Studies toward the synthesis of marine natural products Phormidolides B-D

Alejandro Gil Escolano

Memoria presentada por

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Studies toward the synthesis of marine natural products Phormidolides B-D.

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Do, or do not. There is no try

Yoda to Luke, *The Empire Strikes Back* (1980)

Antes de comenzar la escritura de mi tesis doctoral me gustaría escribir unas líneas para agradecer personalmente a cada persona que me ha ayudado durante este periodo de formación de cuatro años. Intentaré ir al grano.

En primer lugar me gustaría dar las gracias a los supervisores de este trabajo. ***Fernando***, gracias por confiar en mí cuando te contacté en 2013 para hacer la tesis en tu grupo. A lo largo de estos años no hemos hablado mucho de química pero siempre me he sentido respaldado por ti y has estado ahí siempre que lo he necesitado. ***Mercedes***, mi verdadera supervisora del "día a día", estoy muy agradecido de todo lo que he aprendido durante este tiempo trabajando bajo tu tutela. Creo que hemos hecho un buen equipo y hemos obtenido muy buenos resultados trabajando juntos. Sé que te habría gustado acabar este proyecto de una forma más exitosa pero creo que podemos estar orgulloso del progreso obtenido en estos cuatro años. Además, se me ocurren pocos temas y supervisoras mejores a nivel formativo para mi futuro. Un placer.

En segundo lugar querria agradecer a TODA la gente que ha pasado por el laboratorio durante este periodo de mi vida su amabilidad y simpatía conmigo. Tanto la gente que "me acogió" al principio (***Adri***, ***Janire***, ***Kamil***) como el resto de compañeros que he tenido con el paso de los años (***Juan***, ***Marta***, ***Miriam***, ***Gerardo***, ***Jesús***, ***Helena***, ***Judith***, ***Pau***, ***Iván***, ***Anais, Michael***) me habéis tratado muy bien siempre y habéis hecho que este tiempo se haya pasado "volando".

Por supuesto no me puedo olvidar de la gran cantidad de amigos (fuera del Lab) que he hecho estos cuatro años. ***Ernest***, ***Dan***, ***Craig***, ***Salva***, ***Pep***, ***Cris***, ***Juan***, ***Jordi***, ***Jürgen***, ***Ricardo***, ***Enric***, ***Martí***, ***Gemma***, ***Laura***, ***Anna*** gracias por todo chavales (y chavalas), ha sido un placer trabajar con vosotros y me lo he pasado genial en cada actividad que hemos podido hacer juntos. Mucha suerte a todos en el futuro y… keep in touch!

Obviamente también quiero dedicar esta tesis doctoral a las personas que siempre me han apoyado y han confiado en mí cuando decidí iniciar este camino: mi familia. ***Elena*** (y familia), creo que ya sabes bien todo lo que siento por ti pero esta sección de agradecimientos estaría vacía sin ti. Muchas gracias por estar ahí siempre apoyándome (incluso cuando te dejé sola para irme 4 meses a Escocia :P). Como te dije hace poco, saber que tú ibas a estar al final de la meta me ha hecho la "carrera" mucho más fácil. ***Papá***, ***mamá***, gracias por el apoyo sin fisuras que me habéis dado estos cuatro años. ***Wily***, un poco de lo mismo, siempre he sentido que estabas ahí ayudando y algún mensaje tuyo de ánimo del que aún me acuerdo ha hecho mejor cualquier momento de (posible) soledad. Los dos hemos echado de menos vivir juntos en Alicante pero espero que eso cambie pronto ;). ***Al resto de la familia*** muchas gracias por estar pendiente e interesados por mí, os he notado muy cerca desde Barcelona todo este tiempo.

Finalmente, a dos personas que eran muy importantes para mí y que nos dejaron antes de tiempo por culpa del cáncer: ***mi yaya Fina*** y ***mi tio Diego***. Esta tesis no va a curar dicha enfermedad pero creo que toda pequeña contribución con este objetivo es muy valiosa. Pensar en vosotros dos me ha motivado para intentar "construir" una molécula capaz de matar células tumorales. Espero que estéis orgullosos de mí allá donde estéis.

1D-TOCSY Monodimensional Total Correlated SpectroscopY

[α]D optical rotation

Ac acetyl

ACN Acetonitrile

aq. aqueous

Boc *tert*-butoxycarbonyl

bs broad singlet

Bu butyl

Conc. concentrated

***m*-CPBA** 3-chloroperoxybenzoic acid

Cy cyclohexyl

δ chemical shift

d doublet

DIAD diisopropylazodicarboxylate

DIBALH diisobutylaluminium hydride

DIPEA diisopropylethylamine

DMAP 4-(dimethylamino)pyridine

DMF dimethylformamide

DMP Dess-Martin periodinane

DMS dimethyl sulfide

EDC *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide

eq. equivalent

ESI electrospray ionization

Et ethyl

FDA food and drug administration

gCOSY gradient correlation spectroscopy

gHMBC gradient heteronuclear multiple bond coherence

gHSQC gradient heteronuclear single quantum coherence

HPLC high performance liquid chromatography

HRMS high resolution mass spectrometry

iBu *iso*-butyl

iPr *iso*-propyl

IR infrared

J coupling constant

LDA lithium diisopropylamide

LiHMDS lithium bis(trimethylsilyl)amide

m multiplet

M molar

Me methyl

MNPs Marine natural products

MPA methoxyphenylacetic acid

NHTK Nozaki-Hiyama-Kishi-Takai reaction

NMR nuclear magnetic resonance

nOe nuclear Overhauser effect

PM B-D Phormidolides B – D

PMB *para*-methoxybenzyl

Ph phenyl

PPTS pyridinium *p*-toluenesulfonate

pyr pyridine

q quadruplet

ROESY rotating-frame Overhauser

effect spectroscopy

RT room temperature

r.t. room temperature

s singlet

sat. saturated

t triplet

TBAF tetrabutylammonium fluoride

TBAI tetrabutylammonium iodide

tBu *tert*-butyl

TBS *tert*-butyldimethylsilyl

TBDPS *tert*-butyldiphenylsilyl

The present thesis is structured as a compendium of publications which were published in different international scientific journals. Each chapter explains a particular optimization or synthetic achievement needed to set up the conditions to confront, in the last chapter, the total synthesis of this complex family of natural products.

Firstly, **Chapter 1** describes a **General Introduction** about marine natural products (MNPs) and their importance in the current development of drug discovery programs. Different topics and problems that scientific advances are facing related with MNPs are also discussed. Then, a more specific introduction about Phormidolides B-D (PM B-D) explaining their biological relevance, structural properties and all the previous work done before this thesis is reported. Lastly, the last part of **Chapter 1** is a list with the proposed **Objectives** for this work. The following chapters will deal with each of the synthetic objectives.

Chapter 2 is focused on the second generation synthesis (SGS) of the macrocyclic core of PM B-D and it represents an important optimization in terms of yield with the previously reported. A small introduction to give a bit of background will be followed by **Publication 1** where the SGS is fully described.

Chapter 3 describes the first chemical approach to the complex (*E*)-bromo-methoxy-diene (BMD) motif present in the polyhydroxylated chain of Oscillariolide (Osc.) and Phormidolides A-D. Preparation of the C27-C31 east fragment of this family of natural products was performed using model molecules to validate the synthetic strategy. NMR comparison with natural product confirmed, by chemical synthesis, the proposed structure for this challenging moiety. All this work is reported in the **Publication 2**.

After the discovery of an efficient synthesis of the BMD fragment, **Chapter 4** describes an enantioselective synthesis of the complete C19-C31 polyol chain present in Osc. and PM A-D in the **Publication 3**.

Chapter 5 outlines the preparation of the fatty acids present in PM B-D. A brief explanation of the previous attempted methodologies followed by a complete description of the succesfull strategy is reported. These fatty acids were necessary fragments to face the total synthesis of PM B-D.

To conclude, and thanks to all the previous reported work, Chapter 6 describes the first synthetic approach to the synthesis of Phormidolides B-D using a highly convergent synthetic route. The preparation and scale-up of three complex molecules and the reactions to link them are fully described in the Publication 4.

Furthermore, an annex including a review article (Publication 5) about the important role of the Nozaki-Hiyama-Takai-Kishi in the synthesis of natural products. It gathers together all the publications that use this reaction from the year 2000 for the preparation of natural products.

Finally, the General Conclusions section organizes the main achievements after the development of the work herein presented. A list of the Contributions to the Publications is also shown to explain what parts of each article where completely done by me.

Chapter 1

Introduction and objectives

Natural products (NPs) are, usually, small molecules (below 3000 Da) produced by living biological sources such as plants, animals or microorganisms. Generally, they are secondary metabolites used for a variety of purposes like defense against predation, competition for space or food and communication between organisms.[1] NPs are often complex compounds with a well-defined spatial orientation that have evolved for thousands of years to interact with their biological target; therefore, they represent, undoubtedly, validated starting points for drug discovery programs.[2]

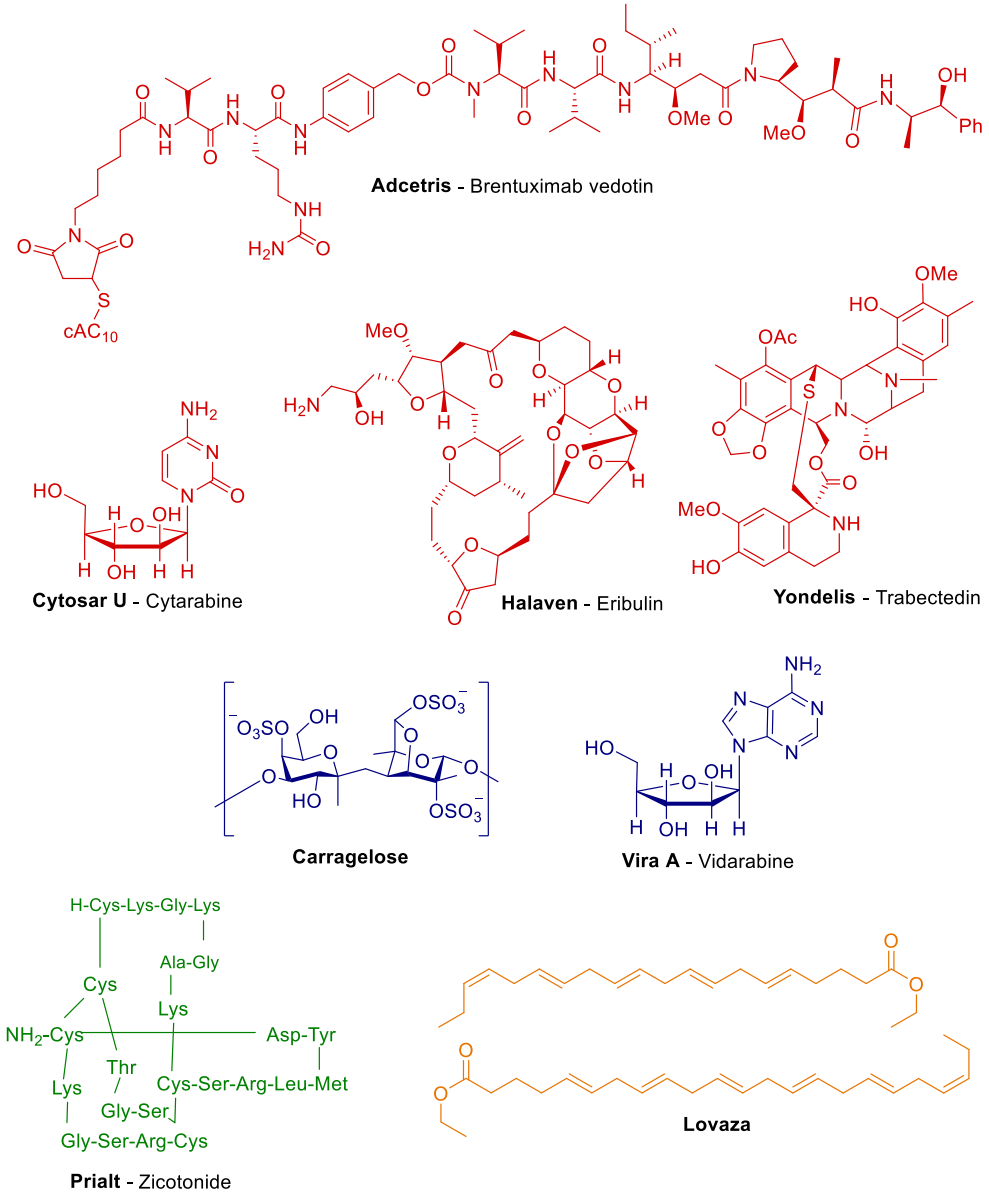


Figure 1. FDA-approved marine drugs on the market classified by their therapeutic target. **Red:** Cancer, **Blue:** Anti-viral, **Green:** Neuropathic pain, **Orange:** Hypertriglyceridemia. Adapted from Mar. Drugs. **2014**, *12*, 1066–1101.

Almost all the current NP-derived therapeutics have been isolated from terrestrial sources. However, Kong and co-workers demonstrated that, statistically, marine natural products (MNPs) are superior to terrestrial NPs in terms of chemical novelty and incidence of significant bioactivity.[3] Seventy per cent of our planet is covered by oceans, seas, lakes and rivers containing more than half of the total worldwide biodiversity.[4] Furthermore, the marine environment is characterized by unique growth conditions which generate very potent compounds that cannot be found from terrestrial sources. MNPs show mainly anti-cancer properties, but photo-protective, antibiotic, pain-killing, lipid-regulating agents and anti-infective agents can also be found.[5,6,7,8]

Cytarabine and vidarabine (Figure 1) were the two first FDA-approved marine-derived compounds as anti-cancer and anti-viral drugs, respectively. Over the past years, a large number of molecular entities have entered the pharmaceutical pipeline but have failed at different stages of the clinical trial process (See Table 1 in ref 5). However, there are currently nine different MNP-drugs that have been approved by the FDA for the treatment of different diseases (Figure 1).

As discussed above, the marine habitat is a prolific source of unique molecules and their rareness leads, sometimes, to the discovery of novel and interesting mechanisms of action or biological targets. For instance, ziconotide (Prialt, Figure 1) has a potent analgesic activity through a totally new mechanism of action. It reversibly blocks N-type calcium channels of neurons,[9,10] being the first marketed drug that interacts with this biological target and the first MNP peptide drug.[11] Surprisingly, ziconotide is 1000-times more potent than morphine and it does not cause tolerance.[12] Other interesting marketed drug that shown a novel mechanism of action during its discovery is anticancer compound trabectedin (Yondelis, Figure 1) marketed by *PharmaMar S.A*. Trabectedin binds to the minor groove of DNA causing DNA damage and inducing apoptosis in cancer cells that show higher acceleration in their gene expression compared with normal cells.[13] Finally, eribulin (Halaven, Figure 1) showed a new microtubule-targeting mechanism capable of causing tubulin aggregation, thereby blocking the growth of the cellular microtubules.[14] Continued efforts in this field will reveal more potent bioactive compounds with new and unusual mechanisms of action. Many other molecular entities are currently under development in their corresponding clinical trials. As shown in Table 1, MNP-derived drugs show a high chemical diversity and a large number of different molecular targets.

	Compound	Marine specie	Chemical class	Molecular target	Disease	Institution
Phase III	Plinabulin	Fungus	DKP	Microtubules	Cancer	BeyondSpring Pharmaceutical
	Plitidepsin	Tunicate	Depsipeptide	Rac1	Cancer	Pharmamar
	Squalamine	Dogfish Shark	Aminosterol	GF of neo-vascularization	Macular degeneration	Ohr Pharmaceutical
	Tetrodotoxin	Pufferfish	Alkaloid	Sodium channel	Chronic pain	Wex Pharmaceutical
	Glembatumumab	Mollusk	ADC	GPNMB & Microtubules	Cancer	Celldex Therapeutics
Phase II	ABT-414	Mollusk	ADC	EGFR & Microtubules	Cancer	AbbVie
	GTS-21	Worm	Alkaloid	α7 nicotinic acetylcholine	Schizophrenia Alzheimer	--
	Denintuzumab	Mollusk	ADC	CD19 & Microtubules	Cancer	Seattle Genetics
	Lurbinectedin	Tunicate	Alkaloid	RNA Pol III	Cancer	Pharmamar
	AGS-16C3F	Mollusk	ADC	ENPP3 & Microtubules	Cancer	Agensys
	Lifastuzumab	Mollusk	ADC	NaPi2b & Microtubules	Cancer	Genentech-Roche
	Pinatuzumab	Mollusk	ADC	CD22 & Microtubules	Cancer	Genentech-Roche
	Polatuzumab	Mollusk	ADC	CD79b & Microtubules	Cancer	Genentech-Roche

Table 1. Phase II/III MNP-derived drugs. Up-to-date 2017 current marine pharmacological pipeline.

MNPs are structurally rich molecular entities that are generally classified by their chemical structure. Primary metabolites are molecules directly involved in normal growth, development, and reproduction of a living system (aminoacids, sugars, nucleobases and fatty acids). Among the secondary metabolites, which are molecules not totally necessary for the development of an organism, peptides and small molecules are the first division due to their different chemical behavior and way of synthesizing them (Figure 2). When used as drugs, peptides have the advantage of being easily and automatically synthesized and present high specificity for their targets because of their many interactions with them, but this comes at a cost of low bioavailability, poor membrane permeability, and metabolic instability. On the other hand, small molecules are normally harder to synthesize but they can still retain high biological activities with improved bioavailability and plasma stability.[15]

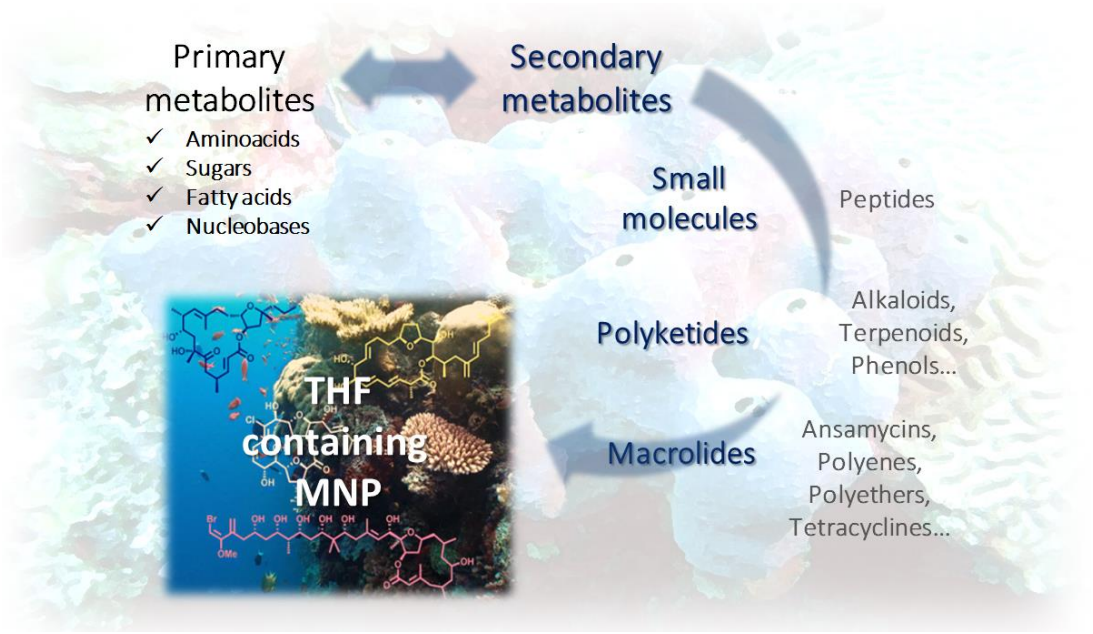


Figure 2. General metabolites classification highlighting our group of interest: THF-containing MNP.

Among the small molecules, MNPs can be classified taking into account their chemical structure. Acyclic NPs are not very common molecular structures and they are outnumbered by a vast amount of cyclic NPs. Cyclic NPs have been recently classified depending on the type of ring they bear: carbocycles, N-containing carbocycles and O-containing carbocycles.[16] As part of the O-containing carbocycles there is a family called polyketides, a structurally diverse group of highly oxygenated secondary metabolites biosynthesized by a complex collection of enzymes known as a polyketide synthases (PKS).[17] Polyketides[18], and more specifically THF-containing NP[19], represent a synthetically challenging family with many interesting biological applications.

Many years ago, the isolation of natural products focused principally on the chemistry of compounds from natural sources, performing their chemical identification before testing any of their possible biological activity. Nowadays, this process is much more "bio-assay guided", meaning that after a preliminary purification, mixtures of compounds are biologically tested and those fractions which give promising results are further purified to isolate and finally characterize the active compound.[20]

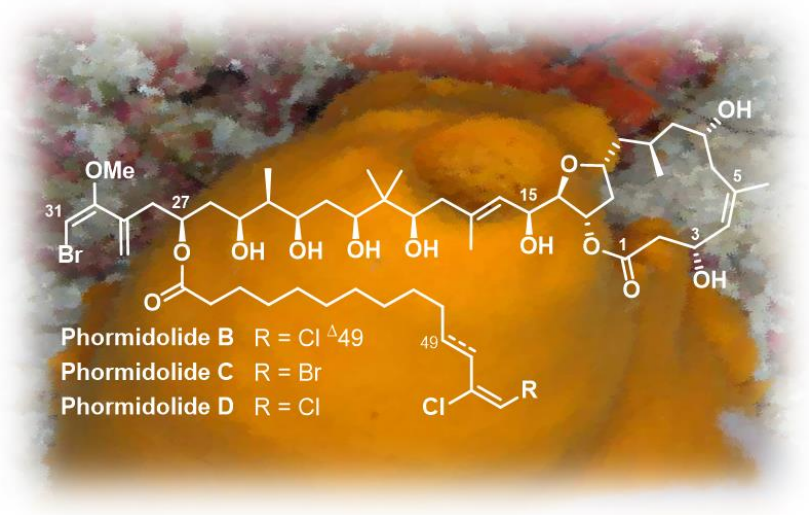
Although discovery of new drugs from marine-derived compounds is undoubtedly very promising, it faces several challenges which need to be resolved in order to improve the efficiency of the whole process. First, there is a need to improve sampling techniques to be able to collect samples from any part of oceans and lakes (not only at shallow depths). Today's

technologies have made it possible to collect samples from the sea bottom at depths greater than 2000 m, which is how Salinosporamide A was discovered.[21,22] Secondly, due to the low amount of natural product obtained after isolation there is a need for highly sensitive NMR characterization techniques that allow the NP structural elucidation even at nano or pico-mole scale.[23,24] Techniques such as atomic-resolution scanning probe microscopy (AFM) are starting to be used in structural elucidation of small molecules. This type of microscopy allows the visualization of a single molecule and it can represent a revolution in the NP characterization field in the near future.[25] Finally, fast and efficient tests for the target identification of the isolated NPs are extremely important to determine which type of illness the new molecular entity can be useful in.

Finding solutions to the "supply issue" is also one of the main challenges that this field is starting to efficiently solve. For that, fermentation (Yondelis) [26] and biotechnology techniques as well as total chemical synthesis are the currently used tools to address the "supply issue" problem. An example showing the importance of total synthesis is the case of Halaven (Figure 1) where the drug is synthesized through an optimized 62-step synthetic route. Reliable chemistry combined with drug safety and efficacy drove this MNP drug to the market.[27] This data reveals the importance of discovering new reactions, improving the ones that already exist and, in general, increase the number of synthetic tools at hand for organic chemists. This doctoral thesis is based on this last idea: finding an efficient way to synthesize a MNP potential drug to solve the "supply issue" problem associated with it: the family of Phormidolides B-D.

The synthetic target: Phormidolides B-D

Phormidolides B, C and D (PM B-D) is the family of MNPs that our group seeks to synthesize (Figure 3). These complex molecules were isolated in 2010 by the pharmaceutical company *Pharmamar S.A.* during an expedition to collect samples in the Pemba Island (Madagascar). The extracts of the *Petrosiidae* sponge shown in Figure 3 rendered a mixture of PM B-D that, once purified, were tested on an IC_{50} assay against three tumour cell lines. The results showed activity in the low micromolar range (Table in Figure 3) with a still unknown mechanism of action.



Compound	A-549	HT-29	MDA-MB-231
Phormidolide B	1.4 μM	1.3 μM	1.0 μM
Phormidolide C	1.3 μM	0.8 μM	0.5 μM
Phormidolide D	1.2 μM	0.3 μM	1.4 μM

Figure 3. Up: General structure of PM B-D. The sponge from where PM B-D was isolated is shown in the background of the molecular structure. Below: Table showing the results of the half maximal inhibitory concentration (IC50) assay for the isolated molecules.

Once the molecules showed their possible biological relevance as a cytotoxic drug a series of studies were started with the objective of determining the structure and stereochemistry of PM B-D. During the course of these studies, PM B-D were found to be structurally closely related to previously isolated MNP phormidolide A[28] and oscillariolide.[29] In

fact, all of them shared the same polyhydroxylated chain with its peculiar terminal bromo-methoxy-diene moiety (Figure 4).

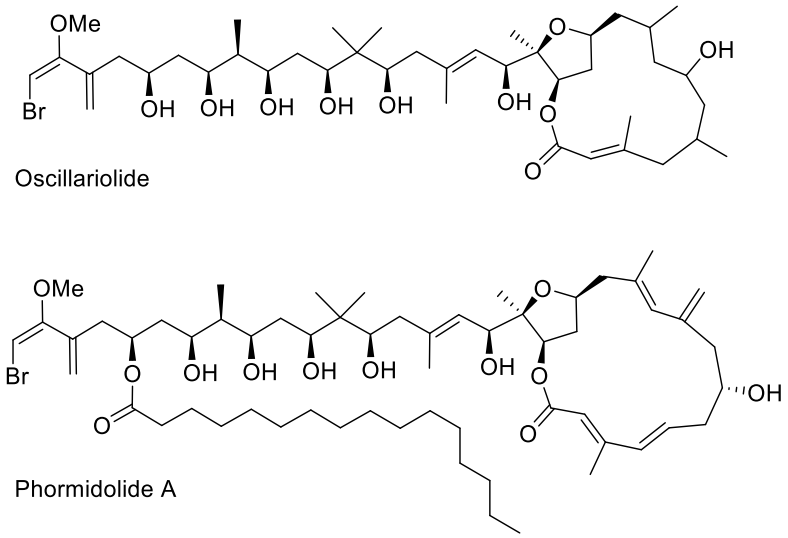


Figure 4. Molecular structures of Oscillariolide and Phormidolide A, parent compounds with Phormidolides B-D.

Connectivity of phormidolides B-D was determined on the basis of comparison of the spectra of the natural product with oscillariolide and phormidolide A and with the study of ^{1}H, ^{13}C, 1D-TOCSY, gCOSY, gHSQC, and gHMBC NMR experiments of isolated compounds.[30] Stereochemistry of the polyol chain was determined by chemical shift and coupling constant comparison with Phormidolide A confirming its identical stereochemistry. The relative stereochemistry present in the macrocyclic core was determined using ROESY combined with J-based configuration analysis and NOE experiments. From all these findings, the structural characteristics of PM B–D were as follows:

- A fourteen member THF-containing macrolactone (C1-C14 fragment) with a methylated *Z* double bond containing and extra methyl group on C9 and two hydroxyl groups on C3 and C7. The relative stereochemistry information was assigned by NMR analysis. However, the configuration of C3 and C14 remained unclear in the structure determination study.

- The polyhydroxylated chain (C15-C31 fragment) is formed by a linear 17 carbon chain substituted by four methyl groups and five free hydroxyl groups, one of them linked

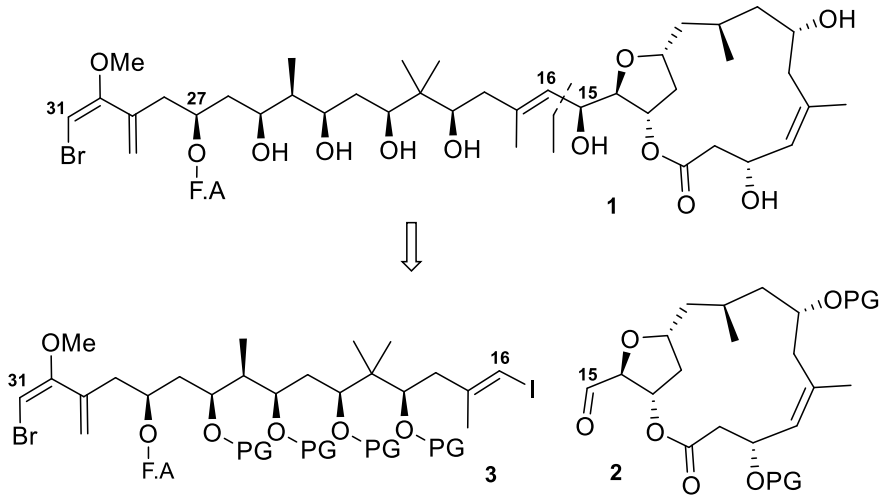
through an ester bond to a fatty acid. The (*E*)-bromo-methoxy-diene moiety is found at the end part of the chain. Beyond any doubt, this motif is the most relevant part of the chain due to its unique structure (only present in this family of MNPs) and its challenging synthesis.

- The previously mentioned fatty acids contain 14 linear carbon chains showing different degree of unsaturation and halogen substitution at their end (Figure 3). PM B bears two conjugated double bond whereas PM C and D have only a terminal olefin. The halogen substitution of PM B and D is the same, having Cl at position C51 and C52 whereas PM C has a Cl at position C51 and a Br at position C52. Stereochemistry studies have shown that the terminal double bonds present in PM B-D have *E* stereochemistry.

Background: Work performed by former PhD students

This project which aims to discern the total synthesis of Phormidolide B-D was started approximately four years before the experimental work of this thesis had started, and, thanks to the work of two former PhD students, the beginning of this doctoral thesis had previous work to rely on. This preliminary work performed by Dr. Adriana Lorente and Dr. Janire Lamariano-Merketegui, provided valuable insight for the progress of this project and, will be briefly described below.

At the beginning of the project, the retrosynthetic analysis of PM B-D was based on a single disconnection between C15-C16 as shown in Scheme 1. To confront this synthesis the first requirements were to achieve efficient syntheses of **2** and **3** and to perform model studies of the possible ways of linking them together.



Scheme 1. 1st Generation retrosynthetic analysis for Phormidolides B-D.

The work of Dr. Adriana Lorente can be summarized in the stereoselective synthesis of three different diastereomers of the macrocyclic core, compounds **4**, **5** and **6** (Figure 5).[31,32] After analysis of the NMR data from these derivatives, it was decided to adopt the macrocycle stereochemistry present in compound **4** as the most plausible one.

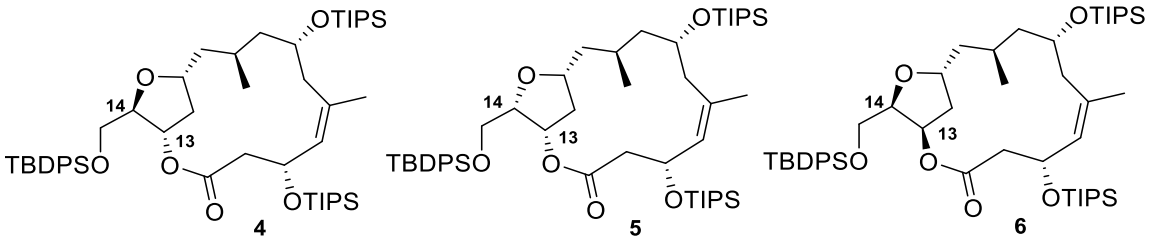
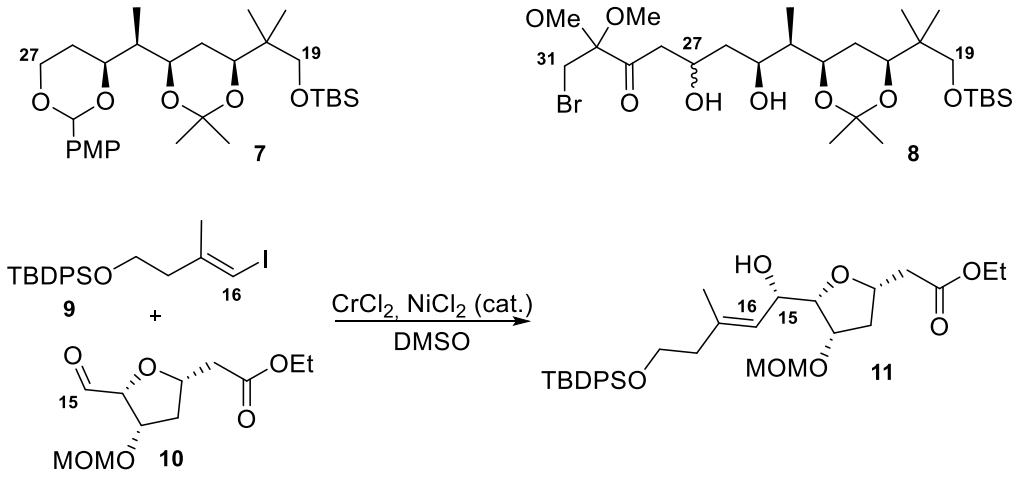


Figure 5. Diastereomers of PM B-D macrocyclic core synthesized by Dr. Adriana Lorente.

On the other hand, Dr. Janire Lamariano-Merketegui focused her work on the polyhydroxylated chain of PM B-D. A synthetic pathway for the protected C19-C27 polyol fragment **7** was found. A preliminary work in the most challenging part of the molecule, the bromo-methoxy-diene C28-C31 fragment, was also successful in achieving the synthesis of a derivative of the C19-C31 complete chain scaffold **8** (Scheme 2). Finally, Dr. Lamariano-Merketegui also explored the formation of the key C15-C16 bond using three different approaches: organolithium generation, direct carboalumination and NHTK coupling. She demonstrated that NHTK was the most robust methodology for this key union using model molecules **9** and **10**.[33]



Scheme 2. Synthetic achievements performed between 2012-2014 by Dr. Janire Lamariano-Merketegui.

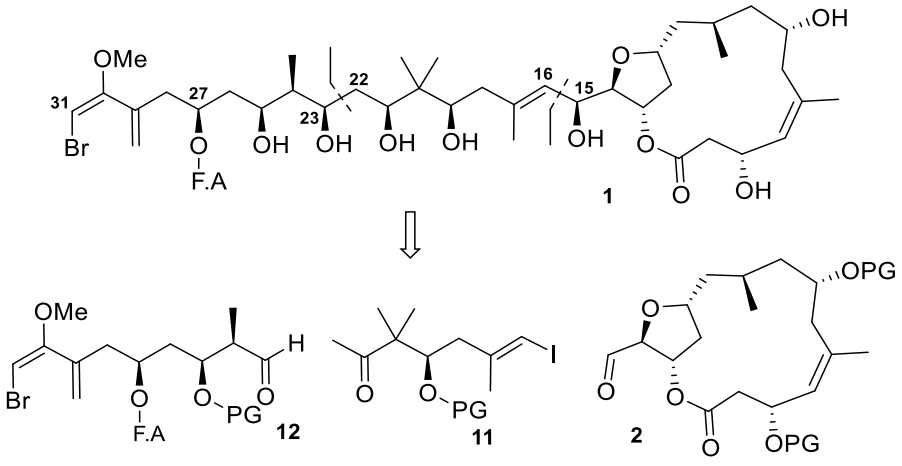
A part of the molecule that was unexplored at the beginning of this thesis was the fatty acid moiety. As it will be shown in this work, these are challenging molecules to prepare, mainly due to the lack of previously reported methodology.

Finding the right retrosynthetic analysis

With the previous results in hand and thinking in terms of the NHTK reaction for linking the macrocycle and the polyol, the previous retrosynthetic analysis (Scheme 1) was modified for the following reasons:

- A high number of linear synthetic steps for the synthesis of **3** would be required rendering, probably, a very low amount of product to perform a reaction (NHTK) that would most likely need some kind of optimization. This linearity would also decrease the overall yield of the total synthesis.
- Synthesis of **3** involved a carboalumination-iodination reaction of the corresponding C19 propargyl derivative. This reaction was shown to be incompatible with the used protecting groups, even with a simplified analogue of **3**.
- NHKT reaction between **2** and **3** might not be chemoselective due to the presence of another possible reacting position such as C31.

Due to all these disadvantages a second generation retrosynthesis was designed using two disconnection points and a central linking fragment to make the route more convergent and therefore higher-yielding. The second generation retrosynthesis adds an additional C22-C23 disconnection to generate three molecular fragments: the C1-C15 macrocyclic core **2**, the central bi-functionalized C16-C22 fragment **11**, and the C23-C31 final part of the polyol chain **12** (Scheme 3).



Scheme 3. 2nd Generation retrosynthetic analysis for Phormidolides B-D.

The union between **11** and **2** would be achieved through NHTK methodology and after that, the methyl ketone at position 22 would react with aldehyde **12** through a Mukaiyama aldol addition to generate the complete PM B-D scaffold. This new proposed retrosynthesis has some advantages compared to the one previously mentioned (Scheme 1):

- The route gains in convergence because the preparation of the C16-C31 fragment will not be too linear. Preparation of **11** and **12** and subsequent union transforms the linear synthesis of **3** into a much more convergent route.
- The central bi-functionalized fragment **11** possesses different reactivity at both their ends. This will allow its union to **2** or **12** in the order that the synthesis requires.

Therefore, the final goal of all the work carried out during this doctoral thesis will be the successful application of this methodology to construct Phormidolides B-D molecular structure.

Objectives

Upon review and understanding of the work previously carried out, the main objectives of this thesis are to achieve the total synthesis of PM B-D and to confirm their proposed structure. To accomplish this, a series of processes as listed below must be optimized first:

1. Develop a more efficient and scalable synthesis of the macrocyclic core to be able to prepare multi-gram quantities of this important part of the natural product.

2. Find out a chemical strategy for the preparation of the never-reported BMD moiety and its introduction at the end of the polyol chain.

3. Develop an enantioselective synthesis of the C19-C31 fragment of the polyol chain.

4. Find suitable strategies for the preparation of the different fatty acids.

5. Use the proposed retrosynthetic analysis to confront the **total synthesis** of Phormidolides B-D. For that, a scale-up for C1-C15, C16-C22 and C23-C31 fragments is required.

6. Finally, if possible, confirm the structural elucidation by comparing the NMR of the synthetic product with the isolated natural product.

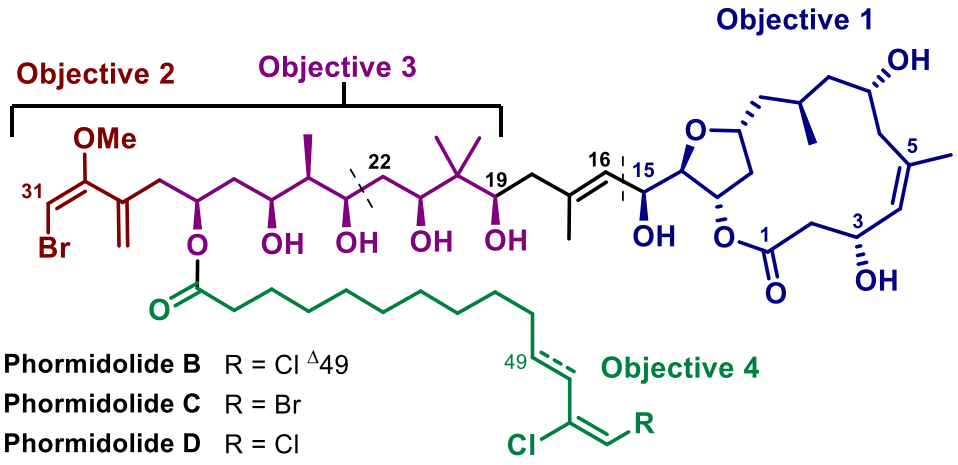


Figure 6. PM B-D showing the different partial synthetic objectives.

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Chapter 2

2nd Generation synthesis of the C1-C15 fragment

Phormidolides B-D macrocyclic core (or C1-C15 fragment) is a 14-member-THF-containing macrolactone bearing 7 stereocenters and a (*Z*)-tri-substituted double bond (Figure 1). The C1-C15 fragment represents, by itself, a synthetic challenge to deal with before facing the total synthesis of the natural product. The retrosynthetic analyses of PM B-D proposed in the group have always included a disconnection through the C15-C16 bond, therefore, an efficient, high-yielding and scalable route of the C1-C15 fragment is an important target to accomplish the total synthesis of these compounds. To that end, Dr. Adriana Lorente reported in her PhD thesis the first enantioselective synthesis of the protected west fragment of PM B-D.[1] That synthetic route provided the preparation of three different diastereomers of the macrocyclic core and a proposal of the previously unknown configuration at positions C3 and C14 based on NMR comparison with the natural product.[2] All this information was of great value for the project and it was used as a reference for all the posterior studies and hence, the *3R*, *14R* stereochemistry will be used from now onwards.

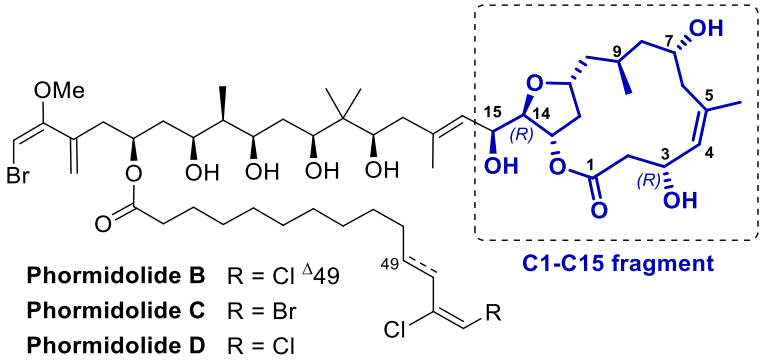
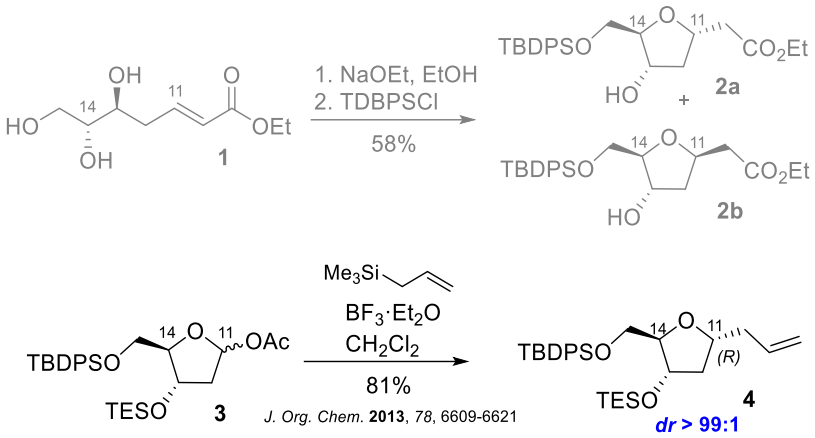


Figure 1. General structure of PM B-D highlighting the synthetic target of this chapter.

However, as is always the case when working in organic synthesis, the first generation synthetic route (FGS) had the possibility of being optimized to make it more convergent and therefore high-yielding, creating the second generation synthesis (SGS). All the ideas and points for improvement are listed and commented below:

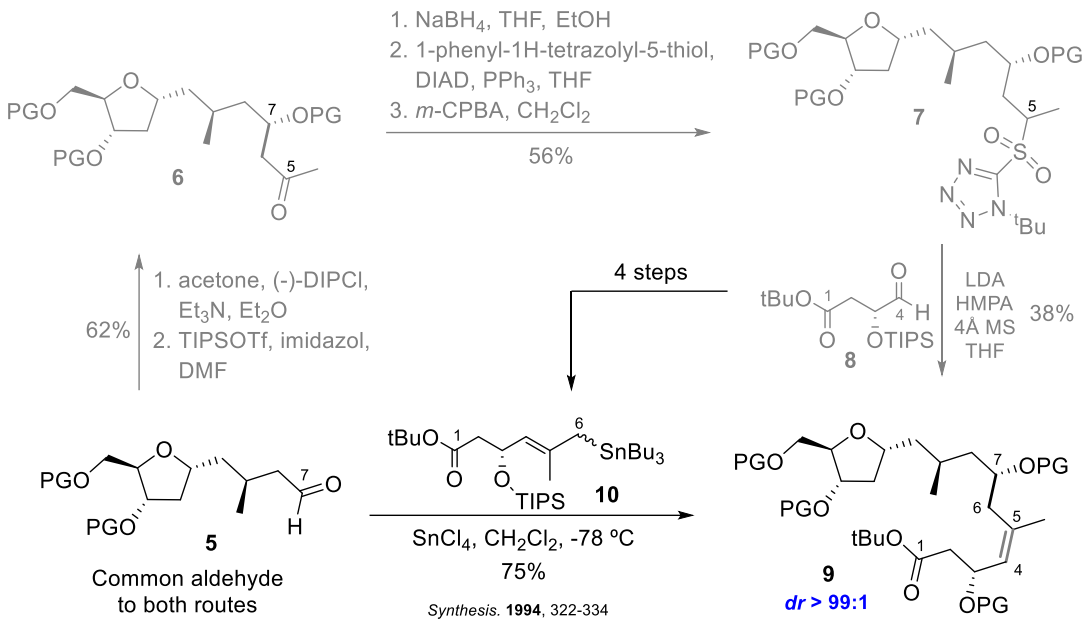
- The formation of the THF core in the FGS was achieved through an oxa-Michael cyclization of α-β unsaturated ester **1** to render a mixture (60:40) of epimers at C11.[3] After TBDPS protection (Scheme 1), a big-scale column chromatography to separate very close TLC spots had to be performed and 40% of the product was not used because of its wrong stereochemistry at C11 (**2b**). To overcome this situation, the application of a reported enantioselective methodology[4] to our substrate **3** gave

excellent results allowing us to isolate enantiopure alkene **4** in 81% yield and great stereocontrol towards the desired (*R*)-C11 epimer.



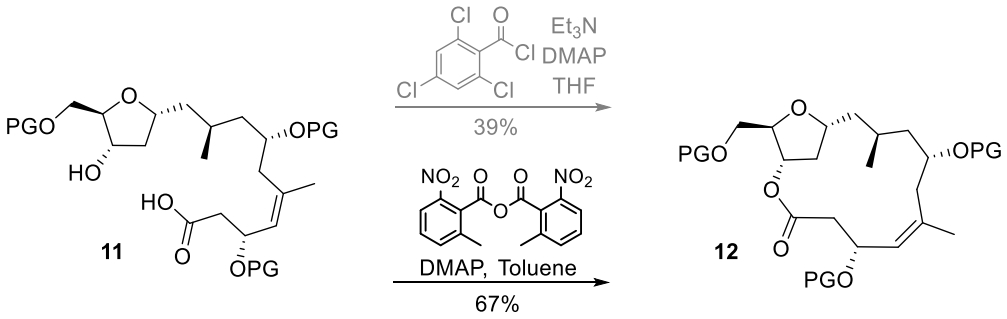
Scheme 1. Differences between the THF core formation between the FGS and the SGS.

- The most important change carried out in the present work was the synthetic disconnection strategy to afford **9**, the protected scaffold of the C1-C15 fragment (Scheme 2). The macrocycle construction in the FGS was conducted through a linear sequence with some low-yield steps including a stereoselective aldol addition of acetone to aldehyde **5**, four protection and functional group conversions to obtain the sulfone **7** and final Julia-Kocienski olefination[5] with aldehyde **8** to give **(*Z*)-9** with the correct stereochemistry (Scheme 2, grey pathway).[6] To reduce linearity and therefore increase the overall yield, a much more convergent route was designed where the whole carbon scaffold would be formed in a single step using the stereoselective addition of allylstannane **10** to the common aldehyde **5.** The methodology described by Thomas et al. about stereo-controlled reactions of alkoxy- and hydroxy-substituted allylstannanes with less functionalized aldehydes was used.[7,8]



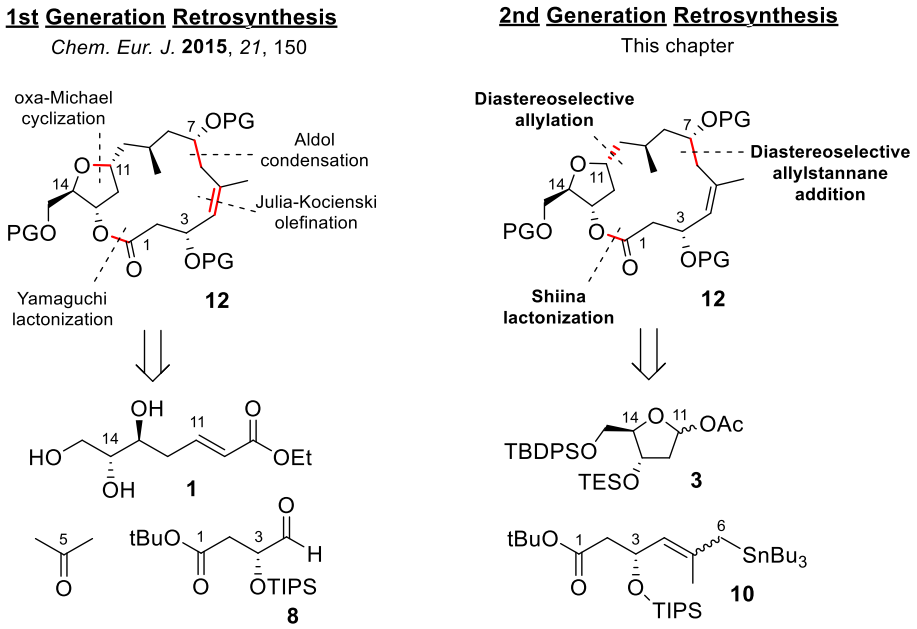
Scheme 2. Comparison between the linear FGS and the designed **convergent approach** to construct the linear C1-C15 carbon scaffold **9**.

- Finally, a change in the cyclization conditions was also introduced (Scheme 3). In the FGS, the cyclization was performed using Yamaguchi conditions[9] with a 39% reaction yield for such macro-cyclization of **11**. To overcome this, Shiina methodology[10] was proposed to try to increase the yield of the protected macrocyclic core resulting in a 1.7-fold increase for this key final step. Furthermore, the new conditions allowed to perform cyclization up to 1.4 mM (considerably higher than using Yamaguchi methodology), thus reducing the amount of anhydrous solvent used in scale up of the synthetic route.



Scheme 3. Yield enhancement caused by a change in the macrolactonization methodology.

To summarize, Scheme 5 shows the different retrosynthetic approaches used in the group for the synthesis of the macrocyclic core of PM B-D. It is easy to note that the second generation retrosynthesis divides the THF-macrolactone through fewer and more effective disconnections, thereby obtaining a more convergent and higher yield synthetic route. The great enhancement of the overall yield for the synthesis of the C1-C15 fragment (10-fold) allowed the synthesis of the macrocyclic core in a multi-gram scale. This fact was of vital importance for the success of the total synthesis project.



Scheme 4. Two different retrosynthetic approaches used in the group for the synthesis of C1-C15 macrocyclic core of PM B-D.

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Stereoselective Allylstannane Addition for a Convergent Synthesis of a Complex Molecule

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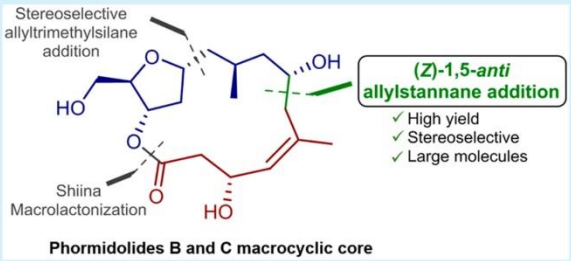
Supporting Information

ABSTRACT: A convergent methodology with 13 lineal steps for the synthesis of phormidolides B and C macrocyclic core is described. Stereoselective formation of the tetrahydrofuran (THF) core was achieved using a stereocontrolled allylation reaction. The key step of the synthesis is a (*Z*)-1,5-*anti* stereoselective allylstannane addition where a new stereocenter and a trisubstituted double bond are formed simultaneously. Finally, Shiina macrolactonization conditions improved the yield of the final cyclization.



Marine natural products have become an important source of drugs for the treatment of different illnesses.[1] Several natural products and their simplified analogs have been approved as drugs for the treatment of various diseases.[2] In particular, compounds with a macrolide motif in their structure are ideal drug candidates because of their interesting biological activities.[3] In this field, phormidolides B and C were isolated from *Petrosiidae* sponge in the coasts of Tanzania.[4] They are cytotoxic in three tumor cell lines in the micromolar range (HT-29, A-549, and MDA-MB-231) with an unknown mechanism of action.

Phormidolides are interesting synthetic targets because of their structural complexity (Figure 1). Their structure can be

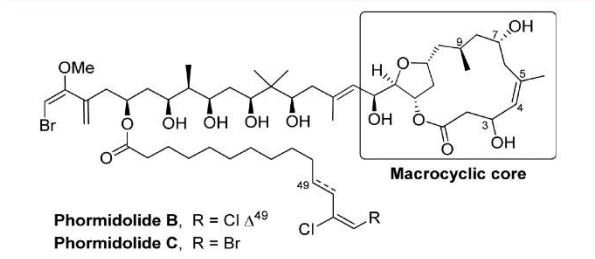


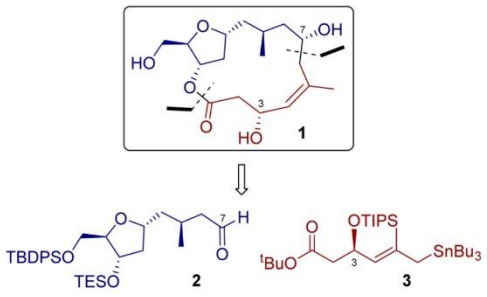
Figure 1. Structures of phormidolides B and C.

divided into three smaller fragments to confront their total synthesis: fatty acids, polyhydroxylated chain, and macrolide ring. A suitable strategy to synthesize these fragments separately is vital to complete their total synthesis and confirm all the stereochemical information. Herein, an improved synthetic approach to the synthesis of the macrocyclic core **1** is described.

The retrosynthetical analysis of **1** is based on a more convergent approach than the previously described by our group.[4] After only two disconnections molecular fragments **2** and **3** were obtained which could be easily synthesized in a few synthetic steps. The formation of the C6−C7 bond was envisioned through a stereoselective allylstannane addition to the aldehyde **2**. The end game of the synthesis will be based on the macrolactonization under Shiina conditions and further removal of the protecting groups (Scheme 1).

The synthesis of aldehyde **2** (Scheme 2) starts with commercially available 2-D-deoxyribose. Oxidation at the anomeric position with bromine followed by chemoselective sequential protection afforded lactone **5**. Then lactone **5** was transformed into acetyl acetal **6** as a 6:4 mixture of epimers. The addition of allyltrimethylsilane promoted by $BF_3{\cdot}OEt_2$ to

Scheme 1. Retrosynthesis of Phormidolides Macrocyclic Core



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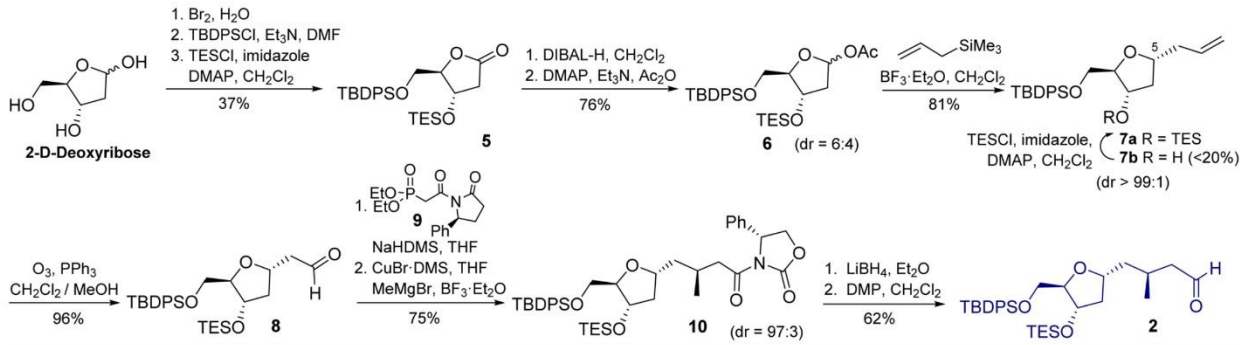
Scheme 2. Synthesis of Aldehyde 2



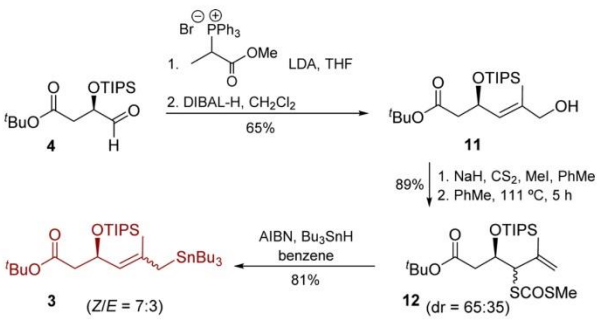
acetylated compound **6**, using the Tran et al. method,[5] gave only the desired 5*R* diastereomer **7a** and its deprotected version **7b**. Alcohol **7b** can be protected in the crude mixture and then purified to obtain **7a** with an 81% yield and excellent diastereoselectivity.[6] One of the advantages of this new synthesis is the diastereoselective formation of the C−C bond in position 5 to furnish the pure enantiomer **7**. This methodology addresses a significant weakness in the previous synthetic route: the unselective installation of the alkyl substituent onto the tetrahydrofuran portion of the core structure.[4]

In order to elongate the chain, allyl derivative **7a** was subjected to an ozonolysis to reach aldehyde **8**. Chiral phosphonate **9**[7,8] was needed at this point to introduce the methyl group by means of a diastereoselective 1,4 addition to afford compound **10** in good yield. Removal of the chiral auxiliary and oxidation with Dess-Martin periodinane (DMP)[9] gave aldehyde **2** in 10 steps with easily scalable procedures.

The synthesis of compound **3** started from previously reported aldehyde **4**.[4] Wittig olefination with (1-methoxycarbonylethyl)triphenylphosphonium bromide[10] and further methyl ester reduction gave alcohol **11** in good yield. Formation of the corresponding xanthate and 3,3-sigmatropic thermal rearrangement furnished compound **12** as an epimeric mixture. Reaction with Bu_3SnH under free radical conditions produced allylstannane **3** as a *Z*/*E* mixture of isomers (7:3 ratio) (Scheme 3).[11] This isomeric mixture was used without separation in the synthetic step described below.

With fragments **2** and **3** in hand, the most important reaction in the synthesis was performed successfully following the procedure described by Thomas et al.[12] The allylstannane addition of **3** to aldehyde **2** resulted not only with a high yield but also with the desired stereoselectivity. In one reaction, a new stereocenter and a trisubstituted double bond were created with complete selectivity for the desired (*Z*)-1,5-*anti* product **13**.[13−15]

Scheme 3. Synthesis of Allylstannane 3



The explanation for this high stereoselectivity is consistent with the mechanism of the reaction depicted in Scheme 4. As reported previously,[11] the stereocenter present in **3** controls the facial selectivity of the transmetalation to give the allyltin trichloride **A** where the prop-1-en-2-yl and OTIPS groups were in a trans relationship on the six-membered oxastannic ring. It is worthy to mention that these kinds of six-membered oxastannic rings have been widely reported[11,16,17] using 6-hydroxystannanes and 6-alkoxystannanes but never using the oxygen of a more oxidated function such as an ester. When aldehyde **2** was added to the reacting mixture it approached this chelated structure to form a new chairlike six-membered transition structure **B** where the group next to tin adopts the preferred axial position to avoid steric hindrance with the apical chloride on the tin. This fact and the preference of the R group of the aldehyde to adopt the equatorial position explain the remote stereocontrol of this reaction to obtain the desired (3*R*,7*S*,*Z*) diastereomer **13**. To the best of our knowledge this has been the first (*Z*)-1,5-*anti* allylstannane stereoselective addition to create a methylated trisubstituted double bond. Furthermore, this addition with multifunctionalized big building blocks such as **2** and **3** shows the utility and robustness of this methodology for the synthesis of natural products.

In the final stage of the synthesis, compound **13** had to be converted to the corresponding seco-acid **14** to perform cyclization. Standard basic conditions were used to protect the homoallylic hydroxyl with TBS. After quantitative conversion, TMSOTf was added to deprotect the *tert*-butyl ester. Then, aqueous workup was necessary and the reaction crude was treated with pyridinium *p*-toluenesulfonate (PPTS) in MeOH obtaining hydroxy-acid **14** in 72% yield for this 2 stage-3 chemical transformation procedure with only one purification (Scheme 5). Following Shiina's methodology,[18] slow addition of **14** to a solution containing 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-dimethylaminopyridine (DMAP) cleanly afforded macrocycle **15** in 67% yield without formation of dimeric or trimeric species. In our previously described synthesis, Yamaguchi's lactonization conditions afforded the protected macrocycle in 39% yield due to the formation of polymeric species.[4]

Macrocycle **15** was transformed into aldehyde **16** by selective deprotection, followed by oxidation. This aldehyde is an essential fragment for the total synthesis of phormidolides B and C using previously studied methodology.[19] In addition,

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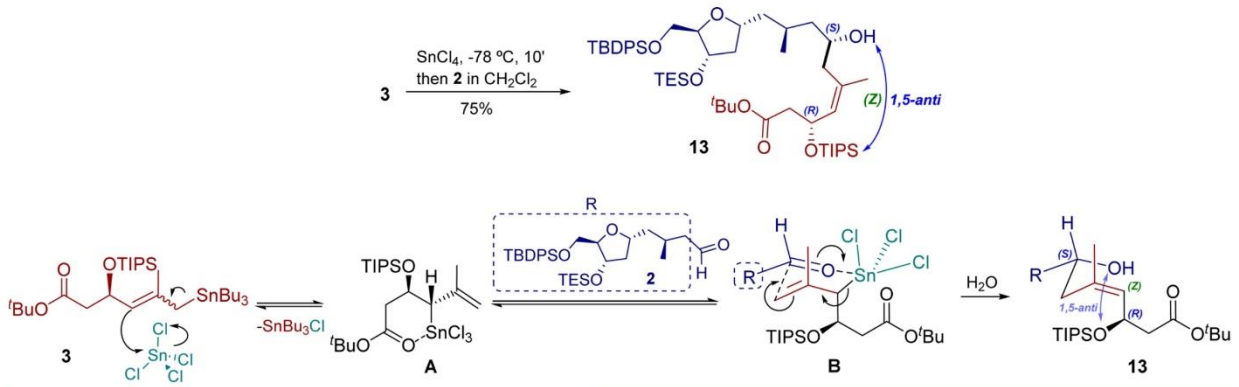
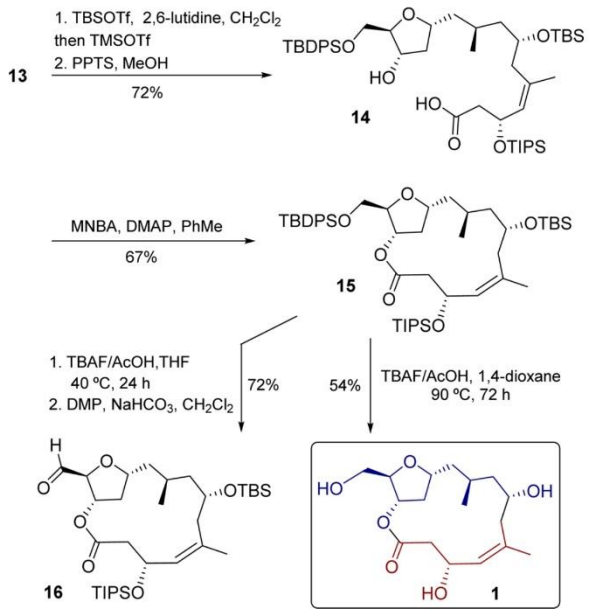
Scheme 4. (*Z*)-1,5-*anti* Allylstannane Addition: Mechanistic Explanation of Its Excellent Stereoselectivity



Scheme 5. Cyclization and Deprotecting Procedures To Obtain 16 or the Desired Macrolide 1



total deprotection gave macrocycle **1** to perform spectral characterization to compare with the natural product and biological tests (IC_{50} tests).[20] Key aspects to control the deprotection included solvent, temperature, and reaction time. An excess of a buffered solution of TBAF/AcOH in THF at 40 °C during 24 h produced selective monodeprotection of **15**. At this temperature di- and trideprotected species were not detected. The obtained alcohol was oxidized with DMP to give aldehyde **16** with high yield. On the other hand, **1** can be obtained by raising the temperature in 1,4-dioxane to 90 °C with a longer reaction time in moderate yield.

In summary, this paper describes a convergent methodology to synthesize **15**, the protected macrocyclic core of phormidolides B and C, with an important improvement in the total yield relative to our previous methodology. The number of linear steps has been reduced from 17 to 13, and the overall yield has been increased 10 times. Three factors contributed to this increase in the overall yield. First, the diastereoselective formation of **7a** by addition of allyltrimethylsilane to the THF core avoided diastereomer separation at the beginning of the synthesis at a multigram scale. Furthermore, this procedure does not produce the nondesired diastereomer that has to be eliminated. Second, the stereoselective link of the two big molecular fragments by the Thomas et al. methodology[12] gave excellent synthetic results in terms of yield and desired stereoselectivity. (*Z*)-1,5-*anti* remote stereocontrol has been achieved through a six-membered oxastannic ring where the coordinating oxygen atom belongs to an ester functionality. This fact broadens the scope for this type of remote stereocontrolled addition with 6-alkyloxycarbonylstannanes. The mild conditions used to perform this reaction and the synthesis of a complex allylstannane opens the possibility to use this methodology in the late stages of a synthesis to link large polyfunctionalized molecular entities with complete stereocontrol.

Finally, the Shiina methodology for macrolactonization instead of Yamaguchi's conditions led to an increase of the yield from 39% to 67% for this important transformation. All of these changes have allowed us to isolate and characterize aldehyde **16** and triol **1**. NMR chemical shifts of macrocycle **1** are in accordance with the described phormidolides B and C. The small differences in chemical shift are caused by the presence of the polyhydroxylated chain in the natural products. Moreover, the lack of this chain would explain the inactivity of macrolide **1**. Further studies to link the polyhydroxylated chain to the macrolactone are under development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03252.

Experimental procedures and characterization of the described compounds (PDF)

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The authors declare no competing financial interest.

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(13) The stereochemistry of the new stereocenter was determined using Mosher's derivatization (see Supporting Information).
(14) The configuration of the double bond was confirmed based on the ^{13}C chemical shift of the olefinic methyl group. Previous published work confirms that if this chemical shift is above 20 ppm the configuration is Z (see ref 15).
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(20) Compound **1** was inactive. It was tested in HT-29, A-549, and MDA-MB-231 cell lines under the same conditions as natural compounds (see ref 4).

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Supporting Information

Stereoselective allylstannane addition for a convergent synthesis of a complex molecule

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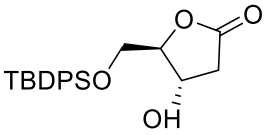
General Procedures.

Tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were dried using a PureSolv solvent purification system. All other solvents and reagents were used as purchased without further purification, unless indicated. Flash column chromatography was performed on SDS silica gel (60A 35-70 μm) as stationary phase. Analytical TLC was done on pre-coated silica gel 60 F_{254} plates (0.2 mm thick, 20x20 cm) and visualized under UV light (254 and 360 nm), with anisaldehyde in conc. H_2SO_4 or with phosphomolybdic acid in ethanol.. Polarimetry studies were performed on a Perkin-Elmer 241 or JascoP-2000 polarimeter equipped with a Na-lamp. IR spectra were recorded on a Thermo Nicolet FT-IR Nexus spectrometer. ^{1}H-NMR and ^{13}C-NMR were recorded on a Varian Mercury 400MHz or a Varian VNMRS500 500MHz. Chemical shifts are reported in ppm referenced to the residual solvent peaks ($CDCl_3$) and coupling constants are reported in Hz. Multiplicity of the carbons was assigned with gHSQC experiments. Standard abbreviations for off-resonance decoupling were employed: s = singlet, d = doublet, t = triplet, q = quadruplet. The same abbreviations were also used for the multiplicity of signals in ^{1}H-NMR, as well as, bs = broad singlet, bd = broad doublet, m = multiplet. High Resolution Mass Spectroscopy (HRMS) was performed an Agilent LC/MSD-TOF 2006 using ESI-MS technique.

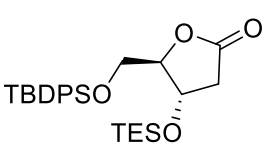
Experimental procedures and characterization

(*4S*,*5R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-hydroxydihydrofuran-2(3*H*)-one (S1)



TBDPSCl (9.7 mL, 37.5 mmol.) was added to a solution of 2-D-deoxyribose (4.5 g, 34 mmol) and imidazole (6.4 g, 95 mmol) in DMF (150 mL). The reaction mixture was stirred at r.t. for 16 h. After this time DMF was evaporated, the mixture was washed with water, extracted with EtOAc, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-acetone (30:70) yielded **S1** (5.1 g, 40%) as a colorless oil. ^{1}H NMR data were in agreement with that reported in the literature.

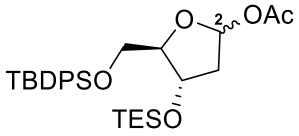
(*4S*,*5R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy)dihydrofuran-2(3*H*)-one (5)



TESCl (1 mL, 5.9 mmol.) was added to a solution of alcohol **S1** (2 g, 5.4 mmol) and imidazole (735 mg, 10.8 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred at r.t. for 45 minutes. After this time, the mixture was washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded **5** (2.41 g, 92%) as a colorless oil. $[\alpha]_D$ = +19.1 (c 1.0, $CHCl_3$). IR (KBr film) ν 2956, 2876, 1788, 1471, 1427, 1113, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (q, *J* = 7.9 Hz, 6H), 0.93 (t, *J* = 7.9 Hz, 9H), 1.05 (s, 9H), 2.43 (dd, *J* = 17.7, 2.6 Hz, 1H), 2.89 (dd, *J* = 17.7, 6.7 Hz, 1H), 3.74 (dd, *J* = 11.6, 2.6 Hz, 1H), 3.84 (dd, *J* = 11.6, 3.3 Hz, 1H), 4.35 (dt, *J* = 3.3, 2.6 Hz, 1H), 4.49 – 4.55 (m, 1H), 7.37 – 7.49

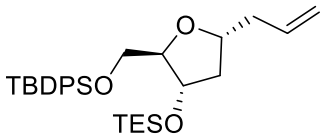
(m, 6H), 7.62 – 7.66 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.6 (t), 6.6 (q), 19.1 (s) , 26.8 (q), 39.1 (t), 63.2 (t), 69.4 (d), 88.1 (d), 127.9 (d), 130.0 (d), 132.1 (s) , 132.7 (s) , 135.5 (d), 135.6 (d), 175.7 (s).HRMS (+ESI): *m/z* calcd. for $C_{27}H_{40}O_4KSi_2$ (M+K) 523.2097, found 523.2103.

(*2RS,4S,5R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy)tetrahydro furan-2-yl acetate (6)



DIBAL 1M in toluene (10.9 mL, 10.9 mmol.) was added to a solution of lactone **5** (2.4 g, 4.95 mmol) in CH_2Cl_2 (50 mL) at -78ºC. The reaction mixture was stirred at this temperature for 60 minutes. After this time, a DMAP (610 mg, 4.95 mmol.) solution in CH_2Cl_2 (8 mL), Et_3N (2 mL, 14 mmol) and Ac_2O (2.4 mL, 25 mmol) were added sequentially. The solution colour changes from colorless to orange. The mixture was warmed to 0 ºC and quenched with sodium potassium tartrate (20 mL) and ammonium chloride (20 mL) saturated solutions. The mixture was extracted three times with CH_2Cl_2 and the organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) and 1% of Et_3N yielded **6** (2 g, 76%) as a 6(A):4(B) epimeric mixture in C2. IR (KBr film) ν 3071, 2956, 2876, 1750, 1471, 1427, 1234, 1112, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 – 0.64 (m, $6H_A$+$6H_B$), 0.90 – 0.99 (m, $9H_A$+$9H_B$), 1.05 (s, $9H_A$), 1.07 (s, $9H_B$), 1.89 (s, $3H_B$), 2.01 (m, $1H_A$), 2.06 (s, $3H_B$), 2.17 – 2.23 (m, $2H_B$), 2.35 – 2.44 (m, $1H_A$), 3.67 – 3.78 (m, $2H_A$+$2H_B$), 3.94 – 3.99 (m, $1H_B$), 4.19 (q, *J* = 3.5 Hz, $1H_A$), 4.46 (dt, *J* = 6.8, 2.6 Hz, $1H_B$), 4.60 (td, *J* = 6.3, 4.7 Hz, $1H_A$), 6.31 (dd, *J* = 5.6, 1.2 Hz, $1H_A$), 6.34 (dd, *J* = 4.7, 3.3 Hz, $1H_B$), 7.34 – 7.46 (m, $6H_A$+$6H_B$), 7.62 – 7.72 (m, $4H_A$+$4H_B$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.7 (t), 4.7 (t), 6.7 (q), 19.2 (s), 19.3 (s), 21.2 (q), 21.4 (q), 26.8 (q), 41.2 (t), 41.7 (t), 63.2 (t), 63.5 (t), 70.4 (d), 71.4 (d), 87.7 (d), 88.7 (d), 98.1 (d), 99.3 (d), 127.7 (d), 127.7 (d), 127.7 (d), 129.7 (d), 129.7 (d), 129.7 (d), 133.0 (s), 133.3 (s), 135.5 (d), 135.6 (d), 135.6 (d), 135.6 (d), 170.4 (s), 170.7 (s). HRMS (+ESI): *m/z* calcd. for $C_{29}H_{48}O_5NSi_2$ (M+NH_4) 546.3066, found 546.3066.

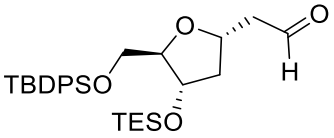
(((*2R,3S,5R*)-5-Allyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(triethylsilyl)oxy) tetrahydrofuran (7a)



Allyltrimethylsilane (2.1 mL, 13.2 mmol) and $BF_3{\cdot}Et_2O$ (0.9 mL, 7.3 mmol) were added sequentially and slowly to a solution of acetal acetate **6** (3.5 g, 6.65 mmol) in CH_2Cl_2 (80 mL) at -78 ºC. The reaction mixture was stirred at this temperature for 5 minutes and then at room temperature for 30 minutes. After this time, the reaction was quenched at -78 ºC with the addition of a mixture of CH_2Cl_2 (15 mL):MeOH (15 mL):Et_3N (15 mL). The mixture was warmed to room temperature and extracted with CH_2Cl_2. The reaction crude was dried over Na_2SO_4. The crude was dissolved in 25 mL of CH_2Cl_2 and TESCl (0.25 mL, 1.5 mmol), imidazole (204 mg, 3 mmol) and DMAP (12 mg, 0.1 mmol) were added to reprotect **7b**. The reaction was stirred for 15 minutes. After this time, the mixture was

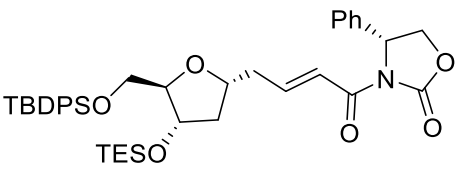
washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **7a** (2.74 g, 81%) as a single diasteromer colorless oil. $[\alpha]_D$ = +19.6 (c 1.0, $CHCl_3$). IR (KBr film) ν 3071, 2956, 2876, 1471, 1427, 1112, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.9 Hz, 6H), 0.94 (t, *J* = 7.9 Hz, 9H), 1.06 (s, 9H), 1.68 (ddd, *J* = 12.6, 7.0, 5.3 Hz, 1H), 2.20 (dt, *J* = 12.6, 6.5 Hz, 1H), 2.28 – 2.38 (m, 1H), 2.47 (ddt, *J* = 13.6, 6.5, 1.4 Hz, 1H), 3.66 (d, *J* = 4.1 Hz, 2H), 3.92 (q, *J* = 4.1 Hz, 1H), 4.09 – 4.18 (m, 1H), 4.50 (ddd, *J* = 6.5, 5.3, 3.9 Hz, 1H), 5.01 – 5.14 (m, 2H), 5.76 – 5.90 (m, 1H), 7.34 – 7.46 (m, 6H), 7.66 – 7.73 (m, 4H).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.7 (q), 6.8 (t), 19.2 (s) , 26.8 (q), 40.5 (t), 40.8 (t), 64.2 (t), 73.0 (d), 78.2 (d), 86.2 (d), 116.6 (t), 127.6 (d), 127.6 (d), 129.6 (d), 129.6 (d), 133.4 (s), 133.5 (s), 135.3 (d), 135.6 (d), 135.7 (d). HRMS (+ESI): *m/z* calcd. for $C_{30}H_{50}O_3NSi_2$ (M+NH4) 528.3324, found 528.3322.

2-((*2S,4S,5R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)acetaldehyde (8)



Ozone was bubbled through a solution of **7a** (2.74 g, 5.37 mmol) in of CH_2Cl_2 (80 mL) and of MeOH (20 mL) at -78 ºC until the solution became intense blue. Then PPh_3 (1.83 g, 7 mmol) was added and the reaction was stirred for 2 h at room temperature. The mixture was evaporated and purified by silica gel column chromatography with hexane-EtOAc (95:5) to yield **8** (2.64 g, 96%) as a colorless oil. $[\alpha]_D$ = +19.6 (c 1.0, $CHCl_3$). IR (KBr film) ν 3071, 2956, 2876, 1471, 1427, 1112, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.9 Hz, 6H), 0.94 (t, *J* = 7.9 Hz, 9H), 1.06 (s, 9H), 1.69 (ddd, *J* = 12.8, 5.4, 4.0 Hz, 1H), 2.35 (ddd, *J* = 12.8, 7.6, 6.1 Hz, 1H), 2.66 (ddd, *J* = 16.6, 5.4, 2.0 Hz, 1H), 2.89 (ddd, *J* = 16.6, 7.6, 2.0 Hz, 1H), 3.57 – 3.69 (m, 2H), 3.97 (dt, *J* = 4.8, 3.4 Hz, 1H), 4.50 (ddd, *J* = 6.1, 4.0, 3.4 Hz, 1H), 4.58 (tt, *J* = 7.6, 5.4 Hz, 1H), 7.35 – 7.46 (m, 6H), 7.63 – 7.71 (m, 4H), 9.81 (t, *J* = 2.0 Hz, 1H).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.7 (t), 6.7 (q), 19.2 (s), 26.8 (q), 40.8 (t), 50.5 (t), 64.2 (t), 73.2 (d), 73.9 (d), 86.9 (d), 127.7 (d), 127.7 (d), 129.7 (d), 129.7 (d), 133.2 (s), 133.3 (s), 135.6 (d), 135.6 (d), 201.6 (d). HRMS (+ESI): *m/z* calcd. for $C_{29}H_{44}NaO_4Si_2$ (M+Na) 535.267, found 535.2676.

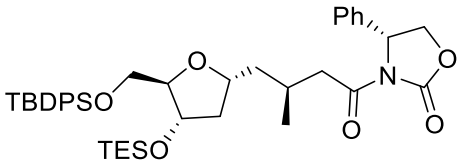
(*R*)-3-((*E*)-4-((*2R,4S,5R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)but-2-enoyl)-4-phenyloxazolidin-2-one (S2).



A 1 M solution of NaHMDS in THF (7.1 mL, 7.1 mmol) was added to a solution of phosphonate **9** (3.6 g, 10.6 mmol) in THF (70 mL). After 10 min, a solution of aldehyde **8** (2.96 g, 5.7 mmol) in THF (15 mL) was added dropwise, and the mixture was stirred at r.t. for 90 minutes. After this time, KH_2PO_4·NaOH pH =7 buffer was added and the solvent was removed under reduced pressure. The residue was disolved in water and

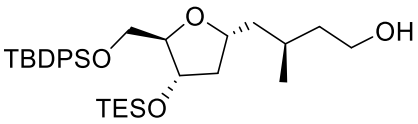
extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10 to 80:20) yielded **S2** (3.26 g, 82%) as a colorless foam. $[\alpha]_D$ = -19.0 (c 1.0, $CHCl_3$). IR (KBr film) ν 2955, 2866, 2857, 1781, 1689, 1629, 1367, 1347, 1196, 1112, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.57 (q, *J* = 7.9 Hz, 6H), 0.93 (t, *J* = 7.9 Hz, 9H), 1.04 (s, 9H), 1.67 (ddd, *J* = 13.0, 6.4, 4.8 Hz, 1H), 2.22 (dt, *J* = 13.0, 6.6 Hz, 1H), 2.49 – 2.59 (m, 1H), 2.63 – 2.74 (m, 1H), 3.62 (dd, *J* = 3.9, 1.1 Hz, 2H), 3.91 (q, *J* = 3.9 Hz, 1H), 4.19 (m, 1H), 4.28 (m, 1H), 4.47 (ddd, *J* = 6.4, 4.8, 3.6 Hz, 1H), 4.69 (t, *J* = 8.7 Hz, 1H), 5.49 (dd, *J* = 8.7, 3.9 Hz, 1H), 7.09 (dt, *J* = 15.4, 7.3 Hz, 1H), 7.29 – 7.44 (m, 12H), 7.62 – 7.69 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.7 (t), 6.8 (q), 19.2 (s), 26.8 (q), 39.7 (t), 40.5 (t), 57.7 (d), 64.1 (t), 69.9 (t), 73.0 (d), 77.5 (d), 86.5 (d), 121.9 (d), 126.0 (d), 127.6 (d), 128.6 (d), 129.1 (d), 129.6 (d), 129.6 (d), 133.2 (s), 133.4 (s), 135.6 (d), 135.6 (d), 139.1 (s), 148.3 (d), 153.6 (s), 164.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{40}H_{53}NNaO_6Si_2$ (M+Na) 722.3304, found 722.3299.

(*R*)-3-((*S*)-4-((*2R,4S,5R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy) tetrahydrofuran-2-yl)-3-methylbutanoyl)-4-phenyloxazolidin-2-one (10)



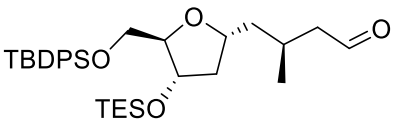
A 3 M solution of MeMgBr in THF (1.36 mL, 4.1 mmol) was added to a solution of $CuBr{\cdot}Me_2S$ (760 mg, 3.7 mmol) in THF (75 mL) at -40 ºC, and the mixture was stirred at -40 ºC for 1 h. The solution was cooled to -78 ºC and $BF_3{\cdot}Et_2O$ (0.46 mL, 3.7 mmol) and a solution of oxazolidinone **S2** (2.81 g, 3.4 mmol) in THF were added. The reaction mixture was stirred at -78 ºC for 1 h, slowly warmed to r.t. during 2 h and stirred at r.t. for 1 hour more. After this time, sat. NH_4Cl was added and the solvent was removed under reduced pressure. The residue was diluted in sat. NH_4Cl and extracted with Et_2O. The organic solution was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10 to 80:20) yielded **10** (2.41 g, 91%) as a colorless oil. $[\alpha]_D$ = -11.6 (c 1.0, $CHCl_3$). IR (KBr film) ν 2956, 2876, 1784, 1707, 1457, 1383, 1322, 1196, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (q, *J* = 7.9 Hz, 6H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 1.05 (s, 9H), 1.47 – 1.54 (m, 1H), 1.56 – 1.61 (m, 1H), 1.61 – 1.66 (m, 1H), 2.10 – 2.17 (m, 1H), 2.20 (dd, *J* = 12.4, 6.3 Hz, 1H), 2.84 (dd, *J* = 16.7, 6.7 Hz, 1H), 2.95 (dd, *J* = 16.7, 6.7 Hz, 1H), 3.64 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.70 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.81 (dt, *J* = 4.8, 3.7 Hz, 1H), 4.07 – 4.13 (m, 1H), 4.24 (dd, *J* = 8.8, 3.6 Hz, 1H), 4.48 (td, *J* = 6.5, 4.6 Hz, 1H), 4.62 (t, *J* = 8.8 Hz, 1H), 5.39 (dd, *J* = 8.8, 3.6 Hz, 1H), 7.26 – 7.46 (m, 11H), 7.64 – 7.75 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.7 (t), 6.8 (q), 19.2 (s), 20.1 (q), 26.8 (q), 27.5 (d), 41.6 (t), 42.3 (t), 42.9 (t), 57.6 (d), 64.1 (t), 69.8 (t), 72.6 (d), 76.8 (d), 85.5 (d), 125.9 (d), 127.6 (d), 128.6 (d), 129.1 (d), 129.5 (d), 129.6 (d), 133.4 (s), 133.5 (s), 135.6 (d), 135.7 (d), 139.2 (s), 153.7 (s), 171.9 (s). HRMS (+ESI): *m/z* calcd. for $C_{41}H_{57}O_6NNaSi_2$ (M+Na) 738.3617, found 738.3617.

(*R*)-4-((*2R,4S,5R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy) tetrahydrofuran-2-yl)-3-methylbutan-1-ol (S3)



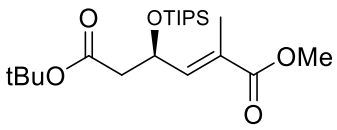
A 2 M solution of $LiBH_4$ in THF (3.1 mL, 6.21 mmol) was added to a solution of oxazolidinone **10** (1.85 g, 2.58 mmol) in Et_2O (65 mL):MeOH (3 mL) at -10 ºC and the reaction mixture was stirred at 0 ºC for 1 h. After this time, a 1 M solution of NaOH was added and the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10 to 85:15) yielded **S3** (0.85 g, 65%) as a colorless oil. $[\alpha]_D$ = +27.1 (c 1.0, $CHCl_3$). IR (KBr film) ν 3404 (br), 2955, 2931, 2875, 1463, 1428, 1239, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (q, *J* = 7.9 Hz, 6H), 0.93 (t, *J* = 7.8 Hz, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H), 1.38 – 1.64 (m, 5H), 1.74 (dt, *J* = 12.8, 6.6 Hz, 1H), 2.24 (dt, *J* = 12.8, 6.5 Hz, 1H), 3.61 – 3.75 (m, 4H), 3.86 (q, *J* = 3.9 Hz, 1H), 4.15 – 4.24 (m, 1H), 4.46 – 4.53 (m, 1H), 7.35 – 7.45 (m, 6H), 7.66 – 7.73 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.7 (t), 6.8 (q), 19.2 (s), 20.4 (q), 26.8 (q), 27.2 (d), 39.7 (t), 41.6 (t), 43.3 (t), 61.1 (t), 64.2 (t), 72.7 (d), 76.8 (d), 85.7 (d), 127.6 (d), 127.6 (d), 129.6 (d), 129.6 (d), 133.4 (s), 133.5 (s), 135.6 (d), 135.7 (d). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{52}O_4NaSi_2$ (M+Na) 579.3296, found 579.3269.

(*S*)-4-((*2R,4S,5R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy) tetrahydrofuran-2-yl)-3-methylbutanal (2)



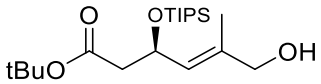
Dess-Martin periodinane (823 mg, 1.94 mmol) was added to a solution of alcohol **S3** (830 mg, 1.5 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred for 30 minutes. The reaction mixture was diluted with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ and the residue was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (9:1) yielded **2** (791 mg, 95%) as a colorless oil. $[\alpha]_D$ = +25.3 (c 1.0, $CHCl_3$). IR (KBr film) ν 2956, 2930, 2857, 1727, 1472, 1428, 1252, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.59 (t, *J* = 7.9 Hz, 6H), 0.94 (t, *J* = 7.9 Hz, 9H), 1.01 (d, *J* = 6.5 Hz, 3H), 1.06 (s, 9H), 1.50 (ddd, *J* = 13.7, 6.7, 5.0 Hz, 1H), 1.62 (ddd, *J* = 12.2, 7.6, 5.9 Hz, 1H), 1.72 (ddd, *J* = 13.7, 8.3, 6.4 Hz, 1H), 2.16 – 2.30 (m, 3H), 2.46 – 2.53 (m, 1H), 3.66 (dd, *J* = 11.0, 3.9 Hz, 1H), 3.71 (dd, *J* = 11.0, 3.9 Hz, 1H), 3.85 (q, *J* = 3.9 Hz, 1H), 4.15 (tdd, *J* = 8.0, 6.4, 5.0 Hz, 1H), 4.46 – 4.52 (m, 1H), 7.33 – 7.46 (m, 6H), 7.65 – 7.72 (m, 4H), 9.72 – 9.74 (m, 1H).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.7 (t), 6.8 (q), 19.2 (s), 20.5 (q), 25.8 (d), 26.8 (q), 41.6 (t), 43.2 (t), 50.6 (t), 64.1 (t), 72.7 (d), 76.3 (d), 85.8 (d), 127.6 (d), 127.6 (d), 129.6 (d), 129.6 (d), 133.4 (s), 133.5 (s), 135.6 (d), 135.6 (d), 202.9 (d). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{51}O_4Si_2$ (M+H) 555.3320, found 555.3326.

6-(*tert*-Butyl) 1-methyl (*R,E*)-2-methyl-4-((triisopropylsilyl)oxy)hex-2-enedioate (S4).



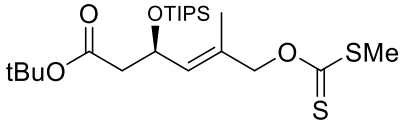
A 2 M solution of LDA in THF (2.7 mL, 5.4 mmol) was slowly added to a solution of (1-mehtoxycarbonylethyl)triphenylphosphonium bromide (2.3 g, 5.4 mmol) in CH_2Cl_2 (140 mL) at -78 ºC. After 5 min, the reaction was warmed to 0ºC and a solution of aldehyde **4** (1.5 g, 4.5 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred 1 h at 0ºC and 1 h at r.t. The reaction was quenched by the addition of 100 mL of NH_4Cl saturated solution. The mixture was extracted three times with CH_2Cl_2 (75 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **S4** (1.6 g, 87%) as a colorless oil. $[\alpha]_D$ = +9.6 (c 1.0, $CHCl_3$). IR (KBr film) ν 2944, 2867, 1723, 1463, 1248, 1159, 887 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 – 1.06 (m, 21H), 1.42 (s, 9H), 1.86 (d, *J* = 1.4 Hz, 3H), 2.39 (dd, *J* = 14.6, 6.3 Hz, 1H), 2.57 (dd, *J* = 14.6, 6.3 Hz, 1H), 3.75 (s, 3H), 5.00 (dt, *J* = 8.7, 6.3 Hz, 1H), 6.72 (dq, *J* = 8.7, 1.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.3 (d), 13.0 (q), 17.9 (q), 28.0 (q), 44.4 (t), 51.9 (q), 66.8 (d), 80.7 (s), 126.4 (s), 143.7 (d), 168.3 (s), 169.6 (s). HRMS (+ESI): *m/z* calcd. for $C_{21}H_{40}O_5NaSi$ (M+Na) 423.2537, found 423.2537.

***tert*-Butyl (*R,E*)-6-hydroxy-5-methyl-3-((triisopropylsilyl)oxy)hex-4-enoate (11).**



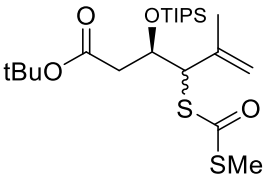
A 1 M solution of DIBAL in THF (31.6 mL, 31.6 mmol) was slowly added to a solution of **S4** (5.76 g, 14.37 mmol) in THF (210 mL) at -78 ºC and the reaction mixture was stirred for 15 minutes. After this time the reaction was warmed to r.t and stirred 1 h. The reaction was quenched by the addition of EtOAc (10 mL) and Rochelle's Salt saturated solution (150 mL). The mixture was stirred 2 h and filtered through celite. The pad was washed several times with EtOAc. The organic solvents were evaporated and the crude was extracted three times with CH_2Cl_2. This organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (9:1) yielded **11** (3.89 g, 75%) as a colorless oil. $[\alpha]_D$ = +8.7 (c 1.0, $CHCl_3$). IR (KBr film) ν 3444 (br), 2943, 2866, 1731, 1464, 1368, 1147, 1084, 883 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 – 1.06 (m, 21H), 1.41 (s, 9H), 1.68 (d, *J* = 1.2 Hz, 3H), 2.34 (dd, *J* = 14.1, 6.9 Hz, 1H), 2.54 (dd, *J* = 14.1, 6.1 Hz, 1H), 3.98 (s, 2H), 4.89 – 4.97 (m, 1H), 5.47 (dq, *J* = 8.8, 1.2 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.3 (d), 14.2 (q), 17.9 (q), 28.0 (q), 45.4 (t), 66.5 (d), 68.1 (t), 80.3 (s), 128.6 (d), 134.9 (s), 170.2 (s). HRMS (+ESI): *m/z* calcd. for $C_{20}H_{40}O_4NaSi$ (M+Na) 395.2588, found 395.2599.

***tert*-Butyl (*R,E*)-5-methyl-6-(((methylthio)carbonothioyl)oxy)-3-((triisopropylsilyl) oxy)hex-4-enoate (S5).**



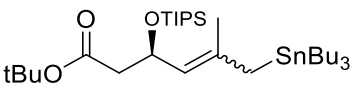
Alcohol **11** (1.3 g, 3.6 mmol) in toluene (5 mL) was added to a suspension of NaH (60% in mineral oil) (290 mg, 7.2 mmol) in toluene (10 mL) at 0 ºC and the mixture was stirred for 30 minutes. After this time, CS_2 was added (1.7 mL, 18 mmol) and the reaction was stirred for 3 h. Finally MeI (2.2 mL, 18 mmol) was added and the reaction was stirred for 1 h at r.t. The reaction was filtered thorugh celite washing the pad with EtOAc, and the solvent was evaporated. The residue was extracted three times with CH_2Cl_2. This organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (97:3) yielded **S5** (1.48 g, 89%) as an orange oil. $[\alpha]_D$ = +10.6 (c 1.0, $CHCl_3$). IR (KBr film) ν 2942, 2866, 1730, 1456, 1367, 1147, 1066, 883 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 – 1.06 (brs, 21H), 1.43 (s, 9H), 1.75 (d, *J* = 1.4 Hz, 3H), 2.36 (dd, *J* = 14.3, 7.0 Hz, 1H), 2.55 (s, 3H) 2.57 (dd, *J* = 14.3, 6.2 Hz, 1H), 4.90 – 5.01 (m, 3H), 5.59 (dd, *J* = 8.9, 1.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.3 (d), 14.8 (q), 17.9 (q), 18.9 (q), 28.1 (q), 45.1 (t), 66.4 (d), 78.4 (t), 80.5 (s), 129.3 (s), 133.6 (d), 169.9 (s), 215.5 (s). HRMS (+ESI): *m/z* calcd. for $C_{22}H_{42}O_4NaS_2Si$ (M+Na) 485.2186, found 485.2191.

***tert*-Butyl (*3R,4RS*)-5-methyl-4-(((methylthio)carbonyl)thio)-3-((triisopropylsilyl) oxy)hex-5-enoate (12).**



Xanthate **S5** (1.94 g, 4.2 mmol) in toluene (155 mL) was heated at reflux temperature for 16 h. The solvent was evaporated to yield **12** (1.94 g, q.) as a 65(A):35(B) mixture of epimers. IR (KBr film) ν 2943, 2867, 1730, 1647, 1463, 1368, 1153, 1110, 864cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 – 1.11 (m, 21H_A+21H_B), 1.46 (s, 9H_A+9H_B), 1.85 – 1.86 (dd, *J* = 1.5, 0.8 Hz, 3H_A), 1.86 – 1.87 (dd, *J* = 1.5, 0.7 Hz, 3H_B), 2.40 (s, 3H_B), 2.41 (s, 3H_A), 2.48 – 2.54 (m, 2H_A+1H_B), 2.70 (dd, *J* = 15.7, 8.6 Hz, 1H_B), 4.40 (dd, *J* = 3.4, 0.8 Hz, 1H_B), 4.49 – 4.59 (m, 2H_A+1H_B), 4.93 – 5.03 (m, 1H_A+1H_B), 5.04 – 5.15 (m, 1H_A+1H_B). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.7 (d, A), 12.9 (d, B), 13.1 (q, A+B), 18.1 (q, A), 18.2 (q, B), 21.5 (q, B), 21.6 (q, A), 28.0 (q, A+B), 41.8 (t, A), 42.7 (t, A), 56.4 (d, A), 57.6 (d, B), 70.5 (d, B), 71.8 (d, A), 81.0 (s, A), 81.0 (s, B) , 115.0 (t, B), 116.7 (t, A), 141.5 (t, A), 142.8 (t, B), 169.8 (s, A+B), 189.1 (s, A+B). HRMS (+ESI): *m/z* calcd. for $C_{22}H_{42}O_4NaS_2Si$ (M+Na) 485.2186, found 485.2186.

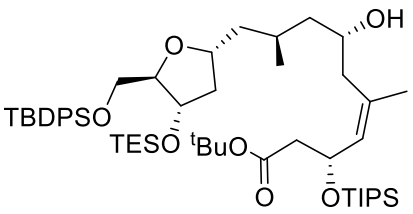
***tert*-Butyl (*ZE,R*)-5-methyl-6-(tributylstannyl)-3-((triisopropylsilyl)oxy)hex-4-enoate (3).**



Tributyltin hydride (0.61 mL, 2.25 mmol) and AIBN (16 mg, 0.1 mmol) were added to a degassed solution of **12** (700 mg, 1.5 mmol)

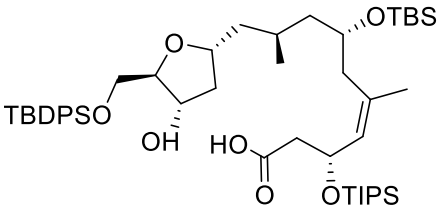
in benzene (40 mL). The reaction was heated at reflux temperature for 6 h (the colour changes from yellow to grey). Then, the solvent was evaporated and the crude was purified by silica gel column chromatography with hexane-EtOAc (99:1) and 1% of Et3N to yield **3** (788 mg, 81%) as a 7(A):3(B) isomeric double bond mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 – 0.89 (m, $6H_A$+$6H_B$), 0.89 (t, *J* = 7.3 Hz, $9H_A$+$9H_B$), 1.02 – 1.06 (m, $21H_A$+$21H_B$), 1.25 – 1.36 (m, $6H_A$+$6H_B$), 1.44 (s, $9H_A$+$9H_B$), 1.45 – 1.52 (m, $6H_A$+$6H_B$), 1.52 – 1.55 (m, $1H_A$), 1.62 (d, *J* = 1.2 Hz, $3H_A$+$3H_B$), 1.66 (d, *J* = 0.8 Hz, $1H_B$), 1.70 (d, *J* = 0.8 Hz, $1H_B$), 1.97 (d, *J* = 11.4 Hz, $1H_A$), 2.22 (dd, *J* = 14.5, 3.6 Hz, $1H_A$), 2.29 (dd, *J* = 14.0, 5.8 Hz, $1H_B$), 2.38 (dd, *J* = 14.5, 8.2 Hz, $1H_A$), 2.47 (dd, *J* = 14.0, 7.0 Hz, $1H_B$), 4.86 – 4.93 (m, $1H_A$+$1H_B$), 4.94 – 4.99 (m, $1H_A$), 5.03 (m, $1H_B$). ^{13}C NMR (100.6 MHz, $CDCl_3$) (cuaternary C not included) δ 9.85 (t, A+B), 12.5 (d, A+B), 13.6 (q, A+B), 15.9 (t, A), 18.1 (q, A+B), 19.0 (q, B), 21.8 (t, B), 26.1 (q, A), 27.3 (t, A+B), 28.1 (q, A+B), 29.2 (t, A+B), 45.5 (t, A), 46.4 (t, B), 67.3 (d, A+B), 124.3 (d, A+B). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{67}O_3SiSn$ (M+H) 647.3876, found 647.3882.

***tert*-Butyl (*3R,7S,9R,Z*)-10-((*2R,4S,5R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)-7-hydroxy-5,9-dimethyl-3-((triisopropylsilyl) oxy)dec-4-enoate (13)**



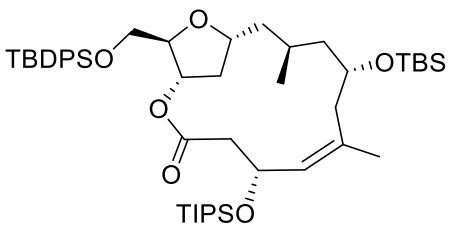
A 1M $SnCl_4$ solution in CH_2Cl_2 (1.26 mL, 1.26 mmol) was added slowly to a solution of allylstannane **3** (780 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) at -78 ºC. After 10 minutes a solution of aldehyde **2** (580 mg, 1.05 mmol) in CH_2Cl_2 (1.5 mL) was added and the reaction was stirred for 2 h at -78ºC and quenched with $NaHCO_3$ saturated solution (10 mL). The crude was extracted two times with Et_2O and the organic phase was washed with 10% NH_3, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (9:1) yielded **13** (717 mg, 75%) as a single diasteromer. $[\alpha]_D$ = +5.2 (c 1.0, $CHCl_3$). IR (KBr film) ν 3436 (br), 2955, 2866, 1726, 1470, 1374, 1112, 880, 702cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (q, *J* = 8.1 Hz, 6H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.00 – 1.04 (m, 21H), 1.05 (s, 9H), 1.42 (s, 9H), 1.41 – 1.43 (m, 2H), 1.54 – 1.66 (m, 3H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.76 – 1.82 (m, 1H), 1.96 (dd, *J* = 13.7, 3.1 Hz, 1H), 2.25 (dt, *J* = 12.5, 6.4 Hz, 1H), 2.39 (dd, *J* = 13.7, 9.7 Hz, 1H), 2.45 (dd, *J* = 15.3, 6.3 Hz, 1H), 2.57 (dd, *J* = 15.3, 6.3 Hz, 1H), 3.65 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.70 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.86 (m, 2H), 4.19 (dd, *J* = 7.7, 6.2 Hz, 1H), 4.49 (td, *J* = 6.4, 4.4 Hz, 1H), 4.87 (dt, *J* = 9.0, 6.3 Hz, 1H), 5.32 (d, *J* = 9.0 Hz, 1H), 7.33 – 7.44 (m, 6H), 7.65 – 7.73 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 4.7 (t), 6.8 (q), 12.4 (d), 18.0 (q), 19.2 (s), 20.9 (q), 23.1 (q), 26.8 (q), 27.5 (d), 28.1 (q), 41.2 (t), 41.5 (t), 42.8 (t), 45.2 (t), 46.0 (t), 64.2 (t), 65.9 (d), 66.7 (d), 72.8 (d), 77.2 (d), 80.6 (s), 85.7 (d), 127.6 (d), 127.6 (d), 129.6 (d), 129.6 (d), 131.6 (d), 133.3 (s), 133.4 (s), 133.6 (s), 135.6 (d), 135.7 (d), 171.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{52}H_{90}NaO_7Si_3$ (M+Na) 933.5887, found 933.5896.

(*3R,7S,9S,Z*)-7-((*tert*-Butyldimethylsilyl)oxy)-10-((*2R,4S,5R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-5,9-dimethyl-3-((triisopropylsilyl)oxy)dec-4-enoic acid (14)



2,6-lutidine (0.1 mL, 0.82 mmol) and TBSOTf (0.05 mL, 0.22 mmol) were added to a solution of **13** (50 mg, 0.055 mmol) in CH_2Cl_2 (3 mL) at 0 ºC. The reaction was stirred 30 minutes at r.t. When the protection is quantitative (TLC) TMSOTf (0.08 mL, 0.44 eq.) was added at 0 ºC and the solution is stirred for 30 minutes at r.t. The reaction was quenched by the addition of saturated NH_4Cl solution (3 mL) and the organic phase was washed two times with 0.1M HCl (2x3 mL). The crude is evaporated and MeOH (2 mL) was added. Then PPTS (55 mg, 0.22) was added and the reaction was stirred for 20 minutes. The mixture was evaporated and purification by silica gel column chromatography with hexane-EtOAc (8:2) yielded seco acid **14** (34 mg, 72%) as a colorless oil. $[\alpha]_D$ = +3.5 (c 1.0, $CHCl_3$). IR (KBr film) ν 3430 (br), 2930, 2864, 1712, 1463, 1252, 1105, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.01 – 1.07 (m, 30H), 1.22 – 1.26 (m, 1H), 1.36 – 1.44 (m, 1H), 1.51 – 1.56 (m, 2H), 1.59 – 1.67 (m, 2H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.98 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.30 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.38 (dt, *J* = 13.0, 6.7 Hz, 1H), 2.54 (dd, *J* = 14.7, 5.6 Hz, 1H), 2.60 (dd, *J* = 14.7, 5.6 Hz, 1H), 3.64 (dd, *J* = 10.4, 6.3 Hz, 1H), 3.78 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.85 – 3.91 (m, 2H), 4.12 – 4.20 (m, 1H), 4.42 (td, *J* = 6.3, 4.3 Hz, 1H), 4.88 (dt, *J* = 8.5, 5.6 Hz, 1H), 5.31 (d, *J* = 8.5 Hz, 1H), 7.35 – 7.46 (m, 6H), 7.63 – 7.69 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.5 (q), -3.9 (q), 12.3 (d), 17.9 (d), 18.0 (q), 18.0 (s), 19.2 (s), 20.9 (q), 24.2 (q), 25.9 (q), 26.8 (q), 27.3 (d), 40.8 (t), 40.9 (t), 43.3 (t), 43.6 (t), 45.0 (t), 65.0 (t), 66.8 (d), 69.4 (d), 74.6 (d), 76.9 (d), 84.3 (d), 127.7 (d), 127.8 (d), 129.8 (d), 129.8 (d), 133.1 (s), 134.2 (s), 135.5 (d), 135.6 (d), 173.2 (s). HRMS (+ESI): *m/z* calcd. for $C_{48}H_{82}NaO_7Si_3$ (M+Na) 877.5261, found 877.5278.

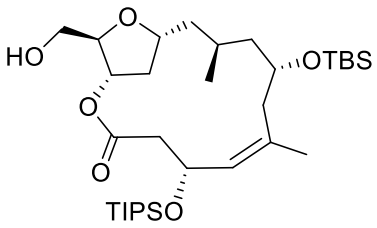
(*1S,5R,9S,11S,13R,15R,Z*)-9-((*tert*-Butyldimethylsilyl)oxy)-15-(((*tert*-butyldiphenylsilyl)oxy)methyl)-7,11-dimethyl-5-((triisopropylsilyl)oxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (15)



A solution of hydroxyacid **14** (223 mg, 0.26 mmol) in toluene (60 mL) was added during 24h using a syringe pump over a solution of DMAP (230 mg, 1.88 mmol) and MNBA (313 mg, 0.91 mmol) in toluene (220 mL) at r.t. The reaction mixture was stirred 2 hours after addition finished and was quenched with a saturated NH_4Cl solution (45 mL). The crude was extracted with CH_2Cl_2 and the organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded macrolactone **15** (145 mg, 67%) as a colorless oil. $[\alpha]_D$ = -11.2 (c 1.0, $CHCl_3$). IR (KBr film) ν 2929, 2864, 1742, 1450, 1112, 1063, 926, 702 cm^{-1}. ^1H NMR (400 MHz,

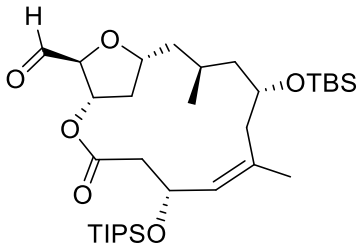
$CDCl_3$) δ 0.02 (s, 3H), 0.06 (s, 3H), 0.84 (s, 9H), 0.93 (d, *J* = 6.2 Hz, 3H), 1.02 – 1.07 (m, 30H), 1.30 – 1.33 (m, 1H), 1.41 – 1.45 (m, 1H), 1.59 – 1.68 (m, 2H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.91 – 1.99 (m, 1H), 2.06 (d, *J* = 13.2 Hz, 1H), 2.25 (ddd, *J* = 13.2, 8.0, 6.2 Hz, 1H), 2.35 (ddd, *J* = 14.1, 11.0, 3.1 Hz, 1H), 2.53 (dd, *J* = 14.1, 7.8 Hz, 1H), 2.68 (dd, *J* = 13.6, 9.7 Hz, 1H), 2.75 (dd, *J* = 14.1, 2.8 Hz, 1H), 3.70 (dd, *J* = 10.9, 3.4 Hz, 1H), 3.86 (dd, *J* = 10.9, 3.1 Hz, 1H), 4.01 – 4.08 (m, 2H), 4.43 – 4.52 (m, 1H), 5.11 (td, *J* = 7.4, 2.8 Hz, 1H), 5.26 (d, *J* = 5.7 Hz, 1H), 5.43 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.43 (m, 6H), 7.63 – 7.71 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.4 (q), -4.1 (q), 12.3 (d), 17.9 (q), 18.0 (q), 18.1 (s), 19.3 (s), 20.9 (q), 23.3 (q), 25.9 (q), 26.7 (d), 26.8 (q), 34.1 (t), 38.5 (t), 41.2 (t), 46.1 (t), 47.0 (t), 65.0 (t), 68.3 (d), 70.7 (d), 77.4 (d), 78.6 (d), 84.7 (d), 127.7 (d), 127.7 (d), 129.6 (d), 129.7 (d), 132.6 (d), 132.9 (s), 133.3 (s), 133.4 (s), 135.6 (d), 135.6 (d), 171.0(s) . HRMS (+ESI): *m/z* calcd. for $C_{48}H_{84}NO_6Si_3$ ($M+NH_4$) 854.5601, found 854.5601.

(*1S,5R,9S,11S,13R,15R,Z*)-9-((*tert*-Butyldimethylsilyl)oxy)-15-(hydroxymethyl)-7,11-dimethyl-5-((triisopropylsilyl)oxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (S6)



A buffered TBAF/AcOH 1:1 solution (1.44 mL, 0.22 mmol of TBAF) was added to a solution of lactone **15** (15 mg, 0.018 mmol) in THF (1 mL) and the mixture is stirred 16 h at 40 ºC. The reaction was quenched with a saturated $NaHCO_3$ solution (1 mL). The crude was extracted twice with EtOAc and the organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded alcohol **S6** (8 mg, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.06 (s, 3H), 0.84 (s, 9H), 0.91 (d, *J* = 6.4 Hz, 3H), 1.02 (s, 21H), 1.25 – 1.30 (m, 1H), 1.41 – 1.48 (m, 1H), 1.57 – 1.65 (m, 1H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.71 – 1.76 (m, 1H), 1.84 (d, *J* = 13.8 Hz, 1H), 2.07 – 2.12 (m, 2H), 2.44 – 2.54 (m, 2H), 2.75 – 2.86 (m, 2H), 3.65 – 3.76 (m, 2H), 4.00 (dt, *J* = 4.2, 2.2 Hz, 1H), 4.08 – 4.15 (m, 1H), 4.42 – 4.50 (m, 1H), 4.99 – 5.03 (m, 1H), 5.15 (t, *J* = 7.6 Hz, 1H), 5.45 (dt, *J* = 7.8, 1.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.4 (q), -4.1 (q), 12.2 (d), 17.9 (q), 17.9 (q), 18.1 (s), 20.7 (q), 22.6 (q), 25.9 (q), 26.6 (d), 33.8 (t), 38.0 (t), 40.4 (t), 45.8 (t), 47.2 (t), 63.4 (t), 68.4 (d), 70.1 (d), 78.7 (d), 84.7 (d), 132.5 (s), 133.0 (d), 171.5 (s). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{62}NaO_6Si_2$ (M+Na) 621.3977, found 621.3961.

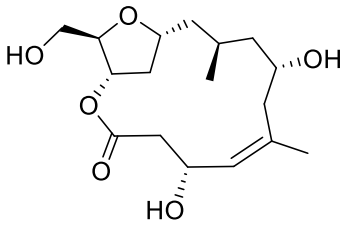
(*1S,5R,9S,11S,13R,15S,Z*)-9-((*tert*-Butyldimethylsilyl)oxy)-7,11-dimethyl-3-oxo-5-((triisopropylsilyl)oxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-ene-15-carbaldehyde (16)



Dess-Martin periodinane (28 mg, 0.064 mmol) was added to a suspension of alcohol **S6** (32 mg, 0.054 mmol) and $NaHCO_3$ (11 mg, 0.128 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred for 45 minutes. The reaction mixture was diluted with sat. $Na_2S_2O_3$ and sat.

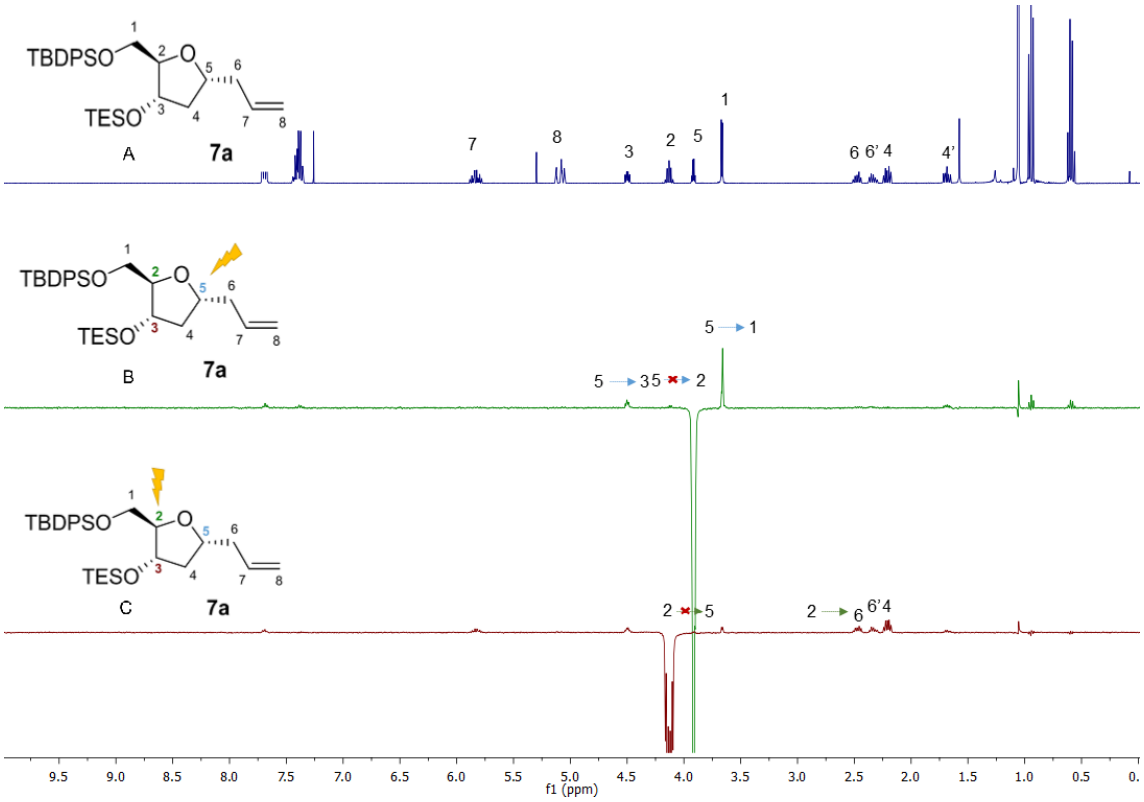
$NaHCO_3$ and the resulting solution was extracted with Et_2O. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (9.1) yielded **2** (31 mg, quant.) as a colorless oil. IR (KBr film) ν 2958, 2921, 1737, 1460, 1378, 1057, 831cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.06 (s, 3H), 0.84 (s, 9H), 0.93 (d, *J* = 6.3 Hz, 3H), 1.03 (s, 21H), 1.37 – 1.41 (m, 1H), 1.42 – 1.46 (m, 1H), 1.62 (dd, *J* = 9.4, 4.6 Hz, 1H), 1.65 – 1.69 (m, 1H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.91 (dd, *J* = 13.6, 3.3 Hz, 1H), 1.97 – 2.02 (m, 1H), 2.13 (d, *J* = 14.3 Hz, 1H), 2.41 (ddd, *J* = 14.2, 11.0, 3.4 Hz, 1H), 2.57 (dd, *J* = 14.1, 7.2 Hz, 1H), 2.68 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.79 (dd, *J* = 14.1, 2.8 Hz, 1H), 4.03 – 4.08 (m, 1H), 4.51 (d, *J* = 1.2 Hz, 1H), 4.55 – 4.63 (m, 1H), 5.09 (td, *J* = 7.4, 2.9 Hz, 1H), 5.27 (dd, *J* = 5.5, 1.2 Hz, 1H), 5.42 (dt, *J* = 7.8, 1.4 Hz, 1H), 9.71 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ -4.4 (q), -4.1 (q), 12.3 (d), 17.9 (q), 17.9 (q), 18.1 (s), 20.8 (q), 23.1 (q), 25.8 (q), 26.6 (d), 33.0 (t), 38.4 (t), 40.9 (t), 45.8 (t), 46.7 (t), 68.1 (d), 70.5 (d), 74.7 (d), 79.8 (d), 88.4 (d), 132.5 (d), 133.0 (s), 170.8 (s), 198.5 (d). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{60}NaO_6Si_2$ (M+Na) 619.3821, found 619.3833.

(*1S,5R,9S,11R,13R,15R,Z*)-5,9-Dihydroxy-15-(hydroxymethyl)-7,11-dimethyl-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (1)



A buffered TBAF/AcOH 1:1 solution (1.3 mL, 0.81 mmol of TBAF) was added to a solution of lactone **15** (45 mg, 0.054 mmol) in 1,4-dioxane (3 mL) and the mixture is stirred 36 h at 90 ºC. The reaction was quenched with a saturated $NaHCO_3$ solution (1 mL). The crude was extracted twice with EtOAc and the organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with EtOAc:MeOH (99:1) yielded triol **1** (9.6 mg, 54%) as a colorless oil. IR (KBr film) ν 3387(br), 2947, 2918, 1728, 1459, 1051 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.0 Hz, 3H), 1.34 – 1.46 (m, 2H), 1.59 – 1.68 (m, 2H), 1.80 (d, *J* = 1.5 Hz, 3H), 2.00 – 2.17 (m, 4H), 2.60 – 2.65 (m, 2H), 2.74 (dd, *J* = 13.4, 7.7 Hz, 1H), 3.62 – 3.71 (m, 2H), 3.97 (td, *J* = 9.9, 7.7, 4.4 Hz, 1H), 4.11 (td, *J* = 4.5, 1.5 Hz, 1H), 4.35 – 4.44 (m, 1H), 4.84 (dt, *J* = 8.7, 5.8 Hz, 1H), 5.14 (dd, *J* = 5.9, 1.5 Hz, 1H), 5.49 (dd, *J* = 8.7, 1.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.6 (q), 24.9 (q), 27.0 (d), 34.8 (t), 39.0 (t), 41.0 (t), 44.3 (t), 44.9 (t), 63.3 (t), 65.9 (d), 69.9 (d), 77.7 (d), 78.3 (d), 84.1 (d), 129.9 (d), 137.1 (s), 171.5 (s). HRMS (+ESI): *m/z* calcd. for $C_{17}H_{28}NaO_6$ (M+Na) 351.1778, found 351.1789.

NOE 1D experiment of 7a

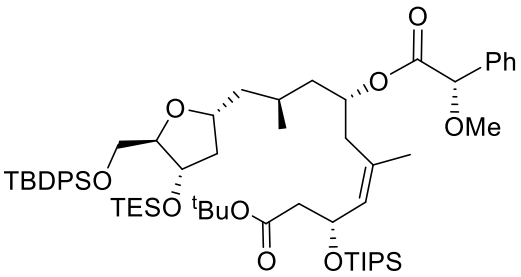


Scheme S1. A) H-NMR of compound **7a**; B) irradiation to proton in position 5 (H5); C) irradiation to proton in position 2 (H2).

Absolute configuration of stereocenters at positions 2 and 3 are determined by the used starting material (2-D-deoxyribose). When proton 5 was irradiated, no NOE correlation with H2 was osbserved, confirming that susbtituents in position 2 and 5 are in anti- relative position. Therefore the created stereocenter in C5 has *R* stereochemistry. Irradiation of H2 has no correlation with H5 (as expected) but it has correlation with the two hydrogens in position 6 (the substituent in C5 is in syn- relation with H2) and with H4 (the hydrogen in position 4 located in syn to H^2).

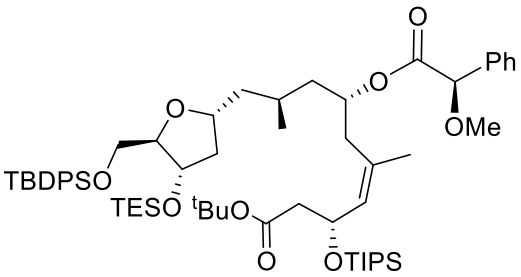
Mosher's derivatization of compound 13

***tert*-Butyl (3*R*,7*S*,9*S*,*Z*)-10-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)-7-((*S*)-2-methoxy-2-phenylacetoxy)-5,9-dimethyl-3-((triisopropylsilyl)oxy)dec-4-enoate (S7)**



(*S*)-α-Methoxyphenylacetic acid (31 mg, 0.19 mmol) and EDC·HCl (30 mg, 0.19 mmol) were added to a solution of alcohol **13** (25 mg, 0.027 mmol) in THF (1 mL), then DMAP (0.3 mg, 0.003 mmol) was added and the solution was stirred for 120 min. The solution was filtered, poured into Et_2O and washed with with aqueous 0.2 M HCl and sat. $NaHCO_3$. The organic residue was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded **S7** (20 mg, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.58 (q, *J* = 7.9 Hz, 6H), 0.91 (m, 3H), 0.92 (m, 1H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.98 – 1.04 (m, 21H), 1.05 (s, 9H), 1.43 (s, 9H), 1.48 (d, *J* = 1.4 Hz, 3H), 1.49 – 1.56 (m, 4H), 2.05 – 2.34 (m, 6H), 3.35 (s, 3H), 3.60 – 3.72 (m, 2H), 3.82 (q, *J* = 3.9 Hz, 1H), 3.98 – 4.07 (m, 1H), 4.45 (td, *J* = 6.5, 4.6 Hz, 1H), 4.86 (td, *J* = 8.1, 4.4 Hz, 1H), 5.16 – 5.23 (m, 2H), 7.30 – 7.46 (m, 11H), 7.66 – 7.72 (m, 4H). HRMS (+ESI): *m/z* calcd. for $C_{61}H_{98}NaO_9Si_3$ (M+Na) 1081.6411, found 1081.6407.

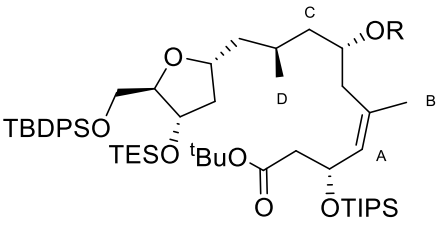
***tert*-Butyl (3*R*,7*S*,9*S*,*Z*)-10-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-((triethylsilyl)oxy)tetrahydrofuran-2-yl)-7-((*R*)-2-methoxy-2-phenylacetoxy)-5,9-dimethyl-3-((triisopropylsilyl)oxy)dec-4-enoate (S8)**



(*R*)-α-Methoxyphenylacetic acid (31 mg, 0.19 mmol) and EDC·HCl (30 mg, 0.19 mmol) were added to a solution of alcohol **13** (25 mg, 0.027 mmol) in THF (1 mL), then DMAP (0.3 mg, 0.003 mmol) was added and the solution was stirred for 120 min. The solution was filtered, poured into Et_2O and washed with with aqueous 0.2 M HCl and sat. $NaHCO_3$. The organic residue was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded **S8** (23 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 0.58 (q, *J* = 7.9 Hz, 6H), 0.70 (d, *J* = 6.6 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.94 (m, 1H), 0.99 – 1.07 (m, 30H), 1.22 – 1.41 (m, 4H), 1.41 – 1.44 (m, 1H), 1.46 (s, 9H), 1.67 (d, *J* = 1.4 Hz, 3H), 2.00 – 2.15 (m, 2H), 2.33 – 2.50 (m, 3H), 3.36 (s, 3H), 3.58 – 3.69 (m, 2H), 3.78 (q, *J* = 3.9 Hz, 1H), 3.81 – 3.89 (m, 1H), 4.42 (td, *J* = 6.5, 4.7 Hz, 1H), 4.66 (s, 1H), 4.95 (td, *J* = 8.2, 4.1 Hz, 1H), 5.18 (dt, *J* = 8.4, 3.8 Hz, 1H), 5.33 (dd, *J* = 8.7,

1.6 Hz, 1H), 7.24 – 7.44 (m, 11H), 7.66 – 7.71 (m, 04H). HRMS (+ESI): *m/z* calcd. for $C_{61}H_{98}NaO_9Si_3$ (M+Na) 1081.6411, found 1081.6400.

Absolute configuration determination:



	δ $\mathbf{H_A}$	δ $\mathbf{H_B}$	δ $\mathbf{H_C}$	δ $\mathbf{H_D}$
R=(*R*)-MPA	**5.33**	**1.67**	**1.31**	**0.70**
R=(*S*)-MPA	**5.19**	**1.49**	**1.47**	**0.91**
$\mathbf{\Delta^{RS}}$	**0.14**	**0.18**	**-0.21**	**-0.21**

Chapter 3

Synthesis and introduction of the bromo-methoxy-diene moiety

PM B-D are large molecules containing several challenging motives that had not been reported before this project. This is the case of their east end, the rare terminal (*E*)-bromomethoxydiene (BMD), present as well in oscillariolide[1] and phormidolide A[2] (Figure 1a). This small part of the molecule represents a synthetic challenge for its high functionality bearing four functional groups and two stereocenters. In our mind, it has always been clear that the easiest way to introduce the BMD moiety at the end of the polyol chain was to disconnect it through the C27-28 bond to give (*E*)-bromomethoxyketone **2** (BMK) and the aldehyde at position C27 of the polyhydroxylated chain **3** (Figure 1b). Both fragments could be linked using a great variety of aldol addition methodologies.

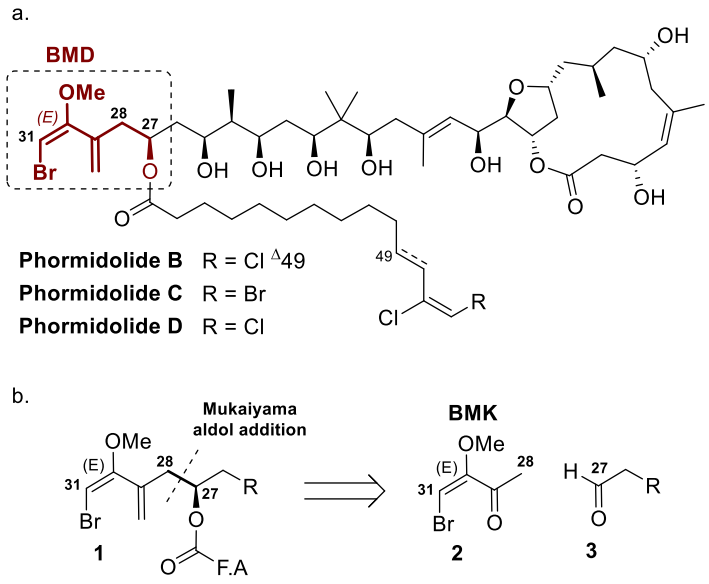
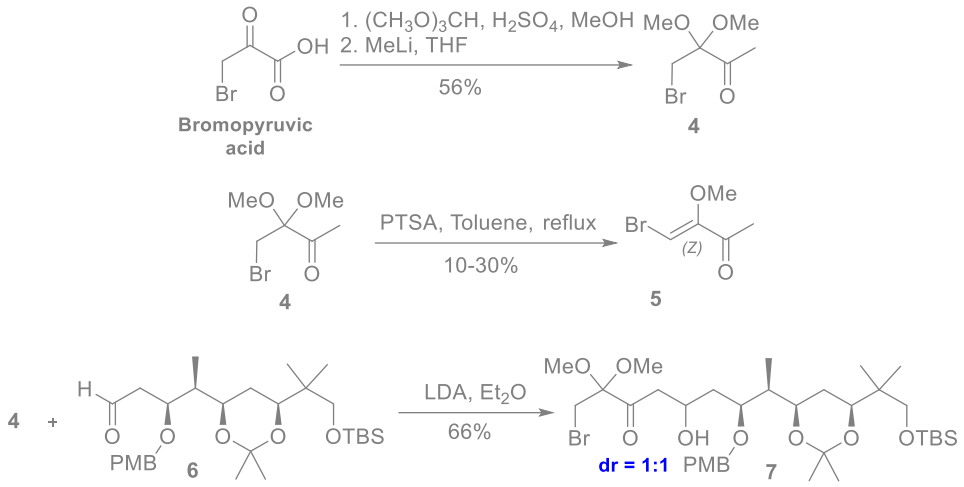


Figure 1. a. Structure of PM B-D highlighting the (E)-bromomethoxydiene C27-C31 fragment, the synthetic target of this chapter. b. General disconnection for the functionalization of the polyol chain with the BMD fragment.

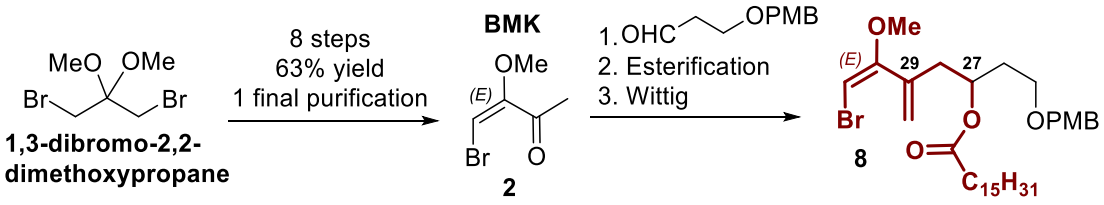
Although it can sound odd, the most challenging part of this chapter was the enantioselective synthesis of the (*E*)-bromoketone **2** mainly because almost all the attempted methodologies rendered low yield and generally the opposite (*Z*) double bond isomer. In her thesis, Dr. Janire Lamariano-Merketegi described the beginning of the work developed in this part of the molecule (Scheme 1).[3] Starting from commercially available bromopyruvic acid ketal **4** was obtained in two simple steps with good yield.[4] However, the MeOH elimination was tested over **4** and the best reaction conditions rendered **5**, the wrong double bond isomer with variable and low yields. Lithium enolate aldol addition of ketal **4** to C19-C27 aldehyde **6** rendered the C19-C31 carbon skeleton **7** with good yield but no diastereoselectivity. Due to the protecting groups incompatibility MeOH elimination from compound **7** was impossible. All these preliminary results showed that aldol addition was a suitable reaction to introduce the BMK

motif but a stereoselective synthesis of (*E*)-bromoketone **2** was necessary in which the double bond would be installed before the aldol condensation.



Scheme 1. Synthetic achievements on the BMK fragment during the thesis of Dra. Janire Lamariano-Merketegi.

An 8-step synthetic route starting from commercially available 1,3-dibromo-2,2-dimethoxypropane was designed, tested, and scaled up successfully (Scheme 2). The route works with outstanding yield (63%) and, more importantly, it only requires a final column chromatography to get a clean sample of **2**. After having access to multi-gram quantities of **2** a validation of our strategy including Mukaiyama addition to **3-(4-methoxybenzyloxy)propanal** (model aldehyde of the polyol chain), fatty acid introduction at position C27, and Wittig olefination at C29 was tested successfully rendering the racemate **8**, a model compound of the BMD moiety.



Scheme 2. Schematic summary of the route to obtain the challenging bromomethoxydiene (BMD) molecular moiety.

This reaction sequence rendered for the first time the C27-C31 (*E*)-bromomethoxydiene moiety present at the end of the polyol chain present in PM and oscillariolide with useful synthetic yields. These results were key for two important aspects:

- NMR comparison of **8** with the natural product allowed us to confirm by chemical synthesis the structural architecture present at the east side of the natural products.[5]
- Having a robust methodology to create the BMD moiety is of vital importance for the synthesis of the whole C19-C31 polyhydroxylated chain (Chapter 4) and to confront the total synthesis of all the members of this family of natural products.

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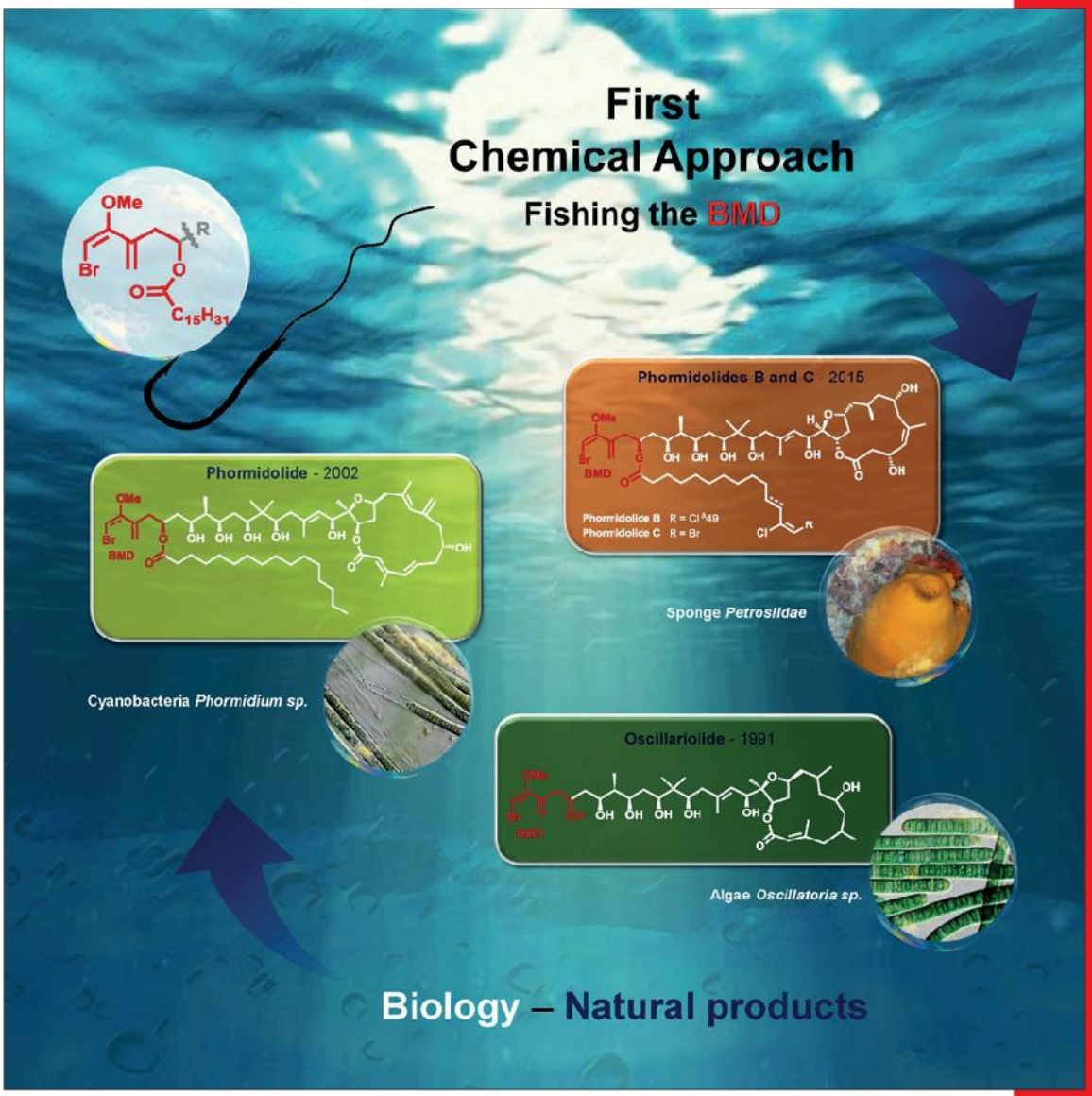

Front Cover Picture:
M. Álvarez et al.
Synthesis of (*E*)-4-Bromo-3-methoxybut-3-en-2-one, the Key Fragment in the Polyhydroxylated Chain Common to Oscillariolide and Phormidolides A–C

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CHEMISTRY A European Journal Cover Profile

Synthesis of (*E*)-4-Bromo-3-methoxybut-3-en-2-one, the Key Fragment in the Polyhydroxylated Chain Common to Oscillariolide and Phormidolides A–C


Adriana Lorente


Alejandro Gil


Fernando Albericio


Janire Lamariano


Mercedes Álvarez

Invited for the cover of this issue is the group of Mercedes Álvarez at the University of Barcelona. The image depicts the Álvarez group's effort to successfully "fish" an efficient strategy for the synthesis of the bromomethoxydiene (BMD) moiety present in marine natural products such as phormidolides and oscillariolides. Read the full text of the article at 10.1002/chem.201600770.

What is the most significant result in this study?

Phormidolides and oscillariolides are marine natural products with complex structures and interesting bioactivities. Bromomethoxydiene (BMD) is a small moiety present at the end of the polyol tail in these families of compounds. The high functionalization of this fragment and the required stereochemistry represented the most complicated challenge for its synthesis. The importance of this BMD motif relies both on its unprecedented presence in such polyketide macrolides and on its strategic position within the structure of the natural product as its synthesis is crucial to link the polyhydroxy chain to distinct fatty acids. BMD has been synthesized for first time and, furthermore, our methodology has enabled us to further confirm the stereochemistry of the polyol by NMR comparison with phormidolide A.

What aspects of this project do you find most exciting?

Confronting a total synthesis is always an attractive challenge and this final objective cannot be achieved without completing minor milestones. One victory for us has been the validation of a synthetic pathway towards the BMD moiety common in these families of natural products after intense work and effort. These small victories are what encourages us to continue and finish the synthesis of phormidolides B and C. In this specific study a difficult moiety has been synthesized for the first time and we were very pleased to observe that the NMR signals were in agreement with the previously reported data.

What was the inspiration for this cover desing?

The work reported in the publication may seem simple but a lot of efforts in terms of time and reagents have been necessary to find out the way to synthesize the appropriate *E*-bromoketone and successfully introduce it in a model of the polyol. After all this work we felt we finally had "fished" an efficient strategy so we decided to design a cover where the effort of synthesizing the BMD moiety was shown as the intricate work of the fishermen.

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Natural Products |*Hot Paper*|

Synthesis of (*E*)-4-Bromo-3-methoxybut-3-en-2-one, the Key Fragment in the Polyhydroxylated Chain Common to Oscillariolide and Phormidolides A–C

Alejandro Gil,[a, b] Janire Lamariano-Merketegi,[a, b] Adriana Lorente,[a, b, f] Fernando Albericio,[b, c, d] and Mercedes Álvarez*[a, b, e]

Abstract: The terminal bromomethoxydiene (BMD) moiety of the polyhydroxylated chain present in phormidolides and oscillariolides has been synthesized for first time. Several strategies for the stereoselective synthesis of the 4-bromo-3-methoxybut-3-en-2-ones are described. Furthermore, a preliminary study to successfully introduce the BMD within the polyol chain and the fatty acid allowed us to corroborate the end structure of the polyol.

Oscillariolide[1] and phormidolides A–C[2,3] are members of a family of compounds isolated from marine organisms[4] with interesting structural and biological activities (Figure 1). They have all shown toxicity against different biological targets, such as fertilized starfish eggs, brine shrimp, and cancer cell lines with an unknown mechanism of action. These natural compounds exhibit characteristic structural similarities such as: a tetrahydrofuran (THF)-containing macrolide ring with a different number of unsaturations and a common polyhydroxylated chain containing six stereocenters in a *syn*-relative configuration. This polyol chain ends with a synthetically challenging common bromomethoxydiene moiety (BMD), an (*E*)-3-substituted-1-bromo-2-methoxybuta-1,3-diene. Phormidolides A–C polyhydroxylated chain differs from that of oscillariolide in one fatty acid linked to a polyol by an ester bond with the hydroxyl closest to BMD. Therefore, the importance of this BMD motif relies both on its unprecedented presence in such polyketide macrolides and on its strategic position within the structure of the natural product as its synthesis is crucial to link the polyhydroxy chain to distinct fatty acids.

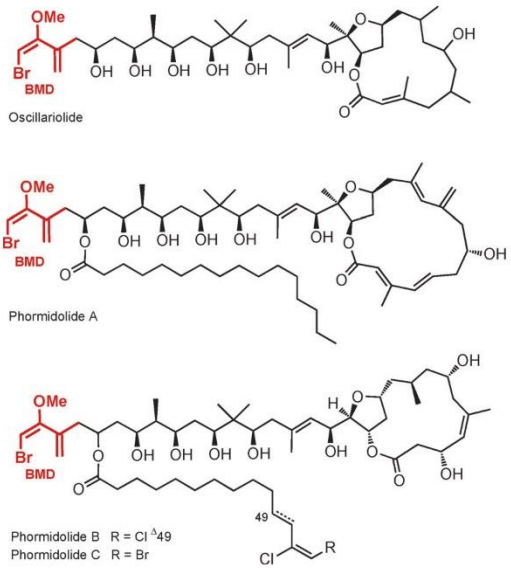

Figure 1. Structures of oscillariolide and phormidolides A–C.

Several strategies for the synthesis of the macrocyclic core present in phormidolides B and C have been reported[3,5] as well as a preliminary study to link the macrocyclic core and the polyol by the formation of the allylic alcohol attached to the THF ring[6] but no publications describing the polyol chain synthesis have been reported yet. To deal with this synthesis, we envisage the formation of the polyol chain BMD moiety by the following reaction sequence: a Mukaiyama aldol addition reaction[7] between 2-bromo-1-methoxyvinyl methyl ketone (BMK) (*E*)-**1** and the corresponding aldehyde, followed by esterification with the appropriate fatty acid and final olefination[8] for the formation of the terminal diene (Figure 2).

For this purpose, the target compound is the (*E*)-4-bromo-3-methoxybut-3-en-2-one (*E*)-**1** as a single isomer. There are few publications reporting the synthesis of bromoenolether ke-

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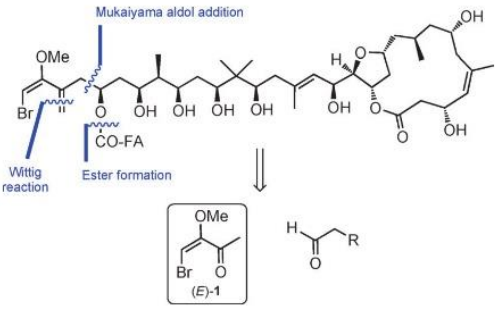
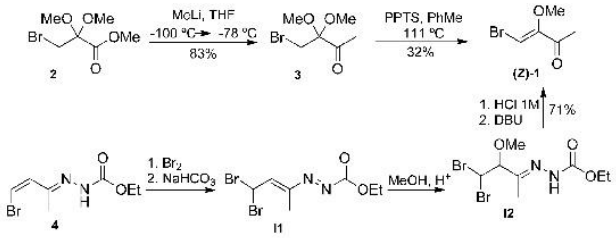


Figure 2. Retrosynthetic analysis for the introduction of key fragment (*E*)-**1**.

tones and generally they report the undesired *Z* isomer.[9,10] Therefore, tremendous efforts have been necessary to develop a suitable strategy that delivers the desired and key compound (*E*)-**1**.

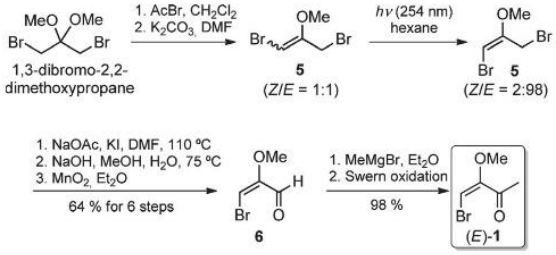
The first attempted methodology was a three-step procedure based on the transformation of bromopyruvic acid into the dimethyl acetal-methyl esther **2**[11] followed by reaction with MeLi at low temperature to give ketone **3**. The final step was the elimination of methanol under acidic conditions to give compound **1** (Scheme 1). After NMR characterization of **1**, NOE 1D studies confirmed the *Z* stereochemistry for the obtained compound. The lack of NOE correlation between the vinylic proton and the methoxy group was significant.[12] It is worth mentioning that photochemical[13] and I_2-promoted isomerization[14] of (*Z*)-**1** to give the desired *E* isomer were tested unsuccessfully due to decomposition or unreactivity of (*Z*)-**1**, respectively.



Scheme 1. Different synthetic strategies to obtain (*Z*)-**1**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; PPTS = pyridinium *p*-toluenesulfonate.

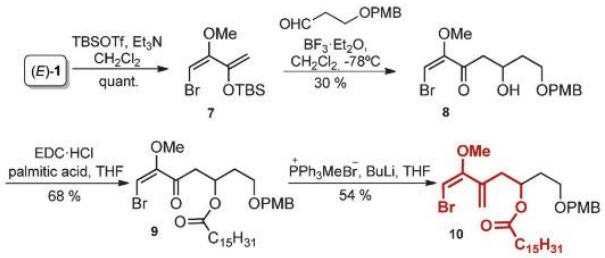
Interestingly, Feuerer and Severin described the synthesis of 3-(benzyloxy)-4-bromo-3-buten-2-one as an isomeric mixture (*E*/*Z* = 10:1).[10] Therefore, their methodology was tested by replacing the benzylic alcohol with methanol (Scheme 1). Bromohydrazone **4** was subjected to a one-pot–five-transformation sequence in which the first steps were bromination and elimination leading to the formation of the corresponding intense red ene–azo compound **I1**. Then, methanol addition in acidic media delivered the dibromo-methoxy intermediate **I2**. Finally, hydrolysis and DBU-promoted HBr elimination afforded again BMK (*Z*)-**1** in a 71% yield relative to **4**. NMR spectroscopy data matched the previously characterized *Z* isomer.

Finally, the effective methodology to synthesize (*E*)-**1** is depicted in Scheme 2. Dibromo compound **5**[13] as an isomeric mixture (*Z*/*E* = 1:1) was obtained, starting from 1,3-dibromo-2,2-dimethoxypropane. This mixture was enriched in the desired *E* isomer by irradiation with UV light at 254 nm in hexane for 8 h. A three-step reaction sequence involving acetylation, hydrolysis, and allylic oxidation led to formyl derivative **6**. The overall yield of this six-step sequence was high and no silica purification was needed during the intermediate steps. Finally, alkylation with MeMgBr and a second allylic oxidation delivered (*E*)-**1** as a single isomer.[15] NOE 1D correlation between the vinyl hydrogen and the methoxy group confirmed *E* stereochemistry.[12] (*E*)-Bromomethoxyvinylmethyl ketone (*E*)-**1** was obtained for the first time by an easily scalable procedure.



Scheme 2. Synthesis of bromoketone (*E*)-**1**.

Once (*E*)-**1** was obtained, a suitable strategy to introduce the BMD moiety into the polyhydroxylated chain was examined (Scheme 3). BMK (*E*)-**1** was converted to the corresponding silylenolether **7** to perform a Mukaiyama aldol addition with 3-[(4-methoxybenzyl)oxy]propanal as a model aldehyde to mimic the polyol chain. Interestingly, the use of the *tert*-butyldimethylsilyl enol ether **7** was mandatory due to the reduced stability of the corresponding trimethylsilyl derivative. Both transformations worked well in terms of yield, delivering ketol **8**. Then, palmitic acid, the fatty acid present in phormidolide A, was introduced using carbodiimide as a condensation agent. Finally, Wittig olefination resulted in the best method to introduce the methylidene extra carbon atom with good yield to give diene **10**. The chemical shifts of the key protons in the BMD moiety of compound **10**[16] matched those obtained for the natural products,[1–3] thereby demonstrating that this route creates the BMD fragment present in this compound family. This is the



Scheme 3. Synthesis of **10**, model of the polyol chain west fragment.

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first synthetic pathway for the challenging BMD west fragment of the polyol chain common to oscillariolide and phormidolides and establishes the route for the condensation of the polyhydroxy chain and the fatty acids to complete their total synthesis.

In conclusion, the synthesis of (*E*)- and (*Z*)-4-bromo-3-methoxybut-3-en-2-ones has been described for the first time with good yields and easy procedures. A robust, high-yielding, efficient, and scalable methodology for the synthesis of key compound (*E*)-**1** BMK is herein described. It is entirely based in spot-to-spot reactions from the commercially available 1,3-dibromo-2,2-dimethoxypropane without intermediate purification, which only requires a final silica column chromatography to give a cleaner sample of (*E*)-**1** with an 63% overall yield after eight synthetic transformations.

In addition, the Mukaiyama aldol addition–esterification–Wittig olefination strategy was shown to be a nice method to introduce the BMD moiety at the end of the polyhydroxylated chain. This synthesis has given access, for the first time, to the west fragment of these challenging molecules. These results are of great significance for the synthesis of the polyol chain, common to oscillariolide and phormidolides. The application of this synthetic strategy to the total synthesis of phormidolides is ongoing.

Acknowledgements

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Keywords: enantioselectivity · Mukaiyama aldol addition · natural products · synthesis · Wittig olefination

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[15] The chemical shift of the vinylic proton in the two stereoisomers of **1** show an important difference due to the influence of bromide and methoxy groups. They are $\delta = 6.93$ ppm for (*Z*)-**1** and and $\delta = 5.64$ ppm for (*E*)-**1**.
[16] See Table 1 in the Supporting Information.

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Synthesis of (*E*)-4-Bromo-3-methoxybut-3-en-2-one, the Key Fragment in the Polyhydroxylated Chain Common to Oscillariolide and PM A-C.

Supporting Information

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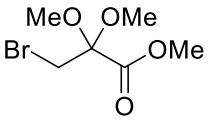
General Procedures.

Tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were dried using a PureSolv solvent purification system. All other solvents and reagents were used as purchased without further purification, unless indicated. Flash column chromatography was performed on SDS silica gel (60A 35-70 µm) as stationary phase. Analytical TLC was done on pre-coated silica gel 60 F_{254} plates (0.2 mm thick, 20x20 cm) and visualized under UV light (254 and 360 nm), with $KMnO_4$ or with phosphomolybdic acid in ethanol. IR spectra were recorded on a Thermo Nicolet FT-IR Nexus spectrometer. Melting points were performed in a Büchi B-540 melting point apparatus. ^{1}H-NMR and ^{13}C-NMR were recorded on a Varian Mercury 400MHz or a Varian VNMRS500 500MHz. Chemical shifts are reported in ppm referenced to the residual solvent peaks ($CDCl_3$) and coupling constants are reported in Hz. Multiplicity of the carbons was assigned with gHSQC experiments. Standard abbreviations for off-resonance decoupling were employed: s = singlet, d = doublet, t = triplet, q = quadruplet. The same abbreviations were also used for the multiplicity of signals in ^{1}H-NMR, as well as, bs = broad singlet, bd = broad doublet, m = multiplet. High Resolution Mass Spectroscopy (HRMS) was performed an Agilent LC/MSD-TOF 2006 using ESI-MS technique. Mass Spectroscopy (MS-CI) was performed in a Shimadzu QP2010 using chemical ionization (CI) technique. HPLC analysis were carried out in a Waters 2695 apparatus with a Waters 996 photodiode array detector. The used column was a C_{18} (4.6 x 150 mm, 5 □m) and linear gradients from 40 to 60% of acetonitrile-water were run over 8 minutes. Photoisomerization reaction was conducted in a Rayonet RMR-600 photochemical reactor with 254 nm UV lamps.

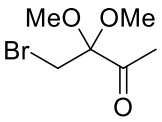
Experimental procedures and characterization

Methyl 3-bromo-2,2-dimethoxypropanoate (2)[1]



Trimethyl orthoformate (12 mL, 112 mmol) and sulfuric acid (1.2 mL, 22.5 mmol) were added to a solution of bromopyruvic acid (3.4 g, 20.5 mmol) in methanol (41 mL). The reaction mixture was stirred at 75 ºC during 24 h. The reaction was quenched with 60 mL of $NaHCO_3$ saturated solution and the mixture was extracted with Et_2O. The organic phase was dried over Na_2SO_4 and evaporated to obtain the crude mixture which was purified by distillation at 3.7 mbar and 82 ºC to obtain **2** (3 g, 67%) as a colorless oil. ^{1}H NMR data were in agreement with that reported in the literature.

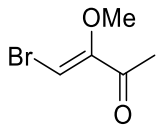
4-Bromo-3,3-dimethoxybutan-2-one (3)



A solution of MeLi 1.6 M in Et_2O (9 mL, 14.5 mmol) was added slowly to a solution of **2** (2.2 g, 9.6 mmol) in THF (60 mL) at -100 ºC and the reaction was stirred 45 minutes at -100 ºC and 45 minutes at -78 ºC. After this time, the reaction was quenched with NH_4Cl saturated solution (60 mL) and extracted with EtOAc. The organic phase was dried with Na_2SO_4 and evaporated to obtain methylketone **3** (1.7 g, 83%) as a colorless oil. IR (KBr film) ν 2944, 2831, 1728, 1352, 1057 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.28 (s, 6H), 3.50 (s,

2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.3 (q), 29.3 (q), 50.0 (t), 101.4 (s), 206.3 (s). MS-CI: *m/z* calcd. for $C_6H_{11}BrO_3$ 210, found 179 (M-CH_3OH+H).

(*Z*)-4-Bromo-3-methoxybut-3-en-2-one (*Z*)-1



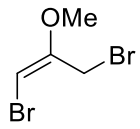
Method 1:

PPTS (125 mg, 0.5 mmol) was added to a solution of **3** (1.1 g, 5.2 mmol) in toluene (50 mL) and the mixture was refluxed during 48h. After this time, the reaction was introduced in a silica column using hexane:EtOAc 93:7 as a mobile phase. The ketone **(*Z*)-1** was isolated as a yellowish oil (300 mg, 32%). IR (KBr film) ν 3094, 2961, 1720, 1575, 1210 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.82 (s, 3H), 6.93 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 26.4 (q), 59.7 (q), 108.0 (d), 156.3 (s), 193.0 (s). MS-CI: *m/z* calcd. for $C_5H_7BrO_2$ 178, found 179 (M+H).

Method 2:

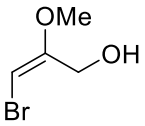
Bromine (180 mg, 1.02 mmol) was added to a solution of **4**[2] (240 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) at -50 ºC. The temperature was allowed to rise to 0ºC and the solution was stirred during 5 minures. After this time, 10 mL of 1M $NaHCO_3$ aqueous solution were added and the reaction mixture was stirred vigorously for 1 h at rt. The red organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The crude material was diluted with MeOH (5 mL) and 1 mL of methanolic sulfuric acid (2 drops of H_2SO_4 in 1 mL of MeOH) was added at 0 ºC and it was stirred until red colour disappeared. Then, HCl 1M (10 mL) and CH_2O 37% solution (1 mL) were added and it was stirred for 1 h at rt. The reaction was extracted three times with Et_2O, washed with brine, dried over $MgSO_4$ and evaporated. DBU (0.3 mL, 2.04 mmol) was added to a solution of the crude mixture in Et_2O (10 mL) producing the formation of an insoluble material. The mixture was stirred for 1h and washed with 1M HCl (5 mL) three times. The crude was purified with silica gel chromatography to obtain **(*Z*)-1** (130 mg, 71%) as a yellowish oil. ^{1}H NMR data were identical to those obtained in Method 1.

(E)-1,3-dibromo-2-methoxyprop-1-ene (5)[3]



A solution of an isomeric mixture of **5** (*Z*:*E* = 1:1) (3.38 g, 14.7 mmol) in dry hexane (220 mL) was bubbled with N_2 for 15 minutes and then it was irradiated under UV light (254 nm) during 8 h. The reaction was monitorized via HPLC analysis using a 40%-60% gradient acetonitrile-water in 8 minutes. The retention times for each isomer are: *Z* = 4.95 minutes, *E* = 6.04 minutes. When the conversion was complete, the solvent was evaporated and **5** was recovered quantitatively as a single *E* isomer. ^{1}H NMR data were in agreement with that reported in the literature.

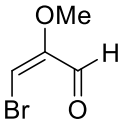
(*E*)-3-Bromo-2-methoxyprop-2-en-1-ol (S1)



NaOAc (18 g, 220 mmol) and KI (500 mg, 2.94 mmol) were added to a solution of **5** (3.22 g, 14 mmol) in DMF (180 mL) and the mixture was stirred at 110 ºC for 1 h. The reaction was cooled down to rt and Et_2O and water were added. The organic phase was washed 5 times with H_2O, dried over Na_2SO_4 and evaporated. The crude was used in the following step without further purification.

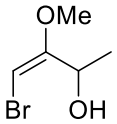
NaOH (11.76 g, 294 mmol) in H_2O were added to a solution of the previous crude in MeOH (200 mL). The mixture was stirred at 75 ºC for 90 minutes. The reaction was cooled down to rt and extracted with CH_2Cl_2. The organic extract was dried over Na_2SO_4 and evaporated to obtain **S1** (1.8 g, 77 %) as an enough pure sample to characterize and continue the synthesis. IR (KBr film) ν 3386 (br), 3106, 2935, 1621, 1204 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 4.36 (s, 1H), 4.37 (s, 1H), 5.25 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.5 (t), 61.1 (q), 78.7 (d), 157.3 (s). MS-CI: *m/z* calcd. for $C_4H_7BrO_2$ 166, found 167 (M+H).

(*E*)-3-Bromo-2-methoxyacrylaldehyde (6)



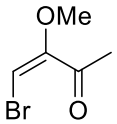
MnO_2 (1 g, 14 mmol) was added to a solution of **S1** (50 mg, 0.3 mmol) in Et_2O (5 mL) and the mixture was stirred vigorously for 16 h. The reaction mixture was filtered through a pad of celite and the solvent evaporated to obtain **6** (41 mg, 83 %) as a yellowish solid. Mp 51.5-53 ºC. IR (KBr film) ν 3088, 2961, 1702, 1586, 1210 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 6.34 (s, 1H), 10.00 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 56.0 (q), 97.6 (d), 151.8 (s), 185.3 (s). MS-CI: *m/z* calcd. for $C_4H_5BrO_2$ 164, found 165 (M+H).

(*E*)-4-Bromo-3-methoxybut-3-en-2-ol (S2)



MeMgBr 3 M in Et_2O solution (6.24 mL, 18.7 mmol) was added to a solution of **6** (1.93 g, 11.7 mmol) in Et_2O at 0 ºC and the reaction was stirred at rt for 60 minutes. The reaction was quenched with water and extracted three times with Et_2O. The ethereal phase was washed with brine, dried over $MgSO_4$ and evaporated to obtain **S2** as a yellowish oil (2.14 g, quant.). IR (KBr film) ν 3392 (br), 2976, 2932, 1618, 1451, 1205, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.6 Hz, 3H), 3.62 (s, 3H), 4.92 (q, *J* = 6.6 Hz, 1H), 5.14 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.7 (q), 55.6 (q), 66.0 (d), 77.0 (d), 159.5 (s). MS-CI: *m/z* calcd. for $C_5H_9BrO_2$ 180, found 163 (M-H_2O+H).

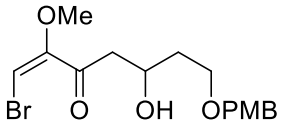
(*E*)-4-Bromo-3-methoxybut-3-en-2-one (*E*)-1



DMSO (0.15 mL, 2.2 mmol) was added to a solution of oxalyl chloride (0.1 mL, 1.1 mmol) in CH_2Cl_2 (2 mL) at -78 ºC and the reaction was stirred for 30 minutes. A solution of **6** (110 mg, 0.6 mmol) in CH_2Cl_2 (1 mL) was added and the mixture was stirred for 45 minutes at the same temperature. Et_3N (0.61 mL, 4.4 mmol) was added and the reaction was stirred for 30 minutes at 0 ºC. The reaction was quenched with NH_4Cl saturated solution and extracted with CH_2Cl_2. The organic

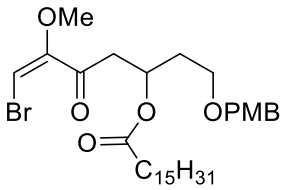
layer was washed with brine, dried over $MgSO_4$ and evaporated. The crude was purified in silica gel chromatography (9:1 hexane:EtOAc) to obtain **(*E*)-1** (105 mg, 98 %) as a yellowish oil. IR (KBr film) ν 3094, 2961, 1720, 1575, 1210 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.66 (s, 3H), 5.64 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.0 (q), 55.9 (q), 83.7 (d), 153.4 (s), 195.4 (s). MS-CI: *m/z* calcd. for $C_5H_7BrO_2$ 178, found 179 (M+H).

(*E*)-1-Bromo-5-hydroxy-2-methoxy-7-((4-methoxybenzyl)oxy)hept-1-en-3-one (8)



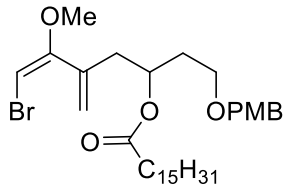
Et_3N (58 μl, 0.42 mmol) and TBSOTf (71 μl, 0.31 mmol) were added sequentially to a solution of **(*E*)-1** (50 mg, 0.28 mmol) in CH_2Cl_2 (3 mL) and the reaction was stirred for 16 h until complete conversion was observed by TLC. The reaction was quenched with saturated NH_4Cl solution (3 mL) and the organic layer was washed three times with saturated NH_4Cl solution, dried over Na_2SO_4, evaporated to give the silyl enol ether **7** used in the next step without further purification. 3-((4-Methoxybenzyl)oxy)propanal (58 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added to a solution of **7** in CH_2Cl_2 (2 mL) at -78 ºC. Then, $BF_3{\cdot}Et_2O$ (35 μl, 0.28 mmol) was added dropwise and the reaction was stirred for 90 minutes at the same temperature. The reaction was quenched by addition of $NaHCO_3$ saturated solution (4 mL) and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4, evaporated and purified with column chromatography to obtain **8** as a colorless oil (31 mg, 30 % for two steps). IR (KBr film) ν 3404 (br), 2958, 2929, 1711, 1612, 1511, 1251, 1089 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.76 – 1.82 (m, 2H), 2.85 – 2.88 (m, 2H), 3.60 – 3.67 (m, 2H), 3.64 (s, 3H), 3.80 (s, 3H), 4.31 (m, 1H), 4.44 (s, 2H), 5.66 (s, 1H), 6.85 – 6.89 (d, 2H), 7.22 – 7.26 (d, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 36.0 (t), 46.7 (t), 55.3 (q), 56.0 (q), 66.3 (d), 67.6 (t), 72.9 (t), 84.4 (d), 113.8 (d), 129.3 (d), 130.1 (s), 152.9 (s), 159.2 (s), 197.4 (s). HRMS (+ESI): *m/z* calcd. for $C_{16}H_{21}BrNaO_5$ (M+Na) 395.0465, found 395.0452.

(*E*)-7-Bromo-6-methoxy-1-((4-methoxybenzyl)oxy)-5-oxohept-6-en-3-yl palmitate (9)



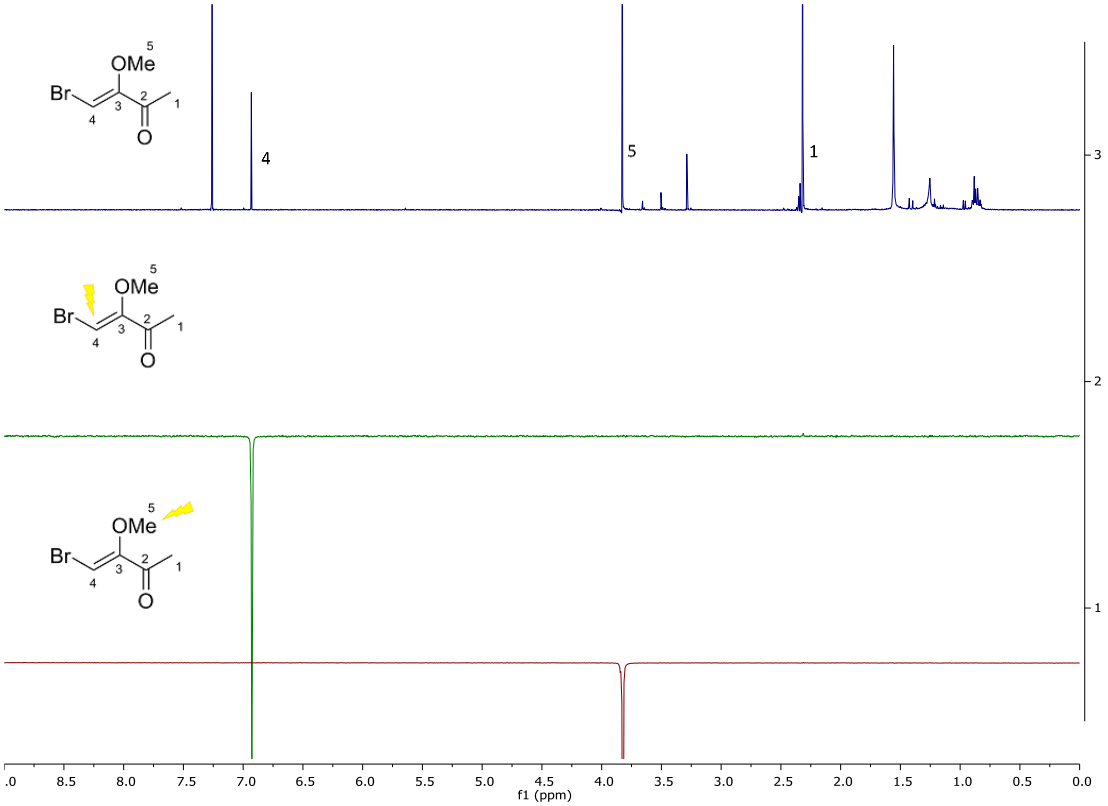
EDC·HCl (26 mg, 0.17 mmol), palmitic acid (43 mg, 0.17 mmol) and DMAP (1 mg, 8 μmol) were added to a solution of **8** (22 mg, 0.06 mmol) in THF (1 mL) and the reaction was stirred at rt for 2 h. The reaction was quenched with NH_4Cl saturated solution (1 mL) and extracted three times with Et_2O. The organic extracts were dried over Na_2SO_4, evaporated and purified with column chromatography to obtain **9** as a colorless oil (17 mg, 68% brsm) and **8** (7 mg). IR (KBr film) ν 2915, 2851, 1728, 1708, 1511, 1248, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.1 Hz, 3H), 1.24 – 1.28 (m, 24H), 1.53 – 1.59 (m, 2H), 1.93 (q, *J* = 6.2 Hz, 2H), 2.21 (td, *J* = 7.1, 1.3 Hz, 2H), 2.90 – 3.05 (m, 2H), 3.49 (m, 2H), 3.62 (s, 3H), 3.80 (s, 3H), 4.40 (s, 2H), 5.38 – 5.49 (m, 1H), 5.62 (s, 1H), 6.84 – 6.88 (d, 2H), 7.22 – 7.26 (d, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1 (q), 24.9 (t), 29.4 (t), 34.1 (t), 34.4 (t), 44.4 (t), 55.3 (q), 55.9 (q), 66.2 (t), 67.7 (d), 72.6 (t), 84.1 (d), 113.7 (d), 129.3 (d), 130.4 (s), 152.9 (s), 159.1 (s), 173.1 (s), 194.2 (s). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{51}BrNaO_6$ (M+Na) 633.2761, found 633.2765.

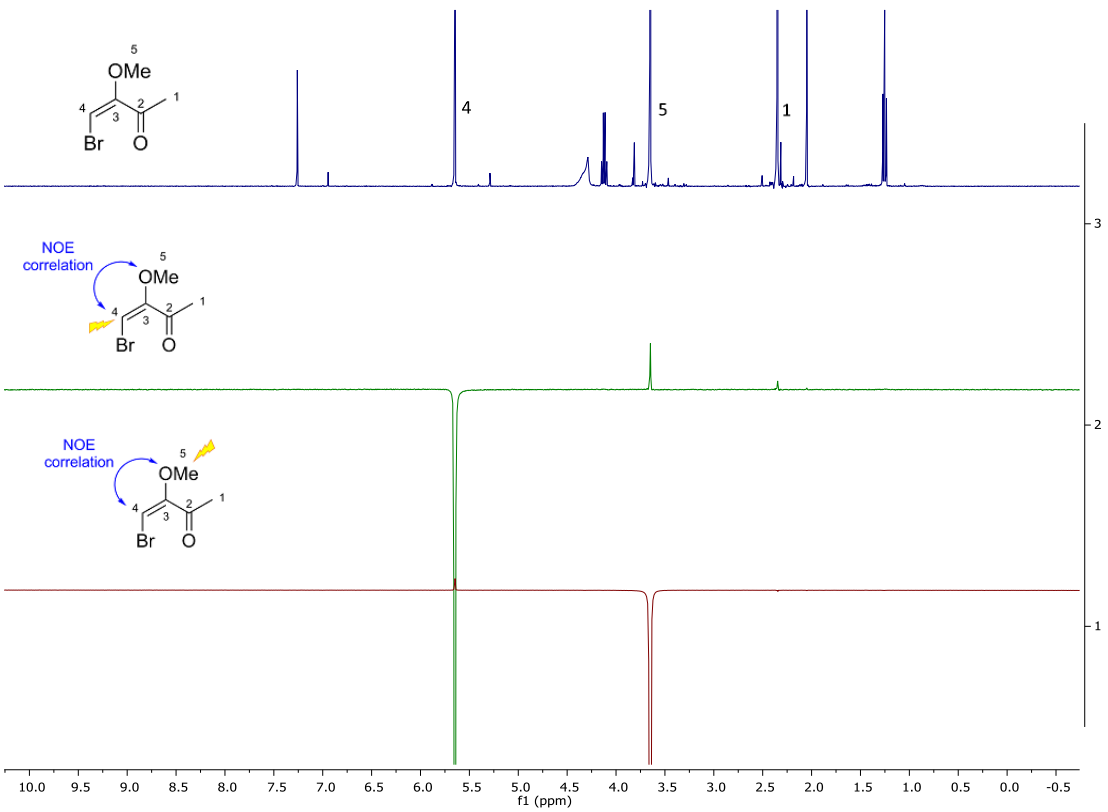
(*E*)-7-Bromo-6-methoxy-1-((4-methoxybenzyl)oxy)-5-methylenehept-6-en-3-yl palmitate (10)



BuLi 2.5 M (32 mL, 0.08 mmol) was added to a suspension of methyltriphenylphosphonium bromide (29 mg, 0.08 mmol) in THF (0.3 mL) at 0 ºC. The intense yellow solution was stirred 15 minutes at 0 ºC, 15 minutes at rt and then it was cooled down to -78 ºC. A solution of **9** (5 mg, 8 μmol) in THF (0.2 mL) was cannulated into the reacting mixture. The solution was stirred 1 hour at -78 ºC and 30 minutes at rt. The reaction was quenched with NH_4Cl saturated solution (1 mL) and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4, evaporated and purified with column chromatography to obtain **10** as a colorless oil (1.6 mg, 54% brsm) and **9** (2 mg). IR (KBr film) ν 2918, 2851, 1734, 1511, 1248, 1147 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.25 (s, 24H), 1.57 (t, *J* = 7.2 Hz, 2H), 1.81 – 1.97 (m, 2H), 2.23 (td, *J* = 7.5, 1.8 Hz, 2H), 2.51 – 2.55 (m, 2H), 3.43 – 3.51 (m, 2H), 3.56 (s, 3H), 3.80 (s, 3H), 4.40 (s, 2H), 5.02 – 5.10 (m, 1H), 5.31 (s, 1H), 5.34 (d, *J* = 1.4 Hz, 1H), 5.40 (d, *J* = 1.4 Hz, 1H), 6.84 – 6.89 (d, 2H), 7.22 – 7.26 (d, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 25.0 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.7 (t, 6C), 31.9 (t), 34.0 (t), 34.6 (t), 38.9 (t), 55.3 (q), 55.6 (q), 66.5 (t), 69.8 (d), 72.6 (t), 78.7 (d), 113.7 (d), 121.9 (t), 129.2 (d), 130.5 (s), 138.4 (s), 158.5 (s), 159.1 (s), 173.2 (s). HRMS (+ESI): *m/z* calcd. for $C_{33}H_{53}BrNaO_5$ (M+Na) 631.2969, found 631.2966.

NOE 1D experiments:





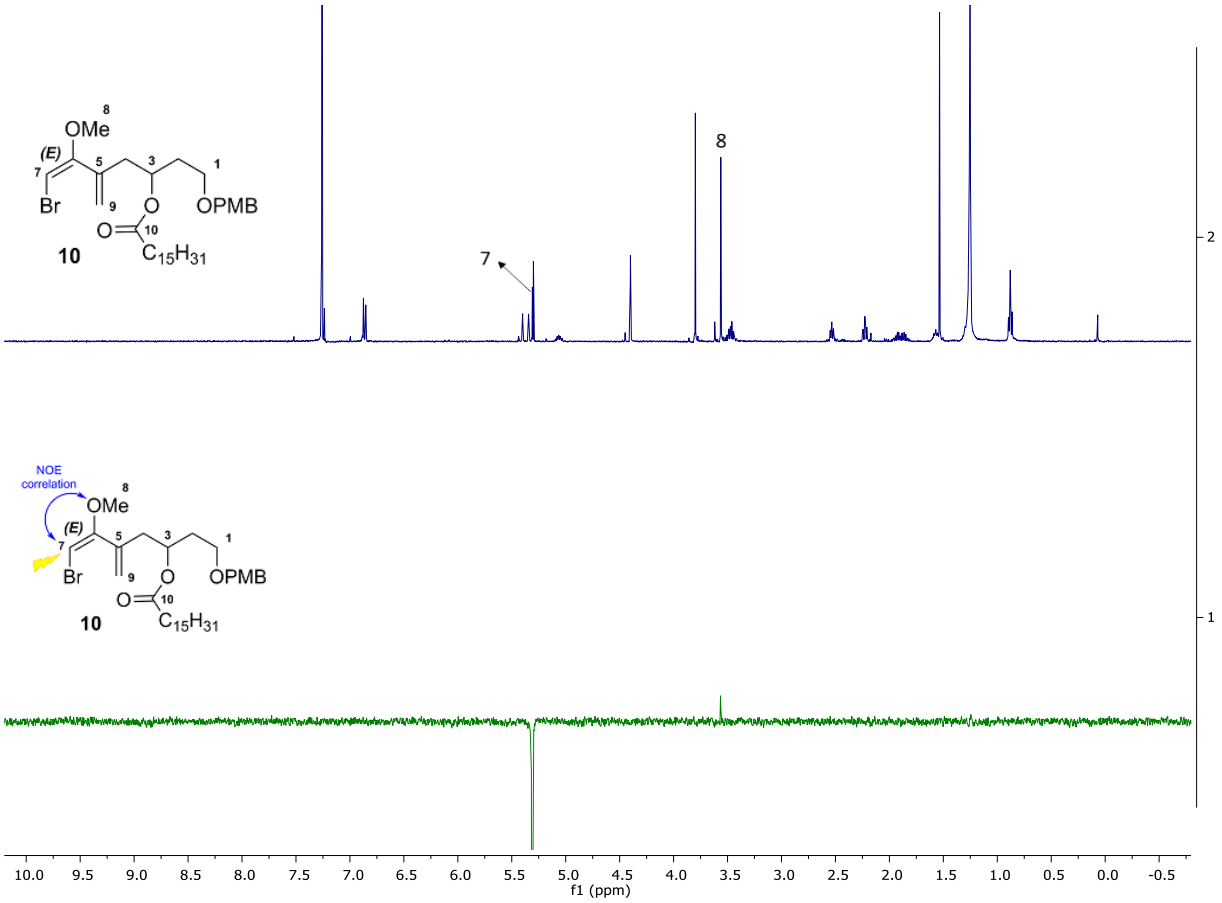
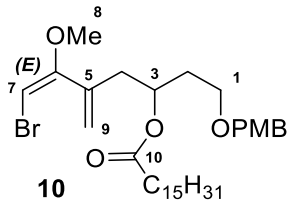


Table 1. Chemical shift comparison between **10** and Phormidolide A.



Position	δ ^{1}H RMN **10**	δ ^{1}H RMN **Ph A**	δ ^{13}C RMN **10**	δ ^{13}C RMN **Ph A**
3	5.06	5.00	69.8	70.5
5	--	--	138.4	138.3
6	--	--	158.5	158.4
7	5.31	5.33	78.6	78.8
8	3.57	3.59	55.6	55.6
9	5.34, 5.40	5.37, 5.42	121.8	122.1
10	--	--	173.2	173.7

Chapter 4

Enantioselective synthesis of the polyhydroxylated chain present on PM B-D

Oscillariolide[1] and phormidolides A-D[2,3] share the same common polyhydroxylated chain located between the macrocyclic core and the corresponding fatty acid (Figure 1).[4] Structure determination of oscillariolide by NMR analysis revealed the (*E*) configuration at C30 position and the relative stereochemistry of the stereocenters in the C19-C27 fragment. With the isolation of phormidolide A it was possible to determine the absolute configuration of the chain. First, Gerwick and co-workers were able to assign the relative stereochemistry of the whole molecule using different *J-based* NMR methodologies. Secondly, they derivatized a bis-acetonide compound of PM A with (R)-methoxyphenylacetic acid at position C16 and using NMR variable T experiments[5] the absolute configuration of that stereocenter was obtained, thus obtaining the absolute stereochemistry of the rest of the molecule. Summarizing, the polyhydroxylated chain common in this family of natural product has 7 stereocenters, 5 hydroxylic positions and a terminal bromomethoxydiene (BMD) moiety (Chapter 3).[6]

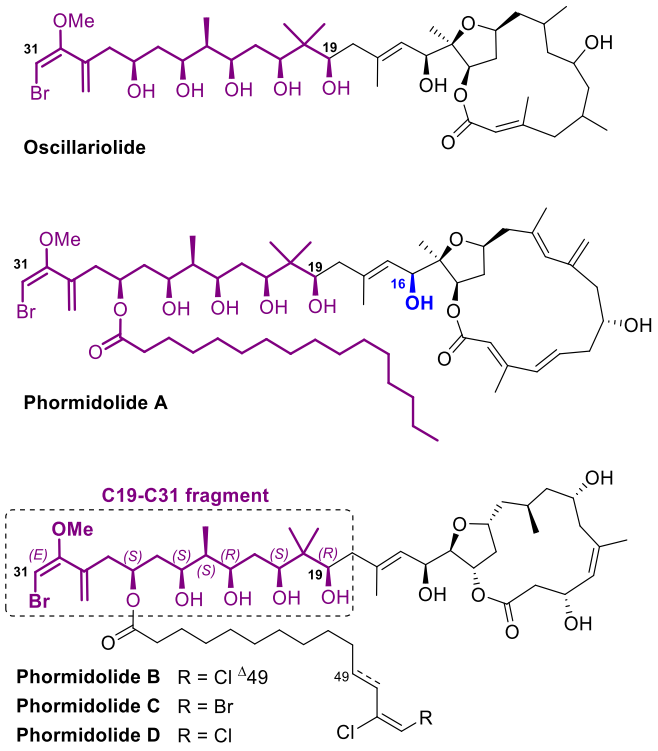
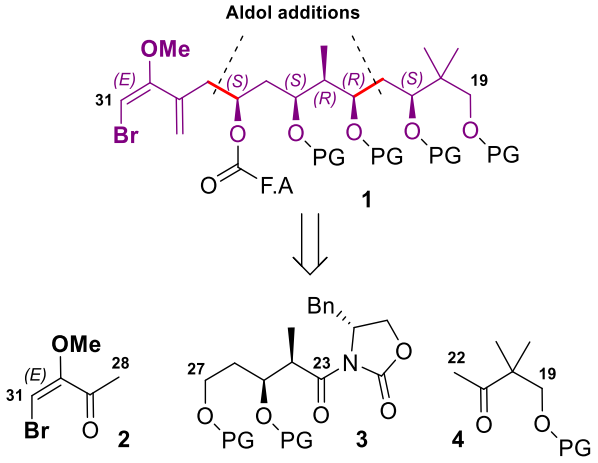


Figure 1. Natural products containing the C19-C31 polyhydroxylated chain present in PM B-D.

In PM B-D, this interesting moiety corresponds numerically to the C19-C31 fragment (**1**) and, as the macrocyclic core, it is an obvious synthetic challenge to face before total synthesis. For its synthesis, a convergent retrosynthetic analysis was designed and validated by Dr. Janire Lamariano Merketegi during here PhD studies in the group and it is still being used for this synthesis (Scheme 1a). On it, C19-C22, C23-C27 and C28-C31 (**4**, **3** and **2** respectively) fragments are separately synthesized and linked using aldol addition methodologies. The general synthetic

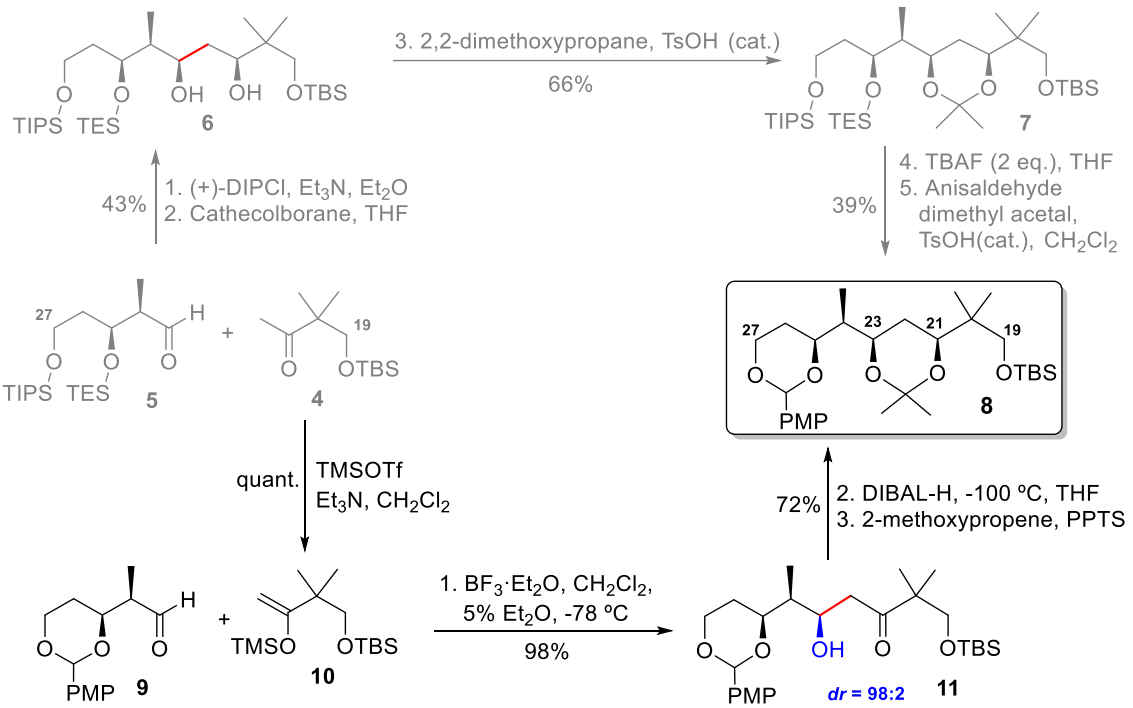
idea is to create the C22-C23 bond in the first place and then obtain a molecule with orthogonal protecting groups at the terminal positions (C19-C27 fragment). Next, selective deprotection and oxidation at C27 gives the possibility to introduce ketone **2** to complete the C9-C31 scaffold. Both parts of the synthesis will be commented individually highlighting their most relevant aspects.



Scheme 1. General retrosynthetic analysis for the synthesis of the C9-C31 polyol chain.

C19-C27 synthetic pathway

After the preparation of compounds **5** and **4** Dr. Janire Lamariano carried out an extensive analysis of silyl protecting groups on **5** and different aldol reaction conditions for the formation of the C22-C23 bond. Thanks to this optimization, she was able to obtain the corresponding ketol using boron enolates in a modest yield but total diastereoselectivity which, after 1,3-*syn* reduction with CatBH and posterior purification, yielded diol **6** (Scheme 2). Protection of C21 and C23 hydroxyl positions as dimethyl ketal gave fully protected compound **7** but two extra steps were required to exchange the C25 and C27 silyl protecting groups by the cyclic *p*-methoxybenzyl ketal to achieve the desired orthogonal C19-C27 scaffold **8**. These additional steps did not work with excellent yield and they were a problem for the overall yield of the C19-C27 synthetic route.



Scheme 2. Comparison between the FGS for the C19-C27 fragment and the newly developed one using PMP as initial protecting group for positions C25 and C27.

With the only objective of improving the yield and the ease of scale-up of key compound **8** we asked ourselves three different questions:

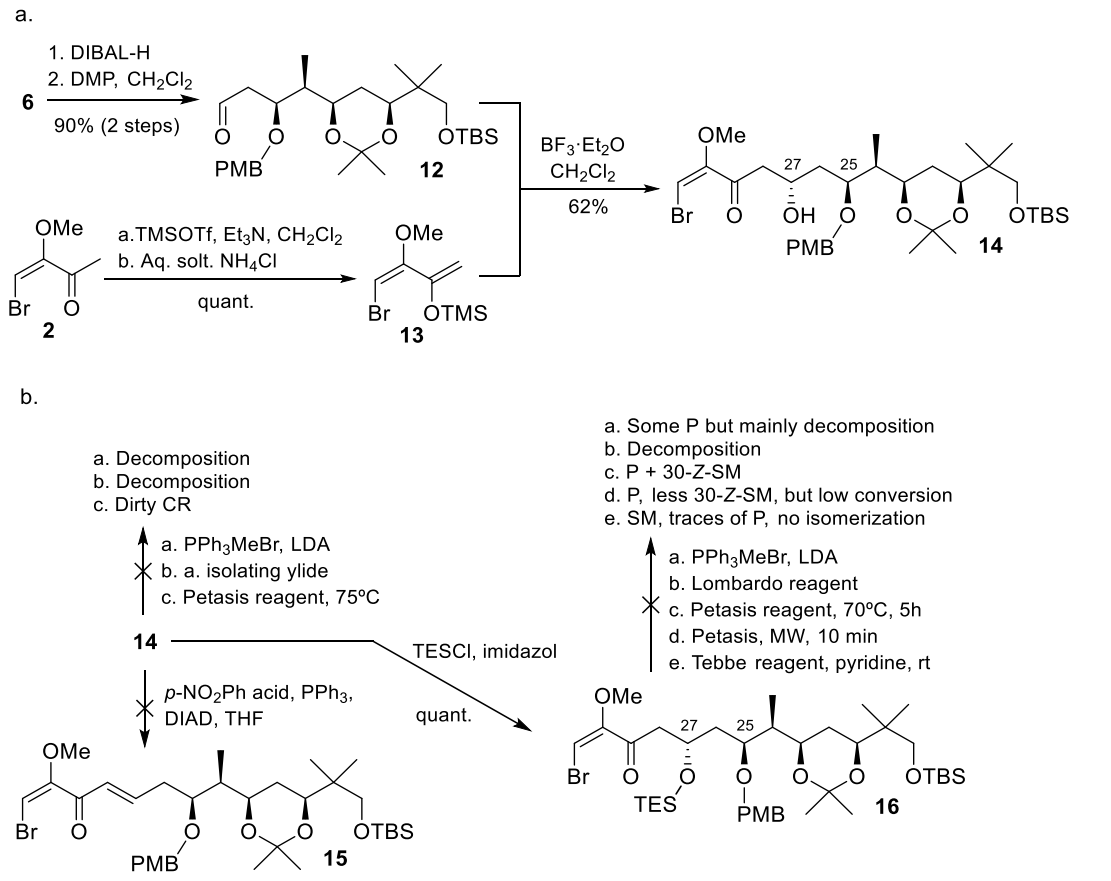
- Can we prepare aldehyde **9** and use the PMB ketal protecting group from the beginning to avoid the extra 2 steps to exchange protecting groups?
- Can we use now Mukaiyama aldol addition for the C22-C23 bond formation?[7]

After some experimentation a short three-step route to **8** was validated. Aldehyde **9** and silylenolether **10** react under optimized Mukaiyama aldol addition conditions[8] to render ketol **11** in almost quantitative yield and total facial selectivity (Scheme 2). Then, the reducing agent was changed to DIBAL-H to have easier purifications and higher yields but again a solvent-temperature optimization[9] was necessary and the final reaction conditions (-100 °C, THF) rendered a *dr* = 84:16 and a final 73% isolation yield of the desired C21-C23-*syn* diastereomer. Protection using 2-methoxypropene worked quantitatively to obtain the protected C29-C27 fragment **8** in three steps from **9** and **10** in a 71% yield. This represents a 6.5-fold increase in comparison with the previous methodology for such a short synthetic sequence.

C19-C31 synthetic pathway

With easy-scalable and high-yielding routes to obtain C19-C27 fragment **8** and bromoketone **2**[10] the end of the enantioselective synthesis of the polyhydroxylated chain needed to be explored. This started with the transformation of compound **6** into aldehyde **12** by chemoselective reduction of the PMP acetal and oxidation of the resulting primary alcohol (Scheme 3). Afterwards, *E*-bromoketone **2** was converted quantitatively into its corresponding silyl enol ether **13** and the crude was reacted directly with aldehyde **12** to render ketol **14** in a 62% yield (*dr* > 95:5). Formation of the 25,27-*anti* diol was expected giving the opposite stereochemistry to the natural product at C27 and confirmed by NOE analysis of the cyclic acetal obtained by oxidation of **16**.[11]

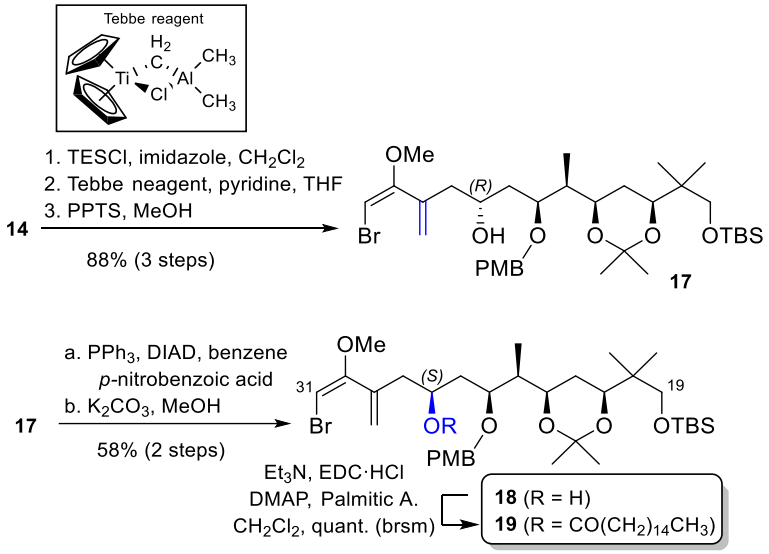
Having synthesized ketol **14**, the most challenging part of the synthesis was to find a strategy to invert the stereocenter at C27 and introduce the terminal double bond at C29 without disruption of the polyol structure and with good yields. A vast amount of possible methodologies to introduce the methylidene functionality were tested (Scheme 2) starting from the simplest to the most complex. Several attempts to olefinate C29 over unprotected alcohol **14** resulted mainly in decomposition of the starting material (SM) and trying to perform the inversion under Mitsunobu conditions to prevent the protection step from rendering the elimination of product **15** due to the high acidicity of the methylene at C28. Under these circumstances, protected compound **16** was obtained and new olefination conditions were tested.



Scheme 3. a.Preparation of the C19-C31 complete fragment **14**. b. Failed attempted strategies to perform C27 inversion and C29 olefination over **14**.

Olefination of **16** using Wittig and Lombardo's reagent[12] resulted in decomposition of the SM; however, Ti-based olefinating compounds such as Petasis reagent[13] started to give satisfactory results (Scheme 3). Under conventional heating it was possible to isolate some olefination product (**P**) but compound **16** was recovered as a *Z-E* mixture of isomers, thereby invalidating the strategy. Microwave activation was also tested with better results but following several optimization attempts, the reaction still did not deliver satisfactory results. The relatively good results showed by Petasis reagent prompted us to move to the generally highly reactive and milder Tebbe's reagent[14] because it is activated by a base and not by temperature and that allow us to work at lower temperatures and avoid isomerization. Unluckily, at room temperature the reagent does not render the olefination product (probably due to the C31-Br steric hindrance) and heating to 50 °C was required.

After finding the suitable strategy the synthesis was completed as shown in Scheme 4. Alcohol **14** was subjected to a very efficient three-step procedure including TES protection, Tebbe olefination and deprotection with an 88% yield. Finally, the configuration of C27 of **17** was inverted using the widely used Mitsunobu-hydrolysis protocol with good yield to give alcohol **18**, the protected C19-C31 fragment of the polyhydroxylated chain of oscillariolide. Alcohol **18** was esterified with palmitic acid under standard conditions to reach ester **19**, the polyhydroxylated chain present in phormidolide A.



Scheme 4. Final steps in the synthesis of the polyol chain present in oscillariolide and phormidolides A-D.

The longest linear sequence to obtain **18** is 17 steps with an average yield of 88% and a 10% overall yield. The absolute configuration of all the stereocenters present in the chain was determined using different NMR methods and the (21*S*, 23*R*, 24*R*, 25*S*, 27*S*, 30*E*) configuration present in the natural products was confirmed. Furthermore, NMR signals of **18** and **19** are in agreement with those reported for the natural products.

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(7) When aldehyde **5** was reacted under Mukaiyama aldol addition conditions the yields were low and non-reproducible probably due to the deprotection of the TES under Lewis acidic conditions.

(8) A solvent screening was performed to determine the optimum reaction conditions. See Supporting Information in *Org. Lett.* **2016**, *18*, 4485-4487.

(9) See Supporting Information in *Org. Lett.* **2016**, *18*, 4485-4487.

(10) See Chapter 3.

(11) See Supporting Information in *Org. Lett.* **2016**, *18*, 4485-4487.

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Organic LETTERS

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Enantioselective Synthesis of the Polyhydroxylated Chain of Oscillariolide and Phormidolides A−C

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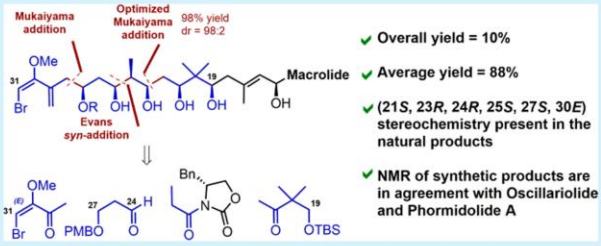
Supporting Information

ABSTRACT: The first enantioselective synthesis of the polyhydroxylated chain common to marine natural products oscillariolide and phormidolides A−C is described herein. This chain represents a synthetic challenge that needs to be solved before the total synthesis of this family of natural products can be approached. It contains seven stereocenters, six of them having a *syn*-hydroxylated functionality, and a tricky terminal (*E*)-bromomethoxydiene (BMD). The described effective enantioselective strategy affords the polyketide chain and represents an important breakthrough to complete the total synthesis of these marine compounds.



Natural products isolated from marine sources have a huge impact on the antitumor drug discovery scenario of the present day.[1] During the past few years, the isolation of polyketide macrolides with the occurrence of oxygen-containing heterocycles has opened a challenging field in structure determination as well as in chemical synthesis of these potent compounds.[2] The complex polyketides oscillariolide,[3] phormidolide A,[4] and phormidolides B and C[5] exhibit similar structures based on a macrocyclic core bonded to a common polyhydroxylated chain. The phormidolides present an extra fatty acid linked by an ester bond to the hydroxyl next to the BMD motif. In phormidolide A, the polyhydroxy chain is linked to palmitic acid, and in phormidolides B and C it is linked to two different halogenated unsaturated fatty acids.

Our group is focused on the total synthesis of phormidolides B and C and has developed approaches for the stereoselective synthesis of their macrocyclic core[5,6] and a model-based study to find the best conditions to link this macrocyclic core to the polyhydroxy chain.[7] Additionally, the first chemical strategy to synthesize the complex BMD moiety present at the end of the polyhydroxylated chain has been recently reported.[8] The retrosynthetic analysis of phormidolides B and C proposed in the previous work[7] (Figure 1) was based on two main disconnections to give three molecular fragments: polyol **A** containing the C19−C31 chain functionalized as an aldehyde at C19, propargylic organometallic **B**, and macrocyclic lactone **C**[6] with C15 functionalized as an aldehyde. From now on, the numeration of carbon in the polyhydroxylated chain will be the same as the one reported in the isolation of phormidolides B and C.[5]

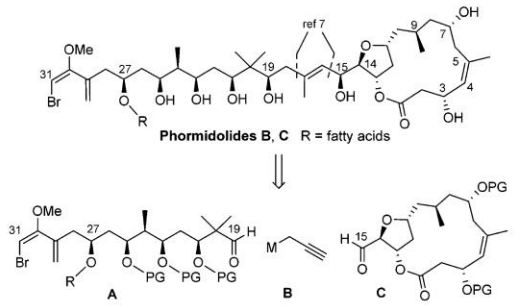


Figure 1. Retrosynthetic plan for phormidolides B and C.

The first enantioselective synthesis of the C19−C31 fragment of the polyol chain present in oscillariolide (**1**) and phormidolide A (**2**) is reported in this paper. Palmitic acid, which is the fatty acid present in phormidolide A, was used in the present work to show the viability of our strategy. The retrosynthetic analysis (Figure 2) starts with the esterification of **1** with the corresponding fatty acid to access the phormidolide chain **2**. The introduction of the terminal

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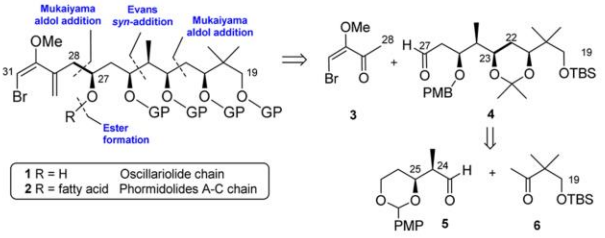


Figure 2. Retrosynthetic analysis of the polyhydroxy chain C19−C31.

bromodiene by means of a Mukaiyama aldol addition[9] of ketone **3**[8] to aldehyde **4** followed by olefination will be used for the synthesis of **1**. The formation of the C22−C23 bond was envisioned through an asymmetric aldol addition between aldehyde **5** and known ketone **6**.[10] It is important to mention that the selection of the protecting groups is a critical part of this project. The possibility of installing the BMD moiety at C27 and the propargyl unit at C19 orthogonally depending on the synthetic requirements is vital for the success of this strategy.

The synthesis of the protected C19−C27 core **11** (Scheme 1) started with the protection of the two hydroxyl groups of aldol **7**[11] by oxidation of the *O*-*p*-methoxybenzyl (PMB) moiety with DDQ to give the *p*-methoxyphenyl (PMP) acetal **8** in high yield. Removal of the oxazolidinone asymmetric inductor and subsequent Dess−Martin periodinane (DMP) oxidation rendered aldehyde **5** in 74% yield for the two steps. Silyl enol ether **9**[12] reacted with aldehyde **5** in an exceptional 98% yield with complete stereocontrol toward our desired 23,24,25-*syn* aldol **10**. Optimization of the conditions[13] was critical to modulate the yield and stereochemical outcome[14] of this key transformation. The 1,3-*syn* reduction using DIBAL-H[15] as the reducing agent instead of catecholborane[16] gave a higher yield[17] (73%, *dr* = 86:14) and simplified the purification. Final protection of the resulting 1,3-diol by acetal formation with 2-methoxypropene under acidic conditions afforded **11** in quantitative yield.

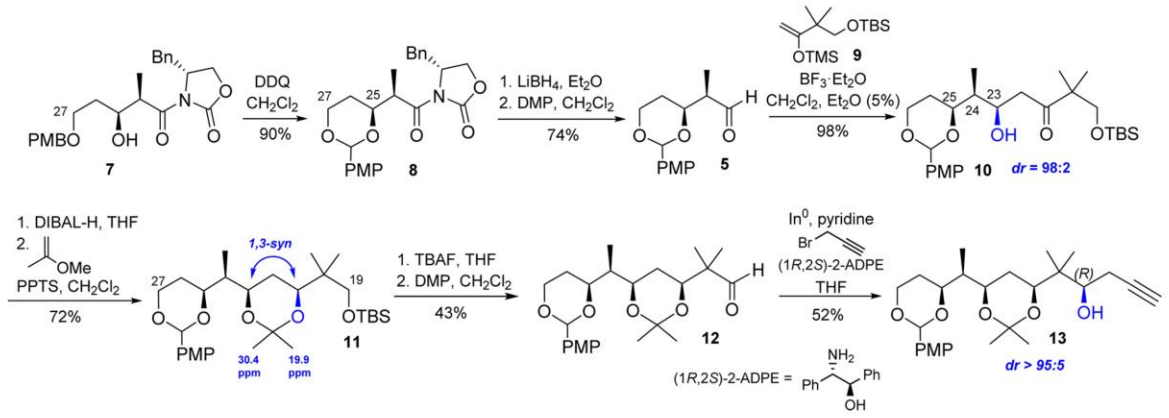
The C21−C23-*syn* relative configuration of **11** was confirmed by ^{13}C NMR analysis of the corresponding acetonide.[18] The orthogonality of the protecting groups has given us the possibility to propargylate C19, transforming compound **11** to **13** in three steps. Thus, chemoselective removal of the TBS protecting group of **11** and oxidation gave aldehyde **12**. The final stereoselective addition using propargylindium following the Singaram procedure[19] afforded compound **13** with an excellent *dr* in 52% yield.[14]

Next, a valid route to install the BMD motif at C27 was investigated. It started with the transformation of compound **11** into aldehyde **4** by chemoselective reduction of the PMP acetal and oxidation of the resulting primary alcohol **14** (Scheme 2). Our strategy takes advantage of an usual consecutive PMB−PMP−PMB manipulation (oxidation−reduction), which allowed efficient transformations **7** → **8** and **11** → **14**. Afterward, (*E*)-bromoketone **3**[8] was converted quantitatively into its corresponding silyl enol ether **15**, and the crude material was reacted directly with aldehyde **4** to render ketol **16** in 62% yield (*dr* > 95:5). Formation of 25,27-*anti* diol **16** was expected[20] and confirmed by NOE analysis of the cyclic acetal obtained by oxidation of **16**.[21]

In order to make the synthesis of the target C19−C31 chain with minimum protection steps, inversion and olefination over unprotected the C27-OH of **16** were tested unsuccessfully.[22] Therefore, a very efficient three-step procedure including TES protection, Tebbe olefination, and deprotection was developed. The methylene was inserted to obtain diene **17** in 88% yield. It is worth mentioning that the Tebbe reagent was not reactive enough at rt and the reaction mixture had to be heated to 50 °C for 2 h. This unreactivity was most likely a result of the steric hindrance caused by the bromine and the triethylsilyl protecting group surrounding the ketone. Finally, the configuration of C27 of **17** was inverted using the widely used Mitsunobu hydrolysis protocol in good yield to give alcohol **1**, the protected C19−C31 fragment of the polyhydroxylated chain of oscillariolide. Alcohol **1** was esterified with palmitic acid under standard conditions to reach ester **2**, the polyhydroxylated chain present in phormidolide A.

In conclusion, we have developed an enantioselective strategy toward the protected polyhydroxylated chains of oscillariolide (**1**) and phormidolide A (**2**) from cheap and accessible starting materials. The longest linear sequence to obtain **1** is 17 steps long with an average yield of 88% and a 10% overall yield. This first method for the synthesis of the polyhydroxylated chain common to oscillariolide and phormidolides A−C is an important requirement to approach their total synthesis. The configurations of all of the stereocenters present in the chain have been determined using different NMR methods, and the (21*S*,23*R*,24*R*,25*S*,27*S*,30*E*) stereochemistry present in the natural products has been confirmed.

Scheme 1. Synthesis of the C19−C27 Protected Fragment (13) and Incorporation of the Propargyl Residue



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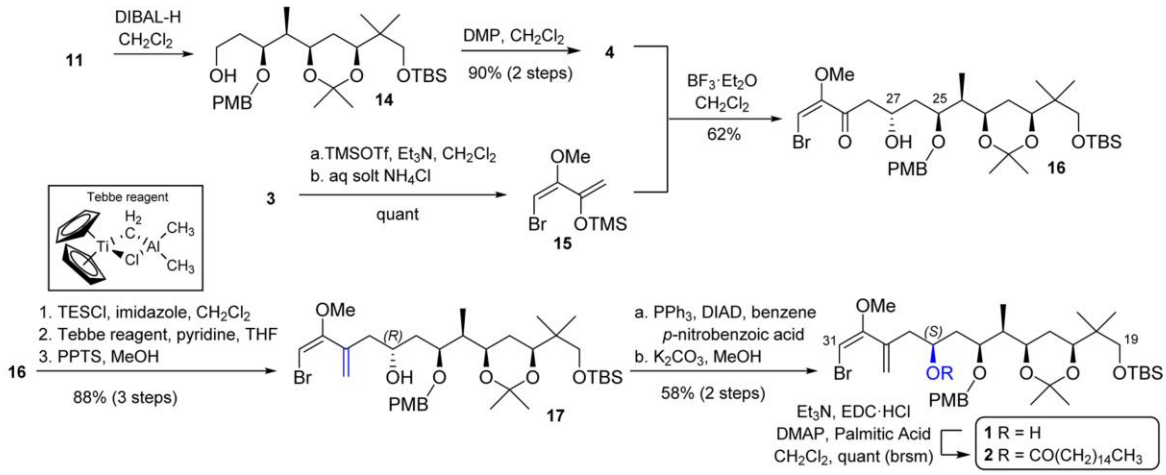
Scheme 2. Synthesis of the C19−C31 Chain of Oscillariolide (1) and Phormidolide A (2)



Furthermore, the NMR signals of **1** and **2** are in agreement with those reported for the natural products.[3,4,23] Remarkable features in the route are the polyvalence and atom economy afforded using the PMB−PMP protecting group moving around different chain positions, the optimization of Mukaiyama addition to obtain compound **10** in excellent yield (98%) and stereoselectivity, and finally, the efficient stereoselective preparation of compound **16** by addition of the C28−C31 fragment **15** over a complex and highly functionalized precursor. This synthetic procedure should pave the way for the total synthesis of this family of intriguing molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02014.

Experimental procedures and characterization of the described compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(13) A table with the detailed data (yield, *dr*, solvents tested) from this optimization is available in the Supporting Information.

(14) The absolute configuration of the new hydroxyl was determined using Mosher's derivatization method. See the Supporting Information.

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(21) 1D NOE experiments on the cyclic acetal of **16** are available in the Supporting Information.

(22) Mitsunobu conditions for inversion led to the elimination product, and all of the tested olefination conditions (Wittig, Petasis, Lombardo, etc.) led to decomposition of the starting material.

(23) A comparison of the key NMR signals in **1** and **2** with those of oscillariolide and phormidolide A is available in the Supporting Information.

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Supporting Information

Enantioselective Synthesis of the Polyhydroxylated Chain of Oscillariolide and Phormidolides A-C.

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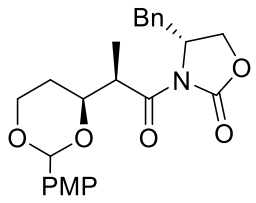
General Procedures

Tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were dried using a PureSolv solvent purification system. All other solvents and reagents were used as purchased without further purification, unless otherwise indicated. Flash column chromatography was performed on silica gel (60A 35-70 μm) as stationary phase. Analytical TLC was performed on pre-coated silica gel 60 F_{254} plates (0.2 mm thick, 20x20 cm) and visualized under UV light (254 and 360 nm), with anisaldehyde in conc. H_2SO_4 or with phosphomolybdic acid in ethanol. Polarimetry studies were performed on a Perkin-Elmer 241 or JascoP-2000 polarimeter equipped with a Na-lamp. IR spectra were recorded on a Varian Mercury 400MHz or a Varian VNMRS500 500MHz. Chemical shifts are reported in ppm referenced to the appropriate residual solvent peaks ($CDCl_3$) and coupling constants are reported in Hz. Multiplicity of the carbons was assigned with gHSQC experiments. Standard abbreviations for off-resonance decoupling were employed: s = singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, bd = broad doublet, m = multiplet. The same abbreviations were also used for the multiplicity of signals in ^{1}H-NMR. High Resolution Mass Spectroscopy (HRMS) was performed an Agilent LC/MSD-TOF 2006 system using the ESI-MS technique.

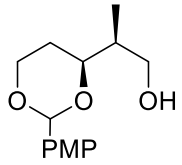
Experimental procedures and characterization

(4*R*)-4-Benzyl-3-((2*R*)-2-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)propanoyl)oxazolidin-2-one (8)



DDQ (6.9 g, 30.3 mmol) was added to a solution of aldol **7** (11.8 g, 27.6 mmol) in dry CH_2Cl_2 (600 mL) and the reaction was stirred for 45 minutes. After this time, the reaction was filtered through a pad of celite. The solution was washed three times with $NaHCO_3$ and the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (9:1) yielded **8** (11.08 g, 90%) as a colorless oil. $[\alpha]_D$ = -34.6 (c 1.0, CH_2Cl_2). IR (KBr film) ν 3028, 2968, 2858, 1777, 1693, 1455, 1382, 1248, 1109 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.34 (d, *J* = 6.5 Hz, 3H), 1.59 – 1.62 (m, 1H), 1.83 – 1.95 (m, 1H), 2.77 (dd, *J* = 13.4, 9.6 Hz, 1H), 3.28 (dd, *J* = 13.4, 3.4 Hz, 1H), 3.79 (s, 3H), 3.95 (ddd, *J* = 12.3, 11.5, 2.6 Hz, 1H), 4.07 – 4.17 (m, 4H), 4.20 – 4.28 (m, 1H), 4.62 – 4.69 (m, 1H), 5.49 (s, 1H), 6.84 – 6.91 (m, 2H), 7.18 – 7.23 (m, 2H), 7.27 – 7.42 (m, 5H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.1 (q), 28.3 (t), 37.9 (t), 42.3 (d), 55.3 (d), 55.5 (q), 66.0 (t), 66.7 (t), 77.6 (d), 100.9 (d), 113.5 (2) (d), 127.2 (2) (d), 127.4 (d), 128.9 (d), 129.4 (d), 131.2 (s) , 135.2 (s) , 153.1 (s), 159.8 (s), 174.4 (s). HRMS (ESI+): *m/z* calculated for $C_{24}H_{28}NO_6$ $[M+H]^+$ 426.1911, found 426.1923.

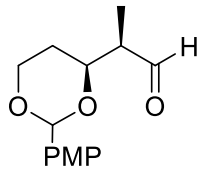
(2*S*)-2-((4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)propan-1-ol (S1)



A 2 M solution of $LiBH_4$ in THF (13.53 mL, 27.1 mmol) was added to a solution of **8** (5.75 g, 13.53 mmol) in Et_2O (210 mL) and MeOH (2.1 mL) at 0°C during 30 minutes and the mixture was stirred at 0°C for 30 minutes more. The reaction was quenched by

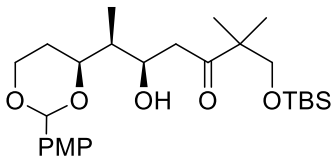
addition of saturated solution of NH_4Cl and extracted three times with Et_2O. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (1:1) yielded **S1** (2.8 g, 82%) as a colorless oil. $[\alpha]_D$ = +13.9 (c 1.0, CH_2Cl_2). IR (KBr film) ν 3436 (b), 2962, 2858, 1614, 1517, 1395, 1249, 1103 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.00 (d, *J* = 7.1 Hz, 3H), 1.40 – 1.46 (m, 1H), 1.93 – 1.99 (m, 1H), 2.00 – 2.07 (m, 1H), 3.59 – 3.65 (m, 1H), 3.74 (d, *J* = 7.7 Hz, 1H), 3.80 (s, 3H), 3.96 (ddd, *J* = 12.2, 11.4, 2.5 Hz, 1H), 4.02 (ddd, *J* = 11.6, 4.2, 2.4 Hz, 1H), 4.29 (ddd, *J* = 11.4, 5.0, 1.5 Hz, 1H), 5.46 (s, 1H), 6.85 – 6.90 (m, 2H), 7.35 – 7.40 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 11.7 (q), 27.1 (t), 39.4 (d), 55.3 (q), 65.5 (t), 67.1 (t), 79.7 (d), 101.3 (d), 113.6 (d), 127.2 (d), 131.2 (s), 159.9 (s). HRMS (ESI+): *m/z* calculated for $C_{14}H_{21}O_4$ $[M+H]^+$ 253.1437, found 253.1434.

(2*R*)-2-((4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)propanal (5)



$NaHCO_3$ (370 mg, 4.4 mmol) and DMP (930 mg, 2.2 mmol) were added to a solution of alcohol **S1** (462 mg, 1.83 mmol) in CH_2Cl_2 (40 mL) and the solution was stirred for 1 h. The reaction mixture was diluted with a saturated solution of $Na_2S_2O_3$ and a saturated solution of $NaHCO_3$ and the residue was extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (9:1) yielded aldehyde **5 (**398 mg, 91%) as a colorless oil. $[\alpha]_D$ = -10.9 (c 1.0, CH_2Cl_2). IR (KBr film) ν 2964, 2839, 1726, 1615, 1518, 1393, 1249, 1102 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21 (d, *J* = 7.1 Hz, 3H), 1.52 – 1.57 (m, 1H), 1.85 – 1.99 (m, 1H), 2.57 – 2.66 (m, 1H), 3.80 (s, 3H), 3.92 – 4.04 (m, 1H), 4.20 – 4.25 (m, 1H), 4.28 (ddd, *J* = 11.5, 5.1, 1.5 Hz, 1H), 5.50 (s, 1H), 6.83 – 6.91 (m, 2H), 7.31 – 7.43 (m, 2H), 9.83 (d, *J* = 1.2 Hz, 1H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.8 (q), 28.3 (t), 50.8 (d), 55.3 (q), 66.7 (t), 76.5 (d), 101.2 (d), 113.6 (d), 127.3 (d), 130.9 (s), 159.9 (s), 203.6 (d). HRMS (ESI+): *m/z* calculated for $C_{14}H_{19}O_4$ $[M+H]^+$ 251.1278, found 251.1282.

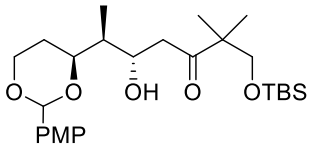
(5*R*,6*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-6-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-2,2-dimethylheptan-3-one (10)



A solution of silylenol ether **9** (1.4 g, 4.71 mmol) in CH_2Cl_2:Et_2O (95:5, 5 mL) was added to a cooled solution (-78ºC) of aldehyde **5** (1.18 g, 4.71 mmol) in CH_2Cl_2:Et_2O (95:5, 50 mL). $BF_3{\cdot}OEt_2$ (0.58 mL, 4.71 mmol) was added via syringe pump with a rate of 0.25 mmol/min. The reaction was stirred at -78ºC for 2 h and quenched with saturated solution of $NaHCO_3$ (50 mL). The residue was extracted three times with CH_2Cl_2, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Purification by silica gel column cromatography with hexane-EtOAc (8:2) affords 1.7 g of **10** and 33 mg of **10(23*S*)** (98 % based in the recovery of **5**) as a separable mixture of diasteromers and 297 mg of **5** as a recovered starting material. $[\alpha]_D$ = +14.5 (c 1.0, CH_2Cl_2). IR (KBr film) ν 3528, 2956, 2857, 1699, 1615, 1517, 1393, 1249, 1105 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01

(d, *J* = 1.5 Hz, 6H), 0.86 (s, 9H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 4.8 Hz, 6H), 1.52 – 1.57 (m, 1H), 1.63 – 1.72 (m, 1H), 1.88 – 2.00 (m, 1H), 2.66 – 2.79 (m, 2H), 3.56 (d, *J* = 1.4 Hz, 2H), 3.80 (s, 3H), 3.97 (ddd, *J* = 12.3, 11.4, 2.6 Hz, 1H), 4.03 (ddd, *J* = 11.5, 5.2, 2.4 Hz, 1H), 4.22 – 4.29 (m, 1H), 4.25 – 4.32 (m, 1H), 5.49 (s, 1H), 6.84 – 6.90 (m, 2H), 7.34 – 7.42 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.5 (q), 8.9 (q), 18.3 (s), 21.5 (q), 25.9 (q), 28.8 (t), 42.2 (d), 42.6 (t), 49.9 (s), 55.4 (q), 67.3 (t), 68.8 (d), 70.4 (t), 79.5 (d), 101.1 (d), 113.7 (d), 127.4 (d), 131.6 (s), 160.0 (s), 216.6 (s). HRMS (ESI+): *m/z* calculated for $C_{26}H_{44}NaO_6Si$ $[M+Na]^+$ 503.2799, found 503.2802.

(5*S*,6*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-6-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-2,2-dimethylheptan-3-one (10(23*S*))

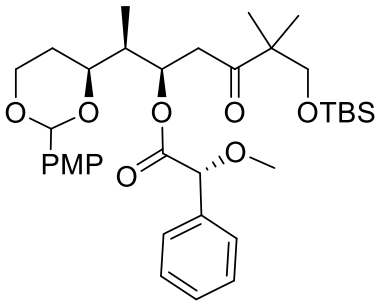


^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.02 (d, *J* = 1.9 Hz, 6H), 0.86 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.09 (s, 6H), 1.56 – 1.62 (m, 1H), 1.66 (dt, *J* = 6.9, 2.3 Hz, 1H), 1.94 – 2.03 (m, 1H), 2.68 (dd, *J* = 17.8, 6.9 Hz, 1H), 2.94 (dd, *J* = 17.8, 6.1 Hz, 1H), 3.54 (d, *J* = 9.8 Hz, 1H), 3.61 (d, *J* = 9.8 Hz, 1H), 3.79 (s, 3H), 3.81 – 3.87 (m, 2H), 4.16 (dt, *J* = 10.0, 2.3 Hz, 1H), 4.45 (td, *J* = 6.5, 2.3 Hz, 1H), 5.56 (s, 1H), 6.77 – 6.95 (m, 2H), 7.30 – 7.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.6 (q), 6.4 (q), 18.2 (s), 21.4 (q), 25.8 (q), 34.5 (d), 35.3 (t), 40.7 (t), 49.7 (s), 55.3 (q), 61.2 (t), 70.0 (t), 76.9 (d), 80.2 (d), 101.6 (d), 113.6 (d), 127.4 (d), 131.1 (s), 159.9 (s), 212.3 (s).

General procedure for derivatization with methoxyphenylacetic acid (MPA):

α-Methoxyphenylacetic acid (5 eq.) and EDC·HCl (5 eq.) were added to a solution of alcohol **10*(5R)*** (1 eq.) in CH_2Cl_2, then DMAP (0.1 eq.) was added and the solution was stirred for 1 h. The solution was filtered through celite®545, poured into Et_2O and washed with 0.2 M aqueous HCl. The organic residue was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded the corresponding esters **S2** and **S3** as colorless oils.

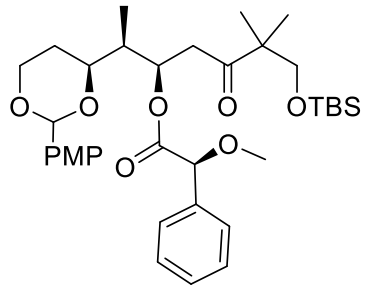
(2*R*,3*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-6,6-dimethyl-5-oxoheptan-3-yl (2*R*)-2-methoxy-2-phenylacetate (S2)



Aldol **10** (20 mg, 0.04 mmol) and (*R*)-MPA (35 mg, 0.21 mmol) afforded MPA derivative **S2** (22 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 1.05 (s, 3H), 1.06 (s, 3H), 1.09 – 1.15 (m, 1H), 1.61 – 1.68 (m, 1H), 1.76 (td, *J* = 6.8, 3.0 Hz, 1H), 2.80 (dd, *J* = 18.0, 5.4 Hz, 1H), 2.91 (dd, *J* = 18.0, 7.4 Hz, 1H), 2.94 – 2.98 (m, 1H), 3.40 (s, 3H), 3.44 – 3.56 (m, 3H), 3.79 (s, 3H), 4.00 – 4.07 (m, 1H), 4.66 (s, 1H), 5.05 (s, 1H), 5.44 (td, *J* = 7.4, 5.4, 3.0 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.29 – 7.46 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.6 (q), -5.6 (q), 9.4 (q), 18.2 (s), 21.3

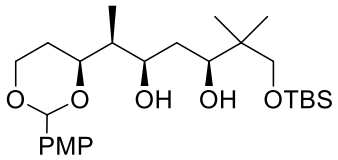
(q,), 25.8 (q), 28.8 (t), 39.5 (t), 40.6 (d), 49.5 (s), 55.3 (q), 57.3 (q), 66.7 (t), 70.0 (t), 70.9 (d), 77.0 (d), 82.2 (d), 100.6 (d), 113.4 (d), 127.1 (d), 127.4 (d), 128.7 (d), 128.8 (d), 131.4 (s), 136.9 (s), 159.7 (s), 169.7 (s), 211.3 (s). HRMS (+ESI): *m/z* calculated for $C_{35}H_{52}NaO_8Si$ $[M+Na]^+$ 651.3324, found 651.3325.

(2*R*,3*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-6,6-dimethyl-5-oxoheptan-3-yl (2*S*)-2-methoxy-2-phenylacetate (S3)



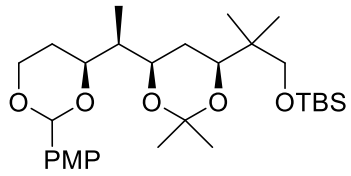
Aldol **10** (20 mg, 0.04 mmol) and (*S*)-MPA (35 mg, 0.21 mmol) afforded MPA derivative **S3** (13 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.03 (s, 3H), -0.03 (s, 3H), 0.83 (s, 9H), 0.92 (s, 6H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.37 – 1.43 (m, 1H), 1.70 – 1.87 (m, 2H), 2.67 (dd, *J* = 18.2, 5.2 Hz, 1H), 2.81 (dd, *J* = 18.2, 7.5 Hz, 1H), 3.32 (s, 3H), 3.42 (s, 2H), 3.50 – 3.56 (m, 1H), 3.72 – 3.77 (m, 1H), 3.79 (s, 3H), 4.13 – 4.19 (m, 1H), 4.67 (s, 1H), 5.31 (s, 1H), 5.48 – 5.53 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.29 – 7.43 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.7 (q), 9.4 (q), 18.1 (s), 21.1 (q), 21.2 (q), 25.8 (q), 29.0 (t), 39.4 (t), 40.9 (d), 49.4 (s), 55.3 (q), 57.2 (q), 66.9 (t), 69.8 (t), 71.3 (d), 77.4 (d), 82.8 (d), 100.8 (d), 113.5 (d), 127.0 (d), 127.2 (d), 128.5 (d), 128.5 (d), 131.5 (s), 136.4 (s), 159.8 (s), 169.9 (s), 211.0 (s). HRMS (+ESI): *m/z* calculated for $C_{35}H_{52}NaO_8Si$ $[M+Na]^+$ 651.3324, found 651.3312.

(3*S*,5*R*,6*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-2,2-dimethylheptane-3,5-diol (S4)



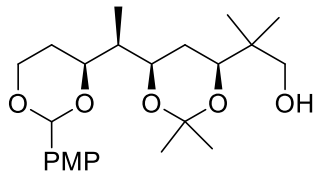
A solution of DIBAL 1 M in THF (7 mL, 7 mmol) was added during 10 minutes to a solution of aldol **10** (1.33 g, 2.79 mmol) in THF (40 mL) at -100°C and the reaction was stirred 90 min at -78°C. After this time, a saturated solution of Rochelle's salt (30 mL) was added and the solution was stirred for 1 h. The residue was extracted with CH_2Cl_2, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (75:25) yielded syn-diol **S4** (957 mg, 73%). $[\alpha]_D$ = -12.8 (c 1.0, CH_2Cl_2). IR (KBr film) ν 3445 (br), 2956, 2930, 2857, 1615, 1250, 1101, 836, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.84 (s, 3H), 0.89 (s, 3H), 0.90 (s, 9H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.50 – 1.69 (m, 4H), 1.87 – 1.99 (m, 1H), 3.45 – 3.54 (m, 2H), 3.72 (d, *J* = 10.6 Hz, 1H), 3.79 (s, 3H), 3.92 – 4.02 (m, 2H), 4.07 (dt, *J* = 9.4, 2.7 Hz, 1H), 4.19 (brs, 1H), 4.23 – 4.29 (m, 1H), 4.37 (brs, 1H), 5.49 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.7 (q), -5.7 (q), 8.9 (q), 18.1 (s), 19.2 (q), 22.2 (q), 25.8 (q), 28.9 (t), 35.0 (t), 38.2 , 43.1 (d), 55.3 (q), 67.2 (t), 73.2 (t), 73.4 (d), 79.3 (d), 80.9 (d), 100.9 (d), 113.5 (d), 127.2 (d), 131.5 , 159.7 . HRMS (ESI+): *m/z* calculated for $C_{26}H_{47}O_6Si$ $[M+H]^+$ 483.3136, found 483.3126.

(4*S*,6*R*)-4-[1-(*tert*-Butyldimethylsilyloxy)-2-methylpropan-2-yl]-6-[(1*R*)-1-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)ethyl]-2,2-dimethyl-1,3-dioxane (11)



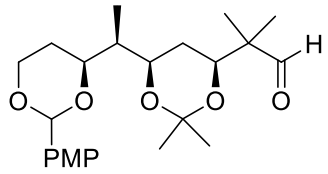
2-Methoxypropene (0.015 mL, 0.16 mmol) was added to a cooled (0ºC) solution of **S4** (30 mg, 0.062 mmol) and PPTS (1.5 mg, 0.006 mmol) in CH_2Cl_2 (0.5 mL). The reaction was stirred 30 minutes at. After this time, a pH=7 buffer was added and the residue was extracted with CH_2Cl_2, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **11** (32 mg, 98%) as a colorless oil. $[\alpha]_D$ = +6.9 (c 1.0, CH_2Cl_2). IR (KBr film) ν 2955, 2861, 1737, 1377, 1249, 1101 cm^{-1}. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.81 (s, 3H), 0.82 (s, 3H), 0.89 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.26-1.29 (m, 3H), 1.33 (s, 3H), 1.37 (s, 3H), 1.42-1.50 (m, 2H), 1.56-1.60 (m, 1H), 1.93 (qd, *J* = 12.4, 5.0 Hz, 1H), 3.20 (d, *J* = 9.2 Hz, 1H), 3.44 (d, *J* = 9.2 Hz, 1H), 3.73 (d, *J* = 2.3 Hz, 1H), 3.75 (d, *J* = 2.3 Hz, 1H), 3.80 (s, 3H), 3.86-3.98 (m, 3H), 4.27 (dd, *J* = 11.3, 3.9 Hz, 1H), 5.47 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$): δ -5.4 (q) 10.3 (q) 18.4 (s), 19.5 (q), 19.9 (q), 20.8 (q), 25.0 (q), 28.2 (t), 28.8 (t), 30.4 (q), 36.7 (s), 43.1 (d), 55.4 (q), 67.4 (t), 68.8 (t), 72.0 (d), 78.0 (d), 98.2 (s), 101.1 (d), 113.6 (d), 127.4 (d), 131.8 (d), 159.9 (s), 190.9 (s). HRMS (+ESI): *m/z* calculated for $C_{29}H_{50}NaO_6Si$ $[M+Na]^+$ 545.3269, found 545.3253.

2-((4*S*,6*R*)-6-((1*R*)-1-((4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylpropan-1-ol (S5)



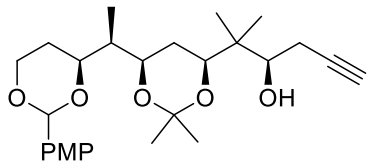
A solution of TBAF 1M in THF (5 mL, 4,9 mmol) was added to a solution of **11** (650 mg, 1.2 mmol) in dry THF (60 mL) at rt under N_2 atmosphere and the reaction was stirred for 16 h. After this time, the reaction was quenched with NaCl saturated solution (40 mL) and the mixture was extracted with AcOEt. The organic layer was dried over MgSO4, filtered and evaporated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (8:2) yielded **S5** (215 mg, 44%) as a colorless oil. $[\alpha]_D$ = +15,3 (c 1,0, CH_2Cl_2). IR (KBr film) ν 3491, 2963, 1737, 1613, 1517, 1378, 1249 cm^{-1}. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 0,87 (s, 3H), 0,91 (s, 3H), 1,05 (d, *J* = 6.9 Hz, 3H), 1,37 (s, 3H), 1,42 (s, 3H), 1,52 (ddd, *J* = 17.7, 8.9, 2.6 Hz, 2H), 1,62-1,69 (m, 2H), 1,84-1,94 (m, 1H), 3,37 (d, *J* = 10.9 Hz, 1H), 3,54 (d, *J* = 10.9 Hz, 1H), 3,75 (dd, *J* = 11.7, 2.6 Hz, 1H), 3,80 (s, 3H), 3,85-3,95 (m, 1H), 3,93-3,99 (m, 2H), 4,24-4,30 (m, 1H), 5,46 (s, 1H), 6,88 (d, *J* = 8.7 Hz, 2H), 7,40 (d, *J* = 8.7 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$): δ 10.2 (q), 19.6 (q), 19.8 (q), 22.4 (q), 28.6 (q), 30.4 (t), 37.8 (s), 42.9 (d), 55.5 (q), 67.4 (t), 69.4 (t), 71.9 (t), 77.9 (d), 78.0 (d), 98.7 (s), 101.2 (d), 113.7 (d), 127.5 (d), 131.8 (s), 160.0 (s). HRMS (ESI+): *m/z* calculated $C_{23}H_{37}O_6$ $[M+H]^+$ 409.2585, found 409.2573.

2-((4*S*,6*R*)-6-((1*R*)-1-((4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylpropanal (12)



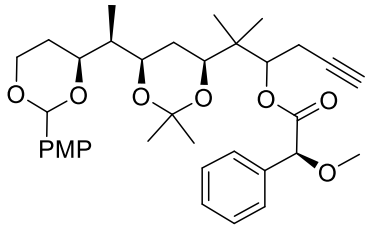
$NaHCO_3$ (16 mg, 0.19 mmol) and DMP (73 mg, 0.17 mmol) were added to a solution of alcohol **S5** (60 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) and the solution was stirred for 30 minutes. The reaction mixture was diluted with a saturated solution of $Na_2S_2O_3$ and a saturated solution of $NaHCO_3$ and the residue was extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure isolating **12** (56 mg, 99%) as a colorless oil. $[\alpha]_D$ = +6,3 (c 1,0, CH_2Cl_2). IR (KBr film) ν 2968, 2853, 1726, 1379, 1249 cm^{-1}. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 1.02-1.05 (m, 9H), 1.33 (s, 3H), 1.36-1.46 (m, 5H), 1.60-1.72 (m, 2H), 1.90-2.00 (m, 1H), 3.79 (s, 3H), 3.82-4.08 (m, 4H), 4.27 (dd, *J* = 11.4, 3.9 Hz, 1H), 5.30 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 9.57 (s, 1H). ^{13}C-RMN (100,6 MHz, $CDCl_3$): δ 10.2 (q), 16.7 (q), 18.9 (q), 19.7 (q), 28.3 (t), 28.5 (t), 30.0 (q), 42.9 (d), 49.1 (s), 55.4 (q), 67.3 (t), 69.1 (d), 73.6 (d), 77.9 (d), 98.6 (s), 101.2 (d), 113.7 (d), 127.4 (d), 131.7 (s), 159.9 (s), 206.5 (d). HRMS (ESI+): *m/z* calculated para $C_{23}H_{35}O_6$ $[M+H]^+$ 407,2428, found 407,2424.

(3*R*)-2-((4*S*,6*R*)-6-((1*R*)-1-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylhex-5-yn-3-ol (13)



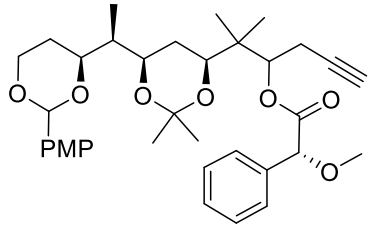
Pyridine (120 µL, 1,5 mmol) and propargyl bromide (220 µL, 1,5 mmol) were added over a solution of Indium (170 mg, 1,5 mmol) and (1*R*,2*S*)-2-Amino-1,2-diphenilethanol (320 mg, 1,5 mmol) in dry THF (3 mL) at rt and the mixture was stirred 30 minutes at the same temperature. The reaction was cooled down to -78 ºC and a solution of the aldehyde **12** (30 mg, 0.074 mmol) in THF (0.5 mL) was added and the reaction was stirred 1h at -78 ºC and 1h at rt. The reaction was quenched by addition of saturated solution of NH_4Cl (4 mL) and extracted three times with Et_2O. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (8:2) yielded **13** (17 mg, 52%) as a colorless oil. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 0,78 (s, 3H), 0,92 (s, 3H), 1,04 (d, *J* = 7,0 Hz, 3H), 1,25-1,27 (m, 1H),1,34-1,36 (m, 1H), 1,36 (s, 3H), 1,45 (s, 3H), 1,47-1,49 (m, 1H), 1,61-1,69 (m, 1H), 1,88-1,99 (m, 1H), 2,05 (t, *J* = 2,6 Hz, 1H), 2,32 (ddd, *J* = 16,6, 9,5, 2,6 Hz, 1H), 2,44 (dt, *J* = 16,6, 3,5 Hz, 1H), 3,70-3,74 (m, 1H), 3,78-3,81 (m, 4H), 3,85-3,93 (m, 1H), 3,92-4,21 (m, 2H), 4,27 (dd, *J* = 11,3, 3,5 Hz, 1H), 5,46 (s, 1H), 6,87-6,89 (m, 2H), 7,37-7,42 (m, 2H). ^{13}C-RMN (100,6 MHz, $CDCl_3$): δ 10,2 (q), 15,3 (q), 19,9 (q), 20,8 (q), 22,5 (t), 28,2 (t), 28,6 (t), 30,2 (q), 40,4 (d), 42,9 (s), 55,4 (q), 67,3 (t), 69,3 (d), 69,8 (d), 77,1 (d), 77,2 (d), 78,0 (s), 82,8 (s), 98,6 (s), 101,2 (d), 113,7 (d), 127,4 (d), 131,7 (d), 159,9 (s). HRMS (ESI+): *m/z* calculated para $C_{26}H_{39}O_6$ $[M+H]^+$ 447,2741, found 447,27455.

2-((4*S*,6*R*)-6-((1*R*)-1-((4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylhex-5-yn-3-yl (2*S*)-2-methoxy-2-phenylacetate (*S6*)



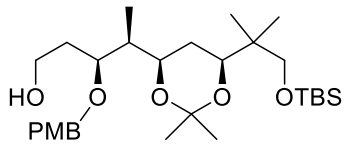
Following the previous general procedure: Aldol **13** (8 mg, 0.018 mmol) and (*S*)-MPA (6 mg, 0.032 mmol) afforded MPA derivative **S6** (6 mg, 56%). ^{1}H-RMN (400 MHz, $CDCl_3$): δ 0,80 (s, 3H), 0,83 (s, 3H), 1,02 (d, *J* = 6,9 Hz, 3H), 1,29 (s, 3H), 1,31 (s, 3H), 1,70-1,75 (m, 3H), 1,85-1,95 (m, 2H), 2,34-2,41 (m, 1H), 2,48-2,53 (m, 1H), 3,42 (s, 1H), 3,47 (s, 3H), 3,51-3,55 (m, 1H), 3,86-3,88 (m, 1H), 3,80 (s, 3H), 3,91-3,97 (m, 2H), 4,27 (dd, *J* = 11,2, 3,8 Hz, 1H), 4,78 (s, 1H), 5,16 (dd, *J* = 9,5, 3,8 Hz, 1H), 5,47 (s, 1H), 6,88-6,90 (m, 2H), 7,29-7,33 (m, 3H), 7,40-7,45 (m, 4H). HRMS (ESI+): *m/z* calculated para $C_{35}H_{47}O_8$ $[M+H]^+$ 595,3265, found 595,32724.

2-((4*S*,6*R*)-6-((1*R*)-1-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylhex-5-yn-3-yl (2*R*)-2-methoxy-2-phenylacetate (*S7*)



Following the previous general procedure: Aldol **13** (14 mg, 0.03 mmol) and (*R*)-MPA (40 mg, 0.24 mmol) afforded MPA derivative **S7** (14 mg, 78%). ^{1}H-RMN (400 MHz, $CDCl_3$): δ0,62 (sa, 6H), 0,99 (d, *J* = 6,9 Hz, 3H), 1,18 (s, 3H), 1,23-1,24 (m, 1H), 1,28 (s, 3H), 1,38-1,41 (m, 1H), 1,44-1,48 (m, 1H), 1,50-1,55 (m, 1H),1,83-1,84 (m, 1H), 1,86-1,97 (m, 1H), 2,43-2,60 (m, 2H), 3,19-3,23 (m, 1H), 3,43 (s, 3H), 3,59-3,69 (m, 1H), 3,80 (s, 3H), 3,81-3,85 (m, 1H), 3,94 (dt, *J* = 12,2, 2,6 Hz, 1H), 4,26 (dd, *J* = 11,4, 3,6 Hz, 1H), 4,78 (s, 1H), 5,13 (dd, *J* = 9,6, 3,6 Hz, 1H), 5,46 (s, 1H), 6,85-6,92 (m, 2H), 7,26-7,32 (m, 3H), 7,40-7,45 (m, 4H). HRMS (ESI+): *m/z* calculated para $C_{35}H_{47}O_8$ $[M+H]^+$ 595,3265, found 595,32711.

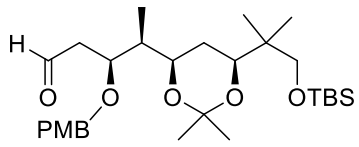
(3*S*,4*R*)-4-[(4*R*,6*S*)-6-(1-(*tert*-Butyldimethylsilyloxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl]-3-(4-methoxybenzyloxy)pentan-1-ol (14)



A solution of DIBALH 1 M in heptane (9 mL, 9 mmol) was added to a solution of acetal **11** (1.04 g, 1.98 mmol) in CH_2Cl_2 (40 mL) at □ ºC. The reaction mixture was stirred at 40 ºC for 16 h until TLC indicated complete conversion. Then a saturated solution of Rochelle's salt (30 mL) was added and the mixture was stirred at 24 h until the formation of two layers. The organic solution was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (72:25) yielded alcohol **14** (920 mg, 95% brsm) as a colorless oil and 69 mg of recovered starting material **11**. $[\alpha]_D$ = -6.0 (c 0.5, CH_2Cl_2). IR (KBr film) ν 3501 (br), 2955, 2857, 1737, 1513, 1377, 1249, 1092 cm^{-1}. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.78 (s, 3H), 0.79 (s, 3H), 0.89 (s, 9H), 0.97 (d, *J* = 7.1 Hz, 3H), 1.24-1.26 (m, 1H), 1.31 (s, 3H), 1.32-1.34 (m, 1H), 1.37 (s, 3H), 1.79-1.84 (m, 3H), 3.19 (d, *J* = 9.2 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.60 (dt,

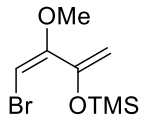
J = 7.1, 4.9 Hz, 1H), 3.71-3.74 (m, 3H), 3.80 (s, 3H), 3.88-3.91 (m, 1H), 4.47 (q, *J* = 11.1, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$): δ -5.4 (q), 10.9 (q), 18.4 (q), 19.5 (q), 19.9 (s), 20.9 (q), 26.1 (q), 28.9 (t), 30.3 (q), 33.3 (t), 38.7 (s), 40.7 (d), 55.4 (q), 61.4 (t), 68.8 (t), 69.4 (d), 71.4 (t), 71.9 (d), 80.7 (d), 98.2 (s), 114.0 (d), 129.5 (d), 130.7 (d), 159.4 (s). HRMS (+ESI): *m/z* calculated for $C_{29}H_{53}O_6Si$ $[M+H]^+$ 525.3606, found 525.3617.

(3*S*,4*R*)-4-[(4*R*,6*S*)-6-(1-(*tert*-Butyldimethylsilyloxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl]-3-(4-methoxybenzyloxy)pentanal (4)



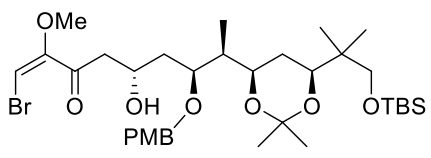
$NaHCO_3$ (88 mg, 1.05 mmol) and DMP (428 mg, 0.98 mmol) were added to a solution of alcohol **14** (370 mg, 0.7 mmol) in CH_2Cl_2 (10 mL) and the solution was stirred for 90 minutes. The reaction mixture was diluted with a saturated solution of $Na_2S_2O_3$ and a saturated solution of $NaHCO_3$ and the residue was extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (9:1) yielded aldehyde **4** (350 mg, 95%) as a colorless oil. $[\alpha]_D$ = -6.0 (c 1.0, CH_2Cl_2). IR (KBr film) ν 2957, 2859, 1725, 1513, 1249, 1090 cm^{-1}. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.78 (s, 3H), 0.79 (s, 3H), 0.89 (s, 9H), 0.96 (d, *J* = 7.0 Hz, 3H), 1.16-1.20 (m, 1H), 1.28 (s, 3H), 1.33-1.34 (m, 1H), 1.35 (s, 3H), 1.71-1.80 (m, 1H), 2.59-2.74 (m, 2H), 3.17 (d, *J* = 9.1 Hz, 1H), 3.41 (d, *J* = 9.1 Hz, 1H), 3.71 (dd, *J* = 11.7, 2.3 Hz, 1H), 3.78 (s, 3H), 3.93-3.95 (m, 1H), 3.96-3.98 (m, 1H), 4.44 (s, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 9.46 (t, *J* = 6.3 Hz, 1H). ^{13}C-RMN (100.6 MHz, $CDCl_3$): δ -5.4 (q), 10.6 (q), 18.4 (s), 19.4 (q), 19.9 (q), 20.9 (q), 26.0 (q), 28.6 (t), 30.3 (q), 38.7 (s), 41.2 (d), 46.1 (t), 55.4 (q), 68.7 (t), 68.8 (d), 71.4 (t), 71.9 (d), 76.2 (d), 98.2 (s), 114.1 (d), 129.4 (d), 130.6 (d), 159.4 (s), 202.5 (s). HRMS (ESI+): *m/z* calculated for $C_{29}H_{51}O_6Si$ $[M+H]^+$ 522.3407, found 522.3412.

(*E*)-((4-Bromo-3-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane (15)



Et_3N (0.062 mL, 0.45 mmol) and TMSOTf (0.065 mL, 0.36 mmol) were sequentially added to a solution of bromoketone **3** (55 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) at 0 ºC. The reaction was stirred for 3 h at rt and quenched with diluted NH_4Cl (5 mL). The organic layer was washed three times with diluted NH_4Cl, dried over $MgSO_4$ and concentrated under reduced pressure to obtain the silylenolether **15** as a brownish oil (65 mg, 86%). The crude was pure enough to continue the synthesis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 3.60 (s, 3H), 4.65 (d, *J* = 1.4 Hz, 1H), 4.75 (d, *J* = 1.4 Hz, 1H), 5.39 (s, 1H).

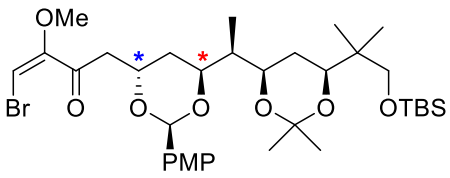
(5*S*,7*S*,8*R*,*E*)-1-Bromo-8-((4*R*,6*S*)-6-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-5-hydroxy-2-methoxy-7-((4-methoxybenzyl)oxy)non-1-en-3-one (16)



A solution of silylenolether **15** (35 mg, 0.122 mmol) in CH_2Cl_2 (0.5 mL) was added to a cooled (-78ºC) solution of aldehyde **4** (46 mg, 0.077 mmol) in CH_2Cl_2 and then $BF_3{\cdot}OEt_2$ (12 □L,

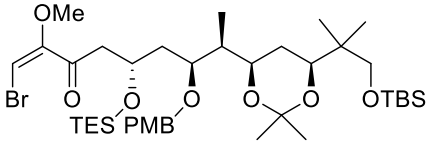
0.092 mmol) was added dropwise. The reaction was stirred at -78ºC for 90 minutes and quenched with saturated solution of $NaHCO_3$ (2mL) andwas extracted three times with CH_2Cl_2. The organic solution was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Purification by silica gel column cromatography with hexane-EtOAc (8:2) afforded **16** (33.3 mg, 62%) as a single diastereomer colorless oil. $[\alpha]_D$ = -1.24 (c 0.5, CH_2Cl_2). IR (KBr film) ν 3485, 2955, 2857, 1708, 1511, 1378, 1254, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.78 (s, 3H), 0.79 (s, 3H), 0.89 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H), 1.21 – 1.39 (m, 3H), 1.30 (s, 3H), 1.36 (s, 3H), 1.62 – 1.82 (m, 3H), 2.81 – 2.85 (m, 2H), 3.19 (d, *J* = 9.2 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.64 (s, 3H), 3.69 – 3.74 (m, 2H), 3.79 (s, 3H), 3.87 – 3.93 (m, 1H), 4.28 – 4.52 (m, 2H), 4.49 (s, 1H), 5.66 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$): -5.6 (q), -5.5 (q), 10.5 (q), 18.2 (s), 19.3 (q), 19.8 (q), 20.7 (q), 25.9 (q), 28.9 (t), 30.2 (q), 37.8 (t), 38.5 (s), 41.1 (d), 47.1 (t), 55.2 (q), 56.0 (q), 64.9 (d), 68.7 (t), 69.2 (d), 71.8 (d), 71.8 (t), 78.3 (d), 84.2 (d), 98.0 (s), 113.8 (d), 129.4 (d), 130.8 (s), 152.9 (s), 159.1 (s), 197.6 (s). HRMS (ESI+): *m/z* calculated for $C_{34}H_{57}BrNaO_8Si$ $[M+Na]^+$ 723.2898, found 723.2894.

(*E*)-4-Bromo-1-((2*S*,4*S*,6*S*)-6-((*R*)-1-((4*R*,6S)-6-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-3-methoxybut-3-en-2-one (S8)



DDQ (15 mg, 0.066 mmol) was added to a solution of aldol **16** (30 mg, 0.042 mmol) in dry CH_2Cl_2 (3 mL) and the reaction was stirred for 30 minutes. After this time, the reaction was filtered through a pad of celite and a saturated solution of $NaHCO_3$ was added to the resulting solution. The solution was washed three times with $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (85:15) yielded **S8** (28 mg, 98%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.79 – 0.81 (m, 6H), 0.88 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.22 – 1.27 (m, 1H), 1.31 (s, 3H), 1.35 (s, 3H), 1.42 – 1.46 (m, 1H), 1.51 – 1.55 (m, 1H), 1.61 (td, *J* = 6.9, 3.9 Hz, 1H), 2.09 – 2.18 (m, 1H), 3.17 – 3.19 (m, 1H), 3.21 – 3.24 (m, 1H), 3.35 – 3.41 (m, 1H), 3.42 – 3.45 (m, 1H), 3.66 (s, 3H), 3.74 (dd, *J* = 11.7, 2.2 Hz, 1H), 3.79 (s, 3H), 3.91 (dt, *J* = 11.5, 3.9, 1.9 Hz, 1H), 4.01 (dt, *J* = 8.8, 3.9, 2.3 Hz, 1H), 4.82 (q, *J* = 6.8 Hz, 1H), 5.67 (s, 1H), 5.75 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$): ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.6 (q), -5.5 (q), 10.0 (q), 18.2 (s), 19.3 (q), 19.7 (q), 20.7 (q), 25.9 (q), 27.9 (t), 30.2 (q), 30.9 (t), 38.5 (s), 41.4 (t), 42.7 (d), 55.3 (q), 56.0 (q), 68.7 (t), 68.9 (d), 69.0 (d), 71.9 (d), 73.2 (d), 84.2 (d), 94.8 (d), 98.1 (s), 113.5 (d), 127.2 (d), 131.5 (s), 153.0 (s), 159.7 (s), 195.1 (s). HRMS (ESI+): *m/z* calculated for $C_{34}H_{56}BrO_8Si$ $[M+H]^+$ 699.2922, found 699.2906.

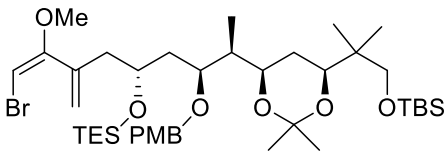
(5*S*,7*S*,8*R*,*E*)-1-Bromo-8-((4*R*,6*S*)-6-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methoxy-7-((4-methoxybenzyl)oxy)-5-((triethylsilyl)oxy)non-1-en-3-one (S9)



Imidazole (85 mg, 1.24 mmol), TESCl (0.16 mL, 0.93 mmol) and DMAP (3 mg, 0.03 mmol) were added sequentially to a

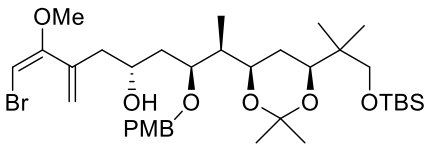
solution of **16** (219 mg, 0.31 mmol) in CH_2Cl_2 (6 mL). The cloudy solution was stirred 90 minutes until TLC analysis showed complete conversion of the starting material. The reaction was quenched with saturated solution of NH_4Cl (6 mL) and extracted three times with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification with deactivated (1% Et_3N) silica gel column cromatography with hexane-EtOAc (95:5) afforded **S9** (235 mg, 96%) as a colorless oil. $[\alpha]_D$ = -1.46 (c 0.5, CH_2Cl_2). IR (KBr film) ν 2955, 2877, 1705, 1517, 1384, 1251, 1083 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.59 (2q, *J* = 7.9 Hz, 6H), 0.75 (s, 3H), 0.76 (s, 3H), 0.89 (s, 9H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.95 (d, *J* = 7.0 Hz, 3H), 1.23 – 1.27 (m, 2H), 1.30 (s, 3H), 1.35 (s, 3H), 1.70 – 1.76 (m, 2H), 2.82 (dd, *J* = 16.2, 5.8 Hz, 1H), 2.94 (dd, *J* = 16.2, 6.4 Hz, 1H), 3.15 (d, *J* = 9.2 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.53 – 3.57 (m, 1H), 3.59 (s, 3H), 3.66 – 3.71 (m, 1H), 3.79 (s, 3H), 3.81 – 3.86 (m, 1H), 4.32 – 4.40 (m, 1H), 4.38 – 4.47 (m, 3H), 5.57 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$) δ -5.6 (q), -5.5 (q), 5.1 (t), 7.0 (q), 10.5 (q), 18.3 (s), 19.1 (q), 19.8 (q), 20.8 (q), 25.9 (q), 29.0 (t), 30.2 (q), 38.5 (s), 39.9 (t), 40.8 (d), 48.5 (t), 55.2 (q), 55.8 (q), 66.8 (d), 68.7 (t), 69.5 (d), 70.3 (t), 71.5 (d), 77.7 (d), 83.5 (d), 97.9 (s), 113.6 (d), 128.9 (d), 131.2 (s), 153.4 (s), 158.9 (s), 195.8 (s). HRMS (ESI+): *m/z* calculated for $C_{40}H_{75}BrNO_8Si_2$ $[M+NH_4]^+$ 832.4209, found 832.4200.

(((5*R*,7*S*,8*R*,*E*)-1-Bromo-8-((4*R*,6*S*)-6-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methoxy-7-((4-methoxybenzyl)oxy)-3-methylenenon-1-en-5-yl)oxy)triethylsilane (S10)



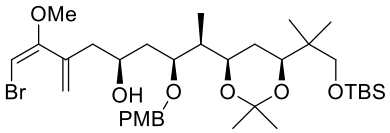
A solution of Tebbe reagent in toluene (0.5M, 1.1 mL, 0.55 mmol) was added to a solution of **S9** (137 mg, 0.17 mmol) and pyridine (0.05 mL, 0.55 mmol) in THF (3.5 mL) at 0 ºC. The reaction mixture was warmed to rt and then heated up at 50 ºC during 2 hours. The reaction was quenched at rt with saturated solution of Rochelle's salt (3 mL) and extracted three times with Et_2O. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **S10** (123 mg, 92%) as a colorless oil. $[\alpha]_D$ = -0.48 (c 0.5, CH_2Cl_2). IR (KBr film) ν 2955, 2874, 1613, 1514, 1373, 1251, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, Chloroform-*d*) δ 0.01 (s, 6H), 0.59 (2q, *J* = 7.9 Hz, 6H), 0.75 (s, 6H), 0.88 (s, 9H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 1.23 – 1.30 (m, 2H), 1.30 (s, 3H), 1.35 (s, 3H), 1.49 – 1.55 (m, 1H), 1.71 – 1.77 (m, 1H), 1.81 – 1.90 (m, 1H), 2.30 (dd, *J* = 13.8, 8.8 Hz, 1H), 2.60 (dd, *J* = 13.8, 4.2 Hz, 1H), 3.15 (d, *J* = 9.2 Hz, 1H), 3.44 (d, *J* = 9.2 Hz, 1H), 3.51 (s, 3H), 3.61 – 3.65 (m, 1H), 3.68 (dd, *J* = 11.2, 2.9 Hz, 1H), 3.80 (s, 3H), 3.80 – 3.85 (m, 1H), 3.94 (dt, *J* = 8.8, 5.2, 4.2 Hz, 1H), 4.37 – 4.48 (m, 2H), 5.27 (s, 1H), 5.34 (s, 1H), 5.39 (s, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$) δ -5.6 (q), -5.5 (q), 5.3 (t), 7.0 (q), 10.6 (q), 18.3 (s), 19.0 (q), 19.8 (q), 20.9 (q), 25.9 (q), 29.1 (t), 30.3 (q), 38.5 (s), 38.8 (t), 41.1 (d), 43.4 (t), 55.2 (q), 55.3 (q), 68.5 (d), 68.7 (t), 69.8 (d), 70.3 (t), 71.5 (d), 77.6 (s), 78.3 (d), 97.9 (s), 113.5 (d), 121.4 (t), 128.6 (d), 131.7 (s), 139.3 (s), 158.8 (s), 158.9 (s). HRMS (ESI+): *m/z* calculated for $C_{41}H_{74}BrO_7Si_2$ $[M+H]^+$ 813.4151, found 813.4151.

(5*R*,7*S*,8*R*,*E*)-1-Bromo-8-((4*R*,6*S*)-6-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methoxy-7-((4-methoxybenzyl)oxy)-3-methylenenon-1-en-5-ol (17)



PPTS (10 mg, 0.03 mmol) was added to a solution of **S10** (123 mg, 0.15 mmol) in MeOH (5 mL) at 0ºC and the reaction mixture was stirred 30 minutes at rt. After this time was quenched with saturated solution of $NaHCO_3$ (5mL) and extracted three times with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (85:15) yielded **17** (107 mg, quant.) as a colorless oil. $[\alpha]_D$ = -1.30 (c 0.5, CH_2Cl_2). IR (KBr film) ν 3470 (br), 2955, 2854, 1607, 1514, 1248, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.78 (s, 3H), 0.78 (s, 3H), 0.89 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H), 1.24 – 1.28 (m, 2H), 1.31 (s, 3H), 1.35 (s, 3H), 1.61 – 1.71 (m, 2H), 1.71 – 1.77 (m, 1H), 2.31 (dd, *J* = 13.8, 8.5 Hz, 1H), 2.44 (dd, *J* = 13.8, 4.1 Hz, 1H), 3.17 (d, *J* = 9.2 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.57 (s, 3H), 3.68 – 3.74 (m, 2H), 3.80 (s, 3H), 3.83 – 3.91 (m, 2H), 4.49 (s, 2H), 5.32 (s, 1H), 5.38 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$) δ -5.6 (q), -5.5 (q), 10.5 (q), 18.3 (s), 19.2 (q), 19.8 (q), 20.8 (q), 25.9 (q), 29.0 (t), 30.2 (q), 38.0 (t), 38.5 (s), 41.3 (d), 43.1 (t), 55.3 (q), 55.7 (q), 66.7 (d), 68.7 (t), 69.3 (d), 71.7 (d), 71.8 (t), 78.4 (d), 78.6 (d), 98.0 (s), 113.8 (d), 122.0 (t), 129.4 (d), 131.0 (s), 139.7 (s), 159.1 (s), 159.1 (s). HRMS (ESI+): *m/z* calculated for $C_{35}H_{59}BrNaO_7Si$ $[M+Na]^+$ 721.3106, found 723.3090.

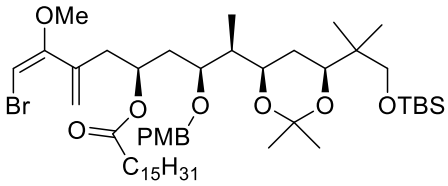
(5*S*,7*S*,8*R*,*E*)-1-Bromo-8-((4*R*,6*S*)-6-(1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methoxy-7-((4-methoxybenzyl)oxy)-3-methylenenon-1-en-5-ol (1)



DIAD (0.21 mL, 1.08 mmol) was slowly added to a solution of **17** (80 mg, 0.11 mmol), *p*-nitrobenzoic acid (160 mg, 0.96 mmol) and PPh_3 (282 mg, 1.08 mmol) in benzene (3 mL) and the yellowish solution was stirred for 3h at rt. The reaction was quenched with saturated solution of $NaHCO_3$ (3 mL) and extracted three times with Et_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was filtered through a plug of silica using hexane-EtOAc 9:1 to eliminate the *p*-nitrobenzoic acid and PPh_3O (R_f = 0.1). After evaporation the resulting crude was dissolved in MeOH (5mL), K_2CO_3 (180 mg, 1.30 mmol) was added and the mixture was stirred for 2 h until TLC indicated total hydrolysis. The reaction was quenched with saturated solution of NH_4Cl (5 mL) and extracted three times with AcOEt. The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by silica gel column chromatography with hexane-EtOAc 9:1 to obtain **1** as a colorless oil (47 mg, 58% for two steps). $[\alpha]_D$ = +1.79 (c 1, CH_2Cl_2). IR (KBr film) ν 3470 (br), 2955, 2854, 1607, 1514, 1248, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.76 (s, 3H), 0.78 (s, 3H), 0.89 (s, 9H), 0.94 (d, *J* = 7.0 Hz, 3H), 1.25 – 1.30 (m, 2H), 1.32 (s, 3H), 1.37 (s, 3H), 1.65 – 1.72 (m, 1H), 1.76 – 1.84 (m, 2H), 2.34 – 2.47 (m, 2H), 3.17 (d, *J* = 9.2 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.57 (s, 3H), 3.62 – 3.66 (m, 1H), 3.67 – 3.75 (m, 2H), 3.79 (s, 3H), 3.84 – 3.91 (m, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 5.32 (s, 1H), 5.37 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$) δ -5.6 (q), -5.5 (q),

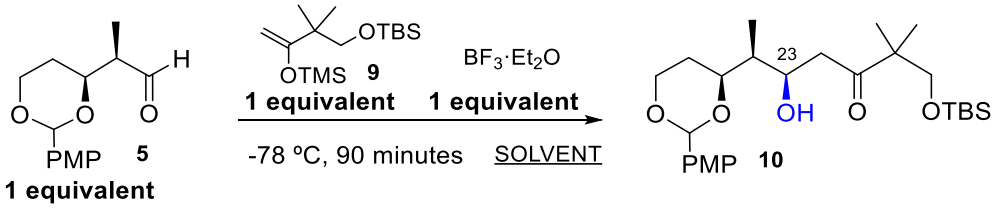
10.8 (q), 18.2 (s), 19.2 (q), 19.8 (q), 20.8 (q), 25.9 (q), 29.0 (t), 30.2 (q), 37.1 (t), 38.5 (s), 40.4 (d), 42.8 (t), 55.2 (q), 55.6 (q), 68.7 (t), 69.1 (d), 69.5 (d), 70.8 (t), 71.6 (d), 78.6 (d), 80.8 (d), 98.0 (s), 113.8 (d), 121.9 (t), 129.3 (d), 130.5 (s), 139.5 (s), 159.0 (s), 159.2 (s). HRMS (ESI+): *m/z* calculated for $C_{35}H_{59}BrNaO_7Si$ $[M+Na]^+$ 721.3106, found 721.3103.

(5*S*,7*S*,8*R*,*E*)-1-Bromo-8-((4*R*,6*S*)-6-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methoxy-7-((4-methoxybenzyl)oxy)-3-methylenenon-1-en-5-yl palmitate (2)



Palmitic acid (13 mg, 0.05 mmol) was added to a solution of EDC·HCl (18 mg, 0.09 mmol), Et_3N (0.013 mL, 0.09 mmol) and DMAP (11 mg, 0.09 mmol) in CH_2Cl_2 (0.35 mL) and the solution was stirred for 20 minutes. **1** (22 mg, 0.031 mmol) dissolved in CH_2Cl_2 (0.15 mL) was added and the solution was stirred for 16h. The reaction was quenched with saturated solution of NH_4Cl (1 mL) and extracted three times with AcOEt. The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by silica gel column chromatography with hexane-EtOAc 95:5 to obtain **2** as a colorless oil (12 mg, cuant. brsm) and **2** (14 mg). $[\alpha]_D$ = +1.86 (c 0.5, CH_2Cl_2). IR (KBr film) ν 2961, 2926, 2848, 1740, 1612, 1511, 1456, 1251, 1089 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.72 (s, 3H), 0.74 (s, 3H), 0.88 (brs, 12H), 0.94 (d, *J* = 7.0 Hz, 3H), 1.11 – 1.21 (m, 2H), 1.25 (brs, 24H), 1.30 (s, 3H), 1.35 (s, 3H), 1.56 – 1.60 (m, 2H), 1.66 (td, *J* = 7.0, 6.4, 3.3 Hz, 1H), 1.82 – 1.95 (m, 2H), 2.15 – 2.29 (m, 2H), 2.54 (qd, *J* = 14.2, 6.4 Hz, 2H), 3.14 (d, *J* = 9.2 Hz, 1H), 3.44 (d, *J* = 9.2 Hz, 1H), 3.45 – 3.49 (m, 1H), 3.55 (s, 3H), 3.65 (dd, *J* = 11.2, 2.9 Hz, 1H), 3.79 (s, 3H), 3.79 – 3.79 (m, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.99 (p, *J* = 6.7 Hz, 1H), 5.31 (s, 1H), 5.34 (d, *J* = 1.4 Hz, 1H), 5.41 (d, *J* = 1.4 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H). ^{13}C-RMN (100.6 MHz, $CDCl_3$) δ -5.6 (q), -5.5 (q), 9.9 (q), 14.1 (q), 18.3 (s), 18.9 (q), 19.8 (q), 20.9 (q), 22.7 (t), 25.0 (t), 25.9 (q), 28.5 (t), 29.3 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.7 (t), 30.2 (d), 34.6 (t), 35.0 (t), 38.5 (s), 39.0 (t), 41.0 (d), 55.2 (q), 55.6 (q), 68.7 (t), 69.9 (d), 70.0 (d), 70.2 (t), 71.4 (d), 75.9 (d), 78.7 (d), 97.9 (s), 113.7 (s), 122.0 (t), 129.2 (s), 131.0 (s), 138.4 (s), 158.5 (s), 159.0 (s), 172.9 (s). HRMS (ESI+): *m/z* calculated for $C_{51}H_{90}BrO_8Si$ $[M+H]^+$ 937.5583, found 937.5559.

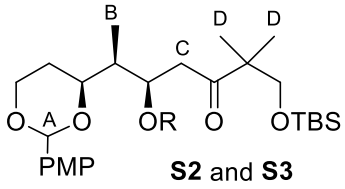
Solvent optimization in transformation 5 → 10



Entry	Solvent	Yield (%)	**10(23*R*):10 (23*S*)**
1	CH_2Cl_2	78[b]	68:32
2	CH_2Cl_2:Et_2O (1:1)	39[c]	100:0
3	Et_2O	0[c]	--
4	Toluene	84[c,d]	94:6
5	**CH_2Cl_2:Et_2O (95:5)**	**98[b]**	**98:2**

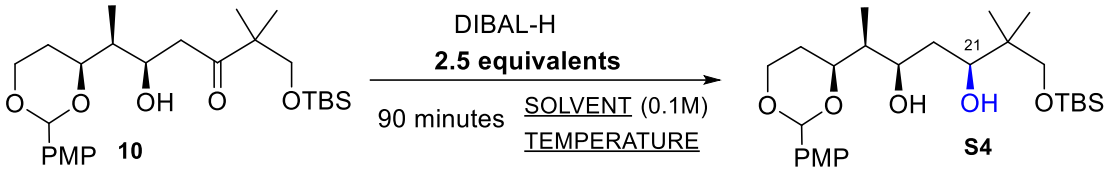
All reactions were carried out with 1 equivalent of BF3·OEt2 in the described solvent at -78 °C during 90 minutes. [b] Yield was based in the recovery of **1** (Y_{brsm}). Diasteromeric ratio was determined separating ***3(5R)*** and ***3(5S)*** via column cromatography. [c] Yield and diasteromeric ratio were determined by integration of the ^{1}H NMR spectrum of the unpurified reaction mixture. [d] The reaction crude had additional ^{1}H NMR signals non-related with **1**, **2** or **3**.

C23 configuration of 10 determination



	δ H_A	δ H_B	δ H_C	δ H_D
S2=*R*-MPA	5.05	0.86	2.86	1.05
S3=*S*-MPA	5.31	0.99	2.74	0.92
Δ^{RS}	-0.26	-0.13	+0.12	+0.13

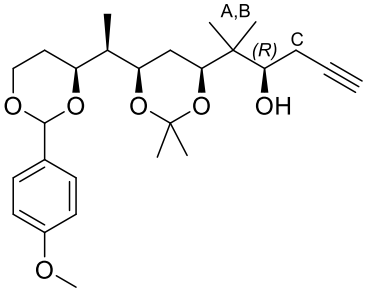
Solvent and temperature optimization in transformation 10 → S4



Entry	Solvent	Temperature	**S4(21*R*):S4(21*S*)**
1	CH_2Cl_2	-78 ºC	52:48
2	Et_2O	-78 ºC	55:45
3	THF	-78 ºC	65:35
4	**THF**	**-100 ºC**	**84:16**

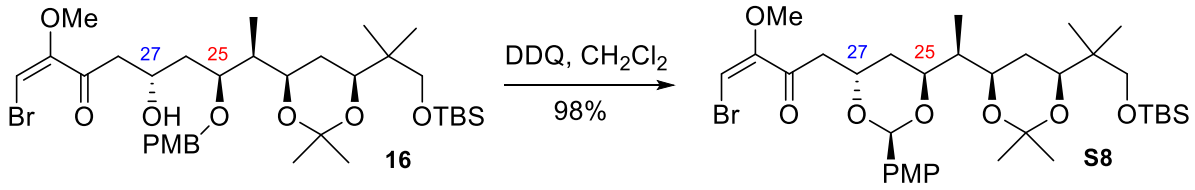
All reactions were carried out with 2.5 equivalents of DIBAL-H the described solvent at the described temperature for 90 minutes. All the starting material was consumed after the reaction time. Diasteromeric ratio was determined by integration of the ^{1}H NMR spectrum of the unpurified reaction mixture.

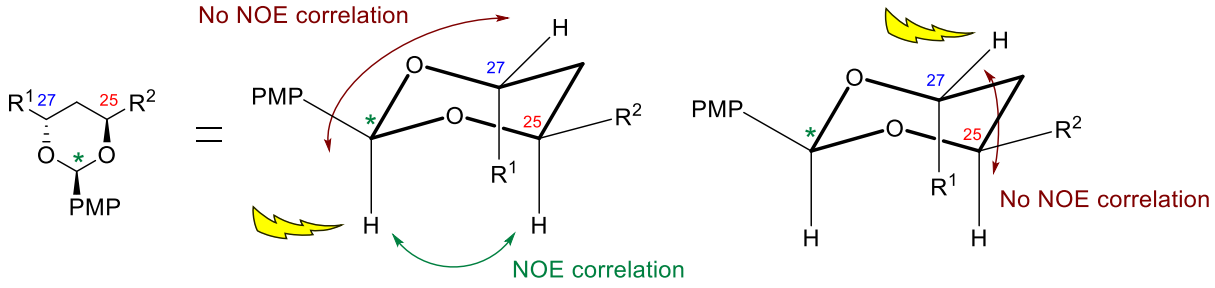
C19 configuration of 13 determination



	δ H_A	δ H_B	δ H_C
S7 = *R*-MPA	0.62 ppm	0.62 ppm	2.51 ppm
S6 = *S*-MPA	0.80 ppm	0.83 ppm	2.37 ppm
Δ^{RS}	-0.18	-0.21	+0.14

C27 Configuration of 16 determination





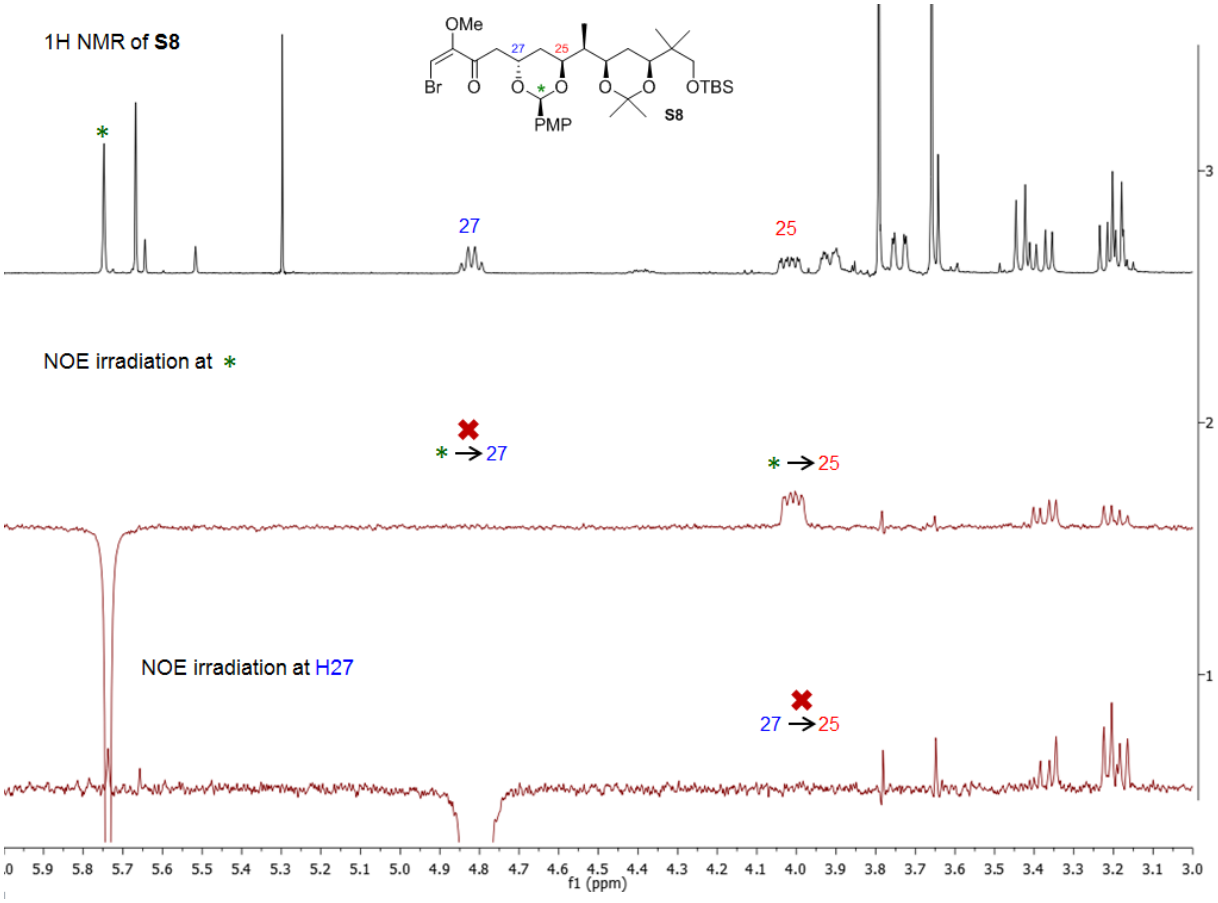
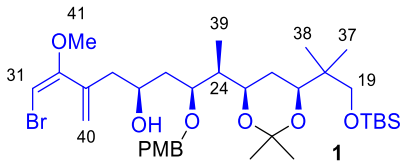
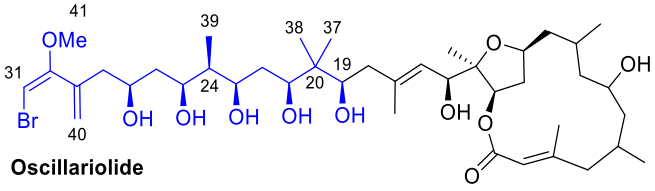


Table 1. H^1- and C^{13}-NMR data of compound 1 and oscillariolide



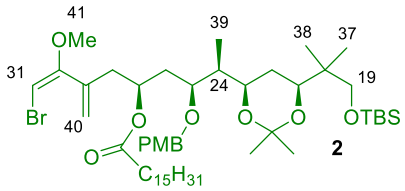
1

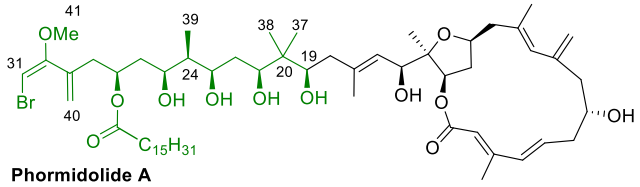


Oscillariolide

Position	δ ^{1}H (**Osc**) d^6-DMSO	δ ^{1}H (**1**) d^6-DMSO	δ ^{1}H (**1**) $CDCl_3$	δ ^{13}C (**Osc**) d^6-DMSO	δ ^{13}C (**1**) d^6-DMSO	δ ^{13}C (**1**) $CDCl_3$
20	--	--	--	41.3	38.1	38.5
24	1.44	1.57	1.79	40.7	40.3	40.4
28	2.21;2.38	2.25;2.45	2.40	42.6	43.0	42.8
29	--	--	--	139.9	139.8	139.5
30	--	--	--	158.7	158.5	159.0
31	5.60	5.63	5.32	79.1	79.1	78.6
37	0.69	0.68	0.76	18.2	18.9	19.2
38	0.82	0.70	0.78	18.7	20.5	20.7
39	0.79	0.83	0.94	6.8	9.6	10.8
40	5.22;5.32	5.25;5.33	5.37	120.3	120.4	121.9
41	3.53	3.53	3.57	55.8	55.8	55.6

Table 2. H^1- and C^{13}-NMR data of compound 2 and phormidolide A





Phormidolide A

Position	δ ^{1}H (**PhA**) $CDCl_3$	δ ^{1}H (**2**) $CDCl_3$	δ ^{13}C (**PhA**) $CDCl_3$	δ ^{13}C (**2**) $CDCl_3$
20	--	--	40.4	38.5
24	1.49	1.66	41.5	40.9
28	2.57	2.54	39.3	39.0
29	--	--	138.3	138.3
30	--	--	158.4	158.5
31	5.33	5.31	78.8	78.7
37	0.91	0.74	13.7	18.9
38	0.74	0.72	21.6	20.9
39	0.92	0.94	5.0	9.8
40	5.37;5.42	5.34;5.41	122.1	122.0
41	3.59	3.55	55.6	55.6

Chapter 5

Chemical synthesis of the fatty acids present in phomidolides C and D

As depicted in Figure 1, the only difference between PM B-D is located in the fatty acid linked through an ester bond to the C27 hydroxyl group of the polyol chain. Each member of the family present a tetradecanoic acid ended by different olefinic functionalities. PM B presents a terminal conjugated (*E*)-dichloro-diene acid whereas PM C and PM D present an (*E*)-bromo-chloro-ene and an (*E*)-dichloro-ene moieties, respectively.[1] The preparation of the different fatty acids **1**, **2** and **3** is a vital synthetic requirement to conclude the total synthesis of the natural products.

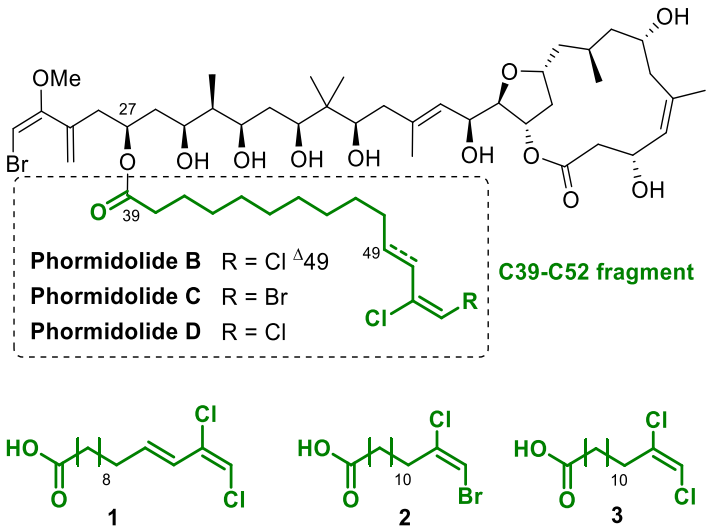
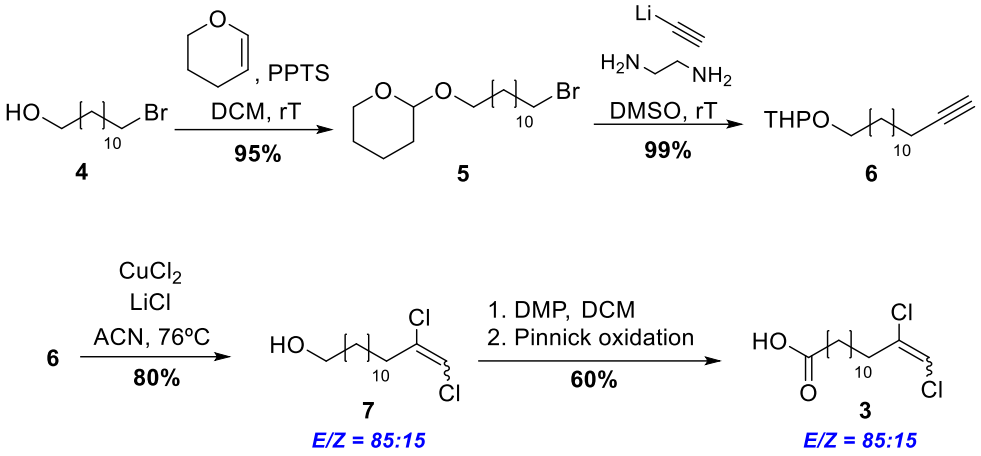


Figure 1. PM B-D general structure highlighting the synthetic targets of this chapter, fatty acids **1**, **2** and **3**.

Our initial investigations started with the preparation of **3**, the fatty acid present in PM D, due to its higher structural simplicity. Thanks to the efforts of a MSc student, José Antonio Fernández, a first generation synthesis for the preparation of **3** was achieved following the route depicted on Scheme 1. Starting from the commercially available 12-bromo-1-dodecanol **4**, protection with tetrahydropyranyl (THP) protecting group and subsequent acetylide substitution of the bromine in halo-derivative **5** rendered the common protected alkyne **6** with good yields in two simple and easily scalable steps. A literature revision about different conditions to perform halogen additions to terminal triple bonds did not give much information, but it was decided to apply the conditions described by Okano et. al.[2] The addition of chlorine to the acetylene moiety in **6** using copper(II) chloride in the presence of lithium chloride proceeded with good yield but due to the harsh conditions, concomitant THP-deprotection ocurred obtaining **7** as an inseparable *E*/*Z* mixture of double bond isomers in 80% yield. During this stage, it was also discovered that a milder two-step oxidation was needed to obtain the acid **3** to keep the molecular architecture intact. Dess Martin oxidation of **7** and subsequent Pinnick oxidation gave acid **3** as an inseparable mixture of double bond isomers. The lack of

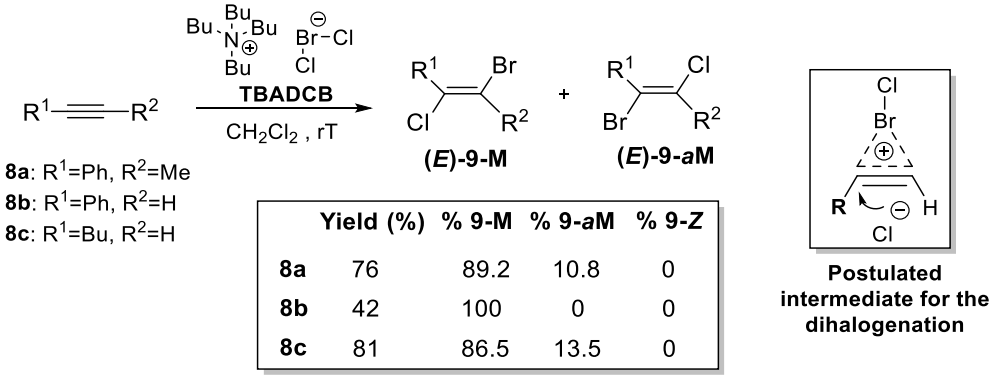
stereoselectivity in the formation of **7** (Scheme 1) invalidated that procedure for the preparation of **3**.



Scheme 1. First synthesis of the fatty acid present in Phormidolide D.[3]

At this point, we put our attention on a publication by Takeshi Negoro[4] where bromo-chlorination of terminal alkynes was investigated with interesting synthetic results (Scheme 2). The alkynes (**8a**-**8c**) reacted with tetrabutylammonium dichlrobromide (TBADCB) in dichloromethane, at room temperature to afford good yield, regio- and stereoselectivity as it is shown in the Table depicted in Scheme 2. For our interest, the main advantages for the use of this methodology applied to the synthesis of the fatty acids were:

- General good yields with easy experimental set-up.
- Mild reaction conditions.
- The reaction is stereospecific only rendering (*E*)-double bonds. This is in agreement with the mechanism proposed by the authors (Scheme 2).
- Regioselectivity toward the (*E*)-Markovnikov isomer (**(*E*)-9-M**), useful later in the synthesis of the fatty acid of Phormidolide C.

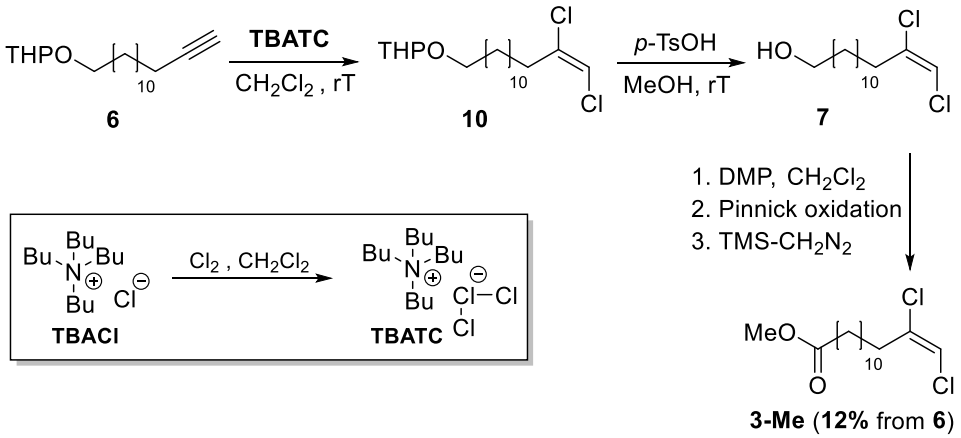


	Yield (%)	% 9-M	% 9-*a*M	% 9-*Z*
8a	76	89.2	10.8	0
8b	42	100	0	0
8c	81	86.5	13.5	0

Scheme 2. Summary of the results obtained in Takeshi Negoro group.[4]

With all this data on hand we hypothesized that reaction with tetrabutylammonium trichloride (TBATC) should render identical results with the additional advantage of absence of regioisomers. So, with the help of another MSc student (Michela Giarrusso), a new synthetic route was designed and validated for the preparation of **3-Me**, the methyl ester of phormidolide D fatty acid. The TBATC was prepared with excellent yield by bubbling Cl_2 over a solution of TBACl in dichloromethane.[5] Then, alkyne **6** reacted with TBATC to render quantitatively **10** as a single (*E*) isomer. Deprotection of **10** in acid conditions followed by two-step oxidation and methyl ester protection, to avoid decomposition during storage, produced methyl ester **3-Me** in a 12% yield from **6**. This route presents the following strengths:

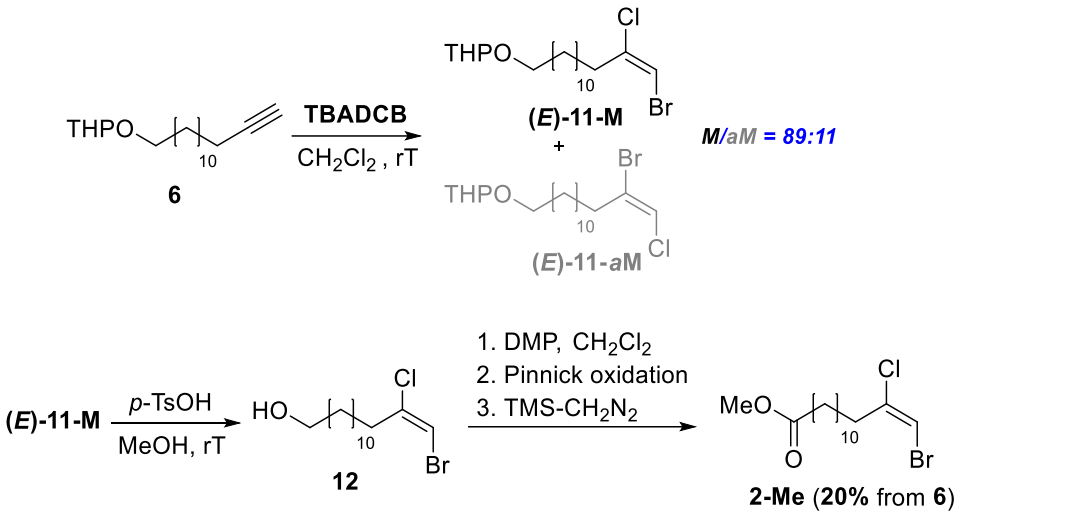
- Clean, mild, quantitative and stereoselective di-halogenation of the triple bond.
- No need to chromatographically purify until the last step.
- Easily scalable (110 mg of **3** were prepared).

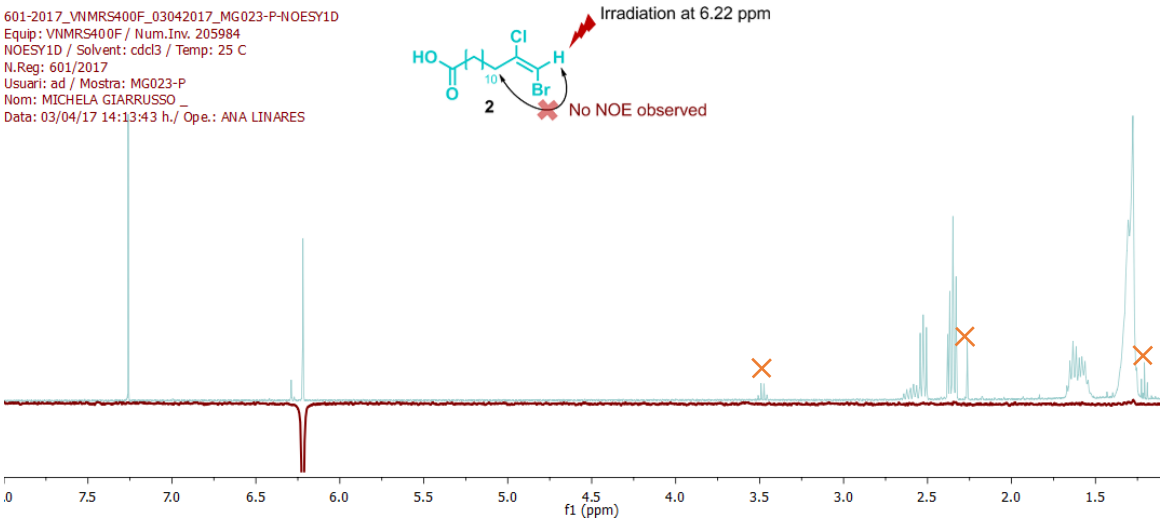


Scheme 3. Efficient preparation of **3-Me**, the methyl ester of PM D fatty acid.

Due to the similarities between PM C and D fatty ester **2-Me** was prepared and alkyne **6** was also used as a starting point (Scheme 4, Up). Compound **6** was treated with commercially available tetra-butyl-ammonium dichlorobromide in dichloromethane following the previously reported[4] procedure rendering a mixture of regio-isomers **(*E*)-11-M** and **(*E*)-11-*a*M**. Fortunately, and as expected from the reviewed literature, the Markovnikov product, constitution present in the natural product, was obtained as the major regioisomer. A postulation for this selectivity would be the existence of a trigonal chloro-bromonium carbocation intermediate (Scheme 2) which, due to the higher stability of the quaternary carbocation, would cause the attack of the chlorine anion to the more substituted position rendering mostly Markovnikov compound **(*E*)-11-M.** The anti- attack of the chlorine anion to the intermediate would also be in agreement with the absence of *Z* double bond isomers. Double bond geometry was determined using NOE-

1D experiments. Irradiation on the olefinic proton (C52) at 6.22 ppm did not produce an increase of the methylene (C50) signal (Scheme 4, Down).[6]





Scheme 4. Up: Synthetic route towards the fatty acids present on PM C and D. **Down:** Light blue: ^{1}H NMR of **2**. Red: NOE-1D irradiation at 6.22 ppm.

Crude material **11** was subjected to a 3-step procedure to introduce the carboxylic acid functionality at the end of the aliphatic chain. Deprotection under acidic conditions, Dess-Martin oxidation, and Pinnick oxidation rendered the fatty acid that was protected as a methyl ester. This synthetic sequence delivered the synthetic objective **2-Me** as a single regio-isomer after a single final purification using preparative RP-HPLC (TELEDYNE ISCO) on column C18 (GOLD REDISEP) with an overall 20% yield from **6**.

In conclusion, fatty acid esters **2-Me** and **3-Me** have been efficiently prepared and scaled to have enough quantity for their use in the total synthesis of PM. All the characterization data matches the presented structures and all the intermediates have been fully characterized. It is important to mention that mass spectrometry analyses of the final compounds confirm unambiguously that the obtained structures have the appropriate number of halogen atoms.

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Note

The experimental section of this chapter can be found within the publication of Chapter 6.

Chapter 6

Towards the Synthesis of Phormidolides, a Journey.

Towards the Synthesis of Phormidolides, a Journey

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ABSTRACT: A convergent and stereoselective approach for the synthesis of marine natural product (MNP) phormidolide D (PM D) is proposed. Two main disconnections divided PM D in three molecular fragments: the macrocyclic core **4**, the stapling iodoalkene **9** corresponding to the central part of PMs and the east fragment **5** that includes the unusual bromo-methoxy-diene moiety and a tetradecanoic acid ended with a (*E*)-dichloro-ene functionality. Procedures for the preparation of compounds **5**, **9** and the never-reported fatty acids **7** and **8**, present in PM C and D have been afforded with good yields and high degree of stereoselectivity. The absolute configuration of all the generated stereocenters has been established. The reaction to link iodoalkene **9** and formylmacrolactone **4**, using the Nozaki-Hiyama-Takai-Kishi coupling, gave an advanced synthetic intermediate with total stereocontrol. Finally, a deeper study of protecting groups and reaction conditions for the last step of the synthesis is needed. All the information gathered in this publication will be of great value to continue performing synthetic studies for the preparation of these NPs. The versatility and the presence of a common polyol chain in oscillariolide and phormidolides A-C would allow applying the same retrosynthesis for syntheses of the mentioned MNP.

INTRODUCTION

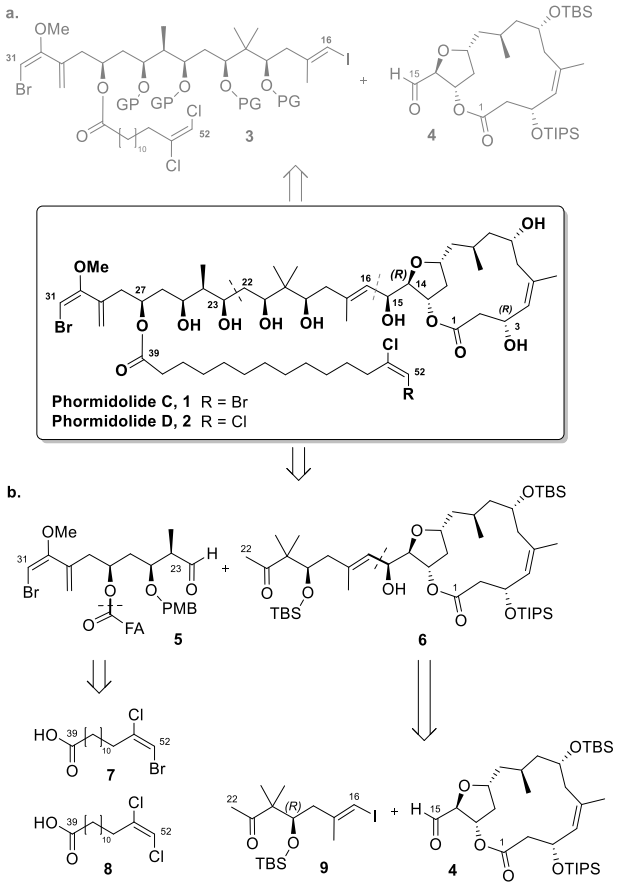
Polyketides, and more specifically macrolides, represent a family of marine natural products of great interest from a biological-therapeutical point of view[1] but, at the same time, they show high complex molecular architectures that make their syntheses a real challenge. Phormidolides C and D (Scheme 1, PM C and D, **1-2**) are marine polyketides isolated by the biotech company *PharmaMar* that showed cytotoxic activity in three tumour cell lines with an unknown mechanism of action.[2] From a structural point of view, PM C-D present thirteen stereocenters and five di- and tri-substituted double bonds distributed in the following moieties: a THF-containing macrolide (C1-C14), a polyhydroxylated chain (C15-C31) terminated with a unusual bromo-metoxy-diene moiety and two different tetradecanoic fatty acids (C39-C52) containing a terminal (*E*)-dichloro-ene or (*E*)-bomo-chloro-ene functionalities linked to the C27 hydroxylic position.[3] So far, and to the best of our knowledge, no total synthesis of phormidolides C-D or the related phormidolide A[4] and oscillariolide[5] has been described.

The structural and stereochemical elucidation of PM C-D was carried out through mono and bi-dimensional advanced NMR tecnhiques (^{1}H, ^{13}C, 1D-TOCSY, gCOSY, gHSQC, and gHMBC) and HRMS.[6] The relative configuration of stereocenters present in the macrocyclic core was determined using ROESY combined with *J*-based configuration analysis and NOE experiments. The two only stereocenters, with unclear configuration after NMR analysis, were C3 and C14 positions. In order to solve this issue, our group reported the chemical syntheses of three different diastereomeric protected macrocyclic cores (C1-C15 fragment). NMR comparison of synthetic and natural product suggested to us that the 3*R*, 14*R* configuration was the most plausible one.[2] A second generation synthesis of the C1-C15 moiety with the after-mentioned stereochemistry, after removal of the protecting groups, enabled a second NMR comparison with the natural product which showed high similarity, hence confirming our 3*R* and 14*R* stereochemical hypothesis.[7]

Stereochemistry of the C15-C31 fragment, common to oscillariolide[5] and phormidolide A[4], was determined by chemical shift and the coupling constant comparison with phormidolide A, whose absolute configuration was previously determined by Gerwick and co-workers. Recently, our group described the synthesis of the C19-C31 polyhydroxylated chain,[8] including the tricky bromo-methoxy-diene motif.[9] This allowed a new NMR chemical shift comparison between the synthetic and the natural products showing high degree of similarity, thereby confirming the absolute configuration of the polyol chain by chemical synthesis.

Our initial proposed retrosynthesis (Scheme 1, a) explained during the enantioselective synthesis of the polyhydroxylated chain was based on a single disconnection through the C15-C16 bond.[8] Both fragments **3** and **4** would be linked in the last step of the synthesis through a Nozaki-Hiyama-Takai-Kishi[10] (NHTK) coupling reaction. However, this approach posed some clear disadvantages. First, a high number of linear synthetic steps for the preparation of **3** would be required and introduction of the C16 iodoalekene functionality would not be trivial. Secondly, a possible lack of chemoselectivity in the formation of the C15-C16 using NHTK conditions bond could have occurred due to the presence of other reactive positions in **3** such as C31 or C52. For these reasons, a new retrosynthetic analysis that overcame all the above-mentioned problems was necessary.

Scheme 2: Phormidolide C and D molecular structures and proposed retrosynthetic analyses.



The new synthetic approach (Scheme 1, b) envisions a disconnection through the C22-C23 bond to create it at the end of the route through a previously optimized[8] Mukaiyama aldol addition from aldehyde **5** (C23-C31) and methyl-ketone **6** (C1-C22). Fatty acids **7** and **8** present in the different phormidolides would be synthesized separately and esterified at the C27 position during the synthetic route toward **5**. Then, fragment **6** would be planned to be prepared by means of the Nozaki-Hiyama-Takai-Kishi[10] coupling of enantiopure iodoalkene **9** (C16-C22) and the previously reported C1-C15 fragment aldehyde **4**.[7] A reliable preparation of central fragment **9** is crucial due to its useful bivalent nature (methy-ketone and iodo-alkene) that allows its use as a "stapling" compound between macrocycle **4** and aldehyde **5**.

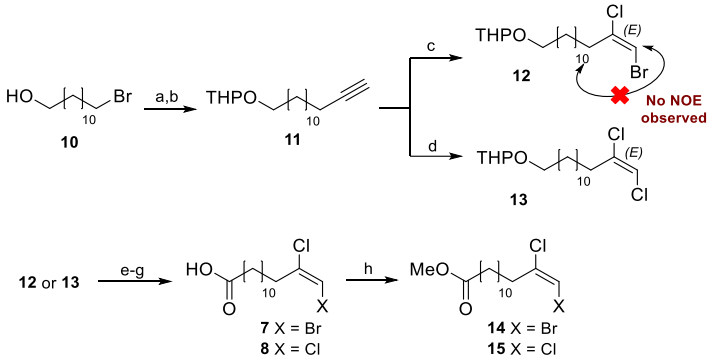
Herein, we report the preparation of fatty acids **7** and **8**, present on both PM C-D, and the synthesis of aldehyde **5** and iodoalkene **9.** Furthermore, with fragments **5**, **9** and **4** in hand the first synthetic approach for the synthesis of marine natural product phormidolide D is discussed.

RESULTS AND DISCUSSION

Fatty acids preparation

Tetradecanoic acids containing (*E*)-di-halogenated terminal double bonds were prepared by direct di-halogenation of the corresponding terminal alkyne using the methodology developed by Negoro et al.[11] The use of these halogenation conditions had important advantages such as good yields, easy experimental setup, mild conditions, stereospecificity toward the (*E*) double bond and regioselectivity for the desired isomer in the case of bromochlorination.

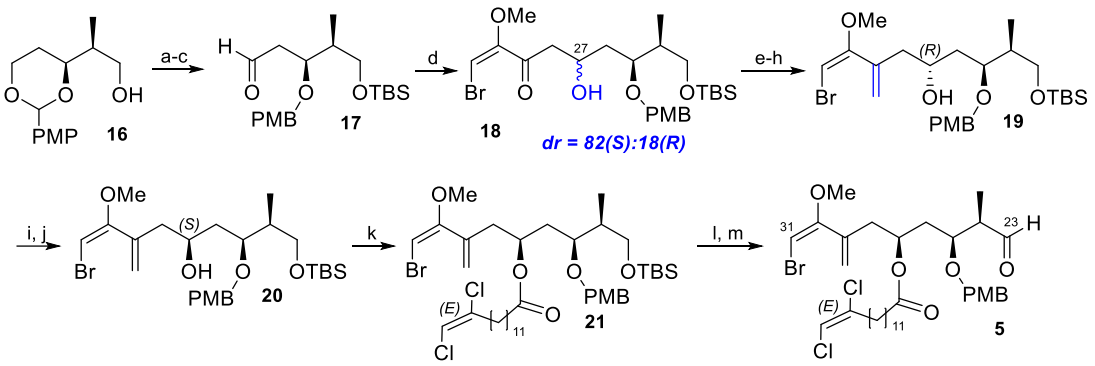
Scheme 3: Preparation of the fatty acids present in phormidolides C and D.[a]



[a]Reagents and conditions: a) PPTS, CH_2Cl_2, 3,4-dihydro-2*H*-pyran, rt, 95%; b) Lithium acetylide-diethylamine complex, DMSO, rt, 99%; c) Tetrabutylammonium dichlorobromide, DCM, rt; d) Tetrabutylammonium trichloride, DCM, rt; e) *p*-TsOH, MeOH, rt; f) DMP, CH_2Cl_2, rt; g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^tBuOH/H_2O$, rt; h) TMS-CH_2N_2, CH_2Cl_2, MeOH. Yields: **14** = 20% from **11**; **15** = 12% from **11**.

The synthetic route was initially started using commercially available 11-bromo-1-dodecanol **10** through protection of the hydroxyl prior to the alkyne introduction, and through triple bond halogenation. The tetrahydropyranyl (THP) protecting group was chosen as the most convenient protecting group for the whole synthetic route.[12] After THP protection of **10** and acetylide introduction, alkyne **11** was obtained in high yield. This compound is common to both synthetic routes for the preparation of fatty acids **7** and **8**. (Scheme 2). The key reaction of **11** with tetrabutylammonium dichlorobromide in CH_2Cl_2 at rt produced terminal alkene **12** as a single (*E*) double bond isomer. (*E*) stereochemistry was confirmed by the lack of NOE correlation between the vinylic and allylic protons.[13,14] However, compound **12** was obtained as a 89:11 mixture of inseparable regioisomers.[15] THP removal followed by a double Dess-Martin and Pinnick oxidation rendered fatty acid **7** found in phormidolide C. Finally, **7** was protected as methyl ester and purified to obtain **14** in good yield with a single final purification from **11**. It is important to mention that this final protection was performed to facilitate the purification process and to enhance the stability of the compound for long-term storage.

Scheme 4: Preparation of compound 5, fragment C23-C31.[a]



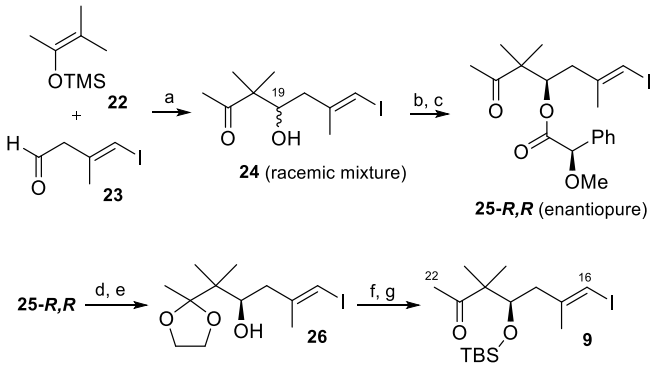
[a]Reagents and conditions: a) TBSCl, imidazole, DCM, 86%; b) DIBAL, DCM, -20 °C to 0 °C, 90%; c) DMSO, $(COCl)_2$, Et_3N, DCM, -78 °C, 80%; d) **(*E*)-((4-bromo-3-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane**, $BF_3{\cdot}Et_2O$, DCM, -78 °C, 47%; e) TESCl, imidazole, DCM, 86%; f) Tebbe reagent, pyridine, THF, 50 °C, 81%; g) PPTS, MeOH, 88%; h) Diastereomer column chromatography separation.; i) PPh_3, *p*-nitrobenzoic acid, DIAD, THF; j) K_2CO_3, MeOH, 59% for two steps; k) **8**, EDC·HCl, Et_3N, DMAP, 61%; l) TBAF, THF, 77%; m) DMP, $NaHCO_3$, DCM, 93%.

A similar synthetic route was followed for the preparation of **8**, using tetrabutylammonium trichloride for the halogenation of **11**. This salt was prepared by reaction of tetrabutylammonium chloride with *in-situ* generated chlorine.[16] Protected alkene **13** was obtained as a single stereoisomer and then, a deprotection-oxidation sequence similar to that used for **7** delivered fatty acid **8**. Finally, methyl ester protection and purification produced ester **15**. These two simple synthetic routes allowed an easy, efficient and scalable preparation of the fatty acids present in phormidolides C-D.

Preparation of fragment C23-C31 (5)

With both fatty acids in hand, the challenging preparation of aldehyde **5**, the east end of the molecule, was investigated. The route was started from the previously reported alcohol **16** (Scheme 3).[8] TBS-hydroxyl protection, DIBAL-H regioselective ketal reduction[17] and Swern oxidation afforded aldehyde **17** with good synthetic yields at gram scale. Then, Mukaiyama aldol addition of **(*E*)-((4-bromo-3-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane**[8] produced ketol **18** as an inseparable mixture of diastereomers (*82:18*) enriched in the undesired C27-(*S*) isomer.[18] Then, as it happened in our previous work,[8] a three-step procedure was necessary to introduce the methylidene moiety including TES protection of **18**, olefination using Tebbe reagent and TES PPTS-mediated removal to afford homoallylic alcohol **19** in good yield. At this point, C27-diastereomers were separated by column chromatography and the absolute configuration of the major isomer was confirmed using Mosher's derivatization.[13,19] Mitsunobu hydroxyl inversion[20] of **19**, followed by basic hydrolysis of the generated nitro-benzoate, cleanly delivered the C27-(*S*) isomer compound **20.** Then, alcohol **20** was esterified with (*E*)-13,14-dichlorotetradec-13-enoic acid (**8**) to obtain the protected C23-C31 fragment of PM D, the ester **21**. TBAF removal at position C23 and Dess-Martin oxidation gave us access to aldehyde **5** in 12 steps with useful yields from alcohol **16**.

Scheme 5: Preparation of compound 9, fragment C16-C22.[a]

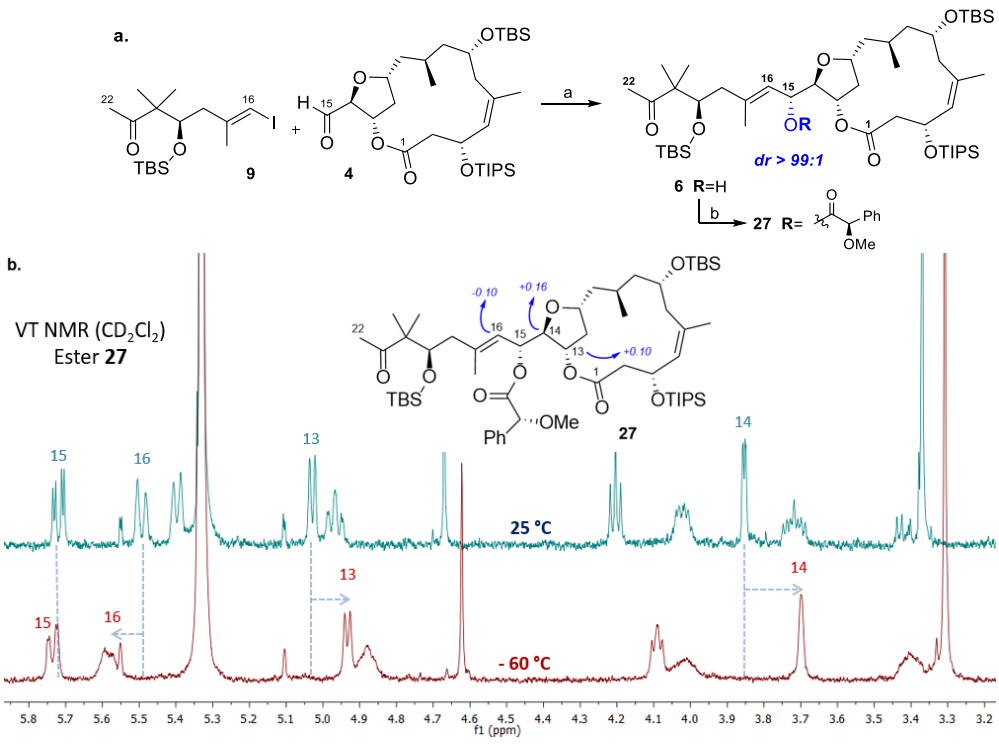


[a]Reagents and conditions: a) $BF_3{\cdot}Et_2O$, DCM, 63%; b) (*R*)-methoxyphenylacetic acid, EDC·HCl, DMAP, THF; c) Column chromatography to isolate C19 diastereomers **25-R,R**, 41% and **25-S,R**, 42%; d) TMSOTf, 1,2-bis(trimethylsiloxy)ethane, -78 °C to rt, 97%, e) $LiOH{\cdot}H_2O$, MeOH, 65 °C, 92%; f) TBSOTf, Et_3N, DCM, 74%; g) PPTS, MeOH, quant.

Preparation of fragment C16-C22 (9)

The synthesis of the central bi-functionalized C16-C22 fragment **9** (Scheme 4) began with the aldol addition of silylenolether **22**[21] to aldehyde **23**[22] to obtain ketol **24** as a C19 epimeric mixture. Several reported enantioselective strategies using *N*-Ts-*L*-valine or a tryptophan-derived oxazaborolidine as chiral inductors for this addition were

Scheme 6: *a.* NHTK coupling to obtain alcohol 6, the C1-C21 fragment. *b.* Determination of C15 absolute configuration using variable temperature Mosher methodology.[27,a]



[a]Reagents and conditions: a) $CrCl_2$, $NiCl_2$, DMF, 48h, 18%; b) (*R*)-methoxyphenylacetic acid, EDC·HCl, DMAP, THF, 48h

tested unsuccessfully.[23,24] The racemic mixture **24** was reacted with the chiral (*R*)-methoxyphenylacetic acid to obtain the corresponding diastereomeric esters that were easily separated via column chromatography to isolate the desired C19-*R* epimer **25-*R,R*** and its diastereomer **25-*S,R***. Taking advantage of the fact that **25-*S,R*** is the enantiomer of **25-*R,S***, and therefore spectroscopically identical, it was possible to identify **25-*R,R*** without additional derivatizations using Mosher's model.[25,26] Ester basic hydrolysis at this point was non-viable probably due to methyl ketone known basic media instability, and therefore C21 position had to be protected. Mild protecting conditions[27] to install the ketone 1,3-dioxolane protecting group were used and subsequent LiOH mediated ester saponification rendered alcohol **26** in high yield for this two-step transformation. Finally, alcohol protection using TBSOTf and ketal removal to recover the methyl ketone delivered the desired iodo-alkene **9** as a single (*R*) enantiomer, as needed.

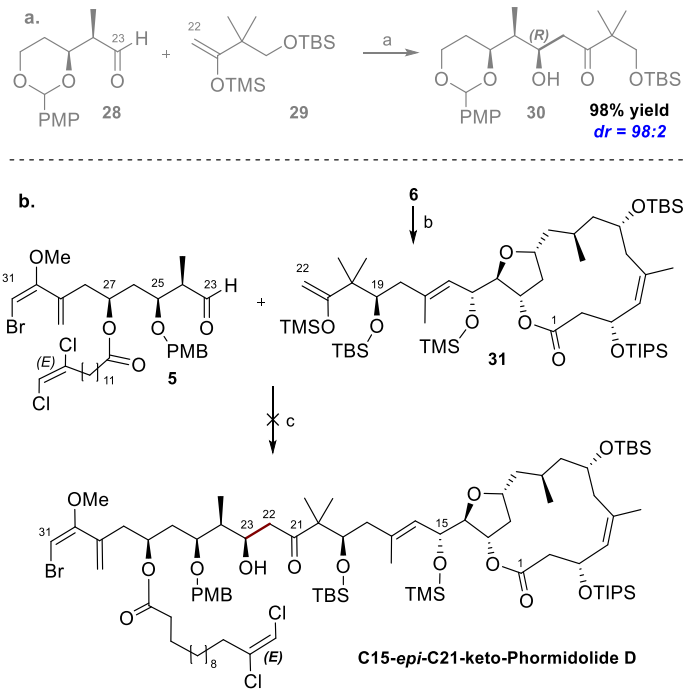
End-game of the synthesis

Having synthesized fragments **5**, **9** and **4**[7] the pieces of the synthetic puzzle should be put together. First of all, the union of aldehyde **4** and iodoalkene **9** using the $CrCl_2$-$NiCl_2$ mediated NHTK coupling (Scheme 5, a) was attempted.[10,29] This methodology allowed the selective formation of the C15-C16 bond in the presence of a methyl ketone due to the well-known chemoselectivity of NHTK coupling towards aldehydes, thereby demonstrating the useful orthogonal reactivity of compound **9**. Allylic alcohol **6** was obtained in an 18% yield, which can be considered a rather acceptable yield, taking into consideration the size and the functionality of both molecular partners.[10] Furthermore, the reaction showed high substrate-controlled diastereoselectivity delivering a single diastereomer. Due to the low amount of compound **6** available, it was decided to use the variable temperature (VT) Mosher determination that allows assigning the absolute configuration of a secondary alcohol performing a single derivatization. [13,27] First, alcohol **6** was converted into its corresponding (*R*)-methoxyphenylacetic ester **27**. Then, ^{1}H NMR of compound **27** in CD_2Cl_2 was recorded at 25 °C and – 60 °C and the C15-(*R*) configuration was confirmed by calculating the increment in chemical shift (Scheme 5, below).[30]

When the synthetic route was planned, the formation of the C22-C23 bond was envisioned as its last step based on our previous outstanding results on the formation of this bond while working in the synthesis of the polyhydroxylated chain. As depicted in Scheme 6 (a) Mukaiyama addition of silylenolether **29**[31] to aldehyde **28** gave not only almost quantitative yield but also total stereoselectivity towards the desired C23-(*R*) diastereomer **30**.[8] Bearing this precedent in mind, the methyl-ketone and the hydroxyl present in compound **6**, were simultaneously transformed into the corresponding silylenoleter and protected hydroxyl in quantitative yield to render the nucleophile for the final Mukaiyama addition, compound **31** (Scheme 6, b). However, when the Mukaiyama addition of silylenolether **31** to aldehyde **5** (using the same conditions applied for the preparation of **30**) was performed,[8] no

conversion towards the product took place, recovering both starting materials after column purification. Modification of the reaction conditions by increasing the equivalents of $BF_3{\cdot}Et_2O$ and the temperature to 0 °C resulted in no reaction either. After these negative results it was concluded that the formation of the C22-C23 bond using Mukaiyama methodology with the coupling partners **5** and **31** was not possible in this case.

Scheme 7: *a*. Precedent work in the formation of C22-C23 bond. *b.* End game of the total synthesis.[a]



[a]Regents and conditions: a) $BF_3{\cdot}Et_2O$, -78 °C, DCM (5% Et_2O), 2h, 98%, *dr = 98:2*; b) TMSOTf, Et_3N, DMAP, CH_2Cl_2, rt, 4h, quant.; c) $BF_3{\cdot}Et_2O$, -78 °C, CH_2Cl_2 (5% Et_2O), 2h, no reaction.

The reason for this lack of reactivity is unknown, but by comparison with our reported precedents, it can be hypothesized that steric congestion around carbons C22 and C23 hinders reagents approximation. The presence of a tetradecanoic acid (C27) and a PMB (C25) in aldehyde **5** reduces somehow the necessary carbonyl activation by $BF_3{\cdot}Et_2O$. In addition, a secondary TBSO-protected hydroxyl (C19) in the large functionalized compound **31** could suppress its reactivity as a nucleophile.

CONCLUSIONS

Highly convergent strategies are the process of choice for the total synthesis of large natural products such as phormidolide D. The synthetic approach reported herein is composed of a total of 73 reactions but the longest synthetic sequence to achieve phormidolide D is only 20 steps long (preparation of **5** from commercially available starting material plus Mukaiyama addition and C21 reduction). The use of highly convergent strategies normally rely on final complex reactions because large molecular entities have to be efficient and stereoselectively linked.

In summary, this publication reports a highly convergent approach towards the natural product phormidolide D. A robust and scalable synthesis of fatty acids **7** and **8**, present in phormidolides C-D, using a stereoselective and regioselective halogenation of an acetylene to obtain (*E*)-dihalogenated terminal double bonds with high yield under mild conditions is described. Stereoselective efficient strategies for the preparation of **5** (C23-C31 fragment) and **9** (C16-C22 fragment) are fully described setting up the conditions to achieve total synthesis. A notable NHTK coupling of macrocyclic fragment **4** and iodoalkene **9** was performed in useful yield and with total substrate-controlled diastereoselectivity.

Finally, the last C22-C23 bond formation using Mukaiyama methodology to link aldehyde **5** and silylenolether **31** did not work despite our previous encouraging results with smaller molecules. These adverse results do not invalidate the proposed retrosynthetic strategy that probably could give good results using less hindered protecting groups. Therefore, a revision of the protecting groups in positions C19 and C25 should be carried out before embarking on the synthesis of these complex natural products. Consequently, all the information reported in this publication will be of great value in the development of the total synthesis of marine natural products phormidolides B-D.

ASSOCIATED CONTENT

Supporting Information. Absolute configuration determinations and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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EXPERIMENTAL SECTION

General procedures

Tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were dried using a PureSolv solvent purification system. All other solvents and reagents were used as purchased without further purification, unless otherwise indicated. Flash column chromatography was performed on silica gel (60A 35-70 µm) as stationary phase. Analytical TLC was performed on pre-coated silica gel 60 F_{254} plates (0.2 mm thick, 20x20 cm) and visualized under UV light (254 and 360 nm), with anisaldehyde in conc. H_2SO_4 or with phosphomolybdic acid in ethanol. Chemical shifts are reported in ppm referenced to the appropriate residual solvent peaks ($CDCl_3$) and coupling constants are reported in Hz. Multiplicity of the carbons was assigned with gHSQC experiments. Standard abbreviations for off-resonance decoupling were employed: s = singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, bd = broad doublet, m = multiplet. The same abbreviations were also used for the multiplicity of signals in ^{1}H-NMR. High Resolution Mass Spectroscopy (HRMS) was performed an Agilent LC/MSD-TOF 2006 system using the ESI-MS technique.

2-((12-Bromododecyl)oxy)tetrahydro-2*H*-pyran. PPTS (282 mg, 1.3 mmol) was added to a stirred solution of commercial 12-bromododecan-1-ol (**10**) (2.00 g, 7.5 mmol) in CH_2Cl_2 (50 mL), the reaction mixture was stirred for 5 minutes and 3,4-dihydro-2*H*-pyran (0.95 g, 11.3 mmol) was added. The reaction mixture was allowed to stir at rt overnight under N_2. The reaction was quenched with saturated solution of $NaHCO_3$ and the organic layer was extracted three times with Et_2O. The organic extract was washed with brine, dried over $MgSO_4$ and filtered. The filtrated was evaporated under reduced pressure. The crude obtained (2.75 g) was purified by silica gel column chromatography with hexane:EtOAc (95:5 to 90:10) to obtain the title compound (2.51 g, 85%). ^{1}H NMR (400 Mz, $CDCl_3$) δ 1.24 – 1.34 (m, 14H), 1.39 – 1.44 (m, 2H), 1.51 – 1.61 (m, 6H), 1.66 – 1.76 (m, 1H), 1.78 – 1.90 (m, 3H), 3.32 – 3.42 (m, 3H), 3.46 – 3.53 (m, 1H), 3.73 (dt, *J* = 9.6, 6.9 Hz, 1H), 3.82 – 3.90 (m, 1H), 4.55 – 4.60 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.7 (t), 25.5 (t), 26.2 (t), 28.2 (t), 28.7 (t), 29.4 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.5 (t), 29.7 (t), 30.8 (t), 32.8 (t), 34.0 (t), 62.3 (t), 67.7 (t), 98.8 (d).

2-(Tetradec-13-yn-1-yloxy)tetrahydro-2H-pyran (11). Lithium acetylide-ethylenediamine complex (1.37 g, 13.35 mmol) was stirred in DMSO (10 mL) at 15-20 ºC for 1 h. Then a solution of the above mentioned bromide (2.51 g, 6.36 mmol) in DMSO (10 mL) was added during 2 h at rt and under N_2. The resulting mixture was stirred for 12 h. The reaction was quenched with water (10 mL) and the organic layer was extracted three times with hexane. The organic extract was washed several times with brine, dried over $MgSO_4$ and filtered. The filtrated was evaporated under reduced pressure. The crude obtained (2.10 g) was purified by silica gel column chromatography with hexane:EtOAc (99:1 to 97:3) to obtain **11** (1.47 g, 79%). ^{1}H NMR (400 Mz, $CDCl_3$) 1.22 – 1.39 (m, 15H), 1.47 – 1.61 (m, 9H), 1.64 – 1.74 (m, 1H), 1.76 – 1.86 (m, 1H), 1.92 (t, *J* = 2.7 Hz, 1H), 2.17 (td, *J* = 7.1, 2.7 Hz, 2H), 3.37 (dt, *J* = 9.5, 6.9 Hz, 1H), 3.45 – 3.52 (m, 1H), 3.72 (dt, *J* = 9.5, 6.9 Hz, 1H), 3.86 (ddd, *J* = 11.1, 6.9, 3.4 Hz, 1H), 4.53 – 4.58 (m, 1H).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.4 (t), 19.7 (t), 25.5 (t), 26.2 (t), 28.5 (t), 28.7 (t), 29.1 (t), 29.5 (t), 29.5 (t), 29.7 (t), 30.8 (t), 62.3 (t), 67.7 (t), 68.0 (d), 84.8 (s), 98.8 (d).

(*E*)-2-((14-Bromo-13-chlorotridec-13-en-1-yl)oxy)tetrahydro-2H-pyran (12). TBADCB (4.16 g, 10.6 mmol) was added to a solution of the alkyne **11** (880 mg, 2.98 mmol) in dry CH_2Cl_2 (20 mL) at rt and under N_2. The reaction mixture was stirred for 2.5 h. The reaction was quenched with water (10 mL) and the organic layer was extracted three times with CH_2Cl_2 . The organic extract was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure to obtain 3.62 g of crude **12** as a *89:11* mixture of regioisomers which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 – 1.30 (m, 12H), 1.44 – 1.55 (m, 8H), 1.61 – 1.71 (m, 6H), 2.14 (td, *J* = 7.1, 2.7 Hz, 1H), 2.44 – 2.52 (m, 1H), 3.43 – 3.49 (m, 1H), 3.61 (t, *J* = 6.7 Hz, 1H), 3.66 – 3.71 (m, 1H), 3.79 – 3.87 (m, 1H), 4.52 – 4.56 (m, 1H), 6.18 (s, 1H).

(*E*)-14-Bromo-13-chlorotetradec-13-en-1-ol. *p*-TsOH (103 mg, 0.60 mmol) was added to a solution of the alkene **12** (1.21 g, 2.97 mmol) in MeOH (20 mL) and the mixture was stirred for 3 hours at rt. The reaction was quenched with a satured solution of $NaHCO_3$ (10 mL) and the organic layer was extracted three times with Et_2O. The organic layer was washed with a saturated solution of $NaHCO_3$ several times, dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure. The crude of the title compound (1.22 g) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (m, 14H), 1.56 (d, *J* = 7.4 Hz, 6H), 2.36 – 2.44 (m, 1H), 2.48 – 2.55 (m, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 6.22 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.7 (t), 26.3 (t), 28.5 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.6 (t), 29.6 (t), 32.8 (t), 35.1 (t), 63.1 (t), 101.0 (d), 136.9 (s).

(*E*)-14-Bromo-13-chlorotetradec-13-enal. DMP (1.18 g, 2.70 mmol) was added to a solution of the above mentioned alcohol (703 mg, 2.15 mmol) in dry DCM (20 mL) at rt and under N_2. The reaction mixture was stirred for 3 hours. The reaction was quenched with saturated solution of $NaHCO_3$ and a saturated solution of NaS_2O_3 and the mixture was left stirring for 20 minutes. The aqueous layer was extracted three times with EtOAc, dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure. The crude of the title compound (751 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (m, 14H), 1.57 – 1.66 (m, 4H), 2.40 – 2.45 (m, 2H), 2.53 (t, *J* = 7.4 Hz, 2H), 6.22 (s, 1H), 9.77 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.1 (t), 26.3 (t), 28.5 (t), 29.2 (t), 29.3 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 35.1 (t), 43.9 (t), 101.1 (d), 136.9 (s), 202.9 (s).

(*E*)-14-Bromo-13-chlorotetradec-13-enoic acid (7). $NaClO_2$ (832 mg, 9.2 mmol) was added to a solution of the above mentioned aldehyde (750 mg, 2.3 mmol) in ^{t}BuOH/H_2O (10 mL/2 mL), in presence of NaH_2PO_4 (1.4 g, 11.5 mmol) and 2-methyl-butene (806 mg, 11.5 mmol), at rt. The reaction mixture was stirred for 2 hours and 30 minutes. The reaction was quenched with water and NaS_2O_3. The organic phase was extracted three times with EtOAc and washed with brine. The organic extract was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude **7** (794 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 – 1.36 (m, 14H), 1.53 – 1.68 (m, 4H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.50 – 2.55 (t, *J* = 7.4 Hz, 2H), 6.22 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.7 (t), 26.4 (t), 28.5 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 33.9 (t), 35.1 (t), 101.1 (d), 136.9 (s), 179.0 (s).

Methyl (*E*)-14-bromo-13-chlorotetradec-13-enoate (14). TMS-CH_2N_2 (778 mg, 6.81 mmol) was added to a solution of **7** (774 mg, 2.27 mmol) in CH_2Cl_2/MeOH (9:1) at 0ºC and under N_2. The reaction mixture was stirred for 3 hours at 0-5 ºC. The solvent was evaporated under reduced pressure and the residue was purified in preparative RP-HPLC to obtain **14** (209 mg). Global yield from **11** to **14** 20%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 – 1.33 (m, 14H), 1.51 – 1.65 (m, 4H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.46 – 2.55 (m, 2H), 3.66 (s, 3H), 6.21 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.9 (t), 26.3 (t), 28.5 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 34.1 (t), 35.1 (t), 51.4 (q), 101.0 (d), 136.9 (s), 174.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{15}H_{27}BrClO_2$ (M+H) 353.0883, found 353.0857.

(*E*)-2-((13,14-Dichlorotetradec-13-en-1-yl)oxy)tetrahydro-2H-pyran (13). TBATC (3.96 g, 10.6 mmol) was added to a solution of the alkyne **11** (880 mg, 2.98 mmol) in dry CH_2Cl_2 (20 mL) at rt and under N_2. The reaction mixture was stirred for 2.5 hours and quenched with water (10 mL). The organic layer was extracted three times with CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure. Crude **13** obtained (957 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 – 1.35 (m, 14H), 1.47

– 1.63 (m, 12H), 2.50 (t, *J* = 7.4 Hz, 2H), 3.38 (dt, *J* = 9.6, 6.7 Hz, 2H), 3.49 (m, 1H), 3.72 (dt, *J* = 9.6, 6.7 Hz, 1H), 3.87 (m, 1H), 4.57 (m, 1H), 6.13 (s, 1H).

(*E*)-13,14-Dichlorotetradec-13-en-1-ol. *p*-TsOH (262 mg, 1.52 mmol) was added to a solution of the alkene **13** (926 mg, 2.54 mmol) in MeOH (20 mL) at rt. The reaction mixture was stirred for 1.5 hours, then quenched with a satured solution of $NaHCO_3$ (10 mL) and extracted three times with Et_2O. The organic layer was washed with a saturated solution of $NaHCO_3$ several times, dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure. The crude of the title compound (819 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 – 1.34 (m, 14H), 1.41 – 1.51 (m, 4H), 1.52 – 1.62 (m, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 6.13 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.7 (t), 26.3 (t), 28.5 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.6 (t), 29.6 (t), 32.8 (t), 33.1 (t), 63.1 (t), 113.5 (d).

(*E*)-13,14-Dichlorotetradec-13-enal. DMP (1.55 g, 3.5 mmol) was added to a solution of the above mentioned alcohol (779 mg, 2.7 mmol) in dry CH_2Cl_2 (20 mL) at rt and under N_2. The reaction was quenched with saturated solution of $NaHCO_3$ and a saturated solution of NaS_2O_3 and the mixture was left stirring for 20 minutes. The aqueous layer was extracted three times with EtOAc, dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure. The crude of the title compound (605 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (m, 14H), 1.44 – 1.66 (m, 4H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 6.13 (s, 1H), 9.76 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.1 (t), 26.3 (t), 28.5 (t), 29.1 (t), 29.3 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 33.1 (t), 43.9 (t), 113.5 (d), 136.6 (s), 203.0 (s).

(*E*)-13,14-Dichlorotetradec-13-enoic acid (8). $NaClO_2$ (734 mg, 8.12 mmol) was added to a solution of the above mentioned aldehyde (565 mg, 2.03 mmol) in ^{t}BuOH/H_2O (14 mL/6 mL), containing NaH_2PO_4 (1.21 g, 10.15 mmol) and 2-methyl-butene (0.711 g, 10.15 mmol), at rt. The reaction mixture was stirred for 2 hours and 30 minutes. The reaction was quenched with water and NaS_2O_3. The organic phase was extracted three times with EtOAc and washed with brine. The organic extract was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Crude **8** (602 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz,$CDCl_3$) δ 1.31 (m, 14H), 1.45 – 1.62 (m, 4H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.49 (d, *J* = 7.4 Hz, 2H), 6.13 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 24.7 (t), 26.3 (t), 28.5 (t), 29.0 (t), 29.2 (t), 29.4 (2C, t), 29.4 (t), 29.5 (t), 33.1 (t), 34.0 (t), 113.5 (d), 136.6 (s), 179.7 (s).

Methyl (*E*)-13,14-dichlorotetradec-13-enoate (15). TMS-CH_2N_2 (0.651 g, 5.7 mmol) was added to a solution of acid **8** (0.562 g, 1.9 mmol) in DCM/MeOH (9:1) at 0ºC and under N_2. The reaction mixture was stirred for 3 hours at 0-5 ºC. The solvent was evaporated under reduced pressure and the residue was purified in preparative RP-HPLC to obtain **15** (0.110 g, 0.35 mmol). Global yield from **11** to **15**: 12%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (m, 14H), 1.59 – 1.65 (m, 4H), 2.30 (t, *J* = 7.5 Hz, 4H), 2.50 (t, *J* = 7.4 Hz, 3H), 3.66 (s, 3H), 6.13 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.0 (t), 26.3 (t), 28.5 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 33.1 (t), 34.1 (t), 51.4 (q), 113.5 (d), 136.4 (s), 174.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{15}H_{27}Cl_2O_2$ (M+H) 309.1388, found 309.1383.

***tert*-Butyl((2*S*)-2-((4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)propoxy)dimethylsilane.** TBSCl (1.25 g, 8.3 mmol.) was added to a solution of alcohol **16**[8] (1.70 g, 6.7 mmol) and imidazole (684 mg, 10.1 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred for 90 minutes. After this time, the mixture was washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded the title compound (2.0 g, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.05 (s, 3H), 0.91 (s, 9H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.45 (dtd, *J* = 13.2, 2.4, 1.4 Hz, 1H), 1.78 (pt, *J* = 6.9, 5.1 Hz, 1H), 1.95 (tdd, *J* = 13.2, 12.3, 11.3, 5.1 Hz, 1H), 3.55 (dd, *J* = 9.9, 5.1 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.9 Hz, 1H), 3.80 (s, 3H), 3.83 – 4.01 (m, 2H), 4.27 (ddd, *J* = 11.3, 5.1, 1.4 Hz, 1H), 5.46 (s, 1H), 6.84 – 6.95 (m, 2H), 7.37 – 7.46 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.4 (q), -5.4 (q), 11.9 (q), 18.3 (s), 25.9 (q), 28.7 (t), 40.6 (d), 55.2 (q), 64.5 (t), 67.2 (d), 77.4 (d), 101.0 , 113.4 (d), 127.2 (d), 131.7 (s), 159.7 (s). HRMS (ESI+): *m/z* calculated for $C_{20}H_{34}NaO_4Si$ $[M+Na]^+$ 389.2119, found 389.2111.

(3*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-4-methylpentan-1-ol. A solution of DIBALH 1 M in heptane (1.3 mL, 1.3 mmol) was added to a solution of the above mentioned acetal (355 mg, 0.97 mmol) in CH_2Cl_2 (15 mL) at -20 ºC. The reaction mixture was stirred at 0 ºC for 2 h. Then a saturated solution of Rochelle's salt (15 mL) was added and the mixture was stirred for 1 h until the formation of two layers. The organic solution was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (8:2) yielded the title compound (285 mg, 90% brsm) as a colorless oil and 43 mg of recovered starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 0.95 (d, *J* = 6.9 Hz, 3H), 1.67 – 1.83 (m, 2H), 1.85 – 2.00 (m, 1H), 2.17 (m, 1H), 3.50 (dd, *J* = 9.9, 6.9 Hz, 1H), 3.62 – 3.78 (m, 4H), 3.80 (s, 3H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 6.83 – 6.92 (m, 2H), 7.22 – 7.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.4 (q), -5.4 (q), 12.6 (q), 18.3 (s), 25.9 (q), 33.6 (t), 39.0 (d), 55.3 (q), 61.2 (t), 64.7 (t), 71.9 (t), 79.2 (d), 113.8 (d), 129.5 (d), 130.7 (s), 159.2 (s). HRMS (ESI+): *m/z* calculated for $C_{20}H_{37}O_4Si$ $[M+H]^+$ 369.2456, found 369.2446.

(3*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-4-methylpentanal (17). DMSO (0.031 mL, 0.44 mmol) was added to a solution of oxalyl chloride (0.019 mL, 0.22 mmol) in CH_2Cl_2 (2 mL) at -78 ºC and the reaction was stirred for 30 minutes. A solution of the above mentioned alcohol (40 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added and the mixture was stirred for 45 minutes at the same temperature. Et_3N (0.123 mL, 0.88 mmol) was added and the reaction was stirred for 30 minutes at 0 ºC. The reaction was quenched with NH_4Cl saturated solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. Purification by silica gel chromatography with hexane:EtOAc (9:1) yielded aldehyde **17** (32 mg, 80 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (2s, 6H), 0.90 (s, 9H), 0.93 (d, *J* = 7.0 Hz, 3H), 1.81 – 1.92 (m, 1H), 2.56 (ddd, *J* = 16.4, 4.6, 2.0 Hz, 1H), 2.71 (ddd, *J* = 16.4, 7.8, 2.0 Hz, 1H), 3.53 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.61 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.80 (s, 3H), 4.03 – 4.10 (m, 1H), 4.49 (s, 2H), 6.83 – 6.88 (m, 2H), 7.20 – 7.25 (m, 2H), 9.76 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.5 (q), -5.4 (q), 12.1 (q), 18.2 (s), 25.9 (q), 39.7 (d), 46.6 (t), 55.3 (q), 64.5 (t), 72.0 (t), 74.8 (d), 113.8 (d), 129.3 (d), 130.5 (s), 159.2 (s), 201.9 (s). HRMS (ESI+): *m/z* calculated for $C_{20}H_{34}NaO_4Si$ $[M+Na]^+$ 389.2119, found 389.2130.

(5*S*,7*S*,8*S*,*E*)-1-Bromo-9-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methylnon-1-en-3-one (18). A solution of silylenolether (*E*)-((4-bromo-3-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane[8] (527 mg, 2.1 mmol) in CH_2Cl_2 (10 mL) was added to a cooled (-78ºC) solution of aldehyde 17 (503 mg, 1.37 mmol) in CH_2Cl_2 (30 mL) and then $BF_3{\cdot}OEt_2$ (155 μL, 1.26 mmol) was added dropwise. The reaction was stirred at -78ºC for 60 minutes and quenched with saturated solution of $NaHCO_3$ (30 mL) and was extracted three times with CH_2Cl_2. The organic solution was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Purification by silica gel column cromatography with hexane-EtOAc (8:2) afforded 18 (312 mg, 47%) as a 82:17 mixture of diasteromers. Mayor diasteromer data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.60 – 1.64 (m, 2H), 1.87 – 1.93 (m, 1H), 2.76 – 2.85 (m, 2H), 3.44 – 3.52 (m, 1H), 3.63 (s, 3H), 3.66 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.80 (s, 3H), 3.80 – 3.81 (m, 1H), 4.23 – 4.35 (m, 1H), 4.46 – 4.57 (m, 2H), 5.66 (s, 1H), 6.82 – 6.89 (m, 2H), 7.24 – 7.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.4 (q), -5.3 (q), 12.5 (q), 18.3 (s), 25.9 (q), 38.3 (t), 39.4 (d), 47.1 (t), 55.3 (q), 56.0 (q), 64.7 (d), 64.8 (t), 72.4 (t), 76.8 (d), 84.4 (d), 113.8 (d), 129.5 (d), 130.9 (s),

152.9 (s), 159.2 (s), 197.7 (s). HRMS (ESI+): *m/z* calculated for $C_{25}H_{41}BrNaO_6Si$ $[M+Na]^+$ 567.1748, found 567.1744.

(5*S*,7*S*,8*S*,*E*)-1-Bromo-9-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-5-((triethylsilyl)oxy)non-1-en-3-one. Imidazole (140 mg, 2 mmol), TESCl (0.14 mL, 0.85 mmol) and DMAP (6 mg, 0.05 mmol) were added sequentially to a solution of 18 (290 mg, 0.53 mmol) in CH_2Cl_2 (10 mL). The cloudy solution was stirred 45 minutes until TLC analysis showed complete conversion of the starting material. The reaction was quenched with saturated solution of NH_4Cl (10 mL) and extracted three times with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification with deactivated (1% Et_3N) silica gel column cromatography with hexane-EtOAc (95:5) afforded the TES-protected title compound (300 mg, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.56 – 0.63 (m, 6H), 0.89 (s, 9H), 0.89 – 0.96 (m, 12H), 1.68 (dt, *J* = 6.6, 5.4 Hz, 2H), 1.89 (qd, *J* = 6.9, 3.2 Hz, 1H), 2.78 (dd, *J* = 16.3, 5.4 Hz, 1H), 2.95 (dd, *J* = 16.3, 6.6 Hz, 1H), 3.41 (dd, *J* = 9.8, 7.0 Hz, 1H), 3.59 (s, 3H), 3.61 – 3.67 (m, 2H), 3.80 (s, 3H), 4.31 – 4.38 (m, 1H), 4.39 – 4.51 (m, 2H), 5.58 (s, 1H), 6.83 – 6.88 (m, 2H), 7.22 – 7.26 (m, 2H). HRMS (ESI+): *m/z* calculated for $C_{31}H_{56}BrO_6Si_2$ $[M+H]^+$ 659.2793, found 659.2762.

(5*R*,7*S*,8*S*,*E*)-1-Bromo-9-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylene-5-((triethylsilyl)oxy)non-1-ene. A solution of Tebbe reagent in toluene (0.5M, 3.62 mL, 1.81 mmol) was added to a solution of the above mentioned ketone (290 mg, 0.45 mmol) and pyridine (0.150 mL, 1.81 mmol) in THF (12 mL) at 0 ºC. The reaction mixture was warmed to rt and then heated up at 50 ºC during 90 minutes. The reaction was quenched at rt with saturated solution of Rochelle's salt (3 mL) and extracted three times with Et_2O. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded the title alkene (235 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.54 – 0.64 (m, 6H), 0.87 – 0.90 (m, 12H), 0.92 – 0.97 (m, 9H), 1.43 – 1.50 (m, 1H), 1.76 – 1.85 (m, 1H), 1.92 (qd, *J* = 6.8, 3.2 Hz, 1H), 2.29 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.61 (dd, *J* = 13.8, 4.2 Hz, 1H), 3.41 (dd, *J* = 9.8, 7.2 Hz, 1H), 3.49 (s, 3H), 3.62 – 3.72 (m, 2H), 3.80 (s, 3H), 3.88 – 3.96 (m, 1H), 4.42 (d, *J* = 11.1 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 5.26 (s, 1H), 5.33 (s, 1H), 5.38 (s, 1H), 6.79 – 6.88 (m, 2H), 7.23 – 7.26 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 5.3 (t), 7.2 (q), 12.1 (q), 26.1 (q), 38.9 (t), 39.4 (d), 43.4 (t), 55.3 (q), 55.4 (q), 65.1 (t), 68.5 (d), 71.0 (t), 77.0 (d), 78.4 (d), 113.5 (d), 121.3 (t), 128.6 (d). HRMS (ESI+): *m/z* calculated for $C_{32}H_{58}BrO_5Si_2$ $[M+H]^+$ 657.3001, found 657.2991.

(5*R*,7*S*,8*S*,*E*)-1-Bromo-9-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenonon-1-en-5-ol (19). PPTS (17 mg, 0.07 mmol) was added to a solution of the above mentioned alkene (235 mg, 0.357 mmol) in MeOH (13 mL) at 0ºC and the reaction mixture was stirred 45 minutes at rt. After this time was quenched with saturated solution of $NaHCO_3$ (5mL) and extracted three times with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (85:15) yielded alcohol 19 (170 mg, 88%) as a colorless oil (mixture of isomers). Separation of diasteromers was performed at this point via silica column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.90 (s, 9H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.52 – 1.65 (m, 2H), 1.84 – 1.93 (m, 1H), 2.28 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.44 (dd, *J* = 13.8, 4.0 Hz, 1H), 3.46 (dd, *J* = 9.9, 6.9 Hz, 1H), 3.56 (s, 3H), 3.67 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.80 (s, 3H), 3.83 (s, 1H), 3.86 (s, 1H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.54 (d, *J* = 10.9 Hz, 1H), 5.32 (s, 1H), 5.38 (s, 2H), 6.84 – 6.89 (m, 2H), 7.25 – 7.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.4 (q), -5.3 (q), 12.5 (q), 18.3 (s), 25.9 (q), 38.4 (t), 39.5 (d), 43.1 (t), 55.3 (q), 55.6 (q), 64.9 (t), 66.5 (d), 72.5 (t), 77.1 (d), 78.6 (d), 113.8 (d), 122.1 (t), 129.5 (d), 131.1 (s), 139.7 (s), 159.1 (s), 159.1 (s). HRMS (ESI+): *m/z* calculated for $C_{26}H_{43}BrNaO_5Si$ $[M+Na]^+$ 565.1955, found 565.1943.

General procedure for derivatization with methoxyphenylacetic acid (MPA):

α-Methoxyphenylacetic acid (5 eq.) and EDC·HCl (5 eq.) were added to a solution of alcohol **10*(5R)*** (1 eq.) in THF, then DMAP (0.1 eq.) was added and the solution was stirred for 2 h at 40 ºC. The solution was filtered through celite®545, poured into Et_2O and washed with NH_4Cl saturated solution. The organic residue was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded the corresponding esters as colorless oils.

(5*R*,7*S*,8*S*,E)-1-Bromo-9-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-yl (*R*)-2-methoxy-2-phenylacetate. Alcohol 19 (4 mg, 0.007 mmol) and (*R*)-MPA (5 eq.) afforded (*R*)-MPA ester (4 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.67 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 1.55 – 1.58 (m, 2H), 1.64 – 1.69 (m, 1H), 2.49 (dd, *J* = 14.5, 6.4 Hz, 1H), 2.58 (dd, *J* = 14.5, 5.8 Hz, 1H), 2.79 (dt, *J* = 8.5, 3.9 Hz, 1H), 3.21 – 3.32 (m, 1H), 3.41 (s, 3H), 3.49 – 3.52 (m, 1H), 3.53 (s, 3H), 3.79 (s, 3H), 3.85 (d, *J* = 10.3 Hz, 1H), 4.07 (d, *J* = 10.3 Hz, 1H), 4.72 (s, 1H), 5.18 – 5.26 (m, 1H), 5.30 (s, 1H), 5.33 (d, *J* = 1.4 Hz, 1H), 5.42 (d, *J* = 1.4 Hz, 1H), 6.81 – 6.85 (m, 2H), 7.15 – 7.20 (m, 2H), 7.30 – 7.37 (m, 3H), 7.43 – 7.47 (m, 2H). HRMS (ESI+): *m/z* calculated for $C_{35}H_{55}BrNO_7Si$ $[M+NH_4]^+$ 708.2926, found 708.2876.

(5*R*,7*S*,8*S*,*E*)-1-Bromo-9-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-yl (*S*)-2-methoxy-2-phenylacetate. Alcohol 19 (4 mg, 0.007 mmol) and (*S*)-MPA (5 eq.) afforded (*S*)-MPA ester S3 (5 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 1.68 – 1.74 (m, 2H), 1.76 – 1.83 (m, 1H), 2.35 (dd, *J* = 14.5, 5.7 Hz, 1H), 2.47 (dd, *J* = 14.5, 6.7 Hz, 1H), 3.32 – 3.36 (m, 1H), 3.38 – 3.41 (m, 1H), 3.41 (s, 3H), 3.45 (s, 3H), 3.61 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.79 (s, 3H), 4.20 (d, *J* = 10.5 Hz, 1H), 4.32 (d, *J* = 10.5 Hz, 1H), 4.72 (s, 1H), 5.03 (d, *J* = 1.4 Hz, 1H), 5.21 (s, 3H), 6.82 – 6.86 (m, 2H), 7.22 – 7.26 (m, 2H), 7.30 – 7.35 (m, 3H), 7.42 – 7.47 (m, 2H). HRMS (ESI+): *m/z* calculated for $C_{35}H_{55}BrNO_7Si$ $[M+NH_4]^+$ 708.2926, found 708.2921.

(5*S*,7*S*,8*S*,*E*)-1-Bromo-9-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-ol (20). DIAD (0.22 mL, 1.06 mmol) was slowly added to a solution of 19 (105 mg, 0.19 mmol), *p*-nitrobenzoic acid (170 mg, 1 mmol) and PPh_3 (294 mg, 1 mmol) in benzene (8 mL) and the yellowish solution was stirred for 4h at 40ºC. The reaction was quenched with saturated solution of $NaHCO_3$ (10 mL) and extracted three times with Et_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude was filtered through a plug of silica using hexane-EtOAc 9:1 to eliminate the *p*-nitrobenzoic acid and PPh_3O (R_f = 0.1). After evaporation the resulting crude was dissolved in MeOH (10 mL), K_2CO_3 (180 mg, 1.30 mmol) was added and the mixture was stirred for 2 h until TLC indicated total hydrolysis. The reaction was quenched with saturated solution of NH_4Cl (10 mL) and extracted three times with AcOEt. The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by silica gel column chromatography with hexane-EtOAc 9:1 to obtain 20 as a colorless oil (60 mg, 59% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H), 1.59 – 1.72 (m, 2H), 1.91 – 2.00 (m, 1H), 2.35 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.45 (dd, *J* = 13.8, 6.8 Hz, 1H), 3.46 – 3.51 (m, 1H), 3.57 (s, 3H), 3.67 (dd, *J* = 9.9, 5.9 Hz, 1H), 3.71 – 3.77 (m, 2H), 3.79 (s, 3H), 4.43 (d, *J* = 10.9 Hz, 1H), 4.55 (d, *J* = 10.9 Hz, 1H), 5.31 (s, 1H), 5.36 (s, 2H), 6.84 – 6.89 (m, 2H), 7.22 – 7.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.4 (q), -5.3 (q), 12.3 (q), 18.3 (s), 25.9 (q), 37.3 (t), 38.7 (d), 42.6 (t), 55.3 (q), 55.6 (q), 64.5 (t), 69.3 (d), 71.5 (t), 78.6 (d), 80.2 (d), 113.8 (d), 121.8 (t), 129.4 (d), 130.5 (s), 139.5 (s), 159.0 (s), 159.2 (s). HRMS (ESI+): *m/z* calculated for $C_{26}H_{43}BrNaO_5Si$ $[M+Na]^+$ 565.1955, found 565.1959.

(5*S*,7*S*,8*S*,*E*)-1-Bromo-9-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-yl (*E*)-13,14-dichlorotetradec-13-enoate (21). (*E*)-13,14-dichlorotetradec-13-enoic acid (8) (82 mg, 0.28 mmol) was added to a solution of EDC·HCl (268 mg, 1.4 mmol), Et_3N (0.195 mL, 1.4 mmol) and DMAP (171 mg, 1.4 mmol) in CH_2Cl_2 (3 mL) and the solution was stirred for 20 minutes. Alcohol 20 (50 mg, 0.092 mmol) dissolved in CH_2Cl_2 (2.5 mL) was added and the solution was stirred for 16h. The reaction was quenched with saturated solution of NH_4Cl (8 mL) and extracted three times with AcOEt. The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by silica gel column chromatography with hexane-EtOAc 95:5 to obtain ester 21 as a colorless oil (35 mg, 56% brsm) and 20 (8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 1.25 – 1.31 (m, 14H), 1.55 (s, 4H), 1.76 – 1.91 (m, 3H), 2.23 (td, *J* = 7.6, 3.8 Hz, 2H), 2.47 – 2.59 (m, 4H), 3.44 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.54 (s, 3H), 3.56 – 3.62 (m, 2H), 3.80 (s, 3H), 4.41 (d, *J* = 11.1 Hz, 1H), 4.48 (d, *J* = 11.1 Hz, 1H), 5.00 (p, *J* = 6.5 Hz, 1H), 5.31 (s, 1H), 5.34 (d, *J* = 1.3 Hz, 1H), 5.41 (d, *J* = 1.3 Hz, 1H), 6.13 (s, 1H), 6.84 – 6.88 (m, 2H), 7.25 – 7.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.4 (q), -5.4 (q), 11.0 (q), 18.2 (s), 24.9 (t), 25.9 (q), 26.3 (t), 28.5 (t), 29.2 (t), 29.3 (t), 29.3 (t), 29.5 (t, 2C), 29.5 (t), 33.1 (t), 34.5 (t), 35.3 (t), 38.8 (t+d, 2C), 55.3 (q), 55.6 (q), 64.9 (t), 70.0 (d), 71.2 (t), 75.7 (d), 78.7 (d), 113.5 (d), 113.6 (d), 122.0 (t), 129.1 (d), 131.2 (s), 136.6 (s), 138.4 (s), 141.7 (s) 158.5 (s), 173.0 (s). HRMS (ESI+): *m/z* calculated for $C_{40}H_{69}BrCl_2NO_6Si$ $[M+NH_4]^+$ 836.3449, found 836.3439.

(5*S*,7*S*,8*S*,*E*)-1-Bromo-9-hydroxy-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-yl (*E*)-13,14-dichlorotetradec-13-enoate. A 1M TBAF solution (0.071 mL, 0.071 mmol) was added to a solution of 21 (29 mg, 0.035 mmol) in THF (0.7 mL) and the solution was stirred at rt for 6h. The reaction was quenched with saturated solution of NH_4Cl (1 mL) and extracted three times with Et_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by silica gel column chromatography with hexane-EtOAc 7:3 to obtain the title alcohol as a colorless oil (19 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 7.1 Hz, 3H), 1.25 – 1.31 (m, 14H), 1.55 – 1.59 (m, 4H), 1.78 – 1.86 (m, 1H), 1.87 – 1.95 (m, 1H), 2.04 – 2.08 (m, 1H), 2.19 – 2.28 (m, 2H), 2.46 – 2.56 (m, 4H), 3.56 (s, 3H), 3.50 – 3.64 (m, 3H), 3.80 (s, 3H), 4.40 – 4.52 (m, 2H), 5.02 (p, *J* = 6.5 Hz, 1H), 5.32 (s, 1H), 5.35 (d, *J* = 1.4 Hz, 1H), 5.43 (d, *J* = 1.4 Hz, 1H), 6.13 (s, 1H), 6.85 – 6.89 (m, 2H), 7.24 – 7.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.2 (q), 24.9 (t), 26.3 (t), 28.5 (d), 29.2 (t), 29.3 (t), 29.3 (t), 29.5 (t), 29.5 (t), 33.1 (t), 34.3 (t), 34.6 (t), 36.9 (d), 39.2 (t), 55.3 (q), 55.6 (q), 66.0 (t), 69.8 (d), 70.9 (t), 77.8 (d), 78.8 (d), 113.5 (d), 113.8 (d), 122.2 (t), 129.4 (d), 130.3 (s), 134.4 (s), 138.2 (s), 158.3 (s), 159.2 (s), 173.3 (s). HRMS (ESI+): *m/z* calculated for $C_{34}H_{55}BrCl_2NO_6$ $[M+NH_4]^+$ 722.2584, found 722.2588.

(5*S*,7*S*,8*R*,*E*)-1-Bromo-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylene-9-oxonon-1-en-5-yl (*E*)-13,14-dichlorotetradec-13-enoate (5). $NaHCO_3$ (4 mg, 0.047 mmol) and DMP (5 mg, 0.118 mmol) were added to a solution of the above mentioned alcohol (2.5 mg, 0.0035 mmol) in CH_2Cl_2 (0.8 mL) and the solution was stirred for 30 min. The reaction mixture was diluted with Et_2O (10 mL) and quenched with saturated solutions of $NaHCO_3$ and $Na_2S_2O_3$ (2+2 mL). The crude was extracted twice with Et_2O and the organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (8:2) yielded aldehyde 5 (2.3 mg, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, *J* = 7.0 Hz, 3H), 1.27 (s, 14H), 1.56 (s, 4H), 1.85 (ddd, *J* = 14.5, 7.5, 4.2 Hz, 1H), 1.98 (ddd, *J* = 14.5, 8.5, 5.8 Hz, 1H), 2.19 – 2.27 (m, 2H), 2.46 – 2.61 (m, 5H), 3.56 (s, 3H), 3.79 (s, 3H), 3.91 (ddd, *J* = 7.5, 5.8, 3.0 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.94 – 5.05 (m, 1H), 5.33 (s, 1H), 5.36 (s, 1H), 5.44 (s, 1H), 6.13 (s, 1H), 6.83 – 6.88 (m, 2H), 7.18 – 7.23 (m, 2H), 9.64 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.5 (q), 24.9 (t), 26.3 (t), 28.5 (t), 29.2 (t), 29.3 (d), 29.5 (t), 29.5 (t), 33.1 (t), 34.5 (t), 35.3 (t), 39.2 (t), 49.2 (d), 55.3 (q), 55.6 (q), 69.3 (d), 70.8 (t), 74.3 (d), 78.9 (d), 113.5 (d), 113.8 (d), 122.4 (t), 129.3 (d), 130.1 (s), 136.6 (s), 138.0 (s), 158.2 (s), 159.2 (s), 173.6 (s), 204.1 (s). HRMS (ESI+): *m/z* calculated for $C_{34}H_{53}BrCl_2NO_6$ $[M+NH_4]^+$ 720.2428, found 720.2447.

(*E*)-4-Hydroxy-7-iodo-3,3,6-trimethylhept-6-en-2-one (24). A solution of silylenol ether 22[21] (1.15 g, 7.3 mmol) in CH_2Cl_2 (10 mL) was added to a cooled solution (-78ºC) of aldehyde 23[32] (1.26 g, 6 mmol) in CH_2Cl_2 (65 mL). $BF_3{\cdot}OEt_2$ (0.58 mL, 4.71 mmol) was added dropwise. The reaction was stirred at -78ºC for 2 h and quenched with saturated solution of $NaHCO_3$ (75 mL). The residue was extracted three times with CH_2Cl_2, dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Purification by silica gel column cromatography with hexane-EtOAc (8:2) afforded 1.13 g of 24 (63%) as a racemic mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.17 (s, 3H), 1.89 (d, *J* = 0.9 Hz, 3H), 2.18 (s, 3H), 2.22 – 2.32 (m, 2H), 3.80 – 3.90 (m, 1H), 6.03 (q, *J* = 0.9 Hz 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.6 (q), 21.6 (q), 23.9 (q), 26.4 (q), 41.9 (t), 51.5 (s), 73.4 (d), 77.2 (d), 145.0 (s), 214.5 (s). HRMS (ESI+): *m/z* calculated for $C_{10}H_{18}IO_2$ $[M+H]^+$ 297.0346, found 297.0340.

(*R*,*E*)-1-Iodo-2,5,5-trimethyl-6-oxohept-1-en-4-yl (*R*)-2-methoxy-2-phenylacetate (25). (*R*)-(-)-α-Methoxyphenylacetic acid (565 mg, 3.4 mmol) and EDC·HCl (862 mg, 4.5 mmol) were added to a solution of alcohol **24** (596 mg, 2 mmol) in THF (15 mL), then DMAP (60 mg, 0.5 mmol) was added and the solution was stirred at 45 ºC for 16h. The solution was poured into Et_2O (15 mL) and washed NH_4Cl saturated solution (2x15 mL). The organic residue was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded the corresponding esters **25-*R*,*R*** (366 mg, 41%) and **25-*S*,*S*** (375 mg, 42%) as colorless oils.

25-*R*,*R* characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H), 0.94 (s, 3H), 1.89 (d, *J* = 0.8 Hz, 3H), 1.90 (s, 3H), 2.20 – 2.35 (m, 2H), 3.43 (s, 3H), 4.65 (s, 1H), 5.36 (dd, *J* = 10.3, 2.5 Hz, 1H), 5.88 (brs, 1H), 7.31 – 7.42 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.6 (q), 21.4 (q), 23.5 (q), 26.0 (q), 40.7 (t), 51.1 (s), 58.0 (q), 74.5 (d), 77.7 (d), 82.6 (d), 127.3 (d), 128.7 (d), 128.9 (d), 136.3 (s), 143.9 (s), 169.7 (s), 210.7 (s). HRMS (ESI+): *m/z* calculated for $C_{19}H_{25}INaO_4$ $[M+Na]^+$ 467.0690, found 467.0692.

25-*S*,*S* characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.12 (s, 3H), 1.76 (d, *J* = 1.1 Hz, 3H), 2.12 (s, 3H), 2.13 – 2.15 (m, 2H), 3.40 (s, 3H), 4.69 (s, 1H), 5.33 (d, *J* = 1.1 Hz, 1H), 5.40 (t, *J* = 6.0 Hz, 1H), 7.32 – 7.40 (m, 5H).

(*R*,*E*)-6-Iodo-2,5-dimethyl-2-(2-methyl-1,3-dioxolan-2-yl)hex-5-en-3-yl (*R*)-2-methoxy-2-phenylacetate. TMSOTf (15 μL, 0.08 mmol) was added over a solution of ketone **25-*R*,*R*** (360 mg, 0.81 mmol) and 1,2-Bis(trimethylsiloxy)ethane (500 mg, 2.43 mmol) in CH_2Cl_2 at -78ºC and the mixture was left to evolve to rt and stirred at rt for additional 48h. The reaction was quenched with 0.1 mL of pyridine and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded title cyclic ketal (335 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (s, 3H), 0.73 (s, 3H), 1.12 (s, 3H), 1.87 (s, 3H), 2.43 (dd, *J* = 14.3, 11.3 Hz, 1H), 2.68 (dd, *J* = 14.3, 1.9 Hz, 1H), 3.43 (s, 3H), 3.69 – 3.88 (m, 4H), 4.63 (s, 1H), 5.19 (dd, *J* = 11.3, 1.9 Hz, 1H), 5.88 (s, 1H), 7.28 – 7.43 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.7 (q), 20.0 (q), 20.5 (q), 23.6 (q), 41.4 (t), 45.8 (s), 58.2 (q), 64.4 (t), 64.7 (t), 75.0 (d), 76.9 (d), 82.7 (d), 112.4 (s), 127.4 (d), 128.4 (d), 128.6 (s), 136.5 (s), 145.1 (s), 169.7 (s). HRMS (ESI+): *m/z* calculated for $C_{21}H_{29}INaO_5$ $[M+Na]^+$ 511.0952, found 511.0962.

(*R*,*E*)-6-Iodo-2,5-dimethyl-2-(2-methyl-1,3-dioxolan-2-yl)hex-5-en-3-ol (26). $LiOH{\cdot}H_2O$ (315 mg, 8.3 mmol) was added to a solution of the above mentioned ketal (320 mg, 0.65 mmol) in MeOH (8 mL) and the solution was stirred at 65 ºC for 16h. The reaction was added to a separatory funnel containing Et_2O (10 mL) and H_2O (10 mL) and it was extracted two times with Et_2O (10 mL). The organic layer was washed with NaHCO3 saturated solution (15 mL), dried over MgSO4 and the solvent was evaporated under reduced pressure yielding

alcohol **26** (205 mg, 0.60 mmol) that was used in the next step without further purification.

(*R*,*E*)-*tert*-Butyl((6-iodo-2,5-dimethyl-2-(2-methyl-1,3-dioxolan-2-yl)hex-5-en-3-yl)oxy)dimethylsilane. Triethylamine (0.33 mL, 2.4 mmol) and TBSOTf (0.23 mL, 1 mmol) were sequentially added to a solution of crude alcohol **26** (205 mg, 0.60 mmol) in CH_2Cl_2 (8mL) at -20 ºC and the mixture was stirred 15 minutes at -20 ºC and then 60 minutes at rt. The reaction was quenched with NH_4Cl saturated solution (10 mL), extracted with CH_2Cl_2 (2x10mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded title TBS-protected compound (200 mg, 68% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.05 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 0.94 (s, 3H), 0.97 (s, 3H), 1.29 (s, 3H), 1.82 (s, 3H), 2.32 (dd, *J* = 14.5, 9.0 Hz, 1H), 2.88 (dd, *J* = 14.5, 2.1 Hz, 1H), 3.70 (dd, *J* = 9.0, 2.1 Hz, 1H), 3.81 – 3.96 (m, 4H), 5.91 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -3.5 (q), -3.2 (q), 18.4 (q), 20.8 (q), 23.0 (q), 23.9 (q), 26.2 (q), 30.3 (s), 45.0 (t), 47.4 (s), 64.3 (t), 64.7 (t), 75.2 (d), 77.9 (d), 113.2 (s), 145.8 (s). HRMS (ESI+): *m/z* calculated for $C_{18}H_{35}INaO_3Si$ $[M+Na]^+$ 477.1298, found 477.1299.

(*R*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-7-iodo-3,3,6-trimethylhept-6-en-2-one (9). PTSA·H_2O (3.8 mg, 0.02 mmol) was added to a solution of the above mentioned ketal (66 mg, 0.15 mmol) in acetone (5 mL) and the reaction was stirred at rt for 30 minutes. The reaction was quenched with two drops of triethylamine and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded entantiopure ketone **9** (59 mg, cuant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.02 (s, 3H), 0.87 (s, 9H), 1.10 (s, 6H), 1.82 (s, 3H), 2.14 (s, 3H), 2.21 – 2.24 (m, 2H), 4.05 – 4.09 (m, 1H), 5.94 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -4.0 (q), -3.7 (q), 18.2 (s), 19.6 (q), 22.9 (q), 23.8 (q), 26.0 (q), 27.1 (q), 44.8 (t), 53.0 (s), 74.0 (d), 78.8 (d), 144.5 (s), 213.4 (s). HRMS (ESI+): *m/z* calculated for $C_{16}H_{31}INaO_2Si$ $[M+Na]^+$ 433.1036, found 433.1039.

(1*S*,5*R*,9*S*,11*S*,13*R*,15*R*,*Z*)-9-((*tert*-Butyldimethylsilyl)oxy)-15-((1*R*,5*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-3,6,6-trimethyl-7-oxooct-2-en-1-yl)-7,11-dimethyl-5-((triisopropylsilyl)oxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (6). DMF was degassed using freeze-thaw-pump technique. $CrCl_2$ and $NiCl_2$ were weighted in a glove box. A mixture of iodoalkene 9 (52 mg, 0.13 mmol) and aldehyde 4[7] (50 mg, 0.083 mmol) in DMF (0.5 mL + 0.2 mL rinse) was cannulated to a solution of $CrCl_2$ (202 mg, 1.64 mmol) and $NiCl_2$ (2 mg, 1% m/m $CrCl_2$) in DMF (1 mL) and the solution was stirred at rt for 48 h. The reaction was filtered through celite and washed with Et_2O. The organic ethereal phase was washed with H_2O (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (8:2) yielded alcohol 6 (13.5 mg, 19%) as single diastereomer as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 0.91 (d, *J* = 6.1Hz, 3H), 1.03 (brs, 21H), 1.09 (s, 3H), 1.12 (s, 3H), 1.27 (m, 1H), 1.42 (m, 1H), 1.60 (m, 1H), 1.70 (m, 1H), 1.71 (s, 3H), 1.72 (s, 3H), 1.91 (m, 1H), 2.03-2.11 (m, 2H), 2.11 (m, 1H), 2.14 (s, 3H), 2.24 (m, 1H), 2.39 (m, 1H), 2.50 (m, 1H), 2.70 (m, 1H), 2.73 (m, 1H), 3.89 (dd, *J* = 4.6, 1.3 Hz, 1H), 4.06 (m, 1H), 4.19 (t, *J* = 6.1 Hz, 1H), 4.33 (m, 1H), 4.43 (m, 1H), 5.05 (m, 1H), 5.15 (d, *J* = 5.6 Hz, 1H), 5.42 (m, 1H), 5.44 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -4.4 (q), -4.1 (q), -3.9 (q), 12.3 (d), 17.4 (q), 17.7 (s), 17.9 (q), 18.1 (s), 19.3 (q), 20.7 (q), 23.0 (q), 23.1 (q), 25.9 (q), 26.0 (q), 26.7 (d), 27.1 (q), 33.9 (t), 38.3 (t), 40.9 (t), 45.0 (t), 46.0 (t), 46.9 (t), 53.1 (s), 68.4 (d), 69.0 (d), 70.3 (d), 74.1 (d), 76.1 (d), 78.5 (d), 87.3 (d), 125.7 (d), 132.7 (d), 138.9 (s), 143.4 (s), 171.1 (s), 213.9 (s). HRMS (ESI+): *m/z* calculated for $C_{48}H_{92}NaO_8Si_3$ $[M+Na]^+$ 903.5992, found 903.5993.

(1*R*,5*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-1-((1*S*,5*R*,9*S*,11*S*,13*R*,15*S*,*Z*)-9-((*tert*-butyldimethylsilyl)oxy)-7,11-dimethyl-3-oxo-5-((triisopropylsilyl)oxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-15-yl)-3,6,6-trimethyl-7-oxooct-2-en-1-yl (*R*)-2-methoxy-2-phenylacetate (27). (*R*)-(-)-α-Methoxyphenylacetic acid (7 mg, 0.04 mmol) and EDC·HCl (10 mg, 0.05 mmol) were added to a solution of alcohol 6 (4.3 mg, 0.005 mmol) in THF (0.25 mL), then DMAP (catalytic) was added and the solution was stirred at 35ºC for 2h. The solution was poured into Et_2O (5 mL) and washed NH_4Cl saturated solution (2x3 mL). The organic residue was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded the corresponding ester 27 (2.2 mg, 48% brsm) and 6 (0.5 mg). ^{1}H NMR (500 MHz, $CDCl_2$-d_2) δ 0.04 (s, 6H), 0.08 (s, 6H), 0.82 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.90 (s, 9H), 1.07 (s, 21H), 1.09 (s, 3H), 1.11 (s, 3H), 1.13 – 1.16 (m, 1H), 1.23 – 1.27 (m, 1H), 1.36 – 1.42 (m, 1H), 1.51 – 1.54 (m, 1H), 1.55 – 1.57 (m, 1H), 1.65 (d, *J* = 13.9 Hz, 1H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.79 (d, *J* = 1.3 Hz, 3H), 1.86 – 1.91 (m, 1H), 2.08 – 2.11 (m, 1H), 2.14 (s, 3H), 2.21 – 2.29 (m, 2H), 2.44 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.62 – 2.69 (m, 2H), 3.40 (s, 3H), 3.75 (ddd, *J* = 12.0, 7.9, 4.5 Hz, 1H), 3.88 (dd, *J* = 3.0, 1.2 Hz, 1H), 4.05 (dd, *J* = 9.9, 3.8 Hz, 1H), 4.23 (t, *J* = 5.8 Hz, 1H), 4.70 (s, 1H), 4.97 – 5.03 (m, 1H), 5.06 (dd, *J* = 6.0, 1.2 Hz, 1H), 5.40 – 5.45 (m, 1H), 5.49 – 5.54 (m, 1H), 5.75 (dd, *J* = 9.3, 3.0 Hz, 1H), 7.32 – 7.49 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_2$-d_2) δ -4.3 (q), -3.9 (q), -3.5 (q), 12.8 (d), 17.9 (q), 18.1 (q), 18.2 (q), 18.4 (s), 18.5 (s), 20.1 (q), 20.8 (q), 22.1 (q), 23.3 (q), 26.1 (q), 26.2 (q), 27.0 (d), 27.0 (q), 33.9 (t), 38.7 (t), 41.6 (t), 45.0 (t), 46.2 (t), 47.1 (t), 57.7 (q), 68.8 (d), 70.8 (d), 71.9 (d), 74.5 (d), 75.7 (d), 78.9 (d), 83.1 (d), 86.0 (d), 121.5 (d), 128.2 (d), 129.0 (d), 129.2 (d), 132.9 (d), 133.5 (s), 137.1 (s), 142.1 (s), 169.9 (s), 170.8 (s), 213.0 (s). HRMS (ESI+): *m/z* calculated for $C_{57}H_{104}NO_{10}Si_3$ $[M+NH_4]^+$ 1046.6963, found 1046.6961.

(1*S*,5*R*,9*S*,11*S*,13*R*,15*S*,*Z*)-9-((tert-butyldimethylsilyl)oxy)-15-((4*R*,8*R*,*E*)-8-((tert-butyldimethylsilyl)oxy)-2,2,6,9,9,12,12-heptamethyl-10-methylene-3,11-dioxa-2,12-disilatridec-5-en-4-yl)-7,11-dimethyl-5-((triisopropylsilyl)oxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (31). Et_3N (14 μL, 0.1 mmol) and TMSOTf (11 μL, 0.06 mmol) were sequentially added to a solution of ketone 6 (8 mg, 0.01 mmol) in CH_2Cl_2 (0.7 mL) at 0 ºC. The reaction was stirred for 3h at rt, diluted with CH_2Cl_2 (2 ml) and quenched with diluted NH_4Cl (1 mL). The organic layer was washed three times with diluted NH_4Cl, dried over $MgSO_4$ and concentrated under reduced pressure to obtain the silylenolether 31 as a brownish oil (10 mg, quant). The crude was pure enough to continue the synthesis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.06 (s, 6H), 0.07 (s, 9H), 0.21 (s, 9H), 0.85 (s, 9H), 0.86 (s, 9H), 0.88 (d, *J* = 2.9 Hz, 3H), 0.93 (s, 3H), 1.02 (s, 3H), 1.05 (s, 21H), 1.28 – 1.29 (m, 1H), 1.66 (s, 3H), 1.72 (s, 3H), 1.73 – 1.76 (m, 1H), 1.93 – 2.04 (m, 3H), 2.07 – 2.17 (m, 3H), 2.20 – 2.30 (m, 2H), 2.47 – 2.58 (m, 2H), 2.68 (dd, *J* = 14.6, 3.7 Hz, 1H), 3.94 – 3.96 (m, 2H), 3.96 – 4.00 (m, 2H), 4.10 (d, *J* = 1.6 Hz, 1H), 4.29 – 4.38 (m, 1H), 4.44 (dd, *J* = 9.1, 2.7 Hz, 1H), 4.89 – 4.95 (m, 1H), 5.21 (d, *J* = 5.7 Hz, 1H), 5.24 – 5.27 (m, 1H), 5.40 – 5.43 (m, 1H).

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Supporting Information

Towards the synthesis of Phormidolides, a Journey

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1. (*E*) stereochemistry confirmation of **12** using NOE 1D NMR[1]

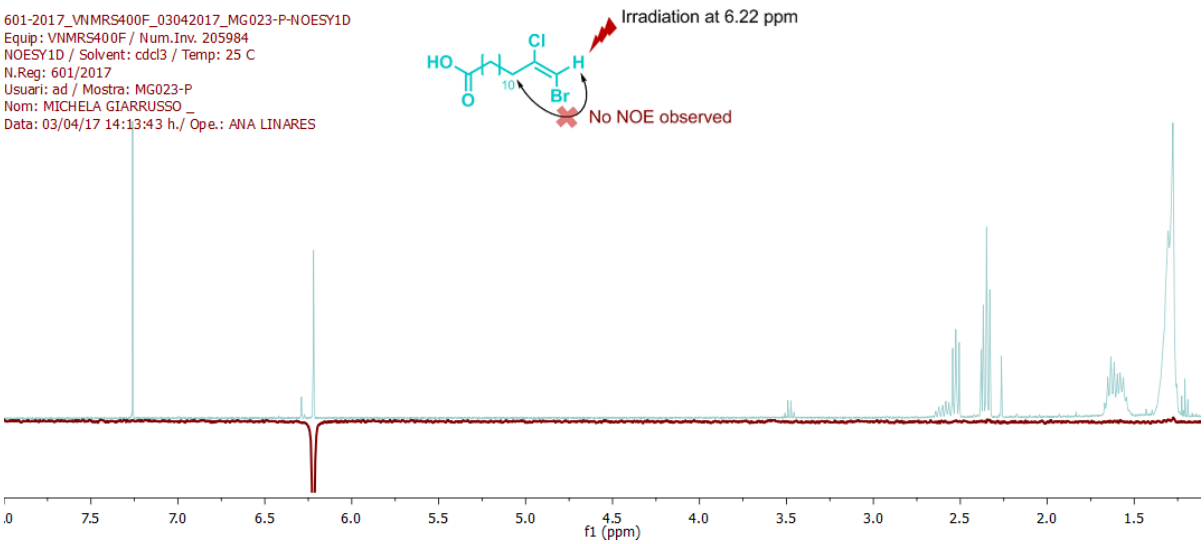
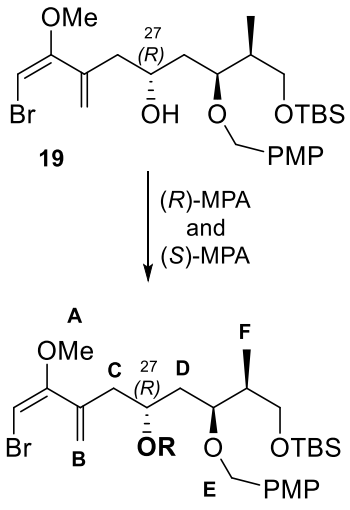


Figure 2: NOE 1D of fatty acid **7**. The absence of NOE correlation between vinylic and allylic protons confirms the (*E*) stereochemistry.

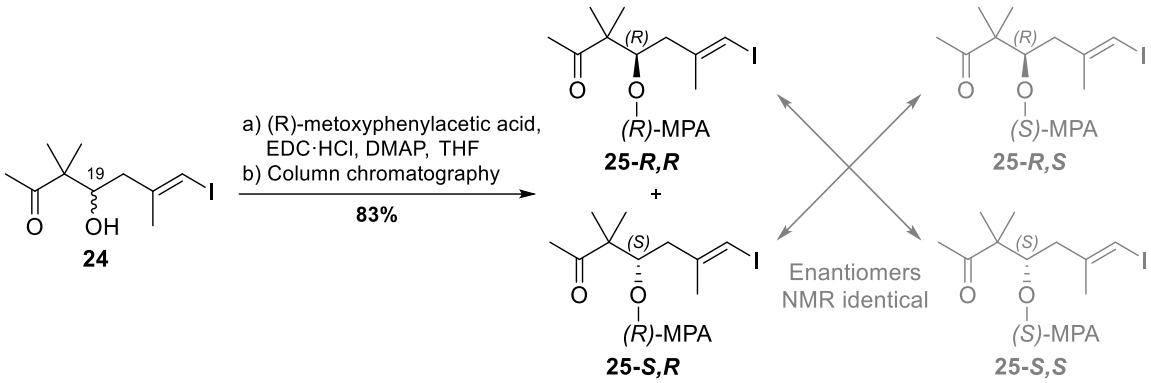
2. C27 absolute configuration determination of alcohol **19**[2,3]



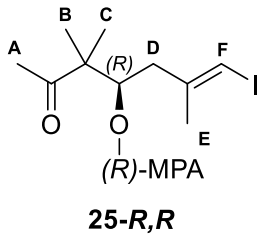
	δ H_A	δ H_B	δ H_C	δ H_D	δ H_E	δ H_F
R = *R*-MPA	3.53	5.37	2.54	1.57	3.96	0.67
R = *S*-MPA	3.41	5.13	2.41	1.72	4.26	0.86
Δ^{RS}	+0.12	+0.24	+0.13	-0.15	-0.30	-0.19

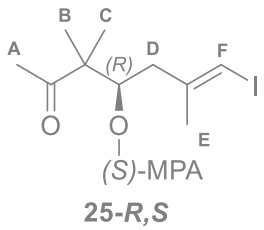
3. C19 absolute configuration determination in compound **25-*R,R***[2,3]

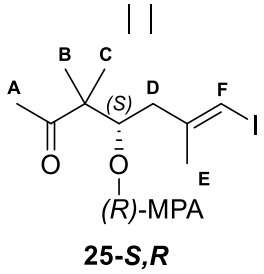
Racemic alcohol **24** was esterified with (*R*)-MPA to obtain diasteromers separable by column chromatography. Once **25-*R,R*** and **25-*S,R*** were isolated Mosher's model was applied (below) to identify each C19 epimers. Taking advantage of the fact that **25-*S,R*** is spectroscopically identical to 25-*R,S* it was possible to directly compare ^{1}H NMR of **25-*R,R*** and **25-*S,R*** and apply Mosher's model to identify the C19-R epimer compound **25-*R,R*.**



Scheme 8: Mosher derivatization of alcohol **24** showing the corresponding enantiomers of the obtained diastereomers **25-*R,R*** and **25-*S,R*.**

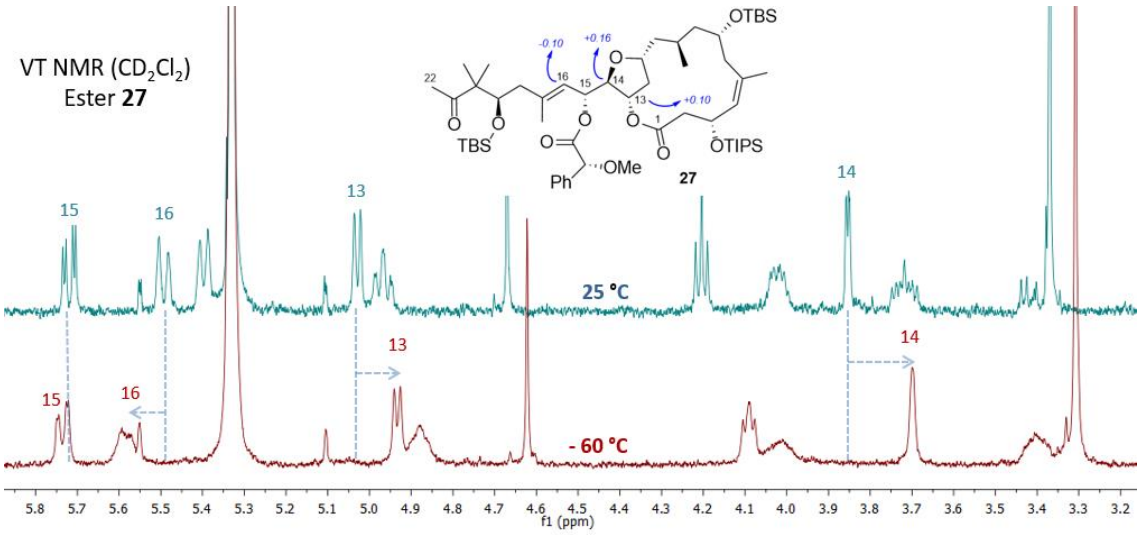




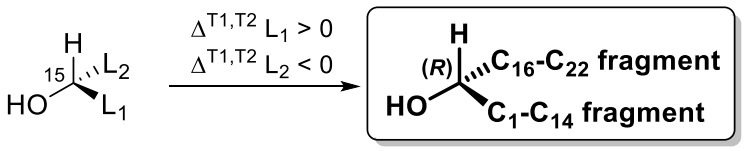


	δ H_A	δ H_B	δ H_C	δ H_D	δ H_E	δ H_F
25-*R,R*	1.90	0.81	0.94	2.27	1.89	5.88
25-*R,S*	2.12	1.05	1.12	2.13	1.76	5.33
Δ^{RS}	-0.22	-0.24	-0.18	+0.14	+0.13	+0.55

4. C15 absolute configuration determination using Mosher VT method in compound **27**[3,4]



	δH_{15}	δH_{14}	δH_{13}	δH_{16}
27 at 25 ºC	5.7	3.85	5.03	5.49
27 at -60 ºC	5.7	3.69	4.93	5.59
$\Delta^{T1,T2}$	0	+0.16	+0.10	-0.10



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Annex

<u>Review article:</u> "Role of the Nozaki-Hiyama-Takai-Kishi reaction in the synthesis of natural products"

CHEMICAL REVIEWS

Review

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Role of the Nozaki–Hiyama–Takai–Kishi Reaction in the Synthesis of Natural Products

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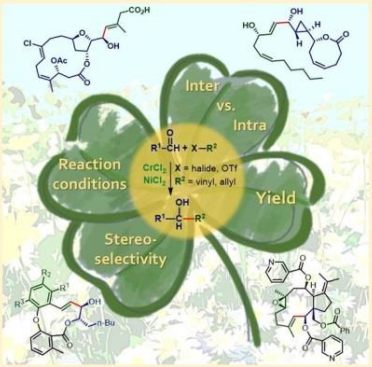
ABSTRACT: The Nozaki–Hiyama–Takai–Kishi (NHTK) reaction was discovered in the late 1970s and, since then, its main application has been its use in total synthesis. In this comprehensive review, the efficiency of the NHKT reaction in the synthesis of a great number of different scaffolds present in complex natural products is analyzed. The preparation of enol and allylic and propargylic alcohol motifs is discussed, highlighting factors such as yield, chemoselectivity, stereoselectivity, or the importance of protecting groups. The review is divided into two main sections: intermolecular and intramolecular NHTK reactions. A final discussion about the current "state-of-art" and future perspectives for the use of this transformation in total synthesis is also included.



CONTENTS

1. HISTORY

The first publication using $CrCl_2$ to create C–C bonds was reported by Tamejiro Hiyama and Hitoshi Nozaki in 1977.[1] In it, a new type of aldehyde allylation using $CrCl_3$ and $LiAlH_4$ as reducing agent to generate a Cr(II) reactive species was described (Nozaki–Hiyama allylation). The new reaction was defined as a "Grignard-type carbonyl addition" due to the inherent similarity with the mentioned reactions. In the following years, several articles exploiting this new methodology were reported by the same authors and Kazuhiko Takai.[2−4] It was not

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until 1986 when, simultaneously, Yoshito Kishi,[5] and Takai and Nozaki[6] discovered the catalytic and necessary effects of $NiCl_2$ for the alkenylation of aldehydes using vinyl halides and vinyl triflates. Because of all of the previous work and the key discovery of the catalytic effect of Ni(II), we believe that the generally called Nozaki–Hiyama–Kishi coupling should be extended to include Takai's name with it.[7] Therefore, in this review, and, hopefully, in future publications this useful reaction for the organic synthesis community will be addressed as the Nozaki–Hiyama–Takai–Kishi (NHTK) reaction.

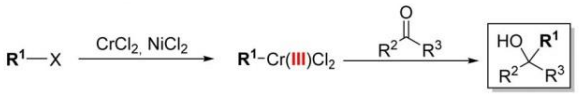
2. THE NOZAKI–HIYAMA–TAKAI–KISHI REACTION. GENERAL FEATURES

Reactions with the ability to create new C–C bonds in a mild and effective manner are essential tools to further develop the synthesis of natural products and other structurally complex compounds. Organolithium and organomagnesium reagents have been used for many years to construct these bonds through a reaction with aldehydes and ketones. However, the lack of chemo- and stereoselectivity or the harsh conditions required pose an important limitation to make these organometallic reagents compatible with the complex structures of natural products. To overcome this problem, organochromium reagents emerged in the late 1970s as a useful alternative to previously used C–C bond-forming protocols.

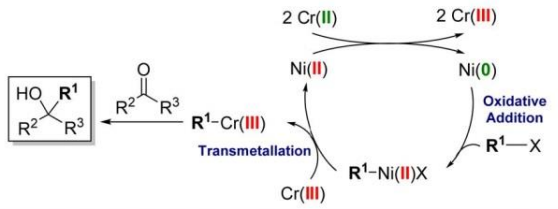
In a broad sense, the NHTK reaction includes chromium(II)-mediated addition of an allyl or propargyl halide with an aldehyde and a Ni-catalyzed chromium(II)-mediated reaction between a vinyl or alkynyl halide (or triflate) and an aldehyde to obtain the corresponding alcohol (Scheme 1.1). In the early years, the process was defined as an oxidative addition through two single electron transfer events; therefore, at least 2 equiv of $CrCl_2$ were required.[8] The reaction could be performed in the presence of functional groups such as esters, amides, nitriles, ketones, acyls, acetals, ketals, ethers, silyl ethers, alcohols, and olefins, showing total chemoselectivity for aldehydes.[4,9] This selectivity could be explained by the fact that Cr–C has a strong covalent nature and thus it reacts easily only with strong electrophiles such as aldehydes. Therefore, NHTK showed itself as a reliable and predictable method for the formation of allylic and homoallylic alcohols that could be used in late synthetic steps.

Scheme 1. General Reaction and Mechanism of NHTK Coupling[6,10]

1.1 General organochromium reaction mechanism



1.2 Mechanism for Ni(II) catalysed NHKT



Several modifications of the original methodology emerged, mainly with the objective of developing catalytic methods to eliminate the problem of the stoichiometric use of toxic chromium salts and enantioselective versions in order to overcome the lack of facial selectivity during the addition.[11−13] Despite this, the use of $NiCl_2$ is still the most widely used methodology in natural product total synthesis to catalyze the initial Cr(II)–Cr(III) oxidation. The most accepted mechanism proceeds through a Ni(II) intermediate generated after oxidative addition of Ni(0) to the alkyl halide, which, after transmetalation with Cr(III), is added to the carbonyl compound.[6] The generated Ni(II) can be reduced again to Ni(0) and start the catalytic cycle again (Scheme 1.2). Recently, some evidence of an alternative free radical mechanistic pathway has been also reported.[14] It is important to keep Ni levels as low as possible (normally 0.1% respect to $CrCl_2$) to avoid homocoupling products between vinyl organonickel species.[5]

One of the most remarkable and pioneering total synthesis accomplished using the NHTK reaction was the total synthesis of palytoxin[15,16] by Kishi and co-workers.[17−20] It was during the studies toward this molecule when it was discovered that the outcome of the reaction was highly dependent on the $CrCl_2$ batch used.[5] This fact made these researchers think that some impurity could be the responsible for increasing the reaction yield. After trying different transition metals, they discovered that $NiCl_2$ was the reason behind this beneficial catalytic effect. Right after this serendipitous discovery, Kishi's group exploited the new methodology in several new total syntheses of relevant natural products, such as (+)-ophiobolin C,[21] halichondrin B and norhalichondrin,[22] altohyrtin A,[23,24] and pinnatoxin A.[25]

The stereoselectivity of the reaction is highly dependent on the substrates used and the corresponding generated transition states. When the reaction is performed with chiral aldehydes, two possible diastereomers can be obtained with a general moderate to good selectivity for the Felkin addition product. As a general trend, α-alkyl aldehydes generate *syn*-alcohols[26] and α-alkoxy ones generate *anti*-alcohols.[5,27] As will be demonstrated in this revision, highly structurally restricted aldehydes give the best results in terms of facial selectivity. It is also possible to use chiral ligands[13] to enhance the stereoselectivity of the addition, but they are not commonly used in total synthesis and the stereochemical outcome is generally dependent on the stereochemistry of the starting materials.

The best solvents for the NHTK reaction are polar aprotic solvents such as DMF, DMSO, and DMSO–DMS that have been thoroughly dried and deoxygenated. Polarity is needed to efficiently solubilize the active $CrCl_2$. The reaction workup is, generally, quite straightforward. Water addition and ether extraction can be used, although in some specific cases the use of sodium serinate, potassium sodium tartrate tetrahydrate, ethylenediamine, or sodium fluoride can help to separate the phases and improve the efficiency of the workup.[28]

In summary, chemoselectivity for aldehydes, mild conditions, good yields, substrate-controlled stereoselectivity, and the possibility of performing the reaction in the presence of many functional groups have shown NHTK to be a very useful methodology for the synthesis of natural products. To date, several complete reviews[10,29−32] and book chapters[33] containing all the general information and application of the reaction have been published, but no total-synthesis-oriented review has been published yet. Therefore, this review seeks to illustrate some interesting features about the use of the NHTK reaction in total synthesis classified by the type of chemical bond obtained after the transformation. In addition, important aspects in synthesis, such as reaction conditions, yield, stereoselectivity, protecting or

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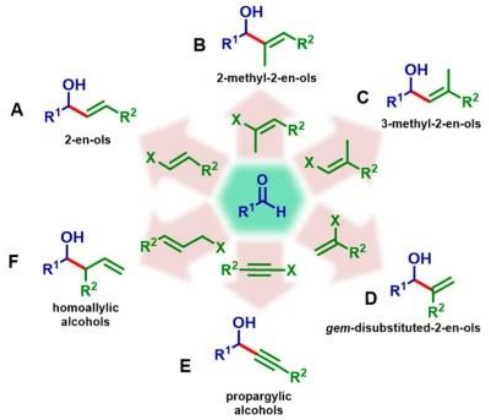
functional group compatibility, are also analyzed in depth. This review can be used as an updated and descriptive version because it includes the most relevant work done between 2000 and 2016.

3. USES OF THE NHTK REACTION IN TOTAL SYNTHESIS

3.1. Intermolecular Version

All the reported NHTK intermolecular reactions used in total synthesis can be classified under six different categories, depending on the resulting bond formation (Scheme 2), the

Scheme 2. Different Intermolecular NHTK Reactions Used in Total Synthesis[a]



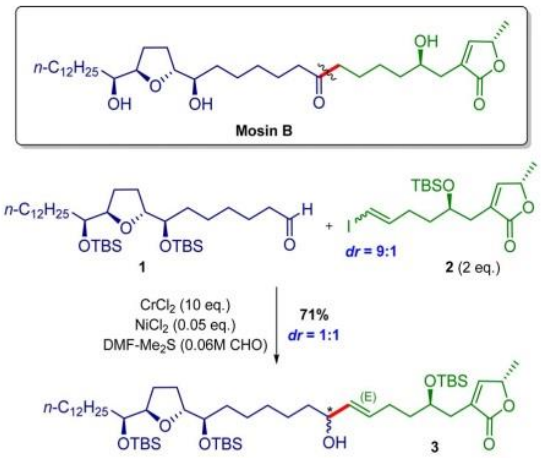
[a]The nascent bond is indicated in red.

alkenylation being the most reported conversion (Scheme 2A–D). From a general point of view, alkenylation can be performed with four different types of vinyl halides rendering di- (A and D) or trisubstituted (B and C) alkenes depending on the starting material. Homoallylic and propargylic alcohols (Scheme 2E,F) have also been used as key intermediates in the synthesis of natural products. NHTK intermolecular reactions used in the synthesis of natural products will be discussed in this section. In addition, a classification of these reactions based on the nature of the bond created during the reaction, along with comments about interesting particularities of each reaction, will also be provided.

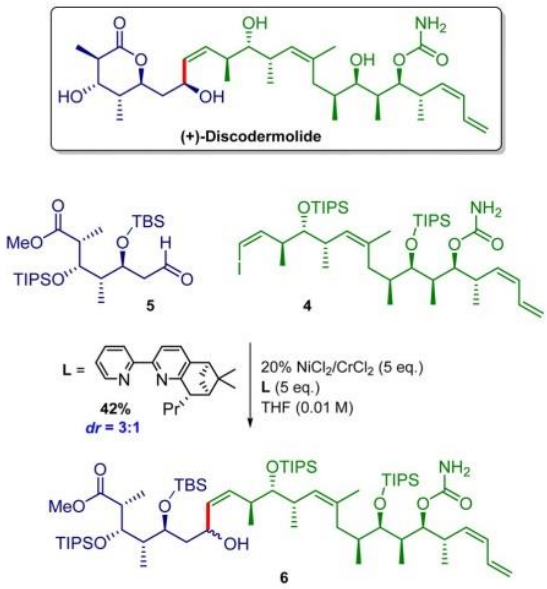
3.1.1. Generation of the 2-En-ol Scaffold. Maezaki et al. reported the NHTK coupling of fragments **1** and **2** in a late-stage part of the synthesis to develop the first total synthesis of mosin B,[34] a selective cytotoxic compound against pancreatic tumor cells (Scheme 3). Interestingly, although they started from a 9:1 (*E*:*Z*) mixture of isomers in **2**, the obtained product was only the (*E*)-allylic alcohol **3**. Although *E*/*Z* isomerization of the organochromium reagent was postulated, there is no evidence about the isomerization, and the low reactivity of the (*Z*)-isomer could cause this high (*E*)-selectivity. The lack of substituents close to the aldehyde and the haloalkene and the absence of structural restrictions caused no facial selectivity in the addition, generating a 1:1 diastereomeric mixture. Alcohol oxidation, double bond reduction, and deprotection delivered mosin B, an aliphatic saturated ketone.[35,36]

One example where the absence of *E*/*Z* iodoalkene is relevant is the total synthesis of (+)-discodermolide by Myles and co-workers (Scheme 4). In it, enantiopure (*Z*)-vinyl halide **4** was coupled with aldehyde **5** under catalytic NHTK conditions using

Scheme 3. Intermolecular NHTK in the Synthesis of Mosin B[35]



Scheme 4. Last Steps in the Synthesis of (+)-Discodermolide[38]



chiral bispyridinyl Kishi's catalyst[37] to render the protected skeleton of (+)-discodermolide **6** and to maintain the *Z* stereochemistry present on **4**.[38] The authors highlight "*The chemoselectivity of this* reaction *allows for optimal convergency in that the carbamate, terminal diene, methyl ester, and β-silyl-oxy aldehyde all can be present during the coupling*", demonstrating the possibility of use the reaction in late-stage synthetic steps when the coupling fragments are highly functionalized.

Natural products bearing a disubstituted vinyl alcohol motif are very common in nature. Therefore, NHTK is a very suitable methodology that enables easy access to these products. An example of this molecular structure is herbarumin I.[39] This product was isolated from *Phoma herbarum* Westend. It has become a very promising scaffold used to develop new herbicides because of its potent phytotoxic activity in vitro on the seedling of *Amaranthus hypochondriacus* (Scheme 5). Sabino and Pilli reported a strategy based on the NHTK reaction followed by macrolactonization.[40] In this approach, the full skeleton of herbarumin I was obtained using standard NHTK conditions for

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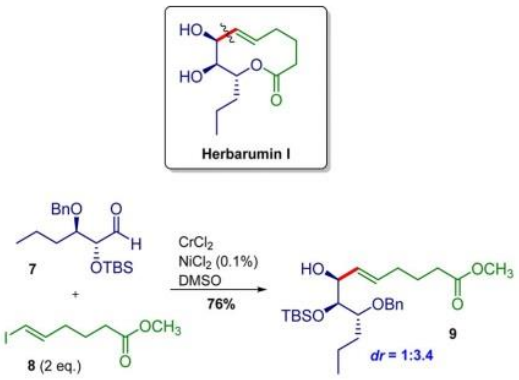
Scheme 5. Intermolecular NHTK in the Synthesis of Herbarumin I[40]

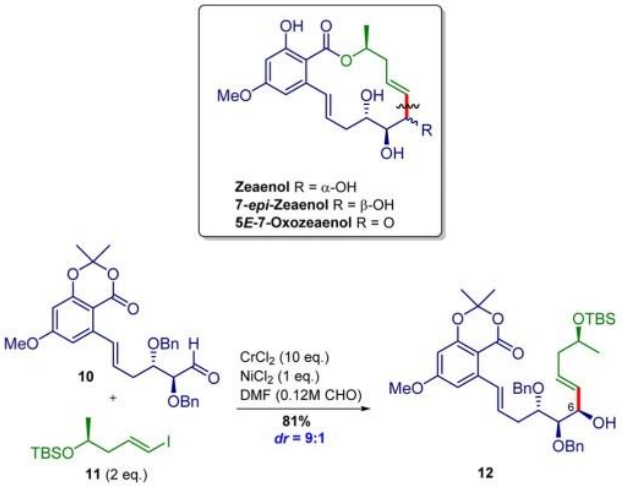


linking fragments **7** and **8** to obtain allylic alcohol **9** as a C7 diastereomeric mixture enriched in the desired (*S*)- or Felkin-type isomer. The stereochemistry of α- and β-substituted positions in the aldehyde **7** was responsible for this modest diastereoselectivity. TBS-protection, benzyl protecting group removal, cyclization, and final di-TBS elimination yielded herbarumin I in 17 steps from L-arabinose in a 6% overall yield.

As observed in the synthesis of herbarumin I, substituents in the position α to the aldehyde moiety can play a critical role in the stereochemical outcome of the reaction.[10] Over the course of their research, Mohapatra et al. performed a model study to determine the best protecting group using simplified analogs of **10** toward the synthesis of paecelomycins E and F.[41] Bulky protecting groups caused better stereochemical control; therefore, OBn was chosen for the good combination of yield and stereoselectivity. Following this study, the total synthesis of zeaenol and several analogs was achieved using NHTK methodology to link aldehyde **10** and iodoalkene **11**.[42] The allylic alcohol **12** was obtained in a very good yield but even better stereocontrol, obtaining the desired 6-(*R*)-diastereomer in a 9:1 ratio (Scheme 6). This is a good example of the importance of substrate-directed stereoselectivity in NHTK reactions.

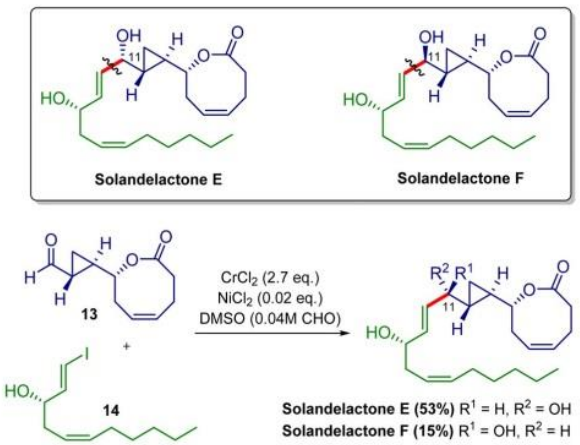
White et al. took advantage of the generally poor stereoselectivity of the NHTK reaction, in the total synthesis of

Scheme 6. Intermolecular NHTK in the Synthesis of 7-Epi-zeaenol and Analogs[42]



solandelactones E and F, to obtain both natural products in the same reaction.[43] The last step of the synthesis was the reaction of aldehyde **13** and vinyl iodide **14** to give an epimeric mixture at C11, which, once purified, yielded solandelactone E and F in good yields (Scheme 7).[44] This reaction also shows the

Scheme 7. Last Reaction in the Total Synthesis of Solandelactones E and F[44]



possibility of using NHTK with unprotected alcohols, displaying the functional group compatibility of the reaction. Later on, this methodology was used in the synthesis of additional members of this family: solandelactones A and B.[45]

One of the most spectacular applications of the NHTK reaction for the synthesis of natural products due to the size and functionalization of the linking fragments is shown in the total synthesis of halichondrin A by Kishi and colleagues (Scheme 8).[46] The point of convergence at the end of the synthesis is the reaction between the iodoalkene **15** and the aldehyde **16** under reported catalytic conditions.[47] This reaction between two molecules of molecular weight around 1000 Da works to render, after DMP oxidation, the α,β-unsaturated ketone **17** with 85% yield. Each linking partner has 9 and 21 stereocenters, respectively, different protecting groups, and different functionalities, such as acetals, terminal double bonds, and esters, and the reaction works selectively without disrupting any of these features. Finally, four steps are required from **17** to obtain the natural product halichondrin A. A similar synthetic strategy was also applied for the synthesis of halichondrin C.[48]

Many other natural products have been synthesized using the formation of a 1,2-disubstituted allylic alcohol (Scheme 2A). In all of these cases, methodologies similar to those mentioned above were used to construct the structure of the final compounds. An intermolecular NHTK reaction was used to create a 1,2-disubstituted alkene in the total synthesis of laulimalide,[49] 11-desmethyllaulimalide and its analogs,[50] eicosanoid,[51] neooxazolomycin,[52] (+)-methynolide,[53] 11,12,15-(*S*)-trihydroxyeicosatrienoic acid,[54] (−)-apicularen A,[55] oxazolomycin A,[56] reveromycin B,[57] (−)-mycalolide A,[58,59] clavosolide A,[60,61] (+)-oxerine,[62] and dictyostatin.[63] All of these compounds are depicted in Figure 1 with the yield of the NHTK transformation.

3.1.2. Generation of the 2-Methyl-2-en-ol Scaffold. 2-Methyl allylic alcohols are a very common motif in natural product architecture (Scheme 2, B). The NHTK reaction allows the link between a 1-substituted vinylic halide and an aldehyde to

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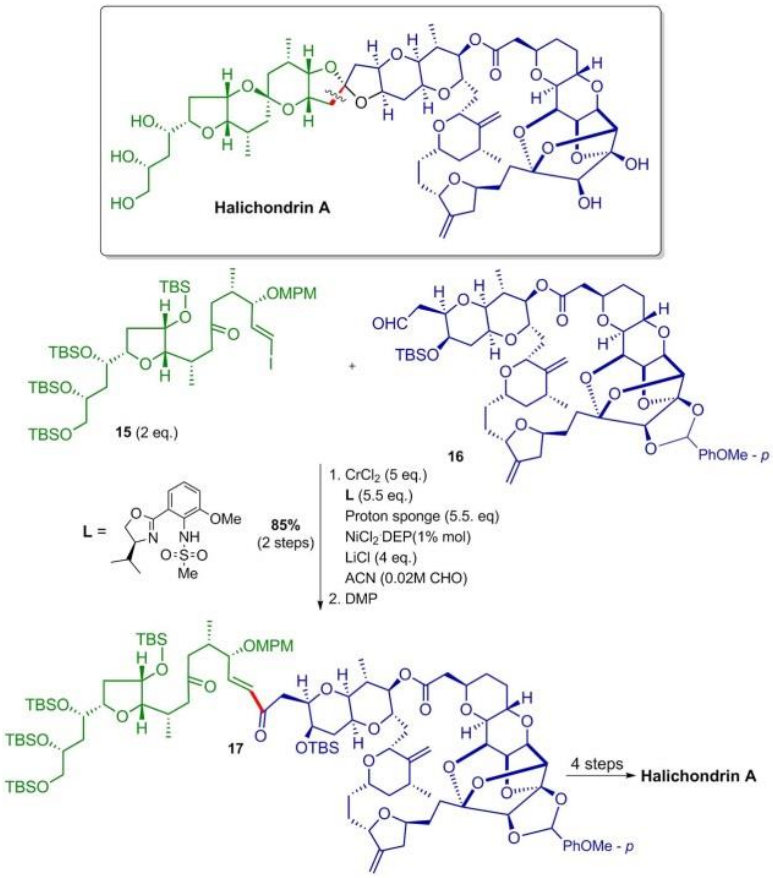
Scheme 8. NHTK Reaction in the Synthesis of Halichondrin A[46]



construct this 2-methyl allylic alcohol structure in a very effective manner. The generated compound is always obtained as a single (*E*) double bond isomer due to the reported possibility of *E*/*Z* equilibration during the reaction process toward the most stable (*E*)-organochromiun intermediate.[6]

Octalactins A and B are very interesting natural products isolated from a marine-derived actinomycete.[64] Octalactin A has significant cytotoxic activity against B-16-F10 murine melanoma and HCT-116 human colon tumor cells, whereas octalactin B is totally inactive. Several syntheses of these natural products have been described.[26,65,66] However, O'Sullivan et al. reported a new concise synthesis using NHTK methodology. The combination of $CrCl_2$ and $NiCl_2$ was used to construct the full octalactin scaffold with excellent 91% yield and a modest stereoselectivity (Scheme 9).[67] The same conversion, changing only the protecting groups, was used by Radosevich et al. with similar results in terms of yield and stereoselectivity.[68] Allylic secondary alcohol **20** was converted into octalactin B by simple oxidation and deprotection.

A particularly interesting modification of the initial synthetic strategy occurred during the synthesis[69,70] of spirocyclic-imine compound (−)-gymnodimine[71] reported by Kong et al. Although their initial plan was to use NHTK intramolecular vinylation to perform cyclization in substrate **21**, it was impossible to reach the heterocyclic scaffold of the natural product **22** (Scheme 10). However, an intermolecular NHTK reaction of fragments **23** and **24** worked with exceptional yield, giving an epimeric mixture at C10. Nevertheless, this mixture could be enriched in the desired (*S*)-diastereomer by oxidation and enantioselective Corey−Bakshi−Shibata reduction.[72] Once compound **26** was obtained, 10 extra synthetic steps were required to reach the natural product (−)-gymnodimine. This example demonstrates the possibility to use NHTK reaction at early medium stages of the synthesis due to the efficiency of the scaling-up process. In this case, 198 mg of aldehyde **23** was converted to almost 600 mg of vinylic alcohol **25**.

Didemnaketal B is a complex natural product isolated from the ascidian *Didemnum* sp. by Faulkner and co-workers (Scheme 11).[73] Fuwa et al. published an elegant total synthesis and structural revision of this fascinating compound.[74] The proposed structure was synthesized and, after detailed NMR spectroscopic analyses and stereochemical studies, it was hypothesized that the relative stereochemistry of C20−C21 and C8−C10 had been originally misassigned. To confirm this theory, a new diastereomer of didemnaketal B was synthesized using NHTK intermolecular coupling as the final step of the synthesis. The process required 20 equiv of $CrCl_2$ and 10 equiv of the iodoalkene **27** to drive the reaction to completion due to the low amount of aldehyde **28** available (9.3 mg), obtaining good yield and modest diastereoselectivity. NMR analysis of each synthesized diastereomer and comparison with the natural product demonstrated that the correct structure of the natural product had an *anti*-C20−21 and *anti*-C8−10 relationship.

Other natural products, such as carolacton,[75] the (+)- and (−)-bisanthraquinone antibiotic BE-43472B,[76] or the common FGHI-ring of ciguatoxins,[77] have been successfully synthesized using NHTK coupling in an intermolecular fashion to construct the 2-methyl-2-en-ol scaffold present in all these compounds.

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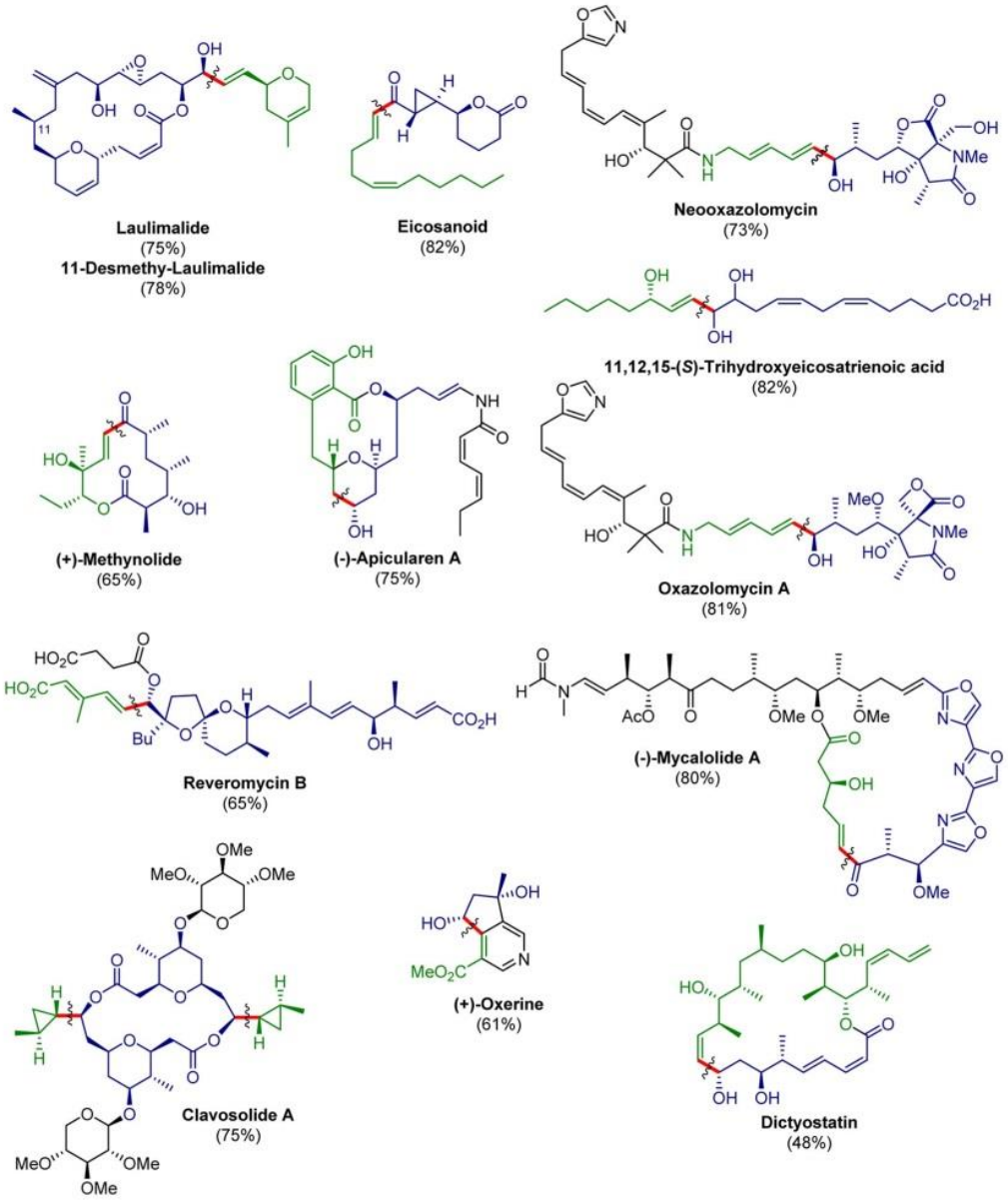
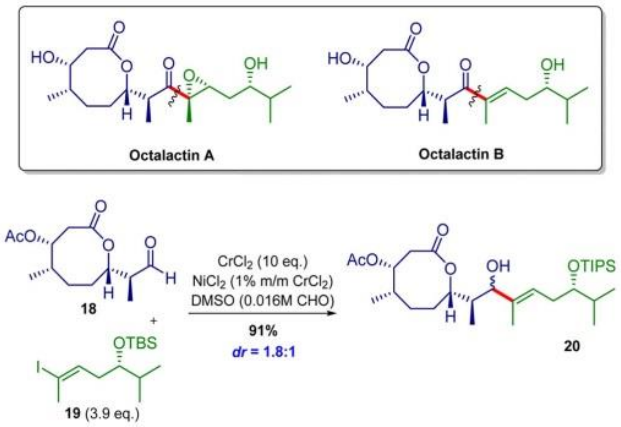


Figure 1. Natural products synthesized using intermolecular NHTK to obtain 1,2-disubstituted alkenes.

Scheme 9. NHTK Coupling in the Synthesis of Octalactins[67]



Norrisolide was synthesized using the NHTK reaction between a quaternary nonmethylated vinyl triflate and the corresponding aldehyde (Figure 2).[78]

3.1.3. Generation of the 3-Methyl-2-en-ol Scaffold. A common retrosynthetic disconnection for natural products bearing a 3-methyl-2-en-1-ol moiety is through the C−C bond between the hydroxylic position and the double bond (Scheme 2C) to give an aldehyde and the corresponding vinylic halide as precursors. These synthons can be linked easily using the NHTK methodology under mild and effective conditions. For this reason, this strategy was used for the synthesis of several important natural products. One relevant example is haterumalide NA, isolated by Uemura and co-workers from an Okinawan sponge.[79] This compound showed interesting biological activities, such as cytotoxicity against P388 cells in the micromolar range. After the first synthesis of *ent*-haterumalide NA methyl ester, the absolute stereochemistry of the natural

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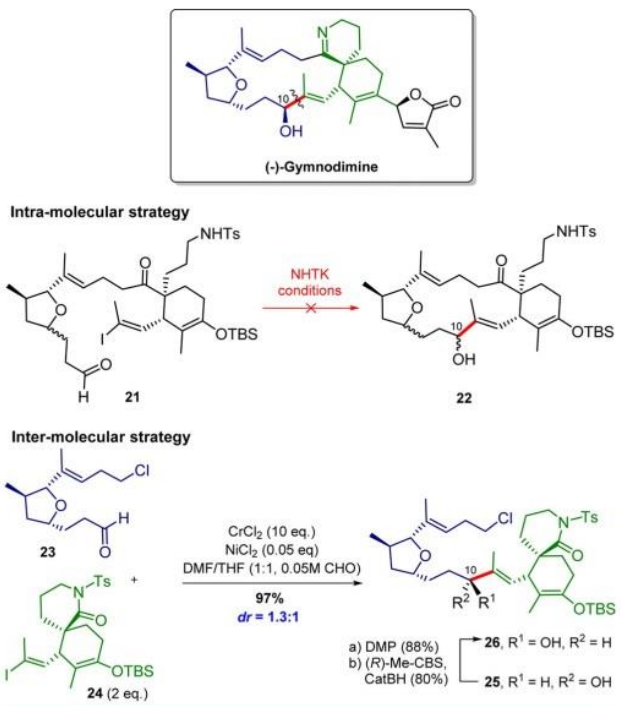
Scheme 10. Different Attempted Synthetic Strategies in the Synthesis of (−)-Gymnodimine[69,70]



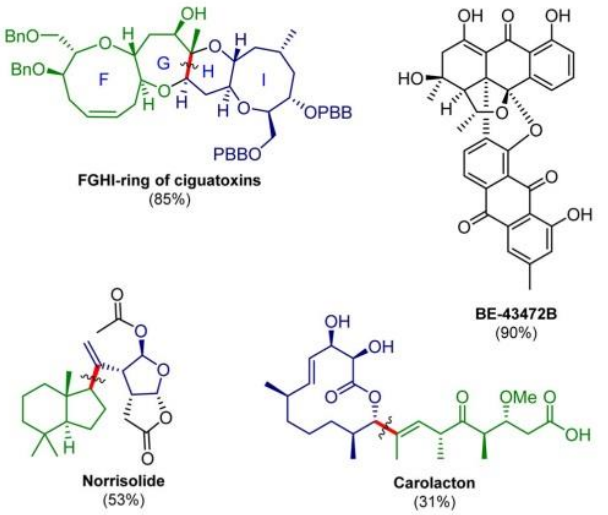
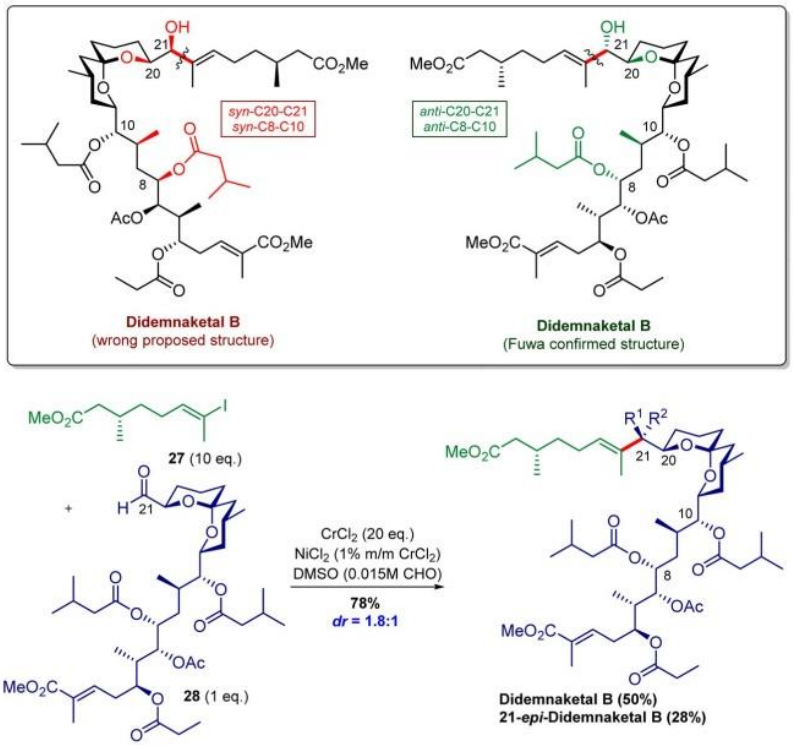


Figure 2. Natural products synthesized using intermolecular NHTK to obtain the 2-methyl-2-en-ol scaffold.

product was unambiguously confirmed.[80] Afterward, several improved or different syntheses of this fascinating natural product were reported.[81−83] All these synthetic routes have one thing in common, which is the use of NHTK methodology to link the carboxylic tail to the macrocyclic core. The different reaction conditions and their results are depicted in Scheme 12. As shown, over the years efforts to reduce the amount of chromium salts and the equivalents of iodide **30** have been performed. The optimal conditions used 6 equiv of **30** and 18.8 equiv of $CrCl_2$ (0.1% $NiCl_2$) without showing a significant decrease in the yield for the transformation.[82] Diastereoselectivity is also another interesting aspect that has remained common to all these total syntheses, mostly delivering the diastereomer with the same absolute configuration in C14 and C15. The driving factor to this substrate-controlled diastereoselectivity is

Scheme 11. NHTK Reaction as the Last Step in the Synthesis of Didemnaketal B[74]



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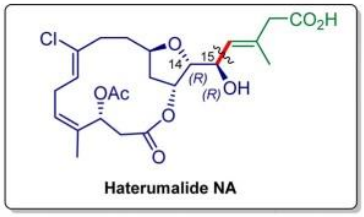
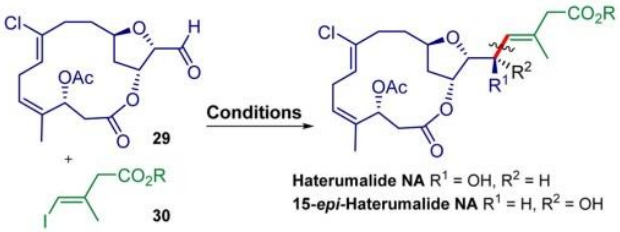
Scheme 12. Different Conditions and Results Obtained in the NHTK Reaction of Haterumalides Syntheses[80−83]





Conditions	Yield	dr (C_{14},C_{15})	Reference
80 eq. **30** - DMSO (0.004M) 170 eq. $CrCl_2$ (1%$NiCl_2$)	**57%** (2 steps)	1:11 (*S*,*R* : *S*,*S*)	80
30 eq. **30** - DMSO (0.01M) 90 eq. $CrCl_2$ (1%$NiCl_2$)	**30%** (2 steps)	n.r	81
n.r eq. **30** - DMSO (n.r) n.r eq. $CrCl_2$ (1%$NiCl_2$)	**50%** (2 steps)	1:10 (*R*,*S* : *R*,*R*)	83
6 eq. **30** - DMSO (0.011M) 18.8 eq. $CrCl_2$ (1%$NiCl_2$)	**49%** (NHTK)	n.r	82

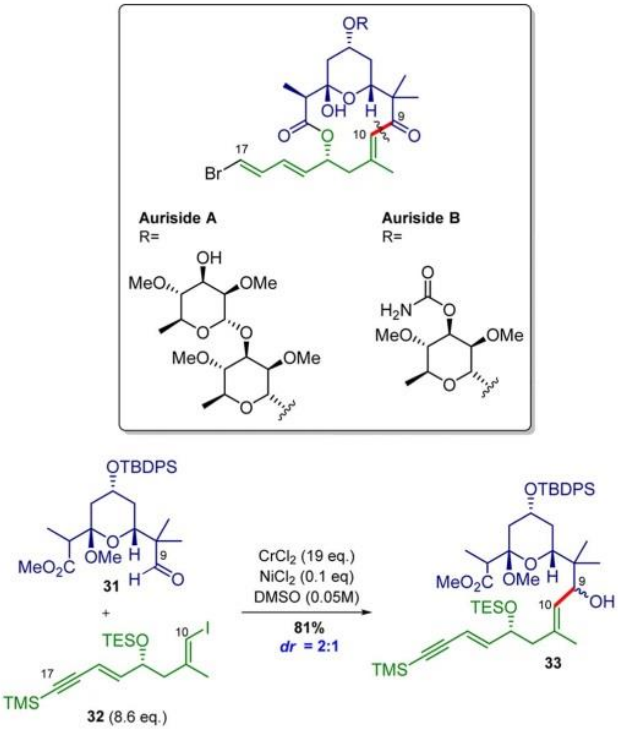
n.r = not reported — 2 steps include DMP oxidation + NHTK

the stereochemistry present in the THF ring, the substituent α with respect to the aldehyde.

One example where the 3-methyl-2-en-ol moiety was used only as intermediate in the synthesis for later modification is given in the total synthesis of marine macrolides aurisides A and B (Scheme 13). Both compounds showed cytotoxic activity in the low micromolar range against HeLa S3 cells. Interesting novel structural features include the bromine-substituted conjugated diene chain and the 14-membered lactone.[84] For their synthesis, Kigoshi and colleagues envisioned the formation of a C9−C10 bond by a NHTK reaction before the construction of the macrolactone scaffold.[85] A high excess of the coupling partner, halide **32**, and $CrCl_2$ was used to achieve good yield and modest stereoselectivity. The stereocontrol was not an important issue for this transformation because a later oxidation, with the subsequent loss of the stereocenter, was needed to install the carbonyl present in the natural product. An additional interesting aspect is the fact that position C17 is protected with an alkyne-TMS to avoid undesired NHTK reactions on the bromodiene. To complete the synthesis of aurisides A and B, nine and eight extra synthetic steps were necessary, respectively, including macrolactonization and coupling with the corresponding sugar.

Phormidolides[86,87] and oscillariolides[88] exhibit a synthetically challenging 3-methyl-2-en-1-ol moiety, and all the efforts[87,89−93] performed toward the total synthesis of phormidolides B and C will use coupling as a late-stage reaction to link the polyhydroxylated chain to the macrocyclic core. Some other natural products, containing the same structural moiety, successfully synthesized using intermolecular NHTK are (+)-massarinolin B[94] and the C31−C46 fragment of phorboxazole A (Figure 3).[95]

Scheme 13. NHTK Coupling in the Synthesis of Aurisides A and B[85]



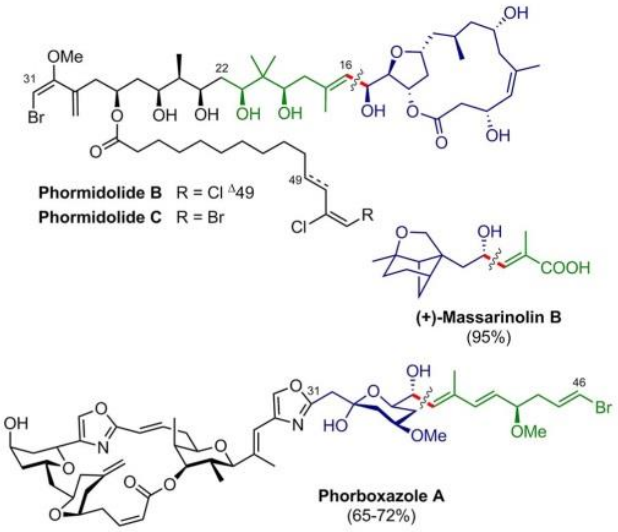


Figure 3. Structures of phormidolides B and C, (+)-massarinolin B, and phorboxazole A.

3.1.4. Generation of *gem*-Disubstituted 2-En-ols. A large number of natural products with a *gem*-disubstituted-alkenols structure have been reported in the literature. Synthetic efforts to construct this interesting scaffold have been facilitated by the introduction of NHTK methodology. Mainly, the NHTK reaction has been applied at an earlier stage to introduce a small fragment, which is modified later on in the synthesis.

Epothilones B and D have been thoroughly studied as promising compounds for the treatment of cancer (Scheme 14).[96] They interact with microtubules in the same fashion as Taxol-type compounds, causing fast and effective cellular death.

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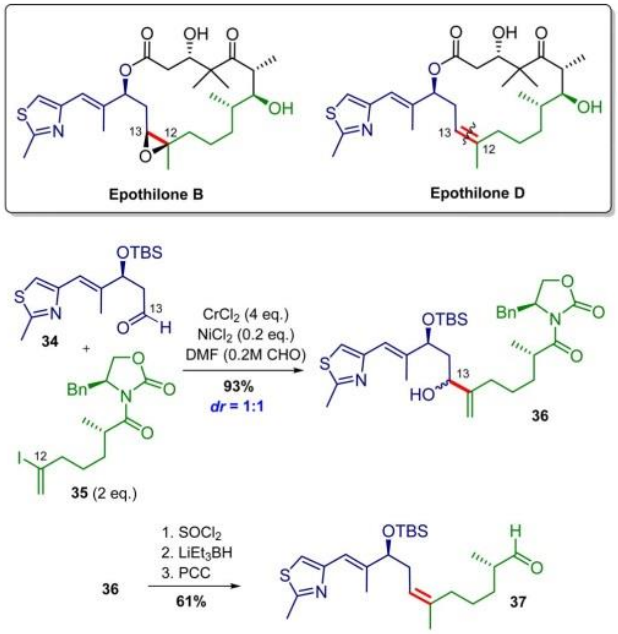
Scheme 14. NHTK Reaction Used in Taylor and Chen's Synthesis of Epothilones B and D[a] [102]



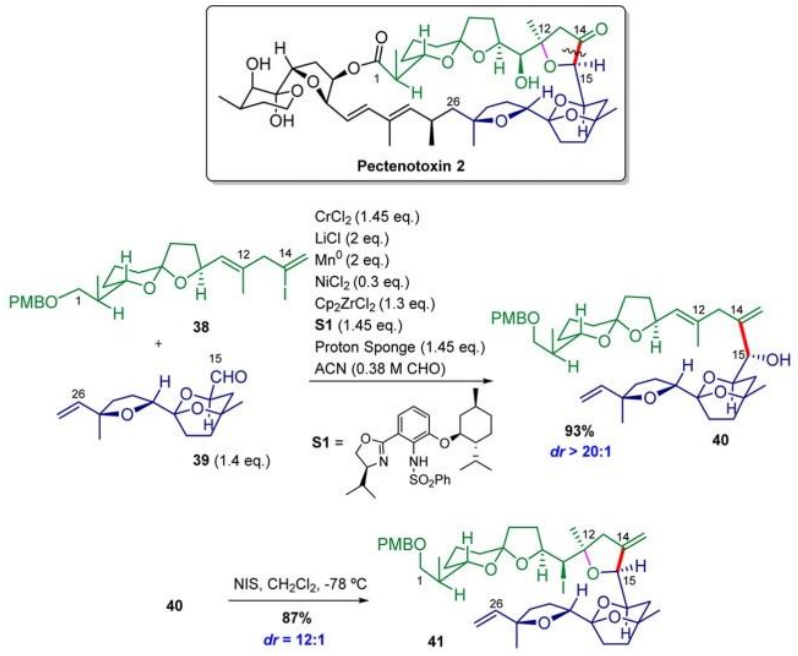
[a]Extra steps are required to build the C7−C21 scaffold.

Several total syntheses have been reported to date.[97−101] One of the most convergent strategies was designed by Taylor and Chen using NHTK as the key step to link fragments C7−C12 and C13−C21.[102] The reaction between **34** and **35** worked with exceptional yield, delivering allylic alcohol **36** without any kind of stereoselectivity. This is a new example where the lack of stereoselectivity in the formation of **36** was not important because the stereocenter is lost in the following steps by formation of alkene **37**. Then, seven and eight extra synthetic steps were carried out to have access to epothilones D and B, respectively, including aldol addition of fragment C1−C6, cyclization, deprotection, and double bond epoxidation.

Micalizio and co-workers[103] reported a spectacular strategy for the C1−C26 hexacyclic subunit of pectenotoxin 2, a rare marine polyether with interesting anticancer properties.[104] A catalytic enantioselective version of the NHTK reaction using the building blocks **38** and **39** was performed, rendering the desired diastereomer **40** in an outstanding yield (Scheme 15).[105] This example clearly illustrates the utility of the NHTK reaction to link two large multifunctionalized fragments in a very efficient and stereoselective fashion if reaction conditions are optimized. After several cyclization trials, a susbtrate-controlled iodoetherification rendered the target compound **41** bearing the THF heterocycle with very good yield and stereocontrol. Due to its high efficiency, this reaction tandem could be added to any synthetic route toward the synthesis of pectenotoxin 2 at any stage to construct the C12−C15 THF ring.

The previously described examples have, as synthetic objective, molecules lacking a *gem*-disubstituted-2-en-ol moiety in their structure. An example where this particular motif is present can be found in amphirionin-4 (AMP-4), which was isolated and structurally elucidated by Tsuda et al.[106] AMP-4 showed important biological activity, such as selective and potent proliferation activity on murine bone marrow stromal ST-2 cells. This can facilitate the use of this molecule in enhancing immune response to disease and bone regeneration. The first total synthesis of AMP-4 was performed by Britton and co-workers, using NHTK as the key late step to assemble the heterocyclic THF core to the remaining polyene tail (Scheme 16).[107] The first synthetic approach was based on a NHTK reaction between vinyl halide **43** and the corresponding aldehyde of the polyene tail **42**. The NHTK reaction worked really well in terms of yield and stereoselectivity, rendering a separable mixture of diastereomers.

Scheme 15. Synthesis of the C1−C26 Hexacyclic Moiety of Pectenotoxin 2 through Sequential Diastereoselective NHTK Coupling−Iodoetherification Cyclization[103]



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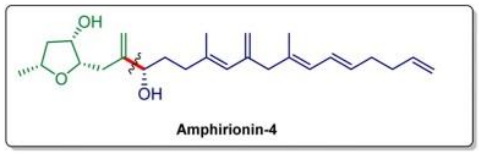
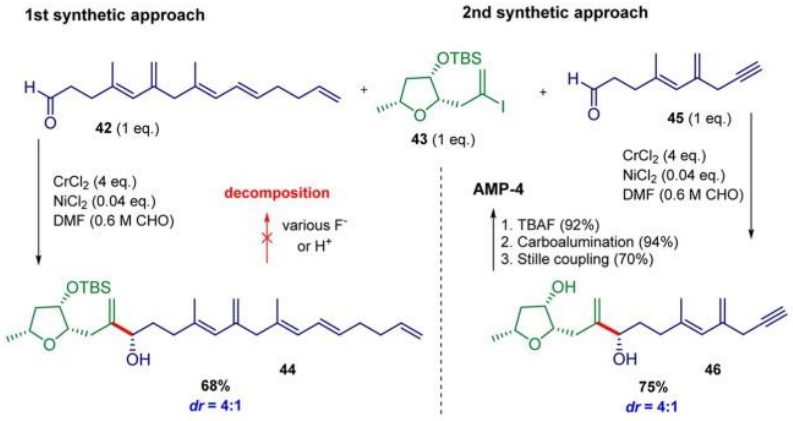
Scheme 16. Different Attempted Strategies in the Late Steps of the First Total Synthesis of Amphirionin-4[107]





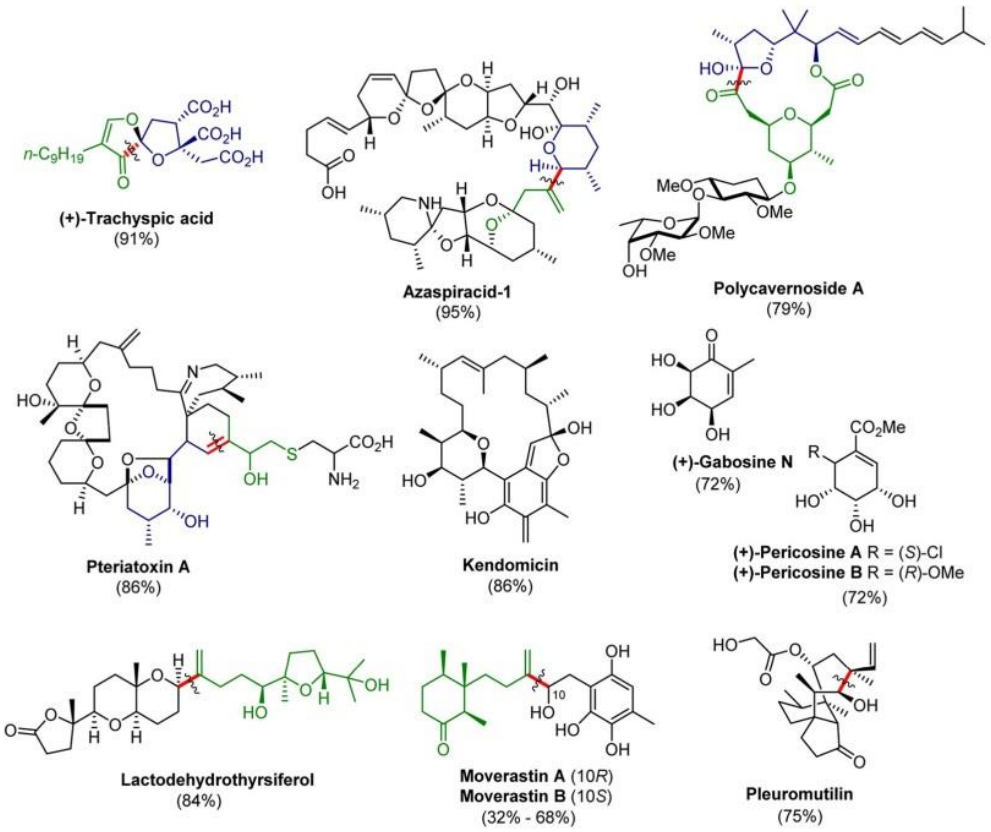


Figure 4. Natural products synthesized using intermolecular NHTK to obtain *gem*-disubstituted 2-en-ol scaffolds.

Unfortunately, all the attempts to remove the silyl protecting group in **44** produced decomposition of the starting material. A slightly longer and less convergent route was used to solve this problem. Maintaining the NHTK reaction as the key one, Britton and co-workers substituted aldehyde **42** with aldehyde **45**, containing a triple bond functionality, as precursor of the unstable polyene tail. The $CrCl_2/NiCl_2$ worked similarly in terms of yield and diastereoselectivity, and later deprotection under TBAF conditions worked with excellent yield. Installation of the rest of the polyenic chain was carried out with a straightforward sequence based on carboalumination and Stille coupling to render the natural product in a very effective manner. Months later, Ghosh and Nyalapatla reported the second enantioselective synthesis of AMP-4.[108] Interestingly, the last deprotection was

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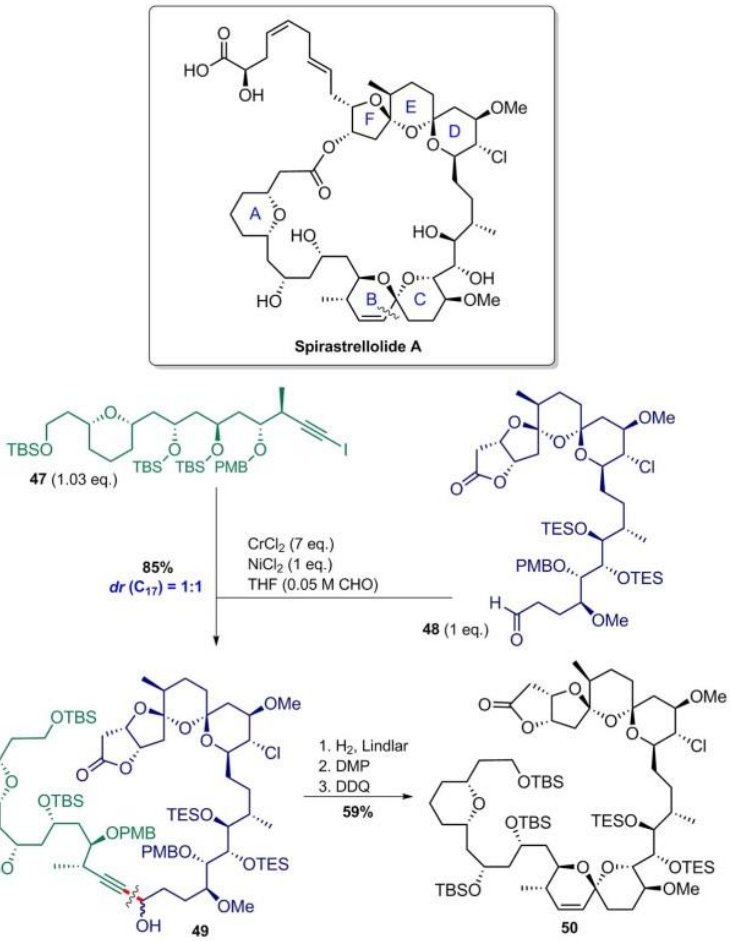
Scheme 17. NHTK Reaction Used in the Second-Generation Synthesis of Spirastrellolide A[130]



carried out with a 98% yield using simply TBAF, under the same conditions used in the first failed approach. In conclusion, both strategies worked well to accomplish the synthesis of this challenging natural product.

Many other products have been synthesized using NHTK to have access to *gem*-disubstituted alkenols, such as (+)-trachyspic acid,[109] azaspiracid-1,[110] polycavernoside A,[111,112] pteriatoxins,[113,114] kendomycin,[115] (+)-gabosine N,[116] lactodehydrothyrsiferol,[117] moverastin analogs,[118] (+)-pericosines A and B,[119,120] pleuromutilin,[121] palhinine A,[122] and (+)-pentandranoic acid A,[123] among others (Figure 4). In all these syntheses, NHTK cannot be considered the key step of the route, but it is still a useful tool to create C−C bonds under very mild conditions.

3.1.5. Generation of Propargylic Alcohols (Alkynylation). Triple bonds are not common motifs in natural products architecture. Nevertheless, the synthetic utility of substituted propargylic alcohols to construct spiroketalic compounds through cyclization is beyond any doubt. The reported uses of NHTK to create alkynyl alcohols motifs in the synthesis of natural products take advantage of this structure (Scheme 2E) and use it as a "chemical tool" to build more complex bicyclic compounds after cyclization. Therefore, the synthetic sequence NHTK−triple bond reduction−oxidation−spiroketalization will be very common in the examples described in this section.

Spirastrellolide A (SP-A) is a marine macrolide isolated from the Caribbean sponge *Spirastrella coccinea* with a potent and selective inhibition of protein phosphatase 2A (Scheme 17).[124] Concretely, SP-A inhibits this protein with an IC50 = 1 nM, and this shows its therapeutic utility to fight against cancer and other metabolic problems.[125] After its structure confirmation,[126,127] two total synthesis of SP-A have been reported by Patterson et al.[128−130] They used alkynyl alcohols to construct the spirocyclic units present in this complex molecule. However, it was only in the second-generation total synthesis that Patterson's group used NHTK to link two large multifunctionalized fragments.[130] They reported that "*after a degree of experimentation*" NHTK resulted to be the most effective method to obtain this union because of its mild reaction conditions. It is interesting to highlight that, due to the molecular complexity of both **47** and **48**, only a scarce excess of alkynyl halide was used, maintaining a high yield for the NHTK reaction. Compound **49** was subjected to Lindlar reduction, alcohol oxidation, PMB removal, and in situ spiroketalization to render **50**, in which rings B and C of the hexacyclic scaffold of SP-A had been generated. A similar spiroketalization strategy was followed in the final part of 7,8-dihydroaigialospirol synthesis by Yeun and Brimble (Figure 5).[131]

Gonzalez and Forsyth described the total synthesis of thyrsiferyl 23-acetate (T-23-A) using NHTK coupling to generate an alkynyl alcohol **53** precursor of pyranopyran moiety present in compound **54** (Scheme 18).[132] T-23-A was isolated from marine red algae of the genus *Laurencia*, showing interesting biological activities.[133] The NHTK reaction between aldehyde **51** and alkynyl bromide **52** gave a good yield of an

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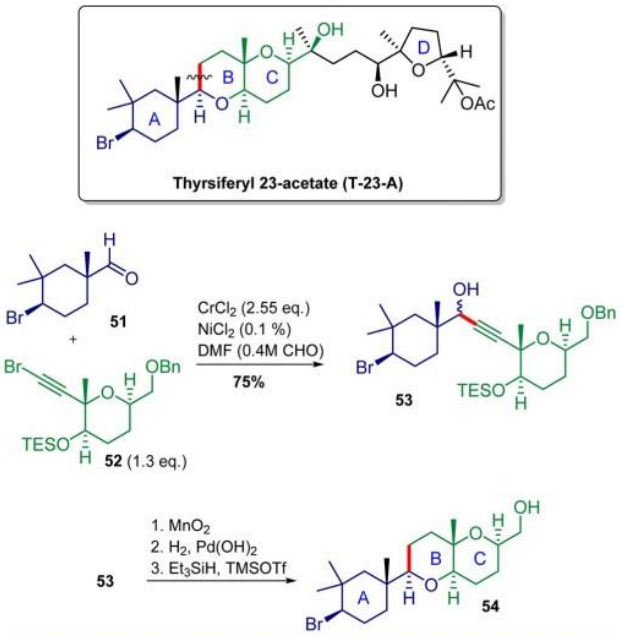
epimeric mixture of alcohols **53**. It is worth mentioning that this reaction was carried out at a 0.4 M concentration of aldehyde (considerably higher than normal). It was also demonstrated that alkynyl bromides are sufficiently reactive under NHTK conditions and the iodine derivative is not necessary. After this transformation, alkynyl alcohol **53** was subjected to oxidation, deprotection−triple bond reduction, and cyclization under Et_3SiH−TMSOTf conditions to reach **54**, the A−C tricyclic core of T-23-A, in a diastereoselective fashion.

Scheme 18. NHTK Reaction in the Synthesis of Thyrsiferyl 23-Acetate[132]



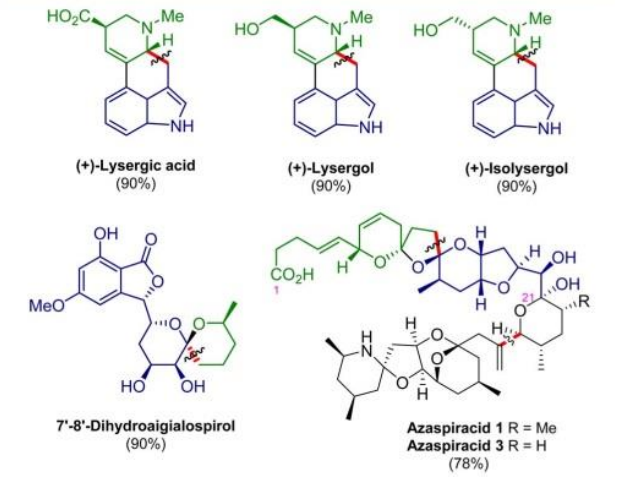
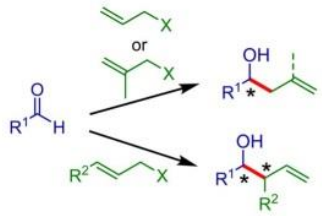


Figure 5. Natural products synthesized with a propargylic alcohol intermediate arising from an intermolecular NHTK reaction.

Other natural products successfully synthesized using similar methodologies are (+)-lysergic acid, (+)-lysergol, (+)-isolysergol,[134] and the C1−C21 domain of azaspiracids **1** and **3** (Figure 5).[135,136]

3.1.6. Generation of Homoallylic Alcohols (Allylation). Homoallylic alcohols are generated through chromium(II)-mediated allylation (Nozaki−Hiyama allylation) of an aldehyde with an allyl halide. The NH-allylation proceeds without addition of a catalytic amount of nickel, which shows sharp contrast to the other chromium(II)-mediated reactions in this review. If the allyl halide is monosubstituted or it is a *gem*-disubstituted vinylic compound, the resulting alcohol will have one new stereogenic center. On the other hand, if the double bond of the halide is a non-*gem*-disubstituted alkene, the reaction will create two new stereocenters (Scheme 19). Normally, allylations proceed

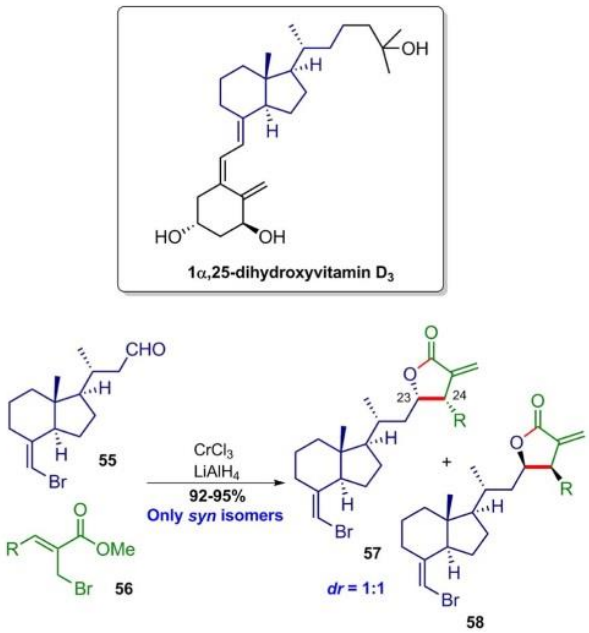
Scheme 19. Different Possible Products Arising from an Intermolecular NHTK Allylation



through six-membered closed transition states, where the aldehyde is chelated with the chromium atom and thus higher levels of stereocontrol are normally achieved, both in its inter- and intramolecular version.[2,137]

A nice and useful application of the NHTK reaction in total synthesis is Nozaki and co-workers' chromium-promoted *syn*-selective lactone generation.[138] This methodology consists of a intermolecular allylation between an aldehyde and a alkyl α-(bromomethyl)acrylate to in situ generate stereoselectively α-methylene-γ-butyrolactones. Due to its high yield and diastereoselectivity, this NHTK−lactonization sequence was useful to prepare a high number of simplified analogs of 25-dehydro-1-α-hydroxyvitamin-D_3 26,23*S*-lactone for biological tests (Scheme 20).[139] Relative stereochemistry of C23−C24 in compounds **57** and **58** was determined using NOE-1D experiments.

Scheme 20. Methodology Applied to the Synthesis of Vitamin D_3 Analogs[139]



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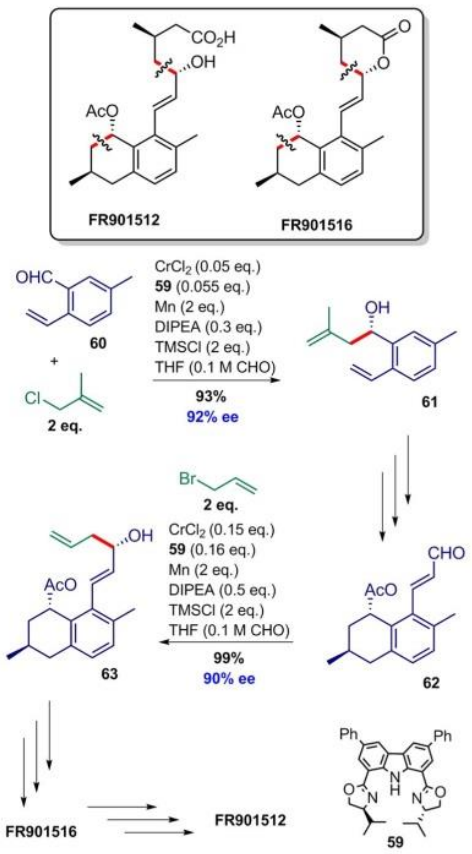
The use of catalysts that control the enantioselective facial addition of the allyl group is also possible, as demonstrated in the enantioselective total synthesis of FR901512 and FR901516, where the carbazol derivative **59** was used as catalyst (Scheme 21).[140] These compounds are strong 3-hydroxy-3-methylglutaryl

Scheme 21. Two Highly Efficient Enantioselective NHTK Allylations towards FR901516 and FR901512[140]



coenzyme A (HMG-CoA) reductase inhibitors. The synthetic strategy is interesting because NHTK is used twice to create C−C bonds with high yield and stereoselectivity. The reaction of benzaldehyde **60** with methanallyl chloride and the reaction between acrylaldehyde derivative **62** and allyl bromide with $CrCl_2$ and Mn, both with **59** as catalyst, afforded the homoallyl alcohols **61** and **63**, respectively, with excellent yield and stereoselectivities. These compounds are precursors of HMG-CoA reductase inhibitors FR901516 and FR901512. It is worth mentioning that this example shows the effectiveness of catalytic $CrCl_2$ procedures (high yield and ee values) for the synthesis of natural products, although until now they have not been very commonly used in total synthesis.[9]

Some other natural product, such as branimycin,[141] have been successfully synthesized using homoallylic alcohols as intermediates during the synthesis achieved through NHTK coupling.

3.2. Intramolecular Version. Particularities of the NHTK Cyclization Reaction

Medium to large sized ring formation is always a challenging aspect in the development of a total synthesis. Among all the possible synthetic tools available, the NHTK cyclization has emerged as a powerful strategy due to several positive factors. First of all, many effective methodologies can be applied to modify a specific substrate in order to obtain the haloalkene aldehyde for the cyclization. In general, haloalkene formation followed by an alcohol deprotection−oxidation sequence is used. Having both reactive functionalities in the same molecule avoids the use of extra equivalents, making the reaction more effective. Second, NHTK ring formation works in good to excellent yield and usually gives better stereochemical control than its intermolecular version, due to more stable transition states. Furthermore, to the best of our knowledge, polymerization of the starting material under reaction conditions has never been reported. Lastly, it has been demonstrated that the reaction works well with highly functionalized fragments, hence making it useful in late-stage synthetic steps.

In total synthesis, the vast majority of synthesized rings using the NHTK reaction can be divided into five groups, depending on the double-bond substitution (Scheme 22). In this section, each cyclic structure will be discussed and the most relevant uses of each reaction in total synthesis will be explained (Scheme 22A−F).

3.2.1. Cyclization To Obtain 2-En-ol Structures. The first total synthesis of a natural product where NHTK was used to perform cyclization to obtain a 2-en-ol scaffold was the synthesis of brefeldin by Schreiber's group (Scheme 22, A).[142] After that, several reports of cyclizations under NHTK conditions started to appear in the bibliography for total synthesis.[143−145] After all these pioneer studies came to light, a burst of examples started to be reported and the methodology began to be extended to many natural products syntheses. Several of these newer examples will be discussed in this section.

Due to the lack of extra substituents on the double bond, this architecture can be easily accessed through two trivial disconnections used in organic synthesis. A ring-closing metathesis (RCM) approach would break the molecule through the double bond, giving rise to the dialkene precursor (Scheme 23).[146] This approach can generally be applied, but the reaction has some drawbacks for stereoselective synthesis. For instance, harsher reaction conditions, an excess of catalyst, a lack of double bond geometry control, depending on the ring size, the possibility of nonselective cross metathesis events, and low reaction progression with hindered double bonds are some negative aspects of RCM. On the other hand, single C−C carbon disconnection to generate a haloaldehyde that can cyclize under NHTK conditions generally offers more advantages for total synthesis. Mild reaction conditions, the absence of polymerization, double bond geometry conservation, and an "atom economy" approach have shown $CrCl_2/NiCl_2$ coupling to be a more suitable strategy in total synthesis. Nevertheless, "not all that glitters is gold", because the NHTK method also possesses some possible problems, such as the lack of facial selectivity for the addition of organochromium. If the reaction fails to show substrate-controlled stereoselectivity, a widely used solution is subsequent oxidation plus enantio- or diasteroselective reduction to achieve the desired configuration at the hydroxylated position. Despite all these considerations, no general rule to choose the best method exists and each substrate will deliver different results, as will be further discussed in this section.

The work by Andrade in the synthesis of different desmethyl analogs of the interesting antibiotic telithromycin (TEL) is of valuable interest to illustrate the possibility of constructing 2-en-ol-containing cycles using RCM or NHTK methodologies (Scheme 24).[147] The reason for the synthesis of these simplified molecules was the search for active compounds against resistant

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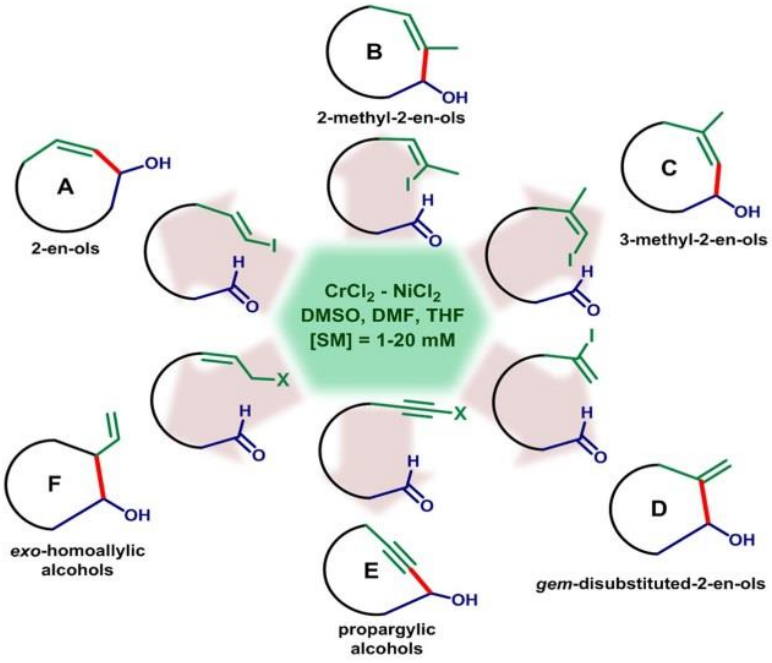
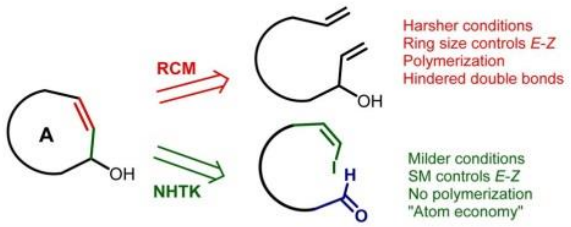
Scheme 22. Most Common NHTK Cyclizations Used in the Synthesis of Natural Products



Scheme 23. Comparison between RCM or NHTK Reaction To Generate 2-En-ol Cyclic Structures



bacteria strains that suffered a ribosomal A2058G mutation.[148] Elimination of the methylated position would mean, theoretically, the disappearance of the steric clash in the mutated active site and thus the end of the antibiotic resistance. In the synthesis of 4,8,10-tridemethyl-TEL, Andrade's group described that the macrocyclic scaffold **66** could be achieved through two similar synthetic pathways.[149] NHTK standard conditions (and posterior DMP oxidation) and second-generation Grubbs catalyst delivered heterocyclic compound **66** with similar yields. However, when a more hindered alkene was attempted, such as compound **68**, for the synthesis of 4,8-didemethyl-TEL bearing a methyl substituent in position 10, the reaction only progressed with moderate yield under NHTK coupling.[150] This is a good example for discussing the viability of both strategies. As is often the case, a fine-tuning optimization is needed for each strategy and a general rule does not exist. Another natural product where NHTK and RCM were tested and compared is (−)-dictyostatin.[151] In this other example, the NHTK methodology afforded even more advantages because, despite the moderate yield obtained, the reaction proceeded with stereoselectivity toward the desired diastereomer.

The example of telithromycin shows that in some cases the facial selectivity of the organochromium addition is not vital, because the generated alcohol in the NHTK reaction should be oxidized to afford the natural product. This kind of methodology (NHTK cyclyzation and oxidation) is used in many total syntheses, such as that of narbonolide,[152,153] 5-(*Z*)-7-oxozeaenol and its analogs,[154] (−)-atrop-abyssomicin C,[155,156] and sacrolide A[157] (Figure 6).

The best-case scenario for this type of cyclization occurs when the reactions take place with not only high yield for the cyclic compound but also a controlled stereochemistry for the aldehyde facial addition. Generally, these reactions occur under substrate-controlled diastereoselective processes, where the bulkiness or electronic properties of substituents close to the cyclization point dictate the stereochemical outcome of the transformation.

The synthesis of aspercyclides by Fürstner's group included an exquisite example where the NHTK cyclization worked exceptionally well in yield and stereoselectivity (Scheme 25).[158,159] In addition, after attempting a RCM approach, which in the end proved to be less effective, NHTK synthesis did work much better for the synthesis of these natural products. Generally, although NHTK reactions proceed through a nonchelated pathway, it has been reported that aldehydes bearing heteroatoms in the α position display variable degrees of diastereoselectivity.[10] In this specific case, this rare and outstanding high stereoselectivity is best explained by a Felkin−Anh chelated transition state (TS), which is very common in reactions with aldehydes with heteroatoms in the α or β position.[160,161]

This chelated TS is preferred even more by the contribution of the ortho substituents in each benzene ring. Because of this, the ester group is forced out of planarity restriction and the available conformational space is preorganized to obtain the mentioned TS. To confirm this theory, an analog of **70** lacking the *o*-methyl group was cyclized under identical conditions, obtaining a modest 3:1 diastereoselectivity. This total synthesis illustrates that each specific substrate will render different degrees of stereoselectivity, depending on small structural differences that are difficult to predict beforehand. However, as previously shown, almost complete stereoselectivity can be achieved under standard NHTK cyclization conditions.

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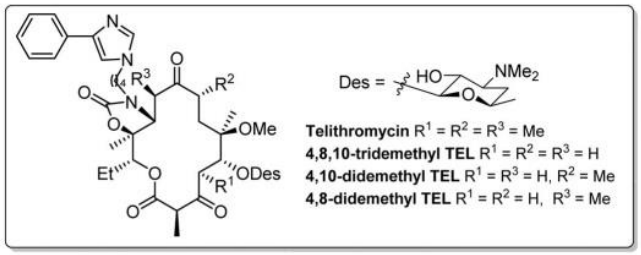
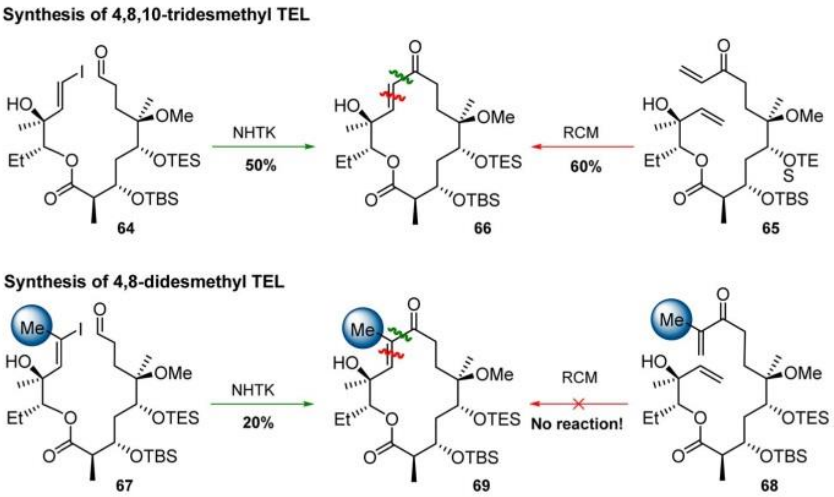
Scheme 24. Comparison between RCM and NHTK Macrocylizations in the Synthesis of Telithromycin Analogs[149,150]





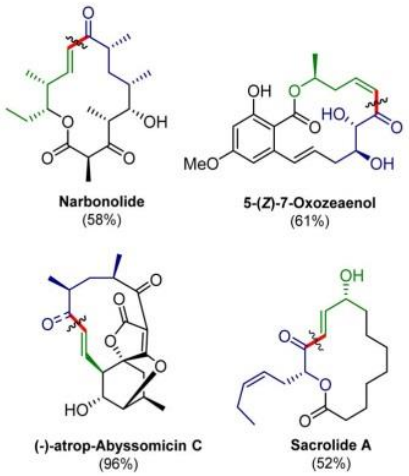
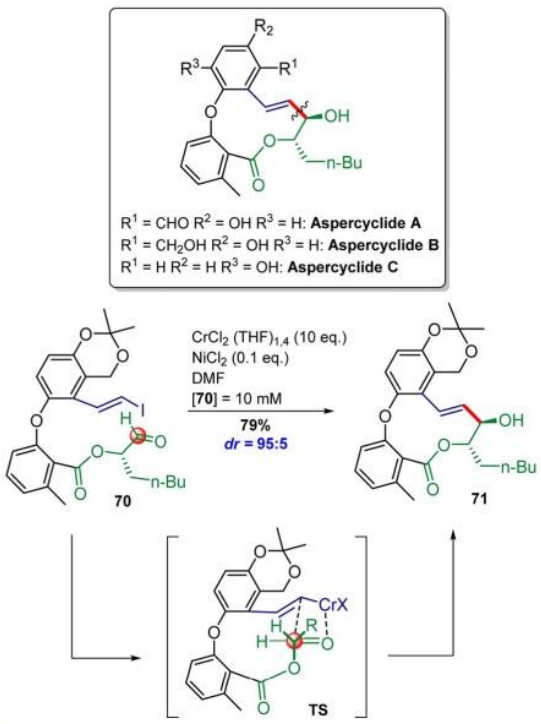


Figure 6. Synthesized natural products using the NHTK cyclization−oxidation sequence.

Another example where excellent levels of diastereoselectivity are achieved is the total synthesis of amphidinolactone A described by Yadav et al.[162] This work highlights the importance of the bulkiness of the protecting groups present in the vinyl halide couple partner. When the conversion depicted in Scheme 26 was performed on substrate **72**, the reaction worked with modest facial selectivity, but when OBn was replaced by the bulky OTBDPS, the reaction delivered exclusively the desired C11-(*S*)-diastereomer **75**. Computational data corroborated the change in diastereoselectivity when the bulkiness of the protecting group on C8 was modified.[162]

As a general issue, cyclization under NHTK conditions can be performed at higher concentrations than in other common

Scheme 25. Stereoselective Macrocylclization in Fürstner's Synthesis of Aspercyclides and the Proposed Transition State[159]



methods used in total synthesis, such as macrolactonization. The synthesis of an hybrid aplyronine A−mycalolide B compound by Kigoshi and colleagues is an example of this (Scheme 27).[163] In

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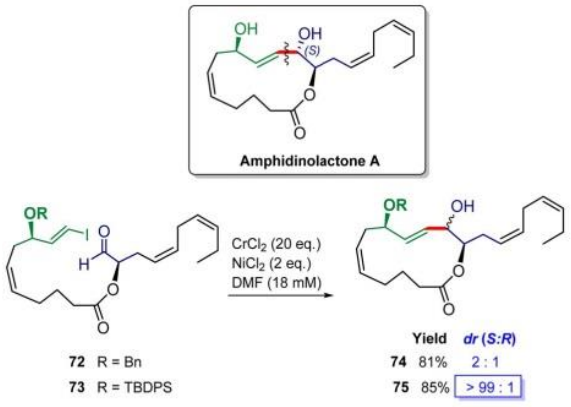
Scheme 26. Protecting-Group-Dependent Diastereoselectivity in the Synthesis of Amphidinolactone A[162]



it, condensation of acid **76** and alcohol **77** through standard Yamaguchi conditions,[164] selective TBS removal, and subsequent oxidation afforded NHTK cyclization precursor **78**. Next, several cyclization conditions were tested in which the concentration of **78** and the $CrCl_2$ equivalents were changed. First, a diluted 1 mM concentration of $CrCl_2/NiCl_2$ in DMSO was used, obtaining both C19 diastereomers in high yield. The reaction works with the identic excellent outcome using a higher 10 mM concentration of **78**, even when the proportion of $CrCl_2$ is reduced. They reported that "*In our aplyronine A synthesis,*[165] *construction of a similar macrolactone via the Yamaguchi method required high-dilution conditions (c = 0.39 mM), which makes this intramolecular NHK* reaction *without the use of high-dilution conditions much more convenient.*"

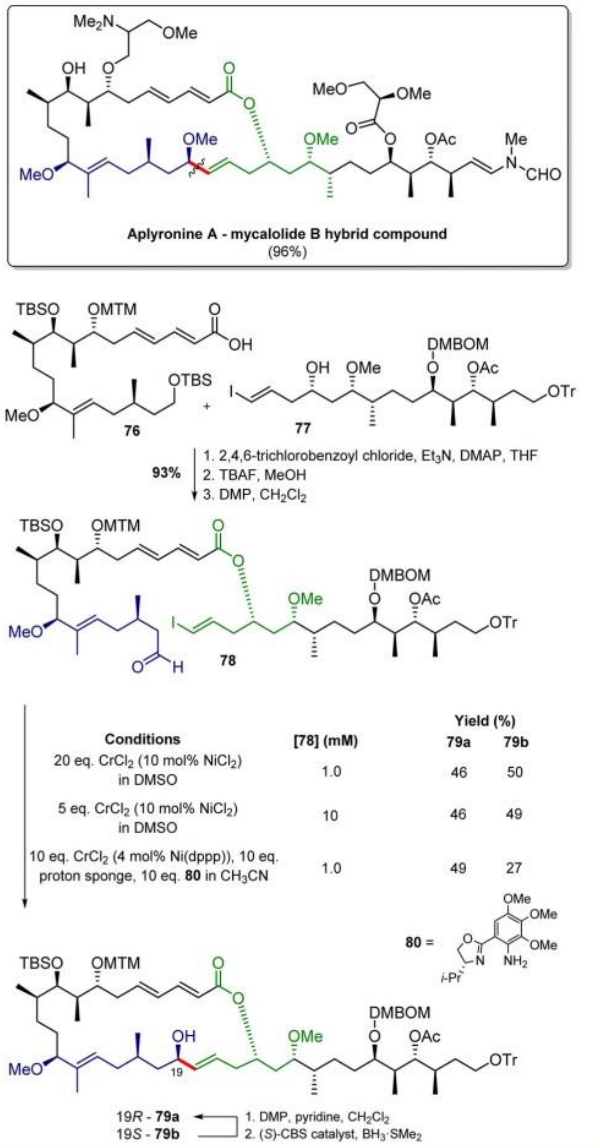
Unfortunately, due to the absence of bulky stereocenters near the cyclization point, the reaction does not show any stereoselectivity. A catalytic asymmetric version using chiral catalyst **80** was tried, but poor stereocontrol was achieved, thereby showing its inefficiency for this specific substrate **78**. After cyclization, the 1:1 diastereometric mixture of **79** was converted into **79a** via oxidation and enantioselective CBS reduction with high yield.

Some other relevant molecules that have been accessed following this NHTK cyclization methodology to reach a 2-en-ol macrocycle are calystegines B_2 and B_3,[166] cochliomycins A and B,[167] 3,6-dihydroxydec-4-enolides,[168] analogs of dictyostatin,[169] modiolide A,[170] the spirotetracyclic carbon core of mangicols,[171] and aspinolide B (Figure 7).[172]

3.2.2. Cyclization To Obtain 2-Methyl-2-en-ol Structures. Several members of the epothilone family, sharing the same mechanism of action as taxol's microtubule-stabilizing capability, inducing cytotoxicity, were isolated from the cellulose-degrading myxobacterium *Sorangium cellulosum*.[96] Danishefsky and co-workers described the total syntheses of epothilones A and B (Scheme 28),[173,174] and this was followed by the first in vivo evaluations published after conductance of in vitro studies.[175,176]

The Suzuki reaction was the key step in the synthesis of epothilone 490. An alternative macrocyclization reaction was necessary for the introduction of heteroatom functionalities on C11, and the NHTK reaction was the proper reaction for that. Oxidation of vinylborane **82** with trimethylamine *N*-oxide gave aldehyde **83**. There were few examples in the literature of NHTK macrocyclization larger than a 12-membered ring, and after some

Scheme 27. Synthesis of a Hybrid Aplyronine A–Mycalolide B Compound (NHKT cyclization under no-high-dilution conditions)[163]



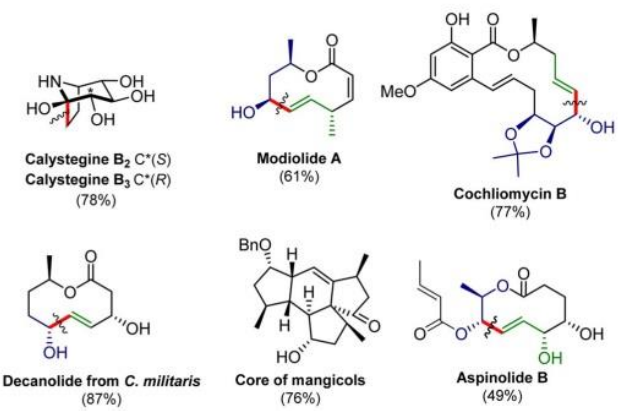


Figure 7. Natural products obtained using NHTK cyclization to obtain 2-en-ol structures.

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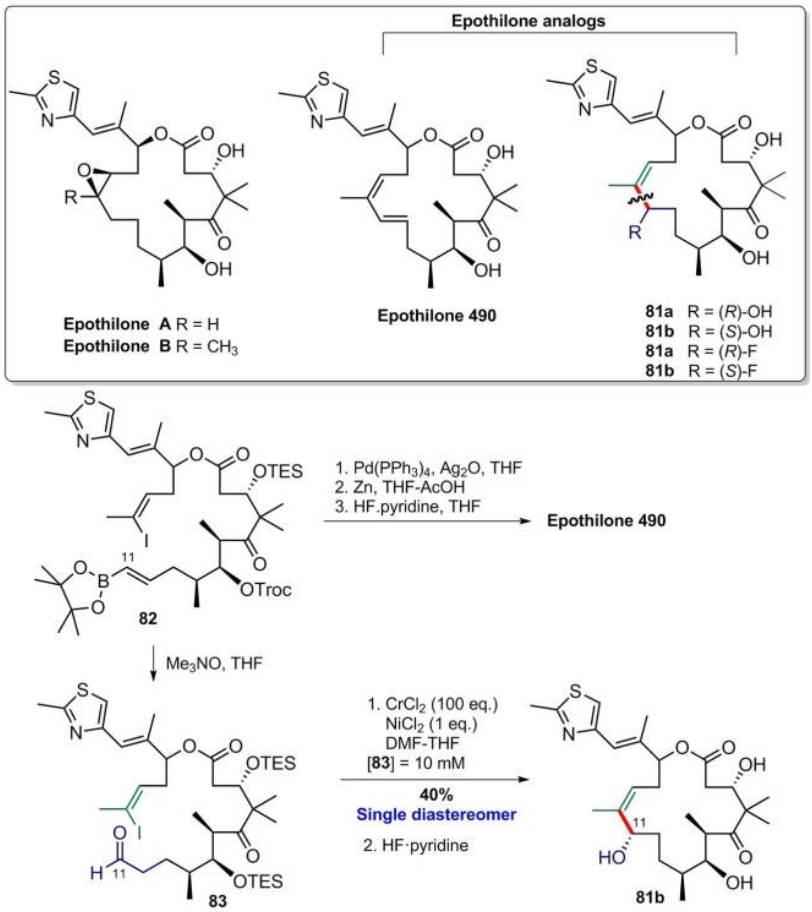
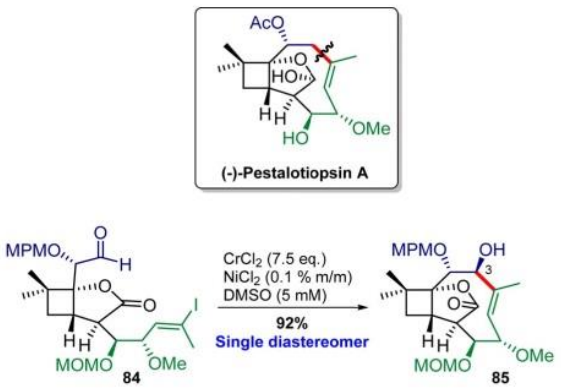
Scheme 28. Synthesis of Epothilone B Analogs[173,174]



experimentation, modified Uguen conditions were used.[144] The macrocyclization proceeded smoothly and produced only one isolated diastereomer in moderate yield that after deprotection gave epothilone analog **81b**.

The construction of the highly strained (*E*)-cyclononene ring of (−)-pestalotiopsin A, the antipode of the natural product, was performed by Tadano and colleagues using as a key step a NHTK macrocyclization with excellent yield and stereoselectivity (Scheme 29).[177] Interestingly, diastereoselectivity is not important for this synthetic sequence, because the nascent hydroxyl groups is removed later in the process to reach the (−)-pestalotiopsin A scaffold. The high yield of the **84** macrocyclization is remarkable considering the highly strained ring formed. The removal of the generated hydroxyl group at C3 in **85**, protecting group removal, and interchange of functional groups rendered (−)-pestalotiopsin A.

Scheme 29. Construction of the (*E*)-Cyclononene Ring of (−)-Pestalotiopsin A[177]



Some other interesting natural products obtained using this NHTK cyclization strategy are neodolabellane-type diterpenoids[178,179] or the interesting eight-membered enone aquatolide.[180−182]

2.2.3. Cyclization To Obtain 3-Methyl-2-en-ol Structures. Cycles with the motif (*E*)-3-methyl-2-en-ol are present in a large number of interesting natural products. To prepare the cyclization substrate, generally, the methyliodoalkene moiety is installed, and then the protection of the oxygenated position is removed and the free alcohol oxidized to obtain the proper aldehyde. The alkene moiety is usually obtained from a terminal alkyne via carboalumination with $AlMe_3$ plus final iodination.[183,184] Depending on the stability of the Lewis acid substrate, this transformation is performed earlier or in the last stages of the synthesis. The following examples will illustrate these considerations and show different results in the synthesis of interesting natural products.

An effective use of NHTK methodology to synthesize this kind of cyclic scaffold was reported in the total synthesis of *ent*-nigellamine A_2 by Ready and co-workers (Scheme 30).[185] By applying modified Nicolaou conditions[186] to compound **86** and using ultrasound sonication, the tricyclic scaffold **87** was

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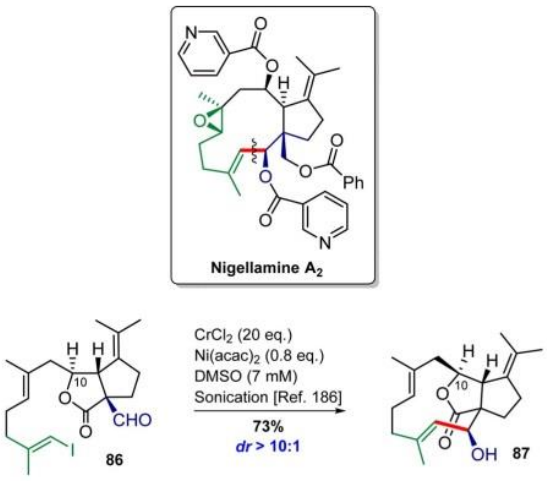
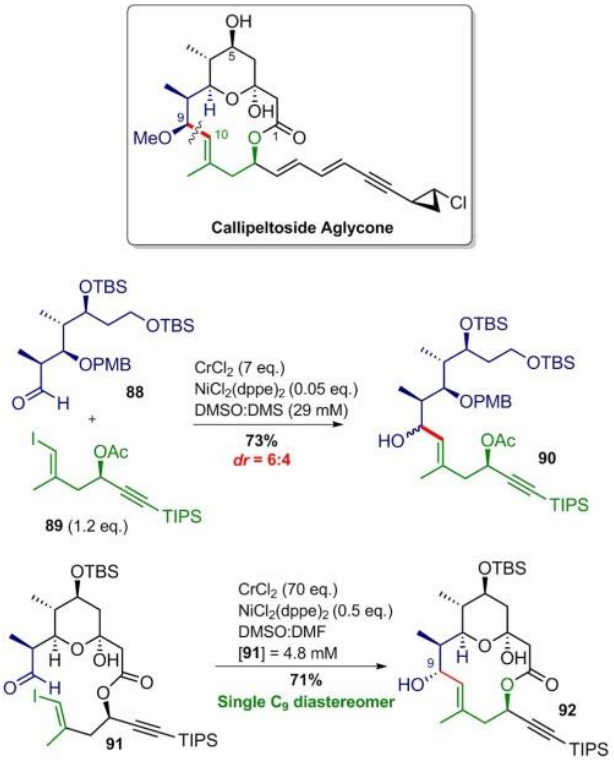
Scheme 30. Highly Stereoselective and Efficient NHTK Cyclization on the Synthesis of *ent*-Nigellamine A_2[185]



obtained with high yield and almost complete diastereoselectivity. It is worthwhile to mention that this cyclization works remarkably well despite "*the hindered nature of the aldehyde component and the formation of a trans-fused ring system*". The presence of a rigid lactone on the C10 stereocenter of **86** helps to rigidify the transition state, thus delivering compound **87** in high yield and facial selectivity.

The importance of structural restrictions in stereoselectivity in the cyclization process is clearly observed in the formal synthesis of the callipeltoside aglycone (Scheme 31).[187] To illustrate this

Scheme 31. Stereoselective Differences Using Intra- or Intermolecular NHTK in the Synthesis of the Callipeltoside Aglycone[187]



general idea, the same C9−C10 bond was formed using NHTK coupling but in an intramolecular fashion. Coupling of aldehyde **88** and iodoalkene **89** under NHTK conditions delivered the desired compound **90** in good yield but poor stereocontrol. On the other hand, using the cyclization precursor **91**, bicyclic structure **92** was obtained with similar yield but total stereocontrol toward the C9-(*R*)-isomer. Unfortunately, the reaction to obtain **92** gave the opposite stereochemistry at C9 compared to that present in the aglycon of the natural product; however, the importance of organized transition states derived from cyclic structures has been clearly demonstrated.

Some other natural products successfully synthesized by applying NHTK cyclization to obtain a 3-methyl-2-en-ol scaffold with good results in terms of yield and stereoselectivity are phomactins A−D,[188] (±)-phomactin G,[189] nitiol,[190] and the pestalotiopsin skeleton (Figure 8).[191]

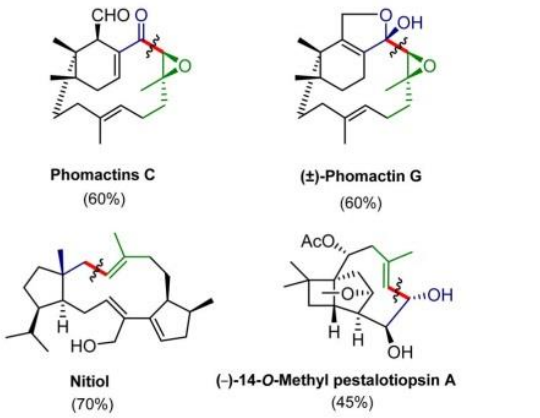


Figure 8. Natural products obtained through 3-methyl-2-en-ol structures derived from NHTK cyclization.

3.2.4. Cyclization To Obtain *gem*-Disubstituted 2-En-ol Structures. NHTK cyclization to generate an exocyclic homoallylic alcohol has been widely used with generally very good results in terms of yield and stereoselectivity. One interesting and useful application of this cyclization was described in the total synthesis of briarellins E and F by Overman and co-workers, where the cyclization was envisioned as the last step of the synthesis (Scheme 32).[192,193] The nine-membered ring is efficiently closed under standard NHTK conditions, and high dilution gives the natural product briarellin E as a single diastereomer with high yield. It is also remarkable to point out that cyclization of substrate **93** works well in the presence of an unprotected alcohol. Extra Dess−Martin oxidation delivered briarellin F. Very similar cyclizations with almost identical results were performed to obtain sclerophytin A[194,195] and (−)-7-deacetoxyalcyonin acetate.[196]

Vibsanins A−F were isolated from the leaves of *Viburum awabuki*, which has been used for many years as fish poison for fishing (Scheme 33).[197] Once every compound was isolated, only vibsanin A was demonstrated to be toxic for fish. Recently, the first total synthesis of this interesting natural product was reported by Takao et al.[198] In this work, the formation of the 11-membered ring occurs through standard NHTK cyclization of **94** to deliver compound **95** as a single diastereomer in high yield. However, the stereoselectvity is not important, because the new stereocenter created during the NHTK is removed in later stages of the process. Allylic rearrangement using Mitsunobu

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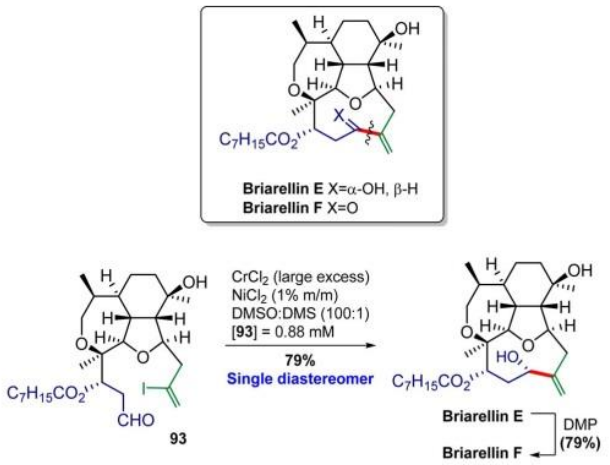
Scheme 32. Last Step in the Synthesis of Briarellin E and F[192,193]

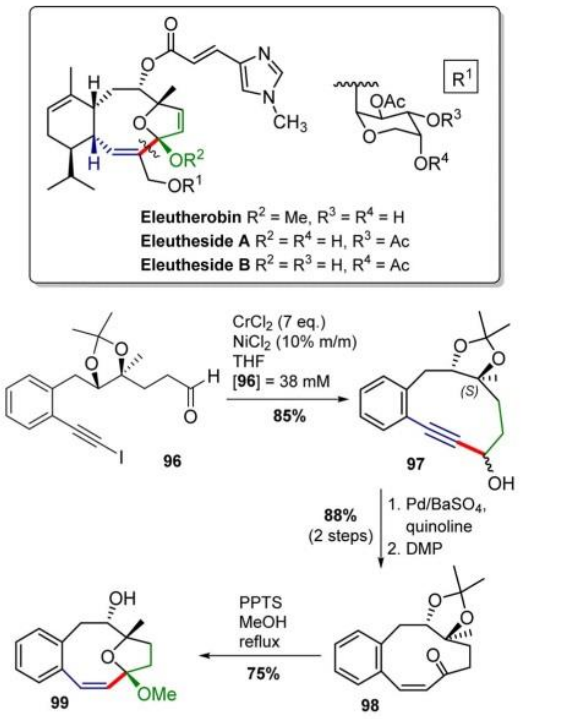


conditions and final ester hydrolysis delivered the natural product with final high yield processes.[199] A similar final strategy was also followed in a recent synthesis of cristaxenicin A.[200]

Sometimes $CrCl_2$–$NiCl_2$ soft Lewis acidic conditions are useful to perform two desired transformations in the same reaction, as was the case in the stereoselective construction of the ABC-ring of fusidane triterpenes. In it, simultaneous NHTK cyclization and dimethylacetal deprotection occurred in the same reaction in 70% yield, hence rendering the desired intermediate for the synthetic process.[201] (−)-Subincanadines A and B were successfully synthesized by Suzuki and Takayama using this type of NHTK cyclization.[202]

3.2.5. Cyclization To Obtain Propargylic Alcohols. As was previously described in section 3.1.5, the cyclic propargylic alcohol motif is not commonly present in natural product architectures; however, this motif may be a useful and versatile synthetic intermediate. The NHTK reaction is, by far, the procedure of choice when this cyclization has to be performed due to its efficiency and its mild conditions. As an example, Scheme 34 shows an original approach toward a 10-membered ring with eleutheside functionality in an attempt to obtain simplified analogs of the natural products that maintain the cytotoxic activity. Bermejo and co-workers describe the NHTK cyclization of iodoalkyne **96** under standard conditions to render **97** as a mixture of epimers.[203,204] It is worth mentioning the high

Scheme 34. Synthesis of the Tricyclic Core of the Eleutherobin–Eleutheside Family[203,204]

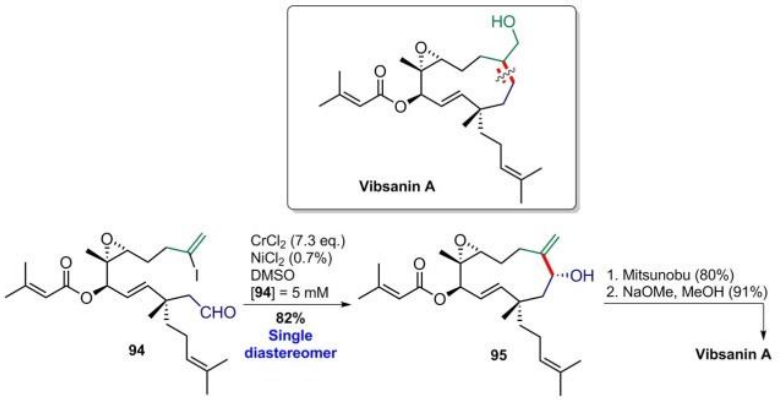


concentration used to cyclize without reported observation of dimeric species. Compound **97** was transformed into a single diastereomer via triple bond reduction and oxidation to obtain ketone **98**, which under acidic deprotective conditions suffered in situ cyclization to construct the THF-fused moiety of compound **99**. This molecule is a simplified analog of the oxatricyclic ring system scaffold present in this family of natural products that can be obtained in a few high-yielding synthetic steps.

Takahashi and co-workers described a study toward the synthesis of the tetracyclic skeleton of landomycinone in which the enediyne precursor for Masamune–Bergmann cyclization is prepared using NHTK reaction.[205]

3.2.6. Cyclization To Obtain *exo*-Homoallylic Alcohol Structures. NHTK is a very versatile methodology that enables the formation of new cycles through an allylic Barbier-type cyclization. These cyclizations have been used since the NHTK

Scheme 33. Macrocyclization in the Synthesis of Vibsanin A[198]



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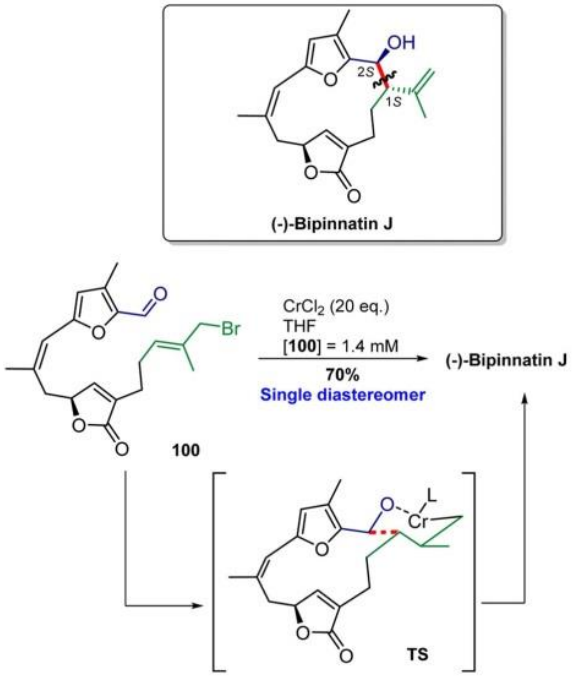
reaction was discovered to prepare natural products, such as asperdiol[206] and gorgiacerone.[207] The resulting products, the architecture of which is present in several natural products, are, in general, cyclic structures with an exocyclic vinyl or methylvinyl moiety. It is worthwhile to mention that in this type of allylic cyclization, two stereocenters are created simultaneously, and therefore, the use of diasteroselective procedures plays a very important role. Luckily, it has been described that when allyl halides are treated with Cr(II), the generated reduction product is always an (*E*)-allylic chromium(III) species, regardless of the geometry of the starting alkene.[1] Furthermore, chromium−aldehyde chelated closed six-membered transition states[2,137] and inherent structural restrictions of cyclization contribute to render the reaction product with high levels of diastereoselective, as will be described later in this section.

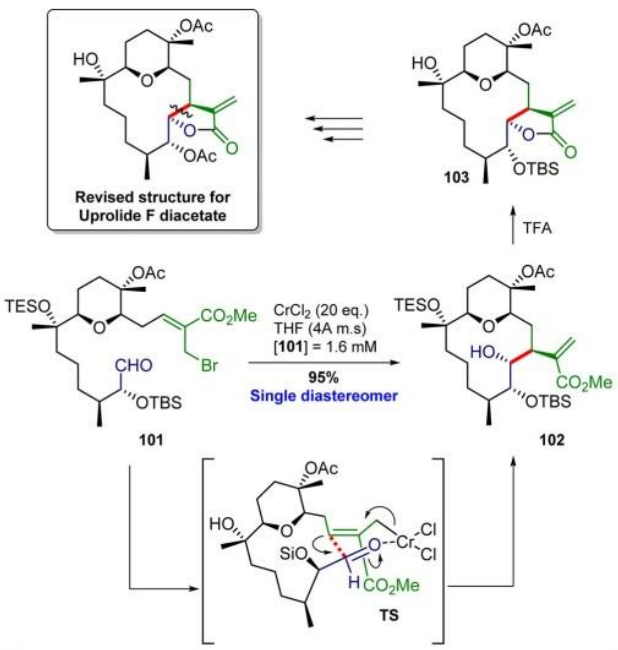
For example, in the total synthesis of (−)-bipinnatin J by Pattenden and co-workers, complete diastereoselective $CrCl_2$-promoted cyclization is used as the last step of the synthesis (Scheme 35).[208] A very stable chairlike TS is thus proposed as the main cause for the complete diasteroselection achieved in the transformation of **100** into (−)-bispinnatin J.

Scheme 35. Last Step in the Total Synthesis of (−)-Bipinnatin J[208]



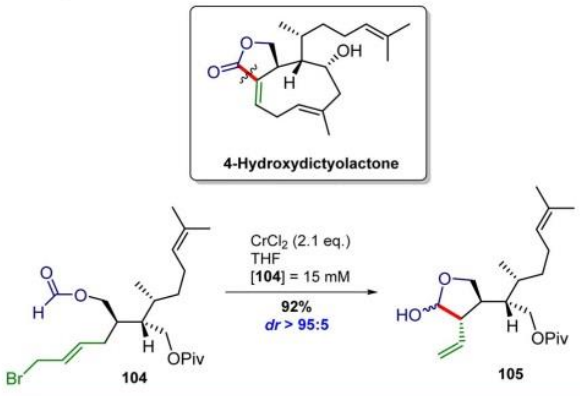
This NHTK variant was very efficiently utilized in the synthesis of uprolide F diacetate by Zhu and Tong (Scheme 36).[209] In the synthetic process, allyl bromide **101** was cyclized to obtain alcohol **102** with almost quantitative yield and total diastereoselectivity for the two created stereogenic positions. This impressive conversion was possible thanks to a Zimmerman−Traxler TS that preorganized the resulting stereochemistry in product **102**. Next, acidic treatment of **102** caused intramolecular lactonization, rendering the uprolide F scaffold **103** in a very efficient manner starting from **101**. A similar type of cyclization was used also in the total synthesis of another member of the family, uprolide D.[210]

Scheme 36. NHTK Cyclization in the Total Synthesis of Uprolide F and the Proposed TS[209]



Another interesting application of these allylic cyclization processes was reported during the synthetic studies toward xenicane diterpenes.[211] Williams and co-workers reported the first NHTK cyclization between an allyl bromide and a formate ester to obtain a lactol. Allyl bromide **104** undergoes $CrCl_2$-mediated cyclization to obtain compound **105** as a single diastereomer, offering versatility and efficiency for the stereoselective synthesis of five- and six-membered lactols and related derivatives (Scheme 37).[212] In this work, a very complete six-membered TS analysis is postulated to justify the stereochemical outcome of the reaction. It is worth mentioning that this kind of cyclization worked at higher concentration than normal without observation of dimerization products.

Scheme 37. First Lactol Formation through a NHTK Reaction in the Synthesis of 4-Hydroxydictyolactone[212]



Another relevant total synthesis where this kind of cyclization was performed is that of (+)-*Z*-deoxypukalide by Pattenden and co-workers.[213]

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4. SUMMARY AND CONCLUSIONS

As previously described in this review, a large number of different scaffolds found in interesting molecules can be efficiently obtained through NHTK methodology. In general, the yield of the transformations is highly substrate-dependent and variable, but if all the synthetic requirements, such as solvent polarity, dryness, and stoichiometric ratio, are strictly taken into account, the reaction offers good to high yields.

An interesting and important factor for a reaction to be useful in total synthesis is its stereoselectivity. Although in the recent years great advances have been achieved in chiral NHTK catalysts, there is a need for a universally easily synthesizable chiral catalyst to tune the stereochemical outcome of the NHTK reactions, especially in the intermolecular version. This catalyst universality is difficult to achieve, because chirality in the starting materials will be more important that the possible chiral catalytic effect. This is why, nowadays, substrate-controlled chiral induction with standard $CrCl_2$−$NiCl_2$ conditions is still mainly used in the synthesis of natural products

Ideal reactions do not exist; therefore, NHTK coupling has some relevant drawbacks that will have to be dealt with in the near future. From a "green chemistry" point of view, the use of an excess of toxic chromium salts generates technical difficulties, especially when a specific transformation needs to be scaled up. To address this problem, several works reporting catalytic chromium versions of the NHTK reaction have been published. However, it is necessary to implement these methodologies in the normal routine work of a synthetic chemist. For that, easy-to-perform procedures and high-yield conversions need to be achieved using catalytic amounts of chromium, independent of the substrate used. Discovery of active chromium-supported catalyst or the use of recyclable chromium precatalysts could be attractive research lines to improve one of the problems of this transformation.

Although the reaction was discovered as its intermolecular variant, cyclization under NHTK conditions has been widely used in the recent years due to highly appealing factors from a synthetic point of view: (1) It is easy to obtain stable molecules with both aldehyde and haloalkene functionalities. (2) There is no need to use an excess of coupling partners. (3) A generally higher stereoselectivity is enjoyed than for intermolecular reactions. (4) There are higher yields than for its corresponding bimolecular analogue. (5) Polymerization products are absent. (6) The standard cyclization concentration ranges between 1 and 20 mM, facilitating the cyclization of linear precursors in relatively high concentration. This is an important factor to scale up synthetic processes. In comparison to other cyclization processes, NHTK affords this possibility without observing polymerization products.

To summarize, the NHTK reaction is an incredibly useful tool for scientists working in total synthesis. Its most significant feature is the easy preparation of allylic, homoallylic, propargylic alcohols precursors, even as motifs of highly functionalized molecules, under mild conditions and high yield. As demonstrated in this review, a vast number of total syntheses have been possible thanks to the discoveries of Nozaki, Hiyama, Takai, and Kishi. The future of this remarkable chemical transformation will rely both on its continuous use in total synthesis and further research to solve the small problems associated with its application.

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Notes

The authors declare no competing financial interest.

Biographies

Alejandro Gil obtained his degree in chemistry and a M.Sc. in applied and pharmacological chemistry from the University Jaume I (Castelló de la Plana, Spain) between 2006 and 2013. In January 2014, he joined the group of Prof. Fernando Albericio and Prof. Mercedes Alvarez to perform his doctoral studies in a project aimed at the total synthesis and structural determination of the marine natural products phormidolides B and C.

Fernando Albericio is a professor at the University of Barcelona, a research professor at the University of KwaZulu-Natal in Durban, South Africa, and a visiting professor at King Saud University in Riyadh, Saudi Arabia. His major research interests cover practically all aspects of peptide synthesis (new reactions, building blocks, coupling reagents, solid-phase supports, protecting groups, and linkers) and combinatorial chemistry methodologies, as well as the synthesis of peptides and small molecules with therapeutic activities. Furthermore, he is also involved in developing new systems for drug delivery and strategies for diagnostics as well. He has published over 850 papers, filed more than 55 patents, and has coauthored four books. He is editor-in-chief of several scientific journals and is on the editorial board of several others. Recently, he has been honored with a Doctorate Honoris Causa by the Universidad de Buenos Aires in Argentina, the Vincent du Vigneaud Award by the American Peptide Society, an A-rating by the National Research Foundation (South Africa), and the Research Medal of the Royal Society of Chemistry (Spain). He is also as a member of the European Academy of Sciences and Arts, and an invited professor at the Universidad de la Habana (Havana, Cuba).

Mercedes Álvarez is full professor at the University of Barcelona, where she received her chemistry degree and Ph.D. in chemistry. She enjoyed a sabbatical year working with Prof. John A. Joule in the Department of Chemistry, University of Manchester, in the U.K. In 2002, she was invited to join with the group led by Prof. Fernando Albericio and to move her research group to the Science Park of Barcelona. She is author of 146 publications, 7 chapters in monographic series, and 40 patents. Her major research interests cover synthesis of natural products, heterocyclic chemistry, combinatorial chemistry, and solid-phase methodology, as well as synthesis of small molecules with therapeutic activity. She is a member of the editorial boards of *Marine Drugs*, *Arkivoc*, *International Journal of Drug Design and Discovery*, and *Reports in Organic Chemistry*. She got a Medal from the Natural Products Division (GEPRONAT) of the RSEQ in 2015. She has got a long history of collaborations with Biomar S.A., Menarini S.A., Medichem S.A., and PharmaMar S.A.

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ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
ACN	acetonitrile
Bn	benzyl
CatBH	catecholborane
Cp	cyclopentadienyl
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMB	2,4-dimethoxybenzyl
DMF	dimethylformamide
DMP	Dess−Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
m.s.	molecular sieves
MOM	methoxymethyl
MTM	methylthiomethyl
NIS	*N*-iodosuccinimide
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PMB = MPM	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluensulfonate
RCM	ring closing metathesis
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tr = Troc	2,2,2-trichloroethyl carbonate
TS	transition state
Ts	tosyl

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General conclusions

Projects that aim at the total synthesis of complex and large natural products can be seen as an endurance long race where the achievement of smaller objectives can take you to the final target. As discussed in this thesis, at the beginning of my doctoral studies there was a background to rely on but, at the same time, there were many things to study, explore and optimize before focusing strictly on the total thesis. It can be said that the first three years (2014-2016, Chapters 2-5) of work were focused on discovering how to efficiently synthesize every single part of our family of natural products: phormidolides B-D (Figure 1). All these efforts and a new retrosynthetic analysis made it possible for us to attempt to accomplish the total synthesis and structural confirmation of PM B-D. All this final work was developed during 2017 (Chapter 6).

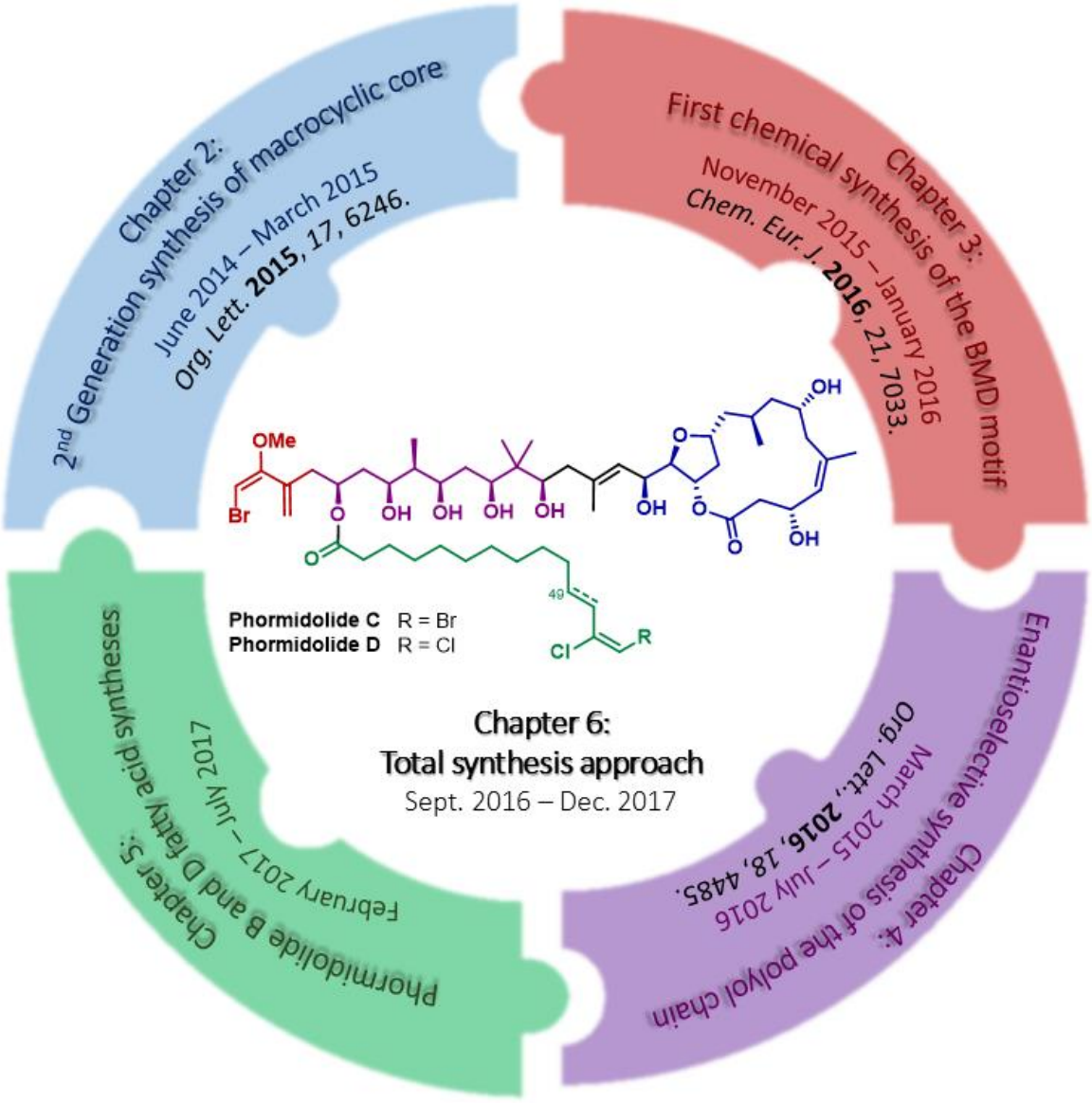

Figure 1. Visual summary of the achievements accomplished between 2014 and 2017 in the synthesis of phormidolides B-D.

To sum up, the following synthetic goals were reached during this doctoral thesis:

- A second generation synthesis of the macrocyclic core present in Phormidolides B-D was designed, developed and scaled-up (Chapter 2). The new route is more convergent than the previous one causing a 10-fold enhancement in the overall yield to obtain PM B-D macrocycle. This increment in the yield allowed us to synthesize this key part of the natural product in the gram-scale. The key step of the route is a (*Z*)-1,5-*anti* substrate controlled allylstannane **10** addition to aldehyde **5** to obtain the macrocylic carbon scaffold. A total removal of protecting groups rendered the C1-C15 fragment of PM B-D. NMR comparison of this fragment with the natural product confirmed our previous 3*R* and 14*R* configuration hypothesis.

- The first methodology to synthesize the complex bromo-methoxy-diene (BMD, Chapter 3) present in the polyhydroxylated chain of oscillariolide (Osc) and phormidolides (PM) is described. This synthetic sequence can be used to efficiently introduce this motif in the total synthesis of any of these natural products. In our case, the methodology was tested with a model aldehyde and the first chemical preparation of the eastern fragment of this family of natural products was reported. ^{1}H and ^{13}C NMR comparison between the synthesized analogue **10** and PM A confirmed, by chemical synthesis, the structure and stereochemistry of the peculiar (*E*)-bromo-metoxy-diene moiety present in oscillariolide and phormidolides.

- After some optimization of the previous designed synthetic sequence and using the new developed methodology to link the BMD motif, a 17-step synthesis of the C19-C31 polyol chain (common to Osc and PM) was described (Chapter 4). The route is efficient (10% overall yield - 88% average yield) and allowed us to study in detail many synthetic transformation that will be of great value to unveil the total synthesis of PM C-D. Finally, the ^{1}H NMR comparison with Osc and PM A demonstrated high similarity between the synthetic (**1** and **2**) and natural compounds, thereby confirming the polyol chain structure and stereochemistry by chemical synthesis.

- A robust, high-yielding, stereospecific and regioselective synthetic route for the preparation of the fatty acids present in phormidolides C and D was designed and validated (Chapter 5). (*E*) stereochemistry in the terminal di-halogenated alkenes was

confirmed using NOE 1D experiments and full characterization (^{1}H, ^{13}C, HSQC and HRMS) of the obtained fatty acids confirmed their chemical structure. Gram-scale synthesis of both fatty acids were prepared resulting in key molecules to try to accomplish the total synthesis of PM D.

- Finally, after efficient synthesis for all the parts of our family of natural products was achieved, it was necessary to address the accomplishment of their total synthesis (Chapter 6). To that end, a highly convergent retrosynthetic analysis that would allow us to reach the complex NP scaffold in only 20 steps was designed. Fragments **4**, **5** and **9** derived from the retrosynthesis were efficiently synthesized following the above mentioned discovered methodologies. A notable NHTK coupling was used to link the macrocyclic core to the central bi-functionalized fragment to obtain fragment C1-C22 (**6**). However, when **6** was reacted in the last step of the synthesis with the east fragment aldehyde **5** no conversion was achieved. Modification of the protecting groups near the reaction point could be a possible solution to overcome possible steric hindrance problems. A deep study of this fact should be taken into account before the total synthesis is approached again.

In conclusion, this doctoral thesis has studied many organic synthetic sequences that could help in the future in the attempt to achieve total syntheses of oscillariolide and phormidolide. Furthermore, some of the developed organic-chemistry tools can be useful for other synthetic chemists aiming at different synthetic targets. Although the final objective of the project was not achieved during the time-period included in this doctoral thesis, every small contribution to try to improve the chemical preparation of cytotoxic natural products is of great value. The addition of these “small-contributions” is what makes organic chemistry in general and total synthesis in particular an inciting ever-changing world with infinite capability for improvement.

Contribution to publications

- *Comparative addition of vinylmetallic reagents to chiral 2-fomyltetrahydrofuran.* J. Lamariano-Merketegi, A. Lorente, A. Gil, F. Albericio, M. Álvarez. *Eur. J. Org. Chem.* 2015, 235.

    - Preparation of compound 1b and NHTK reaction with iodo-alkene 2 to render 3c with good yield and outstanding stereoselectivity.

- *Phormidolides B and C, cytotoxic agents from the sea: Enantioselective synthesis of the macrocyclic core.* A. Lorente, A. Gil, R. Fernandez, C. Cuevas, F. Albericio, M. Álvarez. *Chem. Eur. J.* 2015, *21*, 150.

    - Preparation of macrocycle 1b to validate the route and improve the yield in some key synthetic steps.

- *Stereoselective Allylstannane Addition for a Convergent Synthesis of a Complex Molecule.* A. Gil, A. Lorente, F. Albericio, M. Álvarez. *Org. Lett.* 2015, *17*, 6246.

    - Design of the synthetic plan. Development of the synthesis. Characterization of compounds. Writing of the manuscript.

- *Synthesis of (E)-4-Bromo-3-methoxybut-3-en-2-one, the Key Fragment in the Polyhydroxylated Chain Common to Oscillariolide and Phormidolides A–C*. A. Gil, J. Lamariano-Merketegi, A. Lorente, F. Albericio, M. Álvarez. *Chem. Eur. J.* 2016, *21*, 7033.

    - Design of the synthetic plan using the previous background. Development of the synthesis. Characterization of compounds. Writing of the manuscript. Design and preparation of the cover picture.

- *Enantioselective Synthesis of the Polyhydroxylated Chain of Oscillariolide and Phormidolides A-C.* A. Gil, J. Lamariano-Merketegi, A. Lorente, F. Albericio, M. Álvarez. *Org. Lett.*, 2016, *18*, 4485.

    - Design and optimization of the synthetic plan using the previous background. Development of the synthesis. Characterization of compounds. Writing of the manuscript.

- *Avenços cap a la síntesi de les Formidolides B i C.* A. Gil, F. Albericio, M. Álvarez. *Revista de la Societat Catalana de Química, núm. 15 (2016), p. 42.*

    - Writing of the manuscript.

- *Role of the Nozaki-Hiyama-Takai-Kishi Reaction in the Synthesis of Natural Products.* A. Gil, F. Albericio, M. Álvarez. *Chem. Rev.*, 2017, *117*, 8420.

    - Writing of the review.

- *Towards the Synthesis of Phormidolides, a Journey.* A. Gil, M. Giarrrusso, J. Lamariano-Merketegi, A. Lorente, F. Albericio, M. Álvarez. *Submitted Manuscript*

    - Design of the synthetic plan. Development of the synthesis. Characterization of compounds. Writing of the manuscript.