_2 (30 mL) and the solution stirred in a single-necked flask at room temperature. A few crystals of PTSA were added and stirring was continued for 18 h. The reaction was quenched with the addition of water, the mixture was extracted twice with CH_2Cl_2, the combined organic layers were washed with aqueous NaOH (2 M), dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 20:1) yielded the product as a colorless oil (2.87 g, 17.0 mmol, 85% yield). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.64. **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.59 (dd, J = 4.3, 2.7 Hz, 1H), 3.93 – 3.76 (m, 2H), 3.58 – 3.40 (m, 2H), 2.31 (tdd, J = 6.9, 2.6, 1.0 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.82 (tt, J = 7.1, 6.2 Hz, 3H), 1.75 – 1.64 (m, 1H), 1.64 – 1.45 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 98.9, 84.1, 68.6, 65.9, 62.4, 30.8, 28.8, 25.6, 19.7, 15.5 ppm. **IR (film, $CHCl_3$)** 3296, 2941, 2871, 1441, 1354, 1199, 1120, 1061, 1033, 992, 868, 627 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{10}H_{16}O_2Na$ [M+Na^+]: 191.10430, found 191.10425.

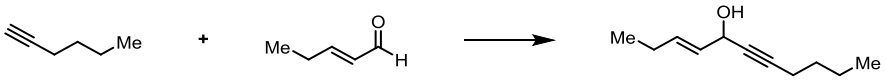
6-((Tetrahydro-2*H*-pyran-2-yl)oxy)hex-2-yn-1-ol - (SI-15)



2-(Pent-4-yn-1-yloxy)tetrahydro-2H-pyran (2.87 g, 17.0 mmol, 1.0 equiv.) was dissolved in THF (50 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. *n*-Butyllithium (11.7 mL, 1.6 M in hexanes, 18.7 mmol, 1.1 equiv.) was added dropwise and the mixture placed on an ice bath for 60 minutes. Then, paraformaldehyde (1.38 g, 45.9 mmol, 2.7 equiv.) was added in one portion and the mixture was stirred for 18 h at room temperature. The reaction was then quenched with saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined organic layers were washed with

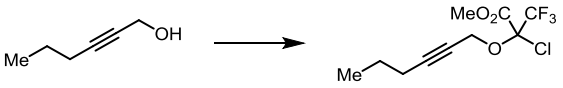
brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, pentane/ethyl acetate, 3:1) yielded the product as a colorless oil (3.21 g, 16.2 mmol, 95% yield). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.24. **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.58 (dd, J = 4.3, 2.8 Hz, 1H), 4.22 (t, J = 2.2 Hz, 2H), 3.91 – 3.77 (m, 2H), 3.57 – 3.42 (m, 2H), 2.33 (tt, J = 7.1, 2.2 Hz, 2H), 2.03 (s, 1H), 1.86 – 1.75 (m, 3H), 1.75 – 1.64 (m, 1H), 1.64 – 1.46 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 98.9, 85.8, 78.9, 66.0, 62.4, 51.4, 30.8, 28.8, 25.5, 19.6, 15.8 ppm. **IR (film, $CHCl_3$)** 3407, 2940, 2869, 1440, 1354, 1135, 1118, 1061, 1018, 986, 900, 866, 809 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{11}H_{18}O_3Na$ [M+Na$^+$]: 221.11482, found 221.11481. Analytical data matched those reported.[21]

Undec-6-yn-5-ol - (SI-16)



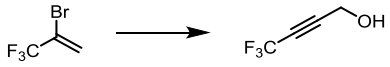
1-Hexyne (2.76 mL, 24 mmol, 1.2 equiv.) was dissolved in dry THF (25 mL) and stirred in an oven-dried Schlenk flask at −78 °C under an argon atmosphere. *n*-Butyllithium (15 mL, 1.6M in hexanes, 24 mmol, 1.2 equiv.) was slowly added and stirring continued at the same temperature for 1 h before neat *(E)*-pent-2-enal (1.96 mL, 20 mmol, 1.0 equiv.) was added in one portion. After 1 h at −78 °C, the mixture was allowed to warm to room temperature and the reaction was quenched with the addition of saturated ammonium chloride solution. The mixture was extracted twice with ethyl acetate, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, pentane/diethyl ether, 10:1) yielded the product as a colorless liquid (2.23 g, 13 mmol, 67% yield). **TLC** (hexanes/MTBE, 15:1), Rf = 0.31. **^{1}H NMR (400 MHz, Chloroform-d) δ** 5.90 (dtd, J = 15.3, 6.3, 1.2 Hz, 1H), 5.58 (ddt, J = 15.3, 6.2, 1.6 Hz, 1H), 4.88 – 4.69 (m, 1H), 2.24 (td, J = 7.1, 2.0 Hz, 2H), 2.13 – 2.04 (m, 2H), 1.80 – 1.75 (m, 1H), 1.54 – 1.46 (m, 2H), 1.46 – 1.36 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H) ppm.**^{13}C NMR (101 MHz, $CDCl_3$) δ** 135.3, 128.7, 87.0, 79.8, 63.4, 30.8, 25.1, 22.1, 18.6, 13.7, 13.3 ppm. **IR (film, $CHCl_3$)** 3337, 2961, 2933, 2873, 1460, 1379, 1147, 1083, 998, 966 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{11}H_{18}ONa$ [M+Na$^+$]: 189.12509, found 189.12498.

Methyl 2-chloro-3,3,3-trifluoro-2-(hex-2-yn-1-yloxy)propanoate[22] - (SI-17)



1-Hexynol (1.10 mL, 10 mmol, 1.0 equiv.) was dissolved in dry toluene (10 mL) and stirred at room temperature in an oven-dried Schlenk flask under an argon atmosphere. Methyl-3,3,3-trifluoropyruvate (1.12 mL, 11 mmol, 1.1 equiv.) was added dropwise and stirring continued for 1 h at room temperature before the mixture was placed on an ice bath. Pyridine (2.43 mL, 30 mmol, 3.0 equiv.) was added followed by dropwise addition of $SOCl_2$ (1.09 mL, 15 mmol, 1.5 equiv.) over 5 minutes. Stirring was continued for another 1 h under ice cooling and then at room temperature with the conversion monitored by TLC. The mixture was then poured onto ice-cold aqueous HCl (2 M) and extracted three times with MTBE. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude yellow residue was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, 20:1) to give the product as a colorless liquid (1.55 g, 5.69 mmol, 57% yield). **TLC** (hexanes/ethyl acetate, 10:1), Rf = 0.73. **^{1}H NMR (400 MHz, Chloroform-d)** δ 4.70 – 4.51 (m, 2H), 3.92 (s, 3H), 2.21 (tt, J = 7.1, 2.2 Hz, 2H), 1.61 – 1.47 (m, 2H), 0.98 (td, J = 7.4, 1.7 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 162.7, 124.8, 122.0, 119.1, 116.3, 89.6, 73.2, 57.4, 54.6, 51.1, 31.1, 21.9, 21.0, 13.6 ppm. **IR (film, $CHCl_3$)** 2966, 2939, 2877, 2242, 1761, 1438, 1382, 1290, 1255, 1193, 1025 1000, 944, 884 907, 794, 744, 680cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{10}H_{12}O_3ClF_3Na$ [M+Na$^+$]: 295.03215, found 295.03193.

4,4,4-Trifluorobut-2-yn-1-ol[23] - (SI-18)



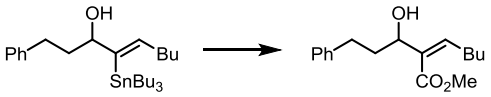
Di-*iso*-propylamine (15.42 mL, 110 mmol, 2.2 equiv.) was stirred in diethyl ether (100 mL) in a two-necked flame-dried flask equipped with a dropping funnel on a dry-ice bath. *n*-Butyllithium (68.8 mL, 1.6 M in hexanes, 110 mmol, 2.2 equiv.) was slowly added via the dropping funnel and stirring continued for 10 minutes before the mixture was placed for 30 minutes on an ice bath. After cooling to −78 °C, 2-bromo-3,3,3-trifluoro-1-propene (5.19 mL, 50 mmol, 1.0 equiv.) was added in one portion followed after 10 minutes by paraformaldehyde (3.0 g, 100 mmol, 2.0 equiv.). The mixture was allowed to stir for 15 minutes before the dry-ice bath was removed and the mixture allowed to reach room temperature over 18 h. The reaction was quenched with the addition of saturated ammonium chloride solution. The mixture was extracted two times

with Et_2O, the combined extracts were washed two times with aqueous HCl (2 M) and once with brine, dried over magnesium sulfate and concentrated under reduced pressure (40 °C, max. 250 mbar). The crude dark red residue was distilled at room temperature (dry-ice trap) via bulb-to-bulb distillation to give the product as a colorless volatile liquid which was carefully dried at room temperature at max. 100 mbar. **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.39 (t, J = 3.4 Hz, 2H), 2.23 (s, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 117.8, 115.3, 112.7, 110.2, 85.3, 73.6, 73.1, 72.6, 72.0, 50.3 ppm. **IR (film, $CHCl_3$)** 3349, 2287, 1274, 1134, 1046, 983, 591 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_4H_4OF_3$ [M+H$^+$]: 125.02132, found 125.02143.

8.3. Hydroxyl-Assisted Carbonylation of Alkenyltin Derivatives: Development and Application to a Formal Synthesis of Tubelactomicin A

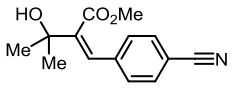
8.3.1. Representative procedure 8: Palladium Catalyzed Oxidative Methoxy Carbonylation of Alkenylstannanes

Methyl (Z)-2-(1-hydroxy-3-phenylpropyl)hept-2-enoate - (249b)



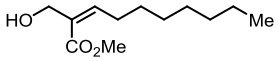
(Z)-1-Phenyl-4-(tributylstannyl)non-4-en-3-ol (1.27 g, 2.5 mmol, 1.0 equiv.) was dissolved in a 0.1 M TFA solution in MeOH (10 mL) and stirred in an oven-dried Schlenk flask under an argon atmosphere. *p*-Benzoquinone (405 mg, 3.75 mmol, 1.5 equiv.), Ph_3As (77 mg, 0.25 mmol, 10 mol%) and $Pd(OAc)_2$ (28 mg, 0.125 mmol, 5.0 mol%) were added in one portion and the mixture was flushed for 2 minutes with CO (balloon) before stirring was continued under positive CO pressure (balloon) at room temperature. The progress of the reaction was monitored by TLC (hexanes/ethyl acetate, 15:1). After 12 h the mixture was diluted with MTBE, and the crude mixture filtered through a plug of Celite®. The volatile materials were removed and the crude material was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, 19:1) to give the product as a colorless oil (660 mg, 2.15 mmol, 86% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.31 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 6.13 (td, J = 7.5, 0.9 Hz, 1H), 4.23 (d, J = 8.7 Hz, 1H), 3.77 (s, 3H), 2.83 – 2.60 (m, 3H), 2.42 (q, J = 7.3 Hz, 2H), 2.04 – 1.86 (m, 2H), 1.47 – 1.24 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 168.2, 143.5, 141.9, 133.7, 128.6, 128.5, 126.0, 74.0, 51.5, 38.2, 32.4, 31.5, 29.3, 22.5, 14.0 ppm. **IR (film, $CHCl_3$)** 3435, 3027, 2954, 2927, 2859, 1706, 1496, 1454, 1435, 1378, 1205, 1143, 1032, 748, 700 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{24}O_3Na$ [M+Na$^+$]: 299.16176, found 299.16188.

Methyl (Z)-2-(4-cyanobenzylidene)-3-hydroxy-3-methylbutanoate - (252)



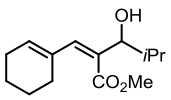
73% yield (89 mg, 0.363 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.64 – 7.54 (m, 2H), 7.36 – 7.29 (m, 2H), 6.86 (s, 1H), 3.64 (s, 3H), 2.49 (s, 1H), 1.52 (s, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 169.7, 145.0, 140.6, 132.2, 128.6, 127.1, 118.7, 111.5, 72.3, 52.3, 29.4 ppm. **IR (film, $CHCl_3$)** 3430, 2977, 2228, 1721, 1638, 1605, 1512, 1435, 1353, 1313, 1286, 1206, 1175, 1041, 966, 944, 893, 824, 759, 677 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{14}H_{15}NO_3Na$ [M+Na^+]: 268.09441, found 268.09435.

Methyl (Z)-2-(hydroxymethyl)dec-2-enoate - (253)



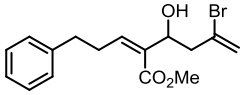
68% yield (145 mg, 0.68 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.23 (tt, J = 7.3, 1.0 Hz, 1H), 4.21 (q, J = 1.0 Hz, 2H), 3.76 (s, 3H), 2.58 – 2.46 (m, 2H), 2.43 (s, 1H), 1.49 – 1.35 (m, 2H), 1.35 – 1.16 (m, 9H), 1.00 – 0.70 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.7, 147.0, 130.5, 65.3, 51.5, 31.9, 29.6, 29.2, 22.7, 14.2 ppm. **IR (film, $CHCl_3$)** 3432, 2954, 2924, 2855, 1706, 1650, 1435, 1380, 1339, 1204, 1145, 1103, 1046, 1011 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{22}O_3Na$ [M+Na^+]: 237.14611, found 237.14618.

Methyl (Z)-2-(cyclohex-1-en-1-ylmethylene)-3-hydroxy-4-methyl-pentanoate - (254)



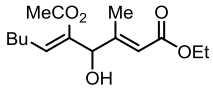
55% yield (65 mg, 0.273 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.17 (p, J = 1.0 Hz, 1H), 5.86 (ddt, J = 4.0, 2.7, 1.2 Hz, 1H), 3.80 (ddd, J = 8.0, 6.2, 0.9 Hz, 1H), 3.76 (s, 3H), 2.22 (d, J = 6.2 Hz, 1H), 2.18 – 2.09 (m, 2H), 2.09 – 2.01 (m, 2H), 1.83 – 1.70 (m, 1H), 1.66 – 1.57 (m, 4H), 1.56 (s, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 170.3, 137.4, 134.5, 133.7, 130.9, 81.7, 51.8, 33.1, 26.4, 26.2, 22.8, 22.0, 19.6, 18.6 ppm. **IR (film, $CHCl_3$)** 3482, 2931, 2868, 1774, 1716, 1635, 1435, 1366, 1214, 1180, 1135, 1102, 1017, 981, 927, 872 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{14}H_{22}O_3Na$ [M+Na^+]: 261.14611, found 261.14632.

Methyl (Z)-5-bromo-3-hydroxy-2-(3-phenylpropylidene)hex-5-enoate - (255)



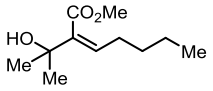
87% yield (147 mg, 0.43 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.29 (ddd, J = 9.1, 6.4, 0.9 Hz, 2H), 7.20 (td, J = 6.5, 1.7 Hz, 3H), 6.35 – 6.27 (m, 1H), 5.63 (dt, J = 1.9, 1.0 Hz, 1H), 5.49 (d, J = 1.6 Hz, 1H), 4.59 (tdd, J = 7.1, 6.0, 0.9 Hz, 1H), 3.78 (s, 3H), 2.83 – 2.68 (m, 6H) ppm**. ^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.5, 143.5, 141.2, 132.5, 130.25, 128.5, 126.2, 119.8, 72.2, 51.7, 48.7, 35.4, 31.3 ppm. **IR (film, $CHCl_3$)** 3463,3026, 2949, 1703, 1631, 1603, 1496, 1435, 1453, 1381, 1332, 1200, 1111, 1050, 1005, 890, 793, 748, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{19}BrO_3Na$ [M+Na^+]: 361.04099, found 361.04241.

Ethyl (2E,5Z)-5-acetoxy-4-hydroxy-3-methyldeca-2,5-dienoate - (256)



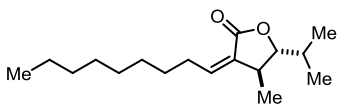
80% yield (113 mg, 0.397 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.20 (td, J = 7.6, 0.7 Hz, 1H), 6.07 (p, J = 1.4 Hz, 1H), 4.81 – 4.73 (m, 1H), 4.16 (qd, J = 7.1, 1.2 Hz, 2H), 3.76 (s, 3H), 3.00 (d, J = 7.2 Hz, 1H), 2.47 (q, J = 7.4 Hz, 2H), 2.05 (dd, J = 1.4, 0.6 Hz, 3H), 1.49 – 1.30 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.7, 166.9, 157.3, 146.7, 130.9, 116.1, 77.8, 60.0, 51.8, 31.3, 29.5, 22.6, 16.0, 14.4, 14.0 ppm. **IR (film, $CHCl_3$)** 3488, 2957, 2930, 2873, 1775, 1713, 1654, 1435, 1368, 1344, 1206, 1144, 1095, 1039 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{24}O_5Na$ [M+Na^+]: 307.15159, found 307.15176.

Methyl (Z)-2-(2-hydroxypropan-2-yl)hept-2-enoate - (257)



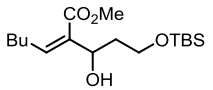
63 yield (63 mg, 0.32 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 5.99 (t, J = 7.5 Hz, 1H), 3.80 (s, 3H), 3.01 (s, 1H), 2.20 (q, J = 7.4 Hz, 2H), 1.41 (s, 6H), 1.40 – 1.22 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 170.0, 139.4, 135.3, 71.8, 51.7, 31.5, 29.6, 29.4, 22.5, 14.0 ppm. **IR (film, $CHCl_3$)** 3436, 2956, 2931, 2860, 1719, 1458, 1434, 1356, 1255, 1204, 1127, 1038, 966 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{11}H_{20}O_3Na$ [M+Na^+]: 223.13046, found 223.13068.

(*anti,Z*)-5-Isopropyl-4-methyl-3-nonylidenedihydrofuran-2(3*H*)-one - (258)



60% yield (79 mg, 0.30 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 6.08 (td, J = 7.6, 2.2 Hz, 1H), 3.75 (t, J = 5.7 Hz, 1H), 2.72 (tdd, J = 7.6, 5.2, 1.6 Hz, 3H), 1.84 (pd, J = 6.8, 5.7 Hz, 1H), 1.54 – 1.37 (m, 2H), 1.37 – 1.23 (m, 12H), 1.19 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.8 Hz, 6H), 0.94 – 0.82 (m, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 170.1, 143.7, 131.0, 89.1, 37.9, 32.5, 32.0, 29.6, 29.4, 27.6, 22.8, 20.1, 18.3, 17.4, 14.2 ppm. **IR (film, $CHCl_3$)** 2960, 2924, 2855, 1751, 1667, 1466, 1370, 1170, 1126, 1094, 1005 953 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{30}O_2$ [M^+]: 266.22403, found 266.22367.

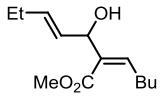
Methyl (Z)-2-(3-((tert-butyldimethylsilyl)oxy)-1-hydroxypropyl)hept-2-enoate - (259)



77% yield (128 mg, 0.387 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.28 (td, J = 7.5, 1.3 Hz, 1H), 4.63 – 4.53 (m, 1H), 3.88 – 3.75 (m, 3H), 3.74 (s, 3H), 2.45 (qdd, J = 7.4, 2.1, 1.0 Hz, 2H), 1.93 – 1.83 (m, 1H), 1.81 – 1.69 (m, 1H), 1.49 – 1.27 (m, 4H), 0.94 – 0.84 (m, 13H), 0.10 – 0.01 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.0, 142.4, 133.5, 72.3, 62.1, 51.4, 38.2, 31.6, 29.3, 26.0, 22.6, 18.3, 14.1, -5.4 ppm. **IR (film, $CHCl_3$)** 3487, 2929, 2954, 2858, 1708, 1435, 1464, 1379, 1254, 1202, 1151, 1096, 1006, 914,

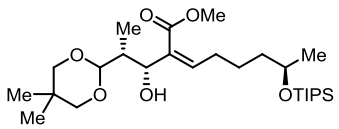
833, 776, 732 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{35}O_4Si$ [M+H^+]: 331.22991, found 331.22998.

Methyl (Z)-2-((E)-1-hydroxypent-2-en-1-yl)hept-2-enoate - (260)



72% yield (81 mg, 0.358 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.17 (td, J = 7.5, 1.0 Hz, 1H), 5.73 (dtd, J = 15.5, 6.3, 1.2 Hz, 1H), 5.54 (ddt, J = 15.4, 6.3, 1.5 Hz, 1H), 4.76 (t, J = 6.5 Hz, 1H), 3.77 (s, 3H), 2.72 (d, J = 6.8 Hz, 1H), 2.43 (q, J = 7.3 Hz, 2H), 2.10 – 1.99 (m, 2H), 1.50 – 1.25 (m, 4H), 0.98 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 168.1, 143.6, 134.7, 133.3, 129.5, 74.6, 51.5, 31.4, 29.3, 25.4, 22.5, 14.0, 13.5 ppm. **IR (film, $CHCl_3$)** 3434, 2959, 2929, 2873, 1707, 1435, 1377, 1204, 1150, 1081, 1021, 966, 911, 799, 731 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{13}H_{22}O_3Na$ [M+Na^+]: 249.14611, found 249.14620.

Methyl (R,Z)-2-((1R,2R)-2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-hydroxy-propyl)-7-((triisopropylsilyl)oxy)oct-2-enoate - (261)



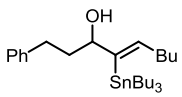
82% yield (345 mg, 0.689 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.28 (td, J = 7.5, 1.5 Hz, 1H), 4.84 (dq, J = 2.9, 1.5 Hz, 1H), 4.53 (d, J = 2.8 Hz, 1H), 3.93 (q, J = 5.6 Hz, 1H), 3.73 (s, 3H), 3.68 – 3.59 (m, 2H), 3.47 – 3.38 (m, 3H), 2.57 – 2.33 (m, 2H), 2.04 – 1.91 (m, 1H), 1.58 – 1.30 (m, 4H), 1.19 (s, 3H), 1.14 (dd, J = 8.4, 6.1 Hz, 3H), 1.05 (s, 18H), 0.99 (dt, J = 9.7, 7.0 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H), 0.72 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.8, 142.6, 131.5, 104.5, 77.4, 70.9, 68.5, 51.4, 40.6, 39.8, 30.5, 29.8, 25.4, 23.7, 23.0, 21.9, 18.3, 18.3, 12.6, 6.9 ppm. **IR (film, $CHCl_3$)** 3514, 2943, 2866, 1719, 1462, 1365, 1202, 1136, 1097, 1061, 1038, 1017, 993, 923, 882, 851, 724, 676, 654 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{27}H_{52}O_6SiNa$ [M+Na^+]: 523.34254, found 523.34334.

8.3.2. Representative procedure 9: Ruthenium Catalyzed *trans*-Hydrostannation of Propargyl Alcohols (25 mmol scale experiment)[24]

1-Phenylnon-4-yn-3-ol (5.4 g, 25 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (100 mL) and the solution stirred at room temperature in an oven-dried Schlenk flask under an argon atmosphere. $[Cp^*RuCl_2]_n$ (77 mg, 0.25 mmol, 1.0 mol%) was added followed by slow addition of Bu_3SnH (7.1 ml, 26.3 mmol, 1.05 equiv.) over 1 h via syringe pump. Stirring was continued for another 5 minutes before the volatile materials were removed under reduced pressure. The crude

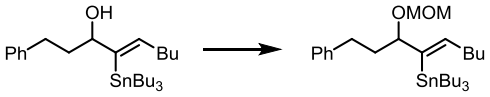
material was purified by flash chromatography (SiO_2, hexanes/ethyl acetate) to give the product as a brownish thick oil.

(Z)-1-Phenyl-4-(tributylstannyl)non-4-en-3-ol - (248)



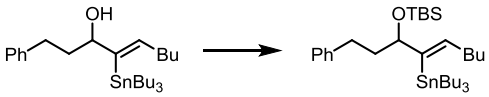
93% yield (11.8 g, 23.3 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.32 – 7.24 (m, 2H), 7.23 – 7.12 (m, 3H), 6.38 – 5.96 (m, 1H), 4.35 – 4.01 (m, 1H), 2.64 (qdd, J = 13.8, 9.8, 6.1 Hz, 2H), 2.13 – 1.95 (m, 2H), 1.83 (dddd, J = 13.3, 9.7, 7.2, 6.0 Hz, 1H), 1.71 (ddt, J = 13.5, 10.0, 6.3 Hz, 1H), 1.60 – 1.40 (m, 8H), 1.40 – 1.21 (m, 10H), 1.04 – 0.79 (m, 20H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.6, 142.3, 141.4, 128.6, 128.5, 125.9, 79.6, 39.4, 34.2, 32.5, 29.4, 27.6, 22.7, 14.2, 13.8, 11.2 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -55.09 ppm. **IR (film, $CHCl_3$)** 2955, 2923, 2871, 2854, 1616, 1496, 1456, 1419, 1376, 1340, 1290, 1201, 1072, 1048, 1002, 961, 926, 863, 746, 697, 664 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{27}H_{48}OSnNa$ [M+Na$^+$]: 531.26186, found 531.26185.

(Z)-Tributyl(3-(methoxymethoxy)-1-phenylnon-4-en-4-yl)stannane - (SI-19)



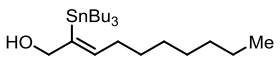
248 (2.53 g, 5.0 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (20 mL) and the solution stirred on an ice bath in an oven-dried Schlenk flask under an argon atmosphere. TBAI (185 mg, 0.5 mmol, 10 mol%) and Hünig's base (1.74 mL, 10 mmol, 2.0 equiv.) were added followed by dropwise addition of MOMCl (570 µL, 7.5 mmol, 1.5 equiv.). The mixture was stirred for 18 h while being allowed to warm to room temperature. The reaction was then quenched with saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 30:1) yielded the product as a colorless oil (2.62 g, 4.75 mmol, 95% yield). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.32 – 7.24 (m, 2H), 7.22 – 7.13 (m, 3H), 6.46 – 5.87 (m, 1H), 4.66 (d, J = 6.5 Hz, 1H), 4.47 (d, J = 6.5 Hz, 1H), 4.25 – 3.92 (m, 1H), 3.37 (s, 3H), 2.80 – 2.51 (m, 2H), 2.07 (dddd, J = 8.8, 7.0, 4.9, 1.8 Hz, 2H), 1.91 (dddd, J = 13.2, 10.5, 7.2, 5.9 Hz, 1H), 1.68 (ddt, J = 13.5, 10.6, 6.1 Hz, 1H), 1.60 – 1.41 (m, 6H), 1.41 – 1.14 (m, 9H), 1.01 – 0.79 (m, 18H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 144.9, 144.1, 142.5, 128.5, 128.5, 93.4, 84.0, 55.6, 38.4, 34.3, 32.6, 29.4, 27.6, 22.8, 14.2, 13.8, 11.3 ppm. **IR (film, $CHCl_3$)** 2954, 2923, 2871, 2855, 1614, 1496, 1455, 1376, 1177, 1147, 1094, 1030, 960, 920, 863, 746, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{29}H_{52}O_2SnNa$ [M+Na$^+$]: 575.28808, found 575.28862.

(Z)-*tert*-Butyldimethyl((1-phenyl-4-(tributylstannyl)non-4-en-3-yl)oxy)silane - (SI-20)



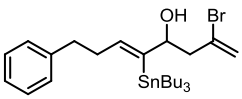
248 (2.53 g, 5.0 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (20 mL) and the solution stirred on an ice bath in an oven-dried Schlenk flask under an argon atmosphere. DMAP (61 mg, 0.5 mmol, 10 mol%) and 1H-imidazole (681 mg, 10 mmol, 2.0 equiv.) were added followed by addition of *tert*-butyldimethylsilyl chloride (1.13 g, 7.5 mmol, 1.5 equiv.). The mixture was stirred for 18 h while being allowed to warm to room temperature. The reaction was then quenched with saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 30:1) yielded the product as a colorless oil (2.89 g, 4.64 mmol, 93% yield). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.32 – 7.22 (m, 2H), 7.22 – 7.11 (m, 3H), 6.08 (td, J = 7.2, 1.0 Hz, 1H), 4.11 (td, J = 6.6, 0.9 Hz, 1H), 2.63 – 2.43 (m, 3H), 2.13 – 1.90 (m, 3H), 1.76 (ddt, J = 13.5, 10.8, 6.2 Hz, 1H), 1.65 (dddd, J = 13.4, 10.8, 6.7, 5.6 Hz, 1H), 1.60 – 1.40 (m, 6H), 1.40 – 1.23 (m, 12H), 1.03 – 0.71 (m, 32H), 0.00 (d, J = 17.2 Hz, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 148.1, 142.8, 140.41, 128.5, 128.4, 125.7, 81.1, 41.0, 34.2, 32.6, 32.5, 29.5, 27.7, 26.2, 22.8, 18.4, 14.3, 13.8, 11.3, -3.9, -4.6 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -57.69 ppm. **IR (film, $CHCl_3$)** 3027, 2926, 2855, 1616, 1496, 1462, 1417, 1377, 1360, 1291, 1251, 1175, 1152, 1066, 1004, 963, 938, 875, 834, 773, 746, 697, 666 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{33}H_{62}OSiSnNa$ [M+Na^+]: 645.34834, found 645.34898.

(Z)-2-(Tributylstannyl)dec-2-en-1-ol - (SI-21)



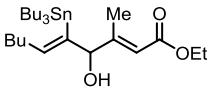
97% yield (3.1 g, 6.96 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.25 (tt, J = 7.2, 1.4 Hz, 1H), 4.28 – 4.12 (m, 2H), 2.04 (q, J = 7.4 Hz, 2H), 1.61 – 1.44 (m, 6H), 1.43 – 1.25 (m, 16H), 1.22 (t, J = 6.0 Hz, 1H), 1.02 – 0.94 (m, 6H), 0.94 – 0.87 (m, 12H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 143.0, 142.2, 70.7, 34.8, 32.0, 30.2, 29.6, 29.4, 29.4, 27.6, 22.8, 14.3, 13.9, 10.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -52.7 ppm. . **IR (film, $CHCl_3$)** 3305, 2955, 2922, 2871, 2852, 1462, 1418, 1376, 1340, 1290, 1181, 1148, 1072, 1000, 960, 862, 806, 769 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{22}H_{45}OSn$ [M-H^+]: 445.24972, found 445.25028.

(Z)-2-Bromo-8-phenyl-5-(tributylstannyl)octa-1,5-dien-4-ol - (SI-22)



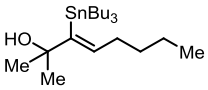
45% yield (1.55 g, 2.72 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.34 – 7.25 (m, 2H), 7.24 – 7.13 (m, 3H), 6.33 (td, J = 7.2, 1.1 Hz, 1H), 5.66 (q, J = 1.0 Hz, 1H), 5.53 (d, J = 1.6 Hz, 1H), 4.61 – 4.38 (m, 1H), 2.75 – 2.62 (m, 2H), 2.60 – 2.47 (m, 2H), 2.43 – 2.29 (m, 2H), 1.69 (d, J = 2.7 Hz, 1H), 1.60 – 1.38 (m, 6H), 1.38 – 1.23 (m, 6H), 1.10 – 0.93 (m, 5H), 0.89 (t, J = 7.3 Hz, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 146.8, 141.8, 140.5, 130.8, 128.5, 128.5, 126.1, 119.6, 76.4, 50.0, 36.5, 36.3, 29.4, 27.6, 13.9, 11.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -53.85 ppm. **IR (film, $CHCl_3$)** 2954, 2922, 2870, 2853, 1629, 1496, 1454, 1376, 1290, 1199, 1123, 1072, 1029, 961, 884, 746, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{26}H_{43}BrOSnNa$ [$M+Na^+$]: 593.14109, found 593.14118.

Ethyl (2E,5Z)-4-hydroxy-3-methyl-5-(tributylstannyl)deca-2,5-dienoate - (SI-23)



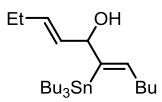
72% yield (2.96 g, 5.74 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.24 (td, J = 7.2, 1.0 Hz, 1H), 6.04 (p, J = 1.4 Hz, 1H), 4.71 – 4.45 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.11 – 2.03 (m, 2H), 2.02 (d, J = 1.2 Hz, 3H), 1.66 (d, J = 3.4 Hz, 1H), 1.44 (dddd, J = 14.1, 8.4, 7.1, 4.0 Hz, 5H), 1.40 – 1.19 (m, 13H), 0.97 – 0.83 (m, 19H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.1, 158.9, 145.1, 144.0, 114.9, 83.7, 59.7, 34.1, 32.3, 29.3, 27.5, 22.7, 16.3, 14.5, 14.2, 13.8, 11.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -49.65 ppm. **IR (film, $CHCl_3$)** 3482, 2955, 2923, 2871, 2854, 1718, 1698, 1650, 1463, 1377, 1340, 1288, 1210, 1142, 1093, 1043 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{25}H_{48}O_3SnNa$ [$M+Na^+$]: 539.25169, found 539.25226.

(Z)-2-Methyl-3-(tributylstannyl)oct-3-en-2-ol - (SI-24)



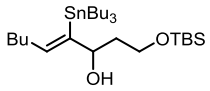
90% yield (3.11 g, 7.21 mmol). 1H NMR (400 MHz, Chloroform-d) δ 6.36 – 5.86 (m, 1H), 2.11 – 1.94 (m, 2H), 1.57 – 1.40 (m, 6H), 1.38 – 1.30 (m, 12H), 1.29 (s, 6H), 0.97 – 0.83 (m, 16H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 153.0, 136.6, 75.4, 33.8, 32.6, 30.9, 29.4, 27.6, 22.8, 14.3, 13.9, 12.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$)** δ -55.51 ppm. **IR (film, $CHCl_3$)** 3456, 2955, 2921, 2871, 2854, 1616, 1462, 1376, 1360, 1133, 1071, 1002, 960, 911, 860, 761, 665 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{21}H_{44}OSnNa$ [$M+Na^+$]: 455.23056, found 455.23087.

(3E,6Z)-6-(Tributylstannyl)undeca-3,6-dien-5-ol - (SI-25)



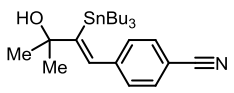
41% yield (1.3 g, 2.84 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.20 (td, J = 7.2, 1.1 Hz, 1H), 5.64 (dtd, J = 15.5, 6.2, 1.3 Hz, 1H), 5.43 (ddt, J = 15.4, 5.9, 1.6 Hz, 1H), 4.63 (ddt, J = 5.9, 3.5, 1.1 Hz, 1H), 2.12 – 1.93 (m, 3H), 1.54 – 1.40 (m, 6H), 1.39 – 1.22 (m, 10H), 0.99 (t, J = 7.4 Hz, 3H), 0.97 – 0.84 (m, 20H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 146.3, 141.1, 133.3, 131.9, 80.2, 34.2, 32.4, 29.4, 27.6, 25.4, 22.8, 14.2, 13.9, 13.5, 11.2 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -53.6 ppm. **IR (film, $CHCl_3$)** 2956, 2922, 2853, 2871, 1458, 1376, 1071, 1001, 966, 863, 666, 594 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{46}OSnNa$ [M+Na^+]: 481.24621, found 481.24621.

(Z)-1-((*tert*-Butyldimethylsilyl)oxy)-4-(tributylstannyl)non-4-en-3-ol - (SI-26)



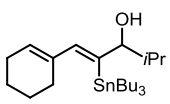
81% yield (1.86 g, 3.31 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.20 (td, J = 7.2, 1.2 Hz, 1H), 4.48 – 4.18 (m, 1H), 3.94 – 3.72 (m, 3H), 3.16 (d, J = 2.2 Hz, 1H), 2.02 (td, J = 8.9, 8.1, 5.9 Hz, 2H), 1.79 – 1.64 (m, 2H), 1.58 – 1.40 (m, 7H), 1.40 – 1.20 (m, 11H), 1.01 – 0.76 (m, 21H), 0.07 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.2, 140.1, 79.3, 62.5, 39.7, 34.1, 32.5, 29.4, 27.6, 26.0, 22.7, 18.3, 14.2, 13.8, 11.2, -5.4 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -55.1 ppm. **IR (film, $CHCl_3$)** 2954, 2926, 2856, 1463, 1377, 1254, 1093, 1004, 961, 939, 834, 775, 729, 664 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{27}H_{58}O_2SiSnNa$ [M+Na^+]: 585.31196, found 585.31235.

(Z)-4-(3-Hydroxy-3-methyl-2-(tributylstannyl)but-1-en-1-yl)benzonitrile - (SI-27)



78% yield (2.63 g, 5.52 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.60 – 7.53 (m, 2H), 7.29 (s, 1H), 7.27 – 7.23 (m, 2H), 1.61 (s, 1H), 1.41 (s, 6H), 1.39 – 1.26 (m, 6H), 1.26 – 1.15 (m, 6H), 0.83 (t, J = 7.2 Hz, 9H), 0.79 – 0.55 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 163.5, 146.0, 135.4, 131.9, 129.0, 119.1, 110.4, 76.2, 31.1, 29.2, 27.5, 13.8, 12.9 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -53.0 ppm. **IR (film, $CHCl_3$)** 3507, 2955, 2921, 2871, 2228, 1602, 1500, 1462, 1362, 1201, 1142, 1073, 1020, 959, 931, 876, 849, 823, 797, 724, 667, 594 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{24}H_{39}NOSnNa$ [M+Na^+]: 500.19451, found 500.19430.

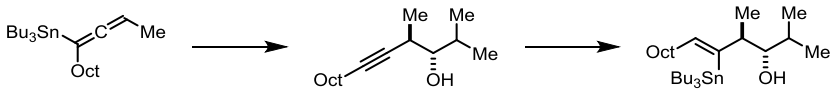
(Z)-1-(Cyclohex-1-en-1-yl)-4-methyl-2-(tributylstannyl)pent-1-en-3-ol - (SI-28)



72% yield (3.36 g, 7.16 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.53 (h, J = 1.1 Hz, 1H), 5.58 (dh, J = 3.5, 1.5 Hz, 1H), 4.03 – 3.64 (m, 1H), 2.18 – 1.86 (m, 4H), 1.68 – 1.53 (m, 6H), 1.53 – 1.36 (m, 7H), 1.36 – 1.25 (m, 6H), 0.99 – 0.78 (m, 20H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.4, 143.3, 139.3, 123.8, 85.3, 33.6, 29.4, 28.9, 27.7, 25.6, 22.7, 22.2, 20.2, 17.7, 13.9, 12.0 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -51.6 ppm. **IR (film,**

$CHCl_3$) 3449, 2955, 2924, 2871, 1597, 1459, 1364, 1266, 1236, 1201, 1137, 1076, 1021, 960, 924, 848, 802, 724, 665, cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{24}H_{45}OSn$ [M-H^+]: 469.24972, found 469.24941.

(*anti*,Z)-2,4-Dimethyl-5-(tributylstannyl)tetradec-5-en-3-ol - (SI-29)

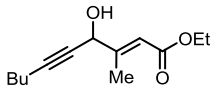


SI-35 (2.73 g, 6.0 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (5 mL) and stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. $SnCl_4$ (6.0 mL, 6 mmol, 1 M in CH_2Cl_2, 1.0 equiv.) was slowly added and stirring was continued for 40 minutes before *iso*-butyraldehyde (1.64 mL, 18 mmol, 3.0 equiv.) in dry CH_2Cl_2 (5 mL) was slowly added. After being stirred at the same temperature for 1 h, the reaction was quenched with the addition of saturated ammonium chloride solution. The mixture was extracted two times with CH_2Cl_2, the combined extracts were washed with water, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 30:1) yielded the product as a pale yellow oil (1.44 g, 6.0 mmol, quant. yield). TLC (hexanes/ethyl acetate, 10:1), Rf = 0.56 (*anti*), 0.44 (*syn*). The crude material could not be readily separated from tin residues so it was used as such.

(*anti*)-2,4-Dimethyltetradec-5-yn-3-ol (1.44 g, 6.0 mmol, 1.0 equiv.) and $[Cp^*RuCl]_4$ (82 mg, 0.3 mmol, 5 mol%) were dissolved in dry CH_2Cl_2 (25 mL) and stirred in an oven-dried Schlenk flask at room temperature under an argon atmosphere. Bu_3SnH (1.78 mL, 6.6 mmol, 1.1 equiv.) was added over 1 h by means of a syringe pump. Upon completion of addition the volatile materials were removed and the crude mixture loaded onto a column. Flash chromatography (SiO_2, hexanes/ethyl acetate, 30:1) yielded the product as a slightly impured pale brown oil (1.56 g, 2.95 mmol, 49% yield over 2 steps, α/β = 10:1). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.37 – 5.94 (m, 1H), 3.16 (dt, J = 9.5, 2.1 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.02 (p, J = 6.4, 5.7 Hz, 2H), 1.87 – 1.75 (m, 1H), 1.52 – 1.41 (m, 6H), 1.40 – 1.19 (m, 24H), 1.03 (d, J = 6.9 Hz, 3H), 0.99 – 0.79 (m, 28H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.7, 143.8, 77.9, 49.6, 34.9, 32.0, 30.5, 29.7, 29.7, 29.4, 29.4, 28.0, 27.6, 27.0, 22.8, 21.1, 18.0(2C), 17.7, 14.3(2C), 13.8, 11.6 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -54.9 ppm. **IR (film, $CHCl_3$)** 2956, 2923, 2872, 2853, 1462, 1377, 1174, 1073, 991, 875, 758, 666, 594, 504 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{28}H_{57}OSn$ [M^-]: 529.34362, found 529.34430.

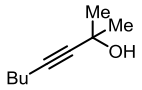
The following compounds were prepared according to representative procedure 6.

Ethyl (E)-4-hydroxy-3-methyldec-2-en-5-ynoate - (SI-30)



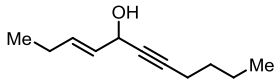
86% yield (3.87 g, 17.3 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.06 (p, J = 1.3 Hz, 1H), 4.77 (q, J = 1.8 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.26 – 2.15 (m, 6H), 1.56 – 1.42 (m, 2H), 1.42 – 1.30 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.9, 155.9, 116.0, 87.8, 78.1, 67.2, 60.1, 30.6, 22.1, 18.5, 15.2, 14.4, 13.7 ppm. **IR (film, $CHCl_3$)** 3434, 2959, 2934, 2873, 1717, 1699, 1657, 1432, 1368, 1344, 1295, 1210, 1146, 1096, 1040, 876 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{13}H_{18}O_3Na$ [M+Na^+]: 245.11481, found 245.11484.

2-Methyloct-3-yn-2-ol - (SI-31)



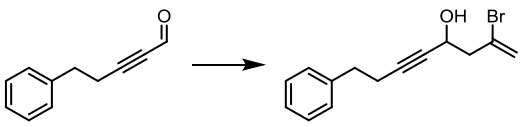
99% yield (2.80 g, 19.7 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 2.18 (t, J = 7.0 Hz, 2H), 1.88 – 1.81 (m, 1H), 1.49 (s, 7H), 1.48 – 1.35 (m, 3H), 0.90 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 85.2, 82.7, 65.5, 31.9, 30.9, 22.1, 18.4, 13.8 ppm. Analytical data in accordance with literature.[25]

(*E*)-Undec-3-en-6-yn-5-ol - (SI-32)



67% yield (2.23 g, 13.4 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 5.90 (dtd, J = 15.3, 6.3, 1.2 Hz, 1H), 5.58 (ddt, J = 15.3, 6.2, 1.6 Hz, 1H), 4.88 – 4.69 (m, 1H), 2.24 (td, J = 7.1, 2.0 Hz, 2H), 2.13 – 2.04 (m, 2H), 1.80 – 1.75 (m, 1H), 1.54 – 1.46 (m, 2H), 1.46 – 1.36 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 135.3, 128.7, 87.0, 79.8, 63.4, 30.8, 25.1, 22.1, 18.6, 13.7, 13.3 ppm. **IR (film, $CHCl_3$)** 3337, 2961, 2933, 2873, 1460, 1432, 1379, 1328, 1147, 1083, 998, 966 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{11}H_{18}ONa$ [M+Na^+]: 189.12498, found 189.12509.

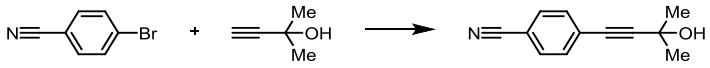
2-Bromo-8-phenyloct-1-en-5-yn-4-ol[26] - (SI-33)



Sn powder (2.04 g, 17.2 mmol, 1.5 equiv.) was suspended in H_2O/Et_2O (25 mL/25 mL) and the suspension stirred vigorously at room temperature. 2,3-Dibromopropene (3.95 mL, 34 mmol, 85% purity, 3.0 equiv.) was added followed by a few drops of concentrated aqueous HBr and 5-phenylpent-2-ynal (1.81 g, 11.4 mmol, 1.0 equiv.) and stirring was continued at room temperature with the conversion monitored by TLC. Upon disappearance of starting material, the mixture was diluted with water and extracted two times with MTBE. The combined extracts

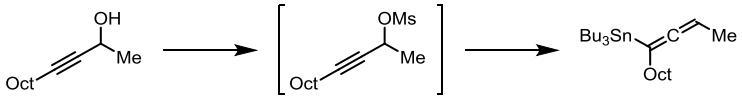
were dried over magnesium sulfate and the volatile materials were removed under reduced pressure to give an orange oil. The crude material was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, 9:1 to 4:1) to give the product as a yellow oil (75% yield, 2.4 g, 8.6 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.38 – 7.31 (m, 2H), 7.26 (td, J = 6.5, 1.6 Hz, 3H), 5.72 (dt, J = 1.9, 1.1 Hz, 1H), 5.56 (d, J = 1.7 Hz, 1H), 4.69 (ddt, J = 7.6, 5.7, 1.9 Hz, 2H), 2.86 (t, J = 7.5 Hz, 3H), 2.84 – 2.71 (m, 2H), 2.55 (td, J = 7.5, 2.0 Hz, 2H), 2.41 (s, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 140.5, 128.6, 128.5, 128.4, 126.4, 120.2, 85.7, 80.5, 60.5, 49.7, 34.9, 20.9 ppm. **IR (film, $CHCl_3$)** 3349, 3027, 2924, 1632, 1603, 1496, 1427, 1453, 1340, 1200, 1113, 1141, 1032, 891, 746, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{14}H_{15}OBrNa$ [M+Na^+]: 301.01986, found 301.01972.

4-(3-Hydroxy-3-methylbut-1-yn-1-yl)benzonitrile[27] - (SI-34)



p-Bromobenzonitrile (2.73 g, 15 mmol, 1.0 equiv.) and 2-methyl-3-butyn-2-ol (1.74 mL, 18 mmol, 1.2 equiv.) were mixed in dry THF (5 mL) and the solution was stirred in an oven-dried Young Schlenk under an argon atmosphere. Et_3N (25 mL) was added followed by bis(triphenylphosphine)palladium(II) dichloride (105 mg, 0.15 mmol, 1.0 mol%) and copper iodide (86 mg, 0.45 mmol, 3.0 mol%). The flask was sealed and the mixture heated to 60 °C for 18 h before being left to cool to room temperature. The reaction was quenched with the addition of ammonium chloride solution. The mixture was extracted two times with MTBE, the combined extracts were washed with aqueous HCl (2 M) and brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 4:1) yielded the product as an orange solid (1.31 g, 7.07 mmol, 47% yield). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.26. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.63 – 7.56 (m, 2H), 7.53 – 7.45 (m, 2H), 2.01 (s, 1H), 1.63 (s, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 131.4, 131.2, 127.0, 117.7, 110.9, 97.4, 79.9, 64.9, 30.5 ppm. **IR (film, $CHCl_3$)** 3404, 2979, 2240, 2225, 1600, 1497, 1456, 1401, 1361, 1272, 1161, 962, 905, 836, 560 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{11}NONa$ [M+Na^+]: 208.07328, found 208.07350.

Tributyl(dodeca-2,3-dien-4-yl)stannane[28] - (SI-35)

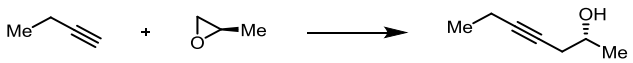


Dodec-3-yn-2-ol (2.73 g, 15 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (20 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. Et_3N (3.14 mL, 22.5 mmol, 1.5 equiv.) and MsCl (1.51 mL, 19.5 mmol, 1.3 equiv.) were slowly added and the mixture was stirred for 15 minutes before it was cooled with an ice bath. After another 30 minutes, the mixture was poured onto aqueous HCl (1 M), extracted two times with CH_2Cl_2, the combined extracts were washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The crude mesylate was used as such.

A Schlenk flask was charged with dry THF (100 mL) and di-*iso*-propylamine (2.31 mL, 16.5 mmol, 1.1 equiv.) and the solution stirred on an ice bath under an argon atmosphere. *n*-Butyllithium (9.4 mL, 15 mmol, 1.0 equiv.) was slowly added followed after 30 minutes by Bu_3SnH (4.04 mL, 15 mmol, 1.0 equiv.). After another 20 minutes, the mixture was cooled with a dry-ice bath and CuBr·Me_2S (3.08 g, 15 mmol, 1.0 equiv.) was added. Another 30 minutes later the crude mesylate was added in THF (10 mL) and stirring was continued for 30 minutes before the mixture was poured onto vigorously stirred NH_4Cl/NH_4OH (9:1). After 10 minutes, the mixture was allowed to settle for 12 h. The layers were then separated, the aqueous layer extracted once with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/Et_3N, 100:1) yielded the product as a colorless liquid contaminated with some $(Bu_3Sn)_2$ (6.02 g, 13.2 mmol, 88% yield). **1H NMR (400 MHz, Chloroform-d) δ** 4.67 – 4.43 (m, 1H), 2.05 (td, J = 7.8, 7.4, 2.8 Hz, 2H), 1.59 (d, J = 6.8 Hz, 3H), 1.54 – 1.45 (m, 7H), 1.44 – 1.15 (m, 24H), 1.02 – 0.80 (m, 29H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 203.2, 93.0, 76.2, 33.3, 32.1, 30.8, 30.1, 29.6, 29.5, 29.4, 29.2, 27.5, 22.9, 14.3, 13.9, 10.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$)** δ -31.9 ppm.

8.3.3. Formal Synthesis of Tubelactomicin A

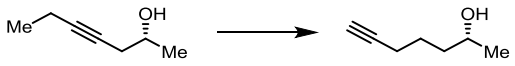
***(R)*-Hept-4-yn-2-ol - (SI-36)**



1-Butyne was condensed into a 500 mL two-necked flask equipped with a dropping funnel and a gas bubbler under dry-ice cooling until about 10 grams of liquid were obtained (175 mmol, 2.5 equiv.). Dry THF (50 mL) was added followed by slow addition of *n*-butyllithium (66 mL, 105 mmol, 1.5 equiv.). After the solution was stirred at the same temperature for a few minutes,

the flask was placed on an ice bath for 1 h. Dry DMPU (50 mL) was added followed by cooling of the mixture to −30 °C. *(R)*-Propylene oxide (4.90 mL, 70 mmol, 1.0 equiv.) in dry DMPU (50 mL) was added and the mixture was allowed to warm to room temperature over the course of 18 h. The reaction was then quenched with slow addition of saturated ammonium chloride solution. The mixture was extracted two times with diethyl ether, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, pentane/diethyl ether, 4:1) yielded the product after careful evaporation of the volatile materials as a pale yellow liquid (6.7 g, 59.7 mmol, 85% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +22.2° (c=1.02 in MeOH); -18.7° (c=1.13 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 3.98 – 3.81 (m, 1H), 2.36 (ddt, J = 16.3, 4.8, 2.4 Hz, 1H), 2.25 (ddt, J = 16.3, 6.8, 2.4 Hz, 1H), 2.18 (qt, J = 7.5, 2.4 Hz, 2H), 2.03 (s, 1H), 1.23 (d, J = 6.2 Hz, 3H), 1.12 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 84.8, 77.5, 66.6, 29.5, 22.3, 14.4, 12.5 ppm. **HRMS (ESI):** *m/z* calculated for $C_7H_{12}ONa$ [$M+Na^+$]: 135.07803, found 135.07811.

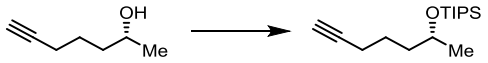
(R)-Hept-6-yn-2-ol[29] - (298)



Freshly distilled 1,3-diaminopropane (100 mL) was placed in a flame-dried two-necked flask under an argon atmosphere at room temperature. Lithium granula (1.25 g, 180 mmol, 6.0 equiv.) were added in one portion and stirring was continued until a dark blue mixture was obtained. The mixture was then heated to 70 °C until the color faded and a pale blueish/grey mixture was obtained which was allowed to cool down to room temperature. At this point and dry [2 h under high vacuum, 120 °C] KO*t*Bu (13.1 g, 117 mmol, 3.9 equiv.) was added in one portion. Stirring was continued for 30 minutes while the mixture turned into a yellowish green. *(R)*-Hept-4-yn-2-ol (**SI-36**) (3.36 g, 30 mmol, 1.0 equiv.) was added dropwise which resulted in a change of color to red and the reaction was quenched after another 30 minutes by pouring the mixture onto ice/water (250 mL). The mixture was extracted three times with diethyl ether, the combined extracts were washed with aqueous HCl (2 M), saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated under reduced pressure to give a pale yellow oil. Flash chromatography (SiO_2, pentane/diethyl ether, 3:1 to 2:1) yielded the product after careful concentration as a colorless liquid which was used directly in the next step. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: −14.5° (c=0.99 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 3.77 (qd, J = 5.9, 1.4 Hz, 1H), 2.17 (tdd, J = 6.7, 2.7, 1.3 Hz, 2H), 2.08 (s, 1H), 1.92 (td, J = 2.7, 1.2 Hz, 1H), 1.69 – 1.54 (m, 1H), 1.54 – 1.44 (m, 3H), 1.15 (dd, J = 6.2, 1.4 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 84.5, 68.6, 67.5, 38.2, 24.7, 23.6, 18.4 ppm. **IR (film, $CHCl_3$)** 3297, 2930, 1457, 1433, 1374, 1327, 1183, 1128, 1085,

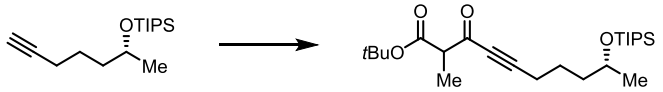
977, 944, 923, 862, 819, 624 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_7H_{12}ONa$ [M+Na^+]: 135.07803, found 135.07809.

(R)-(Hept-6-yn-2-yloxy)triisopropylsilane - (294)



(R)-Hept-6-yn-2-ol (3.36, 30 mmol, 1.0 equiv.) and imidazole (4.08 g, 60 mmol, 2.0 equiv.) were dissolved in dry DMF (60 mL) and the solution was stirred at room temperature in a single-necked flask. Tri-*iso*-propylsilyl chloride (9.63 mL, 45 mmol, 1.5 equiv.) was slowly added and stirring continued for 18 h until TLC showed complete consumption of starting material. The reaction was quenched with the addition of saturated ammonium chloride solution, the mixture was extracted three times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, pentane) yielded the product as a colorless oil (6.4 g, 23.8 mmol, 79% yield over 2 steps). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: −3.4° (c=1.08 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.04 – 3.91 (m, 1H), 2.26 – 2.11 (m, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.66 – 1.49 (m, 4H), 1.17 (d, J = 6.1 Hz, 3H), 1.06 (s, 18H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 84.7, 68.4, 68.2, 39.0, 24.4, 23.6, 18.8, 18.3, 12.6 ppm. **IR (film, $CHCl_3$)** 3314, 2942, 2866, 1462, 1375, 1245, 1136, 1097, 1028, 996, 918, 881, 750, 675, 627 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{16}H_{32}OSiNa$ [M+Na^+]: 291.21146, found 291.21157.

tert-Butyl (9*R*)-2-methyl-3-oxo-9-((triisopropylsilyl)oxy)dec-4-ynoate - (309)

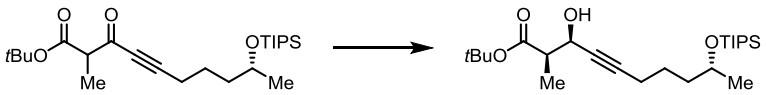


294 (2.27 g, 8.45 mmol, 1.0 equiv.) was dissolved in dry THF (40 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. *n*-Butyllithium (7.93 mL, 1.6 M in hexanes, 12.7 mmol, 1.5 equiv.) was slowly added and stirring continued for 30 minutes before neat methyl chloroformate (1.31 mL, 16.9 mmol, 2.0 equiv.) was added. The mixture was allowed to warm to room temperature and stirred for 30 minutes before the reaction was quenched with saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude material was used without purification.

Di-*iso*-propyl amine (3.55 mL, 25.4 mmol, 3.0 equiv.) was dissolved in dry THF (40 mL) and the solution stirred on an ice bath in an oven-dried Schlenk flask. *n*-Butyllithium (15.9 mL, 25.4 mmol, 3.0 equiv.) was added dropwise and stirring was continued for 10 minutes before the mixture was cooled with a dry-ice bath. *tert*-Butyl propionate (3.82 mL, 25.4 mmol,

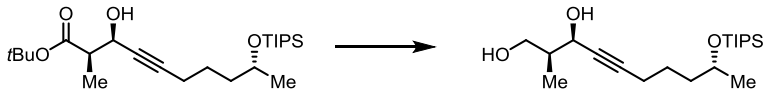
3.0 equiv.) was added and stirring continued for 30 minutes before the above prepared alkynoate in a minimum amount of THF was added dropwise. After being stirred at the same temperature for 2 h, the reaction was quenched with the addition of saturated ammonium chloride solution before being allowed to warm to room temperature. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 40:1) yielded the product as an inseperable mixture of tautomers (3.40 g, 8.0 mmol, 95% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: −1.6° (c=1.10 in $CHCl_3$).**TLC** (hexanes/ethyl acetate, 20:1), Rf = 0.22 and Rf = 0.45. **^{1}H NMR (400 MHz, Chloroform-d) δ** 12.28 (s, 0.65H), 4.03 – 3.90 (m, 1H), 3.48 – 3.38 (m, 0.35H), 2.41 (dt, J = 16.5, 6.8 Hz, 2H), 1.82 (s, 2H), 1.71 – 1.52 (m, 3H), 1.50 (s, 6H), 1.46 (s, 4H), 1.36 (d, J = 7.2 Hz, 1H), 1.16 (d, J = 6.1 Hz, 3H), 1.05 (s, 21H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 183.7, 173.1, 169.0, 152.0, 104.5, 99.8, 96.4, 82.0, 81.8, 75.4, 68.2, 68.0, 56.0, 39.2, 28.4, 28.0, 24.1, 23.7, 19.9, 19.5, 18.3, 18.3, 13.6, 12.9, 12.6 ppm. **IR (film, $CHCl_3$)** 2942, 2866, 2215, 1737, 1680, 1645, 1601, 1459, 1369, 1353, 1252, 1151, 1120, 1026, 995, 882, 846, 817, 757, 675 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{24}H_{44}O_4SiNa$ [M+Na$^+$]: 447.29011, found 447.29049.

***tert*-Butyl (*2R,3R,9R*)-3-hydroxy-2-methyl-9-((triisopropylsilyl)oxy)dec-4-ynoate[30] - (SI-37)**



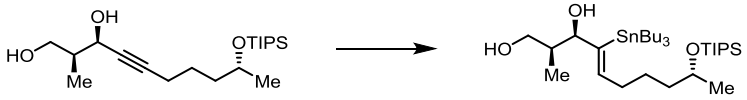
[(*R,R*)-Teth-TsDpen RuCl] (24.8 mg, 0.04 mmol, 0.5 mol%) and formic acid/triethylamine complex (5:2, 7.1 g) were placed in an oven-dried Schlenk flask under an argon atmosphere. **309** (3.4 g, 8.0 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (40 mL) and added to the catalyst solution. The mixture was stirred at room temperature with the conversion monitored by TLC (hexanes/ethyl acetate, 20:1). After 48 h the volatile materials were removed under reduced pressure and the crude yellow residue loaded onto a column. Flash chromatography (SiO_2, hexanes/ethyl acetate, 19:1) gave pure product (2.81 g, 6.59 mmol, 82% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +2.5° (c=1.22 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.52 (ddt, J = 7.2, 4.0, 2.0 Hz, 1H), 4.06 – 3.81 (m, 1H), 3.10 (dd, J = 7.4, 2.3 Hz, 1H), 2.62 (qd, J = 7.2, 4.0 Hz, 1H), 2.21 (tt, J = 4.9, 2.0 Hz, 2H), 1.54 (dddt, J = 8.3, 6.9, 4.4, 2.3 Hz, 4H), 1.47 (d, J = 1.8 Hz, 9H), 1.23 (dd, J = 7.2, 1.8 Hz, 3H), 1.15 (dd, J = 6.1, 1.8 Hz, 3H), 1.05 (d, J = 1.9 Hz, 21H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 173.8, 86.2, 81.6, 78.8, 68.2, 64.3, 46.3, 39.2, 28.2, 24.5, 23.6, 19.1, 18.3, 18.3, 12.6, 12.2 ppm. **IR (film, $CHCl_3$)** 3475, 2942, 2866, 1729, 1460, 1368, 1350, 1254, 1216, 1152, 1095, 1026, 918, 882, 849, 755, 709, 675 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{24}H_{46}O_4SiNa$ [M+Na$^+$]: 449.30576, found 449.30589

(2*S*,3*R*,9*R*)-2-Methyl-9-((triisopropylsilyl)oxy)dec-4-yne-1,3-diol - (310)



SI-37 (2.56 g, 6.0 mmol, 1.0 equiv.) was dissolved in dry THF (25 mL) and MeOH (2.5 mL) and the solution stirred on an ice bath in an oven-dried Schlenk flask under an argon atmosphere. $LiBH_4$ (4.5 mL, 4 M in THF, 18 mmol, 3.0 equiv.) was slowly added and the mixture subsequently heated to 70 °C on an oil bath (CAUTION: vigorus foaming the moment the reaction starts!) with the conversion monitored by TLC (hexanes/ethyl acetate, 4:1). After 15 minutes complete consumption of starting material was observed so the mixture was allowed to cool to room temperature. The mixture was then poured onto ice water and acidified carefully with aqueous HCl (2 M). The mixture was extracted three times with ethyl acetate, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 2:1) yielded the product as a colorless oil (1.97 g, 5.52 mmol, 92% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +7.8° (c=1.06 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.50 (ddt, J = 5.9, 4.0, 2.0 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.87 (ddd, J = 10.4, 8.3, 3.6 Hz, 1H), 3.68 (dt, J = 10.7, 4.2 Hz, 1H), 2.79 (d, J = 5.9 Hz, 1H), 2.25 (tt, J = 6.6, 1.9 Hz, 3H), 2.08 (dqt, J = 8.3, 7.0, 3.9 Hz, 1H), 1.65 – 1.45 (m, 4H), 1.16 (d, J = 6.1 Hz, 3H), 1.05 (s, 21H), 0.93 (d, J = 7.0 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 87.2, 79.2, 68.3, 67.2, 66.2, 40.5, 39.2, 24.7, 23.7, 19.1, 18.3, 18.3, 12.6 ppm. **IR (film, $CHCl_3$)** 3348, 2942, 2866, 1462, 1376, 1256, 1135, 1094, 1013, 917, 882, 756, 674 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{20}H_{40}O_3SiNa$ [M+Na^+]: 379.26389, found 379.26384.

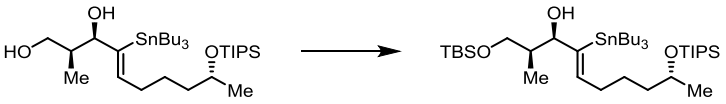
(2*S*,3*R*,9*R*,Z)-2-Methyl-4-(tributylstannyl)-9-((triisopropylsilyl)oxy)dec-4-ene-1,3-diol - (SI-38)



310 (1.95 g, 5.47 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (25 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere at room temperature. $[Cp^*RuCl_2]_n$ (84 mg, 0.27 mmol, 5.0 mol%) was added followed by dropwise addition of Bu_3SnH (1.62 mL, 6.01 mmol, 1.1 equiv.) over 1 h by means of a syringe pump. Upon completion, the volatile materials were removed under reduced pressure and the residue purified by flash chromatography (SiO_2, hexanes/ethyl acetate, 9:1) to give the product as a colorless oil (3.11 g, 4.80 mmol, 88% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +12.0° (c=1.16 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.43 – 6.00 (m, 1H), 4.37 – 4.18 (m, 1H), 3.99 – 3.86 (m, 1H), 3.63 (dd, J = 5.7, 4.8 Hz, 2H), 2.17 (s, 3H), 2.05 (qt, J = 10.3, 5.1 Hz, 2H), 1.96 (t, J = 5.7 Hz, 1H), 1.80 (d, J = 3.1 Hz, 1H), 1.73 – 1.63 (m, 1H), 1.58 – 1.37 (m, 8H), 1.36 – 1.26 (m, 6H), 1.15 (d, J = 6.1 Hz, 3H), 1.05 (s, 21H), 0.97 – 0.91

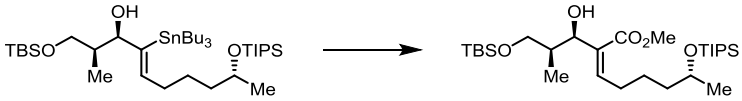
(m, 8H), 0.88 (t, J = 7.3 Hz, 9H) ppm**. ^{13}C NMR (101 MHz, $CDCl_3$) δ** 207.2, 146.7, 140.1, 80.7, 68.6, 67.1, 39.9, 34.9, 29.4, 27.6, 26.1, 23.6, 18.3, 18.3, 13.8, 12.6, 11.0, 10.7 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -55.5 ppm. **IR (film, $CHCl_3$)** 3385, 2925, 2866, 1462, 1376, 1247, 1187, 1133, 1098, 1029, 1013, 970, 918, 881, 758, 674 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{32}H_{68}O_3SiSnNa$ [M+Na^+]: 671.38512, found 671.38501.

(6*S*,7*R*,13*R*,Z)-15,15-Diisopropyl-2,2,3,3,6,13,16-heptamethyl-8-(tributylstannyl)-4,14-dioxa-3,15-disilaheptadec-8-en-7-ol - (308)



SI-38 (3.11 g, 4.8 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (25 ml) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on an ice bath. *tert*-Butyldimethylsilyl chloride (796 mg, 5.28 mmol, 1.1 equiv.) was added followed by the addition of Et_3N (736 µL, 5.28 mmol, 1.1 equiv.) over 20 minutes. Upon disappearance of starting material as determined by TLC, the reaction was quenched with the addition of saturated ammonium chloride solution. The mixture was extracted two times with CH_2Cl_2, the combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 40:1) yielded the product as a colorless oil (3.34 g, 4.38 mmol, 91% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +5.7° (c=1.10 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.24 (td, J = 7.2, 1.5 Hz, 1H), 4.36 (ddd, J = 4.0, 2.5, 1.4 Hz, 1H), 4.00 – 3.86 (m, 1H), 3.70 – 3.58 (m, 3H), 2.52 (d, J = 2.4 Hz, 1H), 2.15 – 1.94 (m, 2H), 1.68 – 1.57 (m, 1H), 1.56 – 1.37 (m, 9H), 1.37 – 1.24 (m, 6H), 1.15 (d, J = 6.1 Hz, 3H), 1.05 (s, 21H), 1.00 – 0.79 (m, 26H), 0.06 (s, 7H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 145.4, 139.5, 79.1, 68.6, 67.6, 40.0, 39.6, 35.0, 29.4, 27.6, 26.2, 26.0, 23.6, 18.3, 13.9, 12.6, 11.0, 10.1, -5.4, -5.4 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -55.9 ppm. **IR (film, $CHCl_3$)** 2955, 2927, 2865, 1463, 1376, 1252, 1202, 1133, 1095, 1005, 918, 882, 835, 775, 724, 673 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{38}H_{82}O_3Si_2SnNa$ [M+Na^+]: 785.47160, found 785.47165.

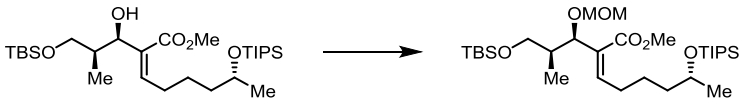
Methyl (*R*,Z)-2-((1*R*,2*S*)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxy-2-methyl-propyl)-7-((triisopropylsilyl)oxy)oct-2-enoate - (311)



308 (761 mg, 1.0 mmol, 1.0 equiv.) was dissolved in TFA solution in MeOH (0.1 M, 10 mL) and stirred in an oven-dried Schlenk flask under an argon atmosphere. 1,4-Benzoquinone (162 mg, 1.5 mmol, 1.5 equiv.), $AsPh_3$ (31 mg, 0.1 mmol, 10 mol%) and $Pd(OAc)_2$ (12 mg, 0.05 mmol, 5.0 mol%) were added and the mixture was flushed for 2 minutes with CO (balloon) before

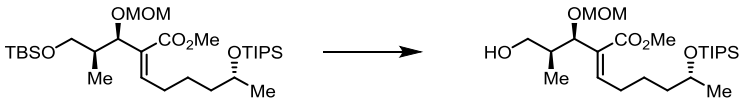
stirring was continued under positive CO pressure at 50 °C. Upon disappearance of starting material as judged by TLC, the mixture was filtered over Celite® with additional MTBE and the filtrate was concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 25:1) yielded the product as a pale yellow oil (373 mg, 0.70 mmol, 70% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +6.0° (c=1.15 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.24 (td, J = 7.5, 1.4 Hz, 1H), 4.65 (tt, J = 3.6, 1.4 Hz, 1H), 3.93 (hept, J = 5.2, 4.7 Hz, 1H), 3.79 (dd, J = 9.8, 3.6 Hz, 1H), 3.72 (s, 3H), 3.65 (dd, J = 9.8, 4.2 Hz, 1H), 3.54 (d, J = 3.7 Hz, 1H), 2.45 (qq, J = 14.1, 6.6 Hz, 2H), 1.85 (tp, J = 7.1, 3.2 Hz, 1H), 1.59 – 1.43 (m, 4H), 1.15 (d, J = 6.0 Hz, 3H), 1.05 (s, 21H), 0.90 (s, 9H), 0.86 (d, J = 7.1 Hz, 3H), 0.06 (d, J = 1.0 Hz, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 168.0, 142.5, 132.2, 74.7, 68.5, 68.1, 51.3, 39.8, 38.3, 29.8, 26.0, 25.3, 23.6, 18.3, 18.3, 12.6, 10.1, -5.45, -5.51 ppm. **IR (film, $CHCl_3$)** 3497, 2930, 2865, 1721, 1463, 1435, 1374, 1252, 1195, 1134, 1096, 1063, 1005, 918, 882, 835, 775, 723 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{28}H_{59}O_5Si_2$ $[M+H^+]$: 531.38956, found 531.38965.

Methyl (*R*,Z)-2-((1*R*,2*S*)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxy-2-methyl-propyl)-7-((triisopropylsilyl)oxy)oct-2-enoate diol - (SI-39)



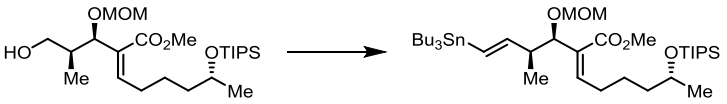
311 (655 mg, 1.23 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (7 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on an ice bath. Hünig's base (860 µL, 4.93 mmol, 4.0 equiv.) and MOMCl (281 µL, 3.70 mmol, 3.0 equiv.) were added in that order and stirring was continued at room temperature with the conversion monitored by TLC (hexanes/ethyl acetate, 10:1). After 24 h full conversion of starting material was observed. The mixture was diluted with CH_2Cl_2 and the reaction was quenched with the addition of saturated ammonium chloride solution. The organic layer was separated, the aqueous layer extracted two times with CH_2Cl_2, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 19:1) yielded the product as a colorless oil (605 mg, 1.05 mmol, 85% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +60.6° (c=1.44 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.05 (td, J = 7.5, 1.0 Hz, 1H), 4.61 (d, J = 6.6 Hz, 1H), 4.52 (d, J = 6.6 Hz, 1H), 4.48 – 4.38 (m, 1H), 4.02 – 3.86 (m, 1H), 3.71 (s, 3H), 3.58 (dd, J = 9.9, 6.1 Hz, 1H), 3.48 (dd, J = 9.9, 6.0 Hz, 1H), 3.37 (s, 3H), 2.42 (dq, J = 14.7, 7.6 Hz, 2H), 1.98 – 1.82 (m, 1H), 1.58 – 1.39 (m, 4H), 1.14 (d, J = 6.1 Hz, 3H), 1.05 (s, 22H), 0.89 (s, 13H), 0.03 (d, J = 2.6 Hz, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.7, 142.7, 131.1, 94.8, 77.0, 68.4, 65.4, 56.1, 51.4, 39.7, 39.6, 29.7, 26.0, 25.3, 23.7, 18.4, 18.3, 12.6, 11.5, -5.2 ppm. **IR (film, $CHCl_3$)** 2930, 2865, 1722, 1463, 1435, 1250, 1210, 1133, 1091, 1032, 921, 882, 835, 774, 674 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{30}H_{62}O_6Si_2Na$ $[M+Na^+]$: 597.39772, found 597.39768.

Methyl (*R*,Z)-2-((1*R*,2*S*)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxy-2-methyl-propyl)-7-((triisopropylsilyl)oxy)oct-2-enoate - (312)



SI-39 (450 mg, 0.78 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and the solution stirred on an ice bath in a Schlenk flask under an argon atmosphere. Aqueous HCl (2 M) was added, the ice bath removed and stirring was continued until disappearance of starting material was judged by TLC. The mixture was diluted with water and extracted two times with CH_2Cl_2. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 4:1) yielded the product as a colorless oil. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +77.8° (c=1.18 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.12 (td, J = 7.5, 1.1 Hz, 1H), 4.57 (d, J = 6.6 Hz, 1H), 4.55 – 4.48 (m, 2H), 3.97 – 3.87 (m, 1H), 3.73 (s, 3H), 3.64 – 3.51 (m, 2H), 3.39 (s, 3H), 2.54 – 2.37 (m, 2H), 2.35 (t, J = 6.0 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.58 – 1.37 (m, 4H), 1.14 (d, J = 6.1 Hz, 3H), 1.04 (s, 21H), 0.87 (d, J = 7.0 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 168.0, 143.2, 130.6, 95.1, 77.1, 68.4, 65.5, 56.2, 51.6, 39.7, 29.7, 25.3, 23.6, 18.3, 12.6, 11.4 ppm. **IR (film, $CHCl_3$)** 3468, 2942, 2891, 2866, 1720, 1462, 1436, 1377, 1210, 1136, 1096, 1029, 919, 882, 850, 675 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{24}H_{48}O_6SiNa$ [M+Na$^+$]: 483.31124, found 483.31142.

Methyl (*R*,Z)-2-((1*R*,2*S*,E)-1-(methoxymethoxy)-2-methyl-4-(tributyl-stannyl)but-3-en-1-yl)-7-((triisopropylsilyl)oxy)oct-2-enoate - (SI-40)

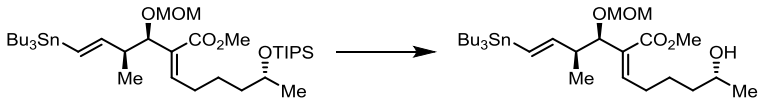


$NaHCO_3$ (341 mg, 4.06 mmol, 8.0 equiv.) and Dess-Martin periodinane (345 mg, 0.81 mmol, 1.6 equiv.) were weighed into an oven-dried Schlenk flask under an argon atmosphere and stirred in CH_2Cl_2 (4 mL) on an ice bath. **312** (234 mg, 0.51 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2 mL) and added to the reagent suspension. Conversion was monitored by TLC (hexanes/ethyl acetate, 4:1), Rf = 0.53. After about 6 h the reaction was quenched with the addition of saturated sodium bicarbonate solution. The mixture was diluted with saturated sodium thiosulfate solution, extracted two times with CH_2Cl_2, the combined organic layers were washed with saturated sodium bicarbonate solution, dried over magnesium sulfate and concentrated under reduced pressure. The crude aldehyde was used as such.

$CrCl_2$·THF (990 mg, 5.08 mmol, 10 equiv.) was weighed under argon into an oven-dried Schlenk flask. THF (10 mL) was added and the mixture stirred at room temperature under an argon atmosphere. DMF (393 µL, 5.08 mmol, 10 equiv.) was added dropwise and stirring continued for

15 minutes. A second oven-dried Schlenk flask was charged with the above prepared aldehyde in THF, the solvent was removed under HV and tributyl(dibromomethyl)stannane (517 mg, 1.12 mmol, 2.2 equiv.) was added. The mixture was dissolved in THF (2 mL) and added under argon to the chromium suspension. The flask was subsequently covered with aluminum foil. A third Schlenk flask was charged with LiI (272 g, 2.03 mmol, 4.0 equiv.) which was molten at ~10 mbar with a Bunsenburner. Upon cooling to room temperature, a stirring bar was added and the salt was solubilized in THF (2 mL) before it was added to the reagent mixture. The reaction was carried out for 18 h before it was quenched with the addition of water. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 40:1) yielded the product as a colorless oil as an inseparable mixture of 85:15 E/Z isomers (225 mg, 0.302 mmol, 60% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +21.5° (c=0.87 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.05 (td, J = 7.5, 0.9 Hz, 1H), 5.93 (d, J = 19.0 Hz, 1H), 5.90 – 5.83 (m, 1H), 4.60 (d, J = 6.7 Hz, 1H), 4.49 (d, J = 6.7 Hz, 1H), 4.24 (d, J = 6.6 Hz, 1H), 3.92 (tt, J = 7.2, 3.6 Hz, 1H), 3.71 (s, 3H), 3.36 (s, 3H), 2.56 – 2.47 (m, 1H), 2.47 – 2.28 (m, 2H), 1.57 – 1.36 (m, 10H), 1.36 – 1.22 (m, 6H), 1.14 (d, J = 6.0 Hz, 3H), 1.04 (s, 24H), 0.88 (t, J = 7.3 Hz, 9H), 0.86 – 0.81 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.6, 151.0, 143.7, 131.2, 127.9, 94.5, 79.9, 68.4, 56.0, 51.4, 45.7, 39.8, 29.8, 29.2, 27.4, 25.3, 23.6, 18.3, 18.3, 15.1, 13.9, 12.6, 9.5 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -49.1 ppm. **IR (film, $CHCl_3$)** 2926, 2867, 1723, 1462, 1376, 1291, 1246, 1194, 1152, 1097, 1030, 991, 920, 882, 675 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{37}H_{74}O_5SiSnNa$ [$M+Na^+$]: 769.42190, found 769.42204.

Methyl (R,Z)-7-hydroxy-2-((1R,2S,E)-1-(methoxymethoxy)-2-methyl-4-(tributyl-stannyl)-but-3-en-1-yl)oct-2-enoate - (272)



SI-40 (160 mg, 0.21 mmol, 1.0 equiv.) was dissolved in dry THF (2 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on an ice bath. TBAF (343 µL, 1 M in THF, 0.34 mmol, 1.6 equiv.) was added and stirring was continued for 18 h while the mixture was allowed to warm to room. The mixture was diluted with MTBE and the reaction quenched with the addition of saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 4:1) yielded the product as a colorless oil (76 mg, 0.215 mmol, 60% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +27.6° (c=1.20 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.07 (td, J = 7.7, 0.9 Hz, 1H), 5.92 (d, J = 19.0 Hz, 1H), 5.85 (dd, J = 19.0, 5.9 Hz, 1H), 4.60 (d, J = 6.7 Hz, 1H), 4.49 (d, J = 6.7 Hz, 1H), 4.24 (d, J = 6.6

Hz, 1H), 3.87 – 3.74 (m, 1H), 3.72 (s, 3H), 3.35 (s, 3H), 2.51 (dddd, J = 13.4, 8.3, 5.8, 3.9 Hz, 2H), 2.41 – 2.30 (m, 1H), 1.57 (d, J = 2.7 Hz, 1H), 1.54 – 1.40 (m, 10H), 1.33 – 1.22 (m, 6H), 1.18 (d, J = 6.2 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.3 Hz, 9H), 0.85 – 0.80 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 167.6, 150.9, 143.5, 131.4, 128.0, 94.5, 79.9, 67.7, 56.0, 51.5, 45.7, 38.9, 29.3, 29.2, 27.4, 25.6, 23.6, 15.1, 13.8, 9.5 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -49.1 ppm. **IR (film, $CHCl_3$)** 2955, 2925, 2871, 1720, 1458, 1436, 1375, 1291, 1211, 1153, 1096, 1029, 991, 961, 921, 863 cm^{-1}. **HRMS (ESI):** *m/z* calculated $C_{28}H_{54}O_5SnNa$ [M+Na^+]: 613.28847, found 613.28840.

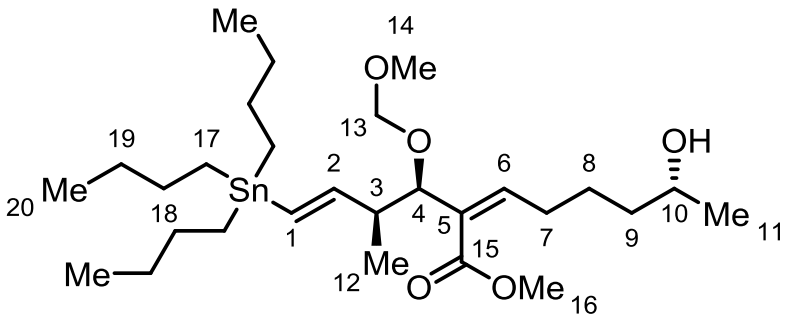
8.3.4. Comparison with published data

^{1}H-NMR

Position	Tadano *et al*[31]. [ppm]	coupling constants	current approach [ppm]	coupling constants	Δ [ppm]
1	5.94	(d, J = 19.1 Hz, 1H)	5.92	(d, J = 19.0 Hz, 1H)	0.04
2	5.86	(dd, J = 19.1, 5.5 Hz, 1H)	5.85	(dd, J = 19.0, 5.9 Hz, 1H)	0.01
3	2.37	(m, 1H)	2.41 – 2.30	(m, 1H)	0.01
4	4.25	(d, J = 6.6 Hz, 1H)	4.24	(d, J = 6.6 Hz, 1H)	0.01
5	-	-	-	-	-
6	6.08	(t, J = 7.6 Hz, 1H)	6.07	(td, J = 7.7, 0.9 Hz, 1H)	0.01
7	2.42-2.61	(m, 2H)	2.51	(dddd, J = 13.4, 8.3, 5.8, 3.9 Hz, 2H)	0.01
8	1.40-1.59	(m, 2H)	1.40-1.54	(m, 2H)	0.02
9	1.40-1.59	(m, 2H)	1.40-1.54	(m, 2H)	0.02
10	3.82	(m, 1H)	3.74-3.87	(m, 1H)	0.01
11	1.19	(d, J = 6.2 Hz, 3H)	1.18	(d, J = 6.2 Hz, 3H)	0.01
12	1.04	(d, J = 6.8 Hz, 3H)	1.03	(d, J = 6.8 Hz, 3H)	0.01
13a	4.62	(d, J = 6.8 Hz, 1H)	4.60	(d, J = 6.7 Hz, 1H)	0.02
13b	4.51	(d, J = 6.8 Hz, 1H)	4.49	(d, J = 6.7 Hz, 1H)	0.02
14	3.37	(s, 3H)	3.35	(s, 3H)	0.02
15	-	-	-	-	-
16	3.73	(s, 3H)	3.72	(s, 3H)	0.01
17	1.40-1.59	(m, 6H)	1.40-1.54	(m, 6H)	0.02
18	1.22-1.37	(m, 6H)	1.22-1.33	(m, 6H)	0.02
19	0.79-0.94	(m, 6H)	0.80-0.85	(m, 6H)	0.03
20	0.89	(t, J = 7.2 Hz, 9H)	0.87	(t, J = 7.3 Hz, 9H)	0.02

^{13}C-NMR

Position	Tadano et al. [31]	current approach	Δ
1	150.8	150.9	-0.1
2	127.9	128.0	-0.1
3	29.2	29.3	-0.1
4	79.8	79.9	-0.1
5	131.3	131.4	-0.1
6	143.4	143.5	-0.1
7	45.6	45.7	-0.1
8	38.8	38.9	-0.1
9	29.1	29.2	-0.1
10	67.6	67.7	-0.1
11	25.5	25.6	-0.1
12	15.0	15.1	-0.1
13a	94.4	94.5	-0.1
13b	94.4	94.5	-0.1
14	55.8	56.0	-0.2
15	167.4	167.6	-0.2
16	51.3	51.5	-0.2
17	23.5	23.6	-0.1
18	27.2	27.4	-0.2
19	9.3	9.5	-0.2
20	13.7	13.8	-0.1

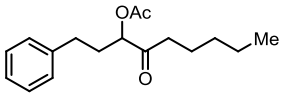


8.4. Oxidation of Alkenylstannanes to (Hydroxy)ketones

8.4.1. Representative procedure 10: Copper Acetate Mediated Oxidation of Alkenylstannanes

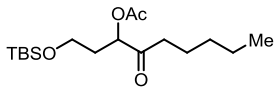
(Z)-1-Phenyl-4-(tributylstannyl)non-4-en-3-ol (**248**) (1.27 g, 2.5 mmol, 1.0 equiv.) was dissolved in reagent grade DMSO (20 mL). Copper acetate monohydrate (998 mg, 5.0 mmol, 2.0 equiv.) and reagent grade Et_3N (1.74 mL, 12.5 mmol, 5.0 equiv.) were added to the mixture and stirring was continued at 45 °C to 50 °C until disappearance of starting material was judged by TLC (hexanes/ethyl acetate, 15:1). The mixture was diluted with MTBE and washed with saturated ammonium chloride solution. The organic layer was separated, the aqueous layer extracted once with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 15:1) yielded the product as a colorless oil.

4-Oxo-1-phenylnonan-3-yl acetate - (396)



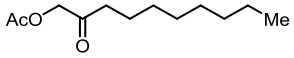
76% yield (527 mg, 1.91 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.33 – 7.27 (m, 2H), 7.24 – 7.14 (m, 3H), 4.99 (dd, J = 8.7, 4.1 Hz, 1H), 2.84 – 2.61 (m, 2H), 2.47 (ddd, J = 17.4, 7.8, 7.0 Hz, 1H), 2.36 (dt, J = 17.4, 7.4 Hz, 1H), 2.16 (s, 3H), 2.14 – 1.93 (m, 2H), 1.56 (dddd, J = 13.6, 9.0, 6.8, 1.2 Hz, 2H), 1.37 – 1.17 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 207.5, 170.7, 140.6, 128.7, 128.5, 126.4, 77.9, 38.7, 32.2, 31.7, 31.4, 22.9, 22.6, 20.8, 14.0 ppm. **IR (film, $CHCl_3$)** 3028, 2931 2956, 2861, 1727, 1742, 1604, 1497, 1455, 1373, 1230, 1041, 749, 700 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{24}O_3Na$ [M+Na$^+$]: 299.16176, found 299.16189.

1-((*tert*-Butyldimethylsilyl)oxy)-4-oxononan-3-yl acetate - (398)



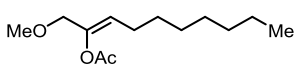
64% yield (106 mg, 0.32 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 5.15 (dd, J = 9.1, 3.7 Hz, 1H), 3.88 – 3.51 (m, 2H), 2.62 – 2.35 (m, 2H), 2.13 (s, 3H), 1.99 (dddd, J = 14.2, 8.1, 6.0, 3.7 Hz, 1H), 1.86 (ddt, J = 14.0, 9.3, 4.8 Hz, 1H), 1.66 – 1.52 (m, 2H), 1.38 – 1.20 (m, 4H), 0.88 (s, 12H), 0.04 (d, J = 1.2 Hz, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 207.5, 170.6, 75.4, 58.6, 38.8, 33.4, 31.5, 26.0, 23.1, 22.6, 20.8, 18.4, 14.1, -5.3, -5.4 ppm. **IR (film, $CHCl_3$)** 2955, 2929, 2858, 1730, 1745, 1471, 1373, 1234, 1094, 1022, 939, 834, 775, 730 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{35}O_4Si$ [M+H$^+$]: 331.22991, found 331.23006.

2-Oxodecyl acetate - (399)



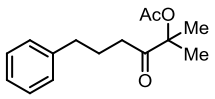
74% yield (79 mg, 0.37 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.65 (s, 2H), 2.40 (t, J = 7.4 Hz, 2H), 2.17 (s, 3H), 1.59 (dt, J = 5.2, 4.6 Hz, 2H), 1.38 – 1.17 (m, 10H), 0.95 – 0.75 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 203.3, 169.5, 67.2, 38.1, 31.1, 28.6, 28.4, 28.4, 22.6, 21.9, 19.8, 13.4 ppm. **IR (film, $CHCl_3$)** 2913, 2848, 2873, 1723, 1750, 1459, 1475, 1407, 1430, 1375, 1335, 1279, 1293, 1259, 1211, 1130, 1105, 1075, 1050, 1009, 982, 960, 897, 857 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{22}O_3Na$ [M+Na^+]: 237.14611, found 237.14611.

(Z)-1-methoxydec-2-en-2-yl acetate - (400)



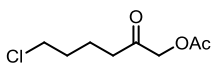
82% yield (94 mg, 0.41 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 5.31 (tt, J = 7.3, 0.7 Hz, 1H), 3.93 (q, J = 0.9 Hz, 2H), 3.32 (s, 3H), 2.18 (s, 3H), 1.97 (q, J = 7.2 Hz, 2H), 1.48 – 1.10 (m, 10H), 0.91 – 0.78 (m, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 169.0, 144.2, 121.3, 72.2, 58.0, 31.9, 29.3, 29.2, 28.9, 25.5, 22.8, 20.8, 14.2 ppm. **IR (film, $CHCl_3$)** 2925, 2855, 1756, 1457, 1369, 1203, 1090, 1017, 942, 914, 587 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{13}H_{24}O_3Na$ [M+Na^+]: 251.16176, found 251.16190.

2-Methyl-3-oxo-6-phenylhexan-2-yl acetate - (401)



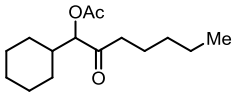
67% yield (83 mg, 0.33 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.32 – 7.23 (m, 2H), 7.18 (ddt, J = 7.1, 3.1, 1.3 Hz, 3H), 2.62 (dd, J = 8.3, 6.9 Hz, 2H), 2.45 (t, J = 7.3 Hz, 2H), 2.03 (s, 3H), 1.99 – 1.83 (m, 2H), 1.45 (s, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 208.8, 170.4, 141.8, 128.6, 128.4, 126.0, 83.7, 35.1, 34.9, 25.1, 23.8, 21.3 ppm. **IR (film, $CHCl_3$)** 2937, 1733, 1719, 1603, 1497, 1454, 1367, 1253, 1146, 1085, 1018, 963, 911, 849, 745, 699 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{20}O_3Na$ [M+Na^+]: 271.13046, found 271.13035.

6-Chloro-2-oxohexyl acetate - (402)



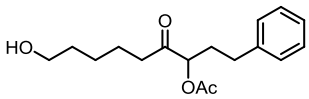
68% yield (65 mg, 0.34 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.64 (s, 2H), 3.64 – 3.47 (m, 2H), 2.46 (td, J = 6.1, 5.3, 1.3 Hz, 2H), 2.16 (s, 3H), 1.91 – 1.67 (m, 4H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 203.4, 170.4, 68.0, 44.6, 37.9, 31.8, 20.6 ppm. **IR (film, $CHCl_3$)** 2938, 1729, 1416, 1373, 1273, 1228, 1073, 1048, 1026, 982, 844, 725, 647 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_8H_{13}O_3ClNa$ [M+Na^+]: 215.04454, found 215.04469.

1-Cyclohexyl-2-oxoheptyl acetate - (403)



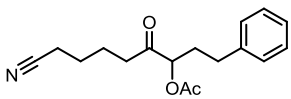
65% yield (82 mg, 0.32 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 4.86 (dd, J = 5.0, 1.7 Hz, 1H), 2.55 – 2.26 (m, 2H), 2.14 (d, J = 1.0 Hz, 3H), 1.87 (tq, J = 6.9, 4.3, 3.6 Hz, 1H), 1.80 – 1.70 (m, 2H), 1.70 – 1.47 (m, 4H), 1.41 – 1.06 (m, 10H), 1.00 – 0.82 (m, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 207.7, 170.9, 82.6, 39.8, 39.4, 31.5, 29.6, 27.5, 26.3, 26.1, 26.1, 22.9, 22.6, 20.8, 14.0 ppm. **IR (film, $CHCl_3$)** 2928, 2855, 1742, 1726, 1451, 1371, 1232, 1082, 1023, 990, 958, 920 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{26}O_3Na$ [M+Na^+]: 277.17741, found 277.17749.

9-Hydroxy-4-oxo-1-phenylnonan-3-yl acetate - (404)



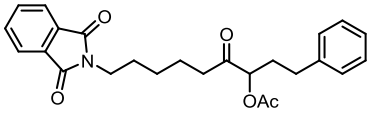
50% yield (73 mg, 0.25 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.34 – 7.26 (m, 2H), 7.24 – 7.13 (m, 3H), 4.99 (dd, J = 8.4, 4.4 Hz, 1H), 3.63 (t, J = 6.5 Hz, 2H), 2.70 (dq, J = 9.0, 6.5 Hz, 2H), 2.58 – 2.27 (m, 2H), 2.15 (s, 3H), 2.12 – 1.93 (m, 2H), 1.68 – 1.48 (m, 4H), 1.48 – 1.24 (m, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 207.2, 170.7, 140.6, 128.7, 128.5, 126.5, 78.0, 62.7, 38.6, 32.5, 32.2, 31.7, 25.4, 23.0, 20.8 ppm. **IR (film, $CHCl_3$)** 3433, 3027, 2933, 2863, 1720, 1603, 1497, 1455, 1373, 1229, 1041, 956, 884, 749, 700 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{24}O_4Na$ [M+Na^+]: 315.15668, found 315.15662.

8-Cyano-4-oxo-1-phenyloctan-3-yl acetate - (405)



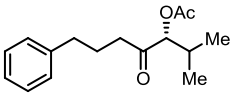
54% yield (78 mg, 0.27 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.34 – 7.27 (m, 2H), 7.25 – 7.19 (m, 1H), 7.19 – 7.12 (m, 2H), 4.99 – 4.91 (m, 1H), 2.82 – 2.65 (m, 2H), 2.54 (dt, J = 18.0, 6.8 Hz, 1H), 2.42 (dt, J = 17.9, 6.6 Hz, 1H), 2.33 (t, J = 6.9 Hz, 2H), 2.16 (s, 3H), 2.11 – 1.99 (m, 2H), 1.84 – 1.56 (m, 4H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 206.4, 170.8, 140.4, 128.7, 128.5, 126.5, 119.5, 77.8, 37.5, 32.1, 31.6, 24.8, 22.2, 20.8, 17.2 ppm. **IR (film, $CHCl_3$)** 3028, 2932, 1724, 1603, 1497, 1454, 1373, 1229, 1080, 1028, 950, 911, 750, 700 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{21}NO_3Na$ [M+Na^+]: 310.14136, found 310.14119.

9-(1,3-Dioxoisoindolin-2-yl)-4-oxo-1-phenylnonan-3-yl acetate - (406)



63% yield (132 mg, 0.31 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.86 – 7.79 (m, 2H), 7.70 (m, 2H), 7.31 – 7.24 (m, 2H), 7.23 – 7.13 (m, 3H), 4.96 (dd, J = 8.7, 4.2 Hz, 1H), 3.66 (t, J = 7.2 Hz, 2H), 2.81 – 2.58 (m, 2H), 2.47 (dt, J = 17.6, 7.3 Hz, 1H), 2.36 (dt, J = 17.7, 7.3 Hz, 1H), 2.14 (s, 3H), 2.12 – 1.94 (m, 2H), 1.71 – 1.51 (m, 4H), 1.38 – 1.24 (m, 2H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 207.1, 170.7, 168.5, 140.5, 134.0, 132.2, 128.7, 128.5, 126.4, 123.3, 77.9, 38.4, 37.9, 32.1, 31.6, 28.5, 26.4, 22.7, 20.8 ppm. **IR (film, $CHCl_3$)** 2937, 2864, 1771, 1740, 1706, 1604, 1497, 1466, 1455, 1436, 1395, 1369, 1229, 1188, 1081, 1041, 947, 874, 851, 794, 750 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{25}H_{27}NO_5Na$ [M+Na$^+$]: 444.17814, found 444.17851.

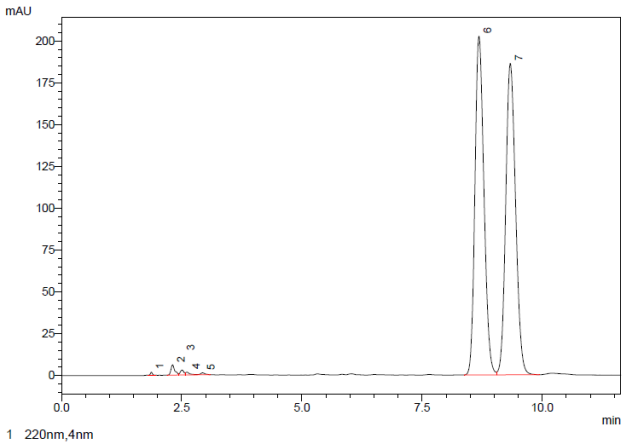
(*R*)-2-Methyl-4-oxo-7-phenylheptan-3-yl acetate - (407)



61% yield (80 mg, 0.31 mmol). $[\alpha]_D^{20}$: +4.7° (c=2.25 in $CHCl_3$). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.33 – 7.24 (m, 2H), 7.23 – 7.13 (m, 3H), 4.86 (d, J = 4.3 Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.58 – 2.31 (m, 2H), 2.26 – 2.14 (m, 1H), 2.13 (s, 3H), 2.02 – 1.85 (m, 2H), 0.98 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 207.2, 170.9, 141.7, 128.6, 128.5, 126.1, 82.8, 38.7, 35.1, 29.6, 24.8, 20.7, 19.4, 17.0 ppm. **IR (film, $CHCl_3$)** 2966, 1742, 1724, 1603, 1496, 1454, 1371, 1231, 1028, 949, 908, 746, 699 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{16}H_{22}O_3Na$ [M+Na$^+$]: 285.14611, found 285.14630.

The **enantiomeric excess** was determined by HPLC analysis to be **94%**.

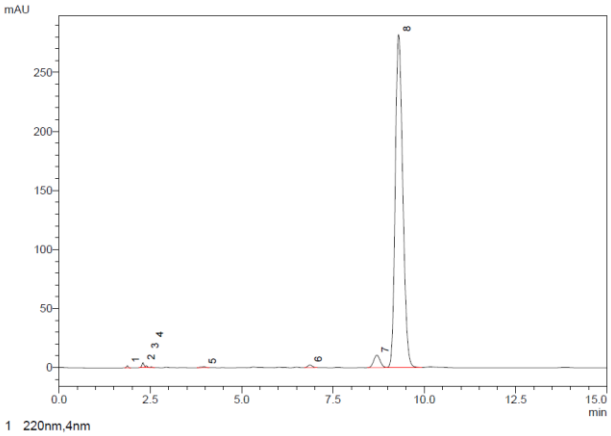
150 mm Chiralpak IC-3, 4.6 mm i.D., n-Heptane/2-Propanol = 98:2, 1.0 mL/min, 4.9 MPa, 298 K, UV 220 nm.



1 220nm,4nm

PDA Ch1 220nm

Peak #	Ret. Time	Area %	Name
1	1.87	0.10	
2	2.31	0.64	
3	2.51	0.29	
4	2.62	0.18	
5	2.93	0.16	
6	8.68	49.14	1. Enantiomer
7	9.33	49.49	2. Enantiomer
Total		100.00	

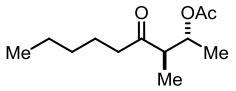


1 220nm,4nm

PDA Ch1 220nm

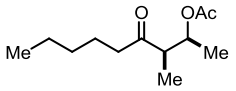
Peak #	Ret. Time	Area %	Name	
1	1.87	0.12		
2	2.30	0.42		
3	2.40	0.15		
4	2.52	0.06		
5	3.97	0.21		
6	6.87	0.47		
7	8.70	3.10	1. Enantiomer	ee = 93.7 %
8	9.29	95.46	2. Enantiomer	
Total		100.00		

(*anti*)-3-Methyl-4-oxononan-2-yl acetate - (408)



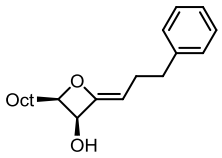
57% yield based on pure α (111 mg, 0.52 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 5.07 (dq, J = 7.9, 6.3 Hz, 1H), 2.77 (dq, J = 7.9, 7.1 Hz, 1H), 2.49 – 2.35 (m, 2H), 1.97 (s, 3H), 1.62 – 1.48 (m, 2H), 1.34 – 1.21 (m, 4H), 1.18 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 7.1 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 212.1, 170.2, 71.8, 50.9, 42.1, 31.5, 23.3, 22.6, 21.3, 17.1, 14.0, 12.3 ppm. **IR (film, $CHCl_3$)** 2957, 2933, 2873, 1736, 1714, 1457, 1408, 1372, 1235, 1090, 1036, 1017, 965, 946, 850 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{22}O_3Na$ [M+Na^+]: 237.14611, found 237.14630.

(*syn*)-3-Methyl-4-oxononan-2-yl acetate - (409)



59% yield based on pure α (114 mg, 0.53 mmol). **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 5.13 (p, *J* = 6.3 Hz, 1H), 2.70 (qd, *J* = 7.0, 6.1 Hz, 1H), 2.43 (td, *J* = 7.3, 4.5 Hz, 2H), 2.01 (s, 3H), 1.58 – 1.48 (m, 2H), 1.37 – 1.19 (m, 4H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 211.9, 170.4, 71.2, 50.7, 42.6, 31.5, 23.3, 22.6, 21.3, 17.9, 14.0, 12.3 ppm. **IR (film, $CHCl_3$)** 2957, 2933, 2873, 1736, 1714, 1457, 1408, 1372, 1235, 1090, 1036, 1017, 965, 946, 850 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{22}O_3Na$ [M+Na^+]: 237.14611, found 237.14630.

1-((*2S,3S*,Z)-3-Hydroxy-4-(3-phenylpropylidene)oxetan-2-yl)octan-1-one - (410)

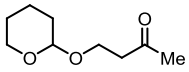


58% yield (87 mg, 0.29 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.32 – 7.25 (m, 2H), 7.20 (dt, J = 8.2, 2.0 Hz, 3H), 4.99 (ddq, J = 8.7, 5.9, 1.3 Hz, 1H), 4.70 (td, J = 7.0, 5.9 Hz, 1H), 4.43 (td, J = 7.5, 1.5 Hz, 1H), 2.78 – 2.58 (m, 2H), 2.32 (qd, J = 7.5, 1.1 Hz, 2H), 2.01 (d, J = 9.2 Hz, 1H), 1.68 (q, J = 6.9 Hz, 2H), 1.49 – 1.18 (m, 12H), 0.95 – 0.83 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 161.1, 142.0, 128.7, 128.3, 125.9, 96.9, 86.5, 69.6, 36.0, 32.0, 29.7, 29.6, 29.4, 29.2, 24.7, 24.6, 22.8, 14.3 ppm. **IR (film, $CHCl_3$)** 3407, 3027, 2924, 2855, 1716, 1604, 1496, 1454, 1365, 1304, 1234, 1201, 1144, 1069, 984, 940, 893, 848, 746, 724 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{20}H_{30}O_2Na$ [M+Na^+]: 325.21380, found 325.21402.

8.4.2. Representative procedure 11: Copper Trifluoroacetate Mediated Oxidation of Alkenylstannanes

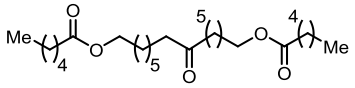
SI-54 (223 mg, 0.5 mmol, 1.0 equiv.) was dissolved in reagent grade DMSO (4 mL). Copper(II) trifluoroacetate hydrate (290 mg, 1.0 mmol, 2.0 equiv.) and reagent grade Et_3N (349 µL, 2.5 mmol, 5.0 equiv.) were added to the mixture and stirring was continued at 45 °C to 50 °C until disappearance of starting material was judged by TLC (hexanes/ethyl acetate, 15:1). The mixture was diluted with MTBE and washed with saturated ammonium chloride solution. The organic layer was separated, the aqueous layer extracted once with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 9:1) yielded the product as a colorless oil.

4-((Tetrahydro-2H-pyran-2-yl)oxy)butan-2-one - (411)



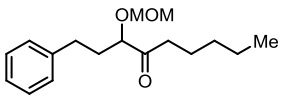
70% yield (60 mg, 0.35 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.55 (dd, J = 4.5, 2.9 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.87 – 3.75 (m, 1H), 3.70 – 3.60 (m, 1H), 3.53 – 3.41 (m, 1H), 2.67 (td, J = 6.2, 1.5 Hz, 2H), 2.15 (s, 3H), 1.81 – 1.69 (m, 1H), 1.69 – 1.57 (m, 1H), 1.57 – 1.41 (m, 4H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 207.3, 99.2, 62.7, 62.4, 43.8, 30.7, 30.6, 25.5, 19.6 ppm. **IR (film, $CHCl_3$)** 2942, 1714, 1355, 1324, 1260, 1201, 1161, 1135, 1120, 1065, 1032, 1019, 979, 904, 869, 813, 755 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_9H_{16}O_3Na$ [M+Na$^+$]: 195.09916, found 195.09925.

7-Oxotetradecane-1,14-diyl dihexanoate - (412)



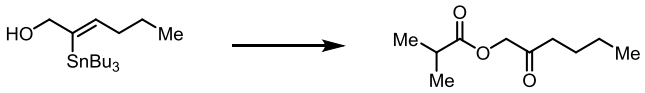
50% yield (55 mg, 0.13 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.04 (t, J = 6.7 Hz, 4H), 2.38 (td, J = 7.4, 2.3 Hz, 4H), 2.28 (t, J = 7.6 Hz, 4H), 1.71 – 1.48 (m, 12H), 1.42 – 1.17 (m, 18H), 0.96 – 0.75 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 211.4, 174.13, 174.12, 64.4, 64.3, 42.9, 42.8, 34.5, 31.5, 29.3, 29.2, 29.0, 28.7, 28.6, 25.9, 24.8, 23.8, 23.8, 22.5, 14.1 ppm. **IR (film, $CHCl_3$)** 2931, 2858, 1734, 1464, 1416, 1359, 1246, 1171, 1099 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{26}H_{48}O_5Na$ [M+Na$^+$]: 463.33939, found 463.33932.

3-(Methoxymethoxy)-1-phenylnonan-4-one - (413)



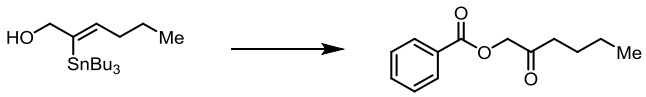
68% yield (95 mg, 0.34 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.34 – 7.24 (m, 2H), 7.24 – 7.14 (m, 3H), 4.66 (d, J = 0.7 Hz, 2H), 4.06 – 3.93 (m, 1H), 3.40 (s, 3H), 2.87 – 2.61 (m, 2H), 2.49 (dd, J = 7.8, 7.0 Hz, 2H), 2.04 – 1.91 (m, 2H), 1.69 – 1.49 (m, 2H), 1.43 – 1.18 (m, 4H), 0.93 – 0.83 (m, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 211.6, 141.3, 128.6, 128.6, 126.3, 96.8, 82.2, 56.3, 38.6, 34.0, 31.7, 31.6, 23.1, 22.6, 14.0 ppm. **IR (film, $CHCl_3$)** 2929, 1715, 1497, 1455, 1148, 1104, 1027, 920, 747, 699, 494 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{26}O_3Na$ [M+Na^+]: 301.17741, found 301.17752.

2-Oxohexyl isobutyrate - (415)



414 (389 mg, 1.0 mmol, 1.0 equiv.) was dissolved in reagent grade DMSO (8 mL). Copper(II) isobutyrate (475 mg, 2.0 mmol, 2.0 equiv.) and reagent grade Et_3N (697 µL, 5.0 mmol, 5.0 equiv.) were added to the mixture and stirring was continued at 45 °C to 50 °C until disappearance of starting material was judged by TLC (hexanes/ethyl acetate, 15:1). The mixture was diluted with MTBE and washed with saturated ammonium chloride solution. The organic layer was separated, the aqueous layer extracted once with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 25:1) yielded the product as a colorless oil (76 mg, 0.41 mmol, 41% yield). **^{1}H NMR (300 MHz, Chloroform-d) δ** 4.63 (s, 2H), 2.67 (p, J = 7.0 Hz, 1H), 2.41 (t, J = 7.4 Hz, 2H), 1.67 – 1.52 (m, 2H), 1.41 – 1.26 (m, 2H), 1.22 (d, J = 7.0 Hz, 6H), 0.90 (t, J = 7.3 Hz, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 204.3, 176.5, 67.9, 38.7, 33.9, 25.5, 22.4, 19.1, 13.9 ppm. **IR (film, $CHCl_3$)** 2935, 2875, 1729, 1469, 1416, 1386, 1253, 1188, 1159, 1126, 1099, 1075, 1022, 979 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{10}H_{18}O_3Na$ [M+Na^+]: 209.11481, found 209.11489.

2-Oxohexyl benzoate - (416)

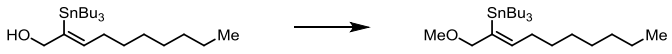


414 (389 mg, 1.0 mmol, 1.0 equiv.) was dissolved in reagent grade DMSO (8 mL). Copper(II) trifluoroacetate hydrate (475 mg, 2.0 mmol, 2.0 equiv.), sodium benzoate (576 mg, 4.0 mmol, 4.0 equiv.) and reagent grade Et_3N (697 µL, 5.0 mmol, 5.0 equiv.) were added to the mixture and stirring was continued at 45 °C to 50 °C until disappearance of starting material was judged by TLC (hexanes/ethyl acetate, 15:1). The mixture was diluted with MTBE and washed with saturated ammonium chloride solution. The organic layer was separated, the aqueous layer extracted once with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 25:1) yielded the product as a colorless oil (136 mg, 0.62 mmol, 62% yield). **^{1}H NMR (300 MHz, Chloroform-d) δ** 8.17 – 8.00 (m, 2H), 7.65 – 7.54 (m, 1H), 7.52 – 7.38 (m, 2H), 4.88 (s, 2H), 2.50 (t, J = 7.4 Hz, 2H), 1.72 – 1.56 (m, 2H), 1.43 – 1.28 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 204.3, 166.0, 133.5, 130.0, 129.4, 128.6, 68.5, 38.8, 25.5, 22.4, 13.9 ppm. **IR (film, $CHCl_3$)** 2959, 2933, 2873, 1718, 1601, 1452, 1414, 1377, 1315, 1272, 1177, 1115, 1060, 1027, 804, 709 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{13}H_{16}O_3Na$ [M+Na^+]: 243.09916, found 243.09929.

Substrate synthesis

The following compounds were prepared according to representative procedure 9.

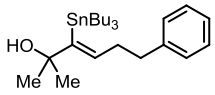
(Z)-Tributyl(1-methoxydec-2-en-2-yl)stannane - (SI-41)



An oven-dried schlenk flask was charged with NaH (180 mg, 7.5 mmol, 1.5 equiv.) under argon. THF (20 mL) was slowly added, the mixture was cooled with an ice bath. **SI-21** (2.23 g, 5.0 mmol, 1.0 equiv.) in a minimum amount of THF was added dropwise. Stirring was continued for 30 minutes at 0 °C before MeI (622 µL, 10.0 mmol, 2.0 equiv.) was slowly added and the mixture allowed to warm to room temperature. After being stirred for 12 h, the reaction was quenched with water at 0 °C and acidified with saturated ammonium chloride solution. The mixture was extracted twice with MTBE, the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 30:1) yielded the product as a colorless oil (2.14 g, 4.65 mmol,

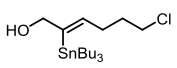
93% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.23 (tt, J = 7.1, 1.2 Hz, 1H), 4.00 – 3.88 (m, 2H), 3.25 (d, J = 0.9 Hz, 3H), 2.02 (q, J = 7.1 Hz, 2H), 1.55 – 1.41 (m, 6H), 1.41 – 1.19 (m, 16H), 1.01 – 0.73 (m, 18H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 143.5, 140.6, 80.6, 57.4, 34.8, 32.0, 30.2, 29.6, 29.4, 29.4, 27.6, 22.8, 14.3, 13.9, 10.4 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -52.5 ppm. **IR (film, $CHCl_3$)** 2955, 2853, 2871, 2815, 1624, 1463, 1419 , 1366, 1376, 1349, 1267, 1291, 1192, 1148, 1110, 1094, 1072, 1002, 1019, 960, 915, 860 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{48}OSnNa$ [M+Na^+]: 483.26186, found 483.26238.

(Z)-2-Methyl-6-phenyl-3-(tributylstannyl)hex-3-en-2-ol - (SI-42)



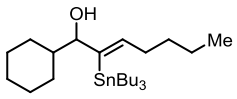
quant. yield (5.16 g, 10.8 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.36 – 7.27 (m, 2H), 7.24 – 7.12 (m, 3H), 6.16 (t, J = 7.2 Hz, 1H), 2.78 – 2.60 (m, 2H), 2.41 – 2.28 (m, 2H), 1.57 – 1.41 (m, 6H), 1.39 – 1.31 (m, 6H), 1.31 (s, 7H), 0.99 – 0.92 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 154.2, 142.0, 135.6, 128.6, 128.5, 126.0, 75.5, 36.7, 35.9, 30.9, 29.4, 27.6, 13.9, 12.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -55.6 ppm. **IR (film, $CHCl_3$)** 2955, 2853, 2871, 2815, 1624, 1463, 1419 , 1366, 1376, 1349, 1267, 1291, 1192, 1148, 1110, 1094, 1072, 1002, 1019, 960, 915, 860 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{25}H_{44}OSnNa$ [M+Na^+]: 503.23056, found 503.23061.

(Z)-6-Chloro-2-(tributylstannyl)hex-2-en-1-ol - (SI-43)



75% yield (1.58 g, 3.73 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.21 (tt, J = 7.1, 1.5 Hz, 1H), 4.28 – 4.12 (m, 2H), 3.54 (q, J = 6.7 Hz, 2H), 2.19 (dddd, J = 7.8, 6.9, 6.0, 1.2 Hz, 2H), 2.00 – 1.74 (m, 2H), 1.70 – 1.38 (m, 6H), 1.38 – 1.27 (m, 6H), 1.24 (d, J = 5.9 Hz, 1H), 1.07 – 0.93 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 145.1, 139.4, 70.5, 44.7, 32.9, 31.8, 29.4, 27.6, 13.9, 10.4 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -52.3 ppm. **IR (film, $CHCl_3$)** 3312, 2955, 2923, 2871, 2851, 1622, 1458, 1376 1340, 1290, 1182, 1072, 999, 961, 866, 767, 727, 657 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{18}H_{36}OClSn$ [M-H^+]: 423.14815, found 423.14812.

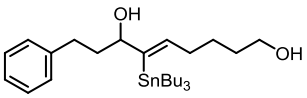
(Z)-1-Cyclohexyl-2-(tributylstannyl)hept-2-en-1-ol - (SI-44)



66% yield (3.2 g, 6.59 mmol). **^{1}H NMR (400 MHz, Chloroform-d)** 6.29 – 5.84 (m, 1H), 3.87 – 3.61 (m, 1H), 2.10 – 1.89 (m, 2H), 1.83 – 1.58 (m, 3H), 1.58 – 1.39 (m, 6H), 1.38 – 1.25 (m, 12H), 1.18 (dtt, J = 20.5, 9.1, 3.3 Hz, 2H),

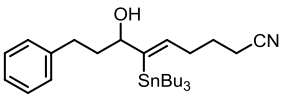
1.02 – 0.68 (m, 22H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.0, 142.1, 85.4, 43.1, 34.2, 32.5, 30.3, 29.4, 28.8, 27.6, 26.7, 26.3, 26.3, 22.8, 14.2, 13.9, 11.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$)** δ -55.5 ppm. **IR (film, $CHCl_3$)** 3482, 2955, 2921, 2851, 1615, 1451, 1376, 1257, 1202, 1148, 1069, 1001, 961, 890, 862 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{25}H_{49}OSn$ [M-H^+]: 485.28102, found 485.28097.

(Z)-9-Phenyl-6-(tributylstannyl)non-5-ene-1,7-diol - (SI-45)



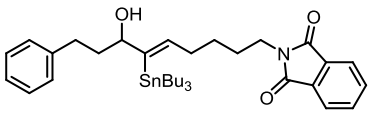
68% yield (2.68 g, 5.12 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.39 – 7.29 (m, 2H), 7.29 – 7.19 (m, 3H), 6.24 (td, J = 7.1, 1.1 Hz, 1H), 4.37 – 4.04 (m, 1H), 3.70 (td, J = 6.4, 5.0 Hz, 2H), 2.86 – 2.53 (m, 2H), 2.15 (q, J = 7.3 Hz, 2H), 1.99 – 1.74 (m, 2H), 1.72 – 1.60 (m, 4H), 1.60 – 1.48 (m, 4H), 1.48 – 1.28 (m, 6H), 1.13 – 0.85 (m, 18H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 148.4, 142.2, 140.5, 128.5, 128.4, 125.8, 79.3, 62.8, 39.4, 34.0, 32.6, 32.4, 29.4, 27.5, 26.4, 13.8, 11.2 ppm. **^{119}Sn NMR (112 MHz, $CDCl_3$) δ** -55.3 ppm. **IR (film, $CHCl_3$)** 3391, 2954, 2924, 2854, 1742, 1727, 1496, 1455, 1374, 1241, 1046, 864, 747, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{27}H_{48}O_2SnNa$ [M+Na^+]: 547.25678, found 547.25751.

(Z)-7-Hydroxy-9-phenyl-6-(tributylstannyl)non-5-enenitrile - (SI-46)



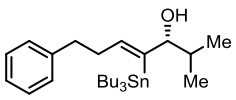
89% yield (2.3 g, 4.44 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.34 – 7.26 (m, 2H), 7.20 (m, 3H), 6.13 (td, J = 7.1, 1.1 Hz, 1H), 4.27 – 4.03 (m, 1H), 2.76 – 2.56 (m, 2H), 2.35 (t, J = 7.2 Hz, 2H), 2.20 (q, J = 7.2 Hz, 2H), 1.89 – 1.64 (m, 4H), 1.55 (d, J = 3.3 Hz, 1H), 1.53 – 1.38 (m, 6H), 1.38 – 1.26 (m, 6H), 1.04 – 0.92 (m, 6H), 0.90 (t, J = 7.3 Hz, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 150.9, 142.0, 137.5, 128.5, 128.5, 125.9, 119.6, 79.0, 39.4, 33.1, 32.4, 29.4, 27.5, 25.9, 16.9, 13.8, 11.2 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$)** δ -54.7 ppm. **IR (film, $CHCl_3$)** 3500, 3027, 2954, 2924, 2870, 2853, 1738, 1604, 1495, 1455, 1422, 1375, 1339, 1243, 1180, 1151, 1046, 961, 915, 877, 748 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{27}H_{45}NOSnNa$ [M+Na^+]: 542.24146, found 542.24170.

(Z)-2-(7-Hydroxy-9-phenyl-6-(tributylstannyl)non-5-en-1-yl)isoindoline-1,3-dione - (SI-47)



76% yield (1.02 g, 1.56 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.87 – 7.77 (m, 2H), 7.74 – 7.64 (m, 2H), 7.26 (ddd, J = 7.8, 7.1, 0.9 Hz, 2H), 7.22 – 7.13 (m, 3H), 6.15 (td, J = 7.2, 1.1 Hz, 1H), 4.28 – 4.00 (m, 1H), 3.69 (t, J = 7.2 Hz, 2H), 2.64 (qdd, J = 13.8, 9.8, 6.1 Hz, 2H), 2.10 (q, J = 7.3 Hz, 2H), 1.87 – 1.77 (m, 1H), 1.71 (dq, J = 9.8, 6.9 Hz, 4H), 1.58 – 1.37 (m, 8H), 1.37 – 1.18 (m, 6H), 1.08 – 0.90 (m, 6H), 0.86 (t, J = 7.3 Hz, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 168.4, 148.6, 142.2, 140.0, 133.9, 132.1, 128.5, 128.3, 125.7, 123.2, 79.2, 39.3, 37.9, 33.8, 32.3, 29.3, 28.4, 27.4, 27.3, 13.7, 11.1 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -55.2 ppm. **IR (film, $CHCl_3$)** 2925, 2854, 1773, 1739, 1712, 1455, 1438, 1395, 1371, 1238, 1044, 961, 918, 873, 849, 792, 747 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{35}H_{51}NO_3SnNa$ [M+Na^+]: 676.27824, found 676.27876.

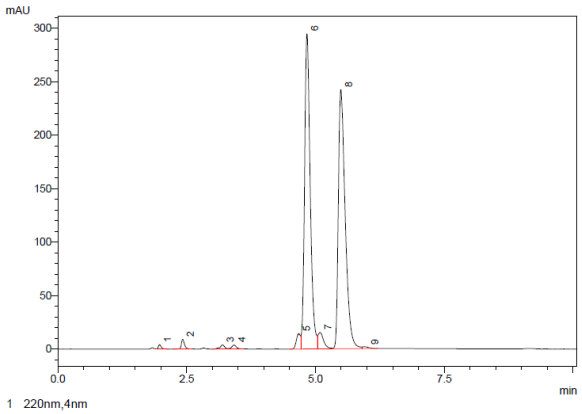
(*R,Z*)-2-Methyl-7-phenyl-4-(tributylstannyl)hept-4-en-3-ol - (SI-48)



91% yield (2.05 g, 4.15 mmol). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: –9.7° (c=2.23 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.33 – 7.24 (m, 2H), 7.24 – 7.11 (m, 3H), 6.16 (td, J = 7.2, 1.1 Hz, 1H), 3.71 (ddd, J = 8.1, 3.2, 1.1 Hz, 1H), 2.69 (dd, J = 9.1, 6.6 Hz, 2H), 2.45 – 2.30 (m, 2H), 1.60 – 1.41 (m, 7H), 1.40 (d, J = 3.2 Hz, 1H), 1.37 – 1.25 (m, 6H), 0.99 – 0.91 (m, 9H), 0.89 (t, J = 7.2 Hz, 9H), 0.79 (d, J = 6.8 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 148.4, 141.9, 140.6, 128.6, 128.5, 126.0, 86.3, 36.6, 36.3, 33.5, 29.4, 27.6, 20.1, 18.3, 13.8, 11.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -55.2 ppm. **IR (film, $CHCl_3$)** 3480, 3027, 2954, 2922, 2870, 2853, 1614, 1496, 1455, 1376, 1273, 1178, 1071, 1004, 959, 874, 745, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{26}H_{46}OSnNa$ [M+Na^+]: 517.24621, found 517.24652.

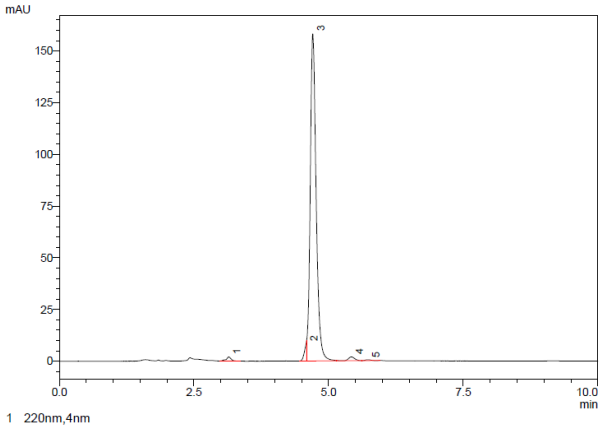
The **enantiomeric excess** was determined by HPLC analysis to be **98%**.

150 mm Chiralpak IA-3, 4.6 mm i.D., Säule 3, n-Heptane/2-Propanol = 99.9:0.1 (v/v), 1.0 ml/min, 6.3 MPa, 298 K, UV 220 nm.



1 220nm,4nm
PDA Ch1 220nm

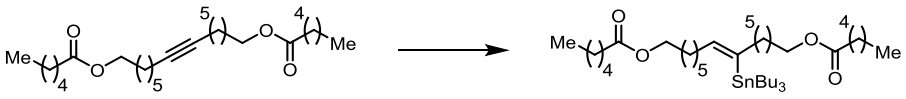
Peak #	Ret. Time	Area %	Name
1	1.97	0.31	
2	2.42	0.79	
3	3.20	0.50	
4	3.42	0.46	
5	4.67	1.69	
6	4.84	46.76	1. Enantiomer
7	5.09	2.44	
8	5.49	46.76	2. Enantiomer
9	6.00	0.29	
Total		100.00	



1 220nm,4nm
PDA Ch1 220nm

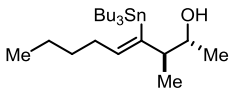
Peak #	Ret. Time	Area %	Name	
1	3.15	0.97		
2	4.58	1.96		
3	4.71	95.66	1. Enantiomer	= 97.5 % ee
4	5.42	1.23	2. Enantiomer	
5	5.73	0.18		
Total		100.00		

(Z)-7-(Tributylstannyl)tetradec-7-ene-1,14-diyl dihexanoate - (SI-49)



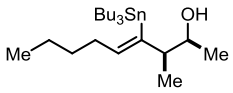
SI-63 (1.69 g, 4.0 mmol, 1.0 equiv.) and $[Cp^*Ru(MeCN)_3]PF_6$ (100 mg, 0.2 mmol, 5.0 mol%) were dissolved in dry CH_2Cl_2 (10 mL) and the solution was stirred at room temperature under an argon atmosphere (high concentration necessary for good conversion). The stannane was added over 2 h by means of a syringe pump. Upon completion of addition, the volatile materials were removed and the crude mixture purified by flash chromatography (hexanes/ethyl acetate, 19:1) to yield the product as a pale brown oil (2.3 g, 3.2 mmol, 81% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.02 (td, J = 6.7, 1.3 Hz, 4H), 2.25 (t, J = 7.5 Hz, 4H), 2.15 – 2.04 (m, 2H), 1.93 (q, J = 6.6 Hz, 2H), 1.70 – 1.49 (m, 6H), 1.51 – 1.36 (m, 6H), 1.28 (dddd, J = 14.4, 11.9, 8.5, 5.4 Hz, 22H), 1.04 – 0.65 (m, 28H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 173.9, 143.4, 140.6, 64.4, 40.7, 35.0, 34.4, 31.4, 30.6, 30.3, 29.4, 29.2, 28.9, 28.8, 28.7, 27.5, 26.0, 25.9, 24.8, 22.4, 14.0, 13.8, 10.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -53.2 ppm. **IR (film, $CHCl_3$)** 2955, 2925, 2855, 1737, 1462, 1377, 1360, 1244, 1205, 1169, 1098, 1000, 862 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{38}H_{74}O_4SnNa$ $[M+Na^+]$: 737.45006, found 737.45014.

(*anti*,Z)-3-Methyl-4-(tributylstannyl)non-4-en-2-ol - (SI-50)



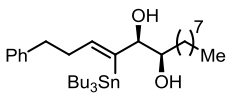
91% yield (9.43 g, 21.2 mmol; α/β = 12:1). **^{1}H NMR (300 MHz, Chloroform-d) δ** 6.17 (td, J = 7.1, 0.8 Hz, 1H), 3.48 (dqt, J = 8.0, 4.6, 1.9 Hz, 1H), 2.26 – 2.12 (m, 1H), 2.12 – 1.97 (m, 2H), 1.86 (dd, J = 1.7, 0.8 Hz, 1H), 1.55 – 1.42 (m, 6H), 1.42 – 1.21 (m, 8H), 1.16 (d, J = 6.0 Hz, 3H), 1.09 – 0.51 (m, 23H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 147.0, 143.7, 70.6, 53.9, 34.6, 32.6, 29.4, 27.6, 22.7, 20.1, 18.0, 14.2, 13.8, 11.5 ppm. **^{119}Sn NMR (112 MHz, $CDCl_3$) δ** -54.4 ppm. **IR (film, $CHCl_3$)** 2923, 2871, 2854, 1457, 1419, 1376, 1340, 1264, 1120, 1071, 1046, 1002, 961, 926, 666 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{22}H_{46}OSnNa$ [M+Na^{+}]: 469.24621, found 469.24663.

(*syn*,Z)-3-Methyl-4-(tributylstannyl)non-4-en-2-ol - (SI-51)



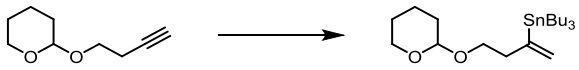
62% yield (5.76 g, 12.9 mmol; α/β = 10:1). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.30 – 5.86 (m, 1H), 3.60 (dddd, J = 9.6, 8.6, 6.3, 3.2 Hz, 1H), 2.40 – 2.19 (m, 1H), 2.01 (pd, J = 6.8, 2.0 Hz, 2H), 1.58 – 1.41 (m, 6H), 1.41 – 1.24 (m, 11H), 1.15 (d, J = 6.3 Hz, 3H), 1.05 – 0.99 (m, 3H), 0.95 – 0.78 (m, 18H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 147.0, 141.1, 69.7, 49.7, 35.1, 32.7, 29.4, 27.6, 22.8, 21.2, 14.4, 14.3, 13.8, 11.0 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ -52.00** ppm. **IR (film, $CHCl_3$)** 3341, 2956, 2923, 2871, 2854, 1458, 1418, 1376, 1340, 1291, 1249, 1151, 1076, 1047, 1019, 960, 923, 899, 862, 768 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{22}H_{45}OSn$ [M-H^{+}]: 445.24972, found 445.24996.

(5S,6R,Z)-1-Phenyl-4-(tributylstannyl)tetradec-3-ene-5,6-diol - (SI-52)



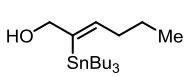
54% yield (1.26 g, 2.12 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.33 – 7.26 (m, 2H), 7.24 – 7.14 (m, 3H), 6.47 – 6.05 (m, 1H), 4.04 – 3.80 (m, 1H), 3.44 – 3.27 (m, 1H), 2.71 (dd, J = 8.8, 6.6 Hz, 2H), 2.45 – 2.34 (m, 2H), 2.29 (dd, J = 16.8, 3.4 Hz, 2H), 1.57 – 1.40 (m, 6H), 1.40 – 1.16 (m, 20H), 0.99 – 0.92 (m, 6H), 0.92 – 0.85 (m, 12H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 145.5, 142.9, 141.6, 128.5, 128.5, 126.1, 83.5, 74.2, 36.4, 36.3, 33.0, 32.0, 29.9, 29.7, 29.5, 29.4, 27.6, 26.0, 22.8, 14.3, 13.8, 11.3 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -53.8 ppm. **IR (film, $CHCl_3$)** 3397, 2922, 2954, 2853, 2870, 1615, 1496, 1455, 1376, 1339, 1288, 1199, 1072, 1029, 961, 904, 866, 746, 723, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{32}H_{58}O_2SnNa$ [M+Na^{+}]: 617.33503, found 617.33546.

Tributyl(4-((tetrahydro-2H-pyran-2-yl)oxy)but-1-en-2-yl)stannane - (SI-53)



2-(3-Butynyloxy)tetrahydro-2H-pyran (784 µL, 5.0 mmol, 1.0 equiv.) and Bu_3SnH (1.41 mL, 5.25 mmol, 1.05 equiv.) were dissolved in dry CH_2Cl_2 (5 mL) and added over 1 h by means of a syringe pump to a stirred solution of $[Cp^*Ru(MeCN)_3]PF_6$ (63 mg, 0.125 mmol, 2.5 mol%) in dry CH_2Cl_2 (20 mL) at room temperature under an argon atmosphere. Upon completion, the volatile materials were removed under vacuum and the residue was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, 50:1) to give the product as a pale yellow oil (1.88 g, 4.21 mmol, 84% yield). **TLC** (hexanes/ethyl acetate, 20:1), Rf = 0.45. **^{1}H NMR (400 MHz, Chloroform-d) δ** 5.94 – 5.49 (m, 1H), 5.31 – 5.09 (m, 1H), 4.58 (dd, J = 4.3, 2.7 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.78 (ddd, J = 9.7, 7.8, 6.7 Hz, 1H), 3.55 – 3.47 (m, 1H), 3.41 (ddd, J = 9.7, 7.9, 7.0 Hz, 1H), 2.54 (ddq, J = 8.0, 6.7, 1.3 Hz, 2H), 1.90 – 1.79 (m, 1H), 1.77 – 1.68 (m, 1H), 1.67 – 1.39 (m, 10H), 1.39 – 1.24 (m, 6H), 1.04 – 0.79 (m, 15H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 151.5, 127.1, 99.0, 67.5, 62.5, 41.2, 30.9, 29.3, 27.6, 25.7, 19.8, 13.8, 9.7 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -43.8 ppm. **IR (film, $CHCl_3$)** 2923, 2871, 2852, 1463, 1377, 1351, 1323, 1260, 1201, 1183, 1135, 1120, 1071, 1031, 981, 960, 915 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{21}H_{42}O_2SnNa$ [M+Na$^+$]: 469.20983, found 469.21016.

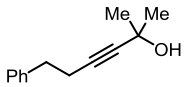
(Z)-2-(Tributylstannyl)hex-2-en-1-ol - (414)



92% yield (7.19 g, 18.5 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 6.52 – 5.93 (m, 1H), 4.28 – 4.09 (m, 2H), 2.10 – 1.87 (m, 2H), 1.63 – 1.41 (m, 6H), 1.41 – 1.23 (m, 7H), 1.16 (t, J = 6.0 Hz, 1H), 0.99 – 0.92 (m, 7H), 0.89 (t, J = 7.3 Hz, 12H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 143.4, 142.0, 70.7, 36.8, 29.4, 27.6, 23.3, 14.0, 13.8, 10.4 ppm. **^{119}Sn NMR (112 MHz, $CDCl_3$) δ** -52.8 ppm. **IR (film, $CHCl_3$)** 3301, 2955, 2924, 2871, 2853, 1622, 1462, 1418, 1376, 1340, 1291, 1182, 1148, 1073, 1045, 1021, 989, 960, 897, 875, 741, 664 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{18}H_{38}OSnNa$ [M+Na$^+$]: 413.18361, found 413.18390.

The following compounds were prepared according to representative procedure 6.

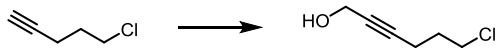
2-Methyl-6-phenylhex-3-yn-2-ol - (SI-54)



97% yield (2.75 g, 14.6 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.35 – 7.27 (m, 2H), 7.26 – 7.16 (m, 3H), 2.82 (t, J = 7.5 Hz, 2H), 2.48 (t, J = 7.6 Hz, 2H),

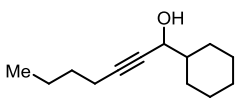
2.07 (s, 1H), 1.49 (s, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 140.7, 128.6, 128.4, 126.4, 86.1, 81.8, 65.3, 35.2, 31.7, 21.0 ppm. **IR (film, $CHCl_3$)** 3379, 3028, 2979, 2930, 2863, 1739, 1604, 1496, 1454, 1362, 1341, 1239, 1163, 1047, 1078, 1030, 949, 833, 861, 748, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{13}H_{16}ONa$ [$M+Na^+$]: 211.10933, found 211.10927.

6-Chlorohex-2-yn-1-ol - (SI-55)



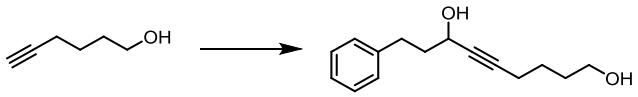
5-Chloro-1-pentyne (2.14 mL, 20 mmol, 1.0 equiv.) was dissolved in THF (20 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. *n*-Butyllithium (12.5 mL, 1.6 M in hexanes, 20 mmol, 1.0 equiv.) was dropwise added and the mixture placed on an ice bath for 15 minutes. Then paraformaldehyde (1.62 g, 54 mmol, 2.7 equiv.) was added in one portion and the mixture was warmed to 45 °C for 2 h with an oil bath. After being cooled again to room temperature, saturated ammonium chloride solution was added. The mixture was extracted twice with MTBE, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/MTBE, 3:1) yielded the product as a colorless oil (2.15 g, 15.4 mmol, 95% purity, 77% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.25 (t, J = 2.2 Hz, 2H), 3.65 (t, J = 6.3 Hz, 2H), 2.42 (tt, J = 6.8, 2.2 Hz, 2H), 1.96 (p, J = 6.6 Hz, 2H), 1.83 – 1.74 (m, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 84.5, 79.5, 51.4, 43.8, 31.3, 16.3 ppm. **IR (film, $CHCl_3$)** 3340, 2918, 1433, 1354, 1290, 1230, 1131, 1010, 859, 726, 652 cm^{-1}. **HRMS (ESI):** *m/z* calculated for C_6H_9OClNa [$M+Na^+$]: 155.02341, found 155.02346.

1-Cyclohexylhept-2-yn-1-ol - (SI-56)



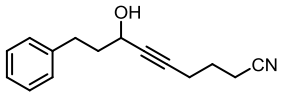
98% yield (5.28 g, 24.5 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.13 (dt, J = 6.0, 2.1 Hz, 1H), 2.21 (td, J = 7.0, 2.0 Hz, 2H), 1.79 (ddtd, J = 29.2, 12.6, 3.2, 1.7 Hz, 3H), 1.67 (dddd, J = 12.8, 5.1, 3.1, 1.7 Hz, 1H), 1.58 – 1.44 (m, 3H), 1.44 – 1.33 (m, 2H), 1.32 – 0.94 (m, 7H), 0.91 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 86.4, 80.2, 67.6, 44.5, 30.9, 28.7, 28.2, 26.6, 26.1, 26.0, 22.1, 18.5, 13.7 ppm. Spectral data in accordance with literature[32].

9-Phenylnon-5-yne-1,7-diol - (SI-57)



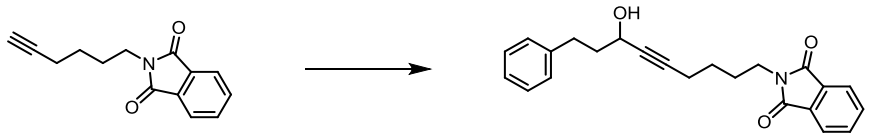
1-Hexynol (1.21 mL, 11 mmol, 1.1 equiv.) was dissolved in dry THF (20 mL) and the solution stirred under an argon atmosphere on a dry-ice bath. *n*-Butyllithium (13.8 mL, 1.6 M in hexanes, 22 mmol, 2.2 equiv.) was added dropwise and stirring continued for 1 h at 0 °C before the mixture was again cooled with a dry-ice bath. Neat phenylpropionaldehyde (1.31 mL, 10 mmol, 1.0 equiv.) was added in one portion, the dry-ice bath was removed and the mixture was allowed to warm to room temperature. After being stirred for 4 h, saturated ammonium chloride solution was added followed by aqueous HCl (2 M) to obtain a clear solution. The mixture was extracted two times with ethyl acetate, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 3:2 to 1:1) yielded the product as a colorless oil (1.76 g, 7.58 mmol, 76% yield). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.33 – 7.24 (m, 2H), 7.21 (m, 3H), 4.36 (tt, J = 6.5, 2.0 Hz, 1H), 3.68 (t, J = 6.2 Hz, 2H), 2.79 (t, J = 7.9 Hz, 2H), 2.28 (td, J = 6.7, 1.9 Hz, 2H), 1.99 (tdd, J = 7.7, 6.5, 3.5 Hz, 2H), 1.93 – 1.76 (m, 2H), 1.76 – 1.51 (m, 4H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 141.6, 128.6, 128.5, 126.1, 85.6, 81.7, 62.5, 62.1, 39.8, 31.9, 31.6, 25.1, 18.6 ppm. **IR (film, $CHCl_3$)** 3331, 2937, 2863, 1722, 1496, 1454, 1374, 1331, 1244, 1156, 1051, 1030, 915, 749, 699 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{20}O_2Na$ [M+Na$^+$]: 255.13555, found 255.13538.

7-Hydroxy-9-phenylnon-5-ynenitrile - (SI-58)



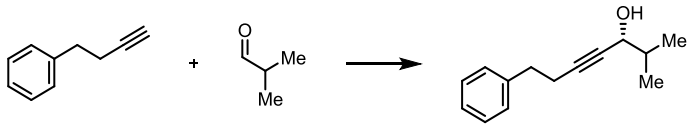
96% yield (2.19 g, 9.64 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.33 – 7.26 (m, 2H), 7.25 – 7.15 (m, 3H), 4.36 (tdd, J = 6.5, 4.7, 3.3 Hz, 1H), 2.78 (t, J = 7.8 Hz, 2H), 2.49 (t, J = 7.1 Hz, 2H), 2.43 (td, J = 6.8, 2.0 Hz, 2H), 2.12 – 1.93 (m, 2H), 1.93 – 1.78 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 141.3, 128.6, 126.2, 119.3, 83.2, 82.9, 77.4, 62.0, 39.6, 31.6, 24.5, 18.0, 16.4 ppm. **IR (film, $CHCl_3$)** 3415, 3025, 2944, 2863, 2249, 1603, 1496, 1454, 1432, 1334, 1218, 1155, 1132, 1056, 1030, 915, 749 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{17}NONa$ [M+Na$^+$]: 250.120233, found 250.120270.

2-(7-Hydroxy-9-phenylnon-5-yn-1-yl)isoindoline-1,3-dione - (SI-59)



HMDS (3.13 mL, 15 mmol, 1.5 equiv.) was dissolved in dry THF (20 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on an ice bath. *n*-Butyllithium (8.13 mL, 1.6 M in hexanes, 13 mmol, 1.3 equiv.) was added dropwise and stirring continued for 30 minutes before the mixture was cooled to −78 °C. *n*-(5-Hexinyl)phthalimide (2.5 g, 11 mmol, 1.1 equiv.) was added and stirring continued for 1 h before neat phenylpropionaldehyde (1.31 mL, 10 mmol, 1.0 equiv.) was added in one portion. The dry-ice bath was removed and the mixture was allowed to warm to room temperature. After being stirred for another 30 minutes, saturated ammonium chloride solution was added followed by aqueous HCl (2 M) to obtain a clear solution. The mixture was extracted two times with ethyl acetate, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 2:1) delivered pure product (746 mg, 2.1 mmol, 21% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.73 (m, 2H), 7.64 – 7.55 (m, 2H), 7.23 – 7.14 (m, 2H), 7.14 – 7.04 (m, 3H), 4.26 (dt, J = 4.6, 2.1 Hz, 1H), 3.62 (t, J = 7.2 Hz, 2H), 2.68 (t, J = 7.9 Hz, 2H), 2.40 (d, J = 4.8 Hz, 1H), 2.19 (td, J = 7.0, 2.0 Hz, 2H), 1.99 – 1.80 (m, 2H), 1.73 (tt, J = 7.9, 6.4 Hz, 2H), 1.47 (dq, J = 9.7, 7.0 Hz, 2H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 168.5, 141.6, 134.0, 132.1, 128.5, 128.4, 125.9, 123.3, 84.8, 82.0, 61.9, 39.6, 37.5, 31.5, 27.5, 25.6, 18.2 ppm. **IR (film, $CHCl_3$)** 3463, 2940, 2864, 1771, 1736, 1704, 1604, 1496, 1467, 1437, 1396, 1372, 1335, 1239, 1188, 1115, 1039, 915, 847, 792 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{23}NO_3Na$ [M+Na^+]: 384.15701, found 384.15727.

***(R)*-2-Methyl-7-phenylhept-4-yn-3-ol[33] - (SI-60)**

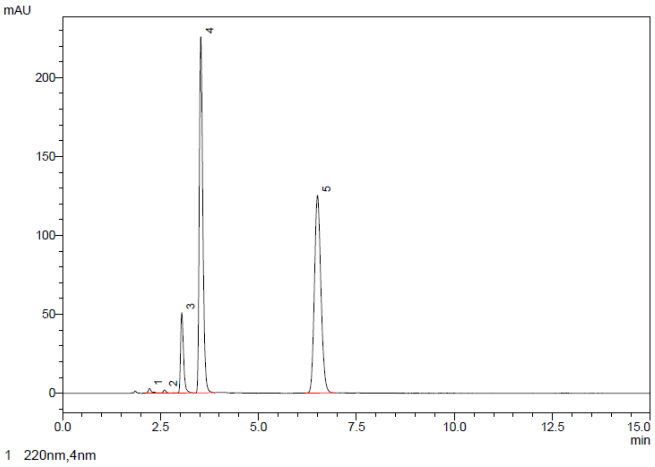


$Zn(OTf)_2$ (2.0 g, 5.5 mmol, 1.1 equiv.) was placed in an oven-dried Schlenk flask under an argon atmosphere at room temperature. (+)-*N*-Methylephedrine (1.08 g, 6.0 mmol, 1.2 equiv.) was added followed by dry toluene (15 mL) and the mixture was stirred for 15 minutes before Et_3N (836 µL, 6.0 mmol, 1.2 equiv.) was added. After being stirred for 2 h, 4-phenyl-1-butyne (844 µL, 6.0 mmol, 1.2 equiv.) was added followed after 15 minutes by *iso*-butyraldehyde (456 µL, 5.0 mmol, 1.0 equiv.). Stirring was continued for 18 h before the reaction was quenched with the

addition of saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 9:1) yielded the product as a pale yellow oil (925 mg, 4.57 mmol, 92% yield).

The **enantiomeric excess** was determined by HPLC analysis to be **97%**.

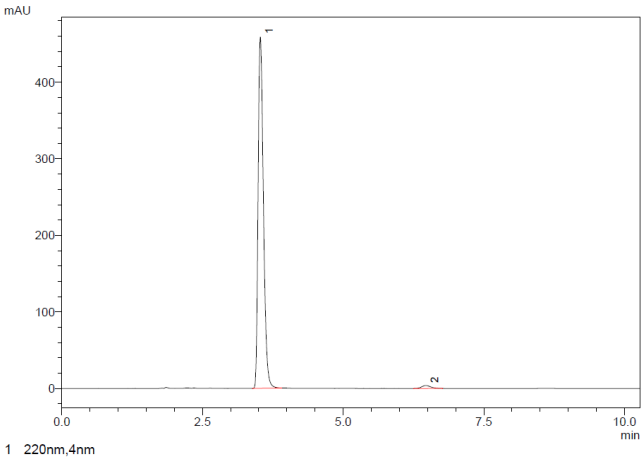
150 mm Chiralcel OD-3, 4.6 mm i.D., n-Heptane/2-Propanol = 90:10, 1.0 ml/min, 7.0 MPa, 298 K, UV 220 nm.



1 220nm,4nm

PDA Ch1 220nm

Peak #	Ret. Time	Area %	Name
1	2.22	0.52	
2	2.60	0.32	
3	3.04	8.48	
4	3.53	44.95	1. Enantiomer
5	6.51	45.73	2. Enantiomer
Total		100.00	



1 220nm,4nm

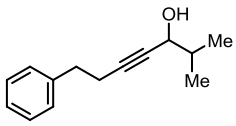
PDA Ch1 220nm

Peak #	Ret. Time	Area %	Name
1	3.53	98.58	1. Enantiomer
2	6.47	1.42	2. Enantiomer
Total		100.00	

ee = 97.2 %

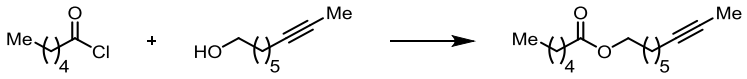
Racemic material was synthesized according to representative procedure 6.

2-Methyl-7-phenylhept-4-yn-3-ol - (SI-61)



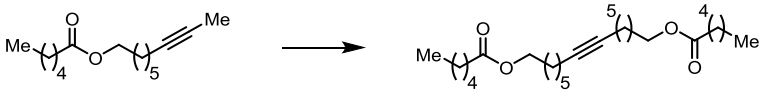
89% yield (1.08 g, 5.34 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.34 – 7.25 (m, 2H), 7.25 – 7.17 (m, 3H), 4.13 (ddt, J = 5.6, 3.7, 2.2 Hz, 1H), 2.83 (t, J = 7.5 Hz, 2H), 2.59 – 2.48 (m, 2H), 1.81 (pd, J = 6.7, 5.6 Hz, 1H), 1.63 (d, J = 5.4 Hz, 1H), 0.95 (dd, J = 6.7, 3.6 Hz, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 140.7, 128.6, 128.5, 126.4, 85.5, 80.9, 68.3, 35.3, 34.8, 21.0, 18.2, 17.6 ppm. **IR (film, $CHCl_3$)** 3382, 3028, 2959, 2929, 2871, 1726, 1604, 1496, 1468, 1454, 1430, 1367, 1256, 1146, 1108, 1077, 1021, 959, 816, 745, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{14}H_{18}O$ [M^+]: 202.13522, found 202.13496.

Non-7-yn-1-yl hexanoate - (SI-62)



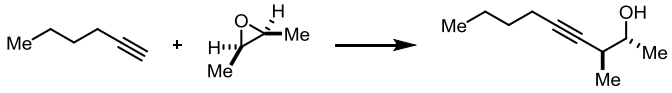
Non-7-yn-1-ol (1.40 g, 10 mmol, 1.0 equiv.) was dissolved in dry THF (20 mL) and stirred on an ice bath in an oven-dried Schlenk flask under an argon atmosphere. Pyridine (1.62 mL, 20 mmol, 2.0 equiv.) was added followed by dropwise addition of the hexanoyl chloride (2.10 mL, 15 mmol, 1.5 equiv.). After 10 minutes, the ice bath was removed and stirring was continued for another 2 h before the reaction was quenched with the addition of aqueous HCl (2 M). The mixture was extracted two times with MTBE, the combined extracts were washed with saturated sodium carbonate solution, aqueous copper sulfate solution (1 M) and brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude material was used as such (2.4 g, 10 mmol, quant. yield). **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 4.05 (t, *J* = 6.7 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.12 (tq, *J* = 7.2, 2.6 Hz, 2H), 1.77 (t, *J* = 2.6 Hz, 3H), 1.69 – 1.56 (m, 4H), 1.53 – 1.17 (m, 10H), 0.94 – 0.80 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 174.2, 79.3, 75.6, 64.4, 34.5, 31.5, 29.0, 28.7, 25.7, 24.9, 22.5, 18.8, 14.1, 3.6 ppm.

Tetradec-7-yne-1,14-diyl dihexanoate[6] - (SI-63)



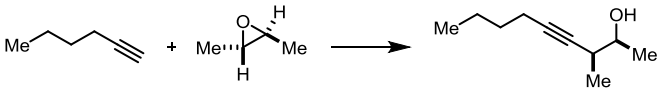
Pre-dried 5 Å mol sieves (~2.0 g) were placed in an oven-dried Schlenk flask under an argon atmosphere and dried again under high vacuum with a blowtorch. After being cooled to room temperature dry toluene (40 mL) was added followed by **SI-62** (2.38 g, 10 mmol, 1.0 equiv.). After being stirred for 5 minutes, (4-methoxybenzylidyne)-*tris*((triphenylsilyl)oxy)molybdenum (208 mg, 0.2 mmol, 2.0 mol%) was added under an argon atmosphere in two portions. After 10 minutes, TLC showed complete conversion of starting material so the mixture was filtered over Celite® with additional MTBE. The volatile materials were removed under reduced pressure and the residue purified by flash chromatography (SiO_2, hexanes/ethyl actetate, 20:1) to give the product as a colorless thick oil (1.69 g, 4.0 mmol, 80% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.04 (t, J = 6.7 Hz, 4H), 2.27 (t, J = 7.6 Hz, 4H), 2.18 – 2.07 (m, 4H), 1.60 (dddd, J = 14.7, 7.4, 5.8, 2.6 Hz, 8H), 1.53 – 1.19 (m, 20H), 0.94 – 0.81 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 174.1, 80.2, 64.4, 34.5, 31.4, 29.1, 28.7, 28.6, 25.6, 24.8, 22.4, 18.8, 14.0 ppm. **IR (film, $CHCl_3$)** 2931, 2859, 1734, 1463, 1352, 1245, 1168, 1098, 730 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{26}H_{46}O_4Na$ [M+Na$^+$]: 445.32883, found 445.32915.

(*anti*)-3-Methylnon-4-yn-2-ol - (SI-64)



1-Hexyne (4.3 mL, 37.5 mmol, 1.5 equiv.) was dissolved in dry THF (50 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. *n*-Butyllithium (23.4 mL, 1.6 M in hexanes, 37.5 mmol, 1.5 equiv.) was added dropwise and stirring continued for 10 minutes. Then, $BF_3{\cdot}Et_2O$ (4.6 mL, 37.5 mmol, 1.5 equiv.) was added followed after 15 minutes by neat (*syn*)-2,3-dimethyloxirane (2.18 mL, 25 mmol, 1.0 equiv.). The mixture was stirred at the same temperature for 2 h before the reaction was quenched with the addition of saturated ammonium chloride solution. The mixture was allowed to warm to room temperature and extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 9:1) yielded the product as a pale yellow liquid (3.6 g, 23.3 mmol, 93% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 3.57 (h, J = 6.0 Hz, 1H), 2.41 (tddd, J = 7.0, 5.6, 4.6, 2.2 Hz, 1H), 2.19 (td, J = 6.9, 2.2 Hz, 2H), 1.96 (d, J = 5.7 Hz, 1H), 1.53 – 1.44 (m, 2H), 1.44 – 1.34 (m, 2H), 1.22 (d, J = 6.2 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 83.7, 80.7, 71.1, 35.2, 31.3, 22.1, 20.9, 18.5, 17.9, 13.8 ppm. **IR (film, $CHCl_3$)** 3386, 2932 2960, 2874, 1454, 1376, 1300, 1265, 1173, 1098, 997, 1011, 955, 913 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{10}H_{18}ONa$ [M+Na^+]: 177.12498, found 177.12498.

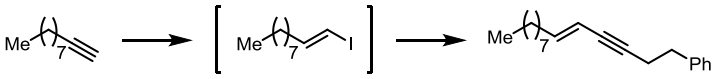
(*syn*)-3-Methylnon-4-yn-2-ol - (SI-65)



1-Hexyne (4.3 mL, 37.5 mmol, 1.5 equiv.) was dissolved in dry THF (50 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. *n*-Butyllithium (23.4 mL, 1.6 M in hexanes, 37.5 mmol, 1.5 equiv.) was added dropwise and stirring continued for 10 minutes. Then, $BF_3{\cdot}Et_2O$ (4.6 mL, 37.5 mmol, 1.5 equiv.) was added followed after 15 minutes by neat (*anti*)-2,3-dimethyloxirane (2.18 mL, 25 mmol, 1.0 equiv.). The mixture was stirred at the same temperature for 2 h before the reaction was quenched with the addition of saturated ammonium chloride solution. The mixture was allowed to warm to room temperature and extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash

chromatography (SiO_2, hexanes/ethyl acetate, 9:1) yielded the product as a pale yellow liquid (3.2 g, 20.8 mmol, 83% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 3.76 – 3.60 (m, 1H), 2.56 (ttd, J = 7.0, 4.9, 2.2 Hz, 1H), 2.16 (td, J = 7.0, 2.3 Hz, 2H), 1.80 (d, J = 6.0 Hz, 1H), 1.53 – 1.31 (m, 4H), 1.21 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 83.1, 81.2, 70.6, 34.3, 31.3, 22.1, 19.5, 18.5, 16.7, 13.8 ppm. **IR (film, $CHCl_3$)** 3384, 2962, 2932, 2874, 1742, 1727, 1454, 1374, 1328, 1298, 1246, 1202, 1168, 1083, 1008, 972, 911 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{10}H_{18}ONa$ [M+Na^+]: 177.12498, found 177.12504.

(E)-Tetradec-5-en-3-yn-1-ylbenzene - (SI-66)

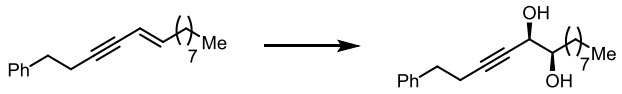


1-Decyne (4.51 mL, 25 mmol, 1.0 equiv.) was placed in an oven-dried Schlenk under an argon atmosphere and stirred at –40 °C. DIBAL-H (22.9 mL, 27.5 mmol, 1.2 M in PhMe, 1.1 equiv.) was added slowly before the mixture was heated to 50 °C for 5 h. After being cooled again to –40 °C, I_2 (7.6 , 30 mmol, 1.2 equiv.) in THF (25 mL) was added slowly over 10 minutes. The mixture was then allowed to warm to room temperature over the course of 12 h. The mixture was poured **carefully onto** a saturated sodium thiosulfate solution/ice mixture. At room temperature, the mixture was extracted two times with MTBE, the combined extracts were concentrated to about 20 mL. The crude mixture was analyzed by GC and showed almost pure vinyl iodide which was used as such as a solution in PhMe.

4-Phenyl-1-butyne (1.4 mL, 10 mmol, 1.0 equiv.) was dissolved in Et_3N (10 mL) and stirred in an oven-dried Schlenk flask under an argon atmosphere at room temperature. Crude (E)-1-iododec-1-ene (solution in PhMe) was added followed by CuI (114 mg, 0.6 mmol, 6.0 mol%) and *bis*-(triphenylphosphine)-palladium(II)-chloride (211 mg, 0.3 mmol, 3.0 mol%) and stirring was continued for 12 h with the conversion monitored by TLC (hexanes/ethyl acetate, 20:1). The reaction was then quenched with saturated ammonium chloride solution and acidified with aqueous HCl (2 M). The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes) yielded the product as a pale yellow oil (1.45 g, 5.4 mmol, 54% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.36 – 7.27 (m, 2H), 7.26 – 7.19 (m, 3H), 6.06 (dt, J = 15.8, 7.1 Hz, 1H), 5.45 (dt, J = 15.8, 1.8 Hz, 1H), 2.97 – 2.77 (m, 2H), 2.58 (td, J = 7.7, 2.1 Hz, 2H), 2.08 (qd, J = 7.1, 1.6 Hz, 2H), 1.46 – 1.12 (m, 12H), 0.96 – 0.84 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 144.0, 140.9, 128.6, 128.5, 126.4, 109.7, 87.9, 80.0, 35.5, 33.1, 32.0, 29.6, 29.4, 29.3, 29.0, 22.8, 21.8, 14.3 ppm. **IR (film, $CHCl_3$)** 3027, 2923, 2853, 1496, 1454, 1340,

1077, 1030, 955, 744, 697, 633, 578, 509 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{20}H_{28}$ [M^+]: 268.21910, found 268.21921.

(*5R*,*6R*)-1-Phenyltetradec-3-yne-5,6-diol - (SI-67)



7.5 g AD-mix β was dissolved in *t*-BuOH (25 mL) and the solution stirred in a cooling Schlenk at 4°C. A solution of $MeSO_2NH_2$ (514 mg, 5.4 mmol, 1.0 equiv.) in water (25 mL) was added followed by (E)-tetradec-5-en-3-yn-1-ylbenzene (1.45 g, 5.4 mmol, 1.0 equiv.). The mixture was stirred at the same temperature for 12 h. TLC indicated complete consumption of starting material. The reaction was quenched with the addition of saturated sodium sulfite solution at 4 °C. The mixture was then extracted three times with ethyl acetate, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 4:1 to 2:1) yielded the product as a colorless oil which solidified upon standing (1.18 g, 3.9 mmol, 72% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +13.3° (c=1.60 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.34 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 4.10 (dt, J = 6.3, 2.0 Hz, 1H), 3.51 (ddd, J = 8.0, 6.3, 3.4 Hz, 1H), 2.83 (t, J = 7.4 Hz, 2H), 2.53 (td, J = 7.4, 1.9 Hz, 4H), 1.65 – 1.16 (m, 14H), 0.97 – 0.84 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 140.5, 128.5, 128.5, 126.5, 86.4, 79.6, 75.2, 66.4, 34.9, 32.4, 32.0, 29.7, 29.7, 29.4, 25.7, 22.8, 20.9, 14.3 ppm. **IR (film, $CHCl_3$)** 3361, 2922, 2854, 1496, 1454, 1260, 1129, 1031, 745, 697, 579, 507 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{20}H_{30}O_2Na$ [M+Na^+]: 325.21380, found 325.21366.

8.5. Fluorination of Alkenylstannanes and Synthesis of Peptide Bioisosters

Synthesis of silver(I) diphenylphosphinate[34]

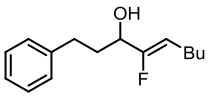
NaOH (1.1 g, 27.5 mmol, 1.1 equiv.) was dissolved in water (10 mL) and the solution stirred vigorously in a 100 mL flask. Diphenylphosphinic acid (5.73 g, 26.3 mmol, 1.05 equiv.) was added and the solution stirred until complete dissolution was realized (a few drops of additional aqueous NaOH were usually necessary to accomplish that task). Then, a solution of $AgNO_3$ (4.25 g, 25 mmol, 1.0 equiv.) in a minimum amount water was added rapidly and a grey precipitate immediately formed. The solids were filtered off with suction, the residue washed two times with water and acetone, then with MTBE followed by drying under high vacuum to

give the product as a grey powder (83% yield, 6.72 g, 20.7 mmol). The material obtained was used as such.

8.5.1. Representative procedure 12: Silver Mediated Fluorination of Alkenylstannanes

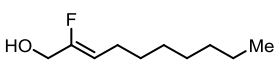
$AgOP(O)Ph_2$ (390 mg, 1.2 mmol, 1.2 equiv.) and F-TEDA-PF_6 (941 mg, 2.0 mmol, 2.0 equiv.) were stirred under argon in an oven-dried Schlenk at room temperature for 10 minutes until a homogenous greyish powder is obtained. Then, dry acetone (15 mL) was added. **248** (507 mg, 1.0 mmol, 1.0 equiv.) was dissolved in dry acetone (5 mL) and the solution added over 60 minutes by means of a syringe pump to the above prepared suspension. Upon complete addition, the mixture was diluted with MTBE and the reaction quenched with saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography of the residue (SiO_2, hexanes/ethyl acetate) provided clean material.

(Z)-1-Phenyl-4-(tributylstannyl)non-4-en-3-ol - (493)



78% yield (184 mg, 0.78 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.34 – 7.26 (m, 2H), 7.21 (m, 3H), 4.82 (dt, J = 37.8, 7.5 Hz, 1H), 4.08 (dt, J = 16.6, 6.7 Hz, 1H), 2.86 – 2.63 (m, 2H), 2.24 – 2.06 (m, 2H), 2.06 – 1.91 (m, 2H), 1.80 (s, 1H), 1.44 – 1.26 (m, 4H), 1.01 – 0.79 (m, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 159.3 (d, J = 255.9 Hz), 141.6, 128.6, 128.5, 126.1, 107.1 (d, J = 14.1 Hz), 70.4 (d, J = 30.5 Hz), 35.6, 31.8, 31.6 (d, J = 1.8 Hz), 23.1 (d, J = 4.5 Hz), 22.4, 14.0 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -126.7 ppm. **IR (film, $CHCl_3$)** 3342, 3027, 2955, 2927, 2859, 1706, 1604, 1496, 1455, 1298, 1179, 1031, 936, 830, 746, 698 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{15}H_{21}OFNa$ [$M+Na^+$]: 259.14686, found 259.14691.

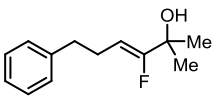
(Z)-2-Fluorodec-2-en-1-ol - (494)



74% yield (64 mg, 0.37 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 4.82 (dt, J = 37.0, 7.6 Hz, 1H), 4.09 (dd, J = 16.0, 6.2 Hz, 2H), 2.09 (qd, J = 7.4, 1.8 Hz, 2H), 1.98 (t, J = 6.3 Hz, 1H), 1.53 – 1.18 (m, 10H), 0.94 – 0.79 (m, 3H) ppm. **^{13}C NMR (75 MHz, Chloroform-d) δ** 157.5 (d, J = 253.2 Hz), 131.3 (d, J = 377.8 Hz), 108.4 (d, J = 14.1 Hz), 61.5 (d, J = 32.6 Hz), 31.9, 29.3 (d, J = 1.7 Hz), 29.2 (d, J = 4.9 Hz), 23.5 (d, J = 4.2 Hz), 22.8, 14.2 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -121.4 ppm. **IR (film, $CHCl_3$)** 3328, 2924, 2856, 1709, 1458,

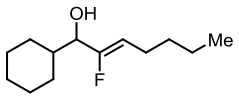
1378, 1214,1114, 1067, 1012, 919, 856, 723, 683 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{10}H_{19}OF$ [M]: 174.14199, found 174.14206.

(Z)-3-Fluoro-2-methyl-6-phenylhex-3-en-2-ol - (495)



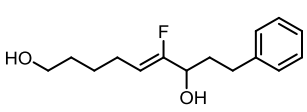
68% yield (71 mg, 34 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.35 – 7.26 (m, 2H), 7.25 – 7.15 (m, 3H), 4.91 (dt, J = 37.9, 7.5 Hz, 1H), 2.70 (dd, J = 8.7, 6.7 Hz, 2H), 2.47 – 2.35 (m, 2H), 1.86 (s, 1H), 1.38 (d, J = 1.2 Hz, 6H). **^{13}C NMR (75 MHz, Chloroform-d) δ** 163.4 (d, J = 257.7 Hz), 141.7, 128.6, 128.4, 126.0, 102.1 (d, J = 14.9 Hz), 70.4 (d, J = 29.3 Hz), 35.7 (d, J = 1.7 Hz), 27.4, 25.2 (d, J = 5.2 Hz) ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -122.6 ppm. **IR (film, $CHCl_3$)** 3380, 2930, 2858, 1702, 1496, 1454, 1364, 1280, 1171, 1094, 1053, 1030, 1002, 955, 877, 841, 782, 747 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{13}H_{17}OFNa$ [$M+Na^+$]: 231.11556, found 231.11565.

(Z)-1-Cyclohexyl-2-fluorohept-2-en-1-ol - (496)



56% yield (60 mg, 0.28 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 4.74 (dt, J = 37.9, 7.5 Hz, 1H), 3.72 (ddd, J = 20.1, 7.3, 6.1 Hz, 1H), 2.09 (dtd, J = 9.6, 7.8, 6.8, 2.7 Hz, 2H), 1.93 (ddq, J = 11.7, 3.5, 1.9 Hz, 1H), 1.77 (d, J = 6.1 Hz, 1H), 1.76 – 1.47 (m, 5H), 1.33 (dq, J = 7.2, 3.6 Hz, 4H), 1.29 – 1.08 (m, 3H), 1.08 – 0.92 (m, 2H), 0.91 (s, 3H) ppm. **^{13}C NMR (75 MHz, Chloroform-d) δ** 158.4 (d, J = 256.5 Hz), 107.9 (d, J = 14.1 Hz), 76.1 (d, J = 29.0 Hz), 40.9, 31.6 (d, J = 1.6 Hz), 29.1 (d, J = 53.6 Hz), 26.5, 26.1 (d, J = 8.8 Hz), 23.1 (d, J = 4.6 Hz), 22.4, 14.0 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -126.7 ppm. **IR (film, $CHCl_3$)** 3373, 2923, 2853, 1706, 1450, 1379, 1308, 1280, 1174, 1110, 1083, 1011, 952, 935, 893, 873, 836, 800 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{13}H_{23}OFNa$ [$M+Na^+$]: 237.16251, found 237.16266.

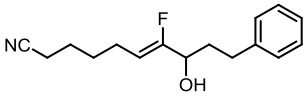
(Z)-6-Fluoro-9-phenylnon-5-ene-1,7-diol - (497)



62% yield (78 mg, 0.31 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.33 – 7.25 (m, 2H), 7.20 (m, 3H), 4.81 (dt, J = 37.6, 7.6 Hz, 1H), 4.06 (dt, J = 16.4, 6.7 Hz, 1H), 3.64 (t, J = 6.4 Hz, 2H), 2.71 (dh, J = 13.9, 7.1 Hz, 2H), 2.14 (qd, J = 7.4, 1.7 Hz, 2H), 2.07 – 1.85 (m, 2H), 1.68 – 1.52 (m, 2H), 1.52 – 1.32 (m, 2H) ppm. **^{13}C NMR (75 MHz, Chloroform-d) δ** 159.6 (d, J = 256.6 Hz), 141.5, 128.6, 128.5, 126.1, 106.5 (d, J = 14.1 Hz), 70.2 (d, J = 30.4 Hz), 62.7, 35.6, 32.2, 31.7, 25.5 (d, J = 1.8 Hz), 23.1 (d, J =

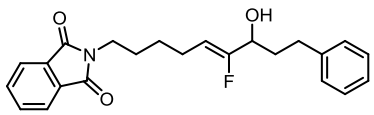
4.6 Hz) ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -125.9 ppm. **IR (film, $CHCl_3$)** 3338, 2932, 2861, 1707, 1496, 1454, 1262, 1032, 933, 836, 748, 698, 494 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{15}H_{21}O_2FNa$ [M+Na^+]: 275.14178, found 275.14184.

(Z)-6-Fluoro-7-hydroxy-9-phenylnon-5-enenitrile - (498)



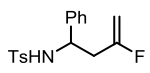
60% yield (74 mg, 0.30 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.36 – 7.27 (m, 2H), 7.21 (m, 3H), 4.82 (dt, J = 36.9, 7.6 Hz, 1H), 4.09 (dt, J = 14.3, 6.6 Hz, 1H), 2.83 – 2.63 (m, 2H), 2.34 (t, J = 7.2 Hz, 2H), 2.30 – 2.22 (m, 2H), 2.21 – 2.15 (m, 1H), 2.08 – 1.90 (m, 2H), 1.75 (p, J = 7.2 Hz, 2H) ppm**. ^{13}C NMR (101 MHz, Chloroform-d) δ** 161.1 (d, J = 259.1 Hz), 141.3, 128.6, 128.5, 126.1, 119.7, 103.9 (d, J = 13.6 Hz), 69.80 (d, J = 30.4 Hz), 35.5, 31.6, 25.0 (d, J = 2.1 Hz), 22.5 (d, J = 5.0 Hz), 16.7 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -122.9 ppm. **IR (film, $CHCl_3$)** 3429, 3027, 2936, 2865, 2249, 1707, 1603, 1496, 1454, 1424, 1295, 1140, 1063, 1030, 1013, 925, 851, 749, 699 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{15}H_{18}NOFNa$ [M+Na^+]: 270.12646, found 270.12649.

(Z)-2-(6-Fluoro-7-hydroxy-9-phenylnon-5-en-1-yl)isoindoline-1,3-dione - (499)



50% yield (96 mg, 0.25 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.86 – 7.77 (m, 2H), 7.73 – 7.65 (m, 2H), 7.32 – 7.22 (m, 2H), 7.22 – 7.12 (m, 3H), 4.79 (dt, J = 37.4, 7.6 Hz, 1H), 4.18 – 3.96 (m, 1H), 3.67 (t, J = 7.3 Hz, 2H), 2.70 (hept, J = 7.1 Hz, 2H), 2.29 (d, J = 5.2 Hz, 1H), 2.15 (qd, J = 7.4, 1.7 Hz, 2H), 2.05 – 1.83 (m, 2H), 1.82 – 1.63 (m, 2H), 1.54 – 1.33 (m, 2H) ppm. **^{13}C NMR (75 MHz, Chloroform-d) δ** 168.5, 159.9 (d, J = 257.2 Hz), 141.5, 134.0, 132.2, 128.5, 128.5, 126.0, 123.3, 106.0 (d, J = 14.0 Hz), 70.1 (d, J = 30.5 Hz), 37.8, 35.5, 31.7, 28.0, 26.4, 22.8 (d, J = 4.7 Hz) ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -125.5 pm. **IR (film, $CHCl_3$)** 3463, 2940, 2861, 1770, 1702, 1604, 1496, 1437, 1396, 1371, 1239, 1187, 1116, 1037, 925, 862, 793, 751, 718, 699 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{23}H_{24}NO_3FNa$ [M+Na^+]: 404.16324, found 404.16349.

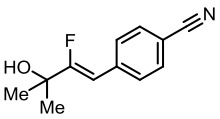
N-(3-Fluoro-1-phenylbut-3-en-1-yl)-4-methylbenzenesulfonamide - (500)



65% yield (103 mg, 0.32 mmol). **^{1}H NMR (500 MHz, Chloroform-d) δ** 7.59 – 7.52 (m, 2H), 7.22 – 7.11 (m, 5H), 7.08 (m, 2H), 5.33 (s, 1H), 4.54 (t, J = 7.2 Hz, 1H), 4.49 (dd, J = 17.2, 3.1 Hz, 1H), 4.17 (dd, J = 49.6, 3.0 Hz, 1H), 2.71 – 2.50 (m, 2H), 2.36 (s, 3H) ppm. **^{13}C NMR (126 MHz, Chloroform-d) δ** 161.9 (d, J = 257.1 Hz), 143.3, 139.7, 137.3,

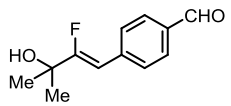
129.5, 128.6, 127.8, 127.3, 126.6, 93.7, 55.3, 40.5 (d, J = 26.9 Hz), 21.6 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -95.7 ppm. **IR (film, $CHCl_3$)** 3245, 1675, 1600, 1497, 1458, 1319, 1290, 1242, 1157, 1095, 1060, 940, 874, 843, 811, 758, 700, 671, 597 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{17}H_{17}NO_2FS$ [M-H$^+$]: 318.09696, found 318.09694.

(Z)-4-(2-Fluoro-3-hydroxy-3-methylbut-1-en-1-yl)benzonitrile - (501)



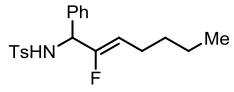
70% yield (72 mg, 0.35 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 7.66 – 7.48 (m, 4H), 5.97 (d, J = 38.8 Hz, 1H), 1.96 (s, 1H), 1.52 (d, J = 1.3 Hz, 6H) ppm. **^{13}C NMR (75 MHz, Chloroform-d) δ** 166.9 (d, J = 276.1 Hz), 138.1, 132.3, 129.2 (d, J = 8.0 Hz), 119.1, 110.5 (d, J = 3.0 Hz), 102.2 (d, J = 6.5 Hz), 71.0 (d, J = 29.0 Hz), 27.7 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -110.1 ppm. **IR (film, $CHCl_3$)** 3432, 2981, 2933, 2872, 2226, 1685, 1605, 1504, 1413, 1072, 1019, 1003, 958, 895, 578 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{12}H_{12}NOFNa$ [M+Na$^+$]: 228.07951, found 228.07953.

(Z)-4-(2-Fluoro-3-hydroxy-3-methylbut-1-en-1-yl)benzaldehyde - (502)



68% yield (71 mg, 0.34 mmol). **^{1}H NMR (500 MHz, Chloroform-d) δ** 9.97 (s, 1H), 7.88 – 7.80 (m, 2H), 7.67 – 7.59 (m, 2H), 6.01 (d, J = 39.2 Hz, 1H), 1.52 (d, J = 1.2 Hz, 6H) ppm. **^{13}C NMR (126 MHz, Chloroform-d) δ** 191.9, 166.7 (d, J = 275.9 Hz), 139.7 (d, J = 2.5 Hz), 134.9 (d, J = 2.0 Hz), 130.1, 129.2 (d, J = 7.8 Hz), 102.6 (d, J = 6.5 Hz), 71.0 (d, J = 29.2 Hz), 27.71 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -110.2 ppm. **IR (film, $CHCl_3$)** 3430, 2979, 1677, 1600, 1566, 1463, 1421, 1363, 1311, 1299, 1254, 1213, 1190, 1169 1071, 1004, 959, 895, 866, 809, 779, 720 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{12}H_{13}O_2F$ [M$^+$]: 208.08996, found 208.08988.

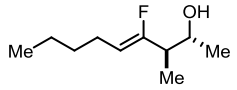
(Z)-N-(2-Fluoro-1-phenylhept-2-en-1-yl)-4-methylbenzenesulfonamide - (503)



87% yield (158 mg, 0.44 mmol). **^{1}H NMR (500 MHz, Chloroform-d) δ** 7.86 – 7.60 (m, 2H), 7.45 – 7.11 (m, 7H), 5.09 (d, J = 25.0 Hz, 1H), 5.02 (d, J = 18.0 Hz, 1H), 4.69 (dt, J = 36.9, 7.5 Hz, 1H), 2.88 (d, J = 7.5 Hz, 1H), 2.41 (s, 3H), 1.97 – 1.81 (m, 2H), 1.33 – 1.09 (m, 6H), 0.85 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (126 MHz, Chloroform-d) δ** 154.8 (d, J = 255.3 Hz), 143.6, 137.4 (d, J = 56.9 Hz), 129.6, 128.8, 128.3, 127.3, 127.1, 109.9 (d, J = 14.0 Hz), 58.4 (d, J = 29.8 Hz), 46.1, 31.2, 23.2 (d, J = 4.1 Hz), 22.3, 21.7, 13.9 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -123.2 ppm. **IR (film, $CHCl_3$)** 3293, 2951, 2858, 1598, 1496,

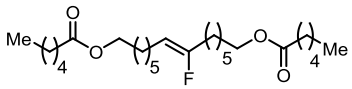
1440, 1382, 1330, 1249, 1155, 1117, 1089, 1054, 1030, 928, 875, 850, 813, 754, 699, 685 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{20}H_{23}NO_2FS$ [M-H^+]: 360.14391, found 360.14397.

(*anti*,Z)-4-Fluoro-3-methylnon-4-en-2-ol - (504)



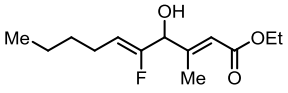
54% yield (47 mg, 6:1 mixture of α:β, 0.27 mmol). Analytical of data pure α: **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.61 (dt, J = 38.7, 7.5 Hz, 1H), 3.86 – 3.69 (m, 1H), 2.22 (dp, J = 24.7, 7.2 Hz, 1H), 2.13 – 2.00 (m, 2H), 1.76 – 1.64 (m, 1H), 1.40 – 1.25 (m, 4H), 1.19 (dd, J = 6.2, 0.7 Hz, 3H), 1.08 (d, J = 7.1 Hz, 3H), 0.93 – 0.84 (m, 3H) ppm. **^{13}C NMR (101 MHz, Chloroform-d) δ** 160.1 (d, J = 255.6 Hz), 107.5 (d, J = 15.6 Hz), 68.9, 45.1 (d, J = 24.4 Hz), 31.8 (d, J = 1.8 Hz), 23.3 (d, J = 5.1 Hz), 22.4, 20.3, 14.0, 13.9 (d, J = 2.9 Hz) ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -116.9 ppm. **IR (film, $CHCl_3$)** 3371, 2959, 2927, 2860, 1702, 1458, 1379, 1277, 1171, 1096, 999, 959, 934, 909, 869, 841, 730 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{10}H_{19}OF$ [M^+]: 174.14199, found 174.14209.

(Z)-7-Fluorotetradec-7-ene-1,14-diyl dihexanoate - (505)



60% yield (133 mg, 0.30 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.44 (dt, J = 38.2, 7.4 Hz, 1H), 4.05 (td, J = 6.7, 1.2 Hz, 4H), 2.28 (t, J = 7.6 Hz, 4H), 2.12 (dt, J = 17.4, 7.4 Hz, 2H), 2.03 (p, J = 6.1 Hz, 2H), 1.68 – 1.53 (m, 8H), 1.53 – 1.41 (m, 2H), 1.31 (ddtd, J = 12.1, 9.9, 6.8, 3.1 Hz, 18H), 0.96 – 0.81 (m, 6H) ppm. **^{13}C NMR (101 MHz, Chloroform-d) δ** 174.2, 174.2, 159.6 (d, J = 252.5 Hz), 105.0 (d, J = 16.1 Hz), 64.4 (d, J = 8.9 Hz), 34.5, 32.2, 31.9, 31.5, 29.6, 28.9, 28.7, 28.7, 28.7, 26.3, 25.9, 25.8, 24.8, 23.5, 23.5, 22.5, 14.1 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -110.0 ppm. **IR (film, $CHCl_3$)** 2930, 2859, 1734, 1707, 1463, 1354, 1244, 1168, 1098, 1050, 992, 891, 729 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{26}H_{47}O_4FNa$ [M+Na^+]: 465.33506, found 465.33544.

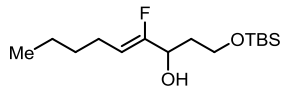
Ethyl (2E,5Z)-5-fluoro-4-hydroxy-3-methyldeca-2,5-dienoate - (506)



71% yield (87 mg, 0.36 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 6.07 (p, J = 1.4 Hz, 1H), 4.91 (dt, J = 37.0, 7.6 Hz, 1H), 4.55 (d, J = 16.0 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.37 (s, 1H), 2.18 – 2.00 (m, 5H), 1.34 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H), 0.94 – 0.82 (m, 3H) ppm. **^{13}C NMR (75 MHz, Chloroform-d) δ** 166.7, 158.1, 154.7, 117.3, 109.5 (d, J = 13.7 Hz), 75.2 (d, J = 31.6 Hz), 60.1, 31.3 (d, J = 1.8 Hz), 23.2 (d, J = 4.0 Hz), 22.3, 15.4, 14.4, 13.9 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -124.3 ppm. **IR (film, $CHCl_3$)**

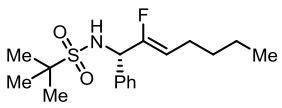
3436, 2958, 2931, 2861, 1698, 1657, 1445, 1369, 1345, 1279, 1212, 1146, 1113, 1096, 1040, 938, 880, 826 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{13}H_{21}O_3FNa$ [M+Na^+]: 267.13669, found 267.13679.

(Z)-1-((*tert*-Butyldimethylsilyl)oxy)-4-fluoronon-4-en-3-ol - (507)



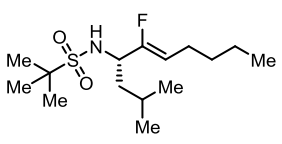
57% yield (82 mg, 0.28 mmol). **^{1}H NMR (300 MHz, Chloroform-d) δ** 4.89 (dtd, J = 38.4, 7.6, 0.8 Hz, 1H), 4.44 – 4.23 (m, 1H), 3.91 (ddd, J = 10.5, 6.5, 4.2 Hz, 1H), 3.79 (ddd, J = 10.2, 7.1, 4.1 Hz, 1H), 3.59 (d, J = 4.4 Hz, 1H), 2.17 – 2.03 (m, 2H), 2.01 – 1.73 (m, 2H), 1.47 – 1.22 (m, 4H), 0.97 – 0.83 (m, 12H), 0.08 (s, 6H) ppm. **^{13}C NMR (75 MHz, Chloroform-d) δ** 159.3 (d, J = 254.3 Hz), 105.9 (d, J = 13.3 Hz), 70.4 (d, J = 33.7 Hz), 61.8, 35.5, 31.6, 26.0, 23.0 (d, J = 4.7 Hz), 22.4, 18.2, 14.0, -5.5 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -125.1 ppm. **IR (film, $CHCl_3$)** 3408, 2955, 2929, 2858, 1709, 1470, 1389, 1362, 1254, 1099, 1006, 939, 832, 775, 732, 664 cm^{-1}. **HRMS (ESI):** m/z calculated for $C_{15}H_{31}O_2FSiNa$ [M+Na^+]: 313.19696, found 313.19696.

(*S*,Z)-N-(2-Fluoro-1-phenylhept-2-en-1-yl)-2-methylpropane-2-sulfon-amide - (531)



76% yield (125 mg, 0.38 mmol). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +3.7° (c=1.01 in MeOH). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.45 – 7.28 (m, 5H), 5.17 (dd, J = 18.2, 9.3 Hz, 1H), 4.92 (dt, J = 36.9, 7.6 Hz, 1H), 4.50 (d, J = 9.2 Hz, 1H), 2.14 (tdq, J = 8.5, 7.0, 2.3, 1.9 Hz, 2H), 1.39 (s, 9H), 1.38 – 1.21 (m, 4H), 0.95 – 0.86 (m, 3H) ppm. **^{13}C NMR (101 MHz, Chloroform-d) δ** 156.6 (d, J = 255.8 Hz), 138.5, 129.0, 128.3, 127.0, 109.5 (d, J = 14.2 Hz), 60.3, 59.2 (d, J = 29.1 Hz), 31.3, 24.3, 23.4 (d, J = 4.1 Hz), 22.4, 13.9 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -122.1 ppm. **IR (film, $CHCl_3$)** 3287, 2957, 2931, 2858, 1705, 1495, 1451, 1438, 1369, 1302, 1249, 1182, 1129, 1061, 1026, 923, 852, 738, 694, 605, 512 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{17}H_{26}NO_2FSNa$ [M+Na^+]: 350.15605, found 350.15569.

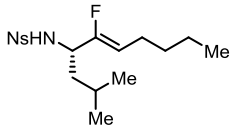
(*S*,Z)-N-(5-Fluoro-2-methyldec-5-en-4-yl)-2-methylpropane-2-sulfon-amide - (532)



81% yield (125 mg, 0.41 mmol). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: −10.2° (c=1.21 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.76 (dt, J = 37.7, 7.6 Hz, 1H), 4.06 – 3.89 (m, 2H), 2.13 – 2.00 (m, 2H), 1.73 – 1.44 (m, 3H), 1.37 (s, 9H), 1.35 – 1.23 (m, 4H), 0.95 (d, J = 6.5 Hz, 3H), 0.93 – 0.86 (m, 6H) ppm. **^{13}C NMR (101 MHz, Chloroform-d) δ** 157.1 (d, J = 255.0 Hz), 108.0, 59.8, 54.7 (d, J = 27.5 Hz), 43.6, 31.4

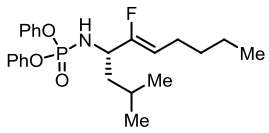
(d, J = 1.6 Hz), 24.9, 24.3, 23.2 (d, J = 4.4 Hz), 22.7, 22.3 (d, J = 12.6 Hz), 13.9 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -128.2 ppm. **IR (film, $CHCl_3$)** 3274, 2957, 2872, 2931, 1706, 1458, 1367, 1301, 1172, 1127, 1061, 1006, 964, 921, 817, 680 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{15}H_{29}NO_2FS$ [M-H^+]: 306.19086, found 306.19105.

(*S*,Z)-N-(5-Fluoro-2-methyldec-5-en-4-yl)-4-nitrobenzenesulfonamide - (533)



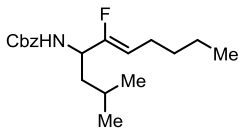
54% yield (100 mg, 0.27 mmol). $[\boldsymbol{\alpha}]_D^{20}$: +40.7° (c=1.11 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 8.36 – 8.27 (m, 2H), 8.06 – 7.94 (m, 2H), 4.77 (d, J = 8.8 Hz, 1H), 4.52 (dt, J = 37.5, 7.5 Hz, 1H), 3.97 (ddt, J = 24.2, 8.9, 7.8 Hz, 1H), 1.79 (dtdd, J = 14.3, 8.0, 6.6, 1.6 Hz, 1H), 1.73 – 1.60 (m, 2H), 1.49 (td, J = 7.7, 7.2, 1.1 Hz, 2H), 1.22 – 1.00 (m, 4H), 0.92 (d, J = 4.9 Hz, 3H), 0.91 (d, J = 4.9 Hz, 3H), 0.81 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (101 MHz, Chloroform-d) δ** 154.8 (d, J = 255.7 Hz), 150.1, 146.9, 128.5, 124.2, 109.0 (d, J = 14.5 Hz), 54.2 (d, J = 27.6 Hz), 42.0, 31.2, 24.6, 22.9 (d, J = 4.2 Hz), 22.4, 22.3 (d, J = 2.6 Hz), 13.8 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -128.6 ppm. **IR (film, $CHCl_3$)** 3301, 2932, 2959, 2871, 1609, 1527, 1352, 1332, 1308, 1158, 856, 813, 738, 682 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{17}H_{24}N_2O_4FS$ [M-H^+]: 371.14463, found 371.14485.

Diphenyl (*S*,Z)-(5-fluoro-2-methyldec-5-en-4-yl)phosphoramidate - (530)



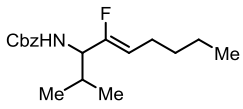
84% yield (176 mg, 0.42 mmol). $[\boldsymbol{\alpha}]_D^{20}$: –6.5° (c=1.11 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.39 – 7.28 (m, 4H), 7.28 – 7.19 (m, 4H), 7.19 – 7.11 (m, 2H), 4.71 (dt, J = 37.7, 7.5 Hz, 1H), 3.89 (ddq, J = 23.4, 10.2, 7.7 Hz, 1H), 3.16 (dd, J = 12.3, 10.2 Hz, 1H), 1.99 (dddt, J = 7.5, 5.9, 3.5, 2.1 Hz, 2H), 1.65 – 1.45 (m, 2H), 1.38 (dt, J = 13.5, 7.4 Hz, 1H), 1.33 – 1.18 (m, 4H), 0.87 (d, J = 1.5 Hz, 3H), 0.87 – 0.83 (m, 6H) ppm. **^{13}C NMR (101 MHz, Chloroform-d) δ** 157.6 (dd, J = 255.5, 3.3 Hz), 151.0 (d, J = 1.6 Hz), 150.9 (d, J = 2.1 Hz), 129.8, 129.7, 125.08 – 125.03 (m), 125.04 – 124.99 (m), 120.4 (d, J = 3.1 Hz), 120.3 (d, J = 3.1 Hz), 107.2 (d, J = 14.7 Hz), 52.4 (d, J = 28.6 Hz), 43.4 (d, J = 7.1 Hz), 31.4 (d, J = 1.7 Hz), 24.7, 23.1 (d, J = 4.3 Hz), 22.4 (d, J = 25.5 Hz), 22.4, 14.0 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -128.8 ppm. **IR (film, $CHCl_3$)** 3212, 2952, 2927, 2869, 1592, 1486, 1456, 1249, 1197, 1158, 1084, 1017, 925, 906, 779, 690 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{23}H_{30}NO_3FP$ [M-H^+]: 418.19529, found 418.19579.

Benzyl (Z)-(5-fluoro-2-methyldec-5-en-4-yl)carbamate - (534)



77% yield (124 mg, 0.39 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.43 – 7.27 (m, 5H), 5.10 (s, 2H), 4.93 – 4.84 (m, 1H), 4.77 (dt, J = 37.9, 7.7 Hz, 1H), 4.26 (dq, J = 22.2, 8.2 Hz, 1H), 2.14 – 1.96 (m, 2H), 1.70 – 1.57 (m, 1H), 1.52 (dt, J = 13.9, 7.1 Hz, 1H), 1.47 – 1.37 (m, 1H), 1.37 – 1.20 (m, 4H), 0.95 – 0.91 (m, 6H), 0.89 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, Chloroform-d) δ** 157.3 (d, J = 255.4 Hz), 155.6, 136.5, 128.7, 128.3, 128.2, 107.2 (d, J = 14.6 Hz), 67.0, 51.2 (d, J = 28.1 Hz), 41.5, 31.5, 24.9, 23.2 (d, J = 4.4 Hz), 22.6 (d, J = 6.5 Hz), 22.3, 14.0 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -127.4. ppm. **IR (film, $CHCl_3$)** 3322, 2956, 2930, 2871, 1696, 1527, 1250, 1112, 1027, 1039, 735, 696 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{19}H_{28}NO_2FNa$ [M+Na$^+$]: 344.19963, found 344.19941.

Benzyl (Z)-(4-fluoro-2-methylnon-4-en-3-yl)carbamate - (535)

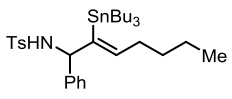


76% yield (116 mg, 0.38 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.43 – 7.28 (m, 5H), 5.11 (s, 2H), 4.96 (d, J = 9.6 Hz, 1H), 4.73 (dt, J = 38.1, 7.5 Hz, 1H), 3.95 (ddd, J = 22.9, 9.6, 7.9 Hz, 1H), 2.15 – 1.96 (m, 2H), 1.88 (dq, J = 13.9, 6.9 Hz, 1H), 1.43 – 1.23 (m, 4H), 0.95 (d, J = 2.7 Hz, 3H), 0.94 (d, J = 2.9 Hz, 3H), 0.92 – 0.85 (m, 3H) ppm. **^{13}C NMR (101 MHz, Chloroform-d) δ** 156.5 (d, J = 255.5 Hz), 155.9, 136.5, 128.7, 128.3, 128.2, 108.0 (d, J = 14.4 Hz), 67.0, 58.6 (d, J = 27.4 Hz), 31.5 (d, J = 1.7 Hz), 30.4, 23.1 (d, J = 4.6 Hz), 22.3, 19.5, 18.8, 14.0 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -125.5 ppm. **IR (film, $CHCl_3$)** 3326, 2959, 2930, 2873, 1697, 1510, 1455, 1264, 1228, 1096, 1022, 936, 836, 736, 696 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{18}H_{26}NO_2FNa$ [M+Na$^+$]: 330.18398, found 330.18378.

Substrate syntheses

The following compounds were prepared according to representative procedure 9.

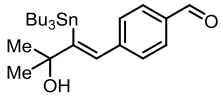
(Z)-4-Methyl-N-(1-phenyl-2-(tributylstannyl)hept-2-en-1-yl)benzene-sulfonamide - (SI-68)



56% yield (1.41 mg, 2.23 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.70 – 7.60 (m, 2H), 7.21 (tdd, J = 7.1, 5.6, 3.3 Hz, 5H), 7.15 – 7.07 (m, 2H), 6.22 – 5.77 (m, 1H), 5.15 – 4.98 (m, 1H), 4.53 (d, J = 7.9 Hz, 1H), 2.40 (s, 3H), 1.92 (qd, J = 7.0, 1.9 Hz, 2H), 1.44 – 1.08 (m, 10H), 0.90 (t, J = 7.1 Hz, 3H), 0.83 (t, J = 7.0 Hz, 15H),

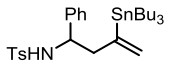
0.66 (ddd, J = 9.1, 5.8, 1.3 Hz, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 143.1, 142.5, 141.8, 140.8, 138.3, 129.5, 128.5, 127.6, 127.6, 127.5, 65.0, 34.4, 32.3, 29.1, 27.5, 22.8, 21.6, 14.2, 13.7, 10.8 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -51.9 ppm. **IR (film, $CHCl_3$)** 3250, 2952, 2922, 2869, 2853, 1453, 1437, 1324, 1303, 1160, 1095, 1067, 1051, 995, 937, 912, 870, 813, 765, 750, 700, 658, 633, 595, 569 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{32}H_{50}NO_2SSn$ [M-H$^+$]: 632.25891, found 632.25941.

(Z)-4-(3-Hydroxy-3-methyl-2-(tributylstannyl)but-1-en-1-yl)benzaldehyde - (SI-69)



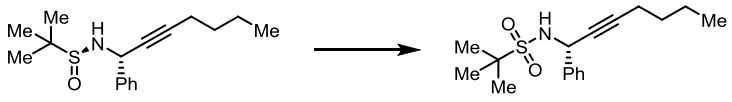
79% yield (3.04 g, 6.35 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 10.00 (s, 1H), 7.84 – 7.75 (m, 2H), 7.40 – 7.29 (m, 3H), 1.57 (d, J = 0.8 Hz, 1H), 1.43 (s, 6H), 1.40 – 1.25 (m, 6H), 1.25 – 1.12 (m, 6H), 0.82 (t, J = 7.2 Hz, 9H), 0.78 – 0.57 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 192.0, 162.9, 147.7, 136.0, 135.0, 129.7, 129.0, 76.2, 31.2, 29.2, 27.5, 13.8, 12.9 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -52.8 ppm. **IR (film, $CHCl_3$)** 2955, 2921, 2871, 2853, 1700, 1600, 1565, 1462, 1418, 1139, 1074, 1048, 1018, 959, 932, 877, 723, 652, 628 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{24}H_{39}O_2Sn$ [M-H$^+$]: 479.19769, found 479.19782.

N-(3-Fluoro-1-phenylbut-3-en-1-yl)-4-methylbenzenesulfonamide - (SI-70)



47% yield (1.12 g, 1.90 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.48 – 7.39 (m, 2H), 7.20 – 7.11 (m, 3H), 7.11 – 7.02 (m, 4H), 5.70 (dt, J = 2.5, 1.3 Hz, 1H), 5.29 (d, J = 2.3 Hz, 1H), 4.74 (d, J = 3.8 Hz, 1H), 4.29 (ddd, J = 9.1, 5.4, 3.8 Hz, 1H), 2.68 – 2.48 (m, 2H), 2.35 (s, 3H), 1.54 – 1.39 (m, 6H), 1.39 – 1.25 (m, 6H), 0.98 – 0.81 (m, 15H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 151.2, 143.0, 140.7, 137.7, 130.1, 129.3, 128.4, 127.5, 127.4, 127.2, 57.2, 49.7, 29.2, 27.5, 21.6, 13.8, 9.8 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -43.6 ppm. **IR (film, $CHCl_3$)** 3273, 2955, 2924, 2871, 2852, 1599, 1495, 1455, 1376, 1325, 1243, 1157, 1094, 1052, 959, 921, 863, 812, 757, 698, 665 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{29}H_{44}NO_2SSn$ [M-H$^+$]: 590.21086, found 590.21190.

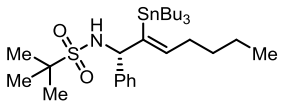
8.5.2. Representative procedure 13: Oxidation of Sulfinimides to the Corresponding Sulfones



SI-83 (1.46 g, 5.0 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (25 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on an ice bath. *m*CPBA (1.62 g, 80% purity, 7.5 mmol, 1.5 equiv.) was added in one portion, the cooling bath removed after 5 minutes and stirring was continued with the conversion monitored by TLC (hexanes/ethyl acetate, 2:1). After 1 h saturated sodium bicarbonate solution was added and stirring continued for 30 minutes before the mixture was extracted twice with CH_2Cl_2. The combined extracts were washed with saturated sodium bicarbonate solution and water, dried over magnesium sulfate and concentrated under reduced pressure. The crude material was used as such for the ensuing hydrostannation.

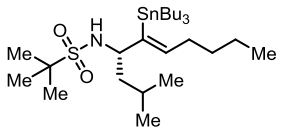
The following compounds were prepared following representative procedure 9.

(*S*,*Z*)-2-Methyl-N-(1-phenyl-2-(tributylstannyl)hept-2-en-1-yl)propane-2-sulfonamide - (SI-71)



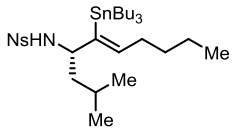
56% yield over 2 steps (1.67 g, 2.79 mmol). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +20.6° (c=1.38 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.40 – 7.28 (m, 4H), 7.28 – 7.17 (m, 2H), 6.43 (td, J = 7.2, 1.4 Hz, 1H), 5.32 – 5.12 (m, 1H), 4.02 (d, J = 9.5 Hz, 1H), 2.17 (q, J = 7.1 Hz, 2H), 1.52 – 1.41 (m, 2H), 1.39 (s, 8H), 1.37 – 1.11 (m, 13H), 1.00 – 0.90 (m, 4H), 0.82 (t, J = 7.1 Hz, 9H), 0.73 – 0.62 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 143.0, 142.1, 141.3, 128.8, 127.8, 127.7, 65.6, 60.1, 34.5, 32.5, 29.1, 27.5, 24.4, 22.8, 14.3, 13.8, 10.8 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -52.5 ppm. **IR (film, $CHCl_3$)** 3279, 2924, 2955, 2854, 2871, 1454, 1377, 1302, 1182, 1127, 1067, 1003, 939, 874, 757, 698, 654, 560 594, 513 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{29}H_{53}NO_2SSnNa$ [M+Na$^+$]: 622.27105, found 622.27143.

(*S*,Z)-2-Methyl-N-(2-methyl-5-(tributylstannyl)dec-5-en-4-yl)propane-2-sulfonamide - (SI-72)



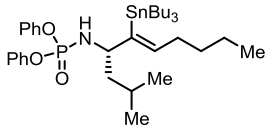
62% yield over 2 steps (1.78 g, 3.08 mmol). $[\alpha]_D^{20}$: –8.6° (c=1.23 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.34 – 5.86 (m, 1H), 4.17 – 3.89 (m, 1H), 3.63 (d, J = 8.9 Hz, 1H), 2.12 – 1.87 (m, 2H), 1.81 – 1.59 (m, 2H), 1.55 – 1.39 (m, 6H), 1.35 (s, 9H), 1.35 – 1.27 (m, 14H), 0.98 – 0.92 (m, 9H), 0.89 (t, J = 7.2 Hz, 12H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 145.3, 141.7, 62.1, 59.5, 48.5, 34.5, 32.3, 29.4, 27.6, 24.8, 24.5, 22.7, 22.6, 14.2, 13.8, 11.1 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -55.1 ppm. **IR (film, $CHCl_3$)** 3273, 2925, 2955, 2871, 1457, 1420, 1377, 1301, 1125, 1061, 692, 663, 594, 539, 512 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{27}H_{57}NO_2SSnNa$ [M+Na$^+$]: 602.30235, found 602.30270.

(*S*,Z)-N-(2-Methyl-5-(tributylstannyl)dec-5-en-4-yl)-4-nitrobenzene-sulfonamide - (SI-73)



67% yield (1.39 g, 2.16 mmol). $[\alpha]_D^{20}$: +9.6° (c=1.35 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 8.30 (dq, J = 9.0, 2.1 Hz, 2H), 8.05 – 7.88 (m, 2H), 6.15 – 5.64 (m, 1H), 4.45 (d, J = 7.6 Hz, 1H), 4.18 – 3.82 (m, 1H), 1.90 – 1.71 (m, 2H), 1.62 (dq, J = 13.4, 6.7 Hz, 1H), 1.49 – 1.33 (m, 7H), 1.33 – 1.19 (m, 12H), 1.19 – 1.09 (m, 2H), 0.91 – 0.87 (m, 9H), 0.86 (s, 6H), 0.83 – 0.77 (m, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 149.9, 147.4, 143.7, 142.3, 128.7, 124.2, 62.1, 46.7, 34.3, 32.3, 29.3, 27.5, 24.7, 22.7, 22.6, 22.3, 14.1, 13.7, 11.1 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -55.3 ppm. **IR (film, $CHCl_3$)** 3285, 2956, 2925, 2871, 1608, 1531, 1464, 1417, 1347, 1310, 1164, 854, 811, 735, 747, 758, 685, 667, 612, 580, 535, 462 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{29}H_{52}N_2O_4SSnNa$ [M+Na$^+$]: 667.25613, found 667.25650.

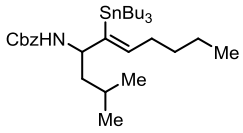
Diphenyl (*S*,Z)-(2-methyl-5-(tributylstannyl)dec-5-en-4-yl)phosphor-amidate - (SI-74)



65% yield (1.62 g, 2.35 mmol). $[\alpha]_D^{20}$: –14.2° (c=1.34 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.37 – 7.25 (m, 5H), 7.22 (tt, J = 8.7, 1.1 Hz, 3H), 7.18 – 7.08 (m, 2H), 6.13 (td, J = 7.2, 0.9 Hz, 1H), 4.07 – 3.81 (m, 1H), 2.92 (dd, J = 12.5, 9.2 Hz, 1H), 1.98 (dtd, J = 12.9, 7.1, 5.8, 3.8 Hz, 2H), 1.60 (dq, J = 13.7, 6.9 Hz, 1H), 1.53 – 1.39 (m, 6H), 1.38 – 1.21 (m, 12H), 0.95 – 0.84 (m, 24H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 151.2, 151.2, 151.2, 151.1, 145.9, 145.8, 141.3, 129.7, 129.6, 124.7, 120.5, 120.4, 120.3, 120.2, 60.2, 47.9, 47.8, 34.3, 32.3, 29.3, 27.6, 24.7, 22.7, 22.7, 22.4, 14.2, 13.7, 11.2 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -56.3 ppm. **IR (film, $CHCl_3$)** 3200, 2924, 2955, 2870,

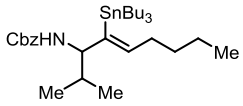
1593, 1491, 1457, 1422, 1376, 1255, 1195, 1220, 1162, 1071, 1025, 929, 899, 753, 687 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{35}H_{58}NO_3PSnNa$ [M+Na$^+$]: 714.30678, found 714.30658.

Benzyl (Z)-(2-methyl-5-(tributylstannyl)dec-5-en-4-yl)carbamate - (SI-75)



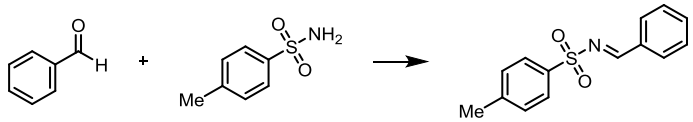
68% yield (1.86 g, 3.14 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.43 – 7.27 (m, 5H), 6.15 (t, J = 7.2 Hz, 1H), 5.15 – 4.99 (m, 2H), 4.56 (d, J = 8.5 Hz, 1H), 4.21 (q, J = 7.8 Hz, 1H), 1.99 (tt, J = 13.6, 7.1 Hz, 2H), 1.68 – 1.54 (m, 1H), 1.54 – 1.38 (m, 6H), 1.38 – 1.19 (m, 10H), 1.01 – 0.77 (m, 26H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 155.4, 144.4, 141.4, 136.9, 128.6, 128.3, 128.2, 66.5, 58.2, 45.6, 34.4, 32.4, 29.3, 27.6, 24.9, 22.7, 14.2, 13.8, 11.0 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -53.4 ppm. **IR (film, $CHCl_3$)** 2954, 2924, 2870, 1707, 1497, 1455, 1403, 1337, 1213, 1027, 864, 734, 695 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{31}H_{55}NO_2SnNa$ [M+Na$^+$]: 616.31463, found 616.31451.

Benzyl (Z)-(2-methyl-4-(tributylstannyl)non-4-en-3-yl)carbamate - (SI-76)



81% yield (2.85 g, 4.93 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.42 – 7.27 (m, 5H), 6.26 – 5.87 (m, 1H), 5.18 – 4.98 (m, 2H), 4.66 (dd, J = 19.2, 8.8 Hz, 1H), 4.05 – 3.74 (m, 1H), 2.12 – 1.92 (m, 1H), 1.62 – 1.38 (m, 6H), 1.31 (h, J = 7.2 Hz, 10H), 0.99 – 0.79 (m, 26H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 155.8, 143.7, 141.3, 136.9, 128.6, 128.2, 128.1, 66.6, 65.6, 34.5, 32.5, 29.3, 27.6, 22.7, 20.7, 17.9, 14.2, 13.8, 10.9 ppm. **^{119}Sn NMR (149 MHz, $CDCl_3$) δ** -54.1 ppm. **IR (film, $CHCl_3$)** 2955, 2924, 2871, 1705, 1497, 1456, 1402, 1338, 1213, 1072, 1024, 873, 752, 695 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{30}H_{53}NO_2SnNa$ [M+Na$^+$]: 602.29898, found 602.29917.

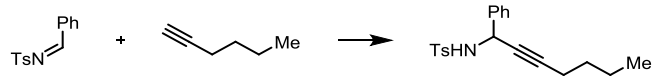
(E)-N-Benzylidene-4-methylbenzenesulfonamide[35] - (SI-77)



Tosylamide (5.14 g, 30 mmol, 1.0 equiv.) and benzaldehyde (3.05 mL, 30 mmol, 1.0 equiv.) were suspended in $(EtO)_4Si$ (7.03 mL, 31.5 mmol, 1.05 equiv.) and the suspension was stirred in a single-necked flask equipped with a Dean-Stark head under an argon atmosphere. The mixture was heated to 160 °C and stirred for 12 h before it was cooled to room temperature. The crude yellow solid was dissolved in ethyl acetate and concentrated until a small amount of precipitate

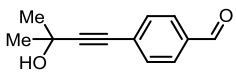
already formed. Then, about 400 mL of hexanes were added, the colorless solid was filtered off, washed once with hexanes and dried under vacuum. The material was used as such.

4-Methyl-N-(1-phenylhept-2-yn-1-yl)benzenesulfonamide - (SI-78)



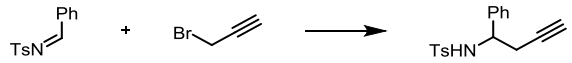
1-Hexyne (1.49 mL, 13 mmol, 1.3 equiv.) was dissolved in dry THF (30 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. *n*-Butyllithium (7.5 mL, 1.6 M in hexanes, 12 mmol, 1.2 equiv.) was slowly added and stirring continued for 30 minutes before a solution of **SI-77** (2.59 g, 10 mmol, 1.0 equiv.) in THF (5 mL) was added. Stirring was continued for 18 h while the mixture was allowed to warm to room temperature. The reaction was then quenched with the addition of saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 9:1 to 4:1) yielded the product as a yellow solid (2.65 g, 7.76 mmol, 78% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.87 – 7.68 (m, 2H), 7.52 – 7.42 (m, 2H), 7.39 – 7.17 (m, 5H), 5.30 (dt, J = 8.9, 2.2 Hz, 1H), 4.81 (d, J = 8.9 Hz, 1H), 2.43 (s, 3H), 1.98 (tt, J = 6.9, 2.2 Hz, 2H), 1.28 (dtdd, J = 7.2, 5.6, 3.4, 1.4 Hz, 4H), 0.98 – 0.75 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 143.4, 138.3, 137.7, 129.5, 128.7, 128.3, 127.6, 127.4, 87.6, 76.7, 49.6, 30.5, 22.0, 21.7, 18.4, 13.7 ppm. **IR (film, $CHCl_3$)** 3282, 2930, 1597, 1493, 1451, 1428, 1326, 1155, 1091, 1037, 937, 905, 815, 751, 698, 666, 635, 571 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{20}H_{23}NO_2SNa$ [M+Na$^+$]: 364.13417, found 364.13414.

4-(3-Hydroxy-3-methylbut-1-yn-1-yl)benzaldehyde - (SI-79)



Following the same procedure as for 4-(3-Hydroxy-3-methylbut-1-yn-1-yl)benzonitrile **SI-34**. The product as obtained as an orange oil (2.8 g, 14.9 mmol, 99% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 9.99 (s, 1H), 7.86 – 7.78 (m, 2H), 7.62 – 7.45 (m, 2H), 2.18 (s, 1H), 1.63 (s, 6H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 191.6, 135.6, 132.3, 129.6, 129.2, 97.9, 81.5, 65.8, 31.5 ppm. **IR (film, $CHCl_3$)** 3392, 2981, 1698, 1601, 1563, 1363, 1303, 1272, 1206, 1163, 962, 905, 828, 789 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{12}H_{13}O_2$ [M+H$^+$]: 189.09101, found 189.09111.

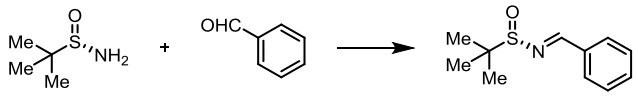
4-Methyl-N-(1-phenylbut-3-yn-1-yl)benzenesulfonamide[36] - (SI-80)



SI-77 (2.59 g, 10 mmol, 1.0 equiv.), propargyl bromide (1.67 mL, 80% in PhMe, 15 mmol, 1.5 equiv.), zinc powder (3.27 g, 50 mmol, 5.0 equiv.) and 1,2-diiodoethane (2.82 g, 10 mmol, 1.0 equiv.) were combined in a Schlenk flask under argon atmosphere. The flask was equipped with an argon balloon and sonicated for 2.5 h at room temperature. The mixture was then poured onto aqueous HCl (2 M) and extracted two times with CH_2Cl_2. The combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in a minimum amount of hot EtOH and then placed for 2 h in the freezer. The liquids were decanted off, the solid washed with hexanes and dried under high vacuum to give a colorless solid (2.06 g, 6.88 mmol, 69% yield). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.63 (d, J = 8.0 Hz, 2H), 7.17 (ddd, J = 11.6, 6.3, 3.0 Hz, 7H), 5.63 (d, J = 7.6 Hz, 1H), 4.51 (q, J = 6.6 Hz, 1H), 2.62 (dd, J = 6.2, 2.7 Hz, 2H), 2.36 (s, 3H), 1.95 (t, J = 2.7 Hz, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 143.3, 139.3, 137.3, 129.5, 128.4, 127.8, 127.2, 126.6, 79.3, 72.1, 56.0, 27.4, 21.5 ppm. **IR (film, $CHCl_3$)** 3258, 1462, 1319, 1156, 1087, 1066, 945, 838, 811, 763, 703, 651, 585, 555 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{17}NO_2SNa$ [M+Na$^+$]: 322.08722, found 322.08729.

8.5.3. Representative procedure 14: Pyrrolidine Catalyzed Condensation of Aldehydes and Amines[37]

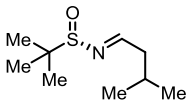
(*S*,E)-N-Benzylidene-2-methylpropane-2-sulfinamide - (SI-81)



(*S*)-*tert*-Butylsulfinamide (2.42 g, 20 mmol, 1.0 equiv.) and benzaldehyde (2.03 mL, 20 mmol, 1.0 equiv.) were dissolved in CH_2Cl_2 (60 mL). Pyrrolidine (334 µL, 4.0 mmol, 0.2 equiv.) and 4 Å mol sieves were added and stirring was continued at room temperature for 4 days. The mixture was then filtered through a plug of silica with additional CH_2Cl_2. The volatile materials were removed under reduced pressure and the oil dried under high vacuum (3.61 g, 17.2 mmol, 85% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +148.9° (c=1.30 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d)** δ 8.59 (s, 1H), 7.90 – 7.78 (m, 2H), 7.58 – 7.42 (m, 3H), 1.27 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 162.9, 134.2, 132.6, 129.5, 129.1, 57.9, 22.7 ppm. **IR (film, $CHCl_3$)** 2960, 2925, 2867, 1572, 1605, 1449,

1474, 1362, 1391, 1171, 1082, 727, 756, 689 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{11}H_{15}NOSNa$ $[M+Na^+]$: 232.076655, found 232.076520.

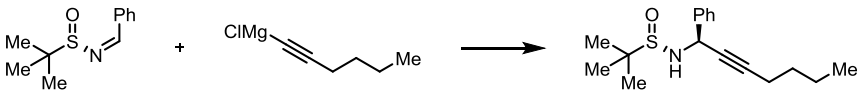
(*S*,E)-2-Methyl-N-(3-methylbutylidene)propane-2-sulfinamide - (SI-82)



96% yield (from 2.0 equiv. of aldehyde, 3.62 g, 19.1 mmol). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +485.5° (c=1.70 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 8.05 (t, J = 5.2 Hz, 1H), 2.40 (ddd, J = 6.6, 5.2, 1.5 Hz, 2H), 2.06 (dt, J = 13.5, 6.7 Hz, 1H), 1.19 (s, 9H), 0.99 (d, J = 1.4 Hz, 3H), 0.97 (d, J = 1.3 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 169.6, 56.7, 45.1, 26.3, 22.8, 22.5 ppm. **IR (film, $CHCl_3$)** 2958, 2871, 1621, 1461, 1363, 1168, 1083, 753, 676, 585, 456, 482 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_9H_{19}NOSNa$ $[M+Na^+]$: 212.10796, found 212.10786.

8.5.4. Representative procedure 15: Diastereoselective Addition of Magnesium Acetylides to Sulfinimides[38]

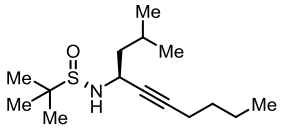
(*S*)-2-Methyl-N-((*S*)-1-phenylhept-2-yn-1-yl)propane-2-sulfinamide - (SI-83)



1-Hexyne (4.36 mmol, 38 mmol, 2.2 equiv.) was dissolved in dry THF (5 mL) and stirred in an oven-dried Schlenk flask under an argon atmosphere on an ice bath. *iso*-Propylmagnesium chloride (17.3 mL, 2 M solution in THF, 34.5 mmol, 2.0 equiv.) was added, the cooling bath removed and stirring continued for 60 minutes. **SI-81** (3.6 g, 17.2 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (80 mL) and stirred in an oven-dried Schlenk flask under an argon atmosphere on a dry-ice bath. The above prepared Grignard reagent was added dropwise by means of a cannula over about 15 minutes and stirring was continued at the same temperature for 2 h and 12 h at room temperature. The reaction was then quenched with saturated ammonium chloride solution. The mixture was extracted two times with MTBE, the combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 4:1) yielded the product as a yellow thick oil (3.4 g, 11.7 mmol, > 20:1 d.r., 68% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +32.3° (c=1.24 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.53 – 7.45 (m, 2H), 7.39 – 7.27 (m, 3H), 5.20 (dt, J = 5.7, 2.2 Hz, 1H), 3.59 (d, J = 5.8 Hz, 1H), 2.25 (td, J = 7.1, 2.1 Hz, 2H), 1.60 – 1.46 (m, 2H), 1.46 – 1.32 (m, 2H), 1.20 (s, 9H), 0.90 (t, J = 7.3 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 139.9, 128.7,

128.2, 127.8, 87.6, 78.9, 56.3, 51.2, 30.7, 22.7, 22.1, 18.7, 13.8 ppm. **IR (film, $CHCl_3$)** 3186, 2931 2956, 2870, 1493, 1455, 1381, 1327, 1251, 1188, 1139, 1061, 1005, 923, 792, 751, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{25}NOSNa$ [M+Na^+]: 314.15491, found 314.15462.

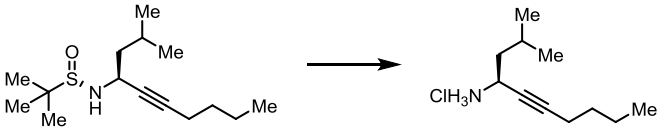
(*S*)-2-Methyl-N-((*S*)-2-methyldec-5-yn-4-yl)propane-2-sulfinamide - (SI-84)



74% yield (3.85 g, 14.2 mmol, > 20:1 d.r.). $[\boldsymbol{a}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +49.5° (c=1.35 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.02 (dddd, J = 8.4, 7.2, 4.2, 2.1 Hz, 1H), 3.18 (d, J = 6.5 Hz, 1H), 2.18 (td, J = 7.1, 2.1 Hz, 2H), 1.83 (dp, J = 13.5, 6.7 Hz, 1H), 1.57 – 1.51 (m, 2H), 1.51 – 1.42 (m, 2H), 1.42 – 1.31 (m, 2H), 1.20 (s, 9H), 0.93 – 0.86 (m, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 85.4, 80.1, 56.1, 46.6, 30.9, 25.1, 22.8, 22.7, 22.2, 22.1, 18.6, 13.7 ppm. **IR (film, $CHCl_3$)** 3198, 2956, 2931, 2869, 1467, 1364 1385, 1159, 1057, 877, 795, 752, 663, 605, 478 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{15}H_{29}NOSNa$ [M+Na^+]: 294.18621, found 294.18593.

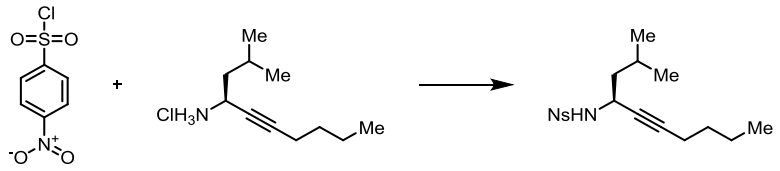
8.5.5. Representative procedure 16: Acid Mediated Deprotection of Sulfonamides[38]

(*S*)-2-Methyldec-5-yn-4-aminium chloride - (SI-85)



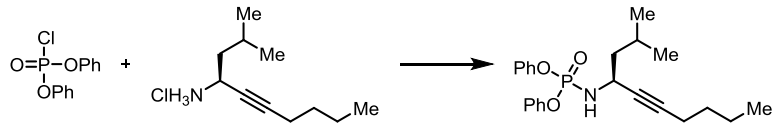
SI-81 (1.61 g, 5.5 mmol, 1.0 equiv.) was dissolved in dry MeOH (20 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on an ice bath. HCl (4.5 mL, 4 M in 1,4-dioxane, 18 mmol, 2.0 equiv.) was added in one portion and stirring was continued with the conversion monitored by TLC (hexanes/ethyl acetate, 2:1). After disappearance of starting material, the volatile materials were removed under reduced pressure and the crude ammonium salt used as such.

(*S*)-N-(2-Methyldec-5-yn-4-yl)-4-nitrobenzenesulfonamide - (SI-86)



SI-85 (917 mg, 4.5 mmol, 1.0 equiv.) was dissolved in dry DMF (20 mL) and stirred at room temperature in an oven-dried Schlenk flask under an argon atmosphere. Et_3N (1.88 mL, 13.5 mmol, 3.0 equiv.) and 4-nitrobenzenesulfonyl chloride (1.2 g, 5.4 mmol, 1.2 equiv.) were added and stirring was continued for 12 h at the same temperature. The mixture was then poured onto saturated ammonium chloride solution. The mixture was extracted two times with CH_2Cl_2, the combined extracts were washed with water, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate) yielded the product as an orange solid (1.13 g, 3.2 mmol, 71% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: −94.2° (c=1.74 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 8.35 (dq, J = 9.0, 2.1 Hz, 2H), 8.22 – 7.96 (m, 2H), 4.65 (d, J = 9.4 Hz, 1H), 4.35 – 3.97 (m, 1H), 1.89 – 1.74 (m, 3H), 1.62 – 1.44 (m, 2H), 1.23 – 1.08 (m, 4H), 0.92 (dd, J = 9.0, 6.6 Hz, 6H), 0.85 – 0.75 (m, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 150.2, 146.7, 128.9, 124.1, 85.8, 77.9, 46.3, 45.1, 30.6, 24.8, 22.3, 22.2, 22.0, 18.1, 13.6 ppm. **IR (film, $CHCl_3$)** 3271, 2933 2958, 2871, 1524, 1346, 1311, 1155, 1090, 1053, 855, 739, 619, 550 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{17}H_{24}N_2O_4SNa$ [M+Na$^+$]: 375.13490, found 375.13471.

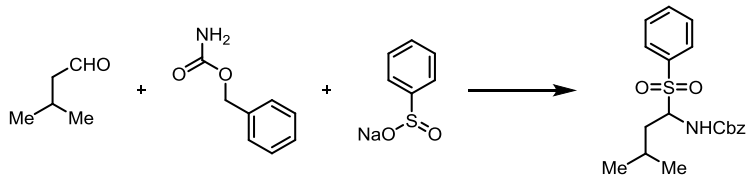
(*S*)-N-(2-Methyldec-5-yn-4-yl)-4-nitrobenzenesulfonamide - (SI-87)



SI-85 (917 mg, 4.5 mmol, 1.0 equiv.) was dissolved in dry DMF (20 mL) and the solution stirred at room temperature in an oven-dried Schlenk flask under an argon atmosphere. Et_3N (1.88 mL, 13.5 mmol, 3.0 equiv.) and diphenylchlorophosphate (1.2 mL, 5.4 mmol, 1.2 equiv.) were added and stirring was continued for 12 h at the same temperature. The mixture was then poured onto saturated ammonium chloride solution. The mixture was extracted two times with CH_2Cl_2, the combined extracts were washed with water, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 9:1) yielded the product as an orange solid (1.45 g, 3.6 mmol, 81% yield). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: −33.1° (c=1.21 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.38 – 7.23 (m, 8H), 7.16 (dddd, J = 8.0, 5.9, 4.2, 1.1 Hz, 2H), 4.14 (dtdt, J = 10.5, 8.7, 6.9, 2.1 Hz, 1H), 3.16 (dd, J = 12.6, 10.1 Hz, 1H), 2.10 (td, J = 6.9, 2.1

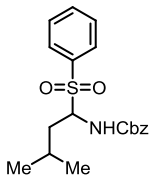
Hz, 2H), 1.77 (ddt, J = 13.1, 8.0, 6.6 Hz, 1H), 1.56 – 1.28 (m, 6H), 0.89 (d, J = 1.7 Hz, 4H), 0.88 – 0.84 (m, 5H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 151.0, 151.0, 150.9, 129.7, 129.7, 125.0, 120.6, 120.6, 120.4, 120.4, 84.1, 80.4, 80.4, 47.7, 47.7, 43.2, 30.8, 25.0, 22.8, 22.0, 18.4, 13.7 ppm. **IR (film, $CHCl_3$)** 3204, 2932 2956, 2870, 1591, 1489, 1255, 1219, 1191, 1162 , 928, 752, 688 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{23}H_{30}NO_3PNa$ [M+Na^+]: 422.18555, found 422.18526.

8.5.6. Representative procedure 17: Synthesis of α-Amidoalkyl Sulfones[39]



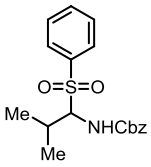
Benzyl carbamate (2.27 g, 15 mmol, 1.0 equiv.) and benzenesulfinic acid sodium salt (2.46 g, 15 mmol, 1.0 equiv.) were dissolved in THF (15 mL) and H_2O (6 mL) and the solution was stirred at room temperature in a single-necked flask. *iso*-Valeraldehyde (1.77 mL, 16.5 mmol, 1.1 equiv.) and HCO_2H (3.96 mL, 105 mmol, 7.0 equiv.) were added and stirring was continued for 18 h. A colorless solid formed over the course of the reaction. The flask was placed for 30 minutes in the freezer before the precipitate was filtered off, washed with ice cold water and dried under high vacuum. NMR showed slightly impured material which was used as such.

Benzyl (3-methyl-1-(phenylsulfonyl)butyl)carbamate - (SI-88)



77% yield (4.18 g, 11.6 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.93 – 7.81 (m, 2H), 7.58 (ddt, J = 8.8, 7.1, 1.3 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.34 (ddt, J = 5.5, 3.8, 2.2 Hz, 3H), 7.24 – 7.13 (m, 2H), 5.32 (d, J = 10.8 Hz, 1H), 4.95 (td, J = 11.1, 3.1 Hz, 1H), 4.88 (d, J = 12.2 Hz, 1H), 4.81 (d, J = 12.2 Hz, 1H), 2.07 – 1.95 (m, 1H), 1.83 – 1.69 (m, 2H), 0.99 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.4 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 154.8, 136.5, 135.7, 134.1, 129.3, 129.1, 128.6, 128.5, 128.3, 70.2, 67.4, 34.7, 24.8, 23.4, 21.2 ppm. **IR (film, $CHCl_3$)** 3279, 3064, 2958, 1718, 1692, 1537, 1448, 1388, 1315,1267 ,1240 1218, 1179, 1140, 1039, 983, 914, 856, 790, 773, 703, 677, 607, 587 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{19}H_{23}NO_4SNa$ [M+Na^+]: 384.12400, found 384.12365.

Benzyl (2-methyl-1-(phenylsulfonyl)propyl)carbamate - (SI-89)

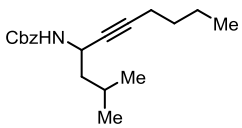


67% yield (2.34 g, 6.74 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.91 – 7.72 (m, 2H), 7.58 (ddt, J = 8.7, 7.1, 1.3 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.38 – 7.33 (m, 3H), 7.23 – 7.17 (m, 2H), 5.44 (d, J = 11.2 Hz, 1H), 4.89 (d, J = 12.2 Hz, 1H), 4.83 (d, J = 12.2 Hz, 1H), 4.77 (dd, J = 11.2, 3.5 Hz, 1H), 2.78 (pd, J = 6.9, 3.5 Hz, 1H), 1.13 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 155.3, 137.7, 135.7, 134.0, 129.1, 129.0, 128.7, 128.5, 128.3, 75.0, 67.6, 26.9, 20.8, 17.0 ppm. **IR (film, $CHCl_3$)** 3330, 2965, 1721, 1525, 1496, 1447, 1390, 1308, 1284, 1228,1138 1098, 1079, 1029, 614, 596, 580, 559 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{18}H_{21}NO_4SNa$ [$M+Na^+$]: 370.10805, found 370.10835.

8.5.7. Representative procedure 18: Alkylation of α-Amidoalkyl Sulfones[39]

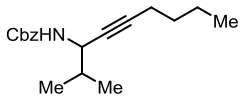
1-Hexyne (1.15 mL, 10 mmol, 2.0 equiv.) was dissolved in dry THF (40 mL) and the solution stirred in an oven-dried Schlenk flask under an argon atmosphere on an ice bath. *n*-Butyllithium (6.56 mL, 1.6 M in hexanes, 10.5 mmol, 2.1 equiv.) was added and stirring continued for 30 minutes before the mixture was cooled with a dry-ice bath. **SI-88** (1.81 g, 5.0 mmol, 1.0 equiv.) dissolved in dry THF (10 mL) was added slowly and stirring was continued at the same temperature for 1 h before the reaction was quenched with of saturated ammonium chloride solution. The mixture was allowed to warm to room temperature and extracted two times with MTBE. The combined extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (hexanes/ethyl acetate, 19:1) yielded the product as a colorless thick oil.

Benzyl (2-methyldec-5-yn-4-yl)carbamate - (SI-90)



97% yield (1.46 g, 4.84 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.40 – 7.27 (m, 5H), 5.24 – 5.00 (m, 2H), 4.82 (d, J = 8.8 Hz, 1H), 4.48 (q, J = 8.2 Hz, 1H), 2.22 – 2.09 (m, 2H), 1.77 (dq, J = 13.4, 6.7 Hz, 1H), 1.57 – 1.31 (m, 6H), 1.00 – 0.78 (m, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 155.5, 136.5, 128.6, 128.3 (2C), 83.7, 79.5, 66.9, 45.9, 42.3, 30.9, 25.2, 22.9, 22.0, 18.4, 13.7 ppm. **IR (film, $CHCl_3$)** 3327, 2956, 2932, 2871, 1697, 1500, 1455, 1368, 1325, 1278, 1241, 1170, 1112, 1038, 912, 751, 696 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{19}H_{26}NO_2$ [$M-H^+$]: 300.19718, found 300.19690.

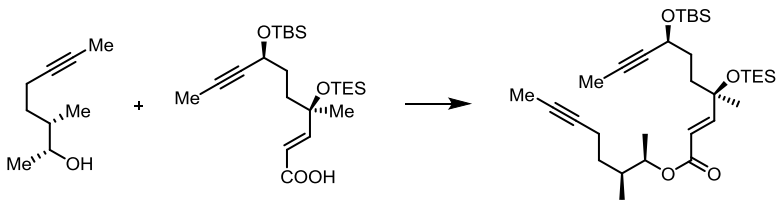
Benzyl (2-methylnon-4-yn-3-yl)carbamate - (SI-91)



91% yield (1.76 g, 6.12 mmol). **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.44 – 7.28 (m, 5H), 5.17 – 5.04 (m, 2H), 4.94 (d, J = 9.0 Hz, 1H), 4.35 (dq, J = 7.5, 2.7 Hz, 1H), 2.17 (td, J = 6.9, 2.2 Hz, 2H), 1.96 – 1.81 (m, 1H), 1.53 – 1.30 (m, 4H), 0.96 (dd, J = 6.8, 4.4 Hz, 6H), 0.90 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 155.6, 136.5, 128.6, 128.3, 128.3, 84.6, 77.6, 66.9, 49.6, 33.3, 30.9, 22.0, 19.0, 18.4, 17.6, 13.7 ppm. **IR (film, $CHCl_3$)** 3325, 2959, 2931, 2872, 1696, 1499, 1455, 1386, 1332, 1302, 1229, 1126, 1026, 736, 696 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{18}H_{25}NO_2Na$ [M+Na^+]: 310.17775, found 310.17765.

8.6. Diverted Total Synthesis of 5,6-Dihydrocineromycin B

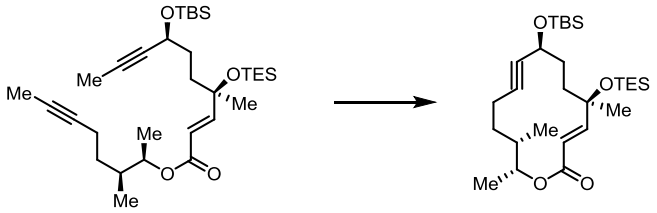
(*2R,3S*)-3-Methyloct-6-yn-2-yl (*4R,7S*,E)-7-((*tert*-butyldimethylsilyl)oxy)-4-methyl-4-((triethylsilyl)oxy)dec-2-en-8-ynoate – (SI-92)



(*2R,3S*)-3-Methyloct-6-yn-2-ol (**648**) (635 mg, 4.53 mmol, 1.05 equiv.) and (*4R,7S,E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-methyl-4-((triethylsilyl)oxy)dec-2-en-8-ynoic acid (**650**) (1.90 g, 4.31 mmol, 1.0 equiv.) were dissolved in dry CH_2Cl_2 (30 mL) and the solution was stirred under ice cooling in an oven-dried Schlenk flask under an argon atmosphere. *N,N'*-Dicyclohexylcarbodiimide (1.16 g, 5.60 mmol, 1.3 equiv.) and DMAP (53 mg, 0.43 mmol, 0.1 equiv.) were added successfully and the conversion was monitored by TLC. After about 30 minutes complete conversion of the starting acid was observed so the mixture was filtered over Celite® with the aid of additional CH_2Cl_2 (200 mL) and the volatile materials were removed under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 40:1 to 30:1) yielded the product as a colorless oil (2.04 g, 4.31 mmol, 84 % yield). **TLC** (hexanes/ethyl acetate, 4:1), Rf = 0.74. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: −13.4° (c=1.0 in MeOH). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.83 (d, J = 15.5 Hz, 1H), 5.91 (d, J = 15.5 Hz, 1H), 4.88 (p, J = 6.3 Hz, 1H), 4.30 (ddt, J = 5.6, 3.7, 2.1 Hz, 1H), 2.29 – 2.15 (m, 1H), 2.10 (dtq, J = 13.6, 8.0, 2.5 Hz, 1H), 1.81 (d, J = 2.1 Hz, 3H), 1.77 (t, J = 2.5 Hz, 3H), 1.75 – 1.61 (m, 4H), 1.59 – 1.49 (m, 1H), 1.36 (s, 3H), 1.29 (dtd, J = 9.3, 8.1, 4.6 Hz, 1H), 1.19 (d, J = 6.4 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.90 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.65 – 0.56 (m, 6H), 0.09 (s, 3H), 0.08 (s, 3H) ppm**. ^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.3, 154.3, 119.1, 80.5, 79.9,

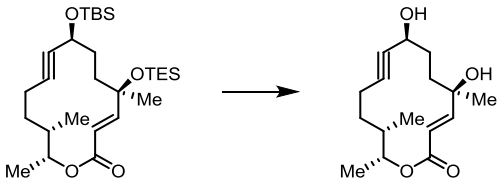
78.6, 75.4, 74.7, 73.8, 62.9, 38.3, 36.4, 34.8, 33.2, 31.5, 27.9, 25.7, 18.1, 16.4, 16.0, 14.2, 6.9, 6.5, 3.3, 3.3, -4.7, -5.2 ppm. **IR (film, $CHCl_3$)** 2955, 2932, 2120, 1717, 1655, 1459, 1362, 1254, 1159, 1082, 1004, 836, 776, 724 cm^{-1}. **HRMS** (ESI): calculated for $C_{32}H_{58}O_4Si_2Na$ [M + Na^+]: 585.37601, found 585.37659.

(*5R,8S,13S,14R,E*)-8-((*tert*-Butyldimethylsilyl)oxy)-5,13,14-trimethyl-5-((triethyl-silyl)-oxy)oxacyclotetradec-3-en-9-yn-2-one – (655b)



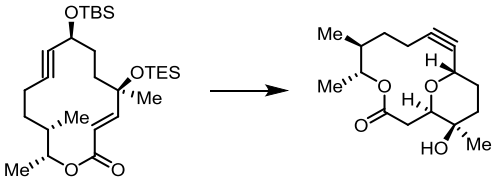
6 g of dry 5Å mole sieves were placed in an oven-dried 2-necked flask and flame-dried under high-vacuum for 10 minutes. After being cooled to room temperature dry toluene (750 mL) and **SI-92** (800 mg, 1.42 mmol, 1.0 equiv.) were added and the mixture was stirred for 1 h at room temperature under an argon atmosphere. Then, potassium benzylidynetetrakis-((triphenylsilyl)oxy)molybdate(VI) (188 mg, 0.14 mmol, 10 mol%) was added and stirring was continued at room temperature with the conversion monitored by TLC (hexanes/ethyl acetate, 2 times 30:1). After 2 h complete conversion of starting material was observed so the mixture was filtered through a plug of Celite® with the aid of ethyl acetate (250 mL) and the volatile materials were removed under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 30:1 to 20:1) yielded the product as a colorless oil (672 mg, 1.32 mmol, 92% yield). **TLC** (hexanes/ethyl acetate, 20:1), Rf = 0.61. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.05 (d, J = 15.3 Hz, 1H), 5.97 (d, J = 15.3 Hz, 1H), 4.68 (dq, J = 9.1, 6.3 Hz, 1H), 4.34 (dq, J = 8.4, 2.1 Hz, 1H), 2.27 (dddd, J = 17.0, 7.0, 5.2, 1.9 Hz, 1H), 2.15 (dddd, J = 17.0, 8.6, 5.2, 2.0 Hz, 1H), 1.95 – 1.76 (m, 2H), 1.66 (dtd, J = 9.1, 6.8, 3.8 Hz, 1H), 1.62 – 1.54 (m, 2H), 1.54 – 1.35 (m, 2H), 1.32 (s, 3H), 1.27 (d, J = 6.3 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.90 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.65 – 0.57 (m, 6H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.6, 155.1, 119.0, 85.4, 81.5, 75.5, 74.9, 63.4, 39.3, 37.6, 33.3, 32.9, 27.5, 25.9, 19.2, 18.3, 17.0, 16.9, 7.2, 6.9, -4.3, -4.8 ppm. **IR (film, $CHCl_3$)** 2955, 2932, 2877, 1715, 1459, 1342, 1251, 1162, 1106, 1081, 1048, 1005, 976, 836, 777, 724 cm^{-1}. **HRMS** (ESI): calculated for $C_{28}H_{52}O_4Si_2Na$ [M + Na^+]: 531.32927, found 531.32964.

(*5R,8S,13S,14R,E*)-5,8-Dihydroxy-5,13,14-trimethyloxacyclotetradec-3-en-9-yn-2-one – (SI-93)



655b (1.31 g, 60% purity, 1.54 mmol, 1.0 equiv.) was dissolved in dry THF (15 mL) and the solution stirred at room temperature in a PTFE vial. Pyridine (1.5 mL, 18.5 mmol, 12.0 equiv.) followed by HF·pyridine complex (795 µL, 70 % in pyridine, 6.18 mmol, 4.0 equiv.) was added and stirring continued with the conversion monitored by TLC (hexanes/ethyl acetate, 2:1). After 5 h some monodeprotected material was left so another 1.0 equiv. of HF pyridine was added and stirring continued for 12 h. The reaction was quenched with the dropwise addition of saturated sodium bicarbonate solution, the mixture was extracted twice with ethyl acetate, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to yield a crude yellowish oil. Purification by flash chromatography (SiO_2, hexanes/ethyl acetate, 2:1 to 1:1 to 1:2) afforded the product as a colorless solid (365 mg, 1.30 mmol, 84% yield). **TLC** (hexanes/ethyl acetate, 2:1), Rf = 0.18. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: –50.2° (c=1.0 in MeOH). **M. p.**: 150-152 °C. **^{1}H NMR (400 MHz, Chloroform-d) δ** 7.17 (d, J = 15.6 Hz, 1H), 6.02 (d, J = 15.6 Hz, 1H), 4.69 (dq, J = 12.5, 6.5 Hz, 1H), 4.50 – 4.37 (m, 1H), 2.39 – 2.25 (m, 1H), 2.25 – 2.13 (m, 1H), 1.87 (ddd, J = 13.8, 10.8, 6.0 Hz, 3H), 1.80 – 1.57 (m, 4H), 1.48 (p, J = 6.3, 5.6 Hz, 2H), 1.34 (s, 3H), 1.29 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.2, 154.2, 119.1, 87.2, 80.6, 75.2, 73.3, 62.7, 39.1, 37.0, 32.9, 31.8, 27.3, 19.1, 17.0, 17.0 ppm. **IR (film, $CHCl_3$)** 3402, 2972, 2934, 1698, 1455, 1379, 1339, 1268, 1102, 1036, 977 cm^{-1}. **HRMS** (ESI): calculated for $C_{16}H_{24}O_4Na$ [M + Na^+]: 303.15665, found 303.15668.

(*1S,5R,6S,11S,14R*)-11-Hydroxy-5,6,14-trimethyl-4,15-dioxabicyclo[12.1.0]-penta-dec-9-yn-3-one – (659)



655b (127 mg, 0.25 mmol, 1.0 equiv.) was dissolved in dry THF (10 mL) and the solution stirred at room temperature. TBAF (750 µL, 0.75 mmol, 1 M in THF, 3.0 equiv.) was added and stirring continued with the conversion monitored by TLC (hexanes/ethyl acetate, 2:1). After 4 h the TLC

showed still a mixture of deprotected starting material and epoxide formation so another 3 equiv. of TBAF was added. Stirring was continued for 12 h at room temperature. The reaction was quenched with the addition of water and the mixture was extracted twice with MTBE. The combined organic layer were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes/ethyl acetate, 6:1 to 4:1 to 2:1 to 1:1) yielded the product as a colorless oil which solidifies upon standing (68 mg, 0.24 mmol, 97% yield). **TLC** (hexanes/ethyl acetate, 2:1), Rf = 0.33. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +57.3° (c=1.0 in MeOH). **Melting point:** 102 °C. **^{1}H NMR (400 MHz, Chloroform-d) δ** 4.79 – 4.69 (m, 2H), 4.59 (dd, J = 11.3, 2.0 Hz, 1H), 2.58 (dd, J = 14.1, 2.0 Hz, 1H), 2.54 (s, 1H), 2.34 (dd, J = 14.1, 11.3 Hz, 1H), 2.23 (ddt, J = 7.8, 5.3, 2.6 Hz, 2H), 2.12 – 1.89 (m, 3H), 1.86 – 1.73 (m, 2H), 1.69 – 1.58 (m, 1H), 1.53 (dddd, J = 14.0, 4.9, 2.4, 1.2 Hz, 1H), 1.28 (d, J = 6.3 Hz, 3H), 1.17 (s, 3H), 1.05 (d, J = 7.2 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 171.2, 90.4, 79.8, 75.3, 75.2, 68.5, 66.2, 37.5, 36.1, 34.4, 29.7, 25.8, 24.3, 19.1, 16.4, 15.0 ppm. **IR (film, $CHCl_3$)** 3468, 2933, 1731, 1449, 1380, 1286, 1247, 1155, 1101, 1061, 1001, 958 cm^{-1}. **HRMS** (ESI): calculated for $C_{16}H_{24}O_4Na$ [M + Na^+]: 303.15674, found 303.15668.

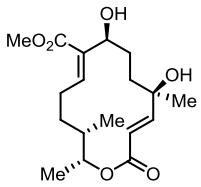
(3E,*5R,8S,9Z,13S,14R*)-5,8-Dihydroxy-5,13,14-trimethyloxacyclotetradeca-3,9-dien-2-one - (658)

Palladium on $BaSO_4$ (0.76 mg, 5% on $BaSO_4$, 0.4 µmol, 0.5 mol%) was suspended in dry pyridine (1 mL) and stirred at room temperature. Hydrogen (balloon) was bubbled through the solution for 10 minutes until the solid particles turned black. The hydrogen balloon was refilled before **655a** (20 mg, 71 µmol, 1.0 equiv.) was added as a solution in dry THF (1 mL). The conversion was monitored by TLC (hexanes/ethyl acetate, 1:1). The starting material and the product share the same Rf value though the product is UV active on TLC. After 3 h the reaction was quenched by passing the mixture through a plug of Celite® with the aid of ethyl acetate (100 mL). The volatile materials were removed under reduced pressure and the residue purified by flash chromatography (SiO_2, hexanes/ethyl acetate, 1:1) to give the product as a colorless foam contaminated with 5% of alkane byproduct (15 mg, 53 µmol, 74% yield). **TLC** (hexanes/ethyl acetate, 2:1), Rf = 0.18. $[\boldsymbol{a}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: –31.1° (c=1.0 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.89 (d, J = 15.7 Hz, 1H), 6.03 (dd, J = 15.7, 1.4 Hz, 1H), 5.48 (tdd, J = 10.0, 5.6, 0.9 Hz, 1H), 5.37 (ddt, J = 10.8, 9.0, 1.1 Hz, 1H), 4.65 (dq, J = 9.9, 6.3 Hz, 1H), 4.31 (tt, J = 9.3, 1.6 Hz, 1H), 2.20 – 2.08 (m,

1H), 2.04 – 1.90 (m, 2H), 1.84 – 1.75 (m, 1H), 1.60 – 1.44 (m, 2H), 1.40 (s, 3H), 1.38 – 1.31 (m, 1H), 1.29 (d, J = 6.3 Hz, 3H), 1.27 – 1.21 (m, 2H), 1.21 – 1.04 (m, 2H), 0.93 (d, J = 6.9 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.0, 153.1, 133.2, 131.3, 120.8, 76.3, 74.0, 69.7, 41.1, 39.2, 35.0, 31.7, 29.0, 27.9, 19.4, 17.3 ppm. **IR (film, $CHCl_3$)** 3402, 2925, 1694, 1454, 1378, 1260, 1043, 730 cm^{-1}. **HRMS** (ESI): calculated for $C_{16}H_{26}O_4Na$ [M + Na^+]: 305.17227, found 305.17233.

Following representative procedure 8.

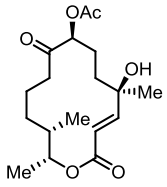
Methyl (2*R*,3*S*,6Z,8*S*,11*R*,12E)-8,11-dihydroxy-2,3,11-trimethyl-14-oxooxacyclotetradeca-6,12-diene-7-carboxylate – (660)



69% yield (10.3 mg, 30 µmol). $[\alpha]_D^{20}$: –58.3° (c=0.83 in $CHCl_3$). **^{1}H NMR (300 MHz, Chloroform-d) δ** 6.77 (d, J = 15.7 Hz, 1H), 6.25 (dd, J = 9.2, 5.0 Hz, 1H), 5.98 (d, J = 15.7 Hz, 1H), 4.63 (dq, J = 9.9, 6.2 Hz, 1H), 4.21 (s, 1H), 3.77 (s, 3H), 2.76 (dddd, J = 16.2, 9.3, 6.8, 4.5 Hz, 1H), 2.60 (s, 1H), 2.31 – 2.10 (m, 1H), 1.96 – 1.81 (m, 2H), 1.81 – 1.65 (m, 2H), 1.65 – 1.40 (m, 2H), 1.35 (s, 4H), 1.31 (d, J = 6.3 Hz, 4H), 0.96 (d, J = 6.9 Hz, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 168.1, 165.8, 153.4, 145.6, 132.3, 120.2, 76.3, 75.6, 73.6, 51.7, 39.3, 38.9, 33.3, 31.6, 28.8, 27.4, 19.2, 18.0 ppm. **IR (film, $CHCl_3$)** 3434, 2954, 2933, 2874, 1703, 1642, 1439, 1377, 1267, 1226, 1153, 1107, 1041, 987 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{18}H_{28}O_6Na$ [M+Na^+]: 363.17781, found 363.17801.

Following representative procedure 10.

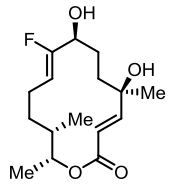
(*2R,3S,8S,11R*,E)-11-Hydroxy-2,3,11-trimethyl-7,14-dioxooxacyclotetradec-12-en-8-yl acetate – (661)



81% yield (12 mg, 35 µmol). $[\alpha]_D^{20}$: –59.5° (c=1.20 in $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-d) δ** 6.68 (d, J = 15.8 Hz, 1H), 5.98 (d, J = 15.7 Hz, 1H), 4.73 – 4.59 (m, 2H), 2.51 (dt, J = 17.2, 7.3 Hz, 1H), 2.16 (dt, J = 17.3, 6.6 Hz, 1H), 2.11 (s, 3H), 1.87 – 1.75 (m, 2H), 1.74 – 1.47 (m, 5H), 1.38 (s, 3H), 1.28 (d, J = 6.3 Hz, 3H), 1.22 – 1.07 (m, 1H), 1.02 (ddt, J = 13.4, 9.0, 7.3 Hz, 1H), 0.90 (d, J = 6.8 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ** 208.1, 170.7, 165.7, 153.0, 120.7, 78.9, 76.9, 73.4, 40.4, 36.8, 36.0, 34.2, 28.9, 24.5, 22.3, 20.9, 19.4, 17.1 ppm. **IR (film, $CHCl_3$)** 3488, 2969, 2934, 2876, 1739, 1711, 1644, 1455, 1374, 1234, 1156, 1107, 1036, 992, 918, 876, 812, 777, 731, 686 cm^{-1}. **HRMS (ESI):** *m/z* calculated for $C_{18}H_{28}O_6Na$ [M+Na^+]: 363.17781, found 363.17764.

Following representative procedure 12.

(3E,*5R,8S,9Z,13S,14R*)-9-Fluoro-5,8-dihydroxy-5,13,14-trimethyloxacyclo-tetra-deca-3,9-dien-2-one – (662)

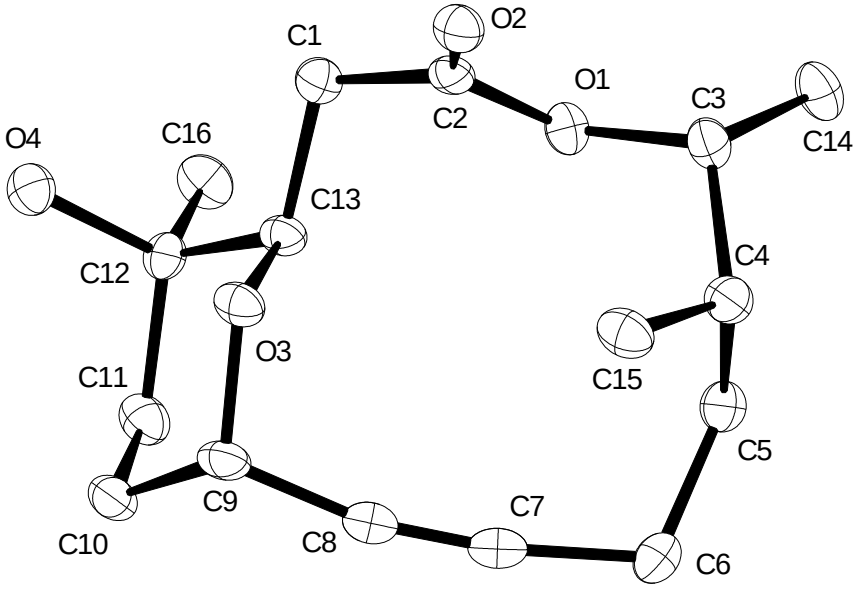


84% yield (11 mg, 37 μmol). $[\alpha]_D^{20}$: –53.0° (c=1.10 in $CHCl_3$). **^{1}H NMR (500 MHz, Chloroform-d) δ** 6.76 (d, J = 15.7 Hz, 1H), 5.99 (d, J = 15.6 Hz, 1H), 4.86 (ddd, J = 36.2, 10.1, 4.9 Hz, 1H), 4.59 (dq, J = 10.1, 6.1 Hz, 1H), 3.93 (ddd, J = 20.7, 10.0, 3.1 Hz, 1H), 2.19 (dddd, J = 14.6, 10.0, 7.8, 4.2 Hz, 1H), 2.03 – 1.92 (m, 2H), 1.87 (ddd, J = 14.9, 9.9, 5.0 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.71 (dddd, J = 14.4, 9.9, 5.5, 3.2 Hz, 2H), 1.54 (tdd, J = 12.2, 6.1, 3.0 Hz, 1H), 1.50 – 1.38 (m, 2H), 1.36 (s, 3H), 1.31 (d, J = 6.1 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.93 – 0.86 (m, 1H) ppm. **^{13}C NMR (126 MHz, Chloroform-d) δ** 165.9, 157.0 (d, J = 257.1 Hz), 152.4, 120.0, 109.1 (d, J = 14.2 Hz), 74.7, 73.0, 72.1 (d, J = 27.7 Hz), 38.8, 37.1, 32.5, 28.9, 27.9, 19.3, 18.6 (d, J = 5.1 Hz), 16.7 ppm. **^{19}F NMR (282 MHz, $CDCl_3$) δ** -124.9 ppm. **IR (film, $CHCl_3$)** 3408, 2958, 2927, 2873, 1697, 1643, 1456, 1377, 1261, 1152, 1103, 1043, 976, 871, 727, 678, 559, 438 cm^{-1}. **HRMS (EI):** m/z calculated for $C_{16}H_{25}O_4FNa$ [$M+Na^+$]: 323.16291, found 323.16327.

9. Appendix

9.1. Crystallographic Data

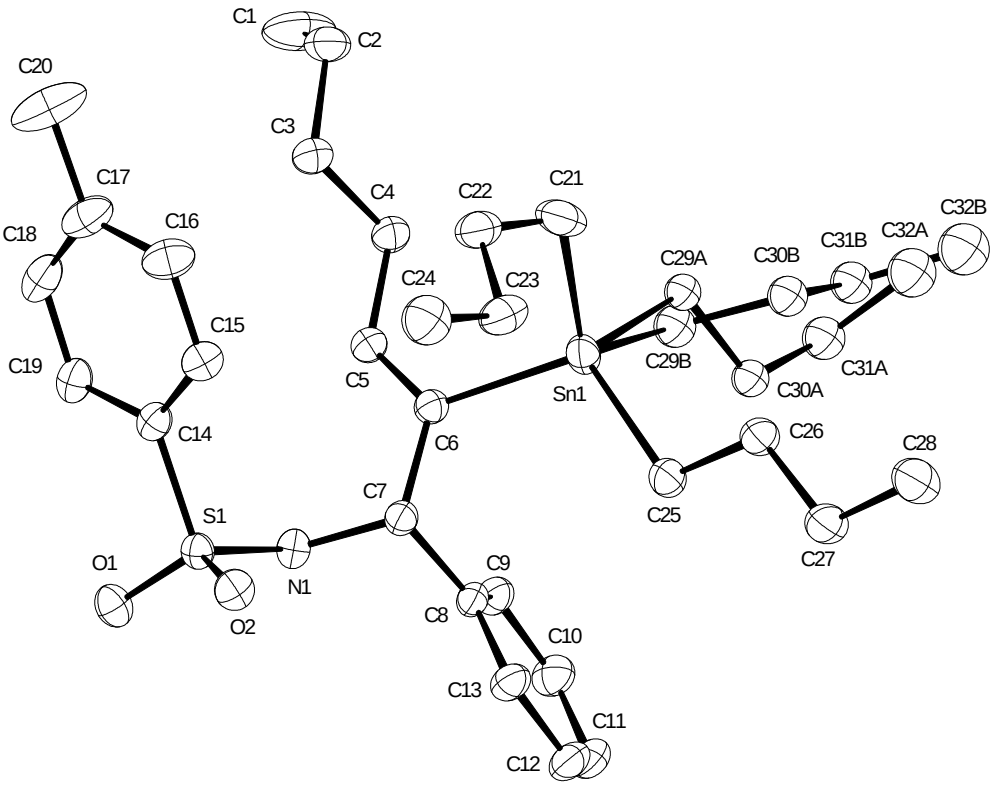
9.1.1. Crystallographic Data of (*1S,5R,6S,11S,14R*)-11-Hydroxy-5,6,14-trimethyl-4,15-dioxabicyclo[12.1.0]-pentadec-9-yn-3-one – (659)



Identification code	8977	
Empirical formula	$C_{16}H_{24}O_4$	
Color	colorless	
Formula weight	280.35 $g \cdot mol^{-1}$	
Temperature	100 K	
Wavelength	1.54178 Å	
Crystal system	ORTHORHOMBIC	
Space group	**$P2_12_12_1$, (no. 19)**	
Unit cell dimensions	a = 7.2789(9) Å	α= 90°.
	b = 10.7001(13) Å	β= 90°.
	c = 19.387(2) Å	γ = 90°.
Volume	1510.0(3) $Å^3$	

Z	4
Density (calculated)	1.233 $Mg \cdot m^{-3}$
Absorption coefficient	0.707 mm^{-1}
F(000)	608 e
Crystal size	0.30 x 0.12 x 0.03 mm^3
θ range for data collection	4.561 to 55.082°.
Index ranges	$-7 \leq h \leq 7, -11 \leq k \leq 11, -20 \leq l \leq 20$
Reflections collected	17540
Independent reflections	1896 [R_{int} = 0.0652]
Reflections with I>2σ(I)	1741
Completeness to θ = 67.679°	70.9 %
Absorption correction	Gaussian
Max. and min. transmission	0.98 and 0.86
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1896 / 0 / 186
Goodness-of-fit on F^2	1.042
Final R indices [I>2σ(I)]	R_1 = 0.0339 wR^2 = 0.0805
R indices (all data)	R_1 = 0.0400 wR^2 = 0.0840
Absolute structure parameter	-0.01(13)
Extinction coefficient	0.0054(8)
Largest diff. peak and hole	0.2 and -0.2 $e \cdot Å^{-3}$

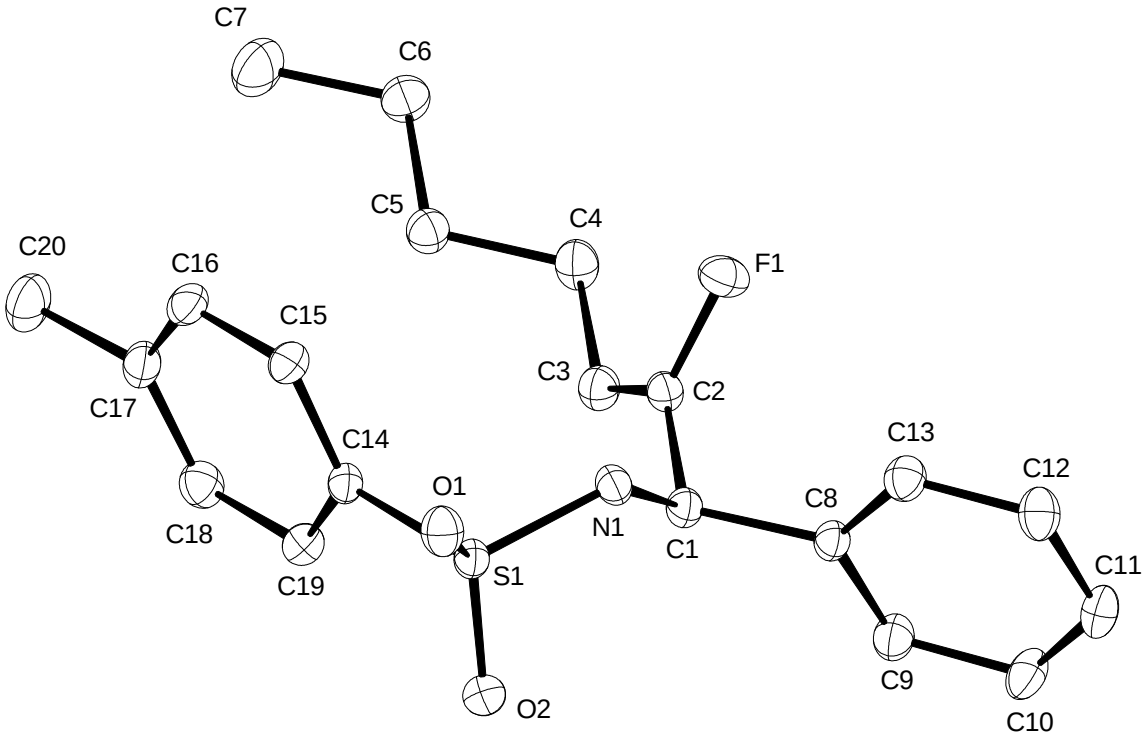
9.1.2. Crystallographic Data of (Z)-4-Methyl-N-(1-phenyl-2-(tributylstannyl)hept-2-en-1-yl)benzenesulfonamide – (503)



Identification code	9954	
Empirical formula	$C_{32}\,H_{51}\,N\,O_2\,S\,Sn$	
Color	colorless	
Formula weight	632.48 $g \cdot mol^{-1}$	
Temperature	100.15 K	
Wavelength	0.71073 Å	
Crystal system	MONOCLINIC	
Space group	**$P2_1/c$, (no. 14)**	
Unit cell dimensions	a = 15.041(3) Å	α= 90°.
	b = 22.972(3) Å	β= 97.301(7)°.
	c = 9.4505(2) Å	γ = 90°.

Volume	3239.0(7) $Å^3$	
Z	4	
Density (calculated)	1.297 $Mg \cdot m^{-3}$	
Absorption coefficient	0.880 mm^{-1}	
F(000)	1328 e	
Crystal size	0.26 x 0.14 x 0.06 mm^3	
θ range for data collection	2.805 to 36.045°.	
Index ranges	$-24 \leq h \leq 24$, $-38 \leq k \leq 38$, $-15 \leq l \leq 15$	
Reflections collected	86733	
Independent reflections	15364 [R_{int} = 0.0360]	
Reflections with I>2σ(I)	12313	
Completeness to θ = 25.242°	99.8 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.95 and 0.83	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15364 / 0 / 335	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2σ(I)]	R_1 = 0.0387	wR^2 = 0.0850
R indices (all data)	R_1 = 0.0551	wR^2 = 0.0946
Largest diff. peak and hole	1.5 and -2.5 e $\cdot Å^{-3}$	

9.1.3. Crystallographic Data of (Z)-N-(2-Fluoro-1-phenylhept-2-en-1-yl)-4-methylbenzenesulfonamide – (508)



Identification code	9977	
Empirical formula	$C_{20}H_{24}FNO_2S$	
Color	colorless	
Formula weight	361.46 $g \cdot mol^{-1}$	
Temperature	100.15 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	**C2, (no. 5)**	
Unit cell dimensions	a = 25.7470(12) Å	α= 90°.
	b = 5.272(2) Å	β= 114.977(13)°.
	c = 15.2010(19) Å	γ = 90°.

Volume	1870.4(8) $Å^3$	
Z	4	
Density (calculated)	1.284 $Mg \cdot m^{-3}$	
Absorption coefficient	0.195 mm^{-1}	
F(000)	768 e	
Crystal size	0.25 x 0.07 x 0.05 mm^3	
θ range for data collection	2.726 to 33.162°.	
Index ranges	$-39 \leq h \leq 39$, $-8 \leq k \leq 8$, $-23 \leq l \leq 23$	
Reflections collected	27424	
Independent reflections	7129 [R_{int} = 0.0518]	
Reflections with I>2σ(I)	6241	
Completeness to θ = 25.242°	99.7 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.99 and 0.97	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7129 / 1 / 232	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2σ(I)]	R_1 = 0.0455	wR^2 = 0.0984
R indices (all data)	R_1 = 0.0572	wR^2 = 0.1053
Absolute structure parameter	0.08(5)	
Largest diff. peak and hole	0.4 and -0.4 e $\cdot Å^{-3}$	

9.2. Abbreviations

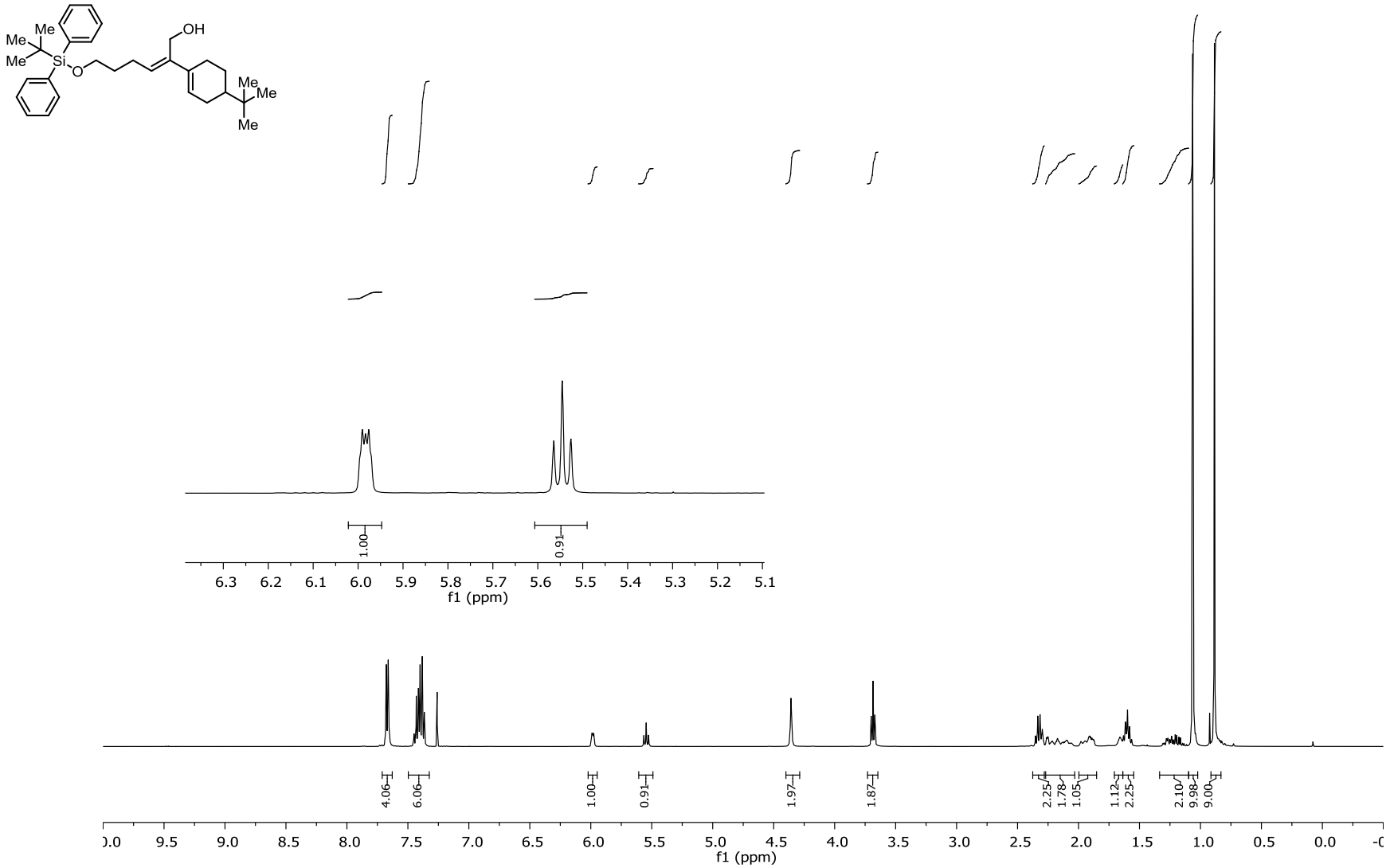
Ac	acetyl
acac	acetylacetonate
Ad	adamantyl
AgDPP	silver diphenylphosphinate
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl
BBN	9-borabicyclo(3.3.1)nonane
BINAL	2,2′-dihydroxy-1,1‘-binaphthyl-lithium aluminum hydride
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Ph-BPE	1,2-Bis[2,5-diphenylphospholano]ethane
BQ	benzoquinone
br	broad
Bu	butyl
Bz	benzoyl
calcd	calculated
CAN	ceric ammonium nitrate
cat.	catalytic
CBS	Corey-Bakshi-Shibata reagent
cm	centimeter
cod	cyclooctadienyl
conc.	concentration
Cp	cyclopentadienyl
Cp*	pentamethyl cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
dd	doublet

DIBAL-H	diisobutylalumnium hydride
DMAP	*N*,*N*-dimethyl 4-aminopyridine
DMF	dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DPP	diphenylphosphinate
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBMP	di-*tert*-butylmethyl pyridine
DTS	diverted total synthesis
ee	enantiomeric excess
ent	enantiomeric
epi	epimeric
eq/equiv.	equivalents
Et	ethyl
F-TEDA	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane
g	gram
h	hour
hep	heptet
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
HRMS	high-resolution mass spectrometry
i	*iso* (branched)
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
ipc	isopinocampheyl
IR	infrared spectroscopy
KHMDS	potassium hexamethyldisilazide
l	liter
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
M	molar (mol/L)
m	multiplet
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl

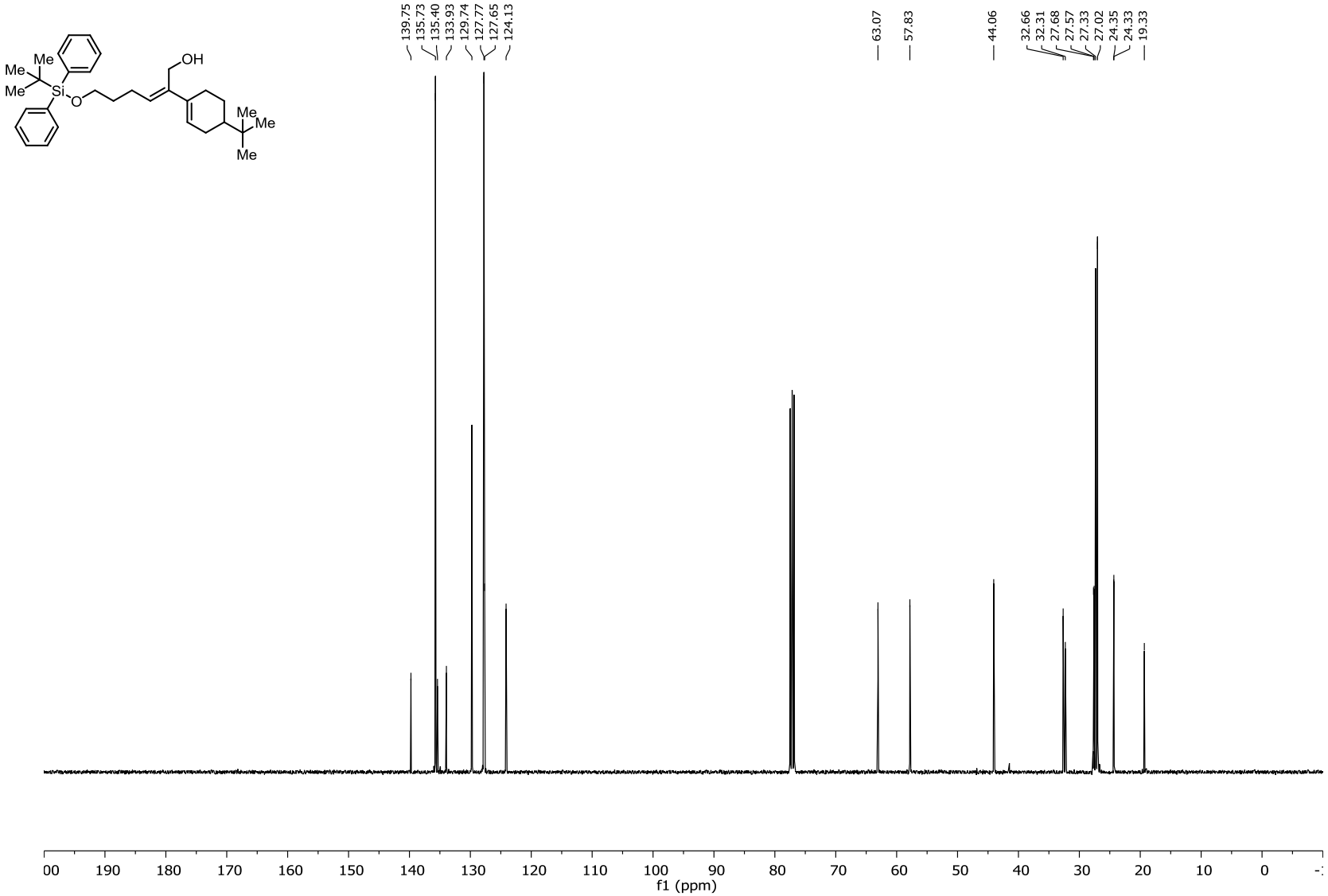
Mes	mesityl
mg	miligram
min	minute
mL	mililiter
MOM	methoxy methyl
mp.	melting point
Ms	methanesulfonyl, mesyl
MTBE	*tert*-butylmethylether
µg	microgram
µL	microliter
NaHMDS	sodium hexamethyldisilazide
n.d.	not determined
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NME	*N*-methylephedrine
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl, Nosyl
Ph	phenyl
pin	pinacol
PG	protecting group
PMB	para-methoxybenzyl
Pr	propyl
q	quartet
quant	quantitative
r.r.	regioisomeric ratio
rac	racemic
RCAM	ring closing alkyne metathesis
RCM	ring closing (olefin) metathesis
r.t.	room temperature
s	singlet
sat.	saturated
Suc	succinimid
t	triplet
TAS	tris(dimethylamino)sulfonium
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl

TBDPP	Tetra-*n*-butylammonium diphenylphosphinate
TBHP	*tert*-butyl hydroperoxide
TBS	dimethyl-*tert*-butylsilyl
TBT	tetrabutyltriazolyl
TC	thiophene-2-carboxylate
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
Thx	thexyl
TLC	thin layer chromatography
TMAO	trimethylamine *N*-oxide
TMS	trimethylsilyl
TMP	tetramesityl porphyrine
Tol	*ortho*-tolyl
Ts	*p*-toluenesulfonyl

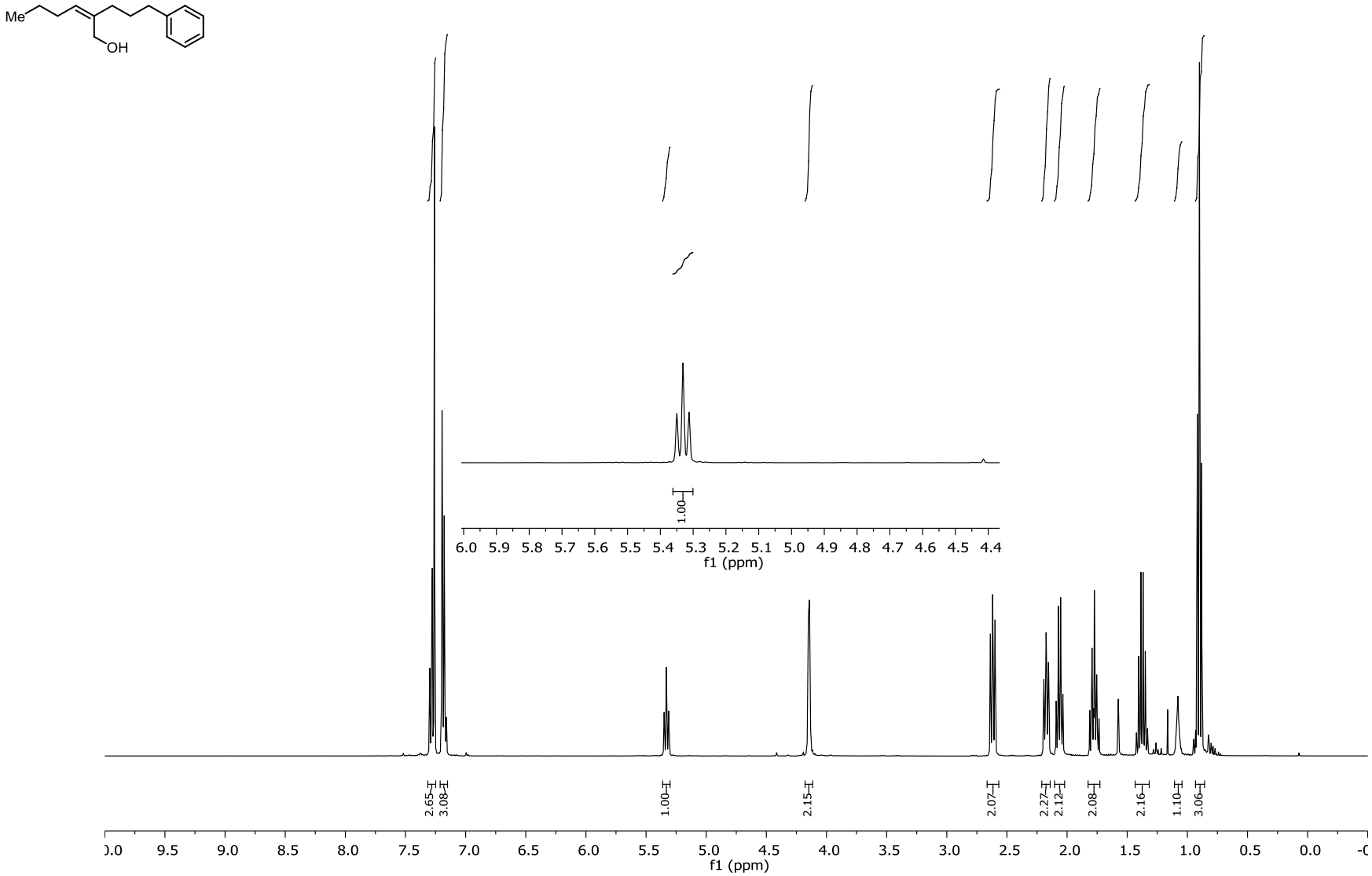
(Z)-2-(4-(*tert*-Butyl)cyclohex-1-en-1-yl)-6-((tert-butyldiphenylsilyl)oxy)hex-2-en-1-ol – (140)



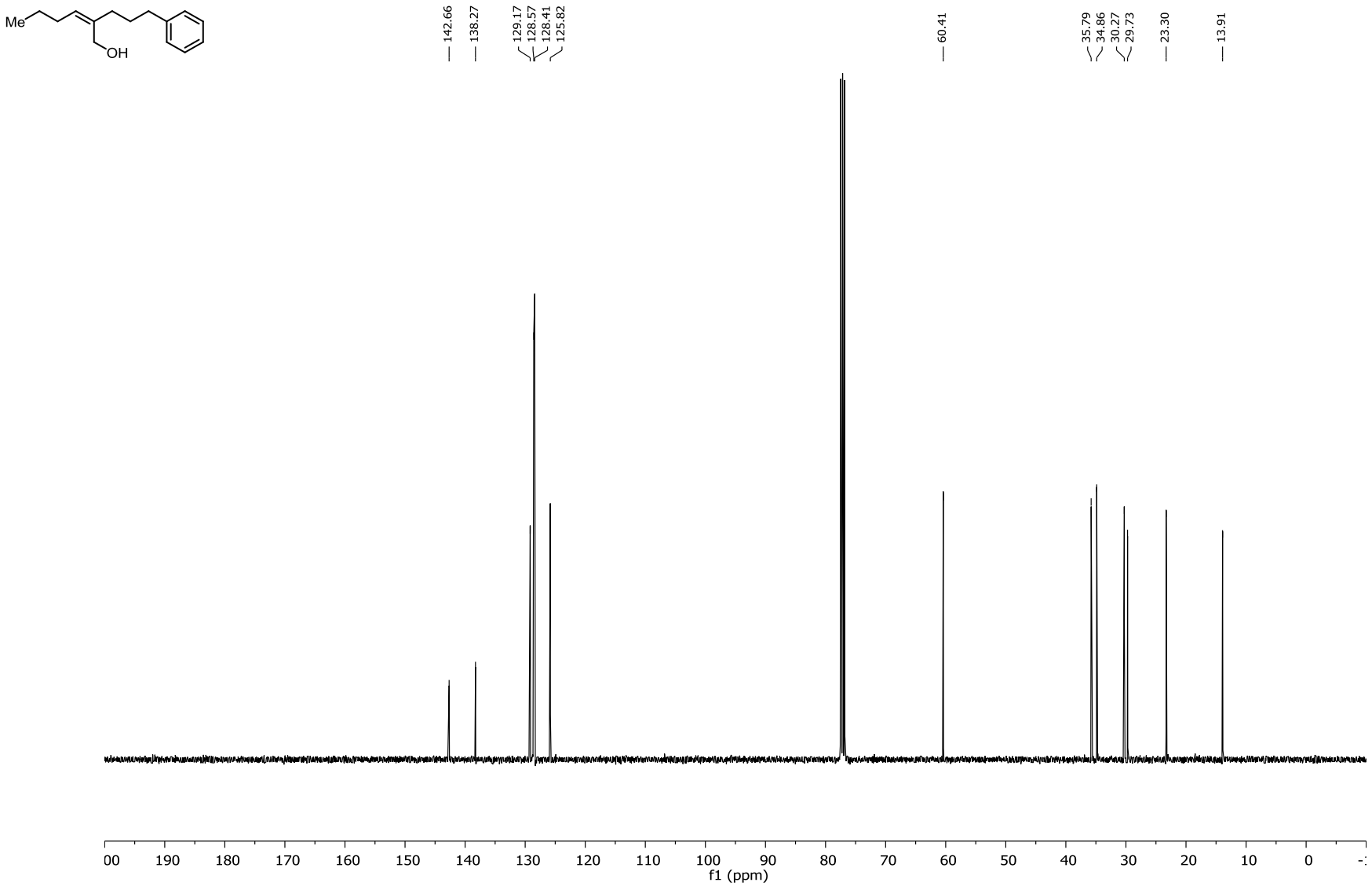
(Z)-2-(4-(*tert*-Butyl)cyclohex-1-en-1-yl)-6-((tert-butyldiphenylsilyl)oxy)hex-2-en-1-ol – (140)



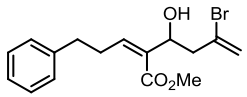
(Z)-2-(3-Phenylpropyl)hex-2-en-1-ol – (167)

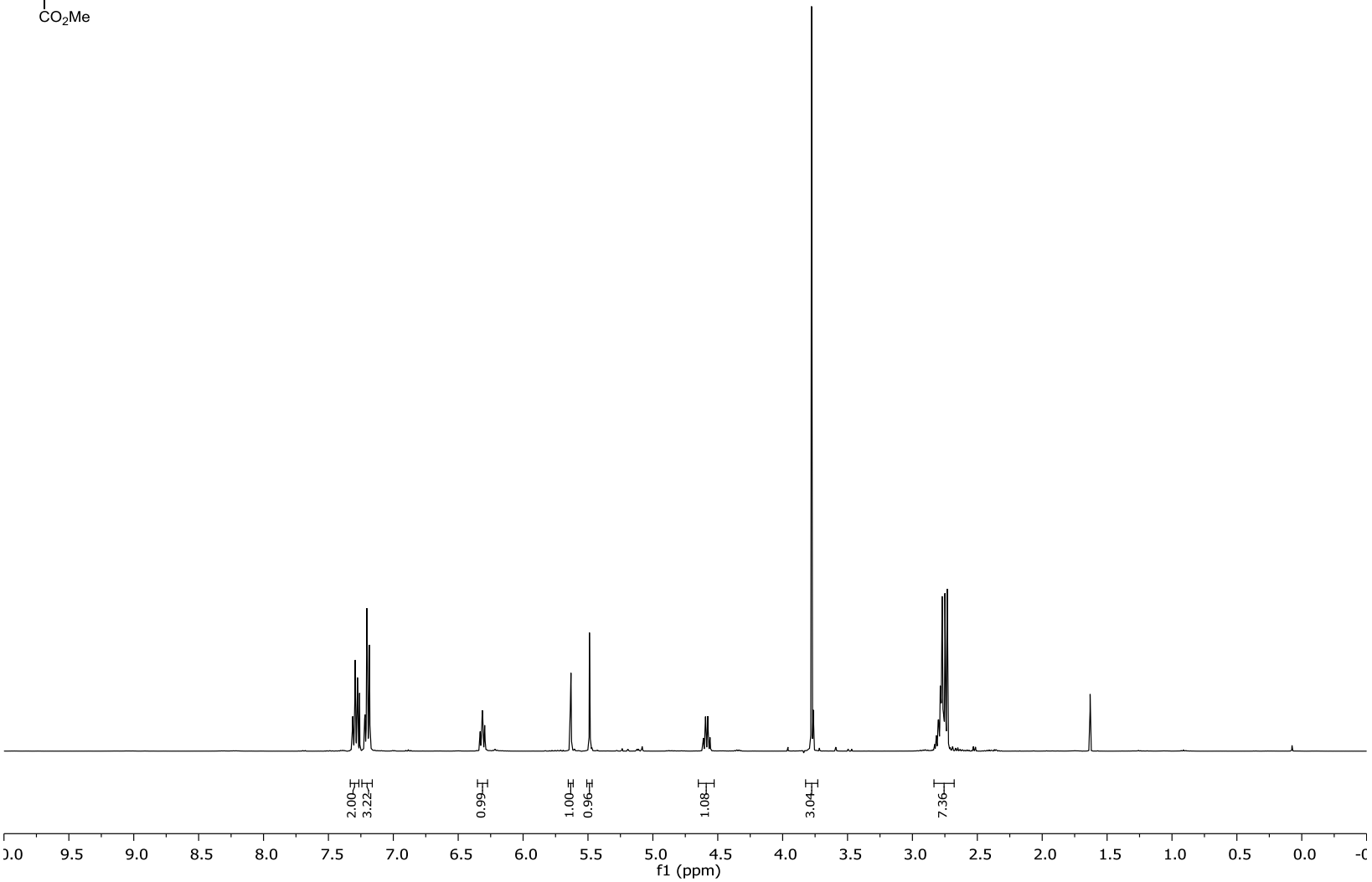


(Z)-2-(3-Phenylpropyl)hex-2-en-1-ol – (167)

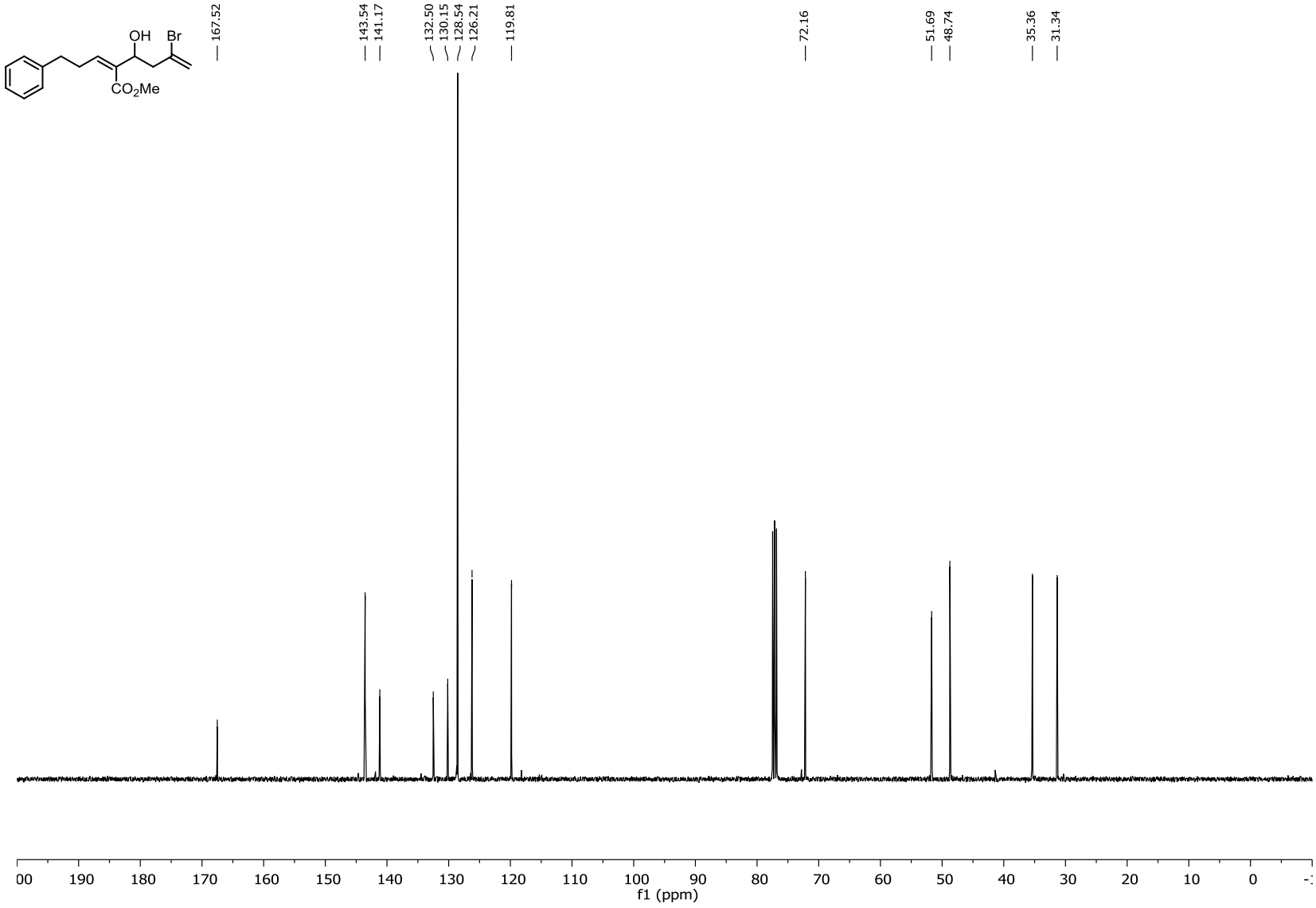


Methyl (Z)-5-bromo-3-hydroxy-2-(3-phenylpropylidene)hex-5-enoate – (255)

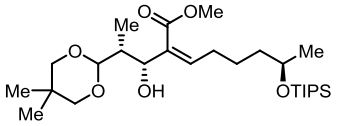




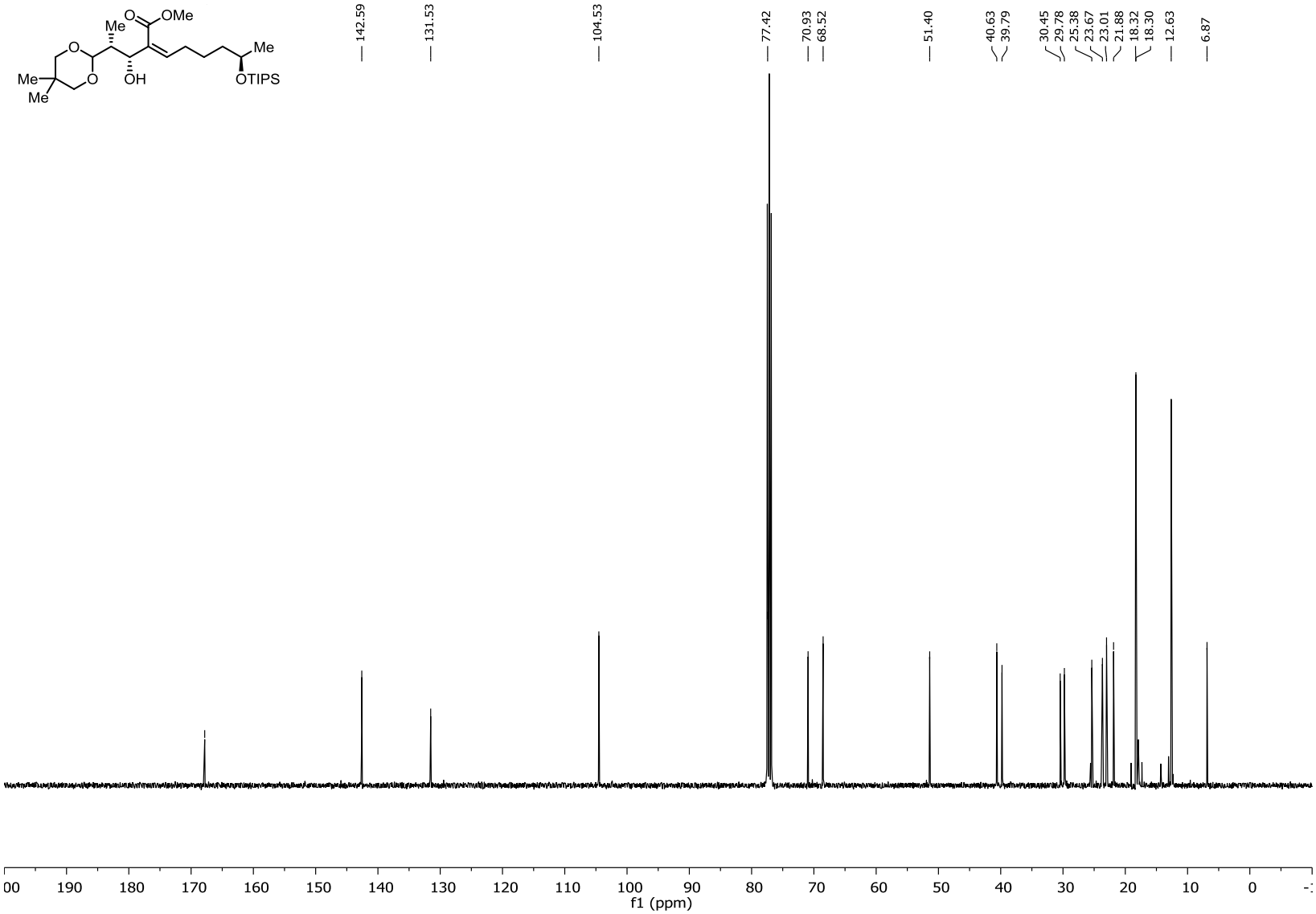
Methyl (Z)-5-bromo-3-hydroxy-2-(3-phenylpropylidene)hex-5-enoate – (255)



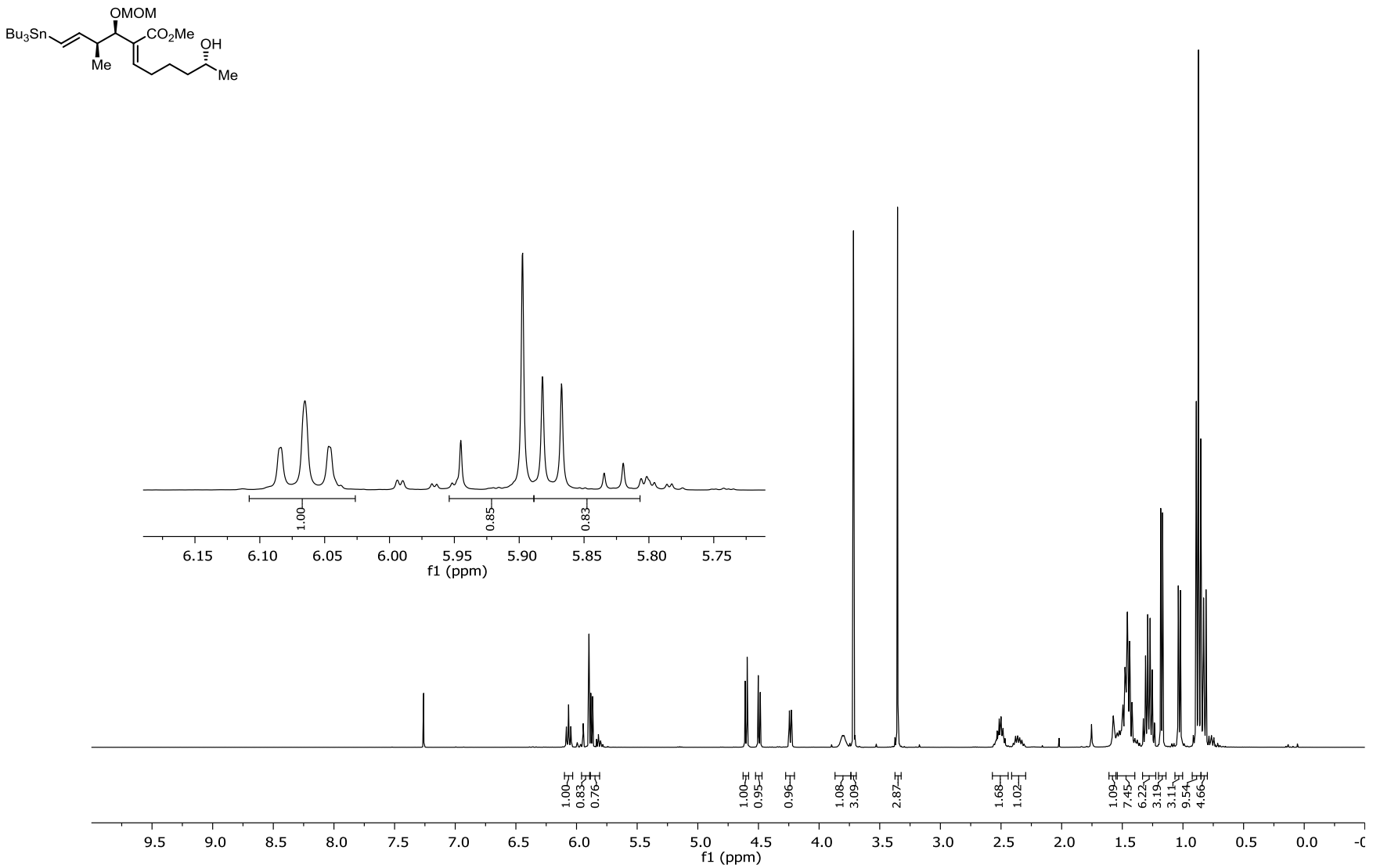
Methyl (R,Z)-2-((1R,2R)-2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-hydroxypropyl)-7-((triisopropylsilyl)oxy)oct-2-enoate – (300)



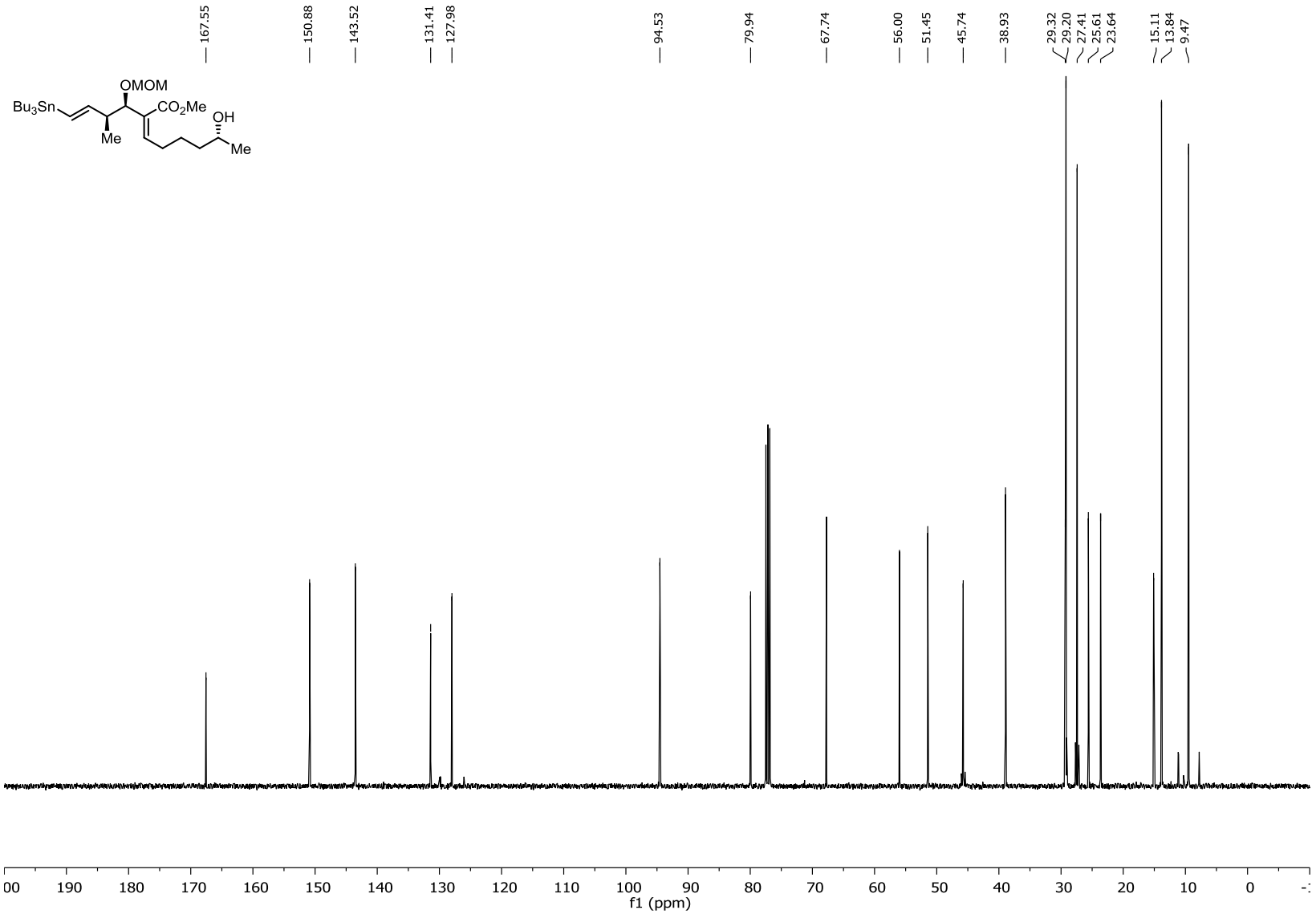
Methyl (R,Z)-2-((1R,2R)-2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-hydroxypropyl)-7-((triisopropylsilyl)oxy)oct-2-enoate – (300)



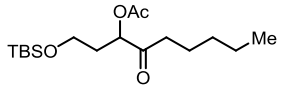
Methyl (*R*,Z)-7-hydroxy-2-((1*R*,2*S*,E)-1-(methoxymethoxy)-2-methyl-4-(tributylstannyl)but-3-en-1-yl)oct-2-enoate – (302)

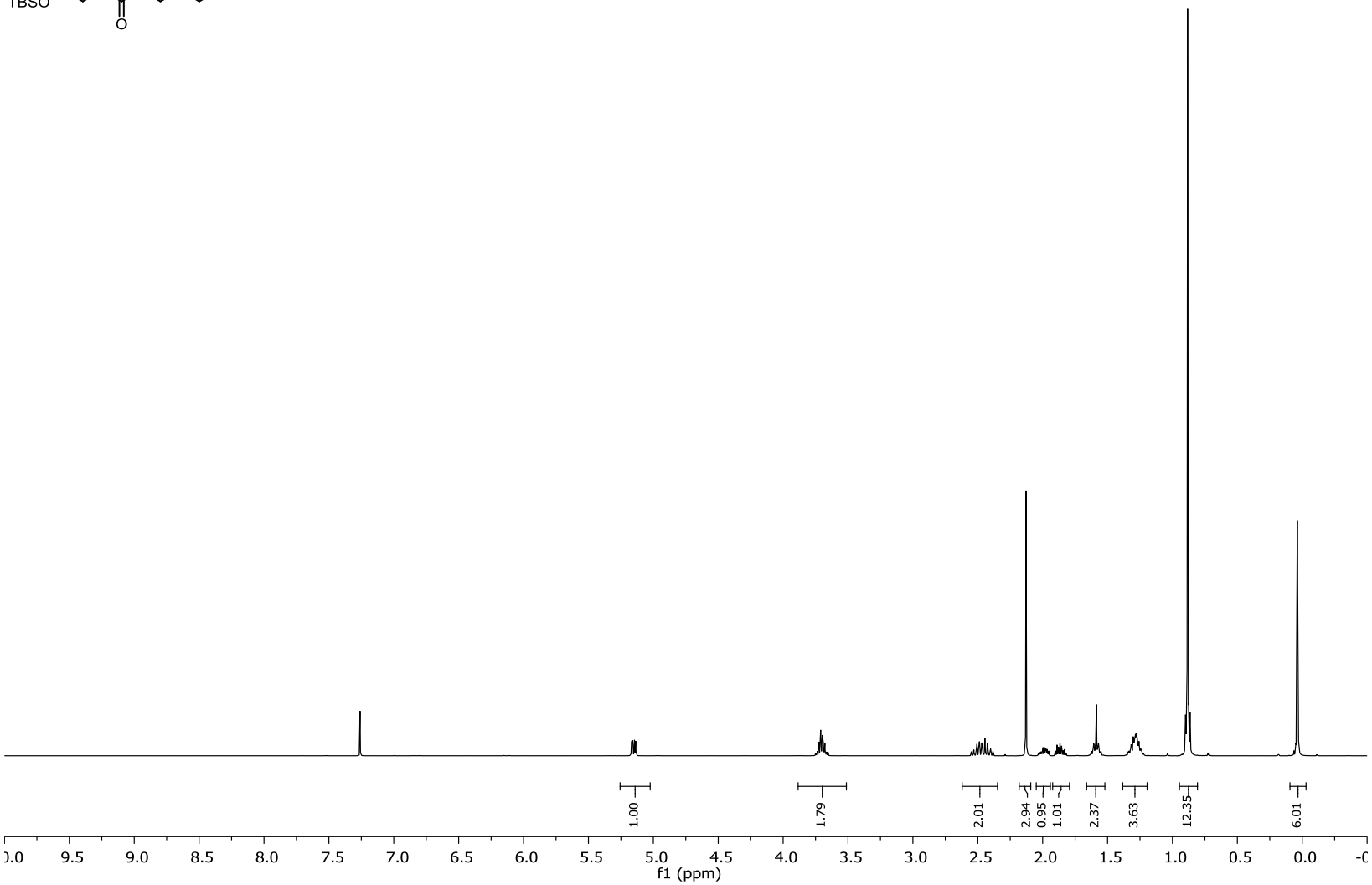


Methyl (*R*,Z)-7-hydroxy-2-((1*R*,2*S*,E)-1-(methoxymethoxy)-2-methyl-4-(tributylstannyl)but-3-en-1-yl)oct-2-enoate – (302)

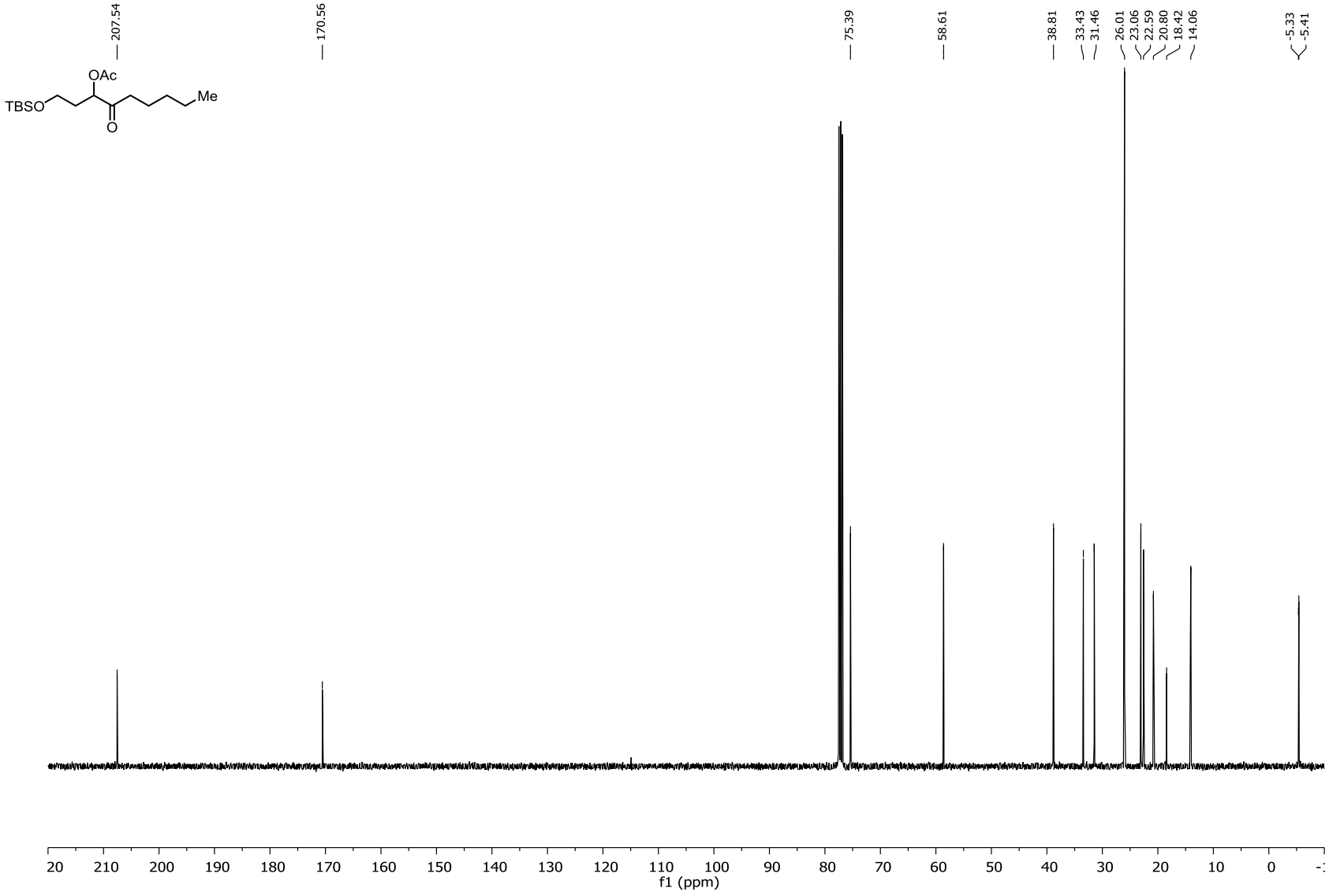


1-((tert-butyldimethylsilyl)oxy)-4-oxononan-3-yl acetate – (398)

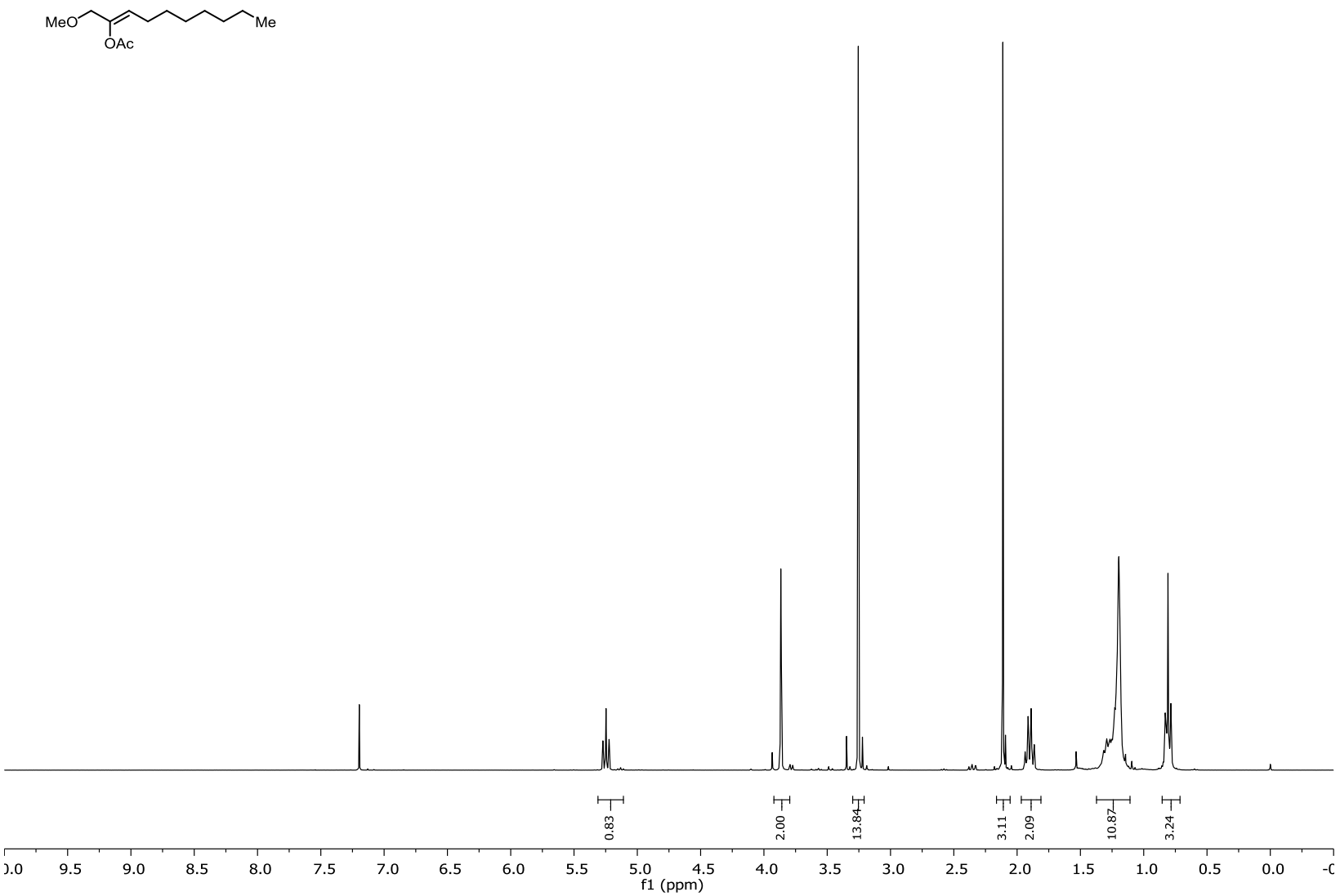




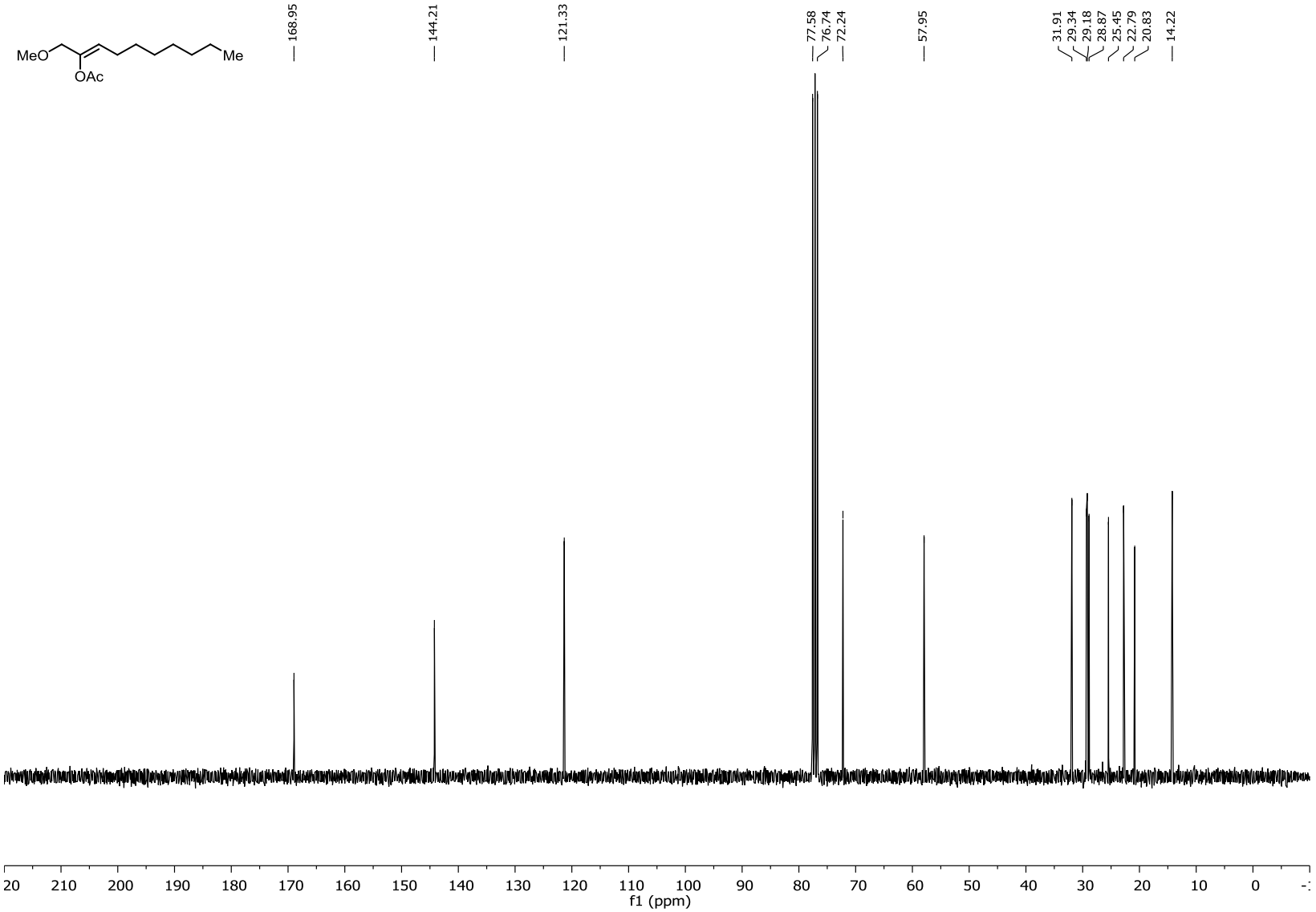
1-((tert-butyldimethylsilyl)oxy)-4-oxononan-3-yl acetate – (398)



(Z)-1-methoxydec-2-en-2-yl acetate – (400)

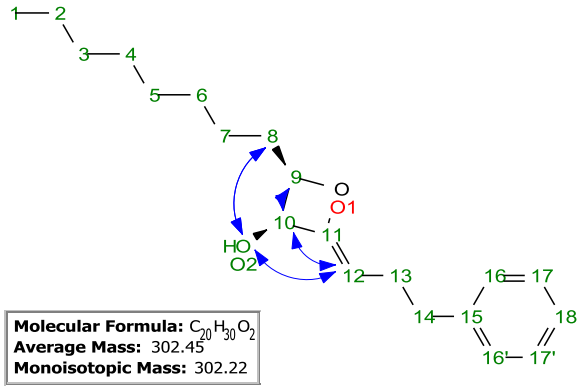


(Z)-1-methoxydec-2-en-2-yl acetate – (400)



SOI-SA-1318

15 mg $CDCl_3$ 298 K



Molecular Formula: $C_{20}H_{30}O_2$
Average Mass: 302.45
Monoisotopic Mass: 302.22

P-ID:	CW00231
Measured on:	14.12.2015
CHIFFRE:	SOI-SA-1318
Client:	Sommer
Group:	Fürstner
Analyst:	Wirtz
Assignment Date:	15.12.2015
Amount:	15 mg
Solvent:	$CDCl_3$
Reference:	solvent
Temperature:	298K
Spectrometer:	AV-400 + BBFO
Experiments:	1H, 13C{1H}, COSYPH
	HSQCed, HMBC,NOESY

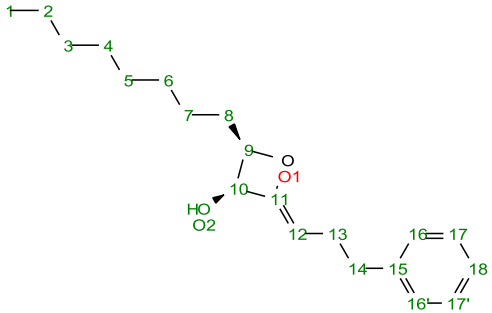
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.98 (11), 141.87 (15), 128.50 (16, 16'), 128.14 (17, 17'), 125.74 (18), 96.74 (12), 86.39 (9), 77.32, 77.00, 76.68, 69.40 (10), 35.85 (14), 31.84 (3), 29.51, 29.43, 29.20, 29.07 (8), 24.58 (7), 24.43 (13), 22.64 (2), 14.08 (1).

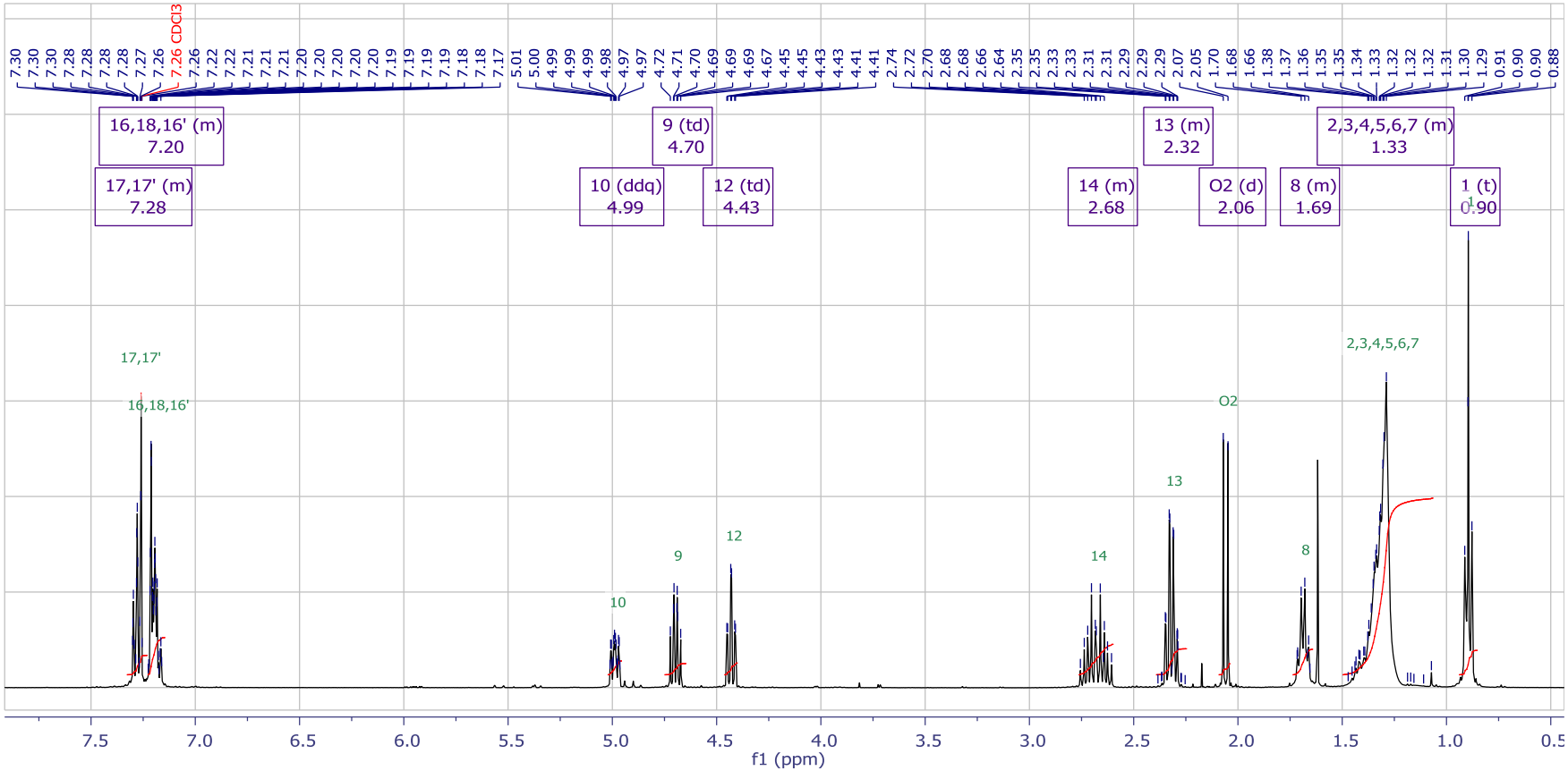
^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.33 – 7.23 (m, 2H), 7.23 – 7.15 (m, 3H), 4.99 (dd, *J*=8.6, 5.9, 1.3, 1H), 4.70 (td, *J*=6.9, 6.0, 1H), 4.43 (td, *J*=7.5, 1.5, 1H), 2.76 – 2.60 (m, 2H), 2.39 – 2.25 (m, 2H), 2.06 (d, *J*=9.1, 1H), 1.73 – 1.64 (m, 2H), 1.50 – 1.06 (m, 12H), 0.90 (t, 3H).

Atom	Chemical Shift	J	COSY	HSQC	HMBC	NOESY
O2 O					9	
H	2.06	9.00(10)	10		11, 9, 10	12, 8
1 C	14.08			1		
H3	0.90		2	1	3, 2	
2 C	22.64			2	1	
H2	1.21..1.49		1	2		
3 C	31.84			3	1	
H2	1.19..1.47			3		
4 C	29.17..29.54			4		
H2	1.21..1.45			4		
5 C	29.18..29.54			5		
H2	1.19..1.49			5		
6 C	29.18..29.54			6		
H2	1.22..1.46			6		
7 C	24.58			7	8, 9	
H2	1.21..1.48		8	7		
8 C	29.07			8		
H2	1.69	6.90(9)	7, 9	8	9, 10, 7	O2
9 C	86.39			9	8, O2	
H	4.70	6.90(8), 6.00(10)	8, 10	9	11, 12, O2, 7	10
10 C	69.40			10	8, 12, O2	
H	4.99	6.00(9), 9.00(O2), 1.30(?)	O2, 9	10	11, 12	9, 12
11 C	160.98				10, 12, 13, 9, O2	
12 C	96.74			12	10, 13, 14, 9	
H	4.43	7.50(13), 1.50(?)	13	12	11, 10, 14	10, O2
13 C	24.43			13	14	
H2	2.32	7.50(12)	12, 14	13	11, 15, 12, 14	
14 C	35.85			14	12, 13, 16, 16'	
H2	2.68		13	14	15, 16', 16, 12, 13	
15 C	141.87				13, 14, 17, 17'	
16 C	128.50			16	16', 18, 14	
H	7.20		17	16	16', 18, 14	
16' C	128.50			16'	16, 18, 14	
H	7.20		17'	16'	16, 18, 14	
17 C	128.14			17	17'	
H	7.28		18, 16	17	15, 17'	
17' C	128.14			17'	17	
H	7.28		18, 16'	17'	15, 17	
18 C	125.74			18	16, 16'	
H	7.20		17, 17'	18	16', 16	

SOI-SA-1318 15 mg $CDCl_3$ 298 K

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.33 – 7.23 (m, 2H), 7.23 – 7.15 (m, 3H), 4.99 (ddq, *J*=8.6, 5.9, 1.3, 1H), 4.70 (td, *J*=6.9, 6.0, 1H), 4.43 (td, *J*=7.5, 1.5, 1H), 2.76 – 2.60 (m, 2H), 2.39 – 2.25 (m, 2H), 2.06 (d, *J*=9.1, 1H), 1.73 – 1.64 (m, 2H), 1.50 – 1.06 (m, 12H), 0.90 (t, 3H).

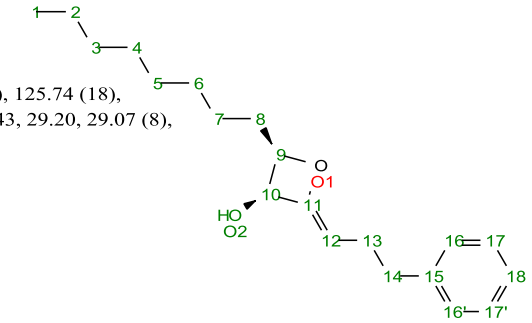


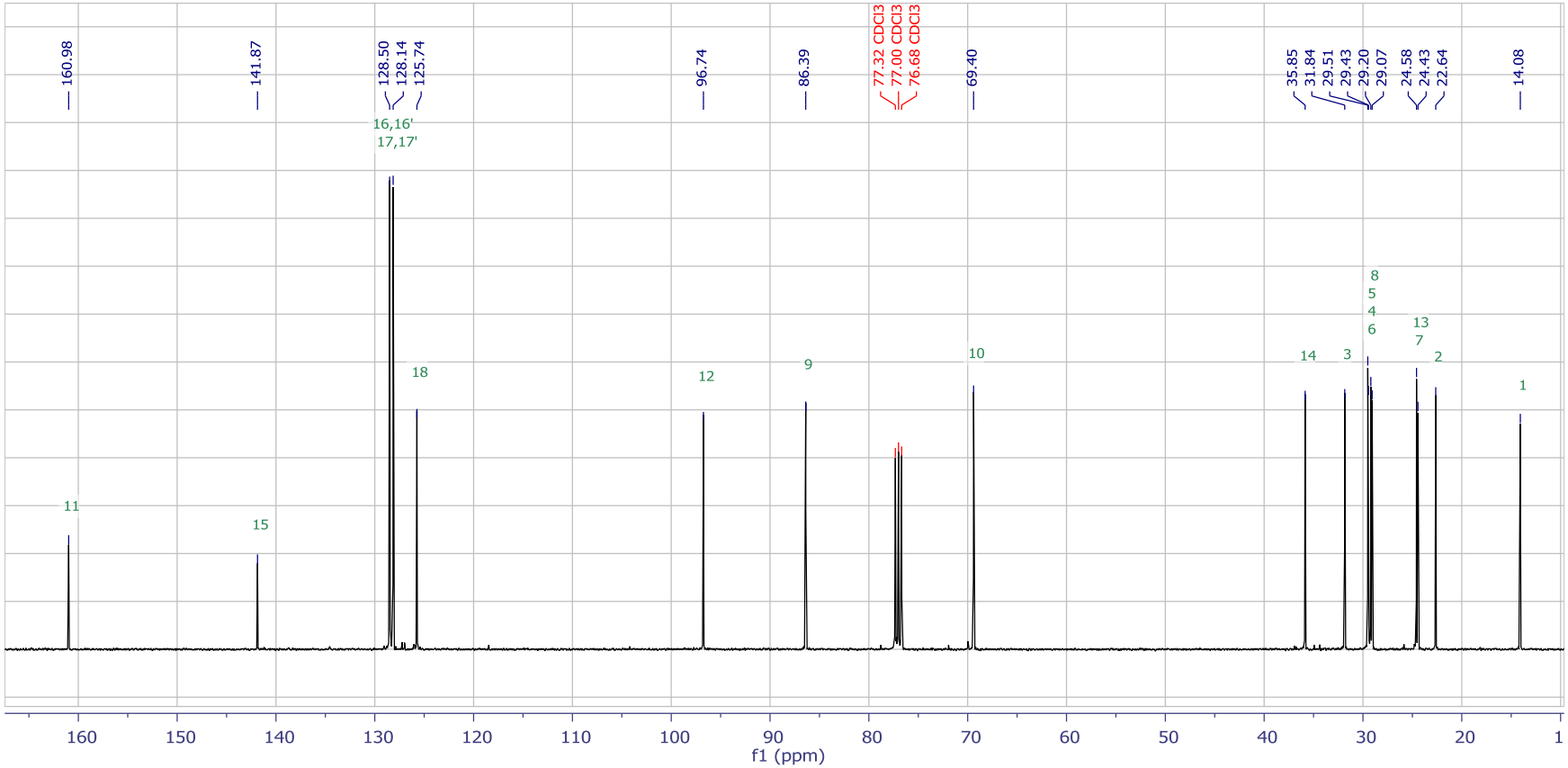


soi-sa-1318-01.1.1.1r — soi-sa-1318-01 — 5mm, CDCl3, 13mg — 1H @ 298K — av400t + BBFO — 14.12.15

SOI-SA-1318 15 mg $CDCl_3$ 298 K

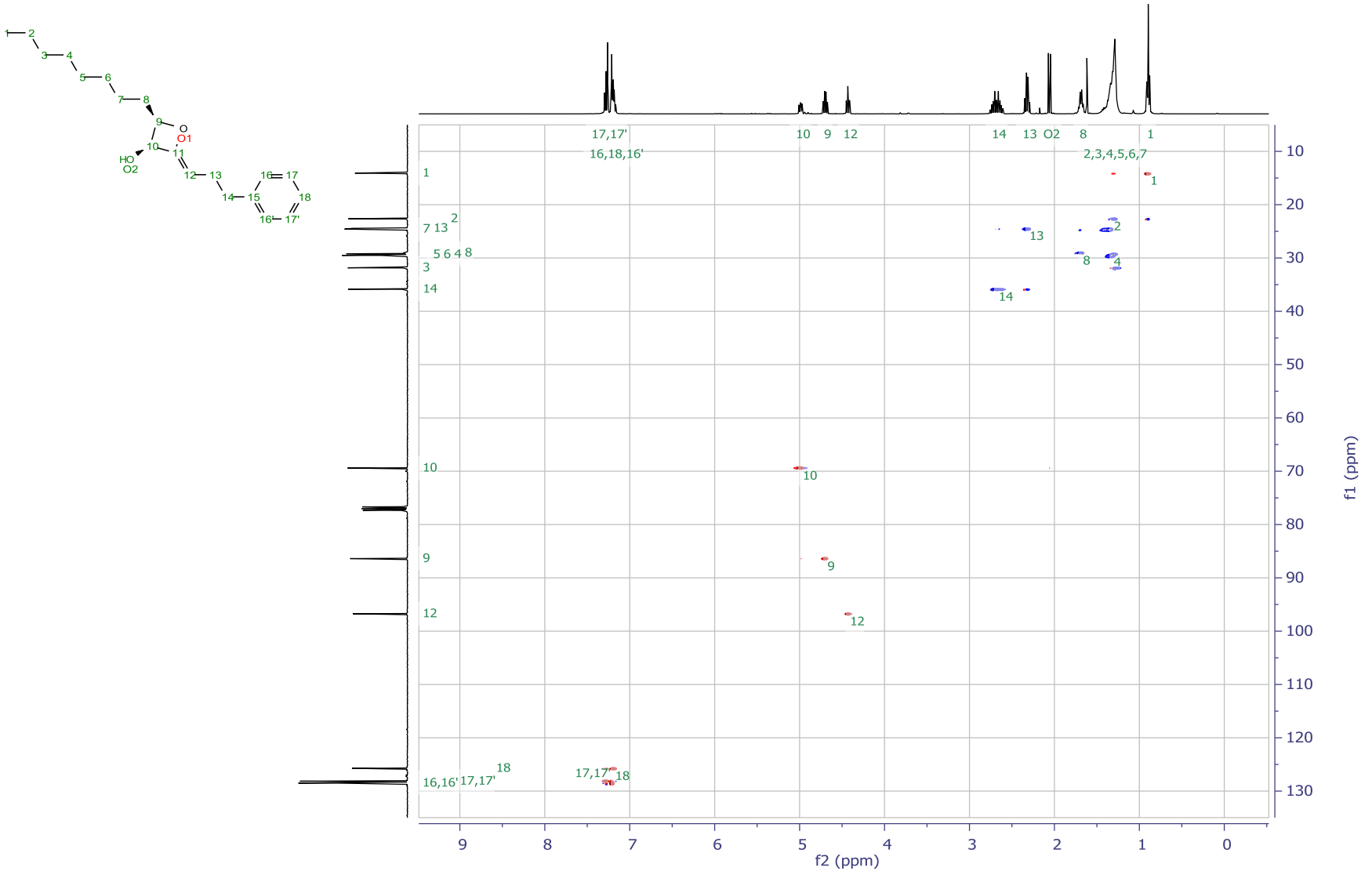
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.98 (11), 141.87 (15), 128.50 (16, 16'), 128.14 (17, 17'), 125.74 (18), 96.74 (12), 86.39 (9), 77.32, 77.00, 76.68, 69.40 (10), 35.85 (14), 31.84 (3), 29.51, 29.43, 29.20, 29.07 (8), 24.58 (7), 24.43 (13), 22.64 (2), 14.08 (1).





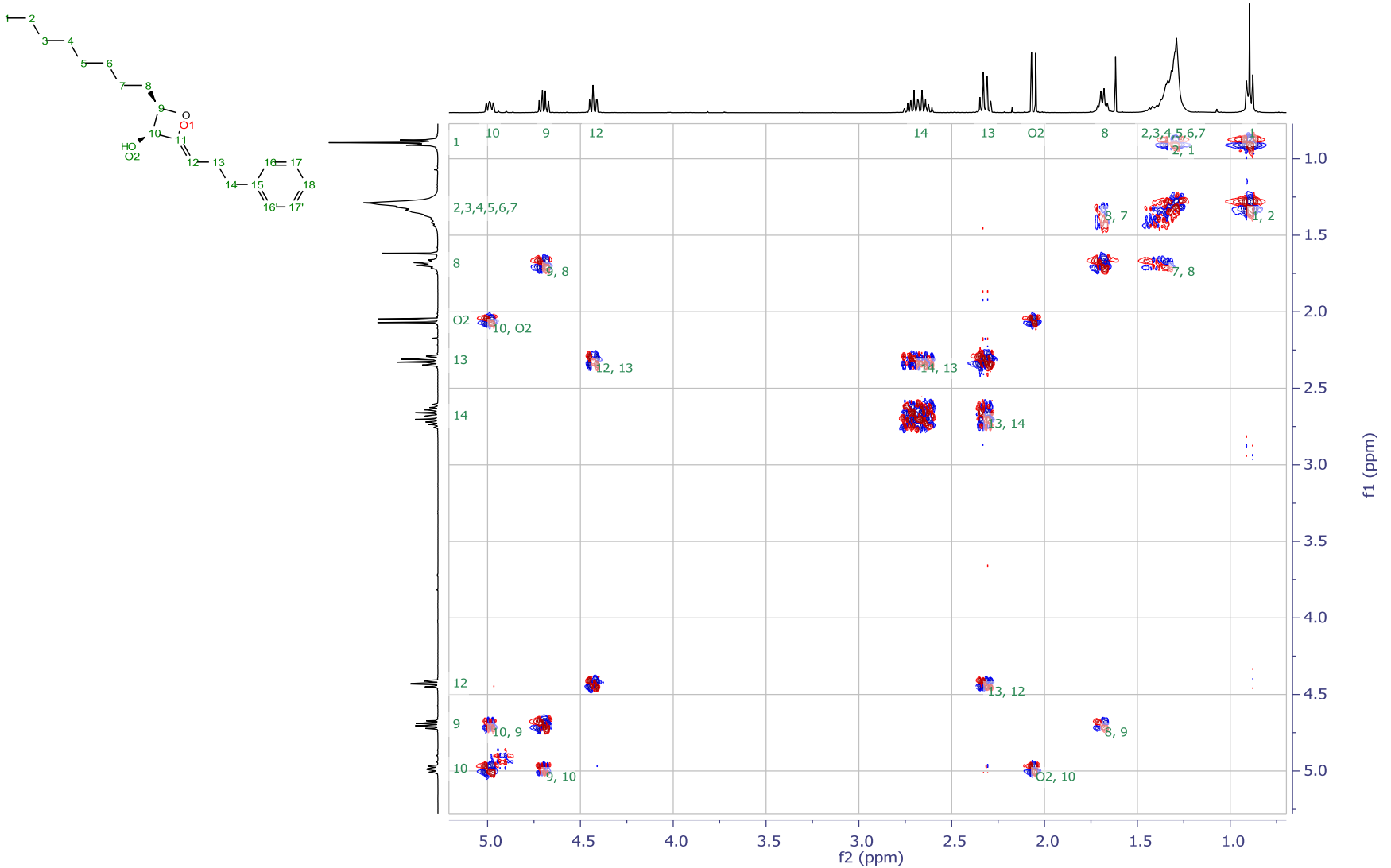
soi-sa-1318-01.2.1.1r — soi-sa-1318-01 — 5mm, CDCl3, 13mg — 13C{1H} @ 298K — av400t + BBFO — 14.12.15

SOI-SA-1318 15 mg $CDCl_3$ 298 K



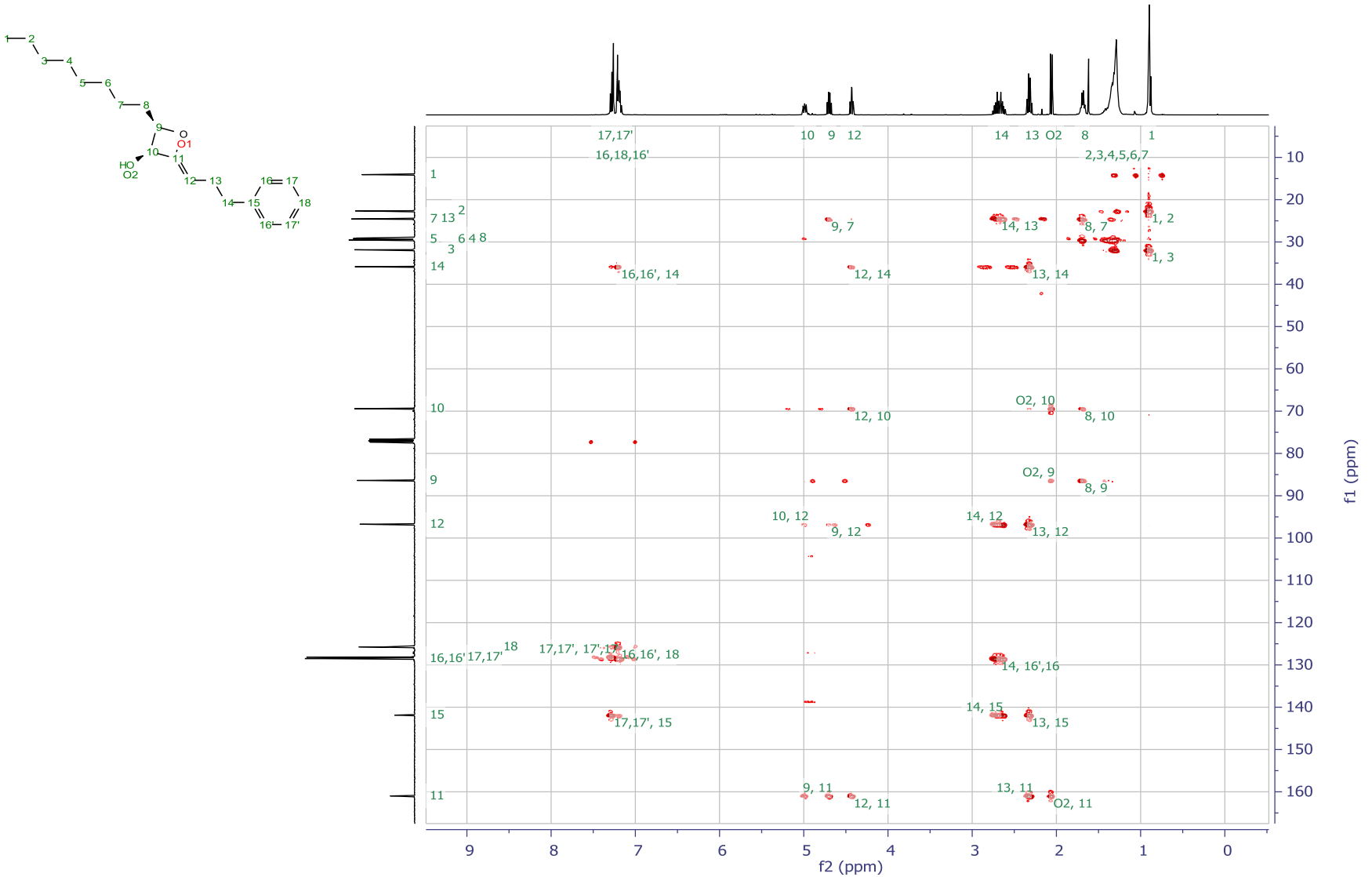
soi-sa-1318-01.3.1.2rr — soi-sa-1318-01 — 5mm, CDCl3, 13mg — 13C-HSQC-ed @ 298K — av400t + BBFO — 14.12.15

SOI-SA-1318 15 mg $CDCl_3$ 298 K

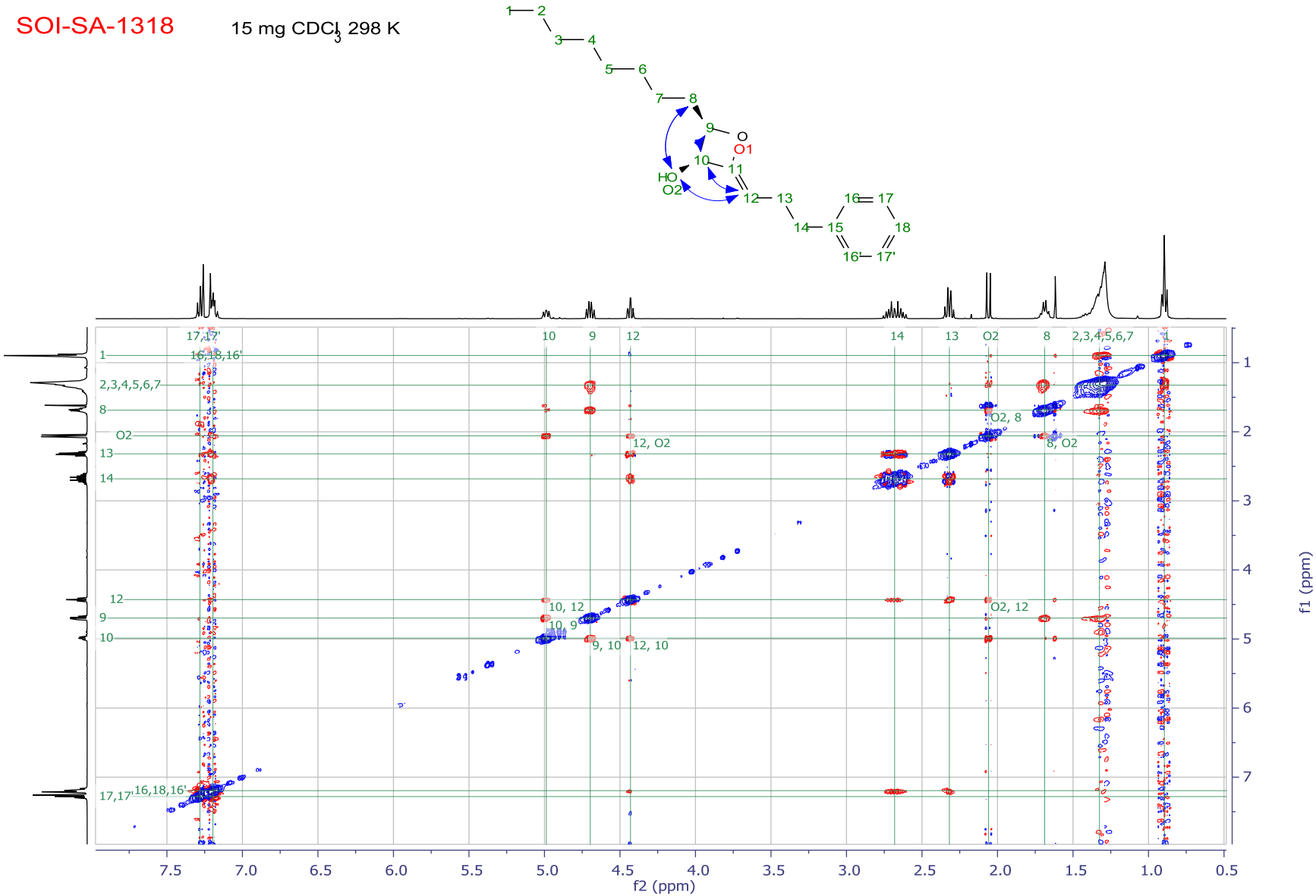


soi-sa-1318-01.5.1.2rr — soi-sa-1318-01 — 5mm, CDCl3, 13mg — COSY @ 298K — av400t + BBFO — 14.12.15

SOI-SA-1318 15 mg $CDCl_3$ 298 K

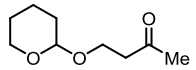


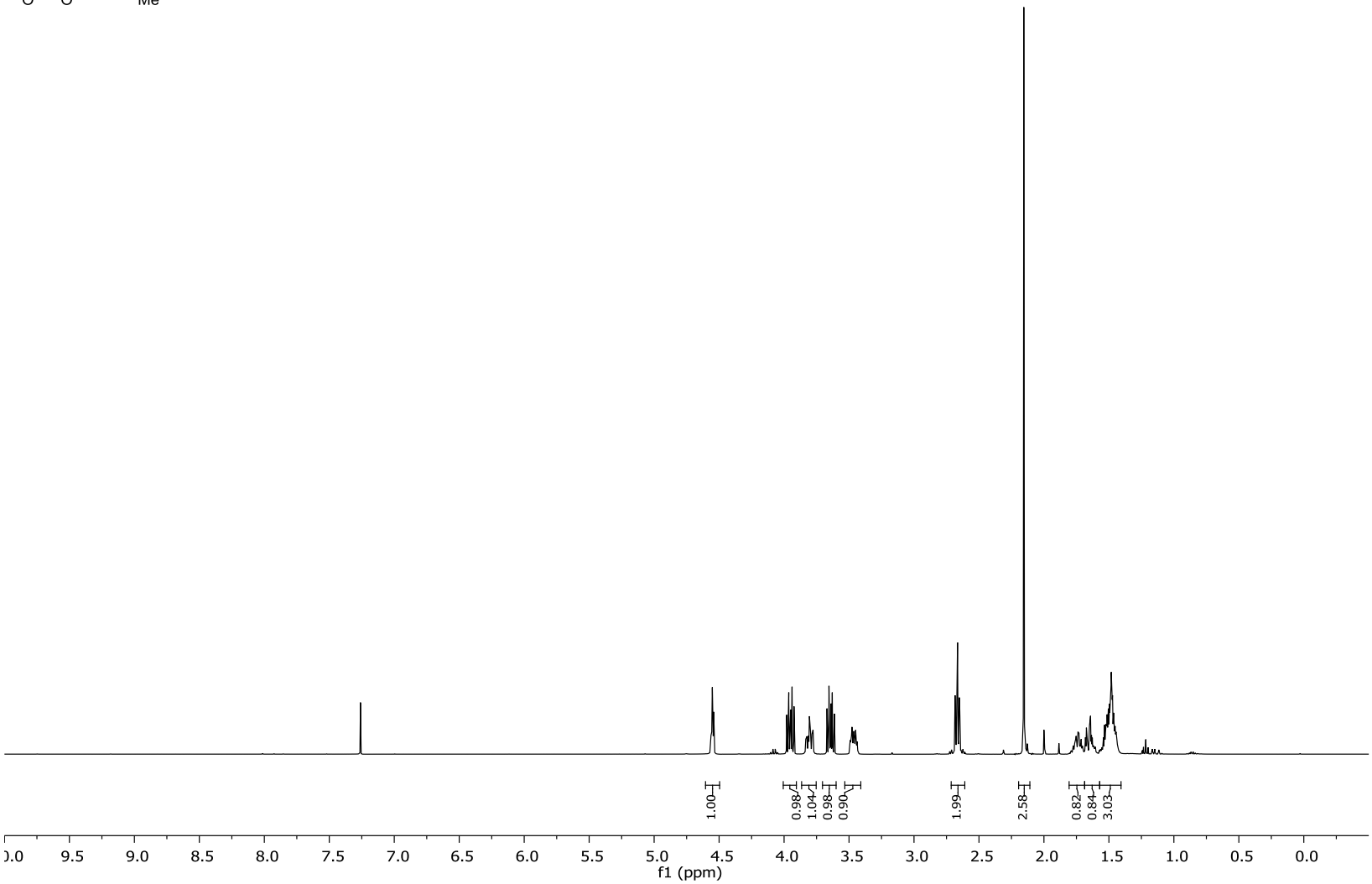
SOI-SA-1318 15 mg $CDCl_3$ 298 K



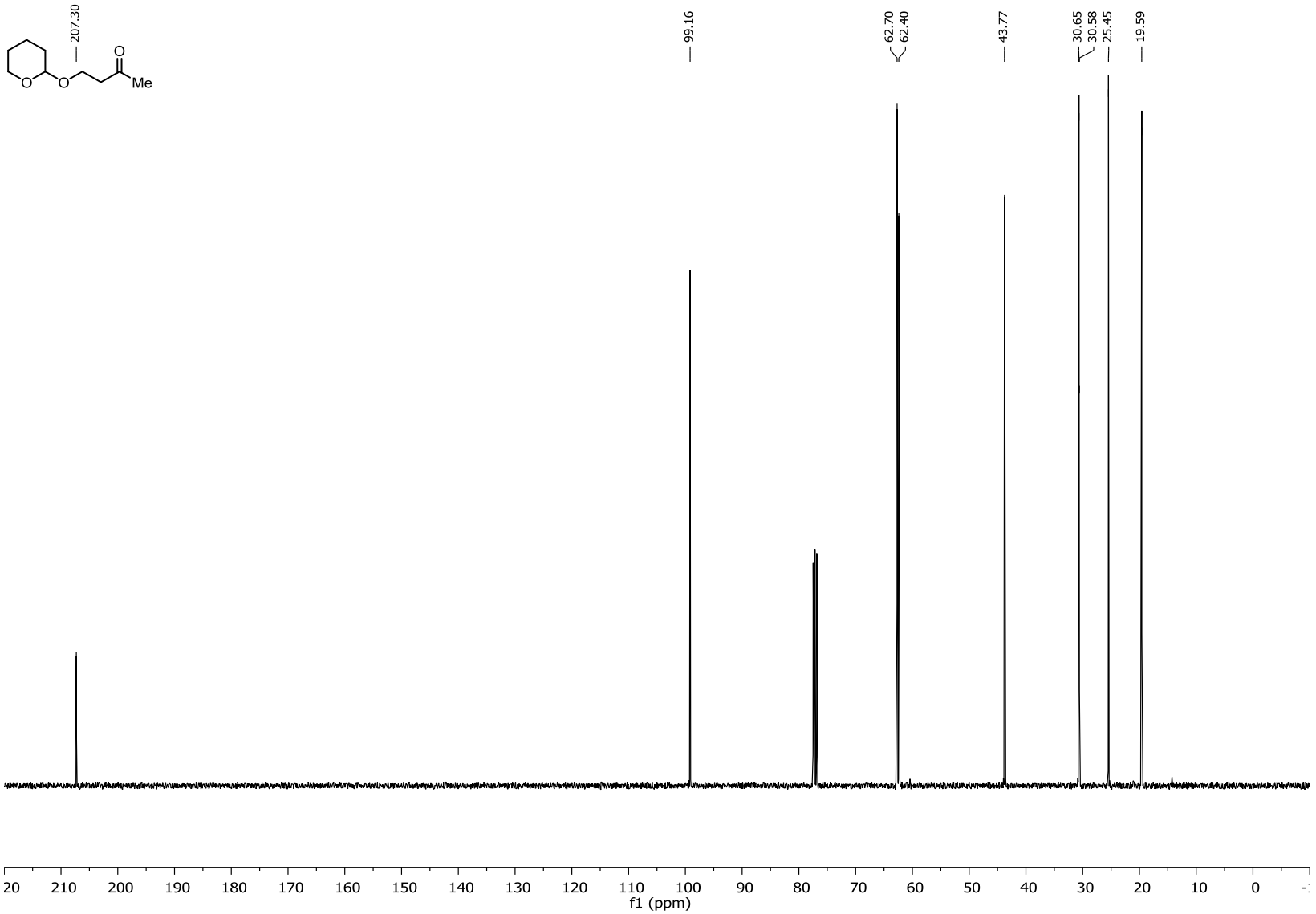
soi-sa-1318-01.6.1.2rr — soi-sa-1318-01 — 5mm, CDCl3, 13mg — NOESY @ 298K — av400t + BBFO — 14.12.15 — AV400t

4-((Tetrahydro-2H-pyran-2-yl)oxy)butan-2-one – (411)

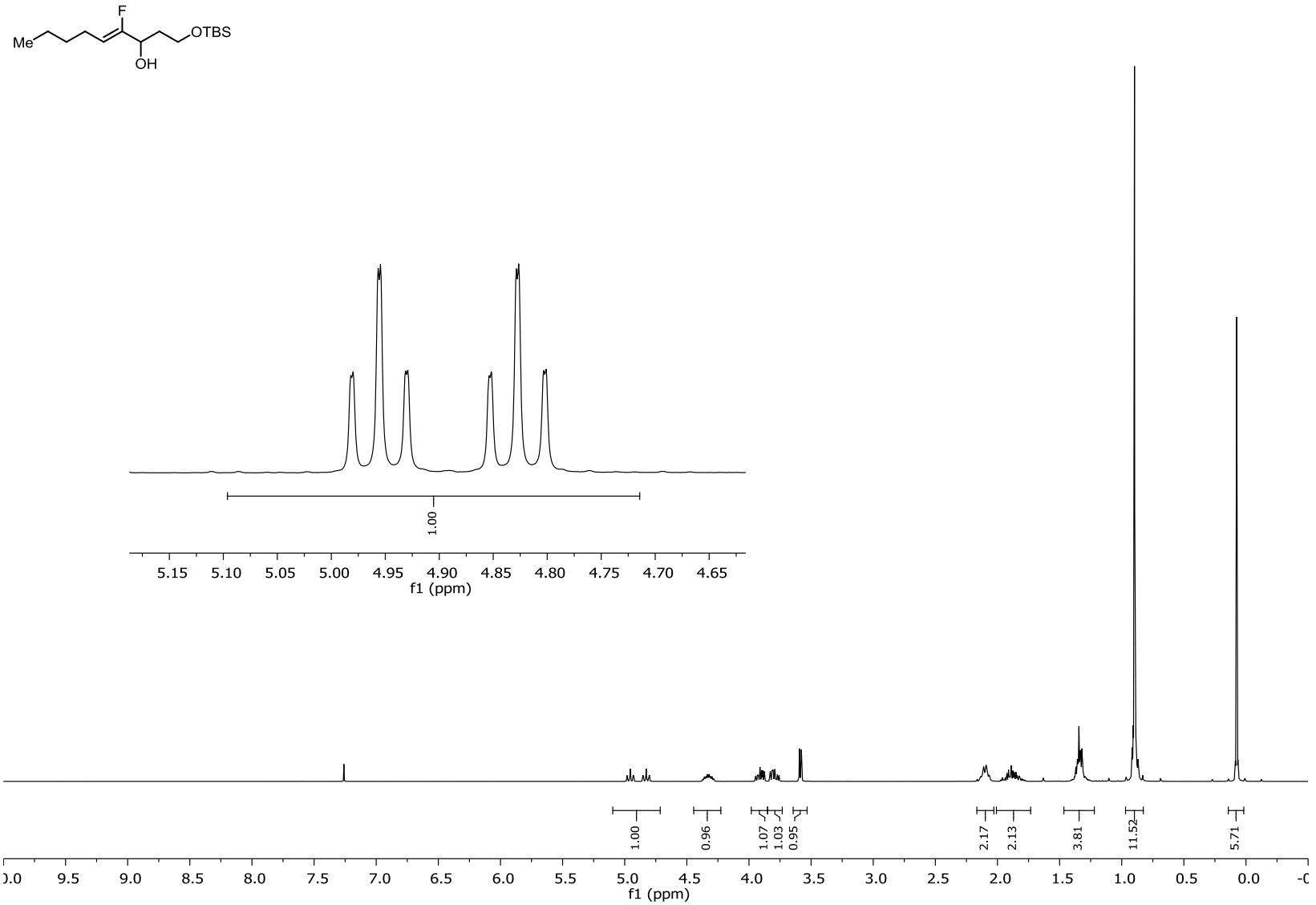




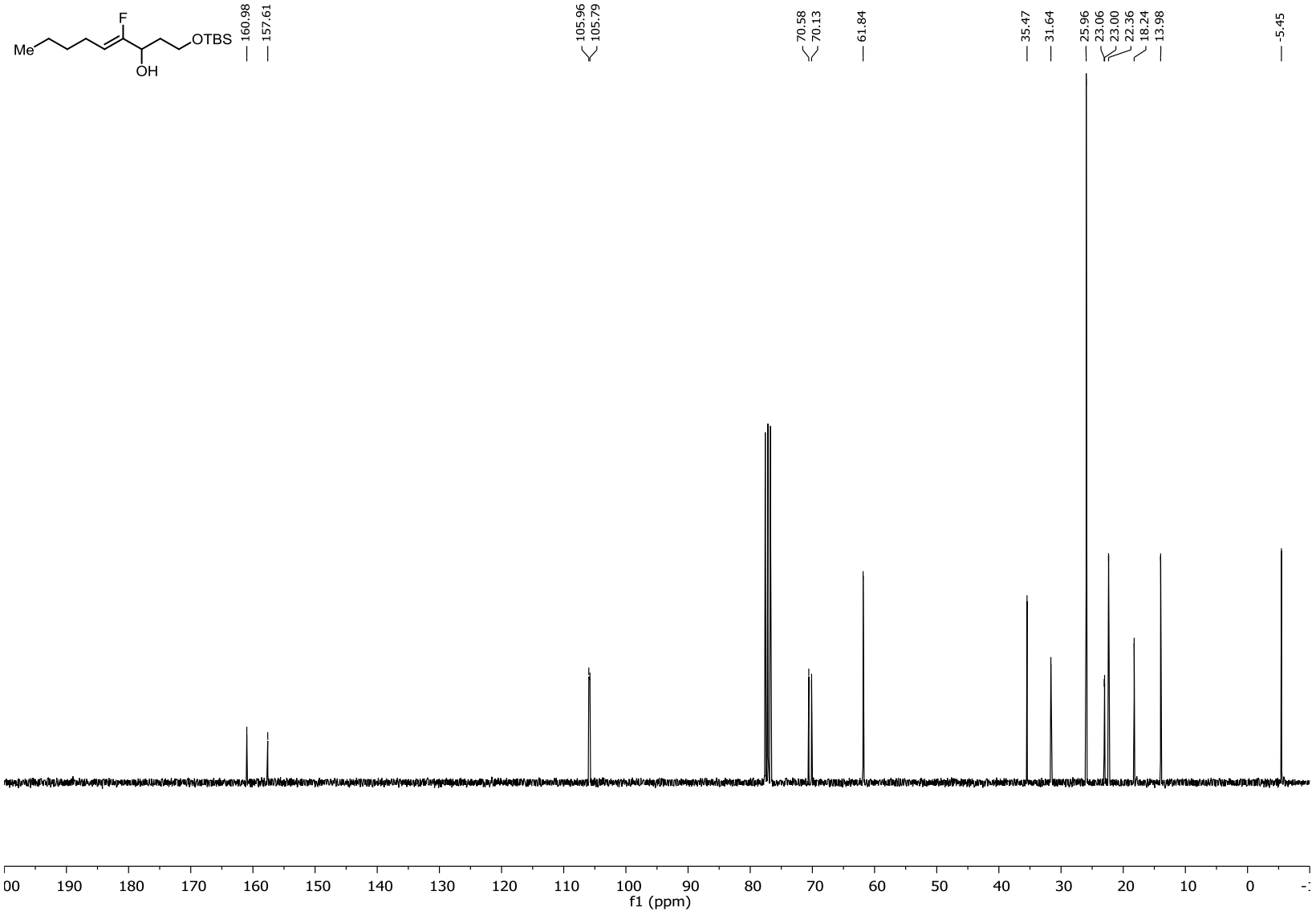
4-((Tetrahydro-2H-pyran-2-yl)oxy)butan-2-one – (411)



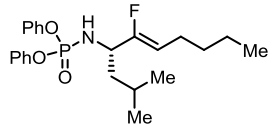
(Z)-1-((*tert*-Butyldimethylsilyl)oxy)-4-fluoronon-4-en-3-ol – (507)

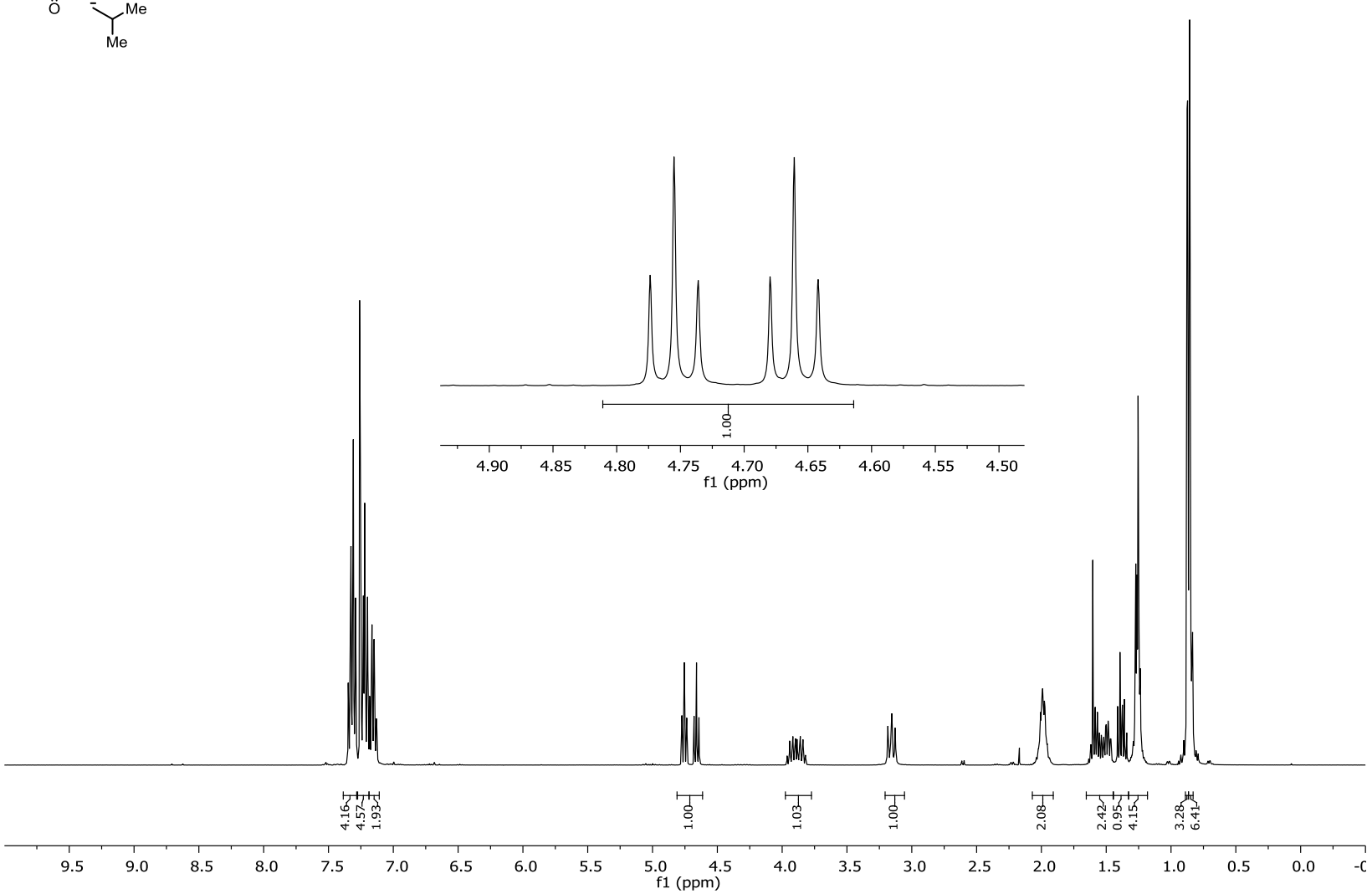


(Z)-1-((*tert*-Butyldimethylsilyl)oxy)-4-fluoronon-4-en-3-ol – (507)

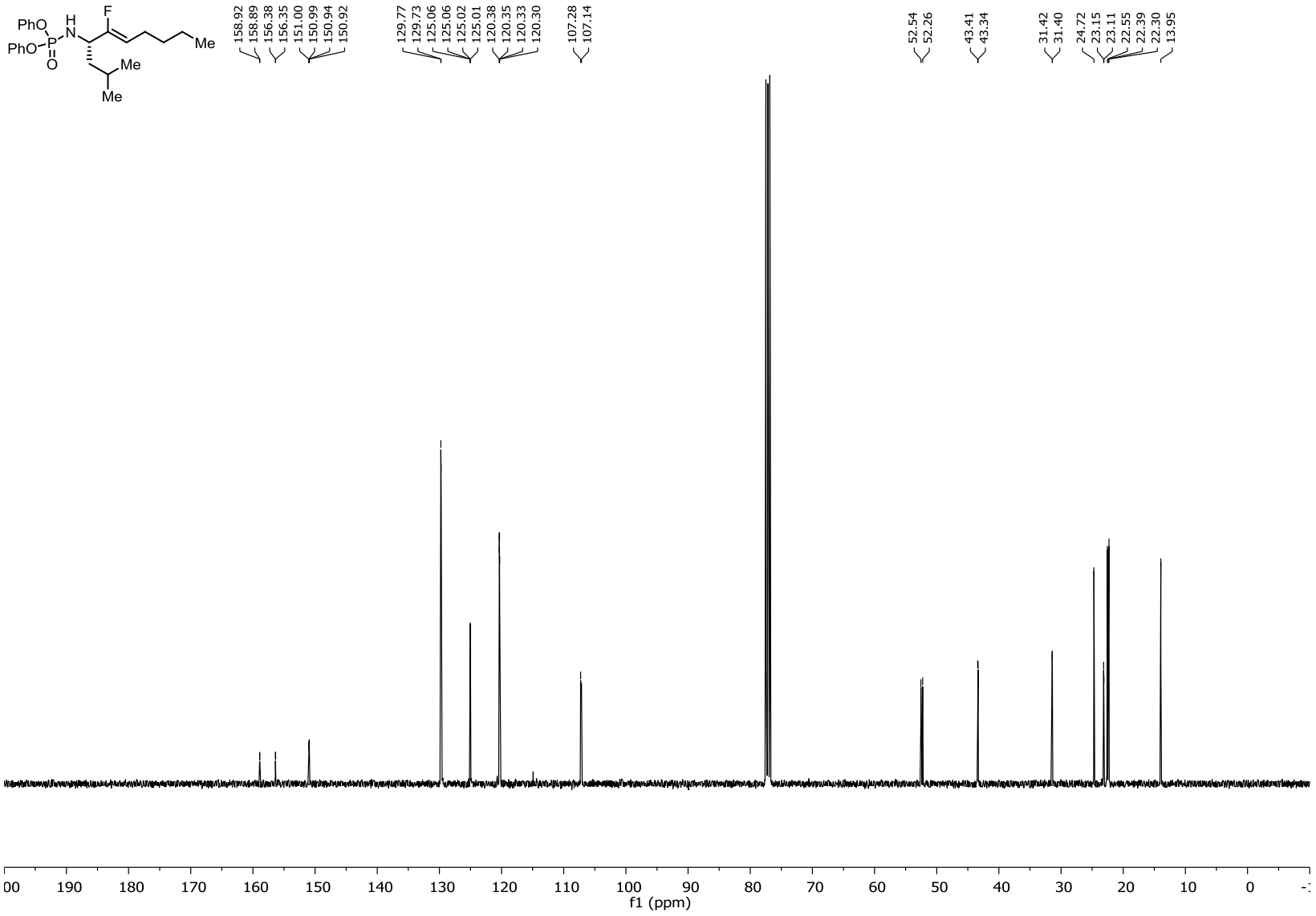


Diphenyl (*S*,*Z*)-(5-fluoro-2-methyldec-5-en-4-yl)phosphoramidate – (530)

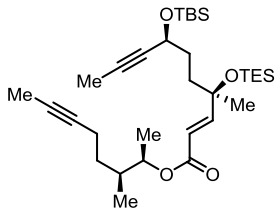




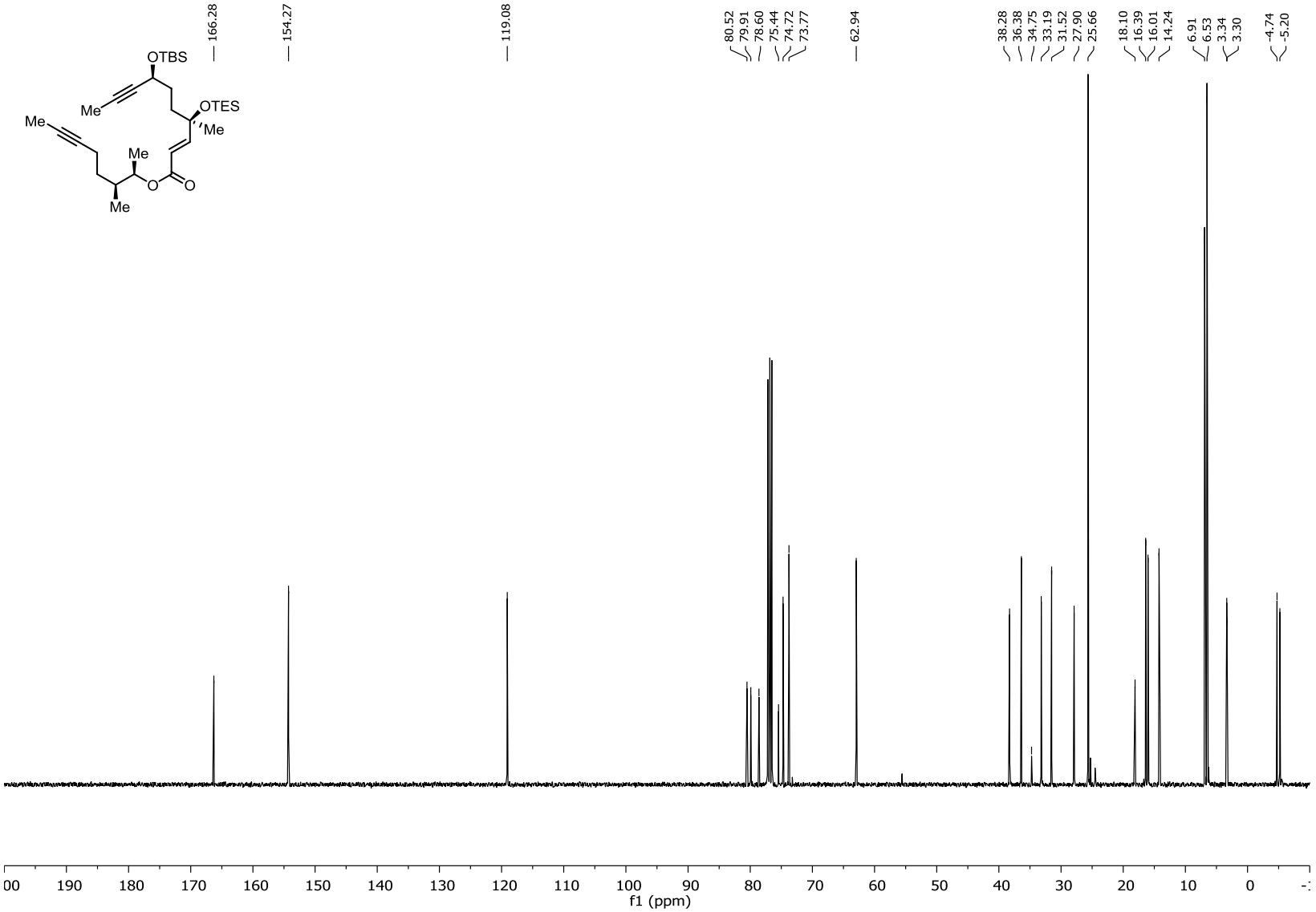
Diphenyl (*S*,*Z*)-(5-fluoro-2-methyldec-5-en-4-yl)phosphoramidate – (530)



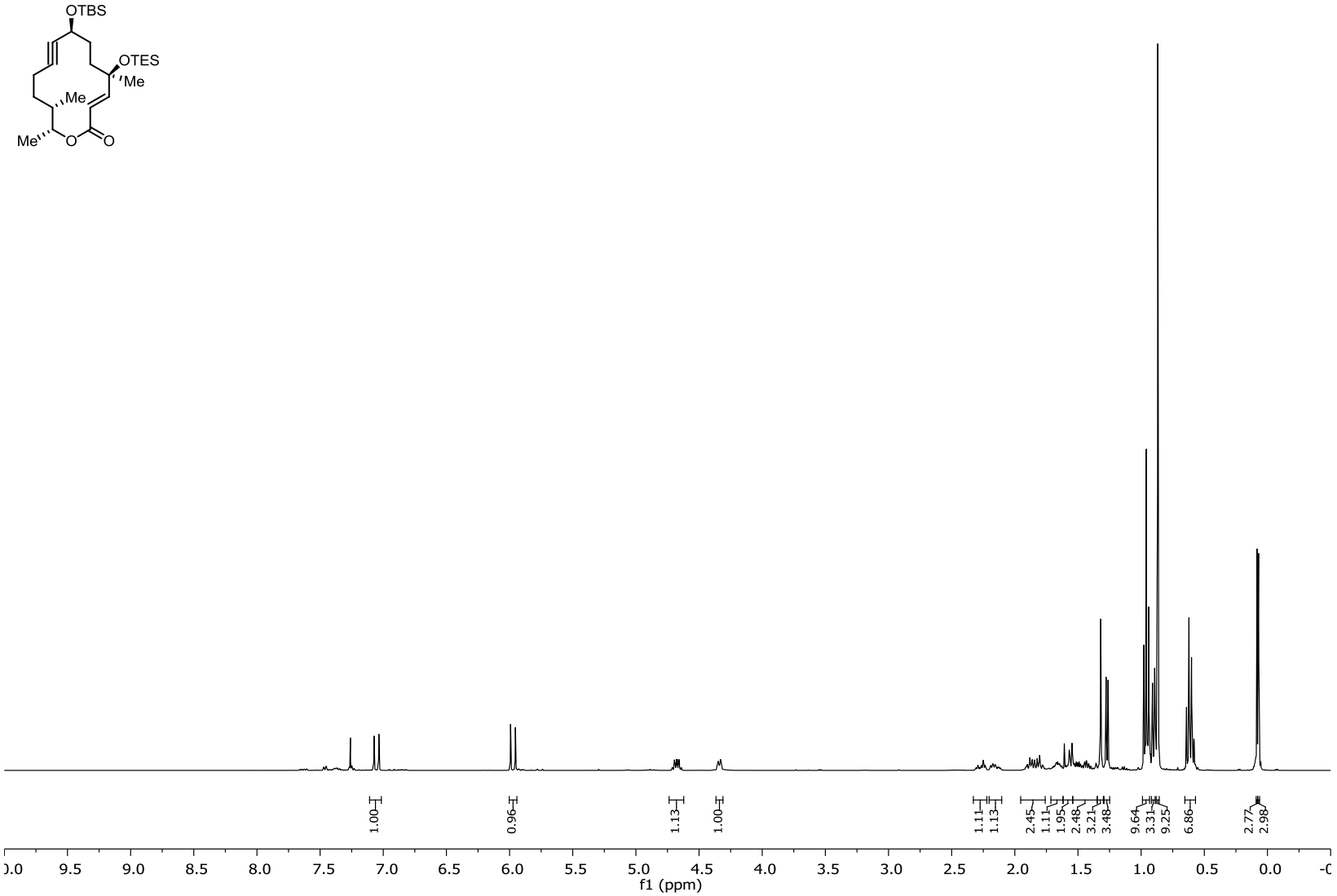
(*2R,3S*)-3-Methyloct-6-yn-2-yl (*4R,7S,E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-methyl-4-((triethylsilyl)oxy)dec-2-en-8-ynoate – (SI-94)



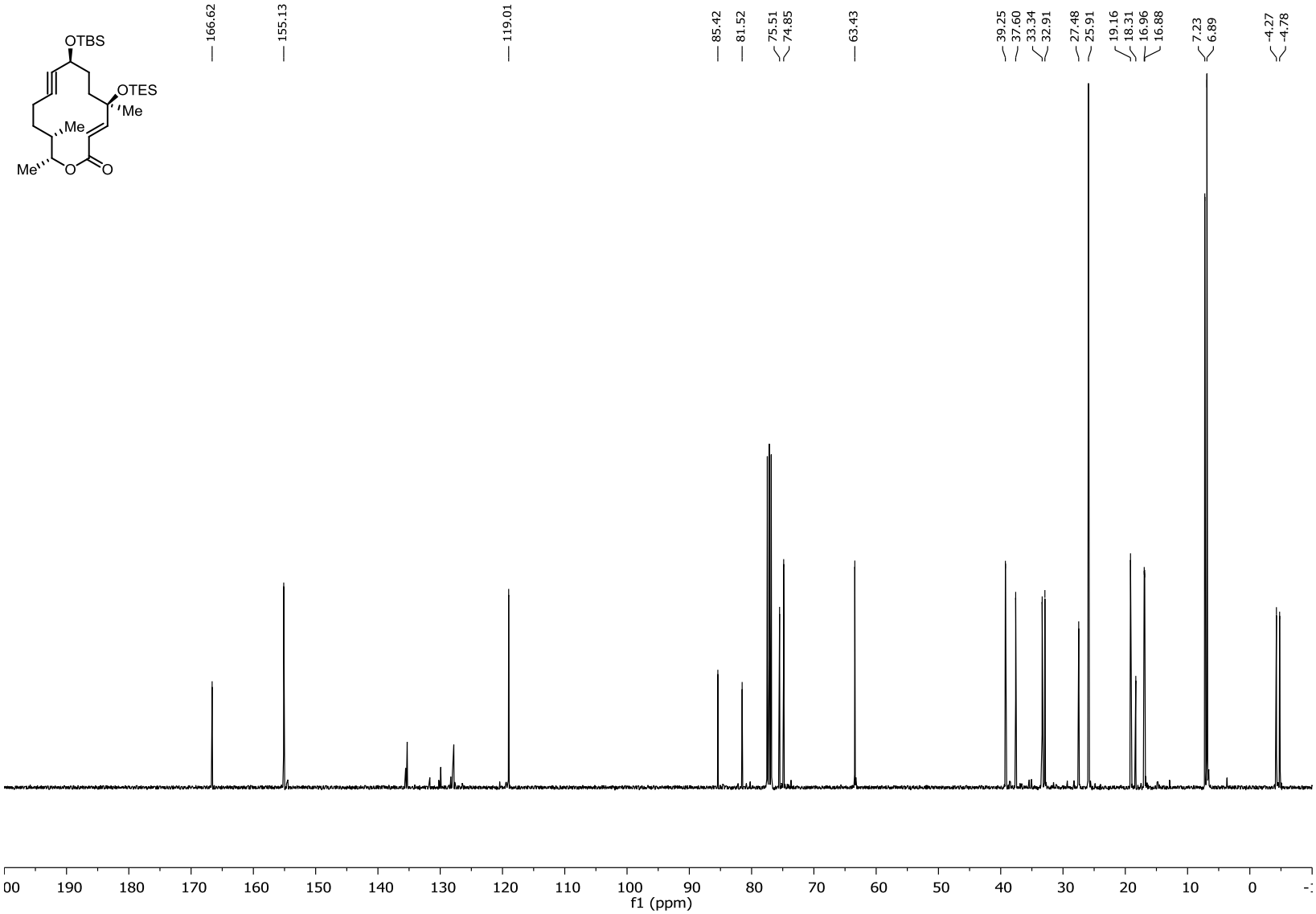
(*2R,3S*)-3-Methyloct-6-yn-2-yl (*4R,7S,E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-methyl-4-((triethylsilyl)oxy)dec-2-en-8-ynoate – (SI-94)



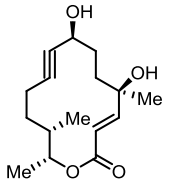
(*5R,8S,13S,14R,E*)-8-((*tert*-Butyldimethylsilyl)oxy)-5,13,14-trimethyl-5-((triethylsilyl)-oxy)oxacyclotetradec-3-en-9-yn-2-one – (655b)



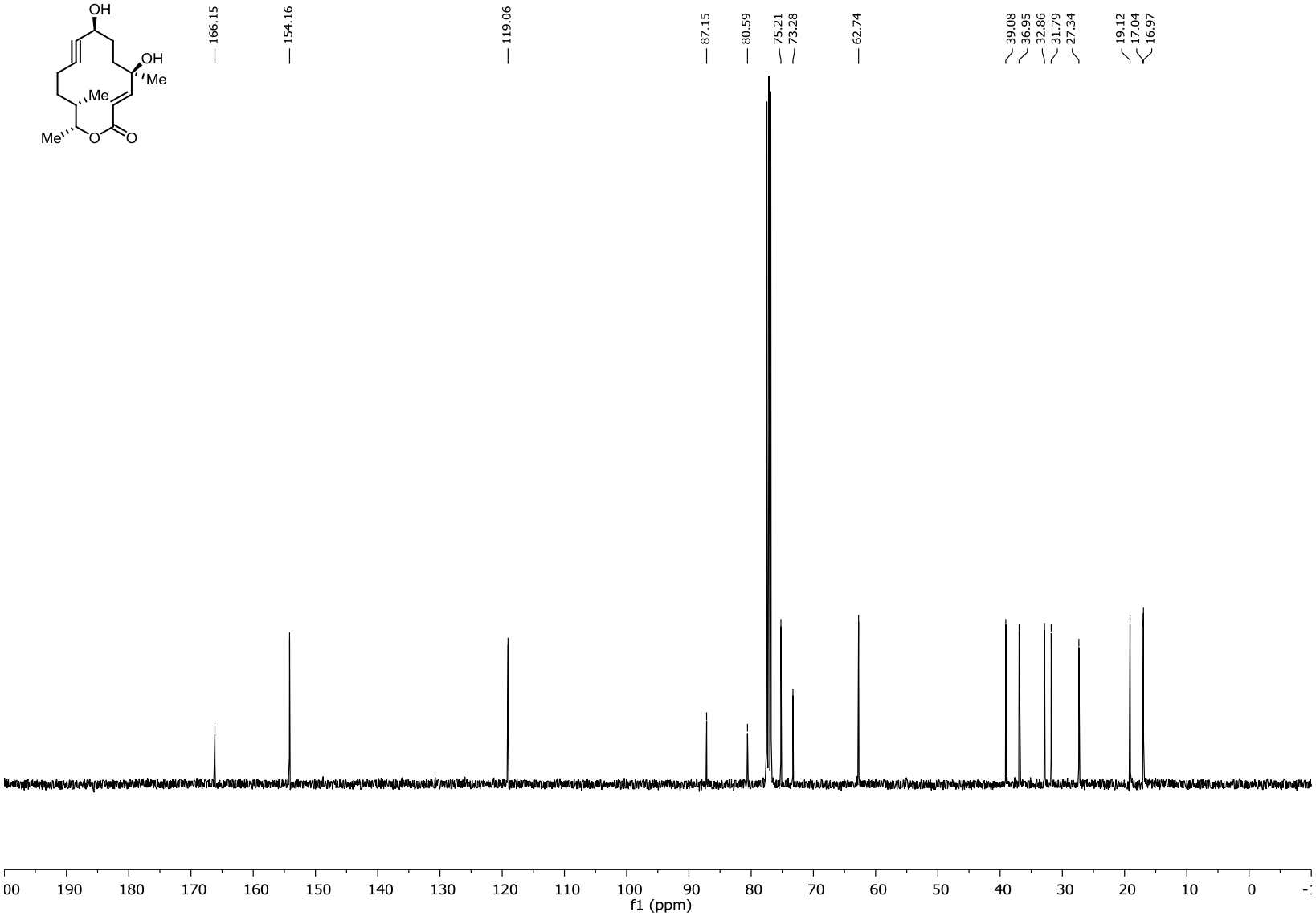
(*5R,8S,13S,14R,E*)-8-((*tert*-Butyldimethylsilyl)oxy)-5,13,14-trimethyl-5-((triethylsilyl)-oxy)oxacyclotetradec-3-en-9-yn-2-one – (655b)



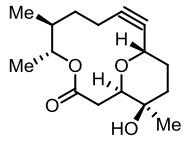
(*5R,8S,13S,14R,E*)-5,8-Dihydroxy-5,13,14-trimethyloxacyclotetradec-3-en-9-yn-2-one - (655a)

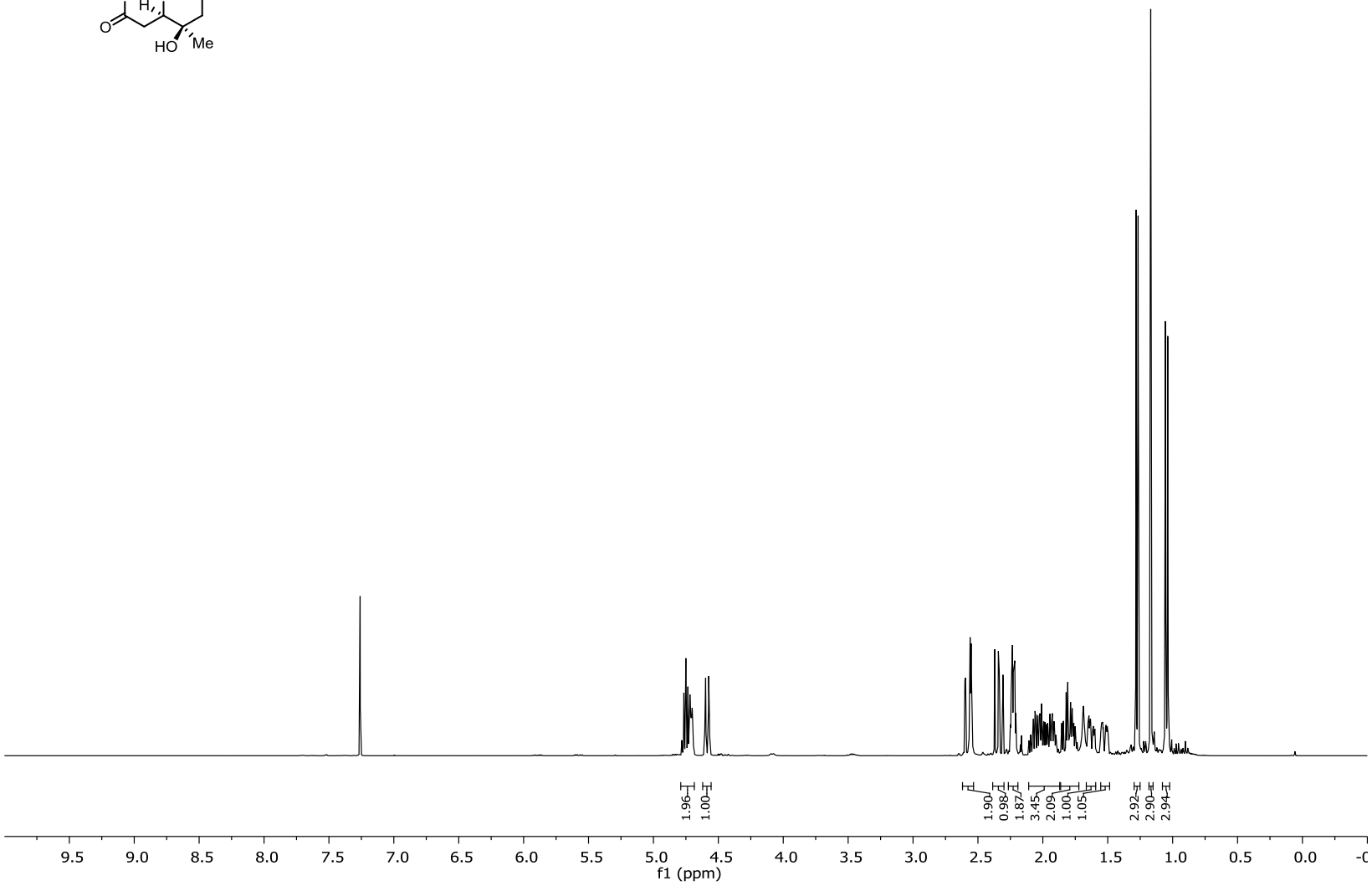


(*5R,8S,13S,14R,E*)-5,8-Dihydroxy-5,13,14-trimethyloxacyclotetradec-3-en-9-yn-2-one – (655a)

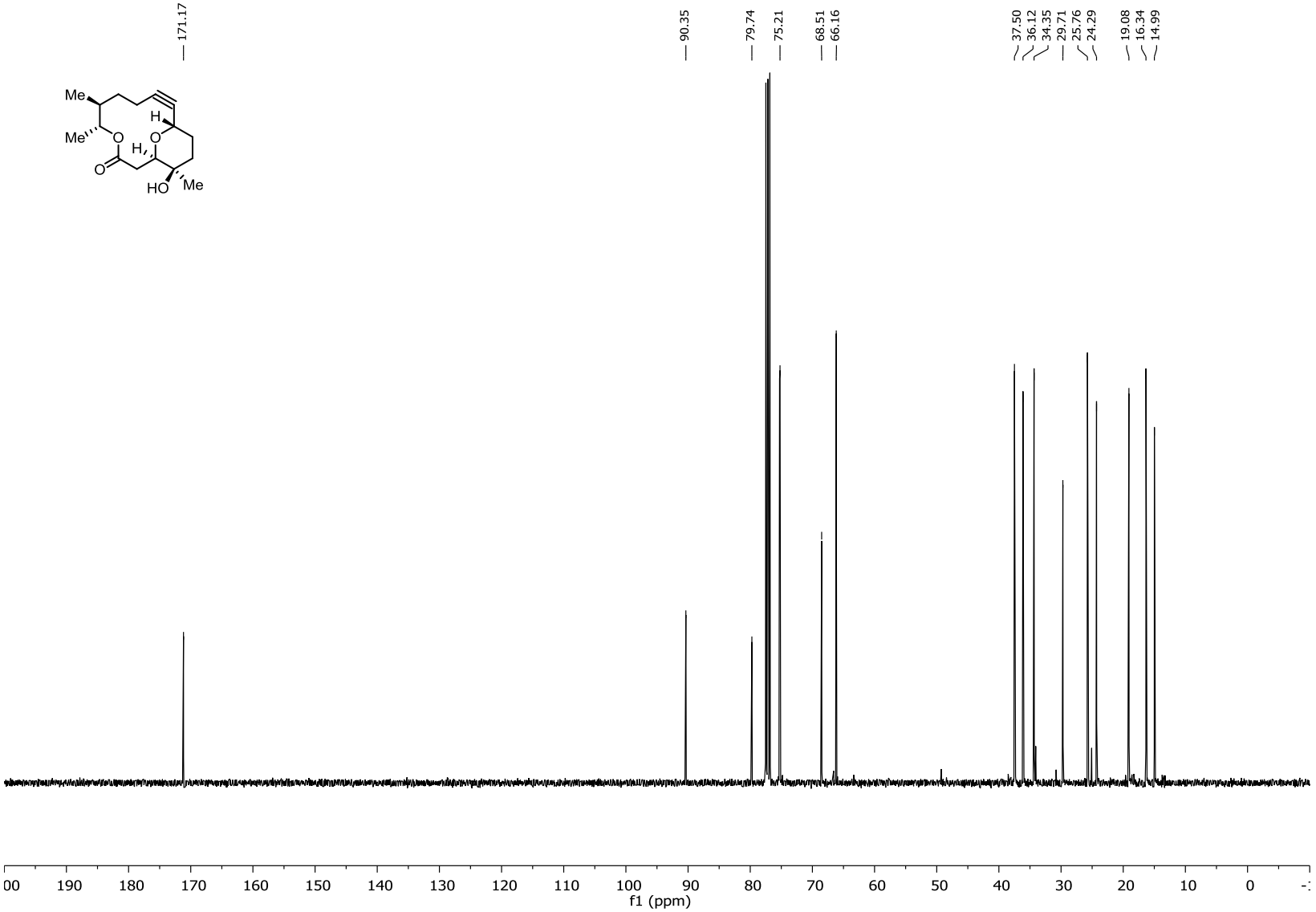


(*1S,5R,6S,11S,14R*)-11-Hydroxy-5,6,14-trimethyl-4,15-dioxabicyclo[12.1.0]-penta-dec-9-yn-3-one – (659)

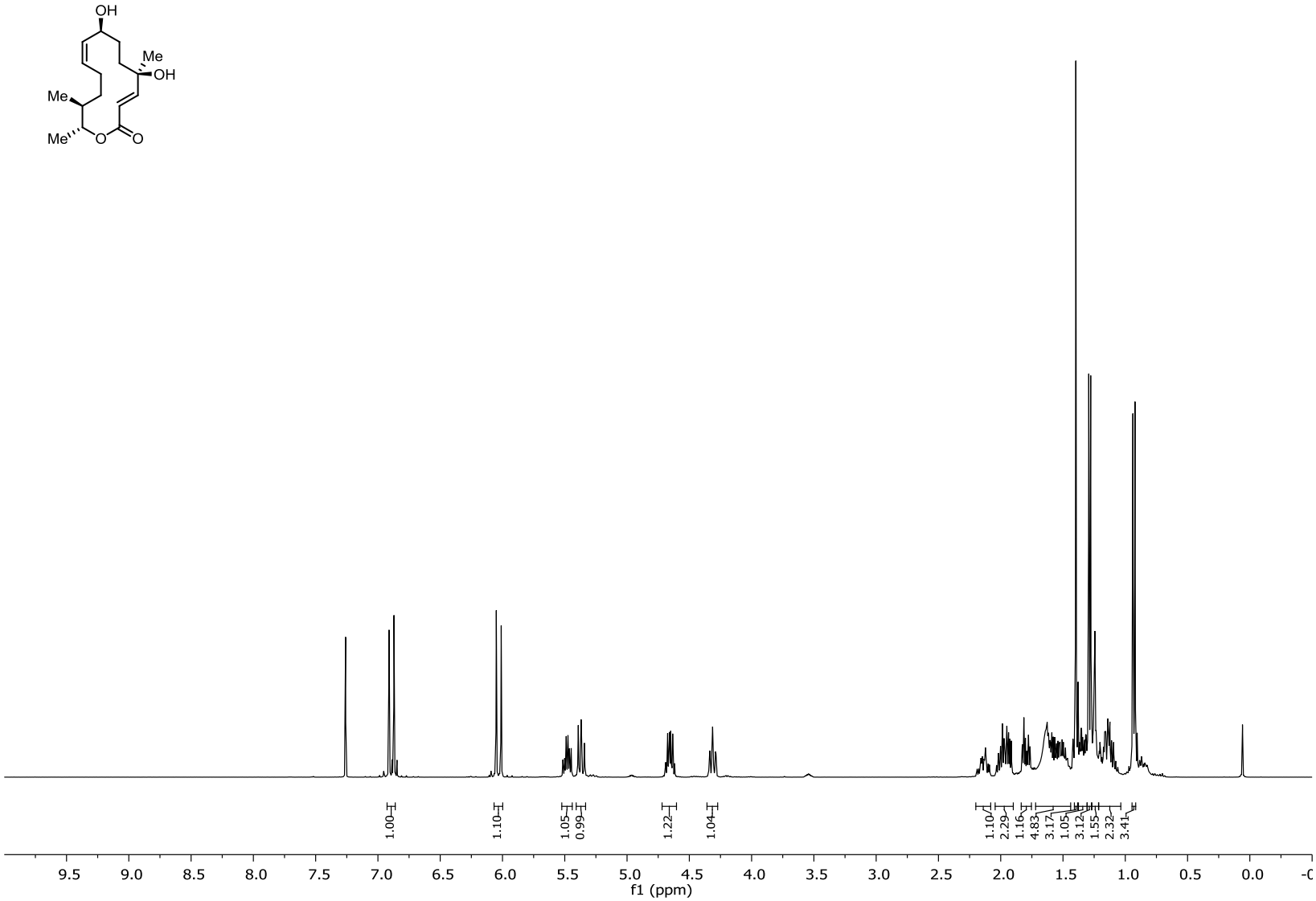




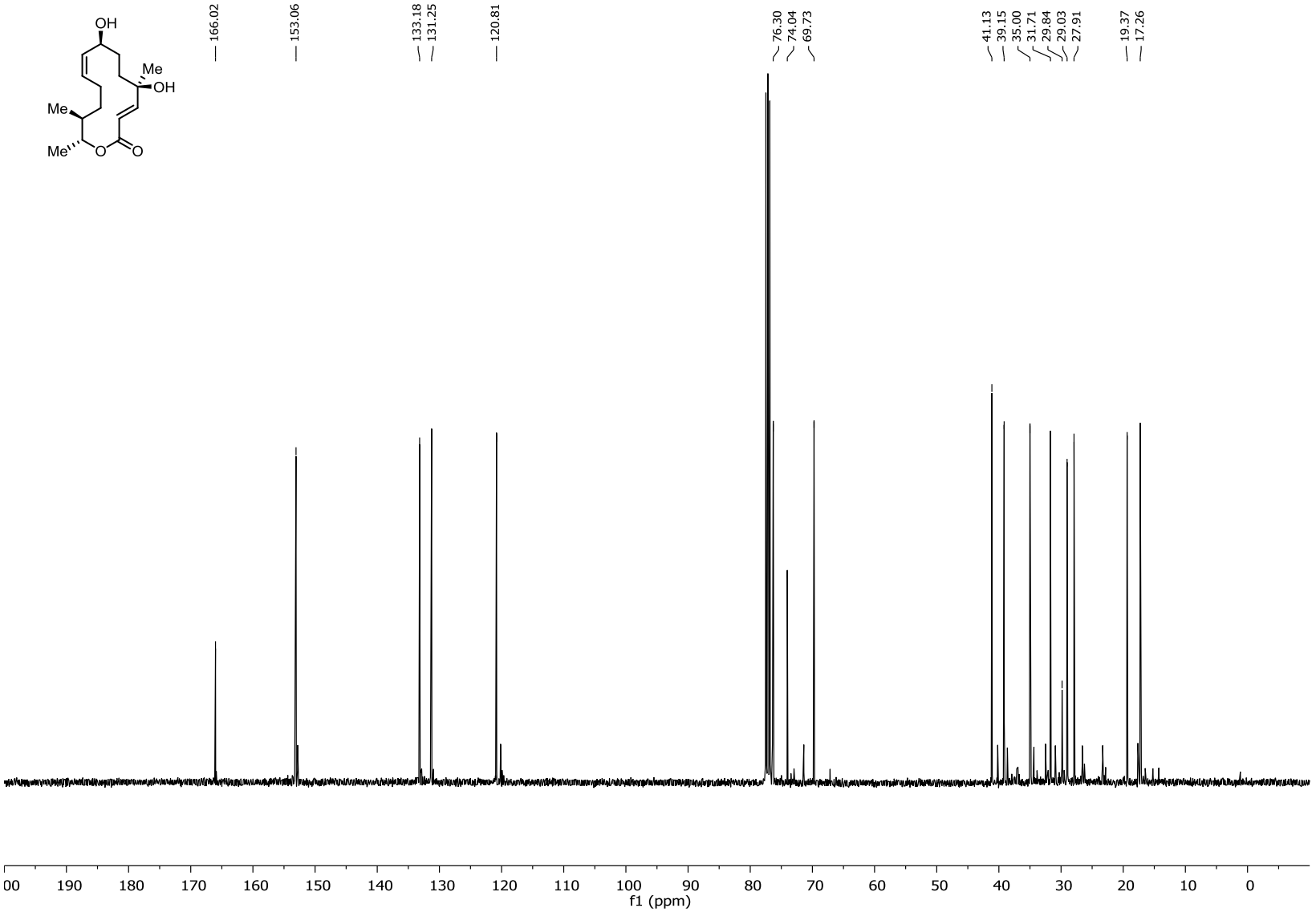
(*1S,5R,6S,11S,14R*)-11-Hydroxy-5,6,14-trimethyl-4,15-dioxabicyclo[12.1.0]-penta-dec-9-yn-3-one – (659)



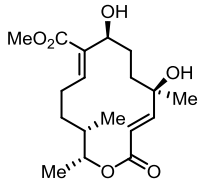
(*3E,5R,8S,9Z,13S,14R*)-5,8-Dihydroxy-5,13,14-trimethyloxacyclotetradeca-3,9-dien-2-one – (658)

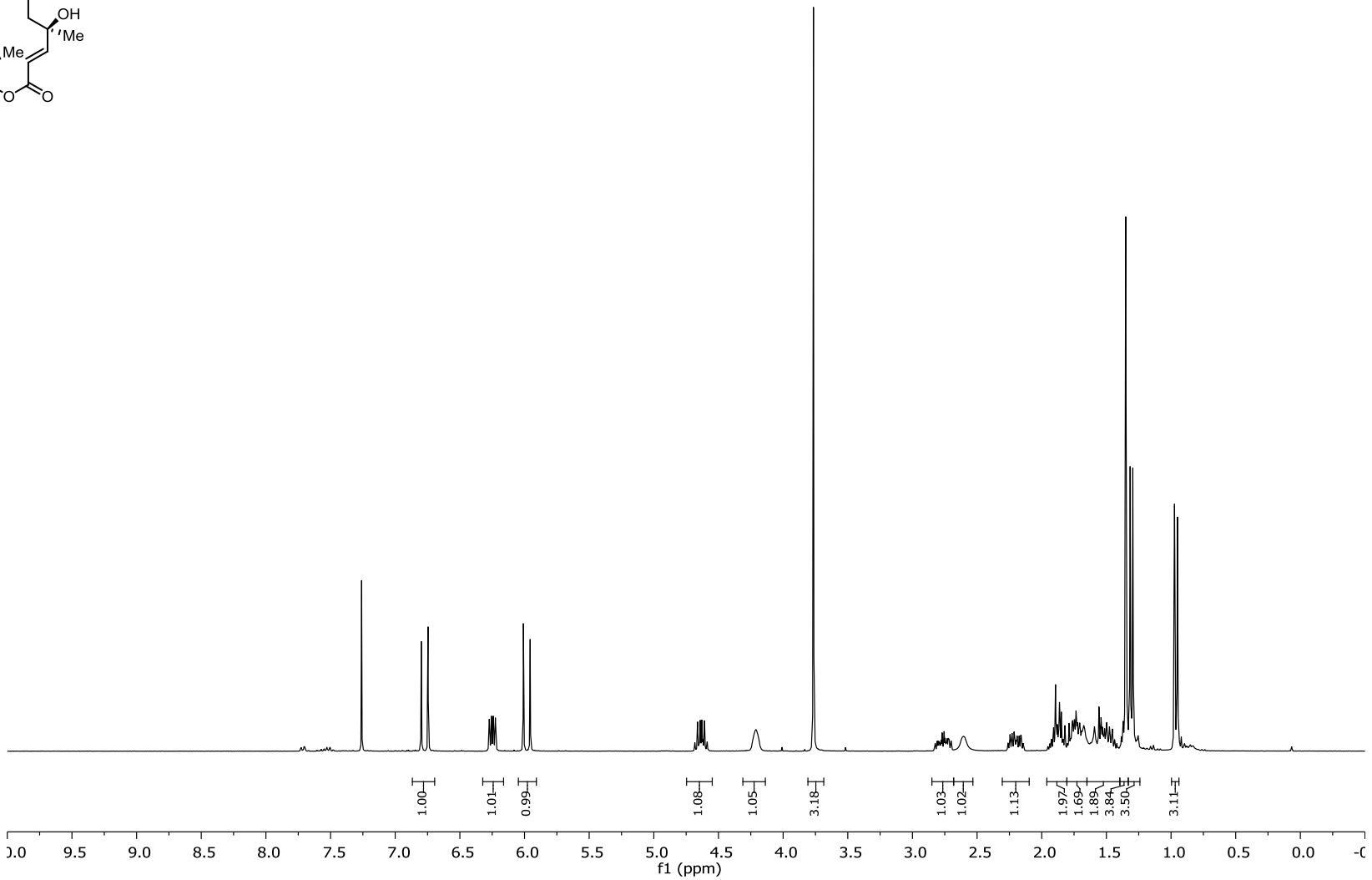


(*3E,5R,8S,9Z,13S,14R*)-5,8-Dihydroxy-5,13,14-trimethyloxacyclotetradeca-3,9-dien-2-one – (658)

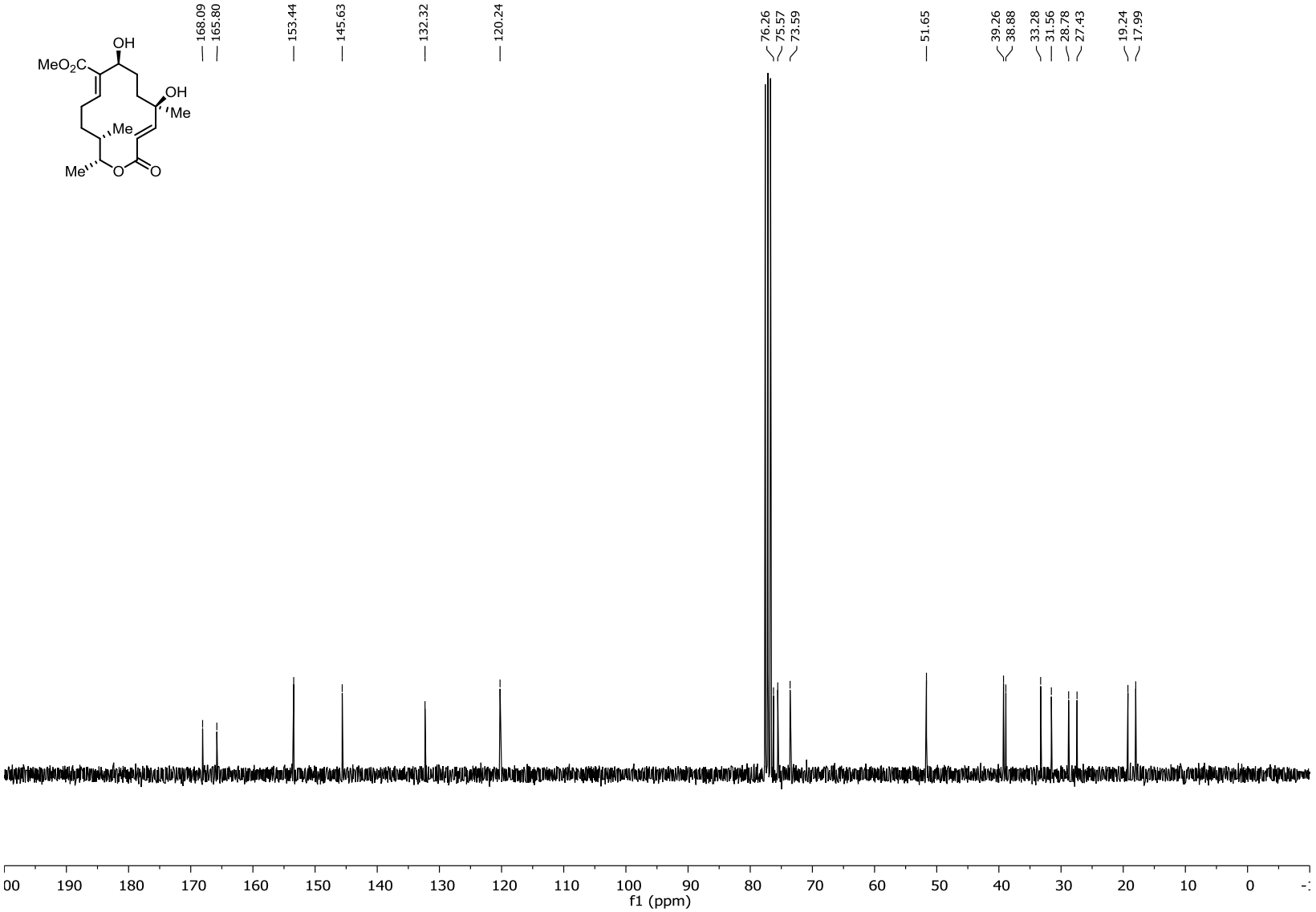


Methyl (*2R,3S,6Z,8S,11R,12E*)-8,11-dihydroxy-2,3,11-trimethyl-14-oxooxacyclotetradeca-6,12-diene-7-carboxylate – (660)

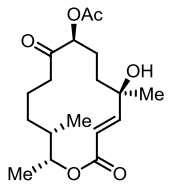




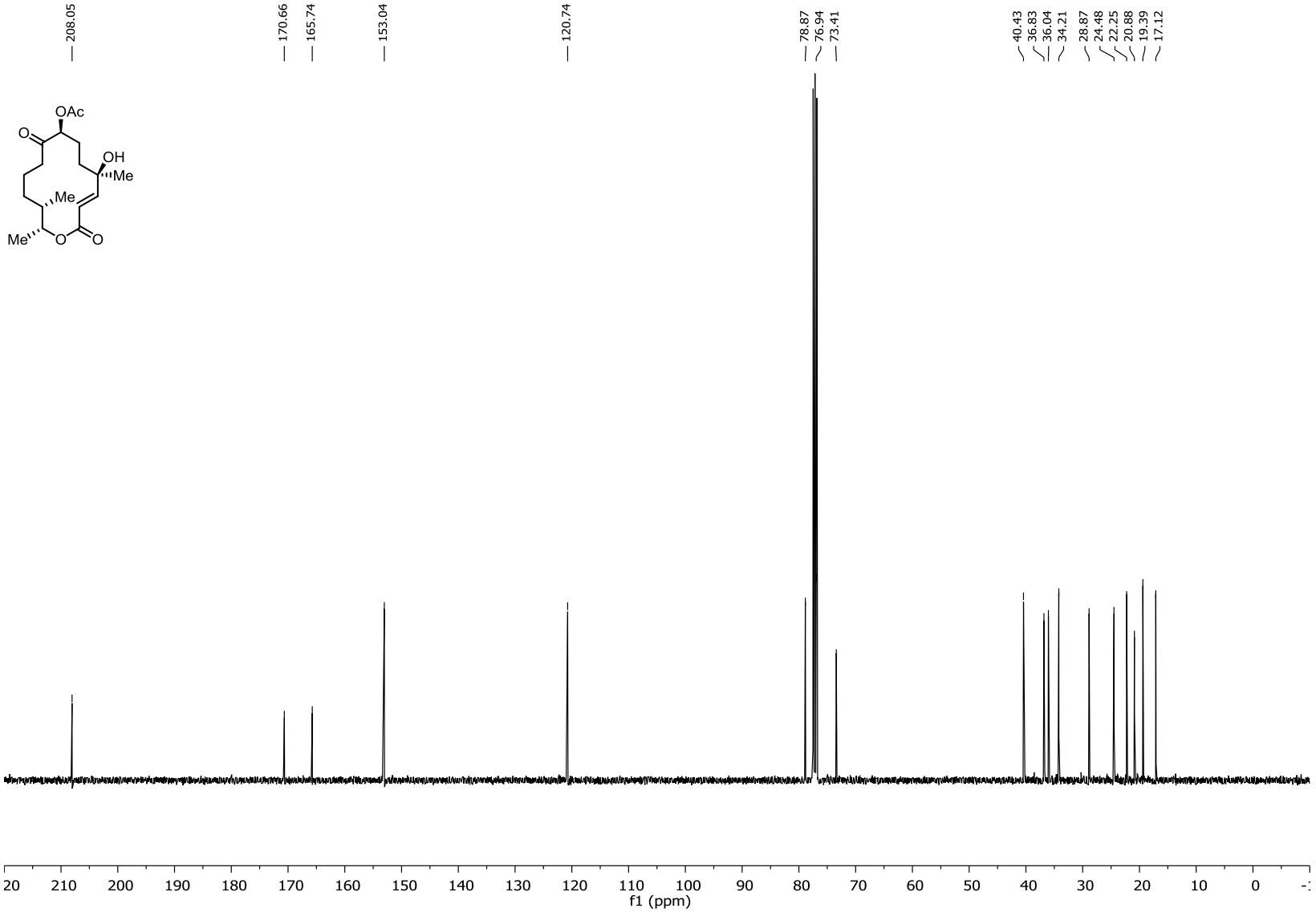
Methyl (*2R,3S,6Z,8S,11R,12E*)-8,11-dihydroxy-2,3,11-trimethyl-14-oxooxacyclotetradeca-6,12-diene-7-carboxylate – (660)



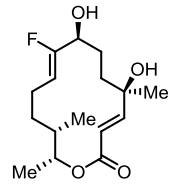
(*2R,3S,8S,11R*,E)-11-hydroxy-2,3,11-trimethyl-7,14-dioxooxacyclotetradec-12-en-8-yl acetate – (661)



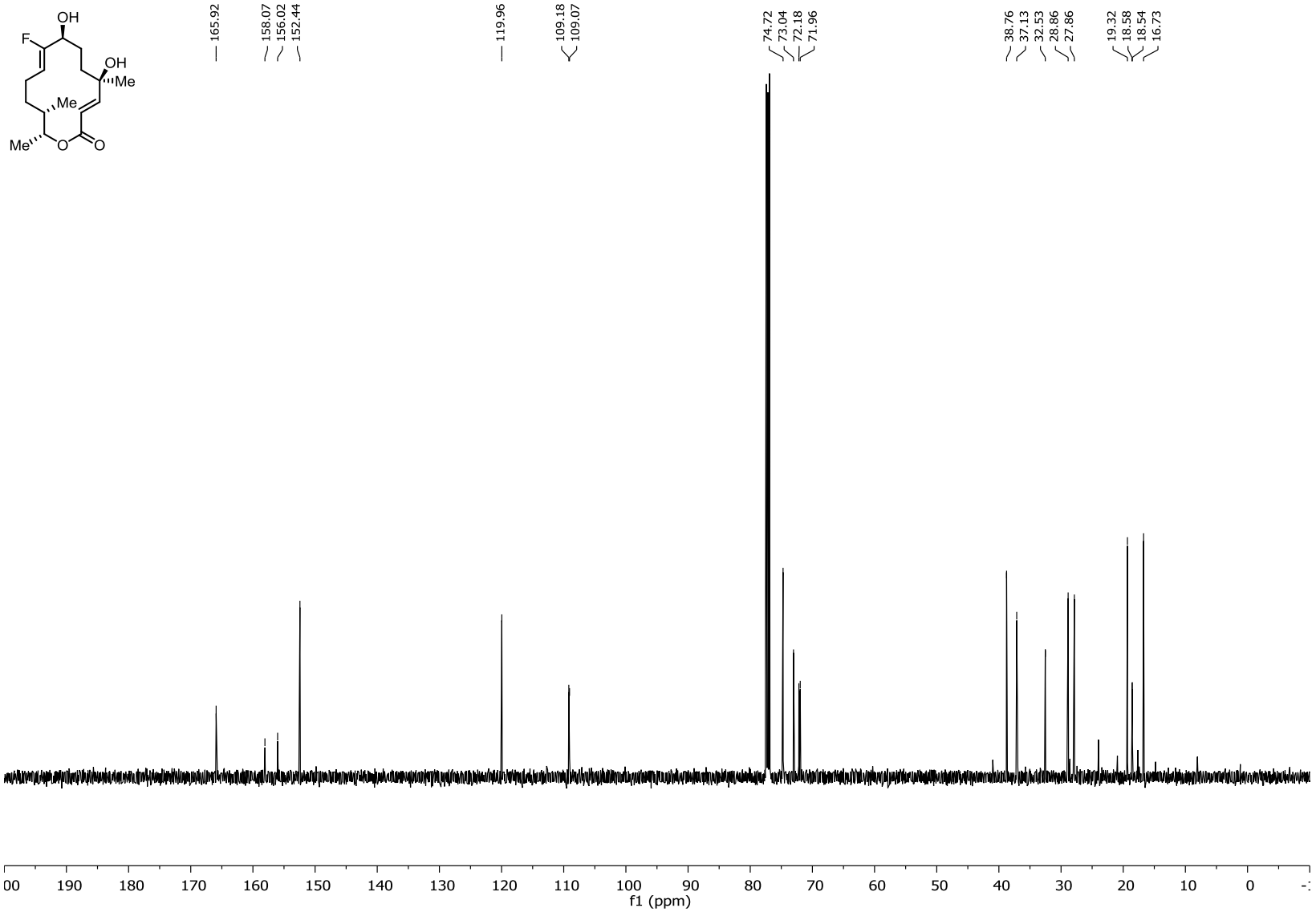
(*2R,3S,8S,11R,E*)-11-hydroxy-2,3,11-trimethyl-7,14-dioxooxacyclotetradec-12-en-8-yl acetate – (661)



(*3E,5R,8S,9Z,13S,14R*)-9-Fluoro-5,8-dihydroxy-5,13,14-trimethyloxacyclotetradeca-3,9-dien-2-one - (662)



(*3E,5R,8S,9Z,13S,14R*)-9-Fluoro-5,8-dihydroxy-5,13,14-trimethyloxacyclotetradeca-3,9-dien-2-one – (662)



9.4. Literature

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