Marine Natural Products. Synthesis and structure determination

Adriana Lorente Crivillé

Memòria presentada per

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Per optar al Grau de Doctora per la Universitat de Barcelona

Programa de Química Orgànica

Marine Natural Products.

Synthesis and structure determination

Dirigida per:

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(Universitat de Barcelona)

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UNIVERSITAT DE BARCELONA

FACULTAT DE QUÍMICA

DEPARTAMENT DE QUÍMICA ORGÀNICA

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2014

“A story should have a beginning, a middle and an end,
but not necessarily in that order”

Jean-Luc Godard

Aquest treball és la finalització d'anys de creixement professional, però també personal. En el camí que m'ha portat a aquest precís moment he passat per tot tipus d'experiències que han fet de mi una persona diferent a la que era al començar aquest projecte. A tots els que m'heu acompanyat en aquest camí, als que encara hi sou i als que ja no hi sou us vull agrair que hagueu fet de mi el que sóc.

The work reported in this doctoral thesis has been carried out at the Institute for Research in Biomedicine of Barcelona (IRB Barcelona), situated in the Barcelona Science Park (PCB).

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Images used as illustrations for each Chapter cover are marine organisms encountered during a scientific expedition to the Antarctica and were given by Dr. C. Ávila.

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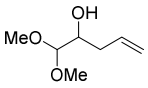
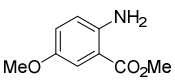
Chapter 2



2 R = H
3 R = Ac



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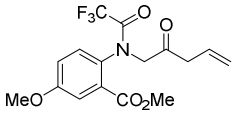

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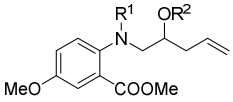
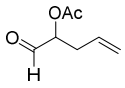


6a: R^1 = H; R^2 = Ac
6b: R^1 = H; R^2 = H
6c: R^1 = H; R^2 = Boc
6d: R^1 = $COCF_3$; R^2 = Boc
6e: R^1 = $COCF_3$; R^2 = OH



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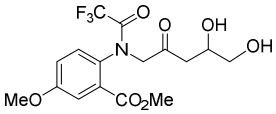

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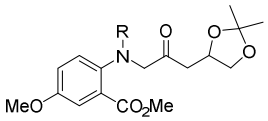
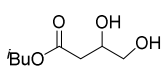


9 R = $COCF_3$
10 R = H



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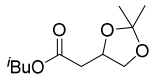

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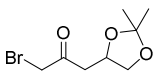

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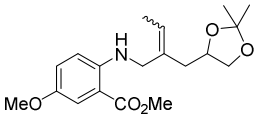

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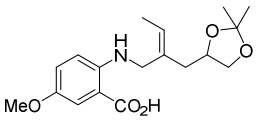

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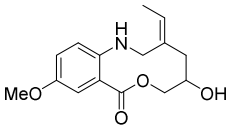

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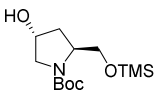

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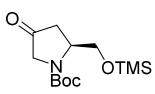

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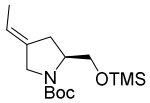

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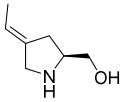

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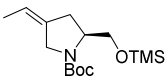

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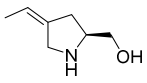

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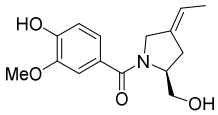

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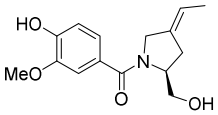

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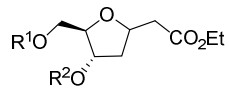
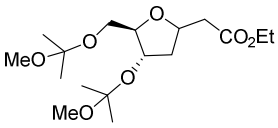
Chapter 4



9 R^1 = H; R^2 = H
S2 R^1 = TBDPS; R^2 = H
11 R^1 = TBDPS; R^2 = TBS



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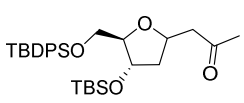

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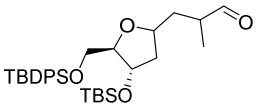

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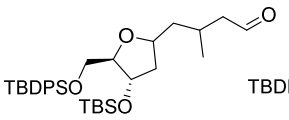

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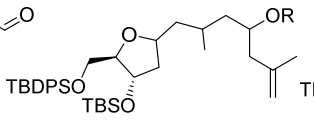
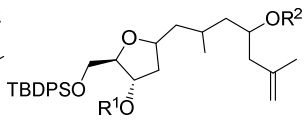
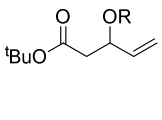


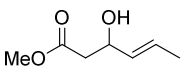
S4 R = Ac
S5 R = Fmoc



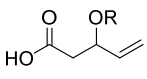
2a R^1 = TBS; R^2 = H
2b R^1 = H; R^2 = Ac
2c R^1 = H; R^2 = Fmoc



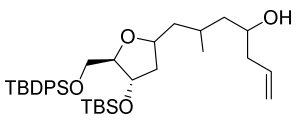
3a R = H
3d R = Ac
S6 R = Fmoc
S7 R = TIPS



3b R = ^{t}Bu
3c R = Me



3e R = Ac
3f R = Fmoc
3g R = TIPS
3h R = Boc



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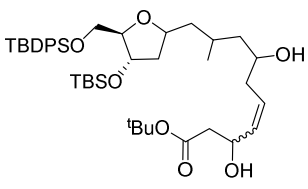

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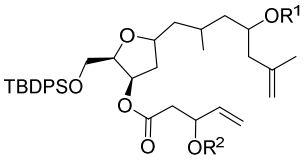
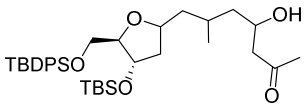


S9 R^1 = Fmoc; R^2 = Fmoc
S10 R^1 = Fmoc; R^2 = TIPS
S11 R^1 = Fmoc; R^2 = Boc
14a R^1 = Ac; R^2 = Ac
14b R^1 = H; R^2 = H
14c R^1 = H; R^2 = TIPS
14d R^1 = H; R^2 = Boc
14e R^1 = MOM; R^2 = MOM
14f R^1 = H; R^2 = H



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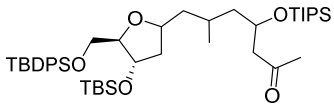

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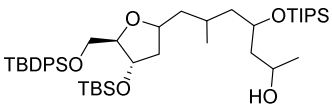

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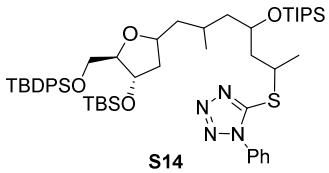

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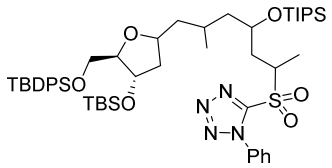

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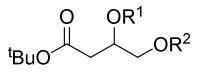
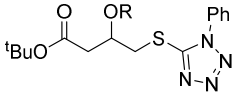
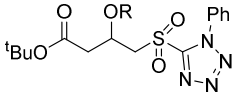


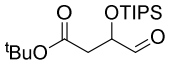
15 R^1 = H; R^2 = Bn
S15 R^1 = TIPS; R^2 = Bn
S16 R^1 = MOM; R^2 = Bn
16a R^1 = TIPS; R^2 = H
16b R^1 = MOM; R^2 = H



S17 R = TIPS
S18 R = MOM



7a R = TIPS
7b R = MOM



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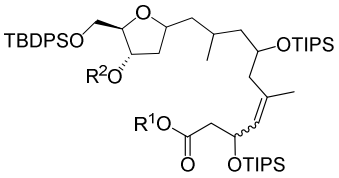
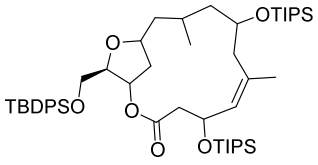


17 R^1 = ^{t}Bu; R^2 = TBS
S19 R^1 = H; R^2 = TBS
18 R^1 = H; R^2 = H



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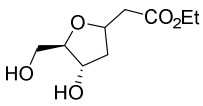
Chapter 5



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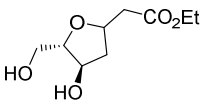
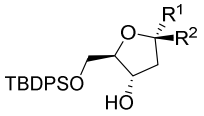
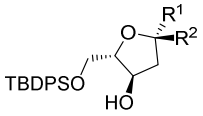


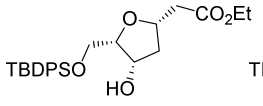
4b



5a R^1 = CH_2CO_2Et; R^2 = H
5b R^1 = H; R^2 = CH_2CO_2Et



5c R^1 = CH_2CO_2Et; R^2 = H
5d R^1 = H; R^2 = CH_2CO_2Et



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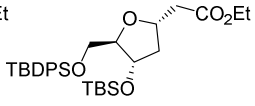
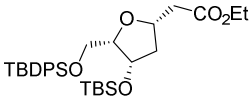
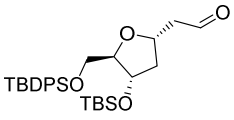


S3a



S3b



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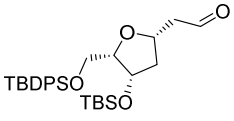

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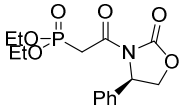

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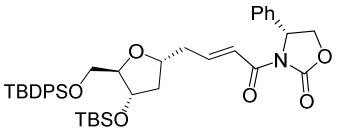

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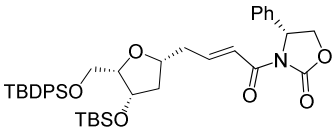
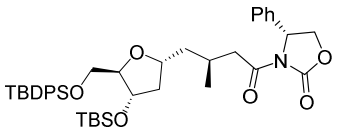


S4b



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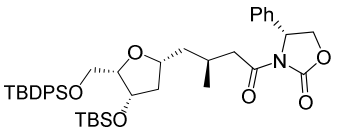

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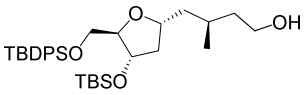
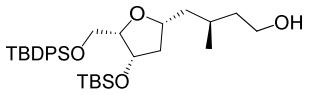
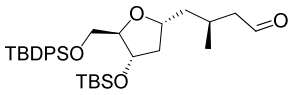


S5a



S5b



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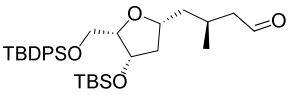

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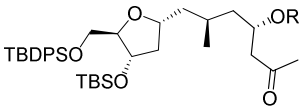
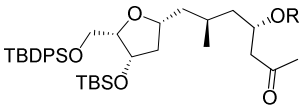
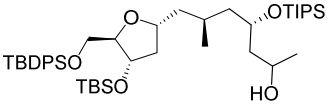


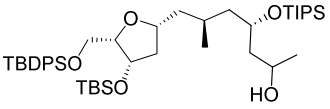
10a R = H
11a R = TIPS



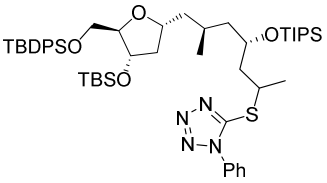
10b R = H
11b R = TIPS



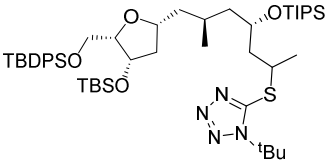
S7a



S7b



S8a



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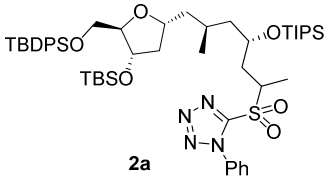

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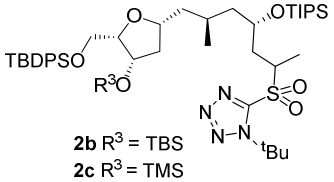
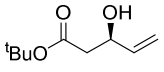
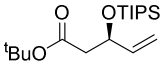


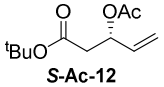
2b R^3 = TBS
2c R^3 = TMS



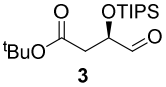
***R*-12**



S10



***S*-Ac-12**



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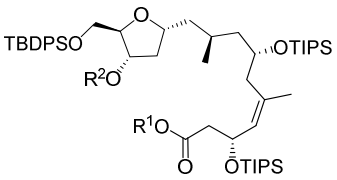
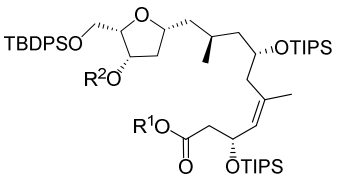
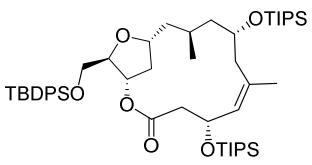


13a R^1 = ^{t}Bu; R^2 = TBS
S11 R^1 = H; R^2 = TBS
14a R^1 = H; R^2 = H



13b R^1 = ^{t}Bu; R^2 = TMS
14b R^1 = H; R^2 = H



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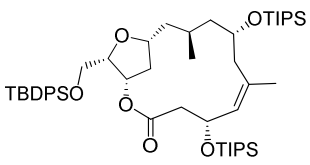
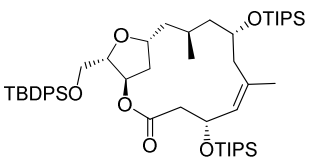
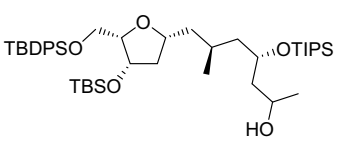


1b



1c

Chapter 6



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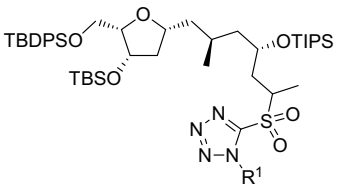
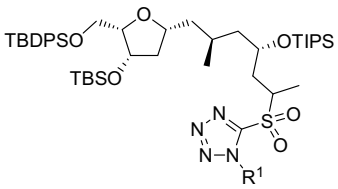
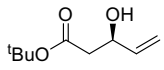


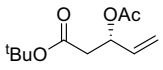
S1a R^1 = Ph
S1b R^1 = ^{t}Bu



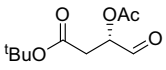
2a R^1 = Ph
2b R^1 = ^{t}Bu



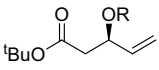
***R*-5**



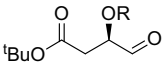
***S*-Ac-5**



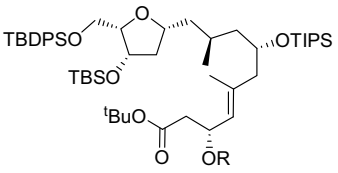
3d



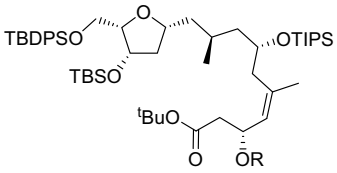
3a R^2 = TIPS
3b R^2 = ^{t}Bu
3c R^2 = MOM



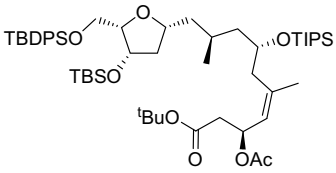
3a R^2 = TIPS
3b R^2 = ^{t}Bu
3c R^2 = MOM



***E*-6a** R = TIPS
***E*-6b** R = ^{t}Bu



***Z*-6a** R = TIPS
***Z*-6b** R = ^{t}Bu
***Z*-6c** R = MOM



***Z*-6d**

ACRONYMS

$[\alpha]_D$	optical rotation
Ac	acetyl
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
(–)-DIPCl	(–)-B-chlorodiisopino-camphehylborane
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
Fmoc	9-fluorenylmethoxycarbonyl
G-II	Grubbs' catalyst 2nd generation
gCOSY	gradient correlation spectroscopy
gHMBC	gradient heteronuclear multiple bond coherence
gHSQC	gradient heteronuclear single quantum coherence
GI_{50}	growth inhibition at 50% concentration
HG-II	Hoveyda-Gurbbs' catalyst 2nd generation
HMPA	hexamethylphopshoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HTS	high throughput screening
^{i}Bu	*iso*-butyl
^{i}Pr	*iso*-propyl
IR	infrared
J	coupling constant
LC_{50}	Lethal concentration at 50%
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
m/z	mass per charge
M	molar
Me	methyl
MOM	methoxymethyl
MPA	methoxyphenylacetic acid
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NRPS	non-ribosomal peptide synthase
Ph	phenyl
PKS	polyketide synthase
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PT	phenyltetrazole
PyBOP	(benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate
pyr	pyridine
q	quadruplet
ROESY	rotating-frame Overhauser effect spectroscopy
RT/r.t.	room temperature
s	singlet
sat.	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
^{t}Bu	*tert*-butyl
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl

TBT	*tert*-butyltetrazole	TGI	tumor growth inhibition
THF	tetrahydrofuran	TIPS	triisopropylsilyl
Tf	trifluoromethanesulfonate	TLC	thin layer chromatography
TFA	trifluoroacetic acid	TMS	trimethylsilyl
TFAA	trifluoroacetic anhydride	TOCSY	total correlation spectroscopy

1 Introduction

Clione antarctica

INTRODUCTION

1. Drug discovery from natural products

Natural products from terrestrial plants and microorganism have long been a traditional source of drugs. For centuries humans have been looking on their environment for medicines to treat illnesses. First written evidence of this fact is the list of plants created by the Sumerians back over 5000 years, describing 12 recipes for drug preparation referring to over 250 various plants. The Chinese book on roots and grasses *Pen T'Sao* written around 2500 BC describes 365 drugs as dried parts of medicinal plants and the ancient Egyptians wrote the *Ebers Papyrus* around 1500 BC, containing information on over 700 plant medicines. Later on, civilizations as the Indian, greek, roman and slavic enlarged in parallel the knowledge around this area and the arabs compiled and combined their wisdom during the middle age.[1]

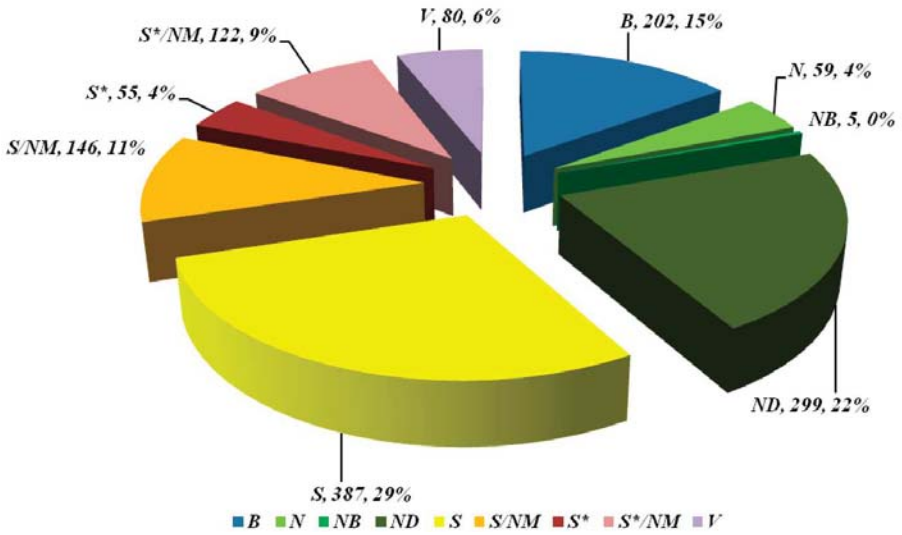
A step forward arrived when Friedrich Sertürner isolated morphine from an opium extract.[2] From then on, a new era where natural products could be in fact isolated, purified and identified began. In 1827 Merck marketed morphine being the first commercially available drug from a natural product and in 1899 Bayer released aspirin, the first pure semisynthetic drug based on a natural product. In 1928, Alexander Fleming discovered penicillin from certain species of *penicillium* fungi,[3] the first known antibiotic, and the massive study of microorganisms that could generate new bioactive molecules began.

During the 90s decade, the interest in natural products decreased on behalf of High Throughput Screening (HTS). HTS is used to create combinatorial libraries of compounds in large numbers, which randomly cover the chemical space, and these are subjected to a variety of tests. Through this process one can rapidly identify active compounds, which are the starting point for a whole new drug development process. Nevertheless, the inefficacy of combinatorial methods to successfully deliver new drug leads in significant numbers changed the idea that new technologies should replace old methods but on the contrary, complement them.

While the generation of combinatorial libraries is constrained by the availability of reagents and suitable reactions, the generation of natural product diversity has occurred in the context of biological utility, meaning that the function and the biosynthetic routes generating these compounds coevolved with the requirements of ligand functionality. Recent studies conclude that combinatorial chemistry should mimic certain properties of natural products and avoid unfavorable modifications such as chirality or conformational constraint elimination and structure simplifications, and suggest using natural products as templates for library design.[4,5]

Nowadays, although technology offers a wide range of opportunities, nature is still the most recurred starting point for drug development.[6] The analysis of worldwide approved drugs with all source categories from 1/1/1981 to 12/31/2010 (Graph 1)[6g] shows the importance of natural products not only as direct source of new bioactive molecules, but also as inspiration to create new structures.

Graph 1. New approved drugs from 1/1/1981 to 12/31/2010 (N= 1335).



B: Biological; usually a large (>45 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in surrogate host.

N: Natural product.

NB: Natural product (Botanical).

ND: Derived from a natural product (usually a semisynthetic modification).

S: Totally synthetic drug (often found by random screening/modification of an existing agent).

S*: Made by total synthesis, but the pharmacophore is/was from a natural product.

V: Vaccine.

/NM Subcategory: Natural product mimic.

The main conclusion extracted from this analysis is that natural products constitute a group of privileged structures. They are selected by evolution to interact with a wide variety of proteins and therapeutic targets with a concrete function and finality, and are excellent candidates for drug development processes.

2. The importance of marine habitat

Unlike terrestrial sources, marine habitat has not been so extensively studied; this field awaited refinements in technologies to collect the source organisms, and development of more advanced analytic techniques to better understand the more complex isolated compounds. Since 1950s this field has suffered an exponential push; considering that water covers around a 70% of the earth's surface, and 32 of the 33 animal phyla are represented in aquatic media, marine habitat represents an extensive source of new bioactive molecules.[7]

Marine organisms produce a big number of structurally diverse secondary metabolites[8] that do not play an essential role in the life of the organism, but offer a complementary function as chemical defence against pathogens, in the fierce competition for survival in marine habitat. As a consequence, natural products isolated from marine sources present diverse and potent bioactivities, and complex structure and stereochemistry, provided that they are the result of more sophisticated biosynthetic pathways created through the combination of evolution and thermodynamics.

The bottleneck for the development of these compounds is supply. Isolation from the natural sources often furnishes small amounts of product, which makes the structure determination and the preparation of enough sample of compound for clinical trials extremely challenging. To illustrate the actual scenario, a short overview of marine derived drugs approved for medical use[9] is outlined (Table 1). Few have arrived to the latter development stage of a drug, but many are on their way, a vast number of them being currently under preclinical and clinical trials.[10]

Table 1. As of February 2014, marine-derived compounds which have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) and are part of the global marine pharmaceutical clinical pipeline.

Compound Name	Trademark	Origin Organism	Chemical Class	Target	Disease Area
Cytarabine	Cytosar-U® Depocyt®	Sponge	Nucleoside	DNA polimerase	Cancer
Ziconotide	Prialt®	Cone snail	Peptide	N-Type Ca chanel	Pain
Trabectedin (EMEA only)	Yondelis®	Tunicate	Alkaloid	Minor groove of DNA	Cancer
Eribulin	Halaven®	Sponge	Macrolide	Microtubules	Cancer
Brentuximab vedotin	Adcetris®	Mollusk	Antibody drug conjugate	CD30 & microtubules	Cancer
Omega-3-acid ethyl esters (FDA only)	Lovaza®	Fish	Omega-3 fatty acids	Trygliceride-synthesizing enzymes	Hypertrigly-ceridemia

Cytarabine

Cytarabine (cytosine arabinoside) (Figure 1), is a synthetic pyrimidone nucleoside developed, after the isolation of spongouridine and spongothymidine from the Caribbean sponge *Tethyacrypta*,[11] from the idea that arabinose nucleosides could indeed be active metabolites and be considered prototypes for drug development processes. Cytarabine received Food and Drug Administration (FDA) approval in 1969, and is available as either conventional cytarabine (Cytosar-U®), for the treatment of acute lymphocytic or myelocytic leukemia, or as liposomal formulations (Depocyt®), for the treatment of lymphomatous meningitis.[12]

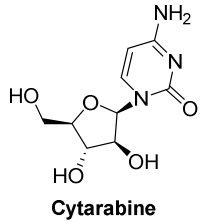


Figure 1. Structure of cytarabine.

Ziconotide, ω-conotoxin MVIIA

ω-Conotoxin MVIIA, a linear peptide with three disulfide bonds in its structure (Figure 2), was discovered in 1979 from the pacific snail *conus magus*,[13] whose venom served as platform for a drug development program. The referred natural product was first obtained by synthesis in 1987[14] and is considered the first marine drug that was approved in the United States and Europe, in 2004, under the trade name Prialt®, for the treatment of chronic pain in spinal cord injury.[15]

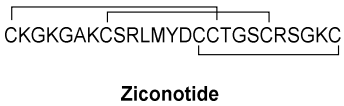


Figure 2. Structure of ziconotide.

Trabectedin and Lurbinectedin

In 1969, extracts of the Caribean tunicate *Ecteinascidia turbinata* showed antitumor activity, but the scarce amounts collected made impossible the identification of the active components.[16] In 1990, the structure of the ecteinascidins was finally revealed[17] being the more active component ecteinascidin-743 (trabectedin, ET-743), which was selected for further development. Some synthetic work has focused on the production of ET-743,[18] but only aquaculture of the tunicate provided enough quantity of product to overcome the first clinical supply needs.[19] Nevertheless, the main push in the development of this compound appeared with the semi-synthetic method developed by Pharmamar, which finally solved the supply issues.[18,20]

In 2007, trabectedin, under the trade name Yondelis®, was approved by the European Union for the treatment of refractory soft-tissue sarcomas (Figure 3).[21] More recently, in 2012, the FDA and the EMEA have given Lurbinectedin,[22] an ecteinsacidin family derivative, the orphan drug designation for the treatment of relapsed ovarian, lung and breast cancers.

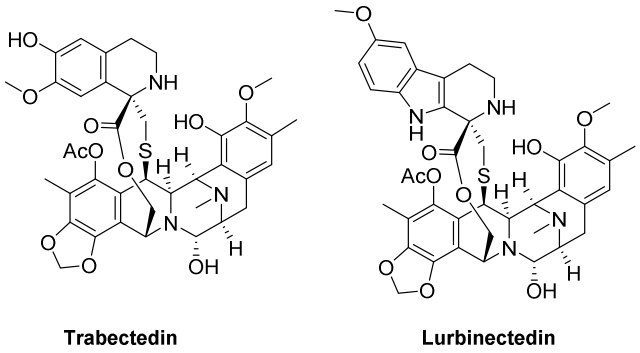


Figure 3. Structures of trabectedin and lurbinectedin.

Eribulin

Halichondrin B was isolated from the sponge *halichondria okadai* in 1986 along with other halichondrins and norhalichondrins.[23] On the course of the drug development program of halichondrin B, scientist at the Eisai pharmaceutics discovered that synthetic analogs of much simpler structures presented similar pharmacological profile, and eribulin was targeted as the next drug candidate.[24] Given the lack of intermediates from naturally occurring sources to support a semi-synthetic strategy, eribulin was, and still is, produced by total synthesis,[25] supposing a breakthrough on the perception of how a druggable chemical lead must look like.

Finally, eribulin was approved in 2010, under the trade name Halaven®, for the treatment of metastatic breast cancer (Figure 4).[26]

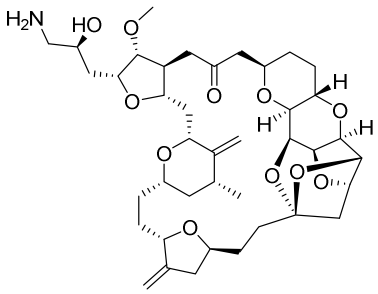


Figure 4. Structure of eribulin.

Brentuximab vedotin

Dolastatin 10, a linear pentapeptide with cytotoxic activity, was isolated in 1987 from the sea hare *Dolabella auricularia*.[27] Some years later, a whole family of compounds was described as the auristatin family.[28] Brentuximab vedotin is an Antibody Drug Conjugate (ADC) with monomethylauristatin E (MMAE) (Figure 5) as warhead[29] and was developed by Seattle Genetics. It was approved in 2011, under the trade name Adcetris®, for the treatment of patients with Hodgkin's lymphoma and patients with systematic anaplastic large cell lymphoma.[30]

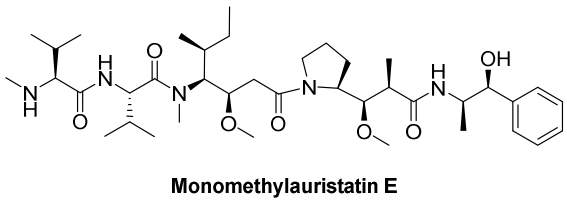


Figure 5. Structure of monomethylauristatin E.

Omega-3 acid ethyl esters

Last on the list is a prescription omega-3 fatty acid formulation containing eicosapentaenoic acid (EPA) (465 mg) and docosahexaenoic acid (DHA) (375 mg) ethyl esters (Figure 6) along with vitamin E (4 mg),[31] which is used for the treatment of hypertriglyceridemia,[32] and is sold under the trade name Lovaza®. Certain fish species yield significant levels of EPA and DHA, and it is considered that intakes of up to 3 g/day of marine omega-3 fatty acids are GRAS (Genereally Recognized as Safe) for inclusion in the diet.[33] Moreover, the FDA has approved a qualified health claim for EPA and DHA omega-3 fatty acids in dietary supplements.[31]

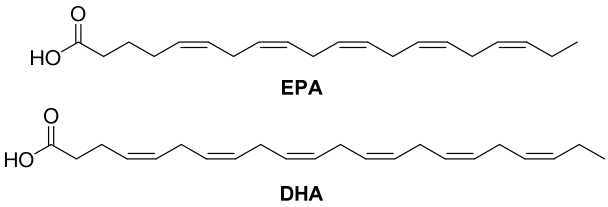


Figure 6. Structure of EPA and DHA.

3. Genetic engineering and marine natural products

During the last years, there has been increasing evidence that the actual producer of some bioactive compounds are not the sponge, tunicate, or invertebrate from which it was isolated, but might well be a symbiotic microbial organism.[34] Concretely, this is stated for compounds derived from polyketide and nonribosomal peptide biosynthetic pathways,[35] since the producing enzymes are so far exclusively known from microorganisms.[36]

As genome sequencing is common, rapid and relatively inexpensive, genetic engineering of cells can be successfully applied to the development of strains dedicaded to the overproduction of a certain natural product. Unlike their invertebrate hosts, genomes of bacteria are small and their biosynthetic pathways tend to be organized in contiguous regions of DNA (operons), which facilitates cloning of these pathways. Expression technology for bacterial genes is well developed, making cloning and expressing biosynthetic genes of cultivable and non-cultivable bacterial symbionts feasible. The strategy lies on determine whether or not symbionts are in fact producing a natural product, and then identify, characterize, and express this bioactive metabolite genes.[37]

Genetic engineering is attracting the attention of many scientists working on marine natural products development, because marine natural products tend to have complex structures difficult to attain using conventional methods. Consequently, this area offers a new possibility facilitating their supply.

4. Current pipeline. The need for scope extension

To date, only a few marine derived drugs are considered suitable for medical use, and the main push has been during the last 10 years. The main cause for the decelerated development of these compounds is supply. Nevertheless, scientists have learned how to overcome these problems, as can be seen from the examples given above, and drug development of complex compounds is now becoming possible.

Although fauna from the deep sea is usually unculturable, or does not produce the same quantity of compounds in a media different from its original, aquaculture of marine invertebrates can be used as supply. On the other hand, the development of efficient and stereoselective methodologies to obtain this targets by synthesis or semi-synthesis seems to be a recurred option; which requires high production yields using the minimum synthetic steps. Finally, a possible bacterial origin of some marine natural products could have important implications for drug development, since it may permit the creation of fermentation based production systems, superior to current procurement methods.

As an important remark, it is worth adding that on the current pipeline, the era of the “me-too” or the “me-slightly-better” has arrived.[38] Thus, the discovery of New Molecular Entities (NME) requires innovation. The way is to look into new places, as oceans, and refocus our mentality with new ideas and processes; what was supposed to work in the past does not provide innovative results anymore, and what was not supposed to work, because it seemed unaffordable, may now be the way to proceed.

SYNTHETIC TARGETS

As stated before, synthesis is a powerful tool to use on our behalf for structure determination and supply of material for clinical tests on the development of new bioactive drugs. On the course of our research to obtain new compounds with antitumor properties from marine habitat, and continuing our collaboration with the spanish pharmaceutical companies Biomar S.A. and Pharmamar S.A., this thesis will be devoted to the development of two projects:

- Synthesis and structure determination of barmumycin.
- Synthesis and structure determination of the macrocyclic core of phormidolides B-D.

1. Barmumycin

Barmumycin was isolated from an extract of the marine actinomycete *Streptomyces sp.* BOSC-022A collected off the Scottish Coast, and was found to be cytotoxic against various tumor cell lines. Its structure was determined by NMR spectroscopy but synthesis was required to confirm the assignment. Compound **1** was depicted as the structure for barmumycin (Figure 7), which is based on a 10 membered lactone fused with an aromatic ring, with the presence of an *E* exocyclic double bond, and two free hydroxyl and amino groups.

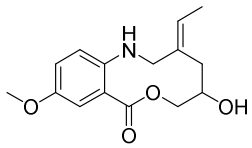


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Figure 7. Proposed structure for barmumycin.

The cytotoxic activity of barmumycin was tested against a variety of tumor cell lines, all activities were within the micromolar range but the best results were obtained against ovarian (IGROV), leukemia (K-562), colon (LOVO-DOX) and pancreas (PANC-1) cell lines (Table 2). Note that acetylation of barmumycin resulted in a loss of activity.

Table 2. GI_{50} values for barmumycin and acetylated barmumycin.

Compound	IGROV	K-562	LOVO-DOX	PANC-1
Barmumycin	0.8 µM	0.8 µM	0.6 µM	0.9 µM
Ac-barmumycin	5.9 µM	5.0 µM	6.5 µM	5.5 µM

2. Phormidolides B-D

Polyketide macrolides are a class of secondary metabolites with interesting biological activities and complex structure and stereochemistry. Phormidolides B-D, related to oscillariolide[39] and phormidolide A,[40] were isolated from an active organic extract of a sponge of the Petrosiidae family collected off the coast of Pemba (Tanzania). As their family congeners, this compounds present high structural and stereochemical complexity (Figure 8).

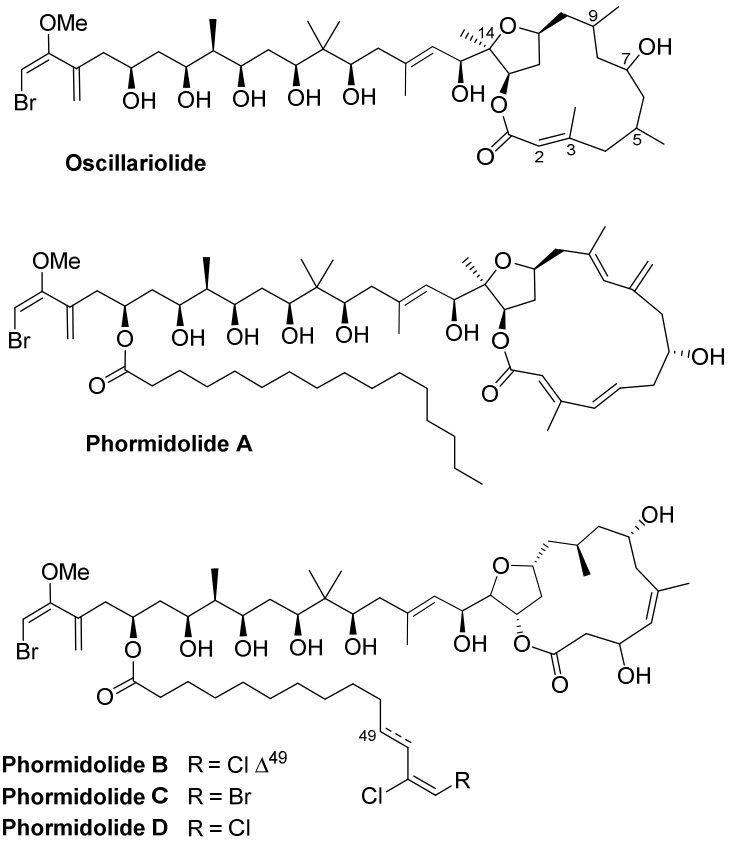


Figure 8. Structures of oscillariolide and phormidolides A-D.

Phormidolides B-D present a common structure based on a macrocyclic lactone, bonded to a polyhydroxylated chain and a fatty acid linked by an ester bond to the polyol. The macrocyclic core has the characteristic presence of a tetrahydrofuran (THF) ring in its structure, two free hydroxyl groups, a branched methyl, and an endocyclic trisubsituted double bond; in total it contains 6 steroceners and the double bond with the *Z* configuration. The polyhydroxylated chain has 5 free hydroxyl groups and one hydroxyl forming an ester bond to the fatty acid, two alkenes in its structure and a rare methyl bromoenol ether motif; in total it contains 7 stereocenters.

The fatty acids are different for each phormidolide, they differ in the insaturations and substitution pattern of the present haloalkenes, also very rare motifs for this kind of structures. Since halogenated compounds are mostly known from marine cyanobacteria,[41] and phormidolide A and oscillariolide were indeed isolated from cyanobacteria, it is feasible to think that these natural compounds have as well a bacterial origin, and the sponge may not be the producing organism itself. Studies towards this direction are not the objective of this thesis but such statement may be considered for the future study of this class of compounds.

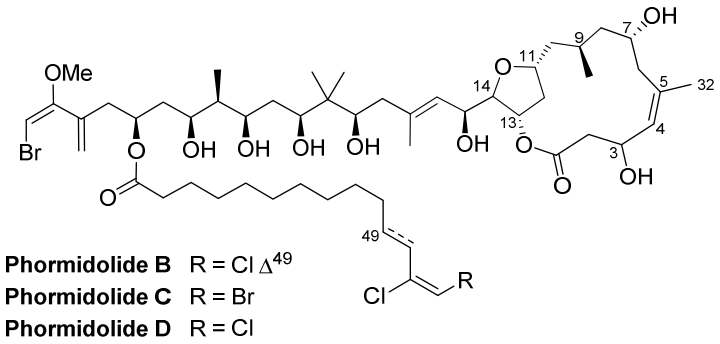
The cytotoxic activity of phormodolides B-D was tested against three human tumor cell lines: lung (A-549), colon (HT-29), and breast (MDA-MB-231). All cell lines exhibited growth inhibition at micromolar concentrations (Table 3).

Table 3. GI_{50} values for Phormidolies B-D.

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

Structure determination

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 (Figure 9).



Phormidolide B R = Cl Δ^{49}
Phormidolide C R = Br
Phormidolide D R = Cl

Figure 9. Structures of phormidolides B-D.

The stereochemistry of the linear polyols was determined by comparison of the chemical shifts and coupling constants with the literature values of phormidolide A.[40] The stereochemistry of the double bonds present on the fatty acid could only be determined in phormidolide B, elucidated to be *E*-*E*.

The relative stereochemistry of the trisubstituted THF ring was determined by ROESY experiments. Although it was clear that H11 and H13 were in a *cis* relationship, the relative disposition of H14 was not clear, although suggested to be in a *cis* relationship with H11 and H13. The relative stereochemistry of C9 and C7 to C11 stereocenter was determined by *J*-based configuration analysis combined with ROESY correlations (Figure 10 and 11). The endocyclic double bond was determined to have the *Z*-stereochemistry based on a strong observed nOe between H4 and H32. However the configuration of the C3 hydroxylated methylene was not determined.

Determination of the relative stereochemistry of C9 and C7 to C11:

Protons $^{10}CH_2$ and $^{8}CH_2$ are systems with the characteristic of having two large *J*-coupling constants and one small, meaning each one has a proton in an anti-relationship.[42]

As an example, assuming that $H10_L$ has H11 in an anti-relationship, and $H10_H$ has H9 in an anti-relationship, for both cases, two dispositions are possible. With the aid of ROESY experiments, the right relative disposition is revealed for each case. Combination of the two relative dispositions C11-C10 and C10-C9 provides the relative disposition of C9-C11 (Figure 10). Same procedure is followed to obtain the relative stereochemistry of C7-C9 (Figure 11).

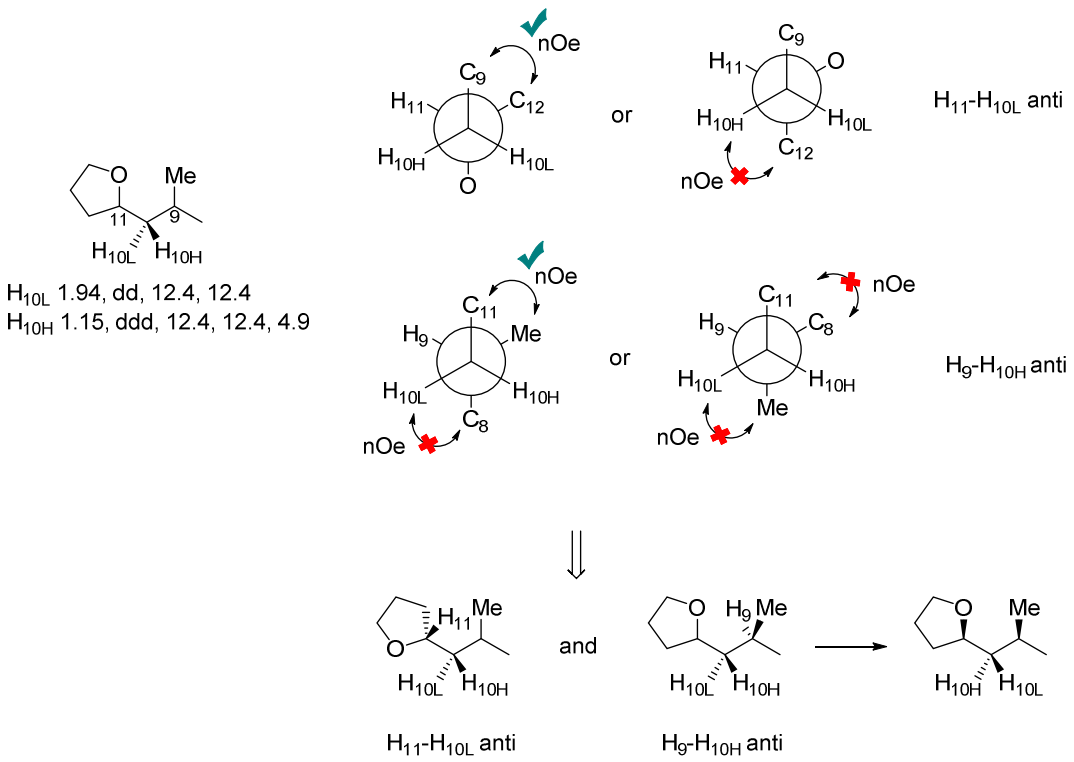


Figure 10. Determination of the relative stereochemistry of C9-11.

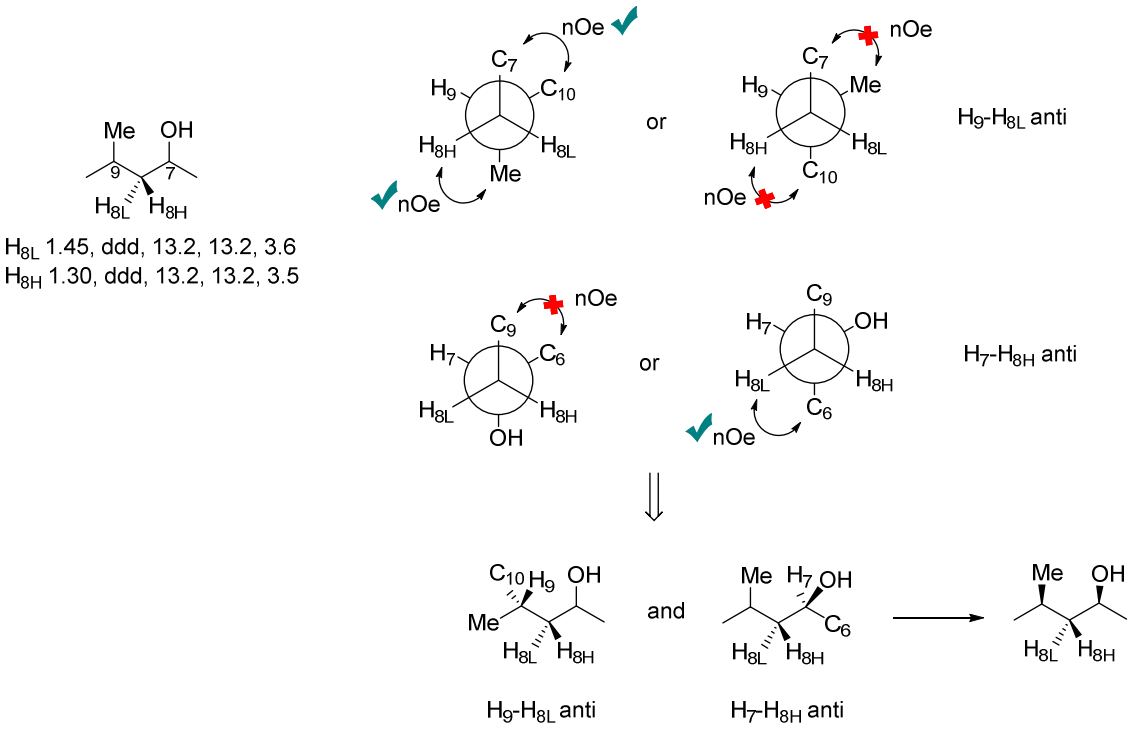


Figure 11. Determination of the relative stereochemistry of C7-C9.

Retrosynthetic analysis of phormidolides B-D

Our retrosynthesis of phormidolides B-D divides the targets in three main fragments. The chosen disconnections were the ester bond that links the fatty acid and the polyhydroxylated chain; and the C15-C16 bond achievable by a diverse number of alkenylation processes (Figure 12). The three fragments that need to be synthesized are the macrocyclic core (**2**), the polyhydroxylated chain (**3**) and the three fatty acids (**4a-c**). Assembling of the fragments will lead to the total synthesis of each phormidolide.

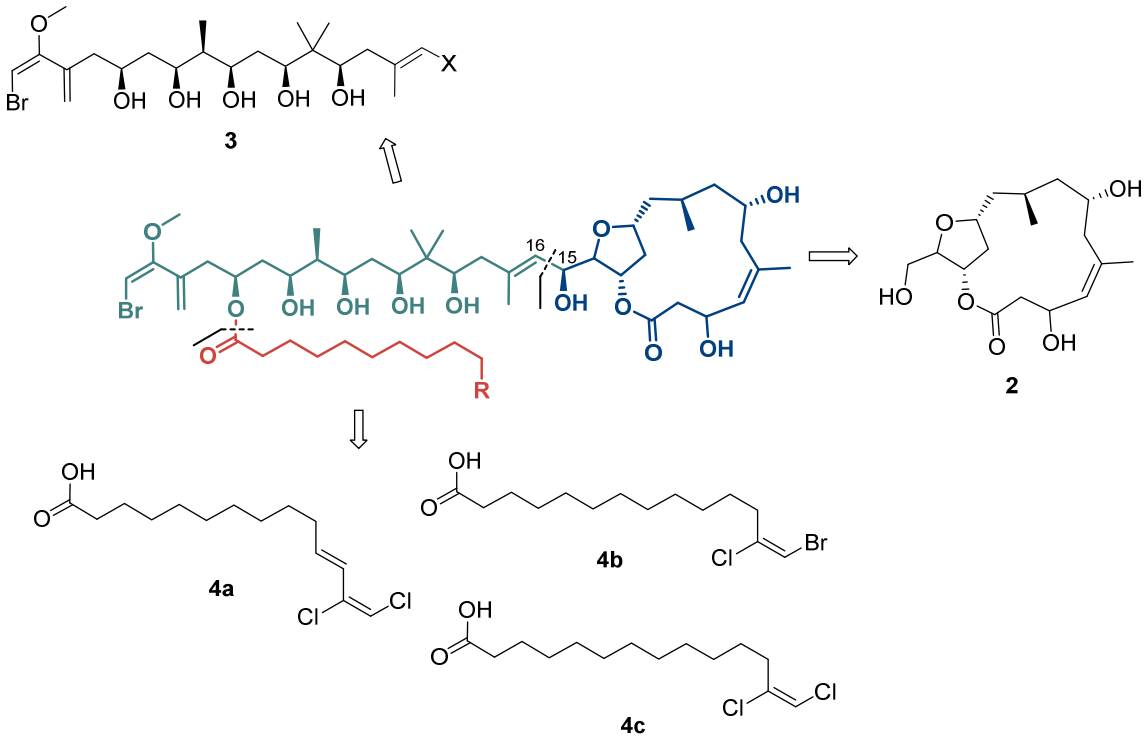


Figure 12. Retrosynthetic analysis of phormidolides B-D.

The second part of this thesis is focused on the development of an efficient methodology to obtain the macrocyclic core of phormidolides B-D (**2**), and, if possible, provide helpful information on the stereochemistry by comparison with the natural product.

The target macrocycle has the characteristic presence of a trisubstituted tetrahydrofuran ring, an endocyclic alkene and 3 hydroxy groups; one of them would need functionalization to link the macrocycle to the polyhydroxy chain. Concerning stereochemistry, it has 6 stereocenters in its structure and the *Z*-trisubstituted double bond. The relative stereochemistry of 4 out of the 6 stereocenters is known, but no more information can be deduced from the spectra of the natural compounds.

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Objectives

Astrotoma agassizii

OBJECTIVES

This thesis is focused on the synthesis and structure determination of bioactive compounds isolated from marine habitat. In addition, other objectives will be addressed in order to complete other aspects of the projects.

- **Synthesis and structure confirmation of barmumycin.** Synthesis to obtain the proposed structure for barmumycin is addressed with the objective of confirming the structure.

- **Overview of bioactive marine macrolides with the characteristic presence of THF motifs in their structure.** Since every year more compounds with this characteristics are isolated from marine sources, a general review compiles the literature addressing its isolation and described total synthesis.

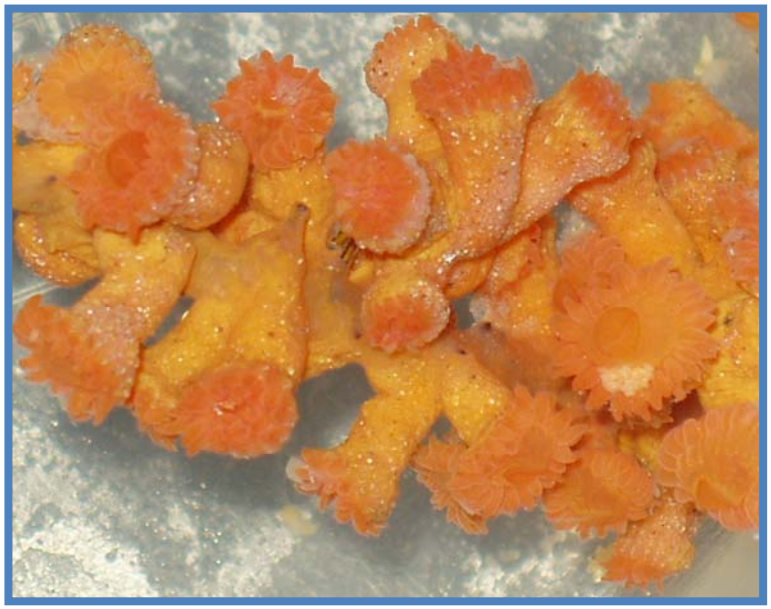
- **Synthesis and structure determination of the macrocyclic core of phormidolides B-D.** This objective is divided in three sections.

    - **Synthetic strategies towards the macrolide core of phormidolides B-D.** Before enrolling to stereoselective procedures, the choice of the best synthetic pathway is performed by a not stereoselective approach.

    - **Development of efficient methodology to construct the *Z*-trisubstituted double bond.** An optimization process for the formation of the *Z*-trisubstituted alkene, key step of the synthesis, is required to complete the total synthesis.

    - **Stereoselective synthesis of the macrolide core of phormidolides B-D.** With an efficient strategy in hand, the best synthetic pathway should lead to the enantioselective synthesis of the macrocycle. The obtained results should permit the comparison with the natural macrolide and provide hints on the stereochemical assignment.

2 Isolation, structural assignment and total synthesis of barmumycin



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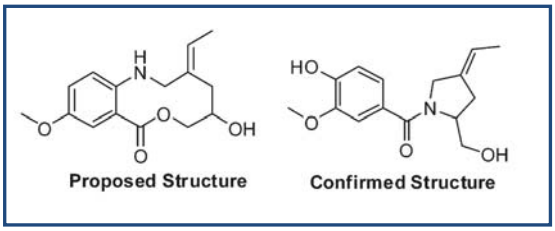
ISOLATION, STRUCTURAL ASSIGNMENT AND TOTAL SYNTHESIS OF BARMUMYCIN



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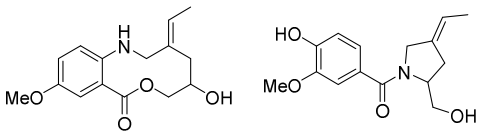
RESUME

Barmumycin was isolated from an extract of the marine actinomycete *Streptomyces* sp. BOSC-022A and found to be cytotoxic against various human tumor cell lines. Macrolactone **1** was assigned on the basis of preliminary mono and bi-dimensional ^{1}H and ^{13}C NMR spectra (Figure 1). Compound **1** was synthesized by two different routes. Both routes converged in one intermediate that was converted by Wittig olefination and macrocyclization to the proposed structure. The main goal of both our synthesis is the alkylation of a weak nucleophilic aniline by this two different methods, which are based on a reductive amination and on a nucleophilic substitution.

However, major spectroscopic differences between isolated barmumycin and **1** led to revision of the proposed structure. The new proposed structure should have similar predicted chemical shifts, and the main difference between the former and the latter should be the connectivity between the aromatic system and the alkyl chain. A new structure based on a pyrrolidine with an exocyclic double bond linked to an aromatic ring by an amide bond was proposed (**2**). On the basis of the enantioselective synthesis of this new compound, and subsequent spectroscopic comparison of it to an authentic sample of barmumycin, the structure of the natural compound was indeed confirmed as that of **2**.



1 **2**

***Figure 1*.** Proposed and revised structures for barmumycin.

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Isolation, Structural Assignment, and Total Synthesis of Barmumycin

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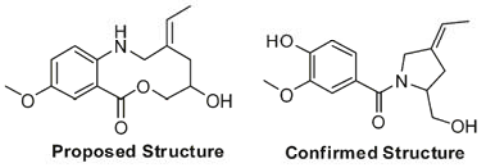

Barmumycin was isolated from an extract of the marine actinomycete *Streptomyces* sp. BOSC-022A and found to be cytotoxic against various human tumor cell lines. On the basis of preliminary one- and two-dimensional ^{1}H and ^{13}C NMR spectra, the natural compound was initially assigned the structure of macrolactone-type compound **1**, which was later prepared by two different routes. However, major spectroscopic differences between isolated barmumycin and **1** led to revision of the proposed structure as *E*-**16**. On the basis of the synthesis of this new compound, and subsequent spectroscopic comparison of it to an authentic sample of barmumycin, the structure of the natural compound was indeed confirmed as that of *E*-**16**.

Introduction

Natural products from terrestrial plants and microorganisms have long been a traditional source of drugs; however, over the past few years, marine organisms have garnered ever-increasing attention as a rich bank of new bioactive compounds.[1] Marine actinomycetes have also proven to be an important source of biologically active compounds.[2]

Among the marine actinomycetes that our group has studied, those of the genus *Streptomyces* have clearly shown the most pharmacological potential; however, in many bioactive cultures they have yielded only compounds that are already known. During ongoing research efforts to explore the biosynthetic potential of rare marine microorganisms, we isolated two known compounds, pretomaymycin[3] and oxotomaymycin[4] (Figure 1), plus the previously unknown compound barmumycin from the culture broth of the marine actinomycete *Streptomyces* sp. BOSC-022A, isolated from a tunicate collected off the Scottish coast. Barmumycin and its diacetate show antitumor activity at micromolar concentrations in all 12 cancer cell lines tested (see Table 1 in the Supporting Information). Herein we report the isolation, total synthesis, and structure elucidation of barmumycin.

Results and Discussion

The molecular formula of barmumycin was determined to be $C_{15}H_{19}NO_4$ by HRMS MALDI-TOF; it gave an $(M + H)^+$ ion at m/z 278.13840 (calcd m/z 278.13869 for $C_{15}H_{20}NO_4$). Reaction of barmumycin with acetic anhydride and pyridine gave a diacetyl derivative, confirmed by MS, pointing the presence of two OH and/or NH protons (see Figure 2).

^{1}H NMR shows three groups of protons (see Table 2 in the Supporting Information). The first group is in the aromatic region and contains three protons at 6.90 (d), 7.03 (d), and 7.08 (s) ppm; the chemical shifts indicated a 1,2,4-substituted electron-rich benzene ring. The second group corresponds to a single vinylic proton at 5.34 ppm (m). The third region comprises an upfield CH shift at 4.67 ppm (m); two methyl

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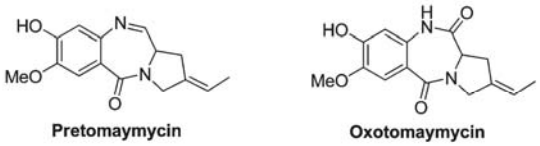

FIGURE 1. Two known compounds isolated from *Streptomyces* sp. BOSC-022A.

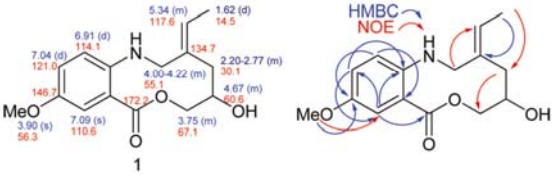

FIGURE 2. Structure of **1** showing ^{1}H NMR (blue) and ^{13}C NMR (red) chemical shifts (left) and its HMBC and NOE correlations (right).

groups, seen at 3.90 ppm (s) and 1.62 ppm (d); and the signals of three CH_2 at 4.07 (bt), 4.18 (bd), 3.75 (m), 2.29 (m) and 2.71 (m) ppm. On the basis of these data, the MS findings, and further data from one-dimensional and two-dimensional (COSY, HMBC, and NOESY) ^{1}H and ^{13}C NMR experiments, we initially proposed that the structure of the isolated natural product was that of benzomacrolactone **1**, derived from 5-methoxy-2-aminobenzoic acid with an exocyclic (*E*)-ethylidene and one alcohol function (Figure 2).

Decanolides are chemical entities abundant in terrestrial organisms, though only a few (e.g., modiolides A and B[5] and xestodecalactones A−C[6]) have been isolated from marine sources. To the best of our knowledge, the aniline moiety within its 10-membered lactone had never been reported in naturally occurring macrocycles.

We sought to synthesize **1** to compare it against an authentic sample of barmumycin in order to assess its structural assignment. Our retrosynthetic analysis of **1** entailed formation of the exocyclic double bond via Wittig reaction; dihydroxylation of a double bond to give the alcohol required for lactonization; and finally, introduction of a functionalized five-carbon chain onto the nitrogen of methyl 2-amino-5-methoxybenzoate (Scheme 1).

The functionalized five-carbon chain on the aniline nitrogen was introduced by two different ways: via reductive amination (Scheme 2) and via *N*-alkylation (Scheme 3).

Homoallylic alcohol **2** was obtained by Barbier reaction of 2,2-dimethoxyacetaldehyde with allyl bromide and indium powder in water (95% yield).[7]

Attempts at direct deprotection of the dimethyl acetal under acidic conditions led to polymerization of **2**;[8] therefore, the alcohol had to be protected. Acetylation of the alcohol to give compound **3**,[7] followed by dimethyl acetal deprotection using $LiBF_4$ in MeCN−H_2O,[9] gave the aldehyde **4** in excellent yield.

Reductive amination of **4** with aniline **5**[10] required special conditions due to the poor nucleophilicity of the aniline (which is deactivated by the methyl ester group in the *ortho* position): thus, reaction of **4**, **5**, phenylsilane, and dibutyltin dichloride under microwave irradiation for short reaction times gave the aminoalkene **6a** in 67% yield.[11,12] Attempts at protecting the aniline NH in **6a** as a ^{t}Bu carbamate failed due to its poor reactivity; therefore, **6a** was treated with K_2CO_3 in MeOH to give the deacetylated derivative **6b**. However, all attempts at oxidizing **6b** to its ketone derivative resulted in decomposition of the starting material.[13] Thus, the aniline had to be protected, but this was not possible in the presence of the unprotected alcohol. Exploiting the lack of reactivity of the aromatic amine toward Boc protection, and using standard conditions, **6b** was converted into its ^{t}Bu carbonate derivative **6c** in 43% yield.[14] The aniline group of **6c** was then orthogonally protected using $(CF_3CO)_2O$ in pyridine to afford the trifluoroacetamide derivative **6d** in quantitative yield. Treatment of **6d** with 10% TFA in CH_2Cl_2 to remove the carbonate gave the free alcohol **6e** in quantitative yield. Compound **6e** was then oxidized with Dess−Martin periodinate (DMP)[15] to yield the ketone **7** in 93% yield. Slow addition of **7** to *N*-methylmorpholine oxide (NMO) and a catalytic amount of OsO_4 in acetone−H_2O to generate the corresponding diol **8** while preventing double-bond isomerization gave **8** in good yield. Diol **8** was further protected by conversion into its 2,2-dimethyl-1,3-dioxolane derivative **9** using 2,2-dimethoxypropane plus pyridinium *p*-toluenesulfonate (PPTS) as catalyst (quantitative yield). Deprotection of the amine in **9** via mild basic hydrolysis gave the free amine **10** in 97% yield.

A faster and better yielding synthesis of **10** (Scheme 3) was done in parallel to the route described above. The first step was dihydroxylation of isobutyl but-3-enoate. The introduction of the bromomethyl residue was planned for a later step. The oxidation conditions described above afforded isobutyl 3,4-dihydroxybutanoate (**11**), which was then further protected as the 2,2-dimethyl-1,3-dioxolane derivative **12**, in excellent overall yield for both steps. The key step, transformation of **12** into the bromoketone **13** using bromomethyllithium, gave **13** in 49% yield. *N*-Alkylation of **5** with **13** under microwave irradiation gave **10**.

Wittig chemistry was employed to introduce the ethylidene chain. Reaction of **10** with the Wittig ylide derived from ethyltriphenylphosphonium bromide yielded **14** (43%) as a mixture of *Z*/*E* diastereomers.[16]

Z/*E*-**14** was transformed into **1** in three successive reactions: hydrolysis of the methyl ester, acetonide deprotection under acidic conditions, and macrocyclization. The acid *Z*-**15** was obtained by purification of the Z/E mixture of acids by semipreparative HPLC.[17]

Racemic *Z*-**1** was obtained in 35% yield by acetal deprotection followed by macrocyclization using EDC·HCl and

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(8) The instability of α-hydroxy aldehydes due to their partial isomerization into α-hydroxy ketones has previously been reported; see: Crestia, D.; Guérard, C.; Bolte, J.; Demuynck, C. *J. Mol. Catal. B: Enzym.* **2001**, *11*, 207–212.
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(10) Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017–3035.
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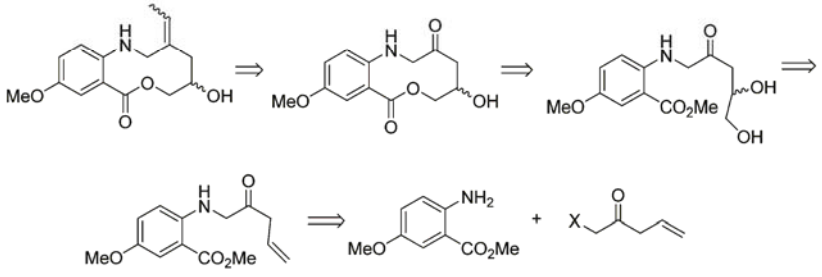
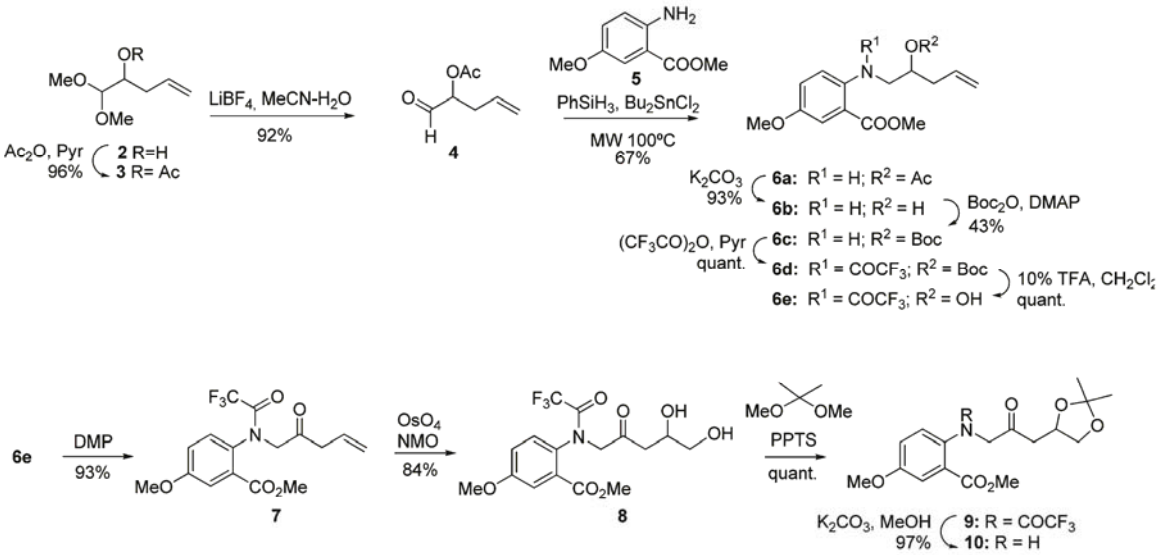
(12) Other reduction conditions proved unsuccessful. These included $NaBH(OAc)_3$ in THF at room temperature for 16 h, $NaBH(OAc)_3$ in CH_2Cl_2/AcOH at room temperature for 5 h, and $NaBH(OAc)_3$ in toluene at 110 °C for 2 h.
(13) The aniline **5** was isolated from the oxidation degradation mixture. Its formation could be rationalized through hydrolysis of the enamine resulting from enolization of the keto compound.
(14) Under these conditions, methyl 2-(5-allyl-2-oxooxazolidin-3-yl)-5-methoxybenzoate was isolated as a byproduct in 27% yield.
(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
(16) The *Z*/*E* stereoisomers were in a ratio of 73:27 (based on NMR signal areas).
(17) The NOESY correlations between $^{4}CH_2$ (2.27 and 2.41 ppm) and the vinyl proton (5.58 ppm) confirmed the stereochemistry of (*Z*)-**15** (see NOESY interactions in the Supporting Information).

SCHEME 1. Retrosynthetic Analysis of Compound 1



SCHEME 2. Route A for the Synthesis of 10



solid-supported DMAP in a 5 mM CH_2Cl_2 solution. The ^1H NMR spectrum of *Z*-**1** showed two doublets for the CH_3 linked to the double bond (1.42 ppm and 1.45 ppm) and two quadruplets for the vinylic proton (5.51 and 5.53 ppm).[18] These data could be explained by the presence of two highly populated conformations of *Z*-**1** at room temperature. Therefore, we studied peak coalescence by ^1H NMR run at different temperatures. Spectra from the initial experiments, run up to 55 °C in $CDCl_3$ as solvent, exhibited this trend, but coalescence was not reached at this temperature limit. Finally, coalescence was almost reached in DMSO-d_6 as solvent at 145 °C (see Table 4 in the Supporting Information). Moreover, comparison of spectroscopic data for barmumycin with those for *Z*-**1** revealed dramatic differences in the chemical shifts (see Tables 2 and 3 in the Supporting Information). This discrepancy, despite the conflicting stereochemistry of the two compounds (*Z*-**1** and *E*-barmumycin), led us to pursue a new structural assignment.

Re-evaluation of all possible alternative structures led us to systematic elucidation of *E*-**16** as a novel structure for barmumycin (Figure 3). Interestingly, the very close structural resemblance of **16** to the pretomaymycin and oxotomaymycin isolated from the extract (Figure 1) suggests that all three molecules could derive from the same biogenetic pathway.

In order to confirm that the structure of barmumycin is actually that of *E*-**16**, we synthesized the latter and subsequently compared it to an authentic sample of the former. This began with selective silyl protection of the primary alcohol in the commercially available *N*-Boc-*trans*-4-hydroxy-L-prolinol followed by oxidation of the secondary alcohol in the derivative **17**, which afforded ketone **18** in 62% yield over two steps (Scheme 4). Wittig chemistry was again employed to introduce the ethylidene chain: reaction of **18** with the Wittig ylide derived from ethyltriphenylphosphonium bromide yielded **19** as a 9:1 mixture of *Z*/*E*-diastereomers. *Z*/*E*-**19** was used directly without separation, as a single purification was planned for the final step of the synthesis. The TMS ether and the *tert*-butyl carbamate of *Z*/*E*-**19** were deprotected with 10% TFA in CH_2Cl_2 to give the pyrrolidine derivative *Z*/*E*-**20**. Condensation of *Z*/*E*-**20** to vanillic acid using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) and *N*,*N*-diisopropylethylamine (DIEA) gave a 9:1 mixture of *Z*/*E*-**16** diastereomers. The configuration of the double bond was established by the NOESY correlations in *Z*/*E*-**16** between $^5CH_2$ (4.00−4.20 ppm) and the CH_3 (1.60 ppm) (see NOESY correlations in the Supporting Information).

None of the Horner−Wadsworth−Emmons reactions tested (using the appropriate phosphonate and different bases[19]) gave

(18) The NOESY correlations between $^2CH_2$ (4.35 and 4.82 ppm) and CH_3 (1.42 and 1.45 ppm), and between $^4CH_2$ (2.09−2.20 ppm) and the vinyl proton (5.51 and 5.53 ppm), confirmed the stereochemistry of (*Z*)-**1** (see NOESY interactions in the Supporting Information).

(19) The reaction was performed with $(EtO)_2P(O)CH_2CH_3$ and either LDA, K^{t}BuO, or NaHMDS as base.

SCHEME 3. Route B for the Synthesis of 10

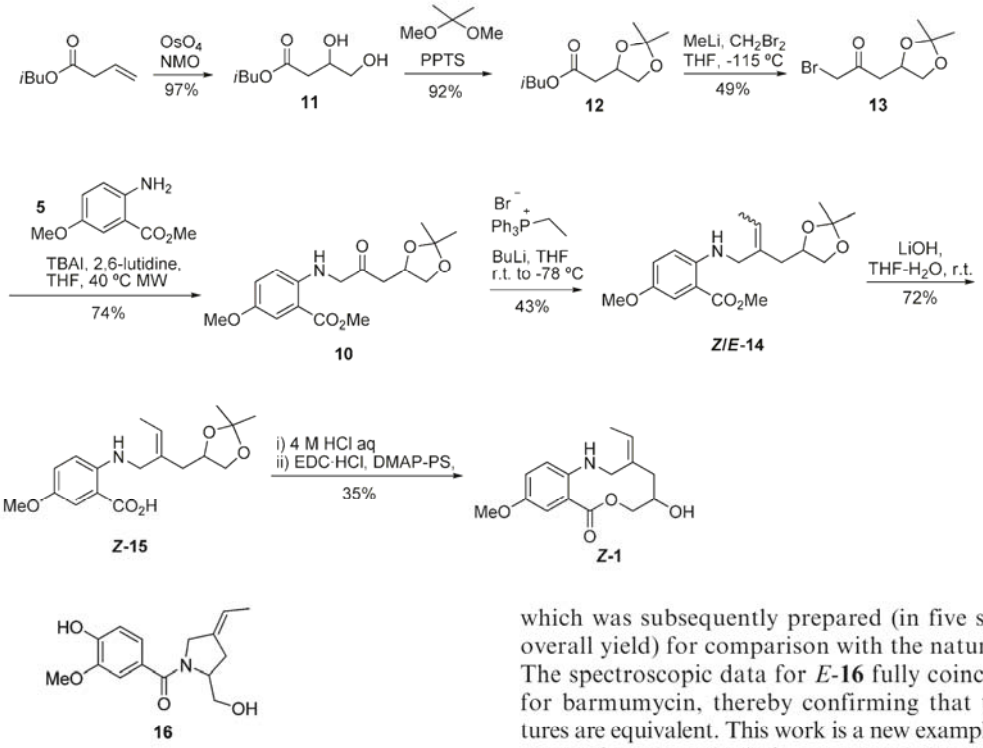


FIGURE 3. Structure proposed for barmumycin upon re-evaluation of NMR data.

the desired *E*-**19**. However, the Kocienski variant of the Julia–Lythgoe olefination[20] afforded a 2:1 mixture of *E*/*Z*-**19**. This process entails nucleophilic addition of 5-(ethylsulfonyl)-1-phenyl-1*H*-tetrazole anion to the ketone followed by transposition and elimination to give the double bond. Again, deprotection of the hydroxyl group and the amine group was obtained using 10% TFA in CH_2Cl_2, and condensation of *E*/*Z*-**20** to vanillic acid using PyBOP and DIEA gave a 2:1 mixture of *E*/*Z*-**16**. This mixture was purified by semipreparative HPLC to obtain *E*-**16** as a single diastereomer. The configuration of the double bond was established by the NOESY correlations in *E*-**16** between $^5CH_2$ (4.00–4.22 ppm) and the vinyl proton (5.30–5.38 ppm) (see the NOESY correlations in the Supporting Information).

Comparison of spectroscopic data obtained for *E*-**16** and barmumycin confirmed that the revised structure is indeed the structure of the natural product.

In summary, the previously unreported marine compound barmumycin was isolated, and its chemical formula was determined via mass spectrometry. On the basis of preliminary NMR data, barmumycin was initially assigned the structure of compound **1**. To confirm this assignment, compound **1** was synthesized following two different strategies starting from an *o*-aminobenzoic ester: one based on reductive amination, and one based on *N*-alkylation, which was shorter and higher yielding. However, comparison of the NMR spectra for **1** with those for isolated barmumycin showed dramatic differences. The structure of barmumycin was reassessed, and most probable option conceived was compound *E*-**16**, which was subsequently prepared (in five steps and 18% overall yield) for comparison with the natural compound. The spectroscopic data for *E*-**16** fully coincided with that for barmumycin, thereby confirming that the two structures are equivalent. This work is a new example of the importance of total synthesis for structural characterization and confirmation of natural products.[21]

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Experimental Section

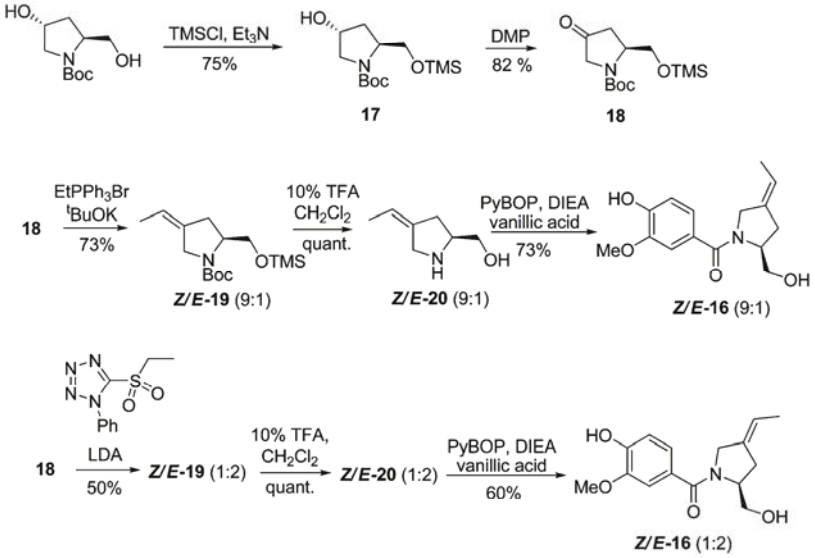
See the Supporting Information for general procedures.

Extraction and Isolation of Barmumycin. The culture broth (10 L) was separated by filtration into a mycelial cake and cultured filtrate (9 L). A 500 mL aliquot of the absorber resin XAD-1180 was added to the filtrate. Compound barmumycin was eluted from the resin by double extraction with a 3:1:1 mixture of EtOAc–MeOH–H_2O (1.8 L). The active fractions were concentrated in the organic phase, which was concentrated to dryness in vacuo to yield 950 mg of crude extract. This extract purified by vacuum flash chromatography using a mixture of *n*-hexane–EtOAc and EtOAc–MeOH, whereby the fractions containing barmumycin (220 mg) were eluted with 9:1 EtOAc–MeOH. The active fractions were purified by silica gel chromatography using CHCl–-MeOH mixtures. Cytotoxicity was detected in the fractions eluted with 96:4 CHCl–-MeOH (20 mg). Further purification with a C18 column by HPLC afforded 6 mg of pure barmumycin (elution with 54:46 H_2O/MeOH). This quantity of barmumycin was treated with 0.5 mL of pyridine and 0.5 mL of Ac_2O to afford 7 mg of the corresponding diacetate. The molecular formula of barmumycin was determined to be $C_{15}H_{19}NO_4$ by HPLC–APESI MS, in which it gave an $(M + Na)^+$ peak at 300 and $(M - H)^-$ 276. Barmumycin gave an $(M + H)^+$ peak at 278 and $(M - H)^-$ 276 in HPLC-APCI MS and it gave an $(M + H)^+$ ion at *m*/*z* 278.13840 (calcd *m*/*z* 278.13869 for $C_{15}H_{20}NO_4$) in HRMALDI-TOF MS.

The diacetyl derivative of barmumycin gave an $(M + H)^+$ peak at 362 and an $(M + Na)^+$ peak at 384 by HPLC–APCI MS and HPLC–ESI MS.

(21) (a) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044. (b) Cornella, I; Kelly, T. R. *J. Org. Chem.* **2004**, *69*, 2191–2193.

SCHEME 4. Preparation of *Z*/*E*-16 Starting from *N*-Boc-*trans*-4-hydroxy-L-prolinol



2-Acetoxypent-4-enal (4). $LiBF_4$ (6.05 g, 64.5 mmol) was added to a solution of **3** (4.05 g, 21.5 mmol) in 98:2 MeCN/H_2O (110 mL), and the mixture was stirred for 72 h at room temperature. The solvents were removed in vacuo. The crude was dissolved in CH_2Cl_2, washed with water and brine, and then concentrated in vacuo to yield **4** (2.82 g, 92%) as a yellowish oil. IR (KBr film): ν 3080, 2932, 1744, 1373, 1237, 1048 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H); 2.32−2.65 (m, 2H); 5.06−5.30 (m, 3H); 5.65−5.87 (m, 1H); 9.54 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.4 (q); 33.1 (t); 77.2 (d); 119.0 (t); 131.4 (d); 170.4 (s); 197.9 (d). MS (ESI-TOF): 143 (M + 1, 100).

Methyl 2-(2-Acetoxypent-4-enylamino)-5-methoxybenzoate (6a). $PhSiH_3$ (2.01 g, 18.6 mmol) was added to a THF solution (12 mL) of **5** (2.02 g, 9.3 mmol), **4** (1.32 g, 9.3 mmol), and Bu_2SnCl_2 (282.3 mg, 0.9 mmol) in a sealed tube. The mixture was heated to 100 °C under MW irradiation for 15 min. The solvents were removed in vacuo. Purification by silica gel column chromatography (100:0 to 95:5 hexane−Et_2O) yielded **6a** (1.93 g, 67%) as a yellowish oil. IR (KBr film): ν 3479, 3370, 2951, 1739, 1691, 1520, 1223, 1042 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H, Me); 2.41−2.46 (m, 2H); 3.35−3.37 (m, 2H); 3.76 (s, 3H, OMe); 3.86 (s, 3H, OMe); 5.09−5.17 (m, 3H); 5.78 (ddt, J = 17.2, 10.1, and 7.1 Hz, 1H); 6.74 (d, J = 9.2 Hz, 1H); 7.04 (dd, J = 9.2, 3.1 Hz, 1H); 7.42 (d, J = 3.1 Hz, 1H); 7.55 (bs, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.0 (q); 36.3 (t); 45.6 (t); 51.5 (q); 55.9 (q); 71.6 (d); 110.2 (s); 112.9 (d); 114.3 (d); 118.3 (t); 123.3 (d); 133.0 (d); 146.0 (s); 149.5 (s); 168.6 (s); 170.6 (s). MS (ESI-TOF): 308 (M + 1, 82). HRMS: m/z calcd. for $C_{16}H_{22}NO_5$ 308.1498, found 308.1504.

Methyl 2-(2-Hydroxypent-4-enylamino)-5-methoxybenzoate (6b). K_2CO_3 (953.5 mg, 6.9 mmol) was added to a solution of **6a** (1.92 g, 6.27 mmol) in MeOH (75 mL). The mixture was stirred for 1 h at room temperature. The solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and then washed with water and brine. The organic extracts were dried over $MgSO_4$ and then concentrated in vacuo. Purification by silica gel column chromatography (85:15 to 75:25 hexane/EtOAc) yielded **6b** (1.55 g, 93%) as a yellow oil. IR (KBr film): ν 3370, 1688, 1518, 1437, 1222, 1073 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.27−2.43 (m, 2H); 3.20 (dd, J = 13.0 and 7.7 Hz, 1H); 3.33 (dd, J = 13.0 and 4.5 Hz, 1H); 3.77 (s, 3H, OMe); 3.87 (s, 3H, OMe); 3.96 (m, 1H); 5.17 (m, 1H); 5.19 (m, 1H); 5.87 (m, 1H); 6.75 (d, J = 9.1 Hz, 1H); 7.04 (dd, J = 9.1, 3.1 Hz, 1H); 7.44 (d, J = 3.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 39.5 (t); 49.3 (t); 51.7 (q); 56.0 (q); 69.3 (d); 110.8 (s); 113.6 (d); 114.5 (d); 118.5 (t); 123.2 (d); 133.9 (d); 145.8 (s); 149.9 (s); 168.6 (s). MS (ESI-TOF): 266 (M + 1, 100). HRMS: m/z calcd for $C_{14}H_{20}NO_4$ 266.1392, found 266.1398.

Methyl 2-(2-(*tert*-Butoxycarbonyloxy)pent-4-enylamino)-5-methoxybenzoate (6c). Boc_2O (823 mg, 3.77 mmol) was added to a solution of **6b** (909.4 mg, 3.43 mmol) and DMAP (125.6 mg, 1.03 mmol) in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred for 40 h at room temperature and then concentrated in vacuo. Purification by silica gel column chromatography (100:0 to 95:5 hexane−EtOAc) yielded **6c** (543 mg, 43%) as a yellowish oil. IR (KBr film): ν 3369, 3078, 1730, 1709, 1500, 1368 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 9H); 2.41−2.48 (m, 2H); 3.39 (d, J = 6.1 Hz, 2H); 3.76 (s, 3H, OMe); 3.85 (s, 3H, OMe); 4.91 (p, J = 6.1 Hz, 1H); 5.12 (m, 1H); 5.17 (m, 1H); 5.82 (m, 1H); 6.74 (d, J = 9.2 Hz, 1H); 7.04 (dd, J = 9.2, 3.1 Hz, 1H); 7.42 (d, J = 3.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 27.7 (q); 36.5 (t); 45.9 (t); 51.6 (q); 56.0 (q); 74.4 (d); 82.2 (s); 110.4 (s); 112.9 (d); 114.4 (d); 118.4 (t); 123.3 (d); 132.9 (d); 145.8 (s); 149.6 (s); 153.2 (s); 168.5 (s). MS (ESI-TOF): 366 (M + 1, 100). HRMS: m/z calcd for $C_{19}H_{28}NO_6$ 366.1917, found 366.1917.

Methyl 2-[*N*-(2-(*tert*-Butoxycarbonyloxy)pent-4-enyl)trifluoroacetamido]-5-methoxybenzoate (6d). TFAA (0.3 mL, 2.2 mmol) was added to a cooled (0 °C) solution of **6c** (542.9 mg, 1.49 mmol) in pyridine (20 mL), and the mixture was stirred at 0 °C for 90 min. The crude was concentrated in vacuo, dissolved in CH_2Cl_2, and then washed with NH_4Cl, water, and brine. The organic extracts were dried over $MgSO_4$ and then concentrated in vacuo to yield **6d** as a mixture of rotamers (685 mg, quant) as a yellowish oil. IR (KBr film): ν 1736, 1707, 1502, 1282 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 and 1.47 (2s, 9H); 2.32−2.40 (m, 2H, CH_2); 3.04 and 3.31 (2dd, J = 14.4, 9.3 and 14.8, 2.2 Hz, 1H, CH_2); 3.86 (s, 3H, OMe); 3.87 (s, 3H, OMe); 4.41 and 4.51 (2dd, J = 14.4, 2.9 and 14.8, 8.9 Hz, 1H, CH_2); 4.82−4.87 and 5.17−5.23 (2 m, 1H, CH); 5.05−5.17 (m, 2H); 5.65−5.81 (m, 1H); 7.04 and 7.10 (2dd, J = 8.8, 3.0 Hz, 1H); 7.24 and 7.51 (2d, J = 8.8 Hz, 1H); 7.55 and 7.57 (2d, J = 3.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 27.6 and 27.7 (3q); 36.7 and 37.1 (t); 52.7 (q); 54.0 and 55.8 (t); 55.7 (q); 73.3 and 73.7 (d); 82.3 (s); 116.4 and 116.8 (d); 118.5 and 118.7 (d); 118.6 (t); 132.2 and 132.3 (d); 132.7 (d); 152.7 (s); 153.1 (s); 159.6 and 159.7 (s); 164.8 and 164.9 (s); 171.1 (s). ^{19}F NMR (376 MHz, $CDCl_3$): δ −68.8 and −69.0 (2s). MS (ESI-TOF): 945 (2M + Na, 15). HRMS: m/z calcd for $C_{42}H_{52}N_2O_{14}F_6Na$ 945.3220, found 945.3208.

Methyl 5-Methoxy-2-[*N*-(2-hydroxypent-4-enyl)trifluoroacetamido]benzoate (6e). A 10% solution of TFA in CH_2Cl_2 (50 mL) was added to **6d** (494.9 mg, 1.07 mmol), and the mixture was stirred at room temperature for 25 min. Elimination of the solvent gave **6e** (387 mg, quant) as a yellow oil. IR (KBr film): ν 3370, 2950, 1688, 1519, 1437, 1222, 1074 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.20−2.30 (m, 2H, CH_2); 3.46−3.49 and 3.54−3.61 (m, 1H); 3.88 (s, 3H, OMe); 3.90 (s, 3H, OMe); 4.02−4.15 (m, 2H); 4.89 (bs, 1H, OH); 5.10−5.14 (m, 2H); 5.72−5.81 (m, 1H); 7.09−7.14 (m, 1H); 7.31 and 7.39 (2d, J = 8.8 Hz, 1H); 7.55 (d, J = 2.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 39.3 and 39.4 (t); 52.9 (q); 55.8 (q); 58.4 and 59.0 (t); 68.2 and 68.8 (d); 114.9 (s); 116.2 and 116.7 (d); 118.8 (t); 118.9 and 119.0 (d); 120.1 (s); 120.9 (s); 122.8 (s); 131.1 (s); 131.9 and 132.1 (d); 133.1 and 133.4 (d); 159.8 (s). ^{19}F NMR (376 MHz, $CDCl_3$): δ −68.7 (s). MS (ESI-TOF): 362 (M + 1, 37). HRMS: m/z calcd for $C_{16}H_{19}NO_5F_3$ 362.1215, found 362.1211.

Methyl 5-Methoxy-2-[*N*-(2-oxopent-4-enyl)trifluoroacetamido]-benzoate (7). Dess−Martin periodinane (606.4 mg, 1.43 mmol) was added to a solution of **6e** (469.6 mg, 1.30 mmol) in anhydrous CH_2Cl_2 (35 mL). The mixture was stirred for 1 h and then diluted with Et_2O and hexane to a final concentration of 30:20:50 CH_2Cl_2/Et_2O/hexane. The solution was filtered through a silica gel pad. The solvents were removed in vacuo to yield **7** (433 mg, 93%) as a yellowish oil. IR (KBr film): ν 1707, 1704, 1502, 1291, 1204, 1153 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.18 (dd, J = 16.8 and 6.7 Hz, 1H); 3.27 (dd, J = 16.8 and 7.2 Hz, 1H); 3.85 (m, 1H); 3.86 (s, 3H, OMe); 3.89 (s, 3H, OMe); 5.13−5.23 (m, 3H); 5.95 (m, 1H); 7.06 (dd, J = 8.8 and 3.0 Hz, 1H); 7.51 (d, J = 3.0 Hz, 1H); 7.59 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.0 (t); 52.7 (q); 55.7 (q); 60.4 (t); 114.7 (s); 116.5 (d); 117.6 (s); 118.4 (d); 119.9 (t); 129.0 (s); 129.1 (d); 131.6 (s); 132.6 (d); 159.8 (s); 165.0 (s); 200.8 (s). ^{19}F NMR (376 MHz, $CDCl_3$): δ −68.8 (s). MS (ESI-TOF): 360 (M + 1, 100). HRMS: m/z calcd for $C_{16}H_{17}NO_5F_3$ 360.1059, found 360.1072.

Methyl 5-Methoxy-2-[*N*-(2,4,5-trihydroxypent-2-enyl)trifluoro-acetamido]benzoate (8). A solution of **7** (775 mg, 2.16 mmol) in acetone (20 mL) was added dropwise over 10 h to a stirring solution of *N*-methylmorpholine oxide (337 mg, 2.37 mmol) and OsO_4 (catalytic amount) in 60:40 acetone/H_2O (64 mL). The mixture was stirred for 20 h at room temperature, quenched with 40% aq $NaHSO_3$ (3 mL), and subsequently concentrated in vacuo. The residue was dissolved in EtOAc, dried over $MgSO_4$, filtered, and then reconcentrated in vacuo. Purification by silica gel column chromatography (100:0 to 90:10 CH_2Cl_2−MeOH) yielded **8** (628 mg, 84%) as a brownish oil. IR (KBr film): ν 1725, 1605, 1503, 1293, 1204 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 3.25−3.30 (m, 1H); 3.36−3.43 (m, 1H); 3.63−3.71 (m, 1H, CH); 3.84 (s, 6H, 2OMe); 4.12−4.13 (m, 1H); 4.16 and 4.33 (2d, J = 18.5 Hz, 1H); 5.14 and 5.33 (2d, J = 18.5 Hz, 1H); 7.27 and 7.29 (2dd, J = 3.0 Hz, 1H); 7.41−7.48 (m, 2H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 52.6 (q); 55.7 (q); 59.4 and 60.2 (t); 61.3 (t); 72.2 and 72.9 (d); 76.0 and 76.1 (d); 116.0 (d); 118.5 (d); 128.6 (s); 128.7 (s); 131.2 (s); 131.9 (d); 159.2 (s); 164.4 (s); 206.2 (s); 207.5 (s). ^{19}F NMR (376 MHz, $CDCl_3$): δ −68.8 (s). MS (ESI-TOF): 392 (M − 1, 100); 394 (M + 1, 40). HRMS: m/z calcd for $C_{16}H_{17}NO_7F_3$ 392.0957, found 392.0946.

Methyl 2-[*N*-(3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-oxopropyl)-trifluoroacetamido]-5-methoxybenzoate (9). Pyridinium *p*-toluene-sulfonate (18.7 mg, 74 mmol) was added to a solution of **8** (584 mg, 1.49 mol) and 2,2-dimethoxypropane (1.82 mL, 14.8 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at 40 °C for 16 h and then concentrated in vacuo. Purification by silica gel column chromatography (90:10 to 40:60 hexane−EtOAc) yielded **9** (642 mg, quant) as a yellowish oil. IR (KBr film): ν 1775, 1730, 1381, 1172, 1087, 1047 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 and 1.36 (2s, 6H); 2.59 and 2.69 (2dd, J = 16.3, 6.8 and 16.7, 6.0 Hz, 1H, CH_2); 2.81 and 2.90 (2dd, J = 16.7, 6.8 and 16.3, 6.0 Hz, 1H, CH_2); 3.54 and 3.60 (2dd, J = 8.4, 6.6 Hz, 1H); 3.77−3.83 (m, 1H); 3.85 (s, 3H, OMe); 3.87 (s, 3H, OMe); 4.12−4.18 (m, 1H); 4.40−4.48 (m, 1H); 5.08 (d, J = 17.9 Hz, 1H); 5.13 (d, J = 17.9 Hz, 1H); 7.048 and 7.051 (2dd, J = 8.8 and 3.0 Hz, 1H); 7.50 (d, J = 3.0 Hz, 1H); 7.55 and 7.57 (2d, J = 8.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.4 (q); 26.8 (q); 44.3 and 44.4 (t); 52.6 (q); 55.7 (q); 61.2 and 61.4 (t); 69.0 and 69.2 (t); 71.3 (d); 109.1 (s); 114.6 (s); 116.4 and 116.5 (d); 117.5 (s); 118.4 (d); 129.0 (s); 131.6 (s); 132.5 and 132.6 (d); 159.8 (s); 164.9 (s); 200.8 (s). ^{19}F NMR (376 MHz, $CDCl_3$): δ −68.8 (s). MS (ESI-TOF): 434 (M + 1, 100).

Isobutyl 3,4-Dihydroxybutanoate (11). A solution of isobutyl but-3-enoate (10.5 g, 73.6 mmol) in acetone (50 mL) was added dropwise over 20 h to a solution of *N*-methylmorpholine oxide (10.9 g, 80.9 mmol) and a catalytic amount OsO_4 in 60:40 acetone/H_2O (250 mL). The reaction was quenched with $NaHSO_3$ 40% aq solution (3 mL) and concentrated in vacuo. The crude was dissolved in EtOAc and filtered through silica gel, and the eluent was concentrated in vacuo to yield **11** (12.6 g, 97%) as a yellow oil. IR (KBr film): ν 3402, 2962, 1729, 1470, 1381, 1170, 1043 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, J = 6.8 Hz, 6H); 2.00−1.89 (m, 1H); 2.51 (dd, J = 16.4 and 4.0 Hz, 1H, CH_2); 2.58 (dd, J = 16.4 and 8.4 Hz, 1H, CH_2); 3.58 (dd, J = 11.2 and 6.4 Hz, 1H, CH_2); 3.69 (dd, J = 11.2 and 3.6 Hz, 1H, CH_2); 3.91 (d, J = 6.8 Hz, 2H); 4.10−4.18 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.2 (2q); 27.8 (d); 37.9 (t); 65.9 (t); 68.8 (d); 71.2 (t); 172.8 (s). MS (ESI-TOF): 177 (M + 1, 45); 199 (M + Na, 100). HRMS (+ESI): m/z calcd for $C_8H_{17}O_4$ (M + 1) 177.1127, found 177.1127; calcd for $C_8H_{16}O_4Na$ (M + Na) 199.0946, found 199.0945.

Isobutyl 2,2-Dimethyl-1,3-dioxolan-4-yl acetate (12). Pyridinium *p*-toluenesulfonate (120 mg, 0.48 mmol) was added to a solution of **11** (15.4 g, 87.26 mmol) in 50:50 2,2-dimethoxypropane/CH_2Cl_2 (300 mL). The reaction mixture was stirred at room temperature for 16 h, and then the solvent was removed in vacuo. Purification by silica gel column chromatography (50:50 hexane−EtOAc) yielded **12** (17.4 g, 92%) as a yellowish oil. IR (KBr film): ν 1736, 1380, 1370 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, J = 6.8 Hz, 6H); 1.35 (s, 3H); 1.41 (s, 3H); 1.98−1.87 (m, 1H); 2.52 (dd, J = 15.7 and 7.6 Hz, 1H, CH_2); 2.72 (dd, J = 15.7 and 6.4 Hz, 1H, CH_2); 3.65 (dd, J = 8.4 and 6.4 Hz, 1H, CH_2); 3.88 (d, J = 6.4 Hz, 2H); 4.16 (dd, J = 8.4 and 6.0 Hz, 1H, CH_2); 4.40−4.51 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.0 (2q); 25.5 (q); 26.9 (q); 27.6 (d); 39.0 (t); 69.2 (t); 70.8 (t); 72.1 (d); 109.1 (s); 170.6 (s).

1-Bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (13). A 1.6 M solution of MeLi in Et_2O (5 mL, 8 mmol) was added to a solution of **12** (865 mg, 4 mmol) and dibromomethane (557 μL, 8 mmol) in THF (20 mL) at −116 °C. The solution was stirred for 3 h and then quenched with satd NH_4Cl (60 mL). The residue was immediately extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. Purification by silica gel column chromatography (80:20 to 70:30 hexane−EtOAc) yielded **13** (460 mg, 49%) as a yellow oil. IR (KBr film): ν 1719, 1370, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3H); 1.42 (s, 3H); 2.82 (dd, J = 16.6 and 6.0 Hz, 1H, CH_2); 3.07 (dd, J = 16.6 and 6.8 Hz, 1H, CH_2); 3.60 (dd, J = 8.4 and 6.4 Hz, 1H, CH_2); 3.94 (s, 2H); 4.18 (dd, J = 8.4 and 6.0 Hz, 1H, CH_2); 4.44−4.51 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.4 (q); 26.8 (q); 34.6 (t); 44.16 (t); 69.2 (t); 71.8 (d); 109.3 (s); 199.7 (s). MS (ESI-TOF): 259 (MBr^{79} + Na, 100); 261 (MBr^{81} + Na, 98). HRMS (+ESI): m/z calcd for $C_8H_{13}O_3NaBr$ (M + Na) 258.9944, found 258.9946.

Methyl 2-[3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-oxopropyl-amino]-5-methoxybenzoate (10). Route A. K_2CO_3 (68 mg, 0.5 mmol) was added to a solution of **9** (50 mg, 0.11 mmol) in MeOH, and the mixture was stirred for 1 h. The solvent was removed in vacuo, and the resulting residue was purified by silica gel column chromatography (95:5 to 80:20 hexane/EtOAc) to yield **10** (38 mg, 97%) as a yellowish oil.

Route B. 2,6-Lutidine (1.6 mL, 13.74 mmol) and tetrabutylammonium iodide (3.08 g, 8.33 mmol) were added to a solution of **5** (1.21 g, 6.66 mmol) and **13** (1.37 g, 5.76 mmol) in 1,4-dioxane

(12 mL). The reaction mixture was stirred at 40 °C for 15 min under microwave irradiation. Purification by silica gel column chromatography (95:5 to 80:20 hexane−EtOAc) yielded **10** (1.44 g, 74%) as a yellow oil. IR (KBr film): ν 3350, 1705, 1692, 1521, 1286, 1225, 1045 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H); 1.40 (s, 3H); 2.64 (dd, J = 16.2, 6.5 Hz, 1H, CH_2); 2.94 (dd, J = 16.2, 6.5 Hz, 1H, CH_2); 3.58 (dd, J = 8.4, 6.7 Hz, 1H); 3.76 (s, 3H, OMe); 3.89 (s, 3H, OMe); 4.08 (bd, 2H, CH_2); 4.18 (dd, J = 8.4 and 6.0 Hz, 1H); 4.46−4.52 (m, 1H); 6.46 (d, J = 9.1 Hz, 1H); 7.02 (dd, J = 9.1 and 3.1 Hz, 1H); 7.45 (d, J = 3.1 Hz, 1H); 7.99 (bt, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.4 (q); 26.8 (q); 44.2 (t); 51.7 (q); 54.2 (t); 55.9 (q); 69.3 (t); 71.8 (d); 109.1 (s); 110.8 (s); 112.7 (d); 114.8 (d); 123.1 (d); 144.7 (s); 149.9 (s); 168.4 (s); 204.7 (s). MS (ESI-TOF): 338 (M + 1, 47); 675 (2M + 1, 100). HRMS: m/z calcd for $C_{17}H_{24}NO_6$ 338.1598, found 338.1603.

(*Z*/*E*)-Methyl 2-[2-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-but-2-enylamino]-5-methoxybenzoate (*Z*/*E*-14). A 2.5 M solution of BuLi in hexane (1.27 mL, 3.17 mmol) was added to a mixture of ethyltriphenylphosphonium bromide (1.18 g, 3.17 mmol) in anhydrous THF (13 mL). The reaction mixture was stirred at room temperature for 1 h and then cooled to −78 °C. A solution of **10** (337 mg, 1.58 mmol) in anhydrous THF (3 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at −78 °C for 30 min and subsequently allowed to warm to room temperature for an additional 30 min. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography with hexane−EtOAc (95:5 to 80:20) to yield *Z*-**14** and *E*-**14** as a yellowish oil (239 mg, 43%; 73:27 *Z*/*E*, as determined by ^1H NMR). IR (KBr film): ν 3373, 1689, 1517, 1222, 1065 cm^{-1}. *Z*-**14**. ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H); 1.40 (s, 3H); 1.74 (d, J = 6.9 Hz, 3H); 2.23−2.44 (m, 2H, CH_2); 3.53 (dd, J = 7.8 and 7.4 Hz, 1H); 3.76 (s, 3H, OMe); 3.82 (bs, 2H, CH_2); 3.85 (s, 3H, OMe); 4.00 (dd, J = 7.8 and 6.0 Hz, 1H); 4.19−4.26 (m, 1H); 5.56 (q, J = 6.9 Hz, 1H); 6.63 (d, J = 9.2 Hz, 1H); 7.03 (dd, J = 9.2 and 3.2 Hz, 1H); 7.42 (d, J = 3.2 Hz, 1H). *E*-**14**: ^1H NMR (100.6 MHz, $CDCl_3$): δ 1.35 (s, 3H); 1.43 (s, 3H); 1.65 (d, J = 6.9 Hz, 3H); 2.23−2.44 (m, 2H, CH_2); 3.56 (dd, J = 7.6 and 7.6 Hz, 1H); 3.75 (s, 3H, OMe); 3.82 (bs, 2H, CH_2); 3.86 (s, 3H, OMe); 4.02−4.05 (m, 1H); 4.19−4.26 (m, 1H); 5.62 (q, J = 6.9 Hz, 1H); 6.63 (d, J = 9.2 Hz, 1H); 7.00 (dd, J = 9.2 and 3.1 Hz, 1H); 7.41 (d, J = 3.1 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 13.4 (q); 25.7 (q); 27.0 (q); 32.6 and 42.8 (t); 40.0 (t); 51.5 (q); 56.0 (q); 69.3 (t); 75.0 (d); 108.9 (s); 112.8 and 114.1 (d); 114.4 (d); 123.3 (d); 125.4 (d); 133.0 (s); 133.7 (s); 146.4 (s); 149.4 (s); 168.6 (s). MS (ESI-TOF): 350 (M + 1, 35); 372 (M + Na, 45); 721 (2M + Na, 100). HRMS: m/z calcd for $C_{19}H_{28}NO_5$ 350.1962, found 350.1961.

(*Z*)-2-[2-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)but-2-enylamino]-5-methoxybenzoic Acid (*Z*-15). LiOH (310 mg, 7.39 mmol) was added to a solution of *Z*/*E*-**14** (258 mg, 0.74 mmol) in 75:25 H_2O/THF (20 mL). The reaction mixture was sonicated at room temperature for 1 h and then stirred at 50 °C for 24 h. The crude mixture was washed with Et_2O. The aqueous phase was cooled to 0 °C, acidified to pH 7 with 4 M HCl (1.7 mL), and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and then concentrated in vacuo to yield *Z*/*E*-**15** (250 mg, quant; 73:27 *Z*/*E*, as determined by ^1H NMR) as a yellowish oil. Purification by semipreparative HPLC performed on a 15.5 g Redisep Gold C_{18} (20−40 μm) column, with UV detection at 254 nm, a flow rate of 18 mL/min, and H_2O−CH_3CN as eluents (gradient: 80:20 to 60:40 in 50 min), yielded *Z*-**15** (80 mg, 72% recovery). IR (KBr film): ν 3375, 2985, 1668, 1577, 1516, 1371, 1216, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H); 1.42 (s, 3H); 1.74 (d, J = 6.9 Hz, 3H); 2.27 (dd, J = 14.3 and 5.7 Hz, 1H, CH_2); 2.41 (dd, J = 14.3 and 7.1 Hz, 1H, CH_2); 3.55 (t, J = 8.0 Hz, 1H); 3.78 (s, 3H, OMe); 3.86 (bs, 2H); 4.02 (dd, J = 8.0 and 6.0 Hz, 1H); 4.20−4.27 (m, 1H); 5.58 (q, J = 6.9 Hz, 1H); 6.69 (d, J = 9.1 Hz, 1H); 7.08 (dd, J = 9.1 and 3.1 Hz, 1H); 7.49 (d, J = 3.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.5 (q); 25.7 (q); 27.0 (q); 39.8 (t); 43.3 (t); 56.0 (q); 69.2 (t); 75.1 (d); 109.1 (s); 109.8 (s); 113.9 (d); 114.6 (d); 124.5 (d); 125.8 (d); 133.3 (s); 146.3 (s); 150.0 (s); 172.5 (s). MS (ESI-TOF): 336 (M + 1, 100); 337 (M + 2, 23).

(*Z*)-3-Ethylidene-5-hydroxy-10-methoxy-1,2,3,4,5,6-hexahydrobenzo[*c*][1,5]oxazecin-8-one (1). *Z*-**15** (30 mg, 0.09 mmol) was stirred with 4 M HCl (4 mL) for 30 min and then concentrated in vacuo to yield (*Z*)-2-(2-ethylidene-4,5-dihydroxypentylamino)-5-methoxybenzoic acid hydrochloride. The resulting residue was used in the following step without further purification. A mixture of EDC·HCl (69 mg, 0.36 mmol), (*Z*)-2-[2-ethylidene-4,5-dihydroxypentylamino]-5-methoxybenzoic acid hydrochloride, solid-supported DMAP (18 mg, 0.09 mmol), and molecular sieves 4 Å (254 mg) in dry CH_2Cl_2 (20 mL) was stirred at room temperature for 3 h. The crude mixture was filtered, treated with satd NH_4Cl, and then extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and then concentrated in vacuo. Purification by silica gel column chromatography (100:0 to 80:20 CH_2Cl_2/MeOH) yielded *Z*-**1** as a brownish oil (9 mg, 35%). IR (KBr film): ν 3397, 1640, 1498, 1436, 1292, 1228, 1039 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 and 1.45 (2d, J = 6.9 Hz, 3H); 2.09−2.20 (m, 2H, CH_2); 3.44−3.51 and 3.59−3.69 (2 m, 2H, CH_2); 3.73 (s, 3H, OMe); 3.79−3.90 (m, 1H); 4.35 (dd, J = 14.3 and 6.1 Hz, 1H, CH_2); 4.82 (dd, J = 14.3, 3.1 Hz, 1H, CH_2); 5.51 and 5.53 (2q, J = 6.9 Hz, 1H); 6.72−6.76 (m, 2H); 6.92 (2d, J = 8.5, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.4 (q); 38.2 and 38.9 (t); 46.9 and 47.1 (t); 55.5 (q); 66.2 and 66.8 (t); 70.4 and 70.9 (d); 111.5 and 111.6 (d); 116.5 (d); 127.0 and 127.1 (d); 127.9 and 128.4 (d); 130.2 and 130.5 (s); 130.7 (s); 136.1 and 136.2 (s); 158.9 (s); 169.1 and 169.2 (s). MS (ESI-TOF): 299 (M + Na, 13); 555 (2M + 1, 100); 577 (2M + Na, 100). HRMS: m/z calcd. for $C_{30}H_{38}N_2O_8Na$ 577.2520, found 577.2521.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-4-hydroxy-2-(trimethylsilyloxymethyl)pyrrolidine (17). TMSCl (0.65 mL, 4.85 mmol) was added to a solution of *N*-Boc-trans-4-hydroxy-L-prolinol (1.054 g, 4.85 mmol), Et_3N (0.67 mL, 4.85 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at 0 °C for 16 h. After this time the reaction 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 (70:30 to 50:50) yielded **17** (1.05 g, 75%) as a colorless oil. IR (KBr film) ν 3434, 1692, 1678, 1408, 1119 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 0.12 and 0.13 (2s, 9H); 1.50 and 1.51 (2s, 9H); 1.90−2.04 (m, 1H, CH_2); 2.18 (dt, J = 17.2 and 5.8 Hz, 1H, CH_2); 3.35−3.48 (m, 2H, CH_2); 3.63 and 3.65 (2d, J = 10.2 Hz, 1H, CH_2); 3.78 and 3.90 (2dd, J = 10.2 and 4.6 Hz, 1H, CH_2); 3.94−4.02 (m, 1H, CH); 4.38−4.44 (m, 1H, CH). ^{13}C NMR (100.6 MHz, CD_3OD) δ −0.5 (q); 28.8 (q); 37.3 and 38.2 (t); 55.9 and 56.4 (t); 58.8 and 58.9 (d); 63.6 and 64.6 (t); 70.1 and 70.6 (d) 80.8 and 81.1 (s); 155.3 (s). HRMS m/z calcd. for $C_{13}H_{28}NO_4Si$ 290.1782, found 290.1784.

(*S*)-1-*tert*-Butoxycarbonyl-2-(trimethylsilyloxymethyl)pyrrolidin-4-one (18). DMP (369 mg, 0.87 mmol) was added to a solution of **17** (228 mg, 0.78 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was stirred at room temperature for 15 min. After this time, satd $NaHCO_3$ and satd $Na_2S_2O_3$ were added, and the reaction mixture was stirred for additional 10 min. The residue was extracted with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane−EtOAc (80:20) yielded **18** (182 mg, 82%) as a colorless oil. IR (KBr film): ν 1765, 1701, 1401, 1106 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 0.12 (s, 9H); 1.54 (s, 9H); 2.41 (d, J = 18.0 Hz, 1H, CH_2); 2.77−2.93 (m, 1H, CH_2); 3.57−3.68 (m, 2H, CH_2); 3.86 (d, J = 18.0 Hz, 1H, CH_2); 3.99 (dd, J = 22.1, 10.0 Hz, 1H, CH_2); 4.38 and 4.40 (2bs, 1H, CH). ^{13}C NMR (100.6 MHz, CD_3OD): δ −0.9 (q); 28.7 (q); 41.1 and 41.7 (t); 54.4 and 54.9 (t); 56.8 and 57.4 (d); 65.3 and 66.1 (t), 81.6 (s). HRMS: m/z calcd for $C_{13}H_{26}NO_4Si$ 288.1626, found 288.1628.

(*S*,*Z*)-1-*tert*-Butoxycarbonyl-4-ethylidene-2-((trimethylsilyloxy)-methyl)pyrrolidine (*Z*-19). ^{t}BuOK (213 mg, 1.9 mmol) was added to a solution of ethyltriphenylphosphonium bromide (705 mg, 1.9 mmol) in THF (5 mL), and the mixture was stirred for 1 h. After this time, **18** (180 mg, 0.62 mmol) was added, and the mixture was stirred for additional 30 min. Water was added, the residue was extracted with Et_2O, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane−EtOAc (95:5) yielded *Z*/*E*-**19** (136 mg, 73%) in a 9:1 ratio as a colorless oil. IR (KBr film): ν 1702, 1397, 1251, 1109 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 9H,); 1.48 (s, 9H); 1.58 (d, J = 6.8 Hz, CH_3); 2.45−2.54 (m, 1H, CH_2); 2.56−2.67 (m, 1H, CH_2); 3.20−3.45 (m, 1H, CH_2); 3.55−3.67 (m, 1H, CH_2); 3.78−4.05 (m, 3H, CH + CH_2); 5.32−5.40 (m, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −0.5 (q); 14.5 (q); 28.5 (q); 34.0 and 34.5 (t); 47.5 (t) 57.5 and 57.7 (d); 62.7 and 63.1 (t); 79.4 (s); 115.9 and 116.2 (d); 136.7 (s); 154.2 (s). HRMS: m/z calcd for $C_{15}H_{30}NO_3Si$ 300.1989, found 300.1990.

(*S*,*Z*)-4-Ethylidene-2-(hydroxymethyl)pyrrolidine (*Z*-20). A solution of *Z*/*E*-**19** in a 9:1 ratio (136 mg, 0.45 mmol) in 10% TFA in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with CH_2Cl_2−MeOH (98:2 to 90:10) to obtain *Z*/*E*-**20** (105 mg) in a 9:1 ratio in quantitative yield. IR (KBr film): ν 3380, 1677, 1435, 1135 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (d, J = 8.0 Hz, 3H, CH_3); 2.34−2.45 (m, 1H, CH_2); 2.58−2.68 (m, 1H, CH_2); 3.65−3.95 (m, 5H); 5.50−5.58 (m, 1H, =CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.7 (q); 32.2 (t); 45.8 (t); 60.5 (t); 61.4 (d); 120.6 (d); 130.9 (s). HRMS: m/z calcd for $C_7H_{14}NO$ 128.1069, found 128.1070.

(*S*,*Z*)-*N*-(4-Hydroxy-3-methoxybenzoyl)-4-ethylidene-2-(hydroxymethyl)pyrrolidine (*Z*-16). PyBOP (135 mg, 0.26 mmol) was added to a solution of DIEA (0.1 mL, 0.55 mmol) and vanillic acid (44 mg, 0.26 mmol) in THF (5 mL), and the mixture was stirred for 10 min. Then, a solution of *Z*/*E*-**20** in a 9:1 ratio (26 mg, 0.21 mmol) in THF was added, and the mixture was stirred for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc and washed with satd $NaHCO_3$ and satd NH_4Cl. Purification by silica gel column chromatography with EtOAc yielded *Z*-**16** (45 mg, 73%) in a 9:1 ratio as a colorless oil. $[\alpha]_D$ = −21.5 (*c* 0.75, CH_2Cl_2). IR (KBr film): ν 3288, 1600, 1585, 1431, 1277, 1207 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (bs, 3H, CH_3); 2.27−2.40 (m, 1H, CH_2); 2.66−2.78 (m, 1H, CH_2); 3.65−3.75 (m, 2H, CH_2); 3.90 (s, 3H, OMe); 4.00−4.20 (m, 2H, CH_2); 4.53−4.69 (m, 1H, CH); 5.30−5.45 (m, 1H); 6.91 (d, J = 8.1 Hz, 1H); 7.05 (dd, J = 8.1 and 1.8 Hz, 1H); 7.09 (d, J = 1.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.5 (q); 34.1 (t); 51.5 (t); 56.1 (q); 59.9 (d); 66.4 (t); 110.4 (d); 114.0 (d); 117.7 (d); 120.7 (d); 128.0 (s); 134.4 (s); 146.6 (s); 147.6 (s); 172.0 (s). HRMS: m/z calcd for $C_{15}H_{20}NO_4$ 278.1387, found 278.1387.

(*S*,*E*)-1-*tert*-Butoxycarbonyl-4-ethylidene-2-(trimethylsilyloxy-methyl)pyrrolidine (*E*-19). A 2 M solution of LDA in THF (0.25 mL, 0.5 mmol) was added to a solution of 5-(ethylsulfonyl)-1-phenyl-1*H*-tetrazole (119 mg, 0.5 mmol) in THF (4 mL) at −78 °C, and the mixture was stirred for 10 min. After this time, **18** (116 mg, 0.4 mmol) was added, and the mixture was stirred for an additional 30 min. The reaction mixture was quenched with satd NH_4Cl and extracted with CH_2Cl_2. The organic fractions were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane−EtOAc (97:3) yielded *Z*/*E*-**19** (58 mg, 50%) in a 1:2 ratio as a colorless oil. IR (KBr film): ν 1702, 1397, 1251, 1109 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) (*E* diastereomer): δ 0.09 (s, 9H); 1.46 (s, 9H); 1.62 (d, J = 6.7 Hz, CH_3); 2.41−2.52 (m, 1H, CH_2); 2.54−2.66 (m, 1H, CH_2); 3.20−3.45 (m, 1H, CH_2); 3.55−3.65 (m, 1H, CH_2); 3.72−3.80 (m, 1H, CH_2); 3.87−4.05 (m, 2H); 5.32−5.42 (m, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) (*E* diastereomer): δ −0.5 (q); 14.4 (q); 28.5 (q); 29.8 and 30.4 (t); 50.8 and 51.4 (t); 57.5 and 57.7 (d); 62.7 and 63.1 (t); 79.4 (s); 115.5 and 116.1 (d); 136.7 (s); 154.2 (s). HRMS: m/z calcd for $C_{15}H_{30}NO_3Si$ 300.1989, found 300.1990.

(*S*,*E*)-4-Ethylidene-2-(hydroxymethyl)pyrrolidine (*E*-20). A solution of *Z*/*E*-**19** in 1:2 ratio (95 mg, 0.31 mmol) in 10% TFA in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with CH_2Cl_2−MeOH (98:2 to 90:10) to obtain *Z*/*E*-**20** in a 1:2 ratio in quantitative yield. IR (KBr film): ν 3380, 1677, 1435, 1135 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) (*E* diastereomer): δ 1.63 (d, J = 6.7 Hz, 3H, CH_3); 2.21−2.30 (m, 1H, CH_2); 2.58−2.68 (m, 1H, CH_2); 3.65−3.95 (m, 5H); 5.50−5.58 (m, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) (*E* diastereomer): δ 14.7 (q); 28.2 (t); 48.7 (t); 60.8 (t); 61.6 (d); 120.6 (d); 130.9 (s). ^{1}H NMR (400 MHz, CD_3OD) (*E* diastereomer): δ 1.68 (d, J = 6.9 Hz, 3H, CH_3); 2.40 (dd, J = 16.4 and 8.4 Hz, 1H, CH_2); 2.75 (dd, J = 16.4 and 7.0 Hz, 1H, CH_2); 3.60−3.98 (m, 5H); 5.55−5.67 (m, 1H, CH). ^{13}C NMR (100.6 MHz, CD_3OD) (*E* diastereomer): δ 14.8 (q); 29.1 (t); 50.1 (t); 61.2 (t); 62.7 (d); 121.0 (d); 133.1 (s). HRMS: m/z calcd for $C_7H_{14}NO$ 128.1069, found 128.1070.

(*S*,*E*)-*N*-(4-Hydroxy-3-methoxybenzoyl)-4-ethylidene-2-(hydroxymethyl)pyrrolidine (*E*-16). PyBOP (93 mg, 0.18 mmol) was added to a solution of DIEA (64 μL, 0.37 mmol) and vanillic acid (30 mg, 0.18 mmol) in THF (5 mL), and the mixture was stirred for 10 min. After this time, a solution of *Z*/*E*-**20** in a 1:2 ratio (19 mg, 0.15 mmol) in THF was added, and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc and washed with satd $NaHCO_3$ and satd NH_4Cl. Purification by silica gel column chromatography with EtOAc yielded *Z*/*E*-**16** (25 mg, 60%) in a 1:2 ratio. Purification by semipreparative HPLC using a Waters XBridge C18 column (10 × 100 mm, 5 μm), UV detection at 254 nm, with a flow of 3 mL/min, and H_2O−CH_3CN 18:82 as solvent system in isocratic conditions yielded *E*-**16** (5.7 mg). The ^{1}H NMR and ^{13}C NMR are identical as described for the natural product in Table 2 in the Supporting Information. $[\alpha]_D$ = −51.2 (*c* 0.25, CH_2Cl_2). IR (KBr film): ν 3288, 1600, 1585, 1431, 1277, 1207 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (d, J = 6.8, 3H, CH_3); 2.20−2.35 (m, 1H, CH_2); 2.67−2.77 (m, 1H, CH_2); 3.75 (bs, 2H, CH_2); 3.90 (s, 3H, OMe); 4.00−4.22 (m, 2H, CH_2); 4.67 (bs, 1H, CH); 5.34 (bs, 1H, CH); 6.91 (d, J = 7.8 Hz, 1H, Ar); 7.04 (d, J = 7.8, 1H, Ar); 7.09 (s, 1H, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.5 (q); 30.1 (t); 55.1 (t); 56.3 (q); 60.6 (d); 67.1 (t); 110.6 (d); 114.1 (d); 117.6 (d); 121.0 (d); 128.3 (s) 134.7 (s); 146.7 (s); 147.8 (s); 172.0 (s). HRMS: m/z calcd for $C_{15}H_{20}NO_4$ 278.1387, found 278.1387.

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Supporting Information Available: General procedures; tables of the bioactivity of isolated barmumycin and of its diacetyl derivative; NMR data Tables 2 and 3; ^{1}H and ^{13}C NMR spectra of compounds **6a**−**e**, **7**−**14**, **17**, **18**, (*Z*/*E*)-**19**, and (*Z*/*E*)-**20**; and the ^{1}H and ^{13}C NMR spectra with two-dimensional NMR experiments for compounds (*Z*)-**15**, (*Z*)-**1**, (*Z*)-**16**, and (*E*)-**16**. This information is available free of charge via the Internet at http://pubs.acs.org.

Supporting information

TABLE OF CONTENTS

1. General Procedures

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 vanillin in conc. H_2SO_4 or with phosphomolybdic acid in ethanol. Column chromatography was run using silica gel 60 (70-230 mesh). Automated flash chromatography was done in a medium-pressure liquid chromatograph with silica gel (47-60 μm) columns. For the isolation, HPLC was used equipped with a photodiode-array and MS detectors; analysis was performed at room temperature using a C18 (5μ) analytical column, MeCN/H_2O as mobile phase (gradient of 45:55 to 85:15 in 25 minutes), a flow rate of 0.3 mL/min, and detection at 220 nm. Under these conditions **barmumycin** elutes at 15.79 min and its acetyl derivative elutes at 23.56 min. For the synthesis, analytical HPLC was performed on a separation module 2695 equipped with a PDA detector (254 nm) and C_{18} column (75 x 4.6 mm, 2.5 μm) in 8-minute long runs. HPLC-ESI-MS and HPLC-APCI-MS analysis were performed with a liquid chromatograph equipped with a gradient pump and a mass spectrometer featuring nebulizer-assisted electrospray and atmospheric pressure chemical ionization sources Microwave-assisted reactions were run in a CEM Discover microwave. Chemical shifts are reported in ppm referenced to the appropriate residual solvent peaks (CD_3OD, d_6-DMSO or $CDCl_3$) and coupling constants are reported in Hz. The multiplicity of signals is indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, bd = broad doublet, m = multiplet. The IR spectra were obtained on a FT-IR spectrometer. Vibration frequencies are expressed in cm^{-1}. Optical rotations were measured on a polarimeter equipped with a Na-lamp.

2. Biological activities of barmumycin and acetylated barmumycin

Table 1. Activities of **barmumycin** and acetylated **barmumycin**

		Prostate	Ovary		Melanoma	NSCL	Leukemia	Pancreas	Colon			Cervix	
		DU-145	IGROV	IGROV -ET	SK-MEL-28	A549	K-562	PANC-1	HT29	LOVO	LOVO-DOX	HELA	HELA-APL
Barmumycin	GI50	1.16E-06	8.37E-07	9.84E-07	2.06E-06	7.03E-06	7.68E-07	9.92E-07	8.29E-06	7.03E-07	6.31E-07	1.06E-06	2.05E-06
	TGI	1.75E-06	1.53E-06	1.97E-06	5.34E-06	1.30E-05	1.58E-06	2.07E-06	2.23E-05	1.23E-06	1.14E-06	1.73E-06	5.70E-06
	LC50	2.62E-06	2.82E-06	5.95E-06	1.37E-05	2.41E-05	3.26E-06	6.35E-06	3.61E-05	2.16E-06	2.06E-06	2.82E-06	1.41E-05
Acetylated Barmumycin	GI50	7.39E-06	5.89E-06	5.89E-06	7.47E-06	2.51E-05	4.98E-06	6.53E-06	>2.77E-05	5.15E-06	5.53E-06	7.17E-06	5.09E-06
	TGI	1.15E-05	1.01E-05	1.03E-05	1.51E-05	>2.77E-05	9.60E-06	1.47E-06	>2.77E-05	8.99E-06	9.77E-06	1.12E-05	1.14E-05
	LC50	1.8E-05	1.73E-05	1.80E-05	>2.77E-05	>2.77E-05	1.85E-05	>2.77E-05	>2.77E-05	1.57E-05	1.73E-05	1.75E-05	2.53E-05

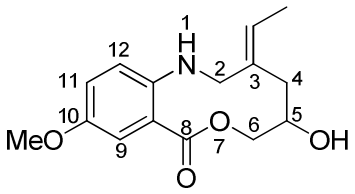
*GI50:Growth Inhibition at 50%; TGI: Tumor Growth inhibition; LC50: Lethal Concentration at 50%

Cell growth inhibition assay

A colorimetric assay using sulforhodamine B (SRB) was adapted to perform quantitative measurement of cell growth and viability, following a previously described method.[1] Cells were seeded in 96-well microtiter plates, at 5 x 10^3 cells per well, in aliquots of 195 µL of RPMI medium, and were allowed to attach to the plate surface by growing in drug-free medium for 18 hours. Afterwards, samples were added in aliquots of 5 µL (dissolved in DMSO:H_2O, 3:7). After 72 hours of exposure, the antitumor effect was measured by the SRB methodology: cells were fixed by adding 50 µL of cold 50% (wt/vol) trichloroacetic acid (TCA) and were incubated for 60 minutes at 4 °C. Plates were washed with deionized H_2O and dried; 100 µL of SRB solution (0.4% wt/vol in 1% acetic acid) was added to each microtiter well and incubated for 10 minutes at room temperature. Unbound SRB was removed by washing with 1% acetic acid. Plates were air-dried and bound stain was solubilized with Tris buffer. Optical densities were read on an automated spectrophotometer plate reader at a single wavelength of 490 nm. Data analyses were generated automatically by LIMS implementation. Using control OD values (C), test OD values (T) and time zero OD values (T_0), the drug concentration that causes 50% Growth Inhibition (GI_{50} value) was calculated from the equation: 100 x $[(T-T_0)/C- T_0)_-] = 50$.

3. Assignation data tables

Table 2. NMR assignation data for **proposed** barmumycin*

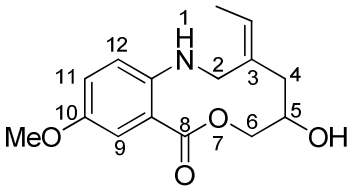


***E*-1**

C /H number	δ_H	δ_C	HMBC	NOESY
2	4.00-4.22 (m)	55.1 (t)	-	H11, CH=
3	-	134.7 (s)	-	-
4	2.20-2.35 (m, 1H); 2.67-2.77 (m, 1H)	30.1 (t)	-	H6, H5, MeC
5	4.67 (bs)	60.6 (d)	-	H6, H4
6	3.75 (bs)	67.1 (t)	-	H4, H5
8	-	172.2 (s)	-	-
8a	-	128.3 (s)	-	-
9	7.09 (s)	110,6 (d)	C8, C12a, C10, C11	OMe
10	-	146.7 (s)	-	-
11	7.04 (d, J = 7.8 Hz)	121.0 (d)	C9, C12a	H12, H2
12	6.91 (d, J = 7.8 Hz)	114.1 (d)	C8a, C10	H11
12a	-	147.8 (s)	-	-
CH=	5.34 (m)	117.6 (d)	-	H2, MeC,
Me CH=	1.62 (d, J = 6.6 Hz)	14.5 (q)	C3, CH=	H4, CH=
-OMe	3.90 (s)	56.3 (q)	C10	H9

* Spectra recorded in $CDCl_3$

Table 3. NMR data for synthetic compound *Z*-1*



***Z*-1**

C /H number	δ_H	δ_C	HMBC	NOESY
2	4.35 (dd, *J* = 14.3, 6.1 Hz, 1H); 4.82 (dd, *J* = 14.3, 3.1 Hz, 1H)	46.9 and 47.1 (t)	C3, C4, C8a, CH=	H11, H4, Me-C
3	-	130.2 and 130.5 (s)	-	-
4	2.09-2.20 (m, 2H, CH_2)	38.2 and 38.9 (t)	C3, C5, CH=	H2, H5, H6, CH=
5	3.79-3.90 (m, 1H)	70.4 and 70.9 (d)	-	H4, CH=
6	3.44-3.51 and 3.59-3.69 (2m)	66.2 and 66.8 (t)	-	H4
8	-	169.1 and 169.2 (s)	-	-
8a	-	130.7 (s)	-	-
9	6.72-6.76 (m, 1H)	116.5 (d)	C8, C8a, C10, C11	OMe
10	-	158.9 (s)	-	-
11	6.92 (dd, *J* = 8.5, 1.3 Hz, 1H)	127.0 and 127.1 (d)	C8a, C12a, C10	H12, H2
12	6.72-6.76 (m, 1H)	111.5 and 111.6 (d)	C9, C10	-
12a	-	136.1 and 136.2 (s)	-	-
CH=	5.51 and 5.53 (2q, *J* = 6.9 Hz)	127.9 and 128.4 (d)	C2, C4, MeC	H4, H5, MeC
Me CH=	1.42 and 1.45 (2d, *J* = 6.9 Hz)	13.4 (q)	C3, =CH	H2, H11, CH=
MeO	3.73 (s, 3H)	55.5 (q)	C10	H9

* Spectra recorded in $CDCl_3$

4. NMR Spectra.

NMR spectra images are available in the supporting information in electronic format.

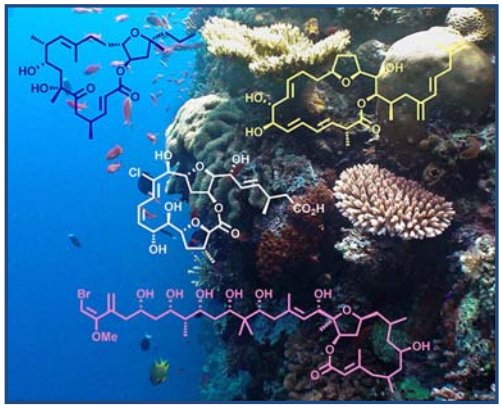
5. References

1. a) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Waren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. New colorimetric cytotoxicity assay for anticancer Drug Screening. *J. Natl. Cancer Inst*., **1990**, *82*, 1107-1112. b) Faircloth, G. T.; Stewart, D.; Clement, J. J. A simple screening procedure for the quantitative measurement of cytotoxicity assay. *J. Tissue Cult. Methods* **1988**, *11*, 201-205.

3 THF-Containing macrolides: A fascinating gift from the deep sea

Acodontaster conspicuus

TETRAHYDROFURAN-CONTAINING MACROLIDES: A FASCINATING GIFT FROM THE DEEP SEA



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RESUME

Marine polyketide macrolides are a class of secondary metabolites with interesting and diverse biological activities and complex structure and stereochemistry. During the last years, the occurrence of THF motifs has appeared as a common feature on new isolated compounds, being such fact an example of how the sea offers a vast array of new molecular entities to be discovered.

In this chapter, an overview of a family of compounds classified as THF-containing macrolides is listed. A short introduction on their biosynthesis explains how nature synthesizes these compounds through the complex machinery of polyketide synthases (PKSs) and post-translational modifications. Discussion is then centered on isolation and reported total synthesis of such structures, emphasizing strategies to obtain the THF motif and key steps towards the whole of the macrolides.

An important conclusion can be extracted from this overview, synthesis is an essential tool for structure determination and procurement of sample for bioactivity studies. Moreover, targeting these structures suppose an advance on chemical synthesis development, because requires innovation on reagents and synthetic strategies, which can be further applied to synthesis of other natural compounds.

CHEMICAL REVIEWS

Review

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Tetrahydrofuran-Containing Macrolides: A Fascinating Gift from the Deep Sea

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CONTENTS

1. INTRODUCTION

Marine organisms have produced a big number of structurally diverse secondary metabolites with important biological activities as a defense mechanism to the persistent aggression of their environment.[1] This structural diversity makes marine natural products excellent candidates for the investigation of new bioactive molecules with high pharmacological potential.[2]

A significant number of marine polyketide macrolides have been isolated in the last years from sponges, algae, dinoflagellate, and other marine invertebrates, characterized by their structural novelty. From a chemical structure point of view, marine polyketide macrolides are fascinating, many of them being highly oxygenated and stereochemically elaborate, such as, for instance, the oxazole containing polyketides kabiramide C,[3] halichondramide,[4] and ulapualide A[5] or the complex polyketide family of the spongistatins[6] (Figure 1).

The determination of full bioactivity, mechanism of action, and further medical application of marine polyketide macrolides is usually unfeasible because their isolation from natural sources very often furnishes very small sample amounts. Thus, synthesis is necessary for further development of these macrolides as pharmacological leads, not only in terms of their supply, but also for structural and stereochemical assignments. Several reviews focusing on the isolation, structure determination, and synthesis of polyketide macrolides have been published until now.[7]

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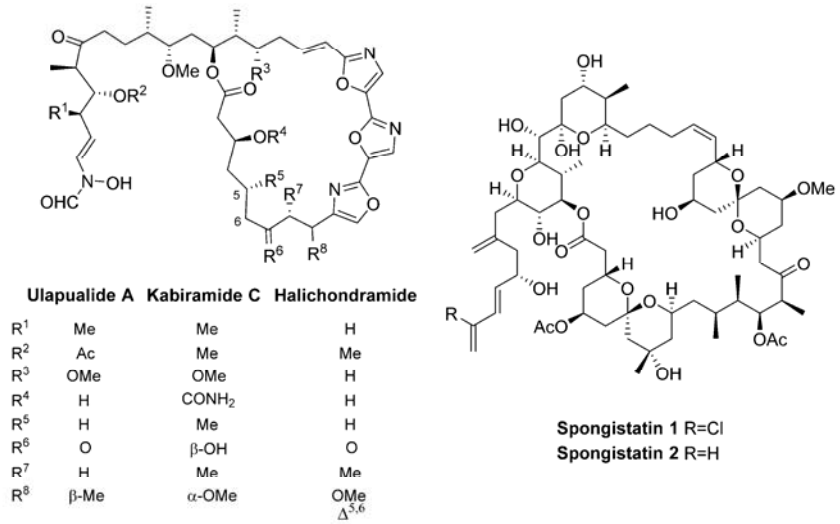

Figure 1. Structures of ulapualide A, kabiramide C, halichondramide, and spongistatin 1 and 2.

Large molecular size tetrahydropyran (THP)-containing polyketide macrolides are a class of marine macrolides with diverse and interesting biological activities. Some of them have reached the clinical trial stage or the market, as is the case of the promising anticancer agents bryostatin 1[8] or eribulin,[9] the analogue of the marine macrolide halichondrin B, respectively (Figure 2). Large molecular size THP-containing macrolides rarely include tetrahydrofuran (THF) rings in their structure. Nevertheless, some natural products are found where both systems are included, such as the above-mentioned eribulin, pectenotoxins,[10] and prorocentrolide[11] toxins, the family of the halistatins,[9a] the family of the antimitotic spirastrellolides,[12] or the actin-targeting marine polyether goniodomin A.[13]

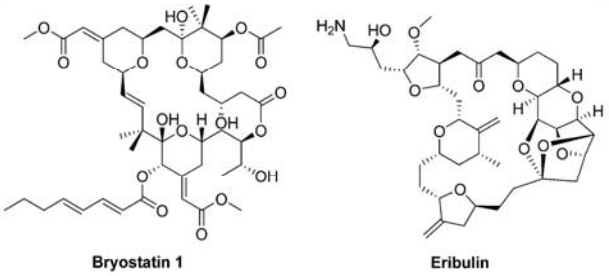

Figure 2. Structures of bryostatin 1 and eribulin.

More recently, THF rings instead of THP rings have occurred in structures of new bioactive compounds. Large molecular size polyketide macrolides with THP and THF rings in their structure were the first reported THF-containing macrolides. Over the last 20 years, more THF- containing polyketide macrolides have been described, and their potential as drug candidates has increased exponentially. It is worth mentioning that THF-containing macrolides are often of smaller molecular weight and less complex than their THP congeners.

This review focuses on the chemical efforts aimed at achieving the isolation and total synthesis of specific marine macrolides, such as macrolides that contain a fused or bridged THF ring, up to 2012. Macrolides containing a fused THF ring share two common carbons with the macrolide, while macrolides containing a bridged THF ring share three or four common atoms with the macrolide. The revision starts with those compounds for which only isolation and structure determination were described and follows with the isolation, structure determination, and synthesis of the rest of the families.

2. BIOSYNTHESIS

On the basis of their biosynthetic origin, metabolites are divided into six classes: ribosomal and nonribosomal peptides, alkaloids, phenylpropanoids, polyketides, terpenoids and steroids, and carbohydrates. Members of each class of metabolites have been shown to exhibit interesting biological activities. Ribosomal peptides and carbohydrates are often referred to as primary metabolites, due to their lack of structural complexity; on the other hand, nonribosomal peptides, alkaloids, phenylpropanoids, polyketides, and terpenoids and steroids are classified as secondary metabolites, because they are formed from a series of enzymatic transformations that employ a much more diverse set of precursors and more sophisticated biosynthetic reactions.[14]

The main push into the investigation of polyketide biosynthesis came from Arthur Birch in the 1950s. His contributions were decisive, recognizing that polyketones could be generated from acetate units by repeated condensation reactions. He tested his theory by feeding an isotopically labeled acetate with ^{14}C at C-1 to a suitable polyketide-producing organism.[15] Later, with the development of genetic techniques in the 1980s and the discovery of enzymes, a new field based on gene sequencing and manipulation appeared.[16] Nowadays, the predictable relationship between the structure and function of modular-type polyketide synthases (PKSs) has enabled the genetic manipulation of biosynthetic pathways for production of novel variants of naturally occurring compounds, such as macrolide antibiotics and antitumor compounds.[17]

Polyketide natural products are constructed by large multifunctional protein complexes PKSs, which use acetate and propionate as building blocks. Different families of PKSs generate very distinct classes of polyketides, but irrespective of the producing organism, polyketides are always formed by decarboxylative Claisen-type 1,2-head-to-tail condensations of thioesters with malonyl-derived extender units. Type I PKSs, or modular PKSs, construct polyoxygenated aliphatic compounds,

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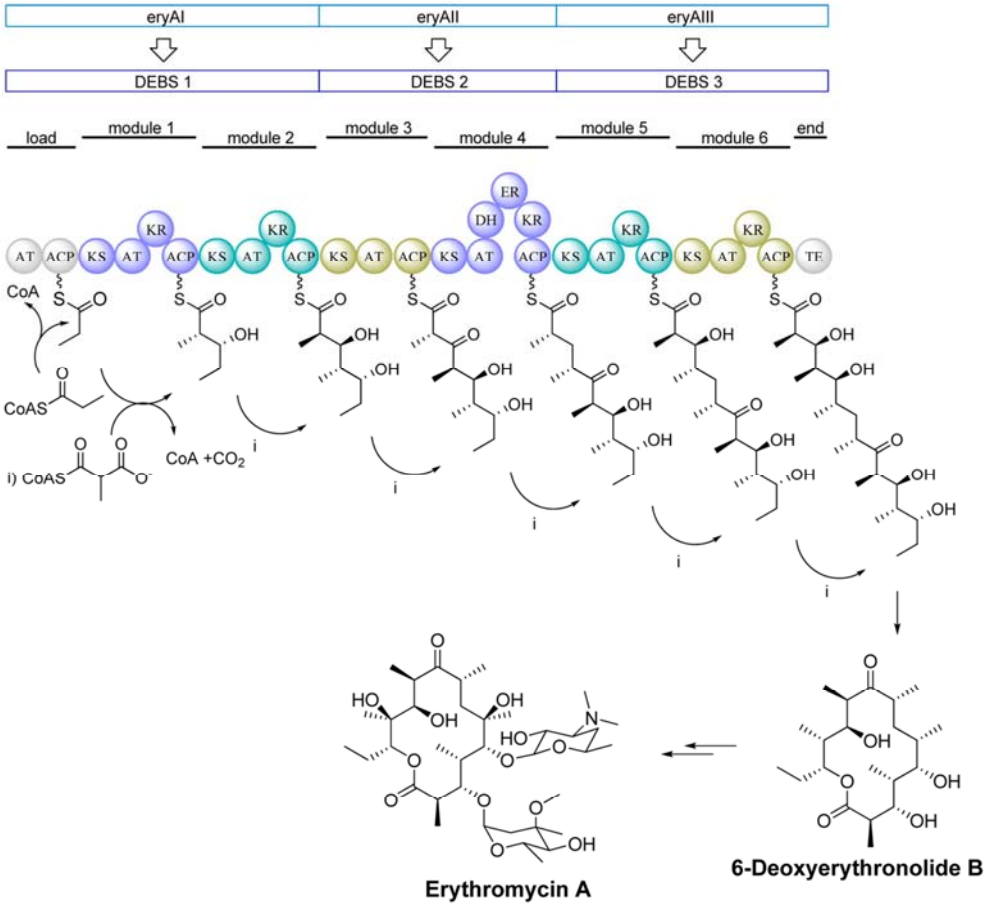


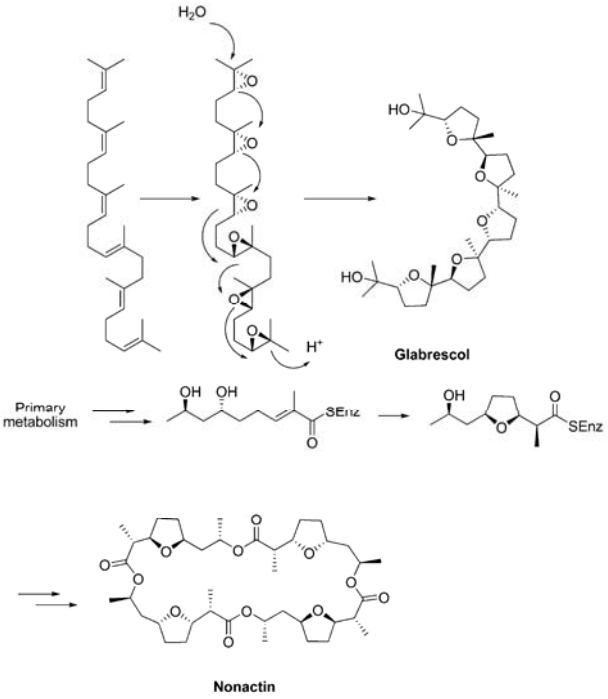
Figure 3. Domain arrangement of erythromycin synthase.

which is the subject of our review. An acyl transferase (AT) domain catalyzes thioester bond formation between an acyl carrier protein (ACP) domain and a coenzyme A (CoA)-bound starter unit. Then, a ketosynthase (KS) domain catalyzes the binding of its cysteine-bound malonyl elongation unit to the growing ACP-bound polyketide. Acetate units are loaded onto cysteine residues of adjacent KS domains, and the chain is elongated via successive Claisen condensations. Complexity and diversity are added to the polyketide chain through ketoreductase (KR), dehydratase (DH), and enoyl reductase (ER) domains. Moreover, PKS and nonribosomal peptide synthase (NRPS) modules can work together to form hybrid PKS–NRPS molecules. The sequence ends in the thioesterase (TE) domain, although the absence of this domain in some PKSs suggests the existence of alternative releasing mechanisms.[18] Figure 3 shows an example of chain elongation; 6-deoxyerythronolide B synthase (DEBS) is the PKS that forms the backbone of erythromycins and is encoded by the three *eryAI-III* genes.[19] Once the resulting linear carbon backbone is released from the PKS, the carbon framework is further processed and modified by various tailoring enzymes, which enhance its functionality to yield biologically active compounds. This post-PKS processing is another source of diversity in polyketide biosynthesis, as there is enormous scope for mixing and matching the tailoring enzymes to produce altered structures. For example, the skeleton can be oxidized or reduced to introduce hydroxy or carbonyl groups (oxygenases [OXs] and ketoreductases [KRs]), methylated at oxygen, nitrogen or carbon centers (methyl transferases [MTs]), or decorated with deoxysugar molecules (glycosyltransferases [GTs]).[20]

Macrolactones are normally formed upon termination/cyclization, provided that the TE domains attached to the terminal modules of PKSs are tolerant toward polyketide chain length as well as substitutions at the C-2 and C-3 positions of the lactone, although with varying efficiencies.[21] On the other hand, the formation of oxacyclic ethers normally occurs in post-PKS processing; (bio)chemically, ether bond formation is not straightforward, but nature has evolved many ways to furnish these structures with high efficiency, and, when necessary, with high enantio- or regioselectivity.[22] Enzymes, such as peroxidases or alkene mono-oxygenases (AMOs), are able to form epoxides from double bonds. The subsequent opening of these epoxides furnished cyclic ethers. This process sometimes occurs in a cascade fashion forming polycyclic natural products, for instance, in the biosynthesis of glabrescol (Scheme 1).[23] Another approach to the formation of oxaheterocycles is the addition of hydroxyl groups to activated double bonds involving the Michael addition reaction, as in the case of the antitumor agent nonactin (Scheme 1).[24]

Another important subject in polyketide biosynthesis is stereochemistry. The PKS-catalyzed assembly process generates stereochemical diversity, because carbon–carbon double bonds may have either *cis*- or *trans*- geometry, and because of the chirality of centers bearing hydroxyl groups and branching

Scheme 1. THF Ring Formation in the Biosynthesis of Glabrescol and Nonactin



methyl groups. More recently, aspects of stereochemistry in polyketide biosynthesis are becoming better understood.[25] Nevertheless, the knowledge around the stereochemical outcome of complex polyketide biosynthesis is still expanding.

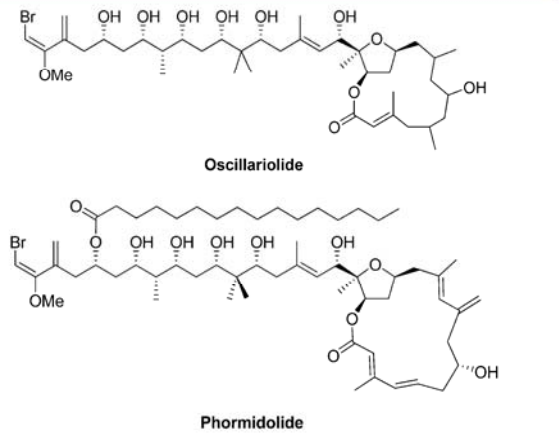


Figure 4. Structures of oscillariolide and phormidolide.[26,27]

3. OVERALL OF THF-CONTAINING MACROLIDES

3.1. Oscillariolide[26] and Phormidolide[27]

Oscillariolide was isolated from a marine blue-green alga *Oscillatoria* sp. collected from Gokashowan-Bay, Mie Prefecture,

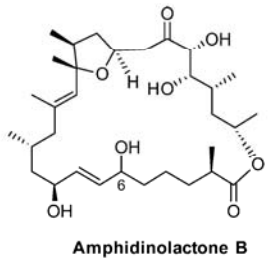


Figure 5. Structure of amphidinolactone B.[29]

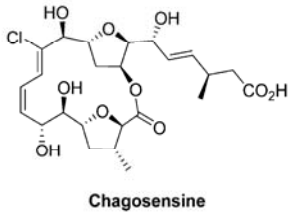


Figure 6. Structure of chagosensine.[30]

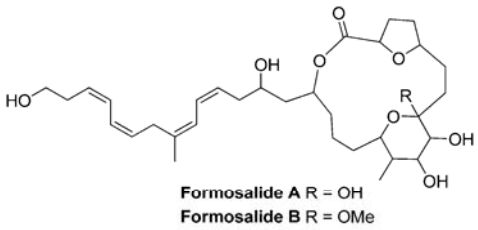


Figure 7. Structures of formosalides A and B.[31]

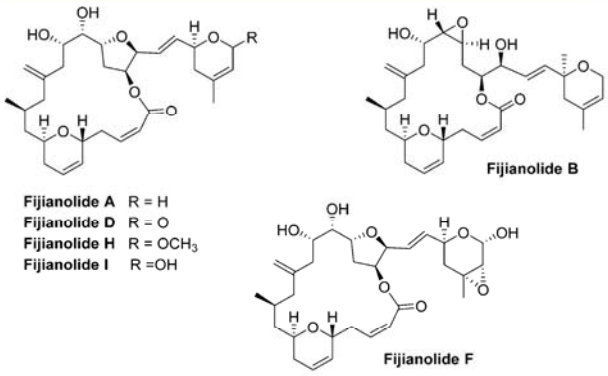


Figure 8. Structures of fijianolides A, B, D, H, I, and F.[32−34]

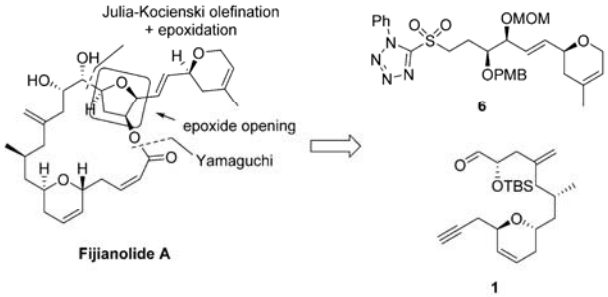


Figure 9. Fijianolide A retrosynthetic analysis by Mulzer.[35]

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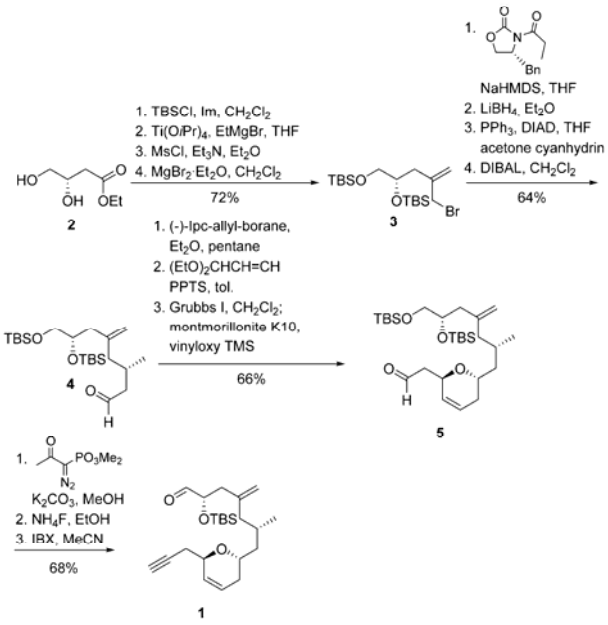
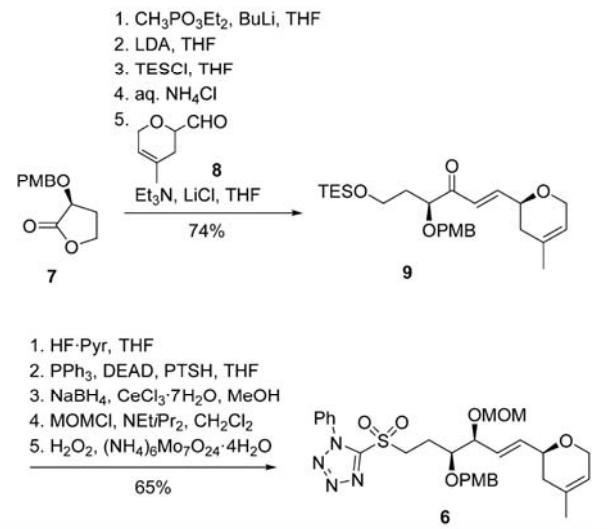
Scheme 2. Synthesis of Aldehyde 1

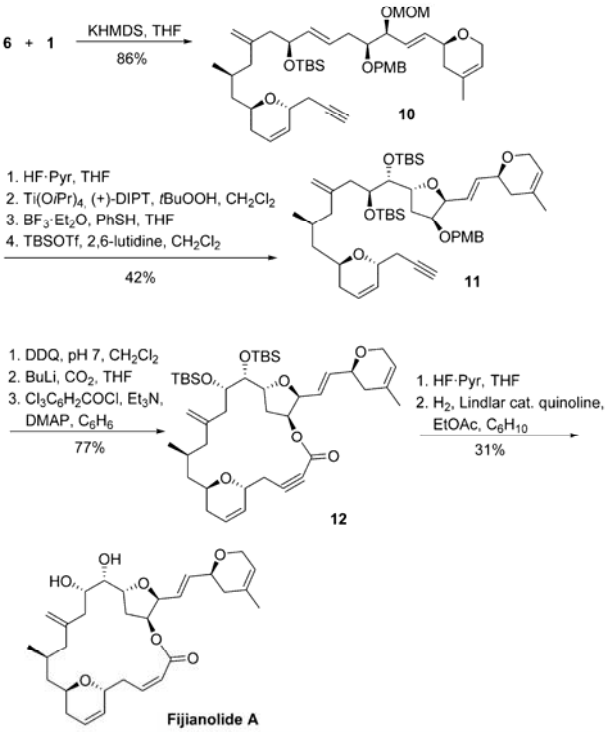


Scheme 3. Synthesis of Sulfone 6



and was shown to cause inhibition of cell division of fertilized starfish eggs.[26] Its structure was elucidated on the basis of spectral data, but the stereochemistry was not defined. A few years later, phormidolide was isolated from the cyanobacteria *Phormidium* sp. and was shown to be toxic to brine shrimp at micromolar concentration.[27] The structure of phormidolide was elucidated using various spectroscopic methods, mostly advanced nuclear magnetic resonance (NMR) techniques. Comparison of spectroscopic data of both compounds demonstrated the same stereochemistry for the polyhydroxy chain and the THF ring (Figure 4). Both compounds share the characteristic structure of a trisubstituted bridged THF macrolactone with a long polyhydroxy chain containing a unique terminal bromo diene. It is worth mentioning that halogenated natural products are compounds typically isolated from cyanobacteria.[28]

Scheme 4. Total Synthesis of Fijianolide A[35]



3.2. Amphidinolactone B[29]

Amphidinolactone B was isolated from a marine dinoflagellate *Amphidinium* sp., and was shown to have modest cytotoxicity. The structure and relative stereochemistry of amphidinolactone B was elucidated on the basis of spectroscopic data. It is constituted by a 26-membered macrocycle containing a 2,5-bridged-tetrasubstituted THF with a quaternary center, a keto carbonyl, four hydroxyl groups and six branched methyls. It affords complex stereochemistry because it has eleven stereocenters and two double bonds (Figure 5). The C-6 stereocenter was not defined due to the limited amount of the sample.

3.3. Chagosensine[30]

Chagosensine was isolated from the Red Sea calcareous sponge *Leucetta chagosensis*, and was described as a chlorinated 16-membered macrolactone containing two 2,3,5-trisubstituted THF rings (Figure 6). The structure and absolute configuration of chagosensine were elucidated by chemical derivatization and spectroscopic techniques.

3.4. Formosalides[31]

Formosalides A and B were isolated from a dinoflagellate, *Prorocentrum* sp., strain PL040104002. They exhibited cytotoxicity against acute lymphoblastic leukemia cells and human colon adenocarcinoma cells. Detailed analysis of NMR spectra was the basis for the structure determination as 17-membered ring macrolides (Figure 7). The compounds have an all-*cis* tetraene system, a tetrahydropyran ring and a tetrahydrofuran ring. Formosalide A has five hydroxyl groups, and formosalide B has four hydroxyl groups and one methoxy group. Both compounds have two branched methyls and a C14 linear side-chain. The stereochemistry of the nine stereocenters was not determined, only the relative stereochemistry of five- and six-bridged rings was established. The substitution of THF and THP rings was elucidated to be a 2,5-*anti*- and 8,12-*syn*-bridged system.

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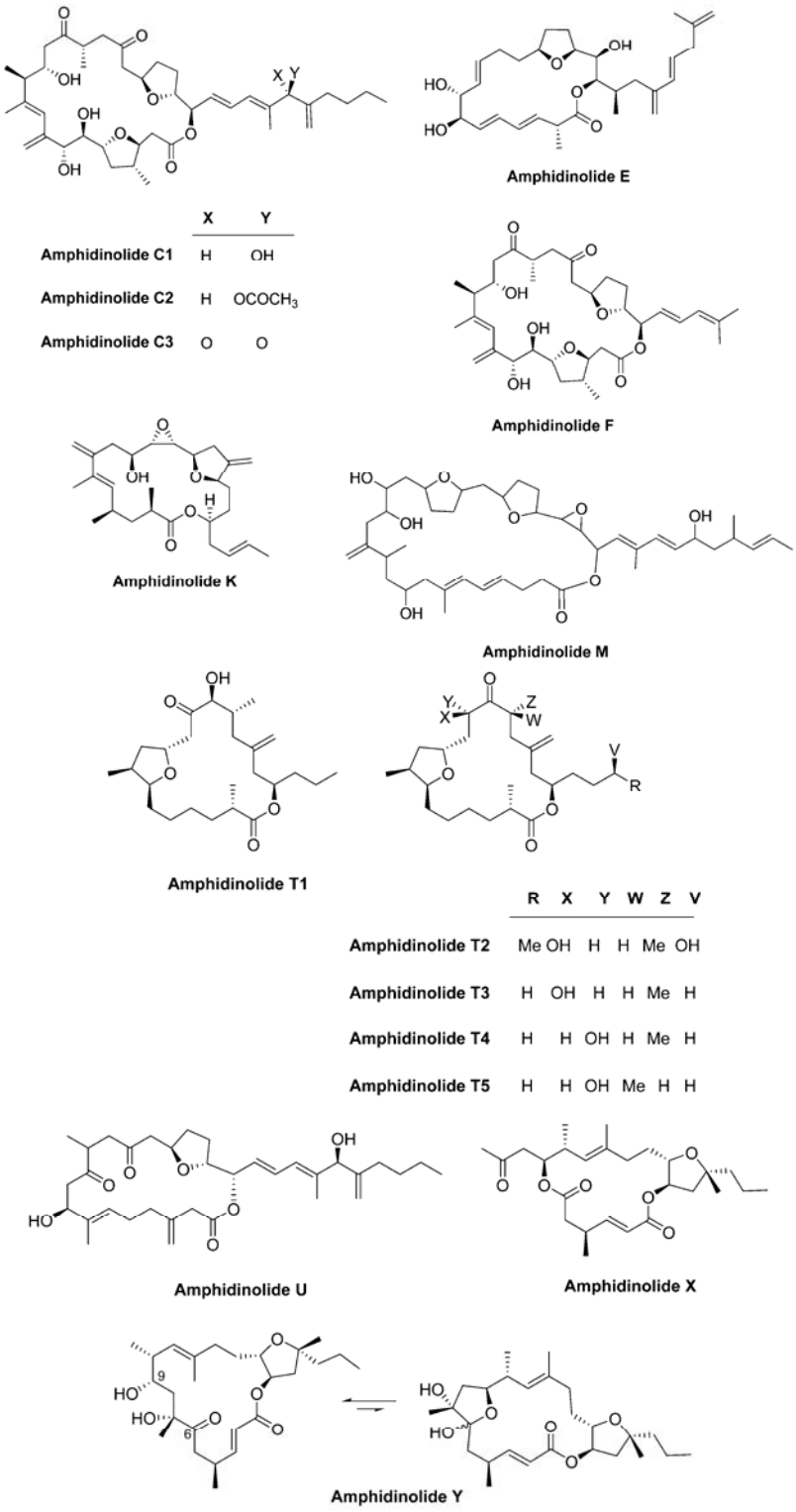

Figure 10. Structure of THF-containing amphidinolides.[39g−u]

3.5. Fijianolides[32−34]

These 20-membered ring macrolides were characterized simultaneously in 1988 as fijianolides A and B from the marine sponge *Cacospongia mycofijiensis*[32] and as isolaulimalide and laulimalide from a *Hyatella* sponge.[33] Several years later new minor components of *C. mycofijiensis* collected from Vanuatu and Indonesia were identified as fijianolides D-I.[34] Fijianolides A and B showed cytotoxicity against two human cancer cell lines, MDA MB 435 and HCT 116, at micromolar concentration.

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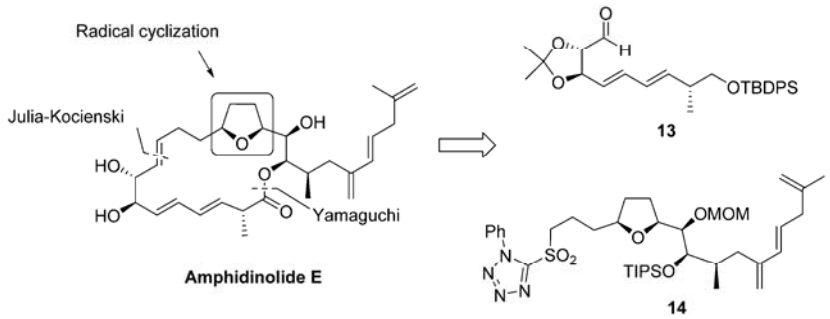
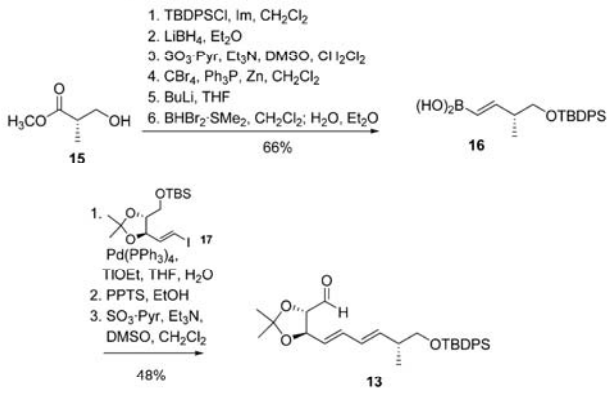


Figure 11. Amphidinolide E retrosynthetic analysis by Lee.[46]

Scheme 5. Synthesis of Aldehyde 13



Fijianolide B was active in the same cancer cell lines at nanomolar concentration. This increase of activity was attributed to the epoxide ring. The structure of these compounds was established by one- and two-dimensional NMR studies. From a structural point of view, these fijianolides were divided into two groups: fijianolides A, D, F, H, and I containing one THF in addition to one dihydropyran (DHP) in the macrolactone ring, whereas the remaining fijianolides were related to fijianolide B containing only one DHP ring in the macrocycle. Fijianolides A, D, H, F, and I have identical macrocycle constitution and configuration and only differ in the functionalization of the pyran lateral chain (Figure 8).

Synthetic efforts toward this family of compounds have focused on the synthesis of fijianolide B (laulimalide), and, to a lesser extent, on the synthesis of the THF-containing macrocycle fijianolide A (isolaulimalide) and related fijianolides D-I. Nevertheless, Mulzer and co-workers have described the synthesis of fijianolide A.[35]

3.5.1. Mulzer's Synthesis of Fijianolide A.[35] Their strategy was developed envisioning a final macrolactonization and the formation of an epoxide precursor of the THF ring from a double bond formed by a Julia−Kocienski olefination (Figure 9).

Aldehyde C2−C16 fragment **1** was synthesized by diprotection of commercially available diol **2** and Kulinkovich reaction,[36] followed by mesylation and $MgBr_2 \cdot Et_2O$ mediated cyclopropyl-allyl rearrangement to obtain allylbromide **3** (Scheme 2). Transformation of compound **3** into aldehyde **4** was obtained by Evans alkylation, reduction to remove the chiral oxazolidinone, Mitsunobu conversion into the nitrile, and final reduction. Trasformation of **4** into dihydropyran **5** was afforded by allylation of **4** with (−)-isopinocamphenyl-allyl-borane, followed by one-pot ring closing metathesis (RCM) and addition of vinyloxytrimethylsilane and montmorillonite K10 for side chain introduction. Conversion of aldehyde **5** into the terminal alkyne was achieved using the Bestmann−Ohira reagent.[37] Further selective removal of the *tert*-butyldimethylsilyl (TBS) protecting group and oxidation furnished aldehyde **1**.

Sulfone **6** was obtained from protected α-hydroxy butyrolactone **7**, which was treated with an equimolar amount of the lithium salt of diethyl methanephosphonate. Further deprotonation led to the dianion that was then silylated with triethylsilyl (TES) chloride. Hydrolysis of the silyl enol ether and Horner−Wadsworth−Emmons (HWE) reaction with aldehyde **8**,[38] under Masamune-Roush conditions, led to enone **9** (E/Z > 40:1). Selective deprotection of primary alcohol and conversion to the sulfide, followed by Luche reduction, yielded *syn*-alcohol with a good diastereomeric ratio (dr >17:1). MOM protection and oxidation to the sulfone furnished **6** (Scheme 3).

Condensation of sulfone **6** and aldehyde **1** afforded coupled compound **10**. TBS deprotection and epoxidation, followed by removal of the methoxymethyl (MOM) protecting group, intramolecular epoxide opening, and TBS protection, afforded THF derivative **11**. *p*-Methoxybenzyl (PMB) removal and C1 elongation led to a seco acid that was then cyclized under Yamaguchi conditions to obtain **12**. Further deprotection of the TBS ethers and reduction of the triple bond to obtain (*Z*)-enoate furnished fijianolide A (Scheme 4).

3.6. Amphidinolides

Amphidinolides are metabolites isolated from *Amphidinium* sp., of a genus of symbiotic marine dinoflagellates of Okinawan marine flatworms *Amphiscolops* sp. Forty members of this big macrolide family have been isolated up to 2010, but only 15 of them have an additional fused or bridged THF in their macrolactone ring (Figure 10). An interesting member of the family is amphidinolide C, which shows potent cytotoxicity in the nanomolar range against murine lymphoma L1210 and human epidermoid carcinoma KB cells (IC_{50} = 5.8 and 4.6 ng/mL, respectively) in vitro. Unique structural features are the presence of exomethylidene units and polyene side chains, as well as the presence of fused or bridged THF systems. Their structural and stereochemical complexity, combined with their important bioactivity, all exhibiting potent cytotoxic activity, make them attractive targets to apply new synthetic methods, thereby encouraging the work of different groups. The isolation, structure elucidation, and activity of this family of macrolides, as well as its biosynthesis, have been extensively reviewed since the discovery of the series was first reported. The last reported macrolide, named amphidinolide C3, was isolated in 2010.[39]

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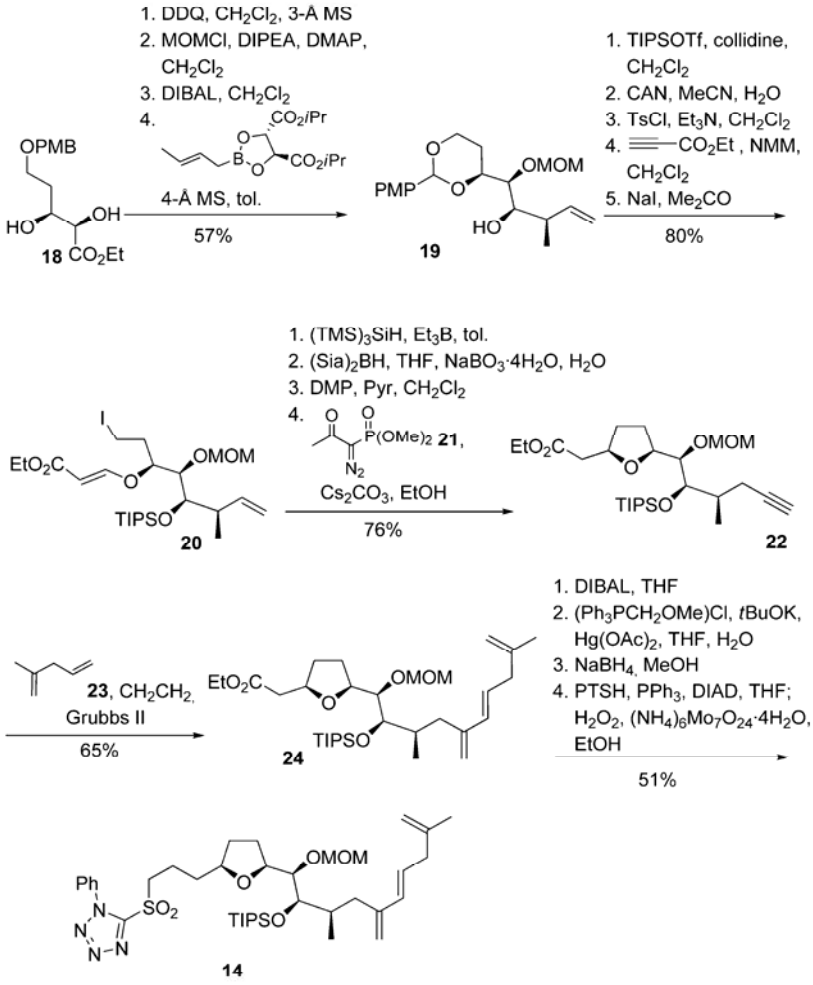
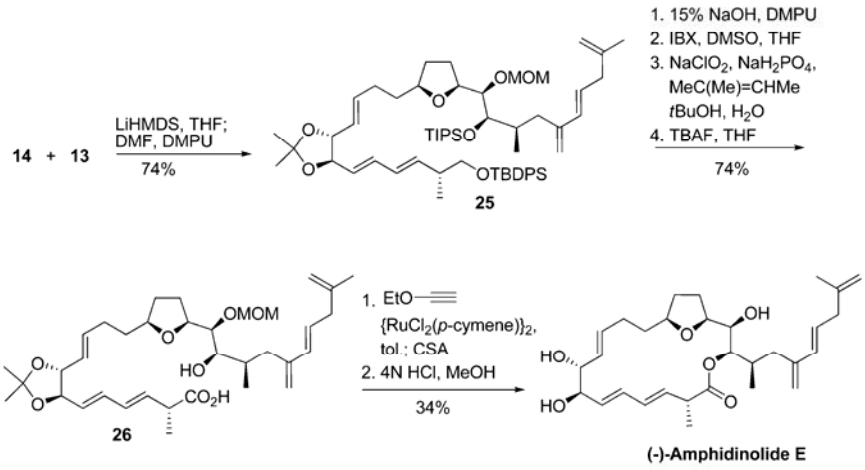
Scheme 6. Synthesis of Sulfone 14



Scheme 7. Total Synthesis of (−)-Amphidinolide E[46]



Synthetic work on amphidinolides up to 2000 has been reviewed.[41] Nevertheless, during the past decade, a major effort has been made on the synthesis of this family of compounds, and several total syntheses have been compiled.[42]

3.6.1. Amphidinolide E. Amphidinolide E is a 19-membered macrolide isolated from the Y-5′ strain of the dinoflagellate *Amphidinium* sp.[39g,h] Several studies aimed at the synthesis of amphidinolide E have been described: Gurjar published the synthesis of the C12−C19 fragment in 2004,[43]

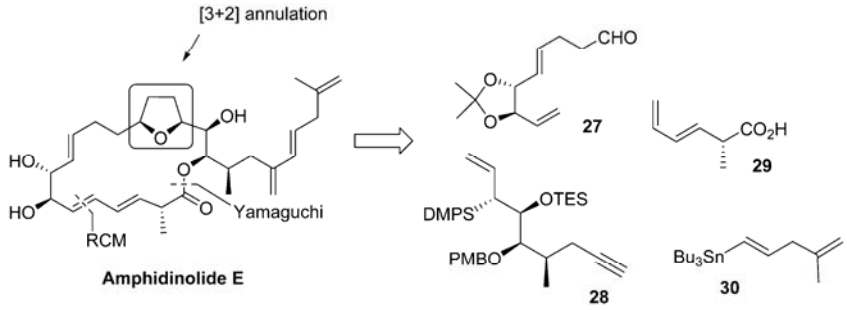
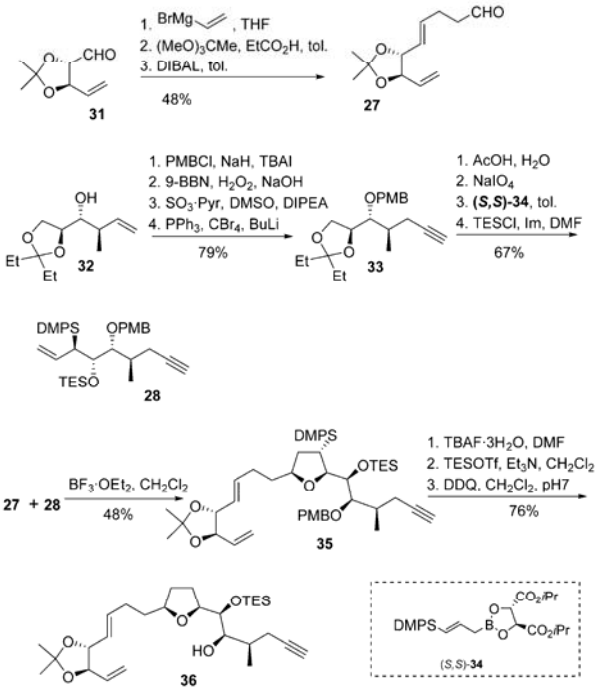
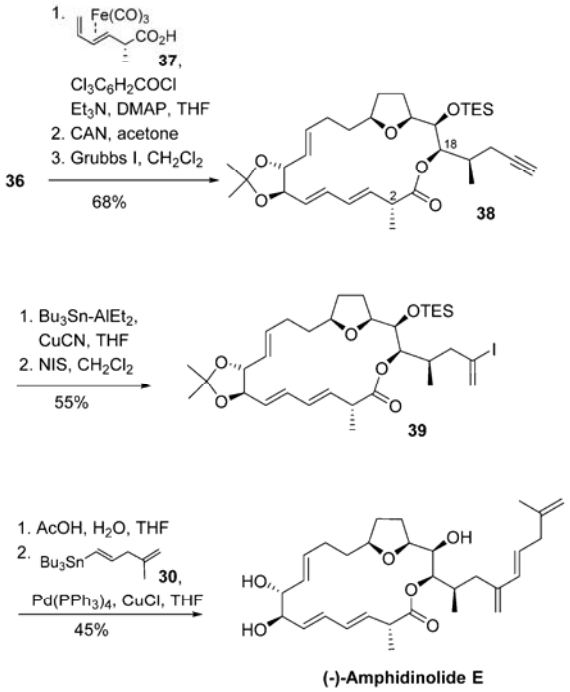


Figure 12. Amphidinolide E retrosynthetic analysis by Roush.[47]

Scheme 8. Synthesis of THF Derivative 36



Scheme 9. Synthesis of (−)-Amphidinolide E[47]



Marshal published the synthesis of the C6−C21 fragment in 2005,[44] and Vilarrasa and co-workers published the synthesis of fragments C1−C7 and C10−C26 in 2008.[45] Total syntheses of amphidinolide E to date are those reported by Lee[46] and Roush.[47]

3.6.1.1. Lee's Synthesis of Amphidinolide E.[46] In 2006, Lee and co-workers described the total synthesis of amphidinolide E; later, they published a detailed account of their attempts toward the synthesis, including pathways that led to a dead end but which were also synthetically interesting.[48] The successful strategy to amphidinolide E focused on lactonization at a late stage, to avoid lability problems at C2. The key intermediates were C1−C9 and C10−C26 fragments **13** and **14** (Figure 11).

Aldehyde **13** was prepared starting from methyl (*S*)-3-hydroxy-2-methylpropanoate **15** and was then converted into vinyl boronic acid **16** by protection as a *tert*-butyldiphenylsilyl (TBDPS) ether, reduction, oxidation, Corey-Fuchs homologation, and hydroboration-hydrolysis. Suzuki cross-coupling of **16** with vinyl iodide **17**,[49] removal of the TBS group, and oxidation afforded aldehyde **13** (Scheme 5).

Fragment C10−C26, sulfone **14**, was prepared from diol **18**[50] by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation to furnish the *p*-methoxyphenyl (PMP) acetal. Protection of the remaining hydroxyl group and reduction, followed by Roush crotylation, led to homoallylic alcohol **19** with good dr (16:1). Triisopropylsilyl (TIPS) protection and removal of the cyclic PMP acetal led to a diol, which was then tosylated at the primary hydroxyl and treated with ethyl propiolate at the secondary hydroxyl. Subsequent substitution of the tosylate with iodide provided **20**. Radical cyclization of iodide **20** permitted the formation of the THF ring. Hydroboration−oxidation and further oxidation led to an aldehyde that treated with diazophosphonate **21** provided alkyne **22**. Cross metathesis with diene **23** led to triene **24**. Reduction of ester **24**, followed by homologation of the resulting aldehyde by Wittig methoxymethylidenation and hydrolysis, reduction with $NaBH_4$, Mitsunobu type introduction of thiol, and oxidation, provided sulfone **14** (Scheme 6).

Julia−Kocienski olefination between sulfone **14** and aldehyde **13** furnished the desired *E*-alkene **25** in good yield (*E*/*Z* 10:1). After removal of the TBDPS group and oxidation to acid, the

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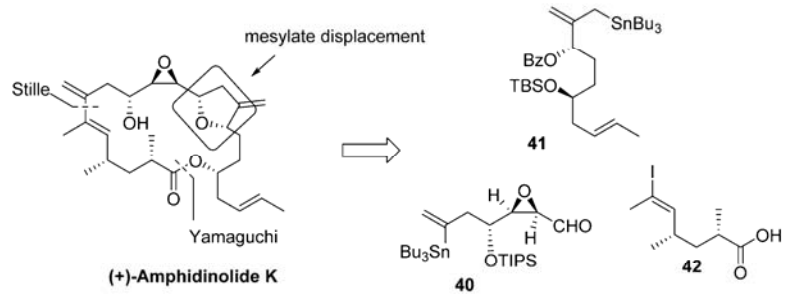
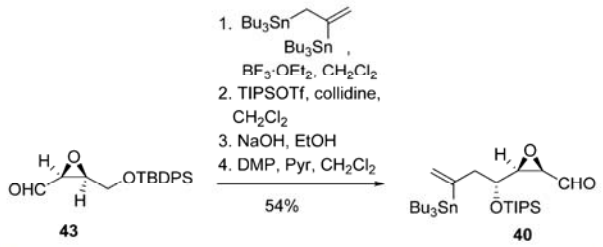


Figure 13. (+)-Amphidinolide K retrosynthetic analysis by Williams.[55]

Scheme 10. Synthesis of Aldehyde 40



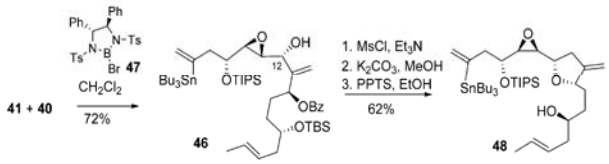
TIPS protecting group was also removed and seco acid **26** was obtained. Macrolactonization was possible using the Kita protocol,[51] and removal of the remaining protecting groups led to (−)-amphidinolide E (Scheme 7).

3.6.1.2. Roush's Synthesis of Amphidinolide E.[47] Roush and co-workers described the synthesis of amphidinolide E, and three of its diastereomers. An unexpected and highly selective C2 inversion observed during an esterification reaction over the course of the natural product synthesis gave to the process an important advantage, enabling a straightforward synthesis of some of its diastereomers.[52] Roush and co-workers envisaged that amphidinolide E could be accessed by elaboration of the THF via a [3 + 2] annulation reaction of aldehyde **27** and allylsilane **28** (Figure 12). The remaining building blocks were dienacid **29** for the lactone construction and tin derivative **30** for the side chain introduction.

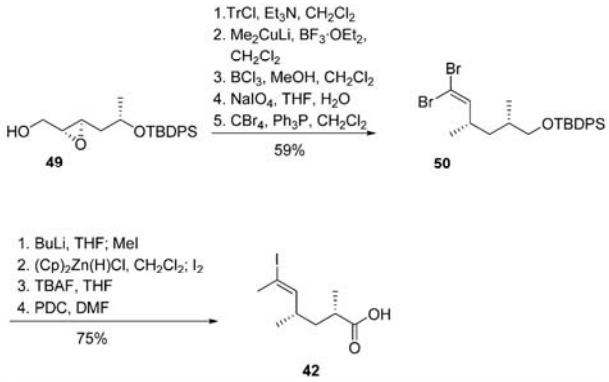
Aldehyde **27** was synthesized starting from aldehyde **31**,[53] which was treated with vinyl magnesium bromide, followed by a Johnson orthoester Claisen rearrangement of the mixture of diastereomeric allylic alcohols. Reduction of the resulting methyl ester afforded aldehyde **27**.

Allylsilane **28** was prepared from homoallylic alcohol **32**.[54] Protection of the hydroxyl of **32** as a PMB ether and hydroboration−oxidation furnished an alcohol that was oxidized

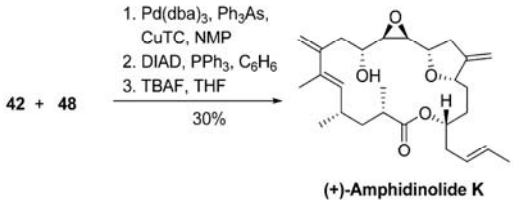
Scheme 12. Synthesis of THF Building Block 48



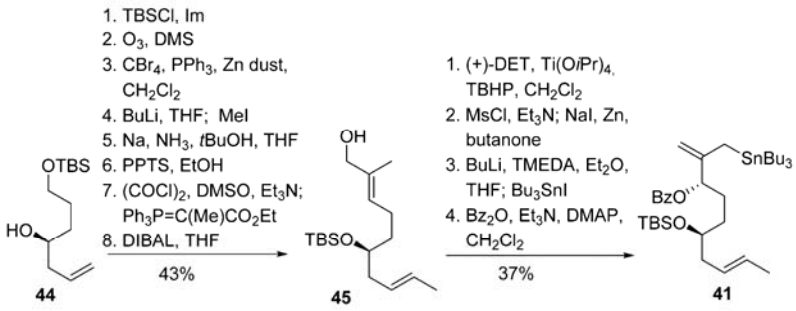
Scheme 13. Synthesis of Vinyl Iodide 42



Scheme 14. Total Synthesis of (+)-Amphidinolide K[55]



Scheme 11. Synthesis of Stannane 41



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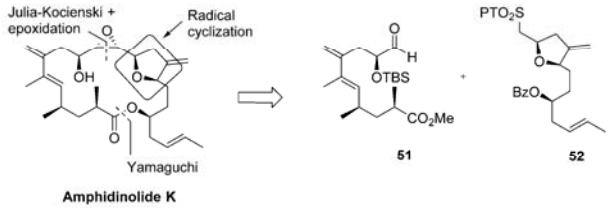


Figure 14. Amphidinolide K retrosynthetic analysis by Lee.[57]

and Corey–Fuchs homologation led to alkyne **33**. Acid hydrolysis of the ketal protecting group and oxidative cleavage of the resulting diol provided an aldehyde. Subsequent treatement with (*S,S*)-**34** afforded silylallylboration with 9:1 selectivity. The protection of the resulting alcohol as a TES ether furnished allylsilane **28**.

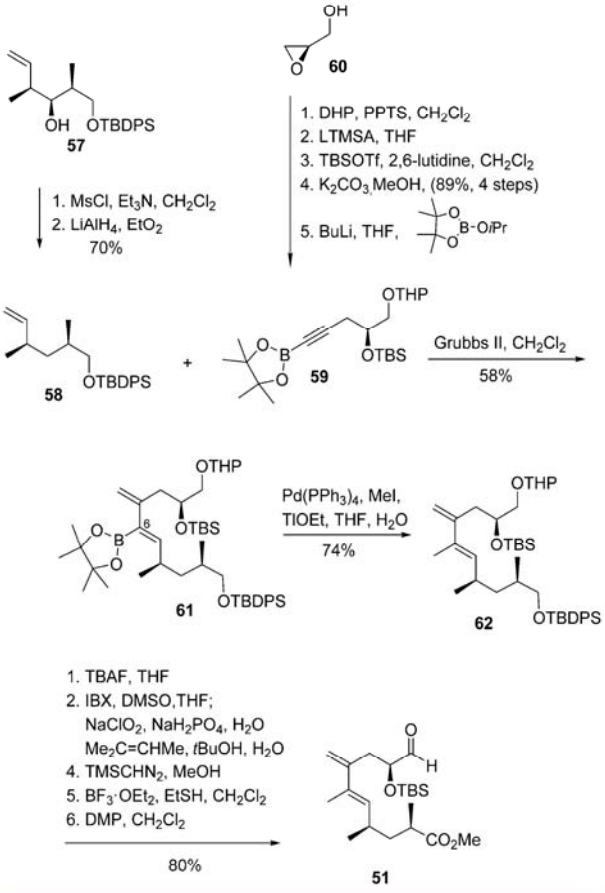
With both fragments in hand, [3 + 2] annulation catalyzed with $BF_3{\cdot}Et_2O$ afforded **35** with dr > 20:1. Cleavage of C–Si bond by treatment with tetrabutylammonium fluoride (TBAF) was not selective and also produced removal of the TES protecting group, which was reintroduced; further removal of the PMB protecting group afforded alcohol **36** for esterification (Scheme 8).

Esterification of the C18 hydroxy group was achieved using "diene protected" acid **37** only to avoid lability problems at C2. Oxidative removal of the $Fe(CO)_3$-unit provided the free diene ready for the Grubbs' first generation catalyzed RCM to obtain macrolactone **38**. Vinyl iodide **39** was obtained after stannylalumination–protonolysis and treatment with NIS. After acidic removal of the acetonide and TES protecting groups, Stille cross-coupling with vinyl stannane **30** afforded (−)-amphidinolide E (Scheme 9).

Several diastereomeric amphidinolide E analogues were prepared with the same strategy changing the acid **37** and allylsilane **28** stereochemistry.[52]

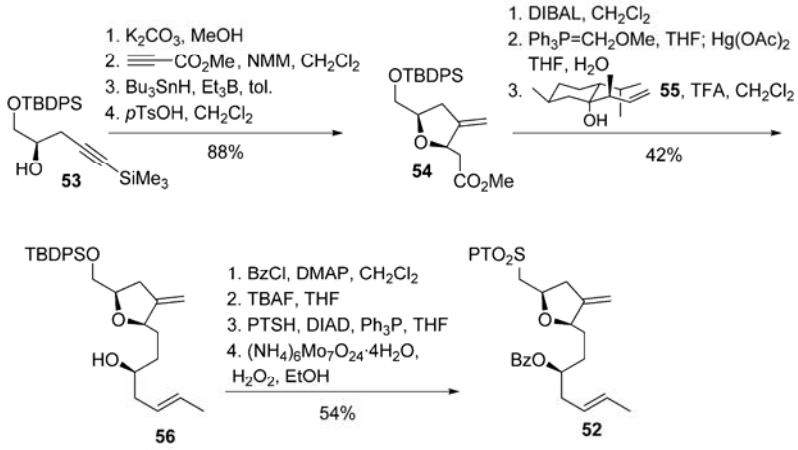
3.6.2. Amphidinolide K. Amphidinolide K is a 19-membered macrolide, the structure of which was described with undetermined stereochemistry at C2, C4, and C18.[39i] Synthetic efforts toward this natural product carried out by Williams and co-workers led to the elucidation of relative and absolute configuration by the synthesis of up to 25 distinct diastereomers.[55] Further work on amphidinolide K consisted of the synthesis of the C9–C22 fragment by Vilarrasa,[56] and the total synthesis of the natural product achieved by Lee.[57]

Scheme 16. Synthesis of Fragment 51



3.6.2.1. Williams's Synthesis of (+)-Amphidinolide K.[55] This work permitted the assignment of the relative and absolute configuration of the isolated natural product. Williams's strategy relied on the synthesis of three building blocks, compounds **40**, **41**, and **42**, which allowed flexibility for the intricate stereochemical issues (Figure 13).

Scheme 15. Synthesis of THF Derivative 52



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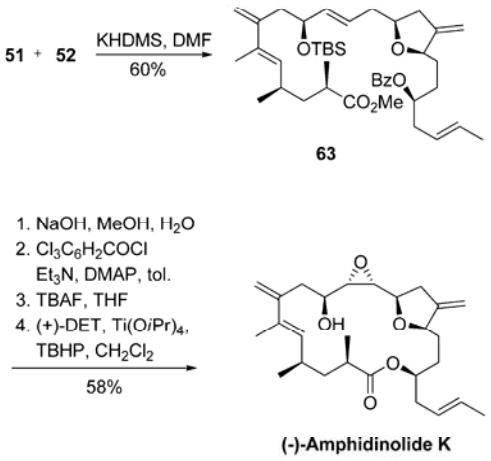
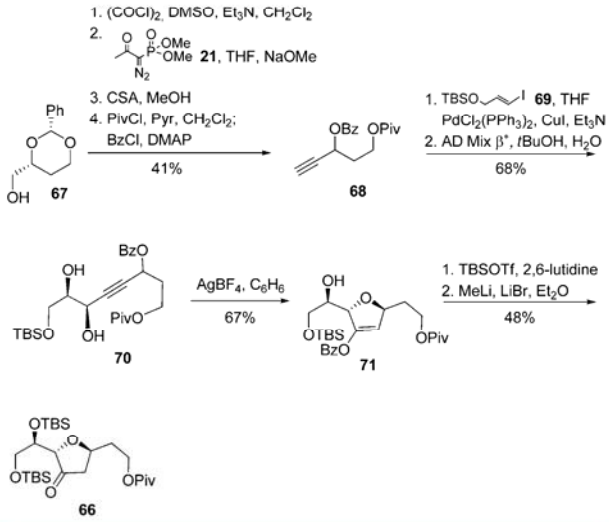
Scheme 17. Synthesis of (−)-Amphidinolide K[57]



Scheme 18. Synthesis of THF Derivative 66



Aldehyde **40** was prepared by allylation of epoxy aldehyde **43** under Felkin-Ahn control (6.9:1 *anti:syn*). The resulting alcohol was protected as a TIPS ether followed by removal of the TBDPS protecting group and oxidation to provide aldehyde **40** (Scheme 10).

Known alcohol **44**,[58] containing the proper configuration, was the starting material for the synthesis of C13−C22 fragment. The eight-step transformation of **44** into allylic alcohol **45** included protection of the free hydroxy group, ozonolysis and homologation to the triple bond, methylation of the terminal triple bond, stereoselective reduction of the triple bond, selective deprotection of the primary alcohol, oxidation, Wittig reaction, and ester reduction. Asymmetric Sharpless epoxidation of **45** and reductive transposition, followed by an alkoxide-assisted allylic deprotonation, furnished stannane **41** (Scheme 11).

Coupling of fragments **41** and **40** to give alcohol **46** was achieved in high diastereomeric control (dr 17:1) by transmetalation of the stannane with borane **47** and subsequent addition of the aldehyde. The desired 2,5-*cis*-tetrahydrofuran was obtained by mesylation of **46** and nucleophilic displacement at C12 on methanolysis of the benzoate. Mild TBS hydrolysis furnished alcohol **48** (Scheme 12).

Acid **42** was prepared from known epoxide **49**[59] by protection as a trityl (Tr) ether, Me_2CuLi addition, and removal of the triphenylmethyl (Tr) protecting group to provide a diol that was subjected to oxidative cleavage and converted to dibromoolefin **50**. Transformation of dibromo compound **50** into the iodo acid **42** was afforded by elimination, methylation, *syn* hydrozirconation−iodination (9:1), removal of the TBDPS group, and oxidation (Scheme 13).

Stille coupling between tin derivative **48** and iodide **42** afforded a seco acid that was subjected to Mitsunobu conditions for macrolactonization, followed by elimination of of the TIPS protecting group to afford (+)-amphidinolide K (Scheme 14).

3.6.2.2. Lee's Synthesis of (−)-Amphidinolide K.[57] Lee and co-workers' total syntesis of (−)-amphidinolide K followed a convergent strategy, which divided the molecule into two main fragments C1−C10 and C11−C22, **51** and **52**, as precursors of

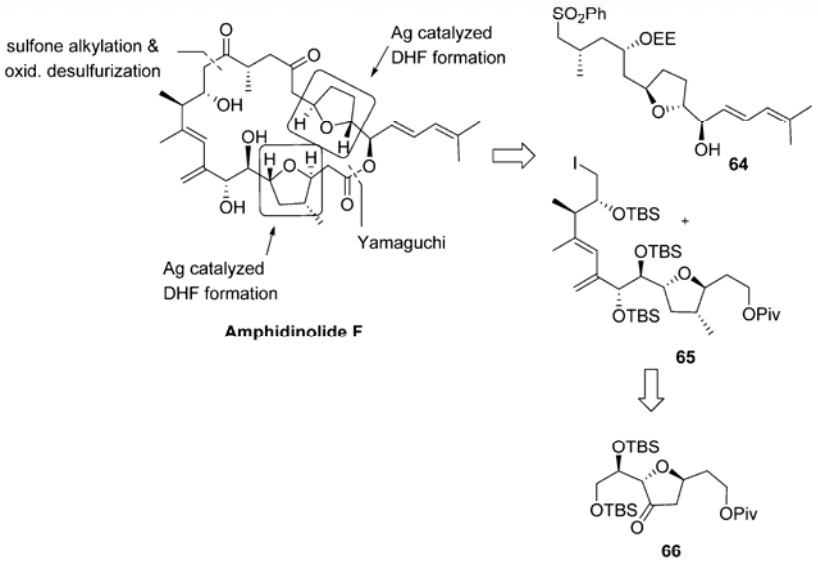


Figure 15. Amphidinolide F retrosynthetic analysis by Carter.[70]

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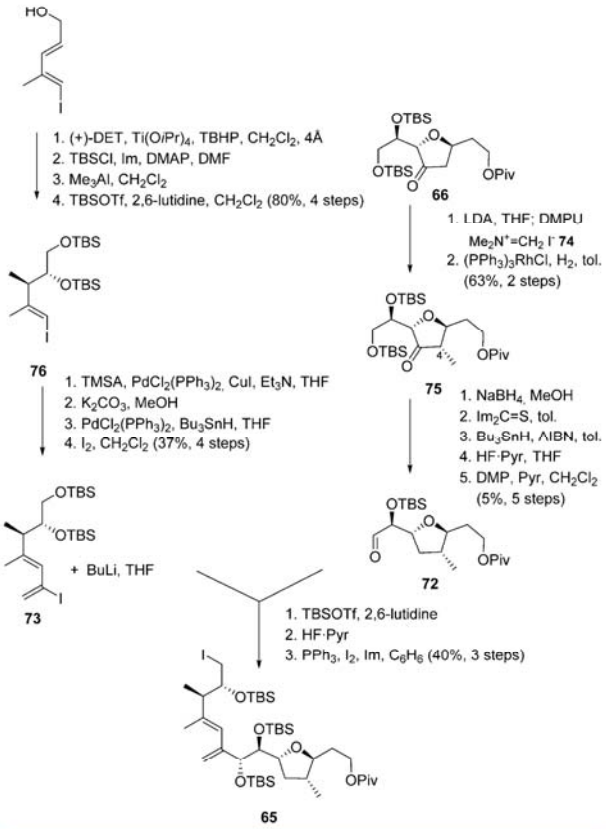
Scheme 19. Synthesis of Building Block 65



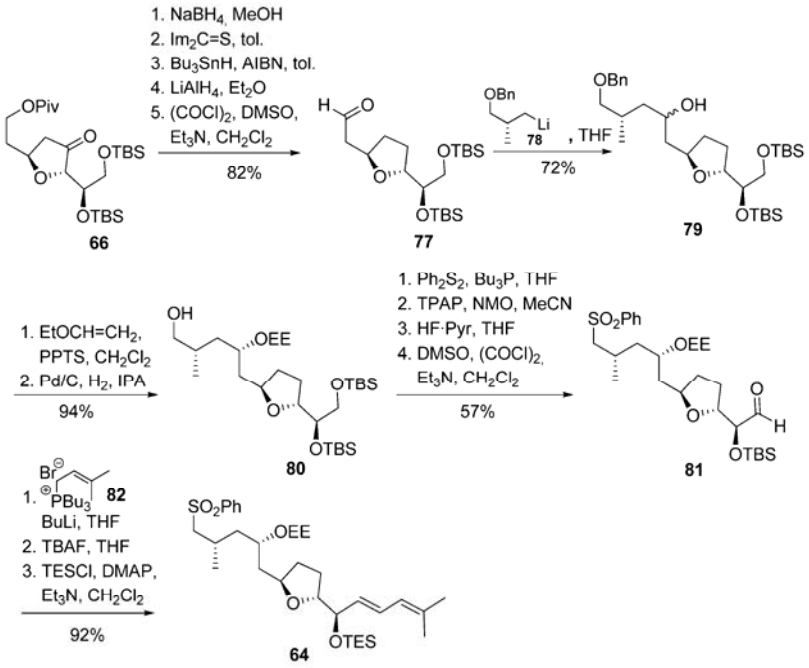
olefin bond formation by Julia–Kocienski reaction and final macrolactonization (Figure 14).

The THF ring of fragment **52** was formed by a stereoselective radical cyclization of a β-alkoxyacrylate with tributylstannane. The known homopropargylic alcohol **53**[60] was the starting material to obtain a β-alkoxyacrylate, which by reaction with tributylstannane and triethylborane, followed by acidic destannylation, gave the *cis*-2,5-disubstituted oxolane **54** (16:1). Reduction of **54** to the aldehyde and Wittig reaction to obtain the homologous aldehyde, followed by reaction with alcohol **55**,[61] furnished the homoallylic alcohol **56**. Protection of the alcohol as a benzoate derivative and functionalization of the deprotected primary alcohol to the sulfone by Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH), followed by oxidation, afforded compound **52** (Scheme 15).

Fragment C1–C10, **51**, was synthesized as shown in Scheme 16 by a reaction sequence in which the key step was the enyne cross-metathesis between olefin **58** and alkynyl boronate **59** to give an enriched mixture of the desired *E* isomer **61** (7.5:1). Olefin **58** was obtained from known alcohol **57**[62] by reduction of the mesyl (Ms) derivative. Alkynyl boronate **59** was prepared from (*R*)-glycidol **60**, via protection of the hydroxyl as a THP acetal, treatment with lithium trimethylsilylacetylide (LTMSA), TBS protection, removal of the timethylsilyl (TMS) protecting group, and formation of the boronate. Introduction of the methyl group at C6 of *E*-**61** was achieved by Suzuki–Miyaura reaction in the presence of thalium ethoxide to give diene **62**. This reaction was not possible using alternative strategies. Transformation of **62** into **51** was performed by succesive selective deprotection of the TBDPS alcohol, oxidation, methyl esterification, removal of the THP protecting group, and oxidation.

E olefin **63** was obtained by Julia–Kocienski reaction of aldehyde **51** and sulfone **52** (Scheme 17). Further transformation into the 19-membered macrocycle was performed by hydrolysis of the ester and Yamaguchi lactonization. After removal of the TBS protecting group and asymmetric

Scheme 20. Synthesis of Building Block 64



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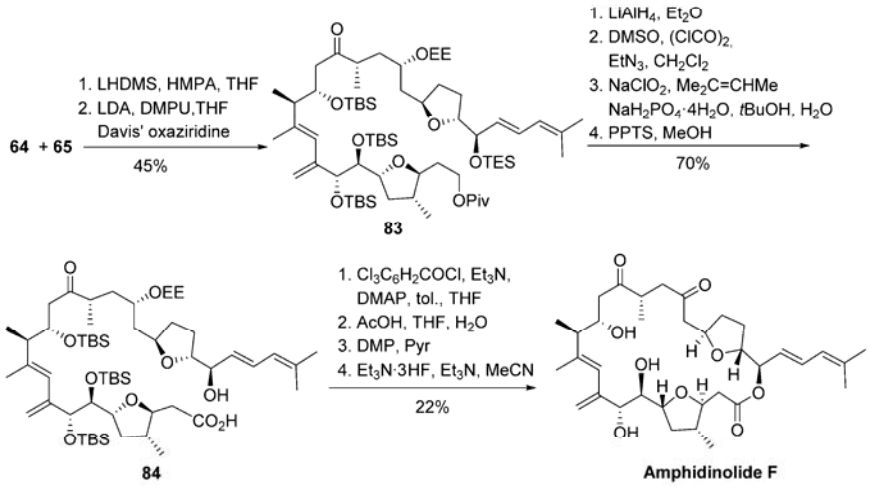
Scheme 21. Total Synthesis of Amphidinolide F[70]



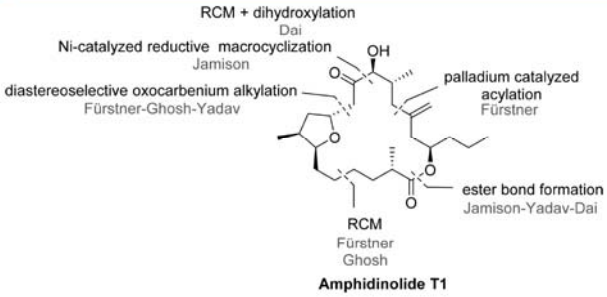


Figure 16. Main bond disconnections for the synthesis of amphidinolide T1.

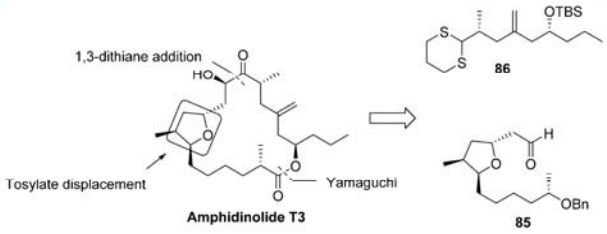


Figure 17. Amphidinolide T3 retrosynthetic analysis by Zhao.

epoxidation of the disubstituted endocyclic double bond, (−)-amphidinolide K was obtained.

3.6.3. Amphidinolides C1, C2, C3, F, and U. Amphidinolides C1, C2, C3 and F are 25-membered macrolactones containing two *trans*-2,5-disubstituted THF rings.[39j−n] Amphidinolide U is a 20-membered macrolactone containing one *trans*-2,5-disubstituted THF ring (Figure 10).[39p] The similarity in their structure and stereochemistry leads to the conclusion that they are biogenetically closely related and the strategies for their synthesis may proceed by similar pathways.

Synthetic work on these amphidinolides compiles several publications where the syntheses of fragments were achieved. Of interest are those published by Roush,[63] Mohapatra,[64] Armstrong,[65] Spilling,[66] Frigadère and Ferrié,[67] and Pagenkopf.[68] Finally, Carter described the total synthesis of the C7−C20 subunit[69] and the total synthesis of amphidinolide F.[70]

3.6.3.1. Carter's synthesis of Amphidinolide F.[70] The retrosynthetic analysis of Carter's group is based on the macrocyclization by lactone formation at the end of the process from a linear precursor containing the two THF rings. They developed a smart strategy where the two building blocks C15−C29 and C1−C4, **64** and **65**, could be synthesized from the same THF intermediate **66** (Figure 15).

Common intermediate **66** was synthesized starting from known alcohol **67**.[71] Oxidation and Bestmann−Ohira reaction, followed by benzylidene acetal removal and orthogonal protection of the free hydroxy-group, furnished **68**, which was subjected to Sonogashira cross-coupling with **69** and Sharpless asymmetric dihydroxylation, to obtain diol **70**. Formation of dihydrofuran (DHF) **71** was achieved with $AgBF_4$ with excellent stereoselectivity (dr > 20:1). Subsequent protection of the free alcohol and removal of the enol benzoate furnished intermediate **66** (Scheme 18).

The synthesis of fragment **65** was performed by stereoselective transformation of **66** into **72**, followed by its condensation with the lithium derivative of vinyl iodide **73** and functional group transformation. The key step for the synthesis of **72** was the introduction of a methylidene in the α-positon of the keto-group using the iminium salt **74**, followed by its stereoselective hydrogenation with Wilkinson's catalyst to give the correct stereochemistry at C4 of the desired **75**. Transformation of **75** into aldehyde **72** was performed by deoxygenation, selective deprotection of the primary TBS, and oxidation. Fragment **73** was synthesized from known iodide **76**,[69] by a regioselective hydrostannation of a Sonogashira formed enyne, followed by iodovinyl formation (Scheme 19).

Subunit **64** was obtained from **66** by keto-deoxygenation and removal of the pivaloyl (Piv) protecting group, followed by oxidation to furnish aldehyde **77**, which was then reacted with lithium derivative **78**,[72] to obtain epimeric alcohols **79** (1.5:1). Protection as ethoxyethyl acetal (EE) permitted separation, and the synthesis went on with **80**, which was obtained after deprotection of the benzyl ether. Alcohol **80** was converted into **81** by introduction of the sulfone, deprotection of the primary TBS alcohol, and oxidation. Reaction of **81** with Vedejs-type tributyl phosphonium salt **82**,[73] and silyl protecting group exchange, led to the desired *E* fragment **64** (Scheme 20).

Coupling of building blocks **64** and **65** was performed successfully with lithium hexamethyldisilazane (LHMDS) and

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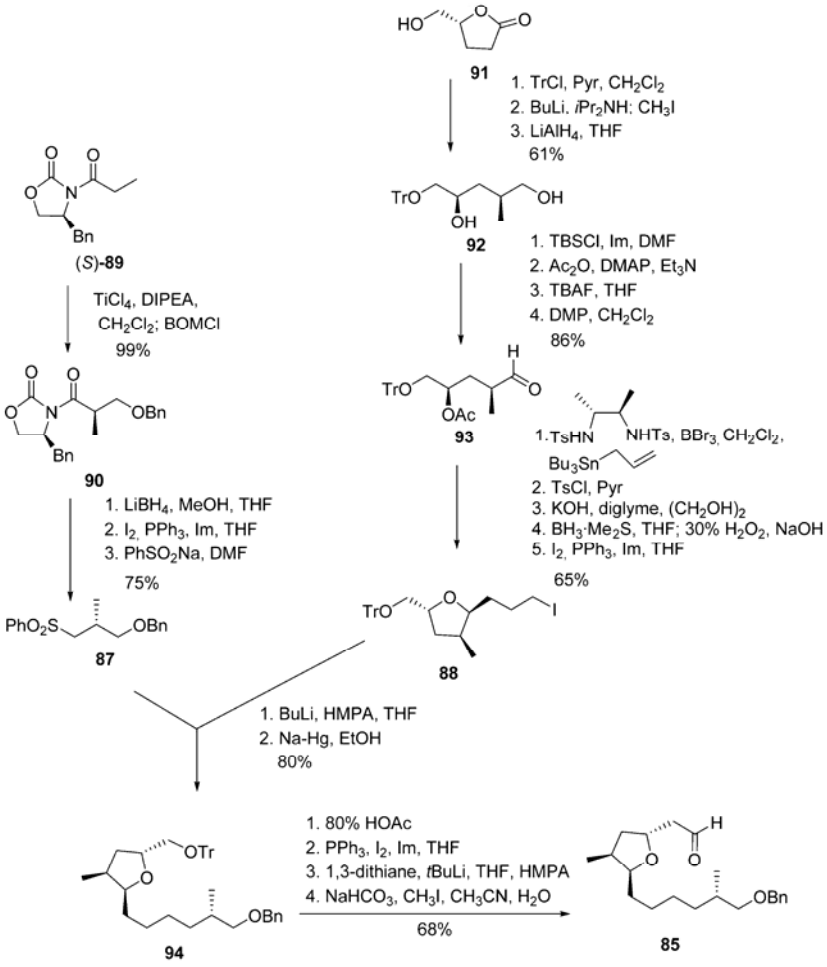
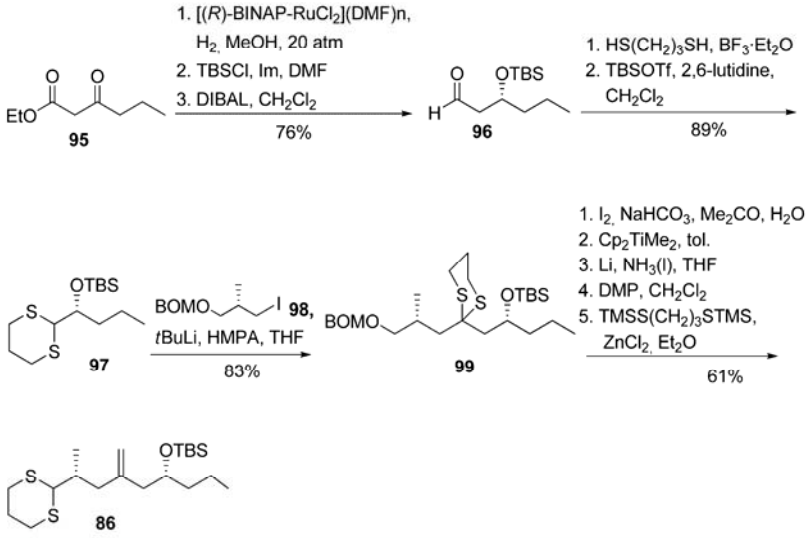
Scheme 22. Synthesis of Trisubstituted THF Building Block 85



Scheme 23. Synthesis of Building Block 86



hexamethylphosphoramide (HMPA). After oxidative desulfurization,[74] ketone **83** was obtained along with Piv-deprotected product. The mixture was converted to seco acid **84**, which, under Yamaguchi conditions, after selective deprotection of the EE ether, oxidation, and desilylation furnished amphidinolide F (Scheme 21).

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Scheme 24. Total Synthesis of Amphidinolide T3[77]

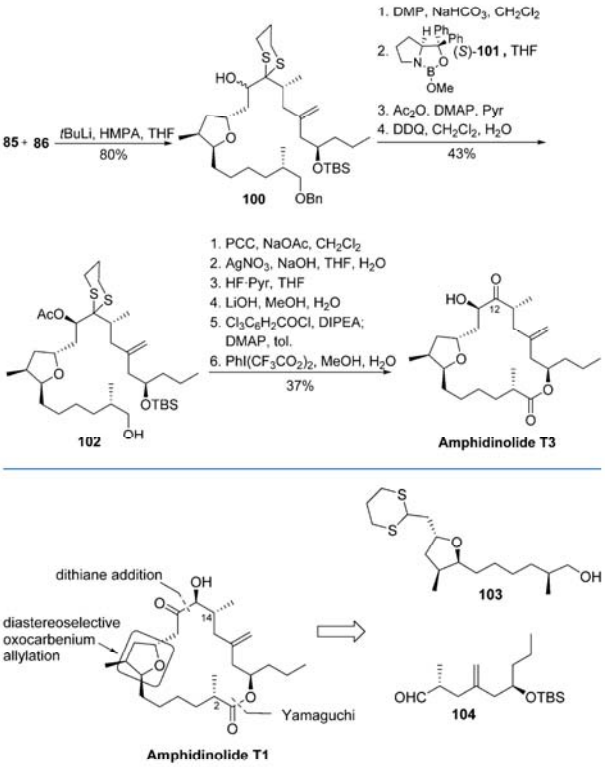


Figure 18. Amphidinolide T1 retrosynthetic analysis by Yadav.[78]

3.6.4. Amphidinolides T1, T2, T3, T4, and T5.

Amphidinolide T series are 19-membered macrolactones containing a *cis,trans,trans*-2,3,5-trisubstituted THF ring and an exocyclic methylidene group.[39p−s] The fact that they are all structurally related permits a diverted strategy for the synthesis of more than one natural product following the same synthetic route.

Synthesis of amphidinolides T was reviewed until 2005,[42a] when the work done by Fürstner, Ghosh and Jamison was compiled. Later in 2011, Fürstner presented a revision of the work done by his own group on the syntesis of amphidinolides, including the T series, and amphidinolides X and Y.[42b]

Further work includes the synthesis of the C1−C12 subunits by Iqbal[75] and Clark[76] and the total syntheses published by Zhao,[77] Yadav,[78] and Dai.[79,80] Figure 16 summarizes the main bond disconnections for the total syntheses of amphidinolide T1.

3.6.4.1. Zhao's Synthesis of Amphidinolide T3.[77] Key steps in this synthesis were the macrolactonization and the 1,3-dithiane addition, which meant the construction of two fragments, aldehyde **85** and dithiane **86** (Figure 17).

Aldehyde **85** was synthesized by condensation of sulfone **87** with iodide **88** (Scheme 22). Enantioselective synthesis of sulfone **87** was performed using oxazolidinone compound **89** as chiral auxiliary to obtain protected alcohol **90**. Removal of the chiral auxiliary and introduction of the sulfone led to compound **87** as shown in Scheme 22. The synthesis of **88** started with the protection of alcohol **91** as a Tr ether. Further alkylation provided good diastereoselectivity (dr 11:1) and reduction with $LiAlH_4$ afforded diol **92**. Aldehyde **93** was obtained by selective protection of **92** as a TBS ether, followed by acetylation of the secondary hydroxyl, desilylation, and oxidation. Asymmetric allylation of **93**, followed by tosyl (Ts) introduction and cyclization, produced the trisubstituted THF ring with the correct stereochemistry. Hydroboration−oxidation and subsequent iodine substitution provided iodide **88**. Addition of lithium derivative of **87** to **88**, followed by reductive removal of the sulfonyl group, furnished **94**. Removal of the Tr protecting group, iodine exchange, and substitution by 1,3-dithiane, followed by removal of dithiane, afforded segment **85**.

Synthesis of dithiane segment **86** started by stereoselective hydrogenation of ethyl 3-oxohexanoate **95**, protection of the formed alcohol, and reduction of the ester to obtain aldehyde **96**. Formation of the dithiane resulted in loss of the TBS ether, so reprotection was mandatory at this stage. The resulting dithiane **97** was reacted with iodide **98** to obtain **99**. Removal of dithiane, Petasis olefination, reductive eliminiation of BOM protecting group and oxidation, followed by dithiane constitution from the aldehyde, resulted in the formation of segment **86** (Scheme 23).

The assembly of **85** and **86** led to epimeric alcohols **100** (1.7:1). Despite the effort of the authors to obtain **100** as a unique stereoisomer, the only possibility was to oxidize the alcohol to the ketone and perform a stereoselective reduction with (*S*)-**101**. Acetylation of the formed hydroxyl and oxidative removal of benzyl protecting group afforded alcohol **102**. A two-step oxidation process was necessary to maintain the dithiane moiety. Removal of TBS and acetyl protecting groups was performed prior to Yamaguchi macrolactonization, and final removal of the dithiane afforded amphidinolide T3 (Scheme 24).

This synthesis of amphidinolide T3 describes the basis for the synthesis of amphidinolide T4, by simply inverting the stereochemistry at C12 in the last steps of the synthesis.

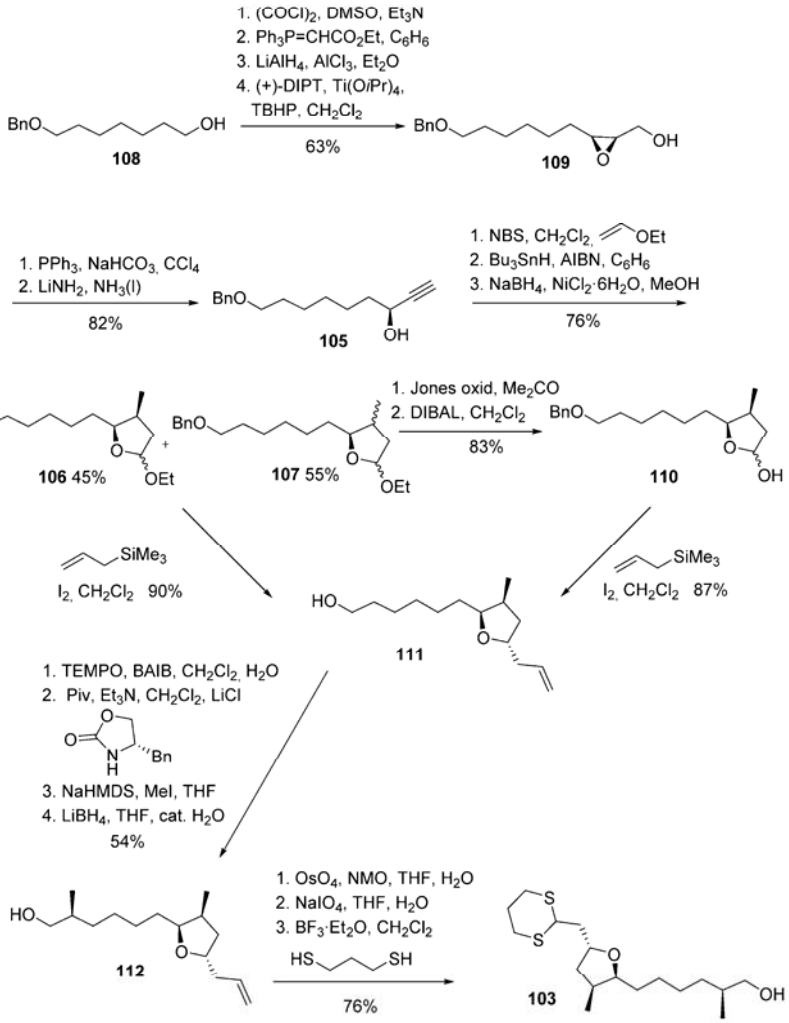
3.6.4.2. Yadav's Synthesis of Amphidinolide T1.[78] Yadav's retrosynthesis of amphidinolide T1 depicted two subunits, **103** and **104**. They based their assembly on a dithiane addition and a macrolactonization. The formation of the THF system was achieved by a new allylation strategy developed in their group (Figure 18).

The key steps for the synthesis of building block **103** were the transformation of alkynol **105** into a bromo acetal that was subjected to radical cyclization and hydrogenation to give ethoxy-THFs **106** and **107**. Alcohol **108** was transformed into **109** by oxidation, Wittig olefination, reduction of the ester to an allylic alcohol, and asymmetric epoxidation. Reaction of **109** with PPh_3 in CCl_4 with $NaHCO_3$, followed by base-induced elimination, resulted in alkynol **105**. Alkynol **105** with NBS and ethyl vinyl ether gave a bromo acetal that was subjected to radical cyclization and hydrogenation to obtain ethoxy-THFs **106** and a diastereomeric mixture of **107**. Mixture **107** was partially recovered for total synthesis by oxidation separation of epimers and reduction of the *syn*-lactone to obtain **110**. Allylation of either lactol ether **106** or lactol **110** was performed using a methodology developed by Yadav,[81] based on the reaction with allyltrimethylsilane in the presence of iodine; the yield and diastereoselectivity of this step proved that it was an effective methodology. Interestingly, the loss of the benzyl protecting group was observed in the presence of 1.2 equiv of iodine.

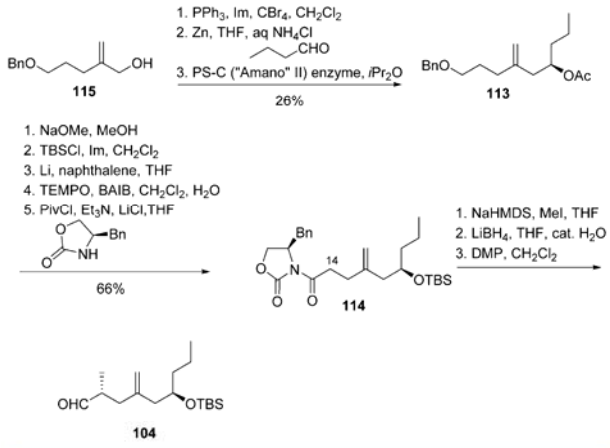
Oxidation of the free alcohol of **111**, followed by introduction of a chiral auxiliary, permitted diastereoselective methylation, and the removal of the chiral auxiliary with $LiBH_4$ afforded alcohol **112**. Dihydroxylation, oxidative cleavage of the diol with $NaIO_4$, and dithiane formation led to segment **103** (Scheme 25).

Enantioselective synthesis of fragment **104** had two important steps for stereochemical results: the enzymatic acetylation of

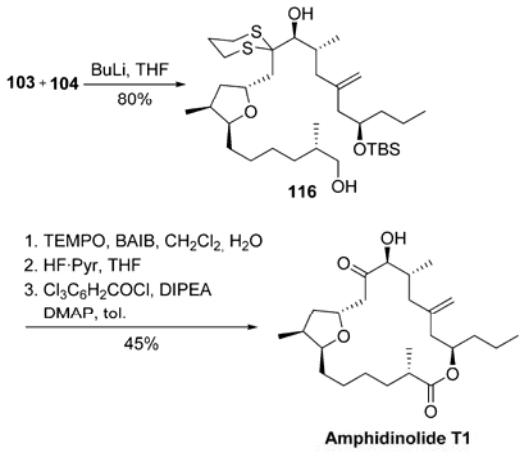
Scheme 25. Synthesis of Trisubstituted THF Derivative 103



Scheme 26. Synthesis of Aldehyde 104



Scheme 27. Total Synthesis of Amphidinolide T1[78]



epimeric alcohols to give **113** and the stereoselective C14 methylation of the acyloxazolidinone **114** precursor of aldehyde **104** (Scheme 26). Alcohol **115** was prepared by malonate synthesis from 3-benzyloxy-1-iodopropane[82] and diethyl malonate followed by reductive elimination. After bromination and allylation of butyraldehyde, the obtained racemic mixture of alcohols was subjected to enzymatic kinetic resolution to give **113**. Successive deacetylation, protection as a TBS ether, removal

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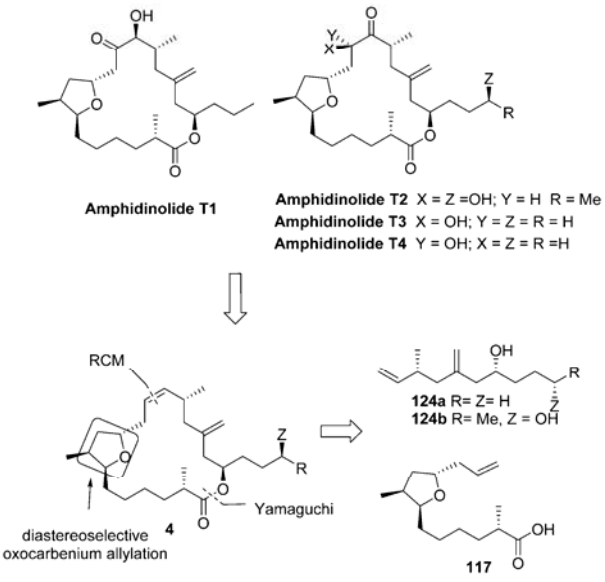
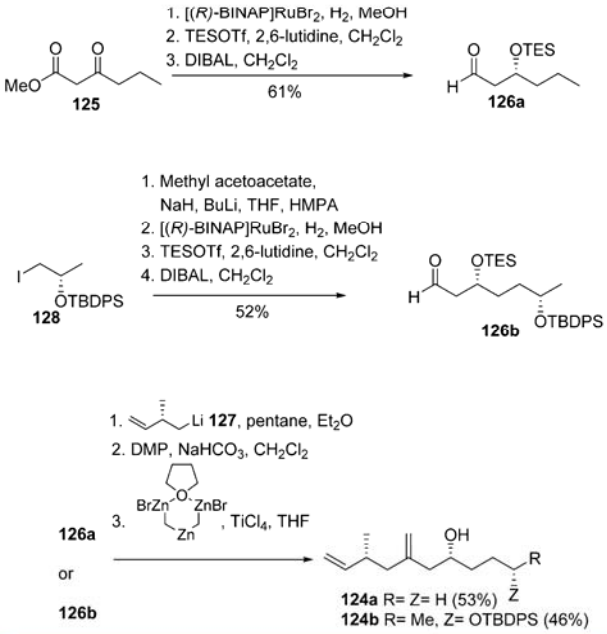


Figure 19. Retrosynthetic analysis of amphidinolides T by Dai.[80]

of the benzyl group, oxidation, and introduction of a chiral oxazolidinone afforded derivative **114**, which, upon methylation and removal of the chiral auxiliary in a two-step process, gave aldehyde **104**.

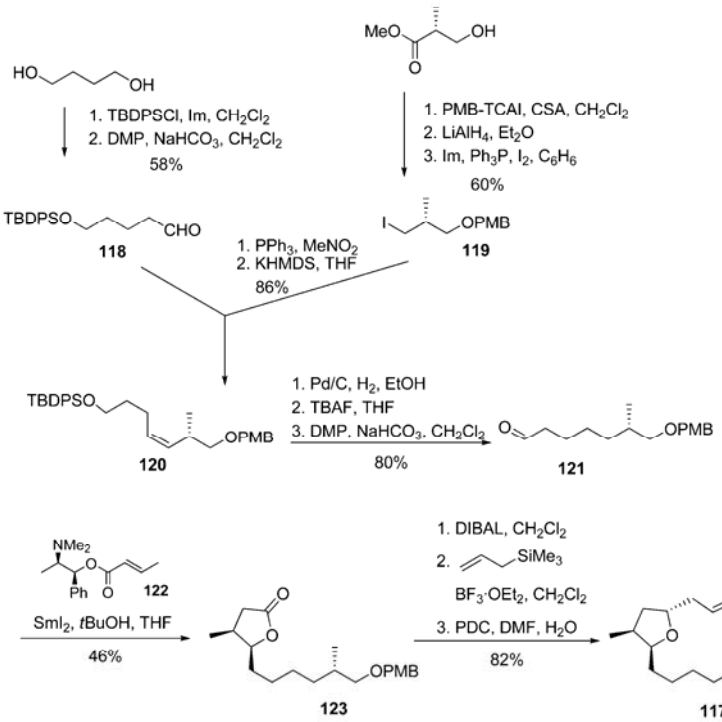
Addition of the lithium derivative of dithiane **103** to aldehyde **104** gave a 4:1 mixture of diastereomers of **116** favoring the *syn* adduct. Chromatographic separation permitted isolation of the major isomer. Selective oxidation of the primary hydroxyl group with loss of the dithiane moiety, removal of the TBS ether, and Yamaguchi lactonization led to amphidinolide T1 (Scheme 27).

Scheme 29. Synthesis of Alcohols 124a and 124b



3.6.4.3. Dai's Syntheses of Amphidinolides T1, T2, T3, and T4.[80] The total synthesis of amphidinolides T1, T2, T3, and T4 by Dai and co-workers took advantage of the components similarity to develop a diverted strategy from an advanced intermediate **117** (Figure 19). The synthesis is based on the union of two fragments by ester formation and RCM to prepare a common macrolactone possessing a double bond precursor of α-

Scheme 28. Synthesis of Acid 117



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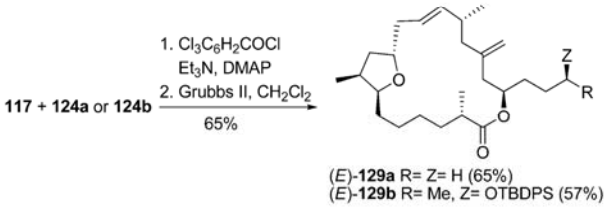
Scheme 30. Synthesis of Macrolactones 129a and 129b



hydroxyketone, which is characteristic of the T series amphidinolide natural products.

Fragment **117**, shared by the four amphidinolides T1, T2, T3, and T4, was synthesized as shown in Scheme 28. Phosphonium salt of iodide **119**, synthesized by known procedures,[83] was reacted with KHMDS and aldehyde **118** to yield alkene **120**, which was then transformed into aldehyde **121** by hydrogenation, removal of TBDPS ether, and oxidation. The stereoselective construction of the trisubstituted THF ring present in fragment **117** was afforded by SmI_2-mediated enantioselective reductive coupling between aldehyde **121** and crotonate **122** to give lactone **123**, which was then transformed into fragment **117** by reduction, allylation−deprotection, and oxidation.

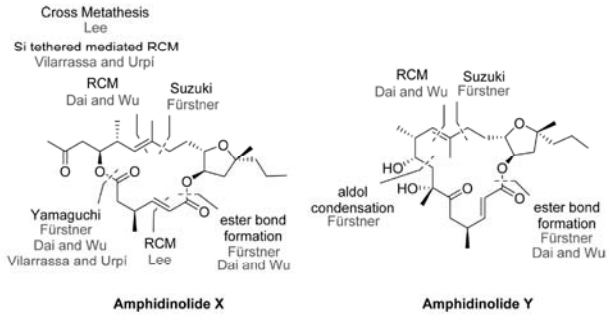
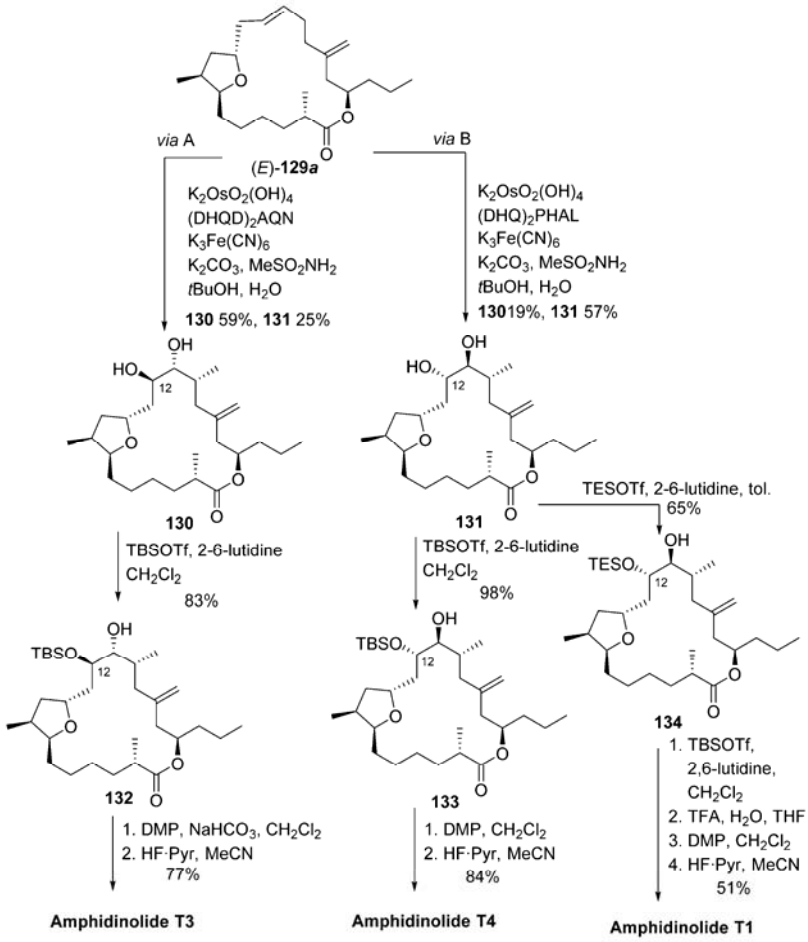


Figure 20. Strategic disconnections for amphidinolides X and Y.

For the synthesis of amphidinolides T1, T3, and T4, fragment **124a** was produced starting from β-keto ester **125**.[80b] Asymmetric reduction of the keto-group, protection of the hydroxyl, and reduction of the ester, afforded aldehyde **126a**. Further reaction of **126a** with lithium derivative **127**, followed by oxidation and methylenation with Nysted's reagent, which resulted in the loss of the TES ether, furnished **124a**. Amphidinolide T2 was synthesized from fragment **124b**.[80a] Protection of methyl (*S*)-lactate, reduction of the ester to the alcohol, and iodine exchange, gave iodine **128**. Methyl acetoacetate was alkylated with **128**. Enantioselective hydro-

Scheme 31. Total Syntheses of Amphidinolides T1, T3, and T4[80]



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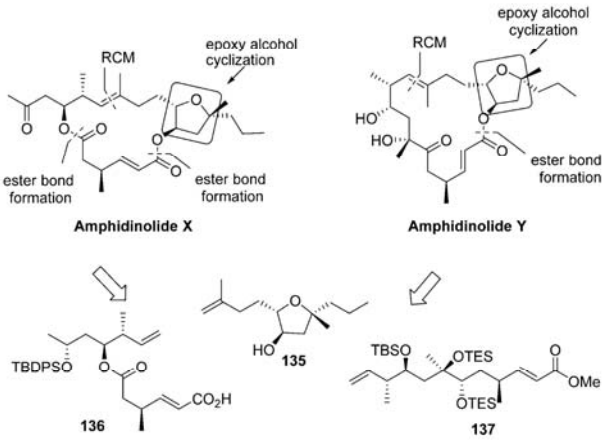
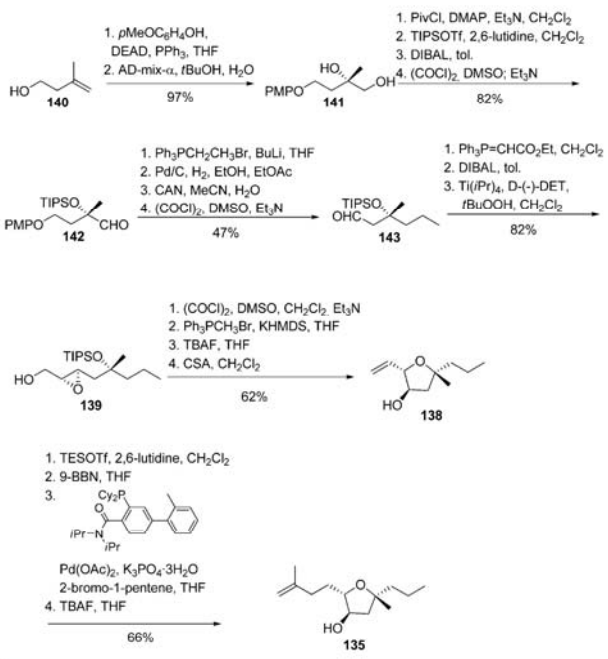


Figure 21. Amphidinolides X and Y retrosynthetic analysis by Dai and Wu.[88]

Scheme 32. Synthesis of Tetrasubstituted THF Building Block 135



genation, TES ether formation, and controlled reduction of the ester, furnished aldehyde **126b**. This aldehyde was transformed into **124b** in a similar reaction sequence as in **124a** (Scheme 29).

Fragments **124** and **117** were condensed by ester formation and further RCM using Grubbs II catalyst to yield macrolactones **129a** and **129b** (Scheme 30).

(*E*)-**129a** was the common synthetic intermediate for the total syntheses of amphidinolides T1, T3, and T4.[80b,c] Asymmetric dihydroxylation of (*E*)-**129a** was performed to obtain either **130**, using 1,4-bis(dihydroquinidine)anthraquinone [$(DHQD)_2AQN$] as a ligand, or **131** with 1,4-bis(9-*o*-dihydroquininyl)phthalazine [$(DHQ)_2PHAL$]. Transformation of **130** into amphidinolide T3 and **131** into amphinidolides T1 or T4 is based on a monoprotection, oxidation, and deprotection process that takes advantage of the selectivity in the protection of the less hindered C12 hydroxyl group of **130** or **131**, obtaining **132**, **133**, or **134** (Scheme 31).

Similar asymmetric dihydroxylation of **129b** using $(DHQD)_2AQN$ protection, oxidation, and deprotection (via A, Scheme 31) afforded amphidinolide T2.[80a]

3.6.5. Amphidinolides X and Y. Amphidinolides X and Y are 16- and 17-membered macrolides, whose structural similarity suggests a close biogenetic relation. Structural characteristics are the 2,3-*trans*-fused 2,3,5,5-tetrasubstituted THF ring and trisubstituted and conjugated *E*-double bonds in both amphidinolides. Amphidinolide Y exists as an equilibrium mixture of 6-keto and 6(9)-hemiacetal form (9:1) in $CDCl_3$ (Figure 10).[39t,u]

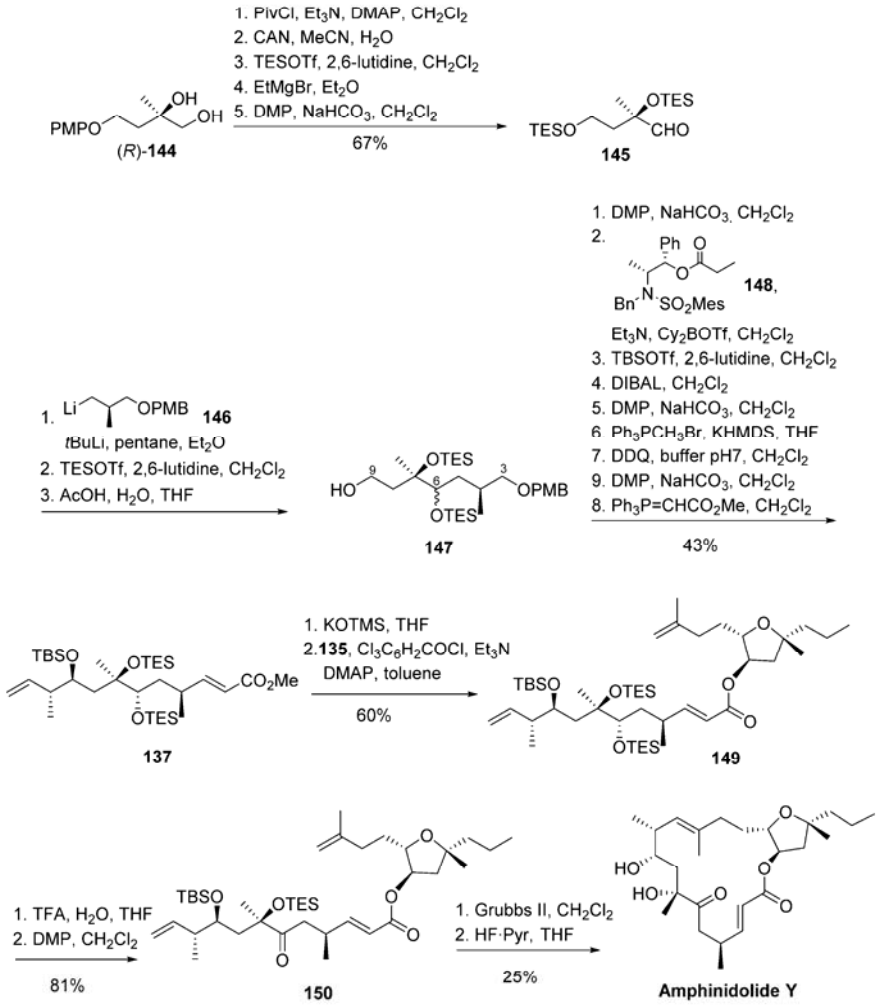
Several groups have been working in the synthesis and mechanism of action of amphidinolides X and Y since they were first reported in 2003. Of interest is the partial synthesis of the THF segment reported by Vatèle,[84] and by Gurjar and Mohapatra.[85] Fürstner and co-workers described the synthesis of amphidinolide X and Y,[86] both compiled in a revision published in 2011,[42b] which reported the synthesis and biological evaluation of some analogues as well.[87] The total synthesis performed by Dai and Wu,[88] Vilarrassa and Urpí,[89] and Lee[90] was reported at a later date. The main bond disconnections for the synthesis of amphidinolides X an Y are summarized in Figure 20.

3.6.5.1. Dai and Wu's Synthesis of Amphidinolides X and Y.[88] The strategy to synthesize amphidinolides X and Y was based on the same THF building block **135**. The main disconnections were macrolactonization and RCM. As shown in Figure 21, three building blocks were proposed for amphidinolide X and amphidinolide Y: the tetrasubstituted THF **135** and the acid derivatives **136** and **137**.

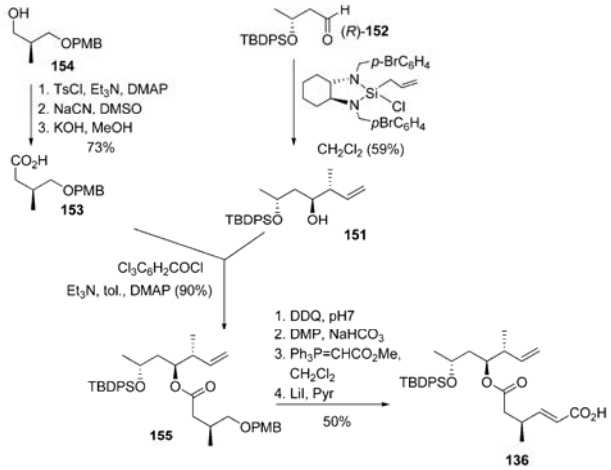
Enantioselective synthesis of tetrasubstituted THF **138** with the appropriate configuration of the four stereocenters was the key for the total synthesis.[88a] Epoxide **139** was synthesized from homoallylic alcohol **140**, using Corey's procedure[91] to obtain diol **141**. Manipulation of protecting groups and oxidation of the primary alcohol led to aldehyde **142**. This aldehyde was subjected to Wittig olefination and reduction, followed by removal of the PMP protecting group and oxidation to obtain aldehyde **143**. Olefination of **143** and reduction, followed by Sharpless epoxidation, furnished epoxy alcohol **139** in high enantioselectivity. Attempts to obtain a cyclized product from epoxy alcohol **139** failed to produce the desired THF fragment. π-Orbital activation by oxidation of the alcohol and Wittig olefination, followed by removal of the TIPS protecting group, and camphorsulfonic acid (CSA) catalyzed cyclization, led to **138**. Transformation of **138** into fragment **135** was afforded by protection of the alcohol, followed by hydroboration, Suzuki cross-coupling, and removal of the protecting group (Scheme 32).

Synthesis of Amphidinolide Y.[88b] Monoprotected triol **144**[91] was transformed to aldehyde **145** by exchanging protecting groups and oxidation. Reaction of **145** with the lithium derivative **146**[83] produced, after protection and selective desilylation, an epimeric mixture of alcohols **147** (3:1.2). The major alcohol (6*S*)-**147** was transformed into **137** by elongation at the two ends. Sequential selective oxidation at C9, aldol reaction with chiral ester **148**, followed by protection of the free hydroxyl, reduction of the ester to the alcohol, oxidation to the aldehyde, Wittig olefination, and oxidation at C3, followed by Wittig reaction, afforded **137**. Methyl ester cleavage and Yamaguchi lactonization with fragment **135** led to RCM precursor **149**. The same procedure was used to obtain **149** 6-epimer from the

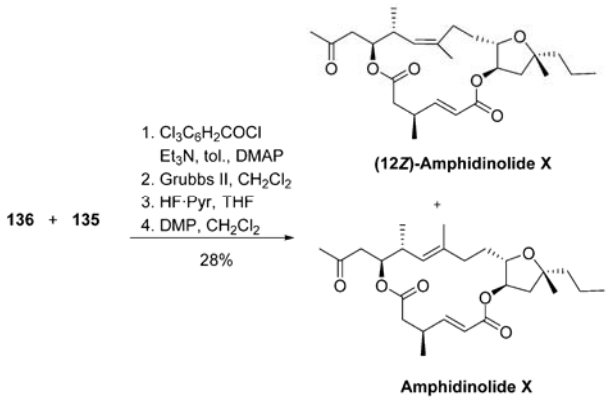
Scheme 33. Total Synthesis of Amphidinolide Y[88b]



Scheme 34. Synthesis of Acid 136



Scheme 35. Synthesis of Amphidinolide X and (12*Z*)-Amphidinolide X[88c]



minority alcohol (6*R*)-**147**. Ketone **150** was obtained from either **149** or its 6-*epi*-**149** by selective desilylation and oxidation. RCM was possible with ketone **150** in a 40% yield. After desilylation, amphidinolide Y was obtained as a 5:1 mixture (Scheme 33).

Synthesis of Amphidinolide X.[88c] Building block **136** for the synthesis of amphidinolide X was prepared starting from homoallylic alcohol **151** and acid **153**. Alcohol **151** was obtained by asymmetric crotylation of known (*R*)-**152**.[92] Acid **153** was synthesized from alcohol **154**[83b] in three steps. Condensation of

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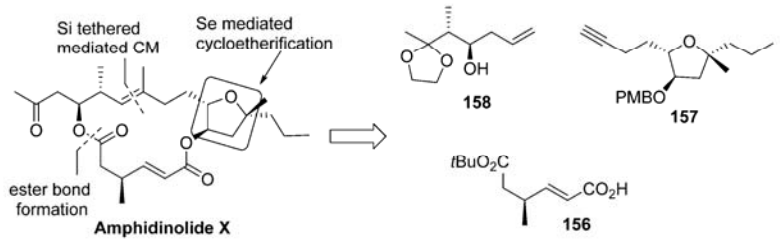
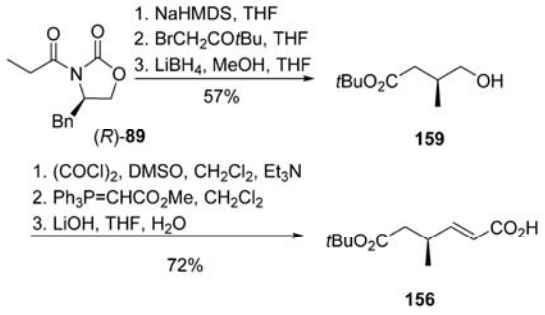


Figure 22. Amphidinolide X retrosynthetic analysis by Vilarrassa and Urpí.[89]

Scheme 36. Synthesis of Building Block 156



151 with **153** was performed under Yamaguchi conditions to obtain **155**. Removal of the PMB protecting group, oxidation, and subsequent Wittig olefination, provided an ester that was transformed into acid **136** (Scheme 34).

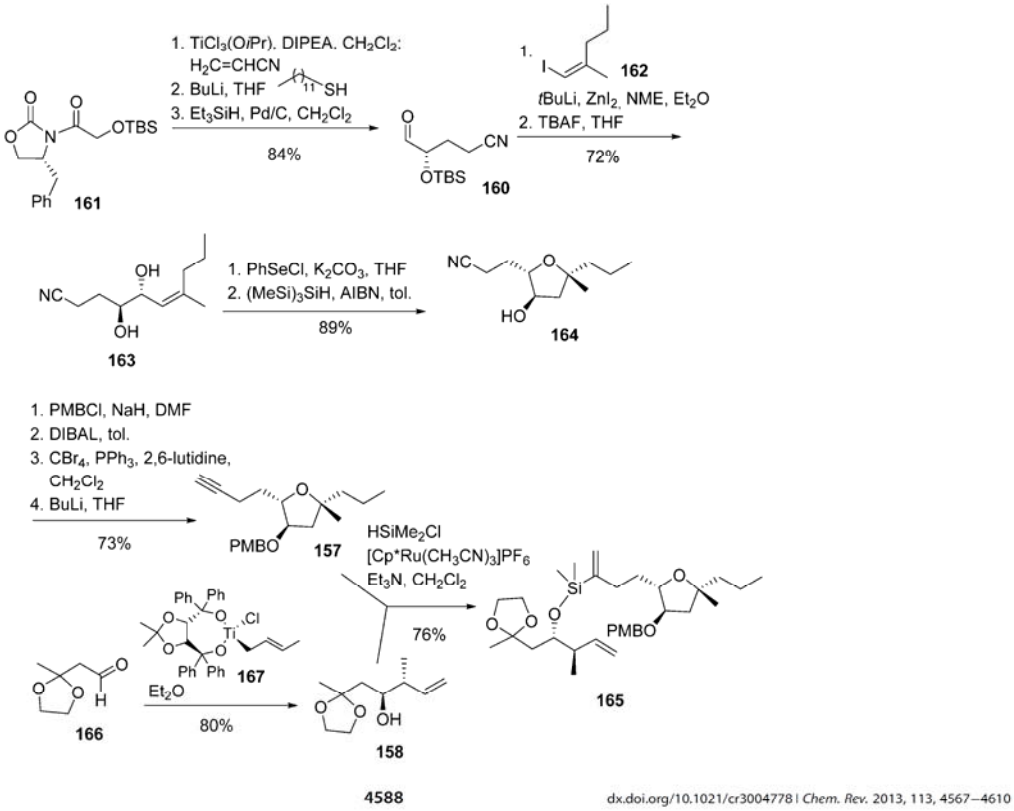
Acid **136** was condensed with THF fragment **135**. Further RCM afforded a mixture of *Z*/*E*-macrodiolides (71:29). Desilylation and oxidation of the mixture produced (12*Z*)-amphidinolide X and amphidinolide X itself (Scheme 35).

3.6.5.2. Vilarrassa and Urpí's Synthesis of Amphidinolide X.[89] Vilarrassa and Urpí's strategy for the synthesis of amphidinolide X depicted three main disconnections to form building blocks **156**, **157**, and **158** (Figure 22). Two ester bond formations and a silicon tethered cross metathesis (CM) reaction were used to build the final macrolide. Authors describe their efforts toward a strategy based on a RCM, but the low reactivity of the 1,1-disubstituted olefin led to a dead end. The construction of a silicon tether proved to be a reasonable solution to the CM problem.

Monoprotected diacid derivative **156** was synthesized by an asymmetric enol alkylation. Elimination of the chiral auxiliary to obtain alcohol **159**, further oxidation, and Wittig reaction, followed by selective hydrolysis, gave **156** (Scheme 36).

Aldehyde **160** was obtained from oxazolidinone **161** by asymmetric addition of the titanium enolate with acrylonitrile and reduction. Reaction of **160** with the alkenylzincate derived from iodide **162** using *N*-methylephedrine (NME) as organic

Scheme 37. Synthesis of Silicon-Tethered Diene 165



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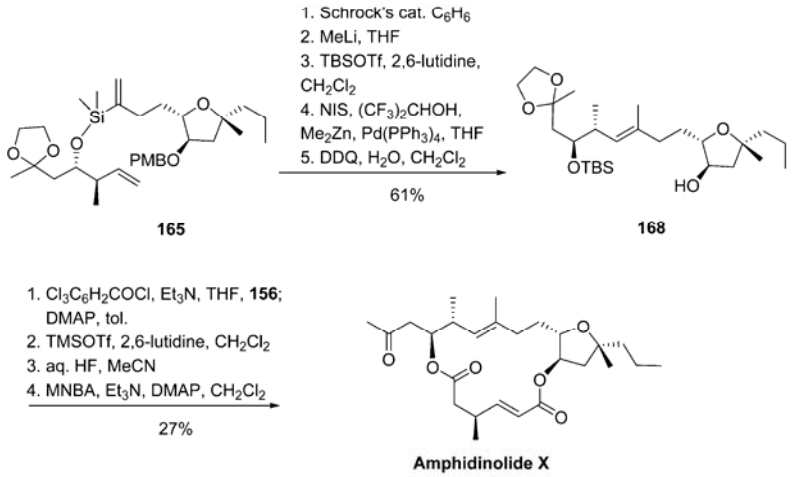
Scheme 38. Total Synthesis of Amphidinolide X[89]



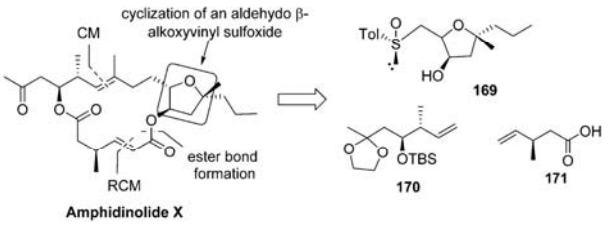
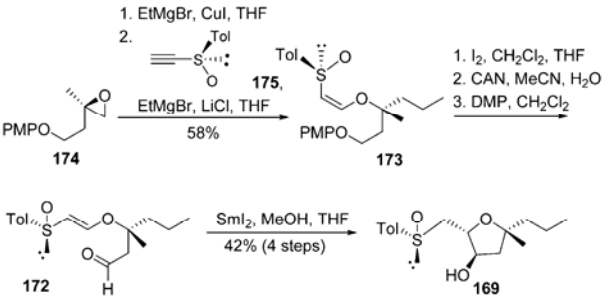


Figure 23. Amphidinolide X retrosynthetic analysis by Lee.[90]

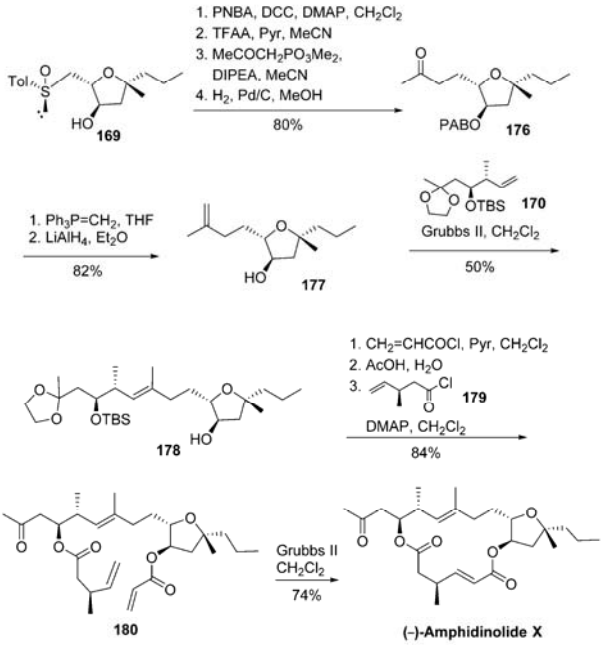
Scheme 39. Stereoselective Synthesis of Tetrasubstituted THF Derivative 169



asymmetric inductor, followed by deprotection of the TBS ether, afforded enantiopure **163**. The synthesis of tetrasubstituted THF **164**,[89a] the key step of this process, was afforded by stereocontrolled PhSeCl-induced cyclization of the *anti*-*Z* α,β-dihydroxy-trisubstituted olefin **163**, followed by deselenylation. Transformation of **164** into **157** was obtained by protection of the free hydroxyl group and homologation of the cyano group to the terminal triple bond. Silicon-tethered fragment **165** was obtained using Trost's catalyst[93] from the addition of dimethylchlorosilane to the triple bond of **157**, followed by silyl ether formation with alcohol **158** (Scheme 37). Alcohol **158** was obtained from aldehyde **166** in a process using Ti-derivative **167**.[94]

Dialkene **165** was reacted with Schrock's catalyst, and the silicon tether was removed by reaction with MeLi. This was followed by protection of the hydroxyl, iododesilylation with *N*-iodosuccinimide (NIS), and Negishi coupling with Me_2Zn. Benzyl removal provided alcohol **168** that was condensed with

Scheme 40. Enantioselective Total Synthesis of (−)-Amphidinolide X[90]



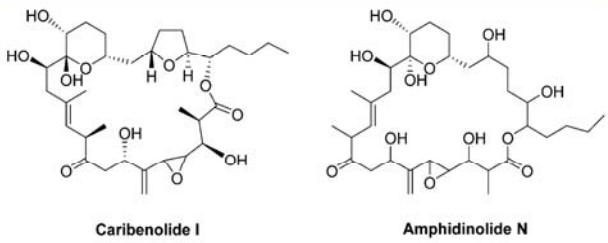


Figure 24. Proposed structures of caribenolide I[97] and amphidinolide N.[39]

building block **156**. Further removal of the *t*Bu ester and the TBS ether, followed by macrolactonization, led to amphidinolide X (Scheme 38).

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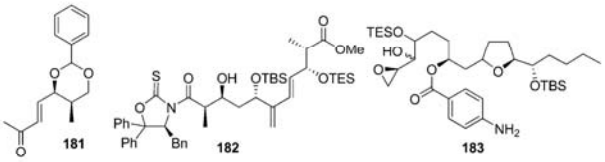


Figure 25. Structures of C1−C6, C1−C11, and C13−C29 building blocks of caribenolide I.[101,102]

3.6.5.3. Lee's Synthesis of Amphidinolide X.[90] The last synthesis of amphidinolide X published to date is the one carried out by Lee and co-workers. They based the construction of the THF onto a cyclization of an aldehydo β-alkoxyvinyl sulfoxide derived from a tertiary alcohol. The retrosynthetic analysis shown in Figure 23 depicts building blocks **169**, **170**, and **171**.

THF **169** was obtained with good stereocontrol by SmI_2 mediated cyclization of vinyl ether **172**. (*Z*)-Alkoxyvinyl sulfoxide **173** was obtained by nucleophilic addition of EtMgBr to known epoxide (*R*)-**174**,[95] followed by reaction of the resulting alkoxide with (*S*)-alkynyl sulfoxide **175**. Isomerization to the (*E*)-alkoxyvinyl sulfoxide by treatment with iodine, followed by ceric ammonium nitrate (CAN) deprotection of the benzyl group, and final oxidation to the aldehyde, led to cyclization precursor **172** (Scheme 39).

Protection of **169** and Pummerer rearrangement afforded an aldehyde that was subjected to a HWE olefination. Hydrogenation produced the double bond as well as the nitro group reduction to give ketone **176**. After Wittig methylenation and $LiAlH_4$ deprotection, hydroxyolefin **177** was obtained. Grubbs II-catalyzed CM between **177** and known olefin **170**,[89b] afforded (*E*)-**178**. Alcohol **178** was condensed with acryloyl chloride, TBS deprotection, condensation with the acid chloride **179**,[96] and subsequent RCM of **180**, furnished (−)-amphidinolide X (Scheme 40).

3.7. Caribenolide I[97]

Caribenolide I is an important cytotoxic metabolite obtained from cultured cells of *Amphidinium* sp. in enriched seawater, under fluorescent illumination, and harvested at the stationary phase in a 0.026% yield from dried cells.[97] Caribenolide I was a cytotoxic agent in the human colon carcinoma cell line (HCT 116) and the corresponding drug-resistant HCT 116 VM/46 with 1.6 nM values for the IC_{50}. Caribenolide I was found to be 100 times more potent than amphidinolide B. This natural compound represents a new type of macrocyclic lactone, which contains one α-methylidene epoxide, one disubstituted THF, one tetrasubstituted THP ring, one keto group, one *E*-double bond, four hydroxyl groups, and one butyl lateral chain (Figure 24). Stereochemical configuration of the natural product, except for the two epoxide stereocenters, was determined by synthetic studies.

Work on the synthesis of caribenolide I is often related to amphidinolide N,[39] due to their similar structure. Nicolaou[98,99] and Franck and Frigadère[100−102] have worked on the complex challenge posed by the synthesis of these structures.

Franck and Figadère's group published an interesting contribution to the total synthesis of caribenolide I.[101,102] They described the stereoselective synthesis of building blocks C1−C6,[100] C1−C11,[101] and C13−C29,[102] **181**, **182**, and **183** of caribenolide I using as key steps asymmetric aldol reactions, to control the absolute configurations of stereogenic centers (Figure 25).

The last contribution to the study of this natural product has been recently published by Trost,[103] who, based on synthetic studies, stated that caribenolide I and amphidinolide N could have more common structural features than those previously reported, since amphidinolide N could also present the THF structural motif.

3.7.1. Nicolaou's Synthesis of Caribenolide I.[99] Nicolaou and co-workers tested three alternative procedures for the synthesis of caribenolide I. The last procedure afforded the enantioselective synthesis of *des*-epoxy-caribenolide I. This work was important to confirm the constitution of the molecule and to establish the configuration of 11 stereocenters and the *E*-alkene. The first strategy tested by Nicolau's group was based on an enyne metathesis for C5 and C6 bond formation. However, following the synthesis of the complete C6−C29 carbon skeleton possessing the terminal acetylene, it was not possible to introduce the C1−C5 chain either intermolecular or intramolecularly.[98] The second strategy focused on a palladium-

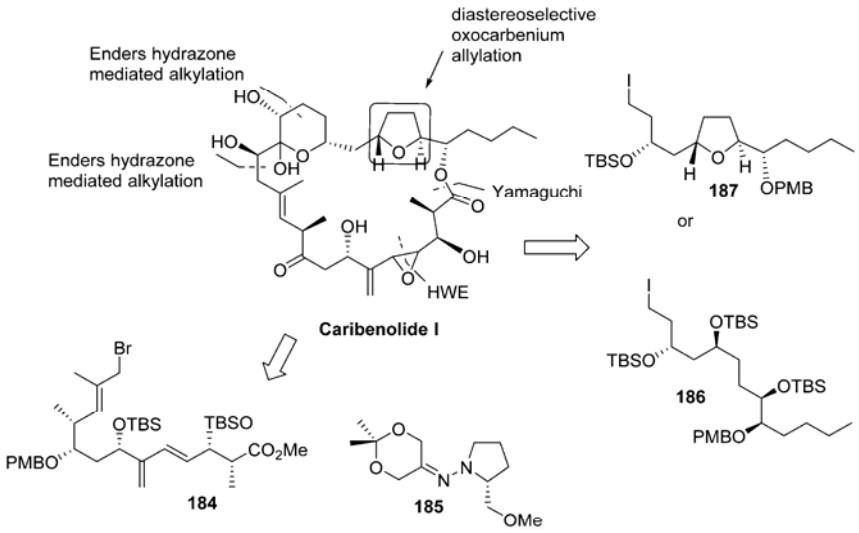
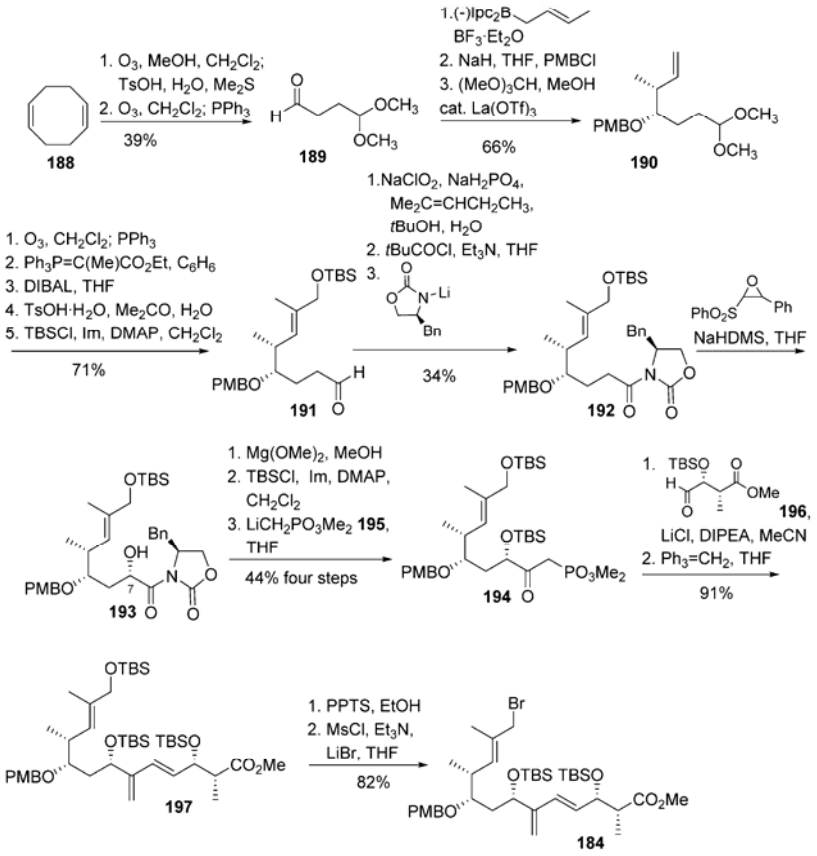
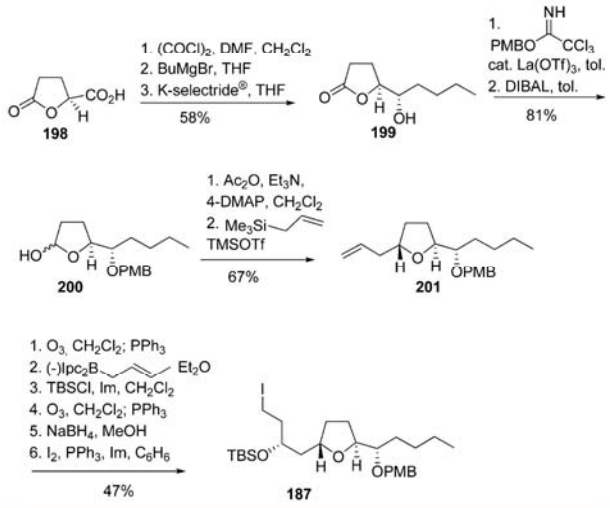


Figure 26. Caribenolide I retrosynthetic analysis by Nicolaou.[99]

Scheme 41. Synthesis of Bromide 184



Scheme 42. Synthesis of Iodide 187



catalyzed cross-coupling to generate the C5−C6 bond by reaction between a vinyl bromide and several functionalized forms of the C1−C5 skeleton.[98] The last strategy, called by the authors the 'HWE approach', has, as a key intermediate, bromide **184** (see Figure 26). The stereoselective assembly of the Enders hydrazone[104] C14−C16 **185** with bromide **184** and iodide **186** affords the full skeleton of amphidinolide N. A similar procedure using iodide **187** affords the full skeleton of caribenolide I.[99]

The 1,5-cyclooctadiene **188** was converted into aldehyde **189** via two sequential ozonolysis reactions.[105] The introduction of the C9−C10 fragment by a Brown crotylboration reaction[106] of aldehyde **189**, followed by secondary alcohol protection as the corresponding PMB ether, gave **190**. Unexpectedly, a significant degree of hydrolysis of the dimethyl acetal group occurred during this step; therefore, the crude reaction mixture was subjected to acetalization prior to purification. Ozonolysis of the terminal alkene in compound **190** then provided the aldehyde, which was subjected to an (*E*)-selective Wittig reaction using stabilized phosphorane, to give trisubstituted alkene as a single geometrical isomer. The alkene was converted into aldehyde **191** by a three-step sequence of ester reduction, acetal hydrolysis, and TBS alcohol protection. The C7 hydroxyl group was introduced through enantioselective α-oxygenation chemistry of *N*-acyl oxazolidinones on **192**.[107] *N*-Acyl oxazolidinone **193** was transformed into the β-ketophosphonate **194** in three steps based on methanolysis, removal of the auxiliary group, TBS protection of the C7-OH, and reaction with the lithium derivative **195**. HWE reaction between **194** and **196** gave exclusively the C4−C5 (*E*)-isomer, which underwent Wittig methylenation to yield diene **197**. Bromine **184** was obtained from **197** by chemoselective deprotection of the primary alcohol and substitution of the hydroxyl group by bromine via mesyl derivative (Scheme 41).

L-Glutamic acid was chosen as the starting material for the synthesis of the C17−C29 fragment **187** (Scheme 42). It was converted into lactone **198**, with retention of configuration, via diazotization and internal displacement.[108] Formation of acid

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Scheme 43. Synthesis of C15 Epimeric Mixture of *des*-Epoxy-caribenolides I 204[99]

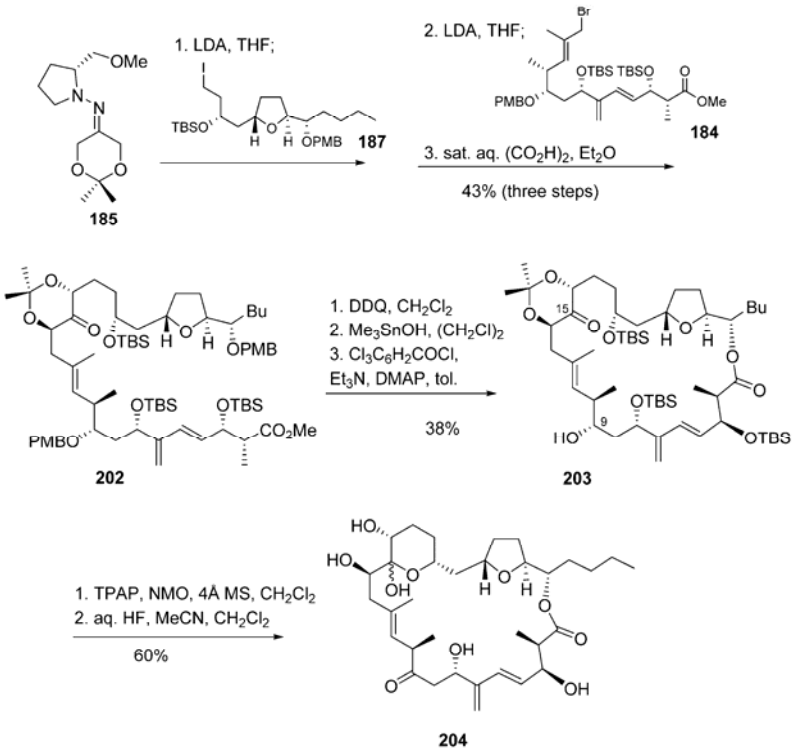
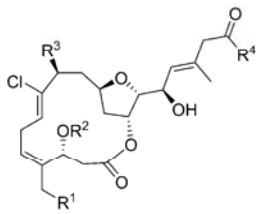
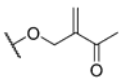
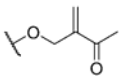
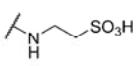


Table 1. Structures of Haterumalides and Biselides



	R^1	R^2	R^3	R^4	Ref. isolation
Haterumalide NA	H	Ac	H	OH	111
Haterumalide NB	H	Ac	H	OBu	111
Haterumalide NC	H	Ac	OH	OBu	111
Haterumalide ND	H	Ac	OH	OH	111
Haterumalide NE	H	H	H	OH	111
Haterumalide B	H	Ac	H		110
Biselide A	OAc	Ac	H	OH	114a
Biselide B	OAc	Ac	H		114a
Biselide C	OH	Ac	H	OH	114b
Biselide D	H	Ac	H		114b

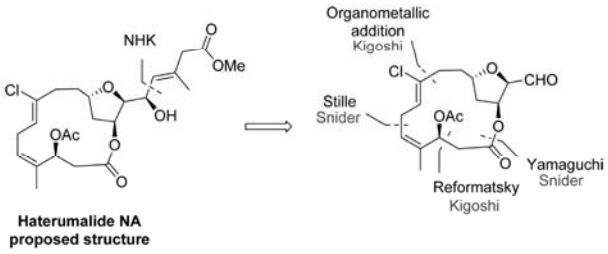


Figure 27. Retrosynthetic disconnections for proposed haterumalide NA.

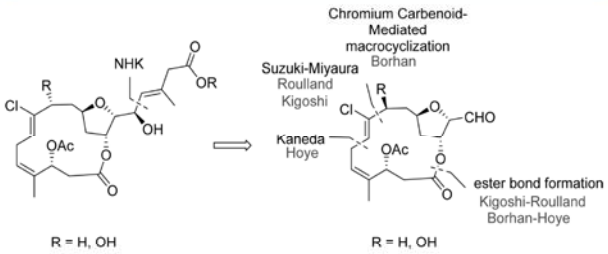


Figure 28. Retrosynthetic disconnections for haterumalide NA/oocydin A, haterumalide B and haterumalide NC.

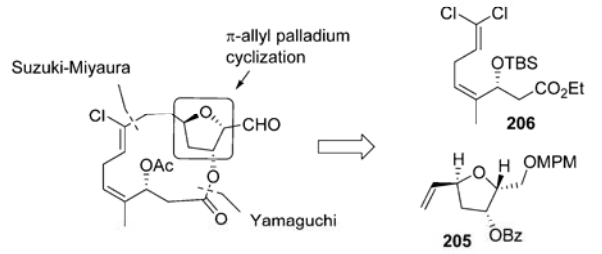
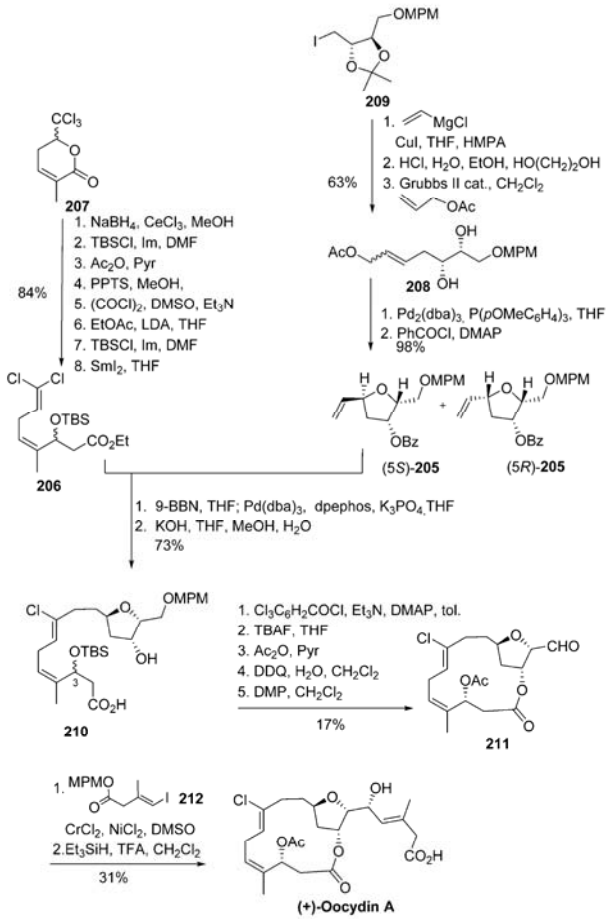


Figure 29. Oocydin A retrosynthetic analysis by Roulland.[123]

chloride, followed by the careful chemoselective addition of butylmagnesium bromide at low temperature, gave a ketone, which, upon reduction using K-Selectride, furnished alcohol **199** as a single stereoisomer. Protection of alcohol as the PMB ether, followed by reduction of lactone using DIBAL, gave lactol **200**, which was converted into anomeric acetate. Further allylation of this acetate, catalyzed with TMSOTf at low temperature to give the (21*S*)-THF product **201**, was then achieved (96%, dr 3.5:1). Iodide **187** was prepared from alkene **201** with a good global yield through a sequence of six further transformations consisting of chain integration and exchange of protecting and functional groups.

The complete carbon framework of target caribenolide I was furnished by the assembly of the building block fragments using Enders chiral hydrazone[104] alkylation methodology. The optimum conditions for the alkylation of hydrazone **185** were depicted as smooth coupling, first with C17−C29 iodide building block **187** and then with C1−C13 bromide building block **184**, following cleavage of the hydrazone auxiliary using aqueous oxalic acid to obtain ketone **202** as a single observable stereoisomer (Scheme 43). From ketone **202**, the fully deprotected core structure of caribenolide I was obtained by removal of both PMB protecting groups by treatment with DDQ, followed by hydrolysis of the ester to the corresponding acid using Me_3SnOH. Macrolactonization of the resulting acid under standard Yamaguchi conditions[109] afforded compound **203**.

Scheme 44. Enantiomeric Total Synthesis of (+)-Oocydin A[123]



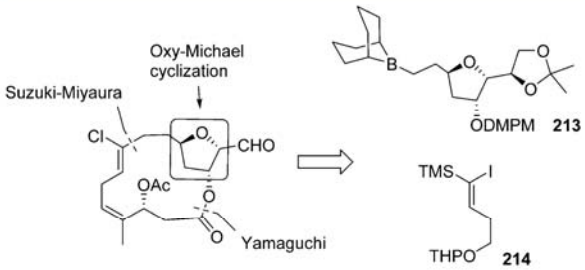


Figure 30. Haterumalide NA retrosynthetic analysis by Kigoshi.[119]

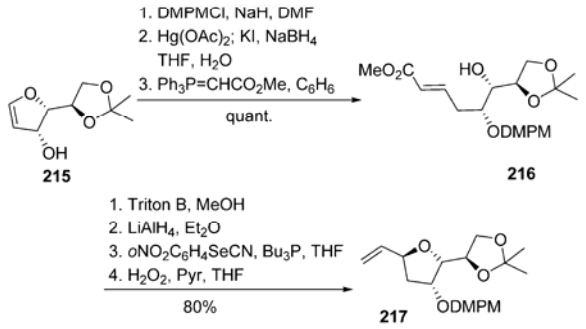
Oxidation of C9-OH group and deprotection of the ketone moiety was accompanied by spontaneous intramolecular hemiacetal formation at the C15 carbonyl group, to generate tricyclic compound **204** (a *des*-epoxy-caribenolide I stereoisomer) as an inseparable 6:1 mixture of anomers. From diene **204**, completion of the first total synthesis of caribenolide I stereoisomer then required the selective epoxidation of the C4−C5 alkene. The oxidation has not yet been described to date.

3.8. Haterumalides, Oocydin A, and Biselides

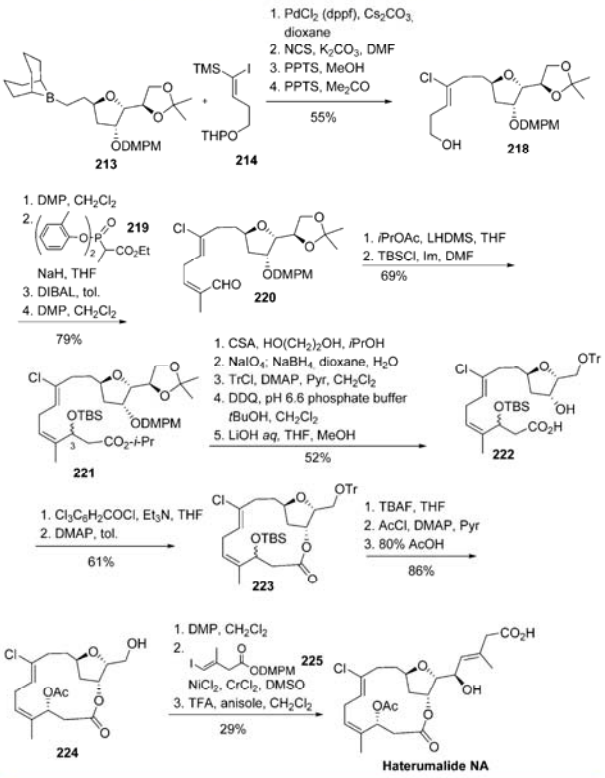
Haterumalides are a series of chlorinated macrolides isolated for the first time in 1999 from an Okinawan sea sponge of the species *Ircinia* and Okinawan ascidian *Lissoclinum* sp.[110,111] In isolation, haterumalide NA was demonstrated to be a strong cytotoxic

dx.doi.org/10.1021/cr3004778 | *Chem. Rev.* 2013, 113, 4567−4610

Scheme 45. Synthesis of Trisubstituted THF 217



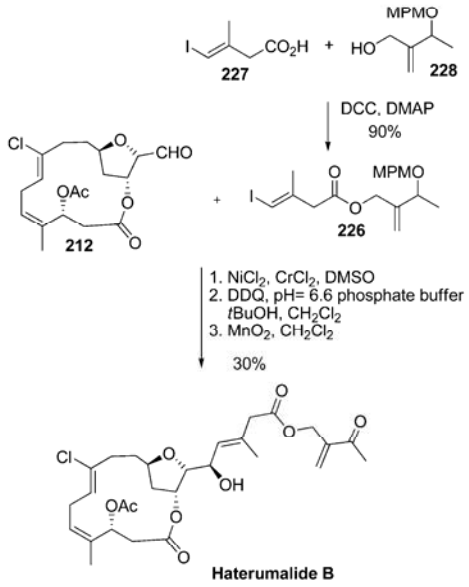
Scheme 46. Total Synthesis of Haterumalide NA[119a]



agent against leukemia cell line (P338) and haterumalide B inhibited fertilized sea urchin eggs at micromolar concentration. Initial proposed stereochemistry was revised upon synthetic production of the proposed haterumalide NA.[112] In the same year, oocydin A, a haterumalide NA diastereomer, was isolated from the South American epiphyte *Serratia marcescens*.[113] Several years later the first biselides were isolated from the Okinawan ascidian *Didemnidae* sp. and after spectroscopic analysis, their structures were established as oxygenated analogs of haterumalides.[114] Researchers at the Fujisawa Pharmaceutical company isolated FR177391 from the soil bacterium *Serratia liquefaciens* and determined its structure as a diastereomer of haterumalide NA.[115] It is worth mentioning that some of the haterumalides were also isolated from the soil bacterium *Serratia plymuthica*.[116]

Spectroscopic data for haterumalide NA, oocydin A, and FR177391 seem to be identical, but there are differences in their reported optical rotations. Therefore, whether the bioactive

Scheme 47. Total Synthesis of Haterumalide B[119b]



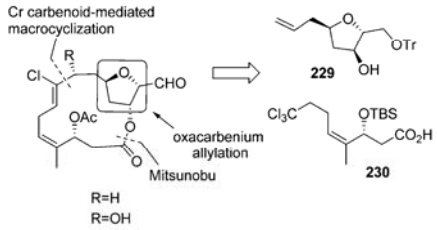


Figure 31. Retrosynthetic analysis of haterumalides NA and NC by Borhan.[124]

metabolite from *Serratia* species is the enantiomer of that derived from the sponge remains unclear. Finally, some advances have been made recently regarding the study of the oocydin A gene cluster and its biosynthesis from a four-plant associated enterobacteria.[117] From a structural point of view, these molecules display many interesting motifs in their complex frameworks, such as the THF ring bridged with a macrocyclic lactone, a Z chlorovinyl functionality, two allylic alcohols, and several stereogenic centers (Table 1). Helpful and complete reviews were published in 2007 and 2009[118] about the isolation, structures, bioactivities, and total synthesis of haterumalides, biselides, and related natural products. In our review, mention is made only to papers after Kigoshi's review.

The widespread family of haterumalides, biselides, oocydin and FR177391 has attracted attention from numerous groups of synthetic chemists who have developed different strategies for the synthesis of these compounds. The synthetic work carried out by Kigoshi and co-workers helped the structural reassignment[112] and later achieved the total synthesis of haterumalides NA and B using two different routes.[119] Recently, the same group has described their results toward the synthesis of biselides A and B.[120] Of interest are also the syntheses developed by Snider,[121] Hoye,[122] Roulland,[123] and Borhan.[124] Figures 27 and 28 summarize the retrosynthetic disconnections in the successful total syntheses of haterumalides and biselides.

The aldehyde itself is the common synthetic precursor in all the total syntheses. Different key strategic bonds have been

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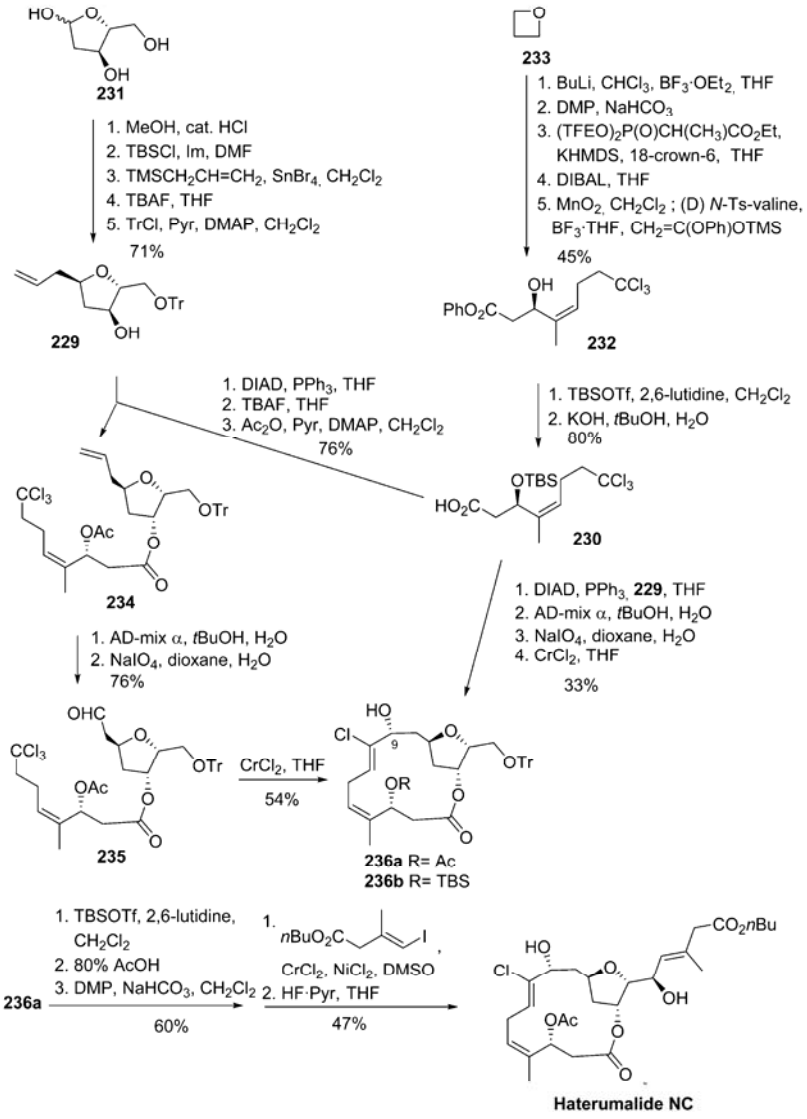
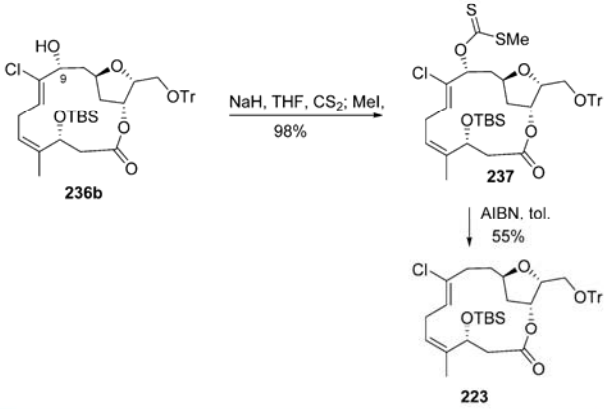
Scheme 48. Borhan's Total Synthesis of Haterumalide NC[124]



Scheme 49. Formal Synthesis of Haterumalide NA[124]



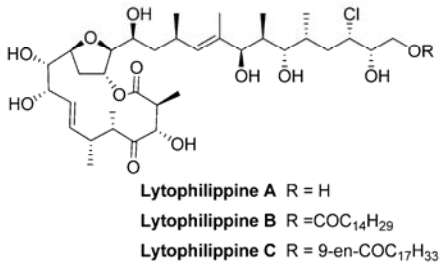


Figure 32. Proposed structures for lytophilippines A–C.[133]

chosen for the syntheses of the aldehydes: macrolactonization,[112,119–124] Suzuki-Miyaura coupling,[112,119,123] Stille coupling,[121] Reformatsky reaction,[112] haloallylation reaction,[122] or the use of chlorovinylidene chromium carbenoids.[124]

3.8.1. Roulland's Synthesis of Oocydin A.[123] The key step for Roulland's total synthesis of oocydin A was the Suzuki–Miyaura cross-coupling of the vinyl THF building block **205** and in situ obtained alkylboronate of the dichlorovinyl derivative **206**,[125] followed by macrocyclization (Figure 29).

dx.doi.org/10.1021/cr3004778 | Chem. Rev. 2013, 113, 4567–4610

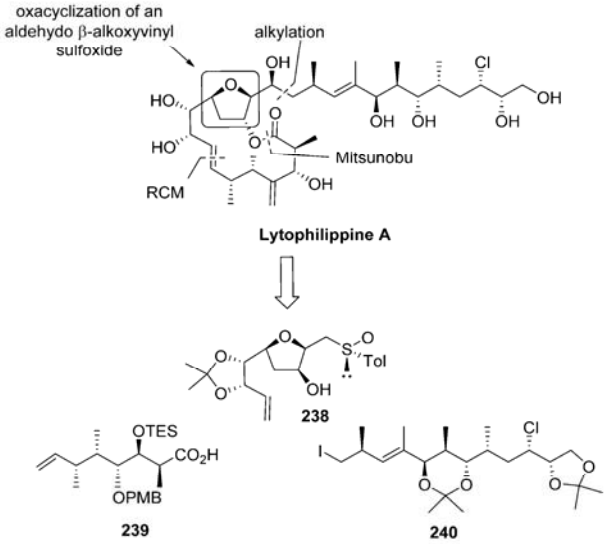
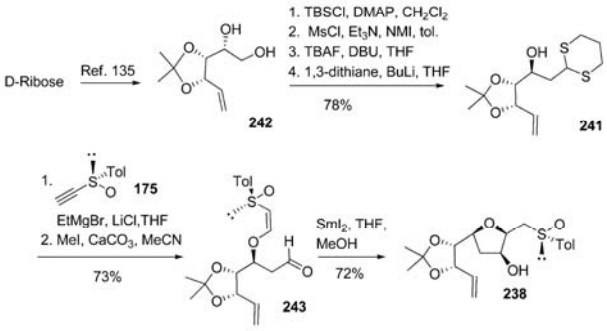


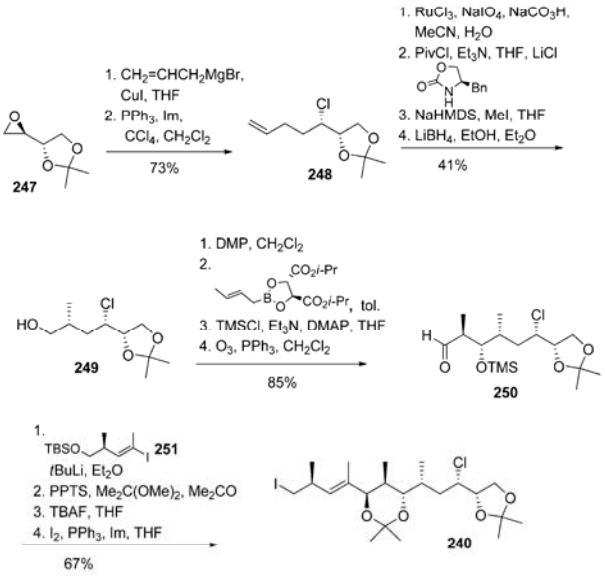
Figure 33. Proposed lytophilippine A retrosynthetic analysis by Lee.[134]

Scheme 50. Synthesis of Trisubstituted THF Building Block 238



The two synthetic precursors of oocydin A **205** and **206** were obtained as shown in Scheme 44. α,β-Unsaturated lactone **207** was the precursor of dichloroalkene **206** by a sequence of eight synthetic steps performed with good yield. THF **205** was obtained in turn, as a C-5 epimeric mixture (96:4), via intramolecular cyclization of the alcohol over the π-allyl palladium of acetate **209**. Separation of the epimers (5*S*)-**205**

Scheme 52. Synthesis of Building Block 240

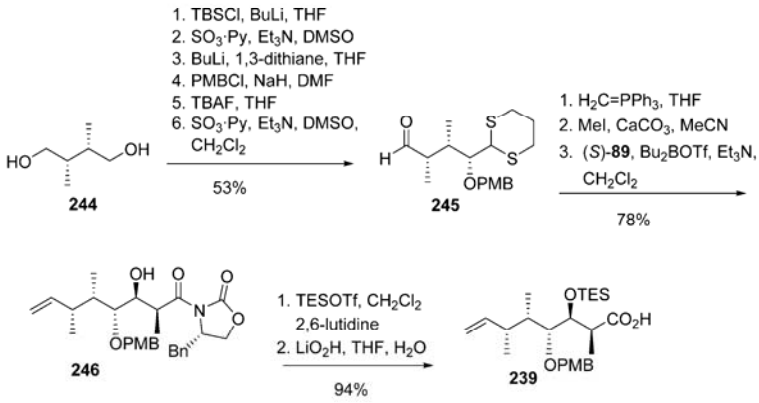


and (5*R*)-**205** was afforded after benzoylation. Acetate **208** was prepared as an *E*/*Z* mixture (95:5) from the iododerivative **209** by copper-catalyzed substitution of iodide with vinylmagnesium chloride, followed by deprotection, and cross-metathesis reaction with allyl acetate using Grubbs II catalyst.

Cross-coupling of (5*S*)-**205** and the epimeric mixture of **206** gave a diester, which was saponified to seco acid **210**. Macrolactonization of **210** under Yamaguchi conditions, removal of TBS protecting group, separation of C3 epimers, and acetylation before *p*-methoxybenzyl (MPM) group removal and oxidation, afforded **211**; the unwanted C3 isomer was recycled under oxidation and Luche reduction to also obtain aldehyde **211**. The condensation of fragment **212**[121] with aldehyde **211** under Nozaki–Hiyama–Kishi (NHK)[126] conditions, furnished an alcohol, which upon final deprotection[127] of the masked carboxylic acid, supplied the target compound (+)-oocydin A, whose chemical data were identical to those of the naturally occurring compound.

3.8.2. Kigoshi's Synthesis of Haterumalides NA and B.[119] A parallel route for haterumalide NA was developed by H. Kigoshi and published in the same year as Roulland's synthesis. Kigoshi's total synthesis of haterumalide NA followed the same

Scheme 51. Synthesis of Building Block 239



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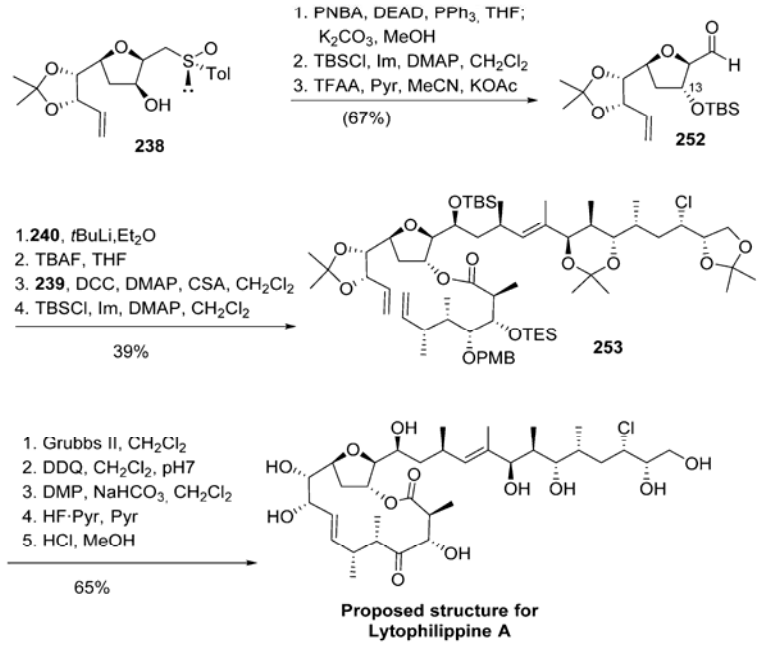
Scheme 53. Synthesis of Proposed Structure for Lytophilippine A[134]



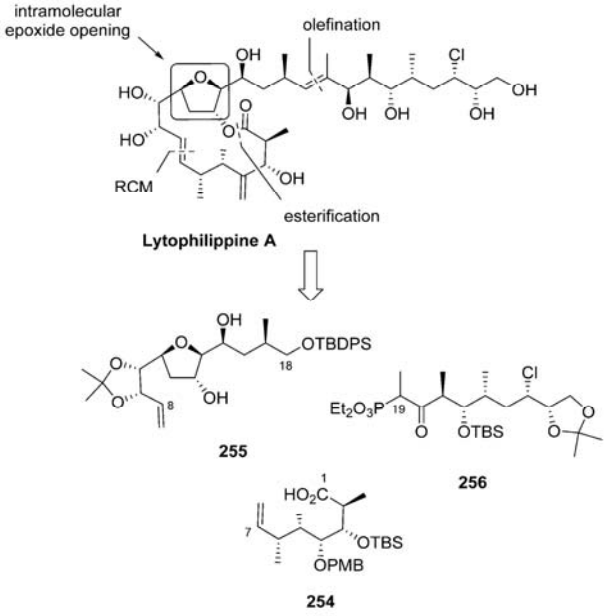


Figure 34. Proposed lytophilippine A retrosynthetic analysis by Hiersemann.[139]

strategy as the one described by the same group when the reassignment of the stereochemistry was done.[112] The two precursor building blocks of the aldehyde were THF **213** with a masked formyl and vinyl iodide **214** (Figure 30).

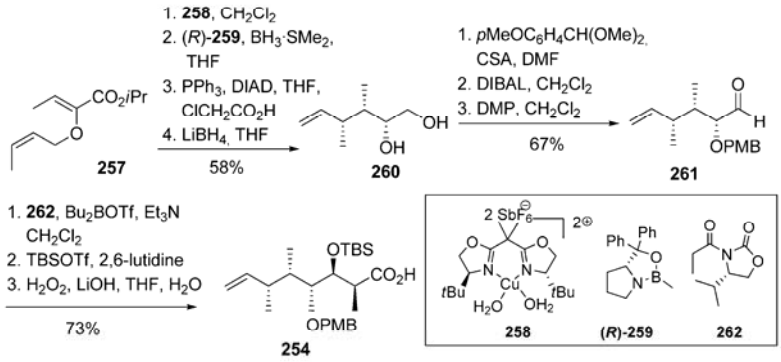
Known glycal **215**[128] was protected as a 3,4-dimethoxybenzyl (DMPM) ether, followed by an oxymercuriation−reduction sequence, and Wittig olefination to afford ester **216**. Oxy-Michael cyclization, reduction of the ester, and elimination, provided the trisubstituted THF **217** with the proper configuration at the three stereocenters (Scheme 45).

Hydroboration of olefin **217** afforded compound **213**. Suzuki−Miyaura cross-coupling between **213**[129] and **214**, followed by transformation of alkenylsi lane into the chloroolefin and acidic removal of THP protecting group, produced the acetonide intermediate **218**. Oxidation of **218** to aldehyde, followed by modified HWE reaction with phosphonate **219** and diisobutylaluminium hydride (DIBAL) reduction, gave an allylic alcohol, which was oxidized to the conjugated aldehyde **220**. The aldol reaction of **220** with isopropyl acetate, followed by protection of the resulting alcohol, yielded ester **221** as a diastereomeric mixture at C-3. A sequence of interchange of protecting groups, oxidative cleavage of the diol, protection of the resulting alcohol, removal of the DMPM protecting group, and hydrolysis of the isopropyl ester gave acid **222**. Macro-lactonization by Yamaguchi conditions[109] gave the desired lactone **223**. Removal of the TBS group in **223** permitted the separation of C-3 isomers by silica gel column chromatography. The undesired isomer was transformed into the desired isomer by oxidation and Luche reduction. The key intermediate **224** was obtained by acetylation of the hydroxyl group at C-3 and removal of the trityl group. **224** was converted into haterumalide NA by oxidation with Dess−Martin periodinane and Nozaki−Hiyama−Kishi coupling with iodide **225** to afford, after ester removal, haterumalide NA (Scheme 46).

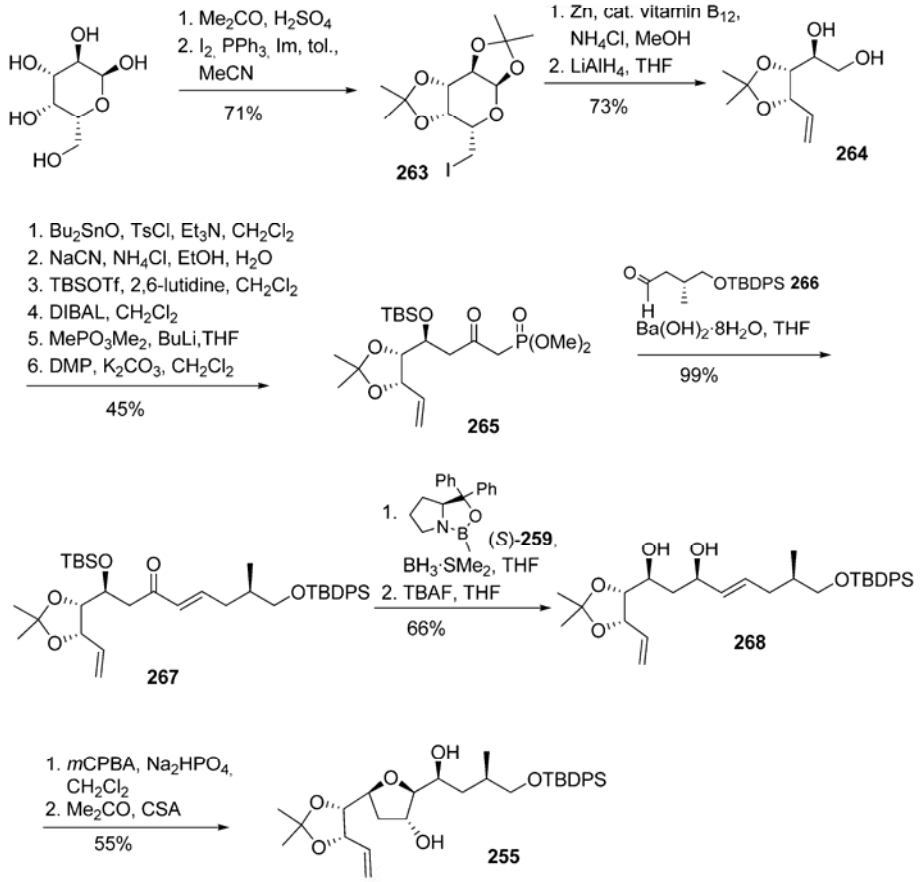
The relative stereochemistry of haterumalide B was established by synthesis.[119b] The synthetic process was performed using the racemic iodide **226** in the NHK coupling reaction with aldehyde **212** to give a diastereomeric mixture of alcohols (dr 5.5:1), followed by removal of the MPM group and subsequent selective oxidation of allylic alcohol with MnO_2 (Scheme 47). Iodide **226**[120] was obtained by condensation of (*E*)-iodo-acid **227** with the monoprotected diallyldiol **228**.[130]

3.8.3. Borhan's Total Synthesis of Haterumalide NC and Formal Synthesis of Haterumalide NA.[124] The total synthesis of haterumalide NC was accomplished via an unprecedented macrocyclization of an aldehyde and a chlor-ovinylidene chromium carbenoid to construct the C8−C9 bond.

Scheme 54. Synthesis of Building Block 254



Scheme 55. Synthesis of Building Block 255



The retrosynthetic analysis shown in Figure 31 depicts two building blocks: trisubstituted THF **229** and trichloroacid **230**. Deoxygenation of the latter product led to the formal synthesis of haterumalide NA.

Enantioselective synthesis of trisubstituted THF **229** was afforded from 2-deoxy-D-ribose **231** by convenient protection, allylation, deprotection, and final protection of the primary alcohol as a Tr ether to yield **229** (Scheme 48).

Preparation of protected hydroxyacid **232** began with the opening of the ring of oxetane **233** with the anion of chloroform, followed by oxidation of alcohol to aldehyde, which was immediately subjected to a Still Gennari olefination[131] to yield the desired *Z*-acrylate. The ester function was reduced to the allylic alcohol. Subsequent oxidation to the unsaturated aldehyde and subsequent asymmetric Mukaiyama aldol reaction[132] furnished **232**. Acid **230** was obtained by protection of the secondary alcohol as a TBS ether and phenyl ester hydrolysis. Mitsunobu esterification of alcohol **229** and carboxylic acid **230** yielded, after exchange of protecting groups, ester **234**. Selective dihydroxylation and oxidation of the terminal alkene afforded aldehyde **235** ready for the intramolecular $CrCl_2$-mediated coupling that furnished **236a**. The stereochemistry of the newly generated C9 center matched the stereochemistry of the natural product, haterumalide NC. The final installation of the side chain

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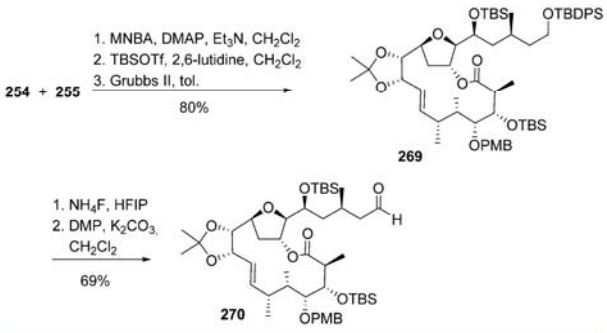
Scheme 56. Synthesis of Lactone 270 Containing the Macrocyclic Core of Lytophilippine A[139]



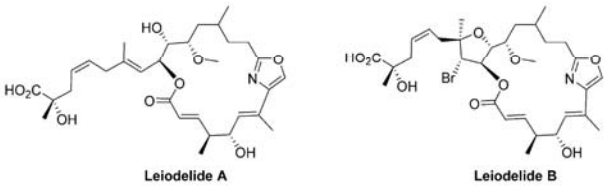


Figure 35. Proposed structures of leiodelides A and B.[141]

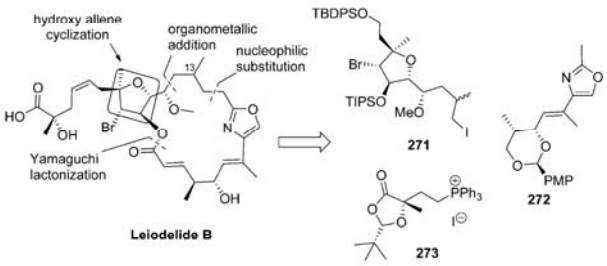


Figure 36. Proposed leiodelide B retrosynthetic analysis by Fürstner.[142]

of haterumalide NC was prepared as illustrated in Scheme 48 in a fashion similar to that reported in prior syntheses for haterumalide NA.[112]

Analogue compound **236b** was subjected to deoxygenation of C9-OH, obtaining **223**, an advanced intermediate of the synthesis of haterumalide NA. This was produced via radical-induced fragmentation of xanthate **237** with azobis(isobutyro)-nitrile (AIBN) in refluxing toluene as shown in Scheme 49.

3.9. Lytophilippines[133]

Lytophilippines A–C are chloro-containing macrolactones isolated from the Red Sea hydroid *Lytocarpus philippinus* in 2004 by Řezanka and co-workers. Lytophilippines A–C showed positive results in the crown gall tumor inhibition test and brine shrimp toxicity assay and demonstrated antibacterial activity against *Escherichia coli*, but were inactive against the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*.

The structure of lytophilippines was elucidated by spectroscopic methods and by chemical degradation (Figure 32). The proposed structure for these compounds was based on a 14-membered macrolactone bridged with a trisubstituted THF containing three methyl ramifications, an *E*-double bond, a ketone and three hydroxyl groups. In addition, lytophilippines possess a chloro-unsaturated-polyhydroxy side chain. The difference between the three members of this group lies in the fatty acid present in lytophilippines B and C. However, further synthetic studies of lytophilippine A claimed that the proposed structure did not correspond to that of the natural compound and that further work should focus on elucidating the correct structure.[134]

3.9.1. Lee's Synthesis of Proposed Lytophilippine A.[134]

The work presented by Lee and co-workers in 2011 established, on the basis of total synthesis, that the proposed structure for lytophilippine A was not matching that of the natural product. Its retrosynthetic analysis divided the molecule into three building blocks, trisubstituted THF derivative **238**, carboxylic acid **239**, and side chain **240** (Figure 33).

Enantioselective transformation of D-ribose into alcohol **241** was afforded by protection as a 2,3-acetonide, followed by Wittig olefination to obtain diol **242**.[135] Diol **242** was then converted to the corresponding epoxide and finally reacted with 2-lithio-1,3-dithiane, to give **241**. Oxiaddition of **241** to alkynyl sulfoxide **175** and hydrolysis of the dithiane unit provided aldehyde **243** (Scheme 50). 5-*Exo* cyclization of **243** with SmI_2 led to 3-hydroxyoxolane **238** (dr 9:1).

Monoprotection and oxidation of diol **244**[136] furnished an aldehyde that was reacted with 2-lithio-1,3-dithiane with moderate stereocontrol (dr 4.6:1). The resulting alcohol was protected as PMB ether. Further deprotection of the TBS and oxidation provided aldehyde **245**. Wittig olefination and dithiane hydrolysis provided an aldehyde ready to be reacted with boron enolate to furnish compound **246** in good yield and stereoselectivity (dr > 19:1). Acid **239** was obtained by TES protection and removal of the chiral inductor (Scheme 51).

Side chain **240** was obtained starting from the known epoxide **247**[137] by reaction with allylmagnesium bromide, followed by substitution of the hydroxyl with the chloride, to give **248**. The terminal double bond was oxidized to the acid. Stereoselective α-methylation via Evans oxazolidinone induction and reduction with lithium borohydride afforded alcohol **249**. Aldehyde **250** was obtained by oxidation of alcohol **249**, Roush crotylation (dr > 19:1), protection of the obtained alcohol as a TMS ether, and reductive ozonolysis. Building block **240** was obtained by addition of the vinyllithium reagent prepared from known vinyl iodide **251**,[138] followed by acetonide formation, TBS ether cleavage and iodide substitution of the resulting terminal hydroxyl group (Scheme 52).

Condensation of building blocks **238** and **239** by a Mitsunobu reaction, followed by ring closing metathesis, and introduction of side chain **240**, furnished protected lytophilippine A with only a 10% yield and low diastereoselectivity (dr 4:1).

An alternative route, based on the introduction of the side chain before macrocyclization, was developed starting from THF **238** (Scheme 53). Inversion of the stereochemistry at the C-13 via a Mitsunobu reaction, followed by protection of the hydroxyl group as a TBS ether, and subsequent Pummerer rearrangement, led to formyl hydroxyoxolane **252**. Side chain **240** was introduced at this stage with moderate yield and diastereoselectivity (dr 1.6:1). Deprotection of the TBS ether provided a diol that was converted to diene **253** by condensation with acid **239** and TBS ether formation of the free alcohol. A single macrolactone was then obtained via RCM, removal of the PMB protecting group, oxidation of the free alcohol with Dess–Martin periodinane (DMP), and final elimination of the remaining protecting groups (Scheme 53).

Dramatic ^1H and ^{13}C NMR differences between the isolated lytophilippine A and the synthesized product led to the conclusion that the structure proposed by Řezanka and co-workers was not adequate.

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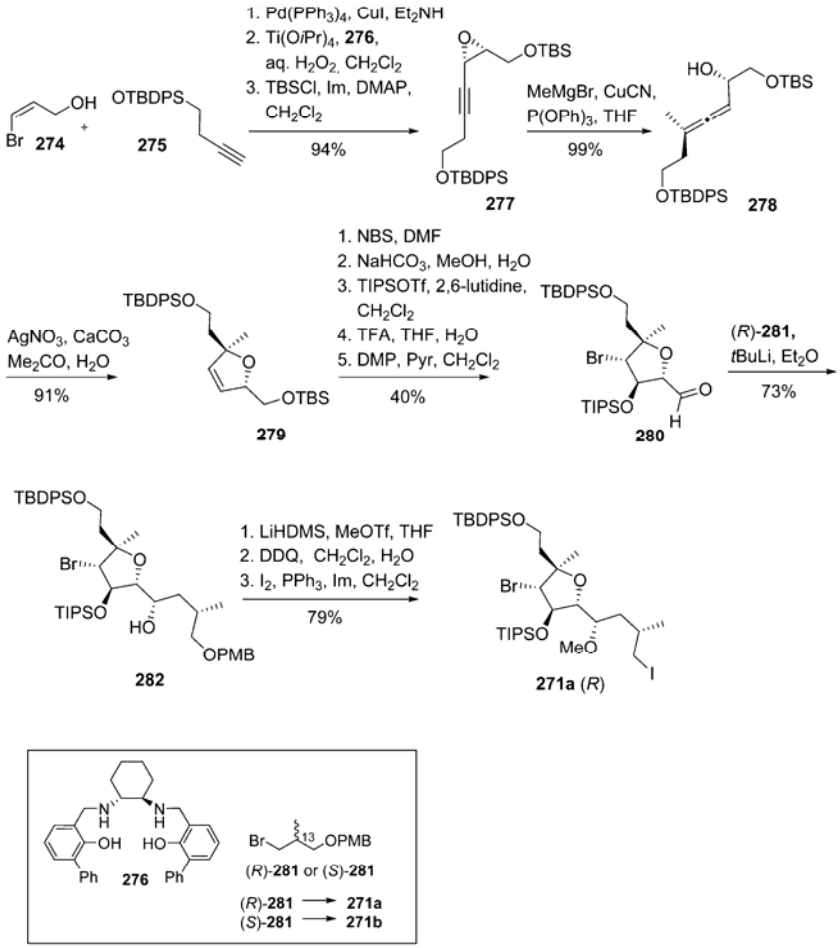
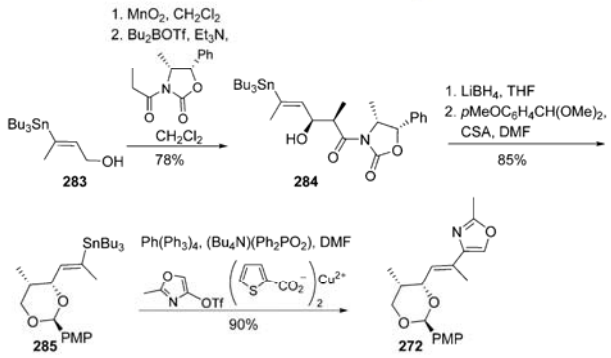
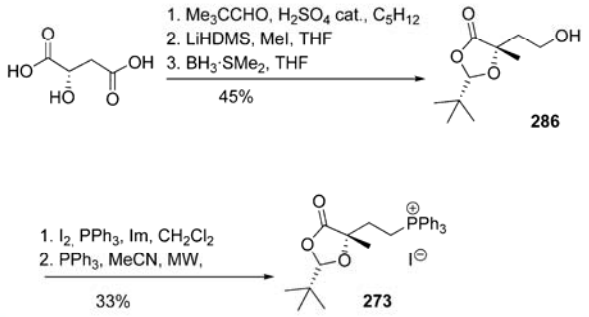
Scheme 57. Synthesis of the Northern Sector of Proposed Leiodelide B



Scheme 58. Synthesis of Oxazole Building Block 272



Scheme 59. Enantioselective Synthesis of Phosphonium Iodide 273



3.9.2. Hiersemann's Synthesis of C1−C18 Building Block of Proposed Lytophilippine A.[139] In 2010 Hiersemann and co-workers described the synthesis of the C1−C18 building block. The synthesis of this fragment is introduced in this review because it is an advanced building block of the natural product containing the macrolactone and lacking only the side chain introduction. Its retrosynthetic analysis shown in Figure 34 proposes three building blocks: the C1−C7 segment **254**, the C8−C18 segment **255**, and the appropriate C19−C27 segment **256**.

Building block **254** was synthesized starting from allyl vinyl ether **257** by a reaction sequence based on asymmetric Gosteli−Claisen rearrangement, configuration inversion, and further reduction to provide diol **260**. Transacetalization with *p*-methoxybenzaldehyde dimethyl acetal, followed by reductive cleavage, and oxidation of the resulting primary alcohol gave aldehyde **261**. Diastereoselective Evans aldol reaction, protection of the hydroxyl group, and removal of the chiral auxiliary led to fragment **254** (Scheme 54).

Building block **255** was synthesized starting from D-galactose by bis(acetonide) protection, followed by substitution of the

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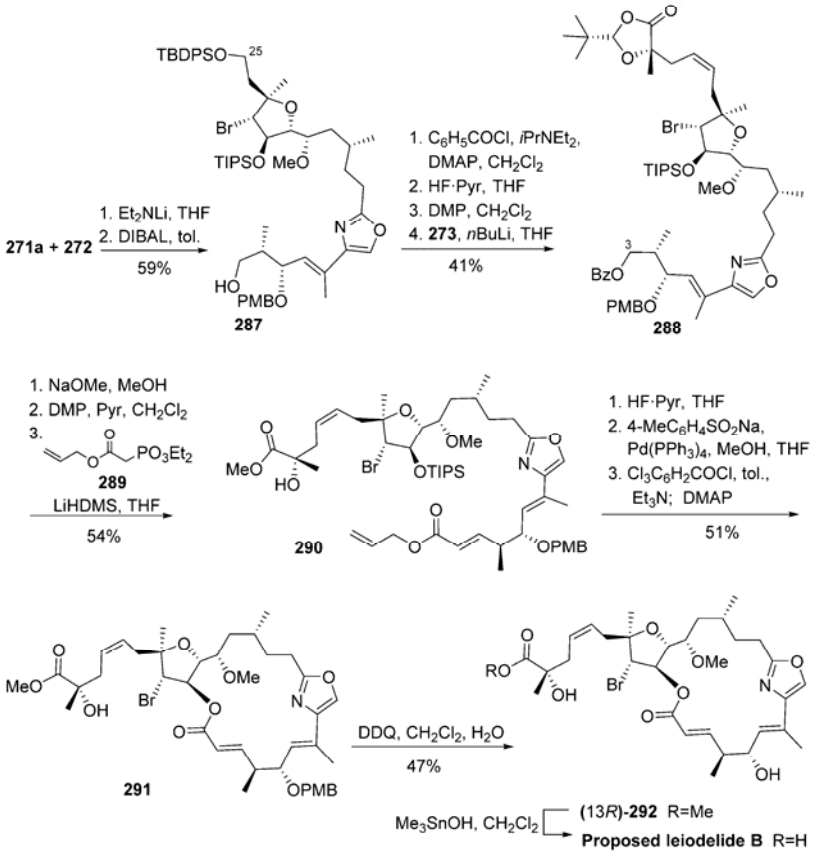
Scheme 60. Synthesis of Proposed Leiodelide B[142]



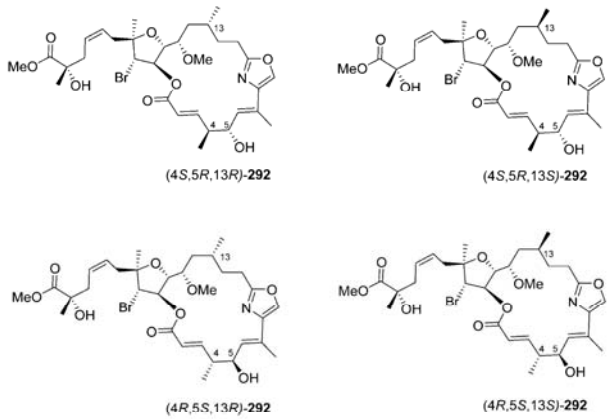


Figure 37. Four stereoisomers of leiodelide B.[142]

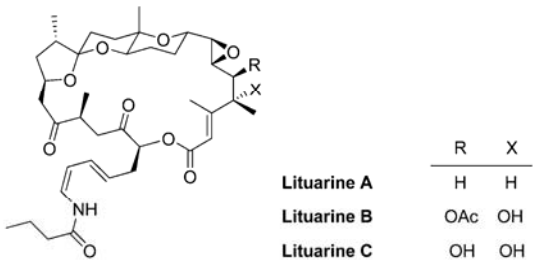


Figure 38. Proposed structures of lituarines A–C.[147]

remaining hydroxyl group by iodide to obtain **263**. β-Elimination led to a cyclic hemiacetal that was reduced to diol **264**. The primary alcohol was subjected to a Kolbe nitrile synthesis, and the secondary hydroxyl group was protected as TBS ether. Reduction of the nitrile was followed by transformation of the resulting aldehyde into β-keto phosphonate **265** for HWE reaction with known aldehyde **266**[140] to give enone **267**. Compound **267** containing the C8–C18 fragment of lytophilippine A was reduced at the enone carbonyl with a dr > 95:5, and chemoselective removal of the silyl protecting group delivered diol **268**. Diastereoselective epoxidation of the double bond was not possible in reasonable diastereomeric ratios, and thus the best conditions were obtained with 3-chloroperoxybenzoic acid (CPBA) to give a 3:2 mixture of the corresponding diastereomeric oxiranes in 95%. Finally, chromatographic separation was mandatory after diastereomeric differentiating acetalization of the mixture with CSA to obtain the desired enantiomerically pure segment **255** (Scheme 55).

The targeted macrolide was formed by regioselective ester bond formation between acid **254** and alcohol **255**, followed by subsequent RCM, obtaining **269**. Selective removal of the primary TBDPS protecting group in front of the secondary TBS ethers was achieved with NH_4F in hexafluoroisopropanol (HFIP), and oxidation of the resulting alcohol furnished aldehyde **270** containing the macrocyclic core of lytophilippine A (Scheme 56). Authors claim the preparation of the side chain is under construction for introduction.

dx.doi.org/10.1021/cr3004778 | Chem. Rev. 2013, 113, 4567–4610

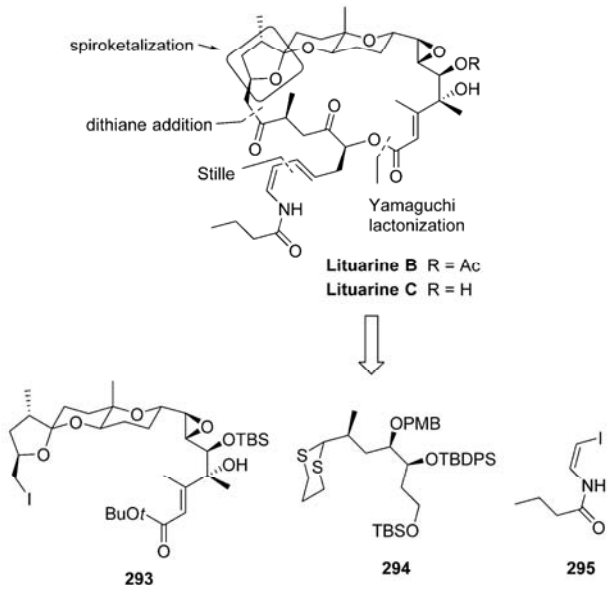


Figure 39. Retrosynthetic analysis of lituarines B and C by Smith III.[150]

3.10. Leiodelides[141]

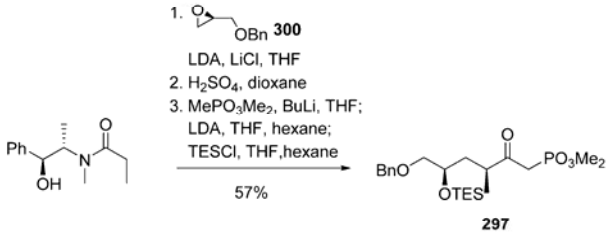
Leiodelides A and B (also named leiodolides A and B) are cytotoxic macrocyclic lactones extracted from a sponge, identified as a member of the rare genus *Leiodermatium* (order Lithistida, Azoricidae family) and collected at a depth of 720 feet near Uchelbeluu Reef in Palau. Leiodelide B represents the first member of a new class of 19-membered ring macrolides and incorporates several unique functional groups including a pentasubstituted THF with four stereocenters, a conjugated oxazole ring, a bromine substituent, and a α-hydroxy-α-methyl carboxylic acid side-chain terminus. Leiodelide B was found to be active against HCT 116 human colon carcinoma. The structure of leiodelides A and B was established by spectroscopic analysis, chemical modification, and degradation. The relative and absolute stereochemistries at most chiral centers were assigned on detailed interpretation of spectroscopic data, coupled with chemical degradation and application of the modified Mosher ester method. Structure of leiodelide B was established by comparison of spectral data for leiodelide B with data for leiodelide A, suggesting that leiodelide B was a related macrolide (Figure 35). The authors proposed a bromonium ion induced formation of the THF ether bridge in leiodelide B from leiodelide A. Synthetic work on this natural product concluded that the proposed structure is in error and should be revised.[142]

3.10.1. Fürstner's Synthesis of Proposed Leiodelide B.[142] Only one synthetic approach to leiodelide B has been published until now by Fürstner's group. Their synthesis was based on the disconnections shown in Figure 36, considering the union of building blocks **271**, **272**, and **273**. Because the configuration of C-13 stereocenter was not established, two building blocks with the precursor of (*R*)-C13 and (*S*)-C13 were tested in this work. Of interest in this synthesis is the enantioselective preparation of the pentasubstituted THF moiety by Ag-induced cyclization of a α-allenol to give a DHF ring with the proper configuration at positions 2 and 5 of the ring. The subsequent step was stereoselective bromo-esterification of the ring double bond to the proper pentasubstituted THF.

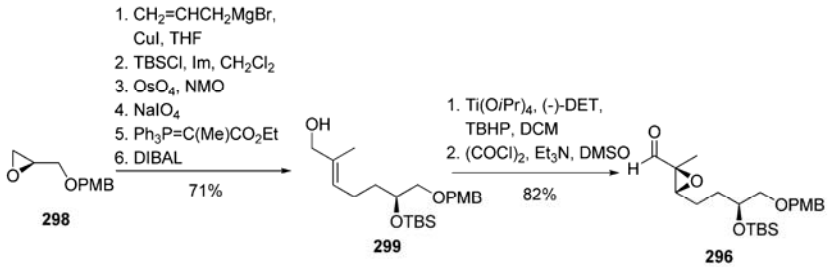
The polysubstituted THF **271** containing four stereocenters was afforded starting from the allylic alcohol **274** and alkyne **275** as building blocks for the construction of **277** (Scheme 57). This epoxide was transformed into the axially chiral allene intermediate **278** by conjugate addition of the reagent derived from MeMgBr, a stoichiometric amount of CuCN, and $P(OPh)_3$. Subsequent $AgNO_3$-induced cyclization of allenol **278** to DHF **279**,[143] bromo-esterification, protecting-group manipulations, and oxidation gave aldehyde **280**. After chain extension with the building block (*R*)-**281**[144] by metal–halogen exchange with *t*BuLi in Et_2O, followed by transmetalation with freshly prepared $MgBr_2$, epimeric alcohols at C15 were obtained in 73% yield in a 1:4 ratio. The minor isomer could be recycled by oxidation/Luche reduction to **282**. Subsequent *O*-methylation, oxidative cleavage of the PMB ether, followed by conversion of the resulting alcohol into the corresponding iodide **271a**, completed the preparation of the northern sector of proposed leiodelide B in one of the two possible diastereomeric forms. Epimer **271b** was obtained in a similar way using (*S*)-**281** for the reaction with aldehyde **280**.

Oxazole building block **272** was obtained as indicated in Scheme 58 from stannylated alcohol **283**. Oxidation of **283** to the aldehyde, which was then subjected to an Evans boron-aldol reaction,[145] yielded **284**. Reductive cleavage of the auxiliary and protection of the resulting diol as acetal gave product **285**, which was then prepared for cross-coupling with the known 2-methyl-oxazol-4-yl triflate[146] to finally give building block **272**.

Scheme 62. Synthesis of Phosphonate 297[149a]

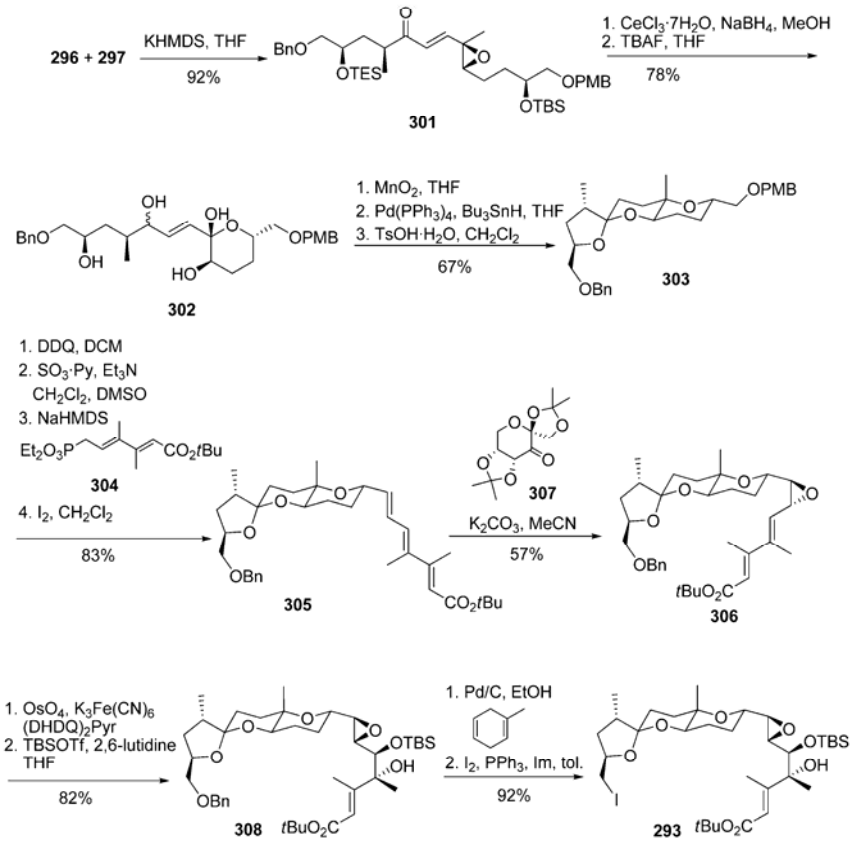


Scheme 61. Synthesis of Aldehyde 296.[149a]

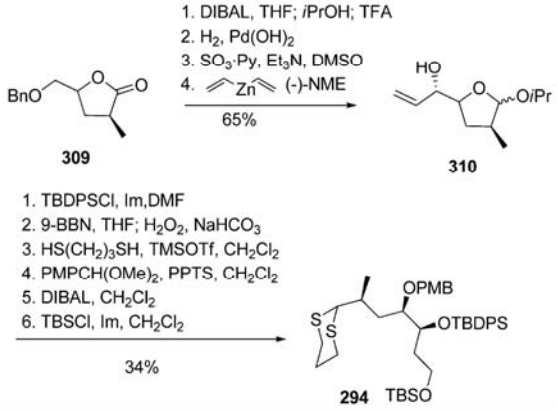


dx.doi.org/10.1021/cr3004778 | *Chem. Rev.* 2013, 113, 4567–4610

Scheme 63. Synthesis of Building Block 293[149]



Scheme 64. Synthesis of Building Block 294[150]



The third building block **273** was prepared from L-malic acid by a reaction sequence based on the simultaneous protection of the acid and the α-hydroxy groups, followed by diastereoselective α-methylation and reduction, to give alcohol **286**. Transformation of **286** into **273** was performed using the normal procedures (Scheme 59).

The connection of the three building blocks started with the alkylation of **272** with iodide **271a** using Et_2NLi as the optimal base. Reductive opening of the PMP acetal released primary alcohol **287**. Further exploratory macrocyclization studies showed that the installation of the side chain should have been given priority, and consequently macrolactonization was depicted as the final step of the synthesis (Scheme 60).

Protection of **287** as benzoate ester, selective removal of the TBDPS ether at C25 and oxidation, followed by reaction of the resulting aldehyde with the ylide derived from **273**, gave alkene **288** in good yield. Benzoate at C3 was removed and the cyclic acetal was converted at the acid terminus into the corresponding methyl ester. DMP oxidation of the primary alcohol at C3, followed by a HWE olefination with phosphonate **289**, gave product **290**, which comprised the complete carbon backbone of leiodelide B. Selective TIPS deprotection and Pd-catalyzed cleavage of the allyl ester, followed by Yamaguchi lactonization[109] of the resulting seco acid, gave the desired macrocycle **291**. Removal of the residual PMB protecting group completed the total synthesis of the putative leiodelide B methyl ester (13*R*)-**292**. The epimeric product (13*S*)-**292** was prepared analogously from **271b** and **272**. Authors describe that neither of the synthesized methyl esters matched the reported data of leiodelide B, with small but non-negligible deviation being scattered over the entire framework. The free acid (13*R*)-leiodelide B obtained by saponification of (13*R*)-**292** with excess Me_3SnOH showed important differences in the chemical shifts in the C2−C9 region of the molecule. To check the originally assigned configuration of 4*S* and 5*R*, enantiomeric oxazole building block ent-**272** was prepared (Figure 37).

The four isomers (Figure 37) were synthesized; however, none of them reproduced the published data of the natural product well enough to claim identity.

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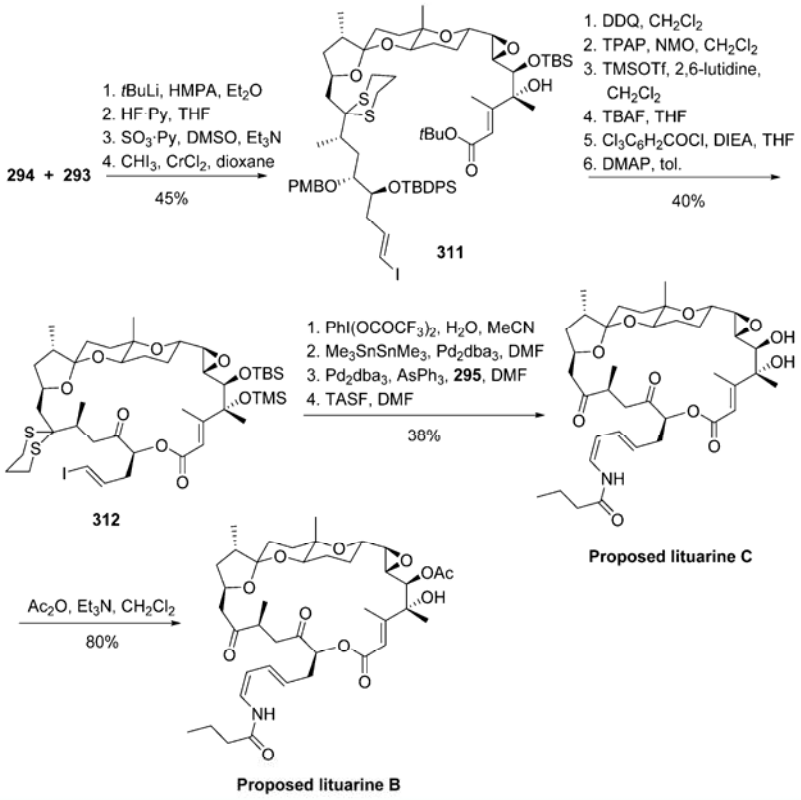
Scheme 65. Synthesis of Proposed Lituarines B and C[150]



3.11. Lituarines[147]

Lituarines A−C were isolated from the New Caledonian sea pen, *Lituaria australasiae* and exhibited antifungal, antineoplastic, and significant cytotoxicities. The IC_{50} of lituarines A−C toward KB cells are 3.7−5.0 nM, 1.0−2.0 nM, 5.0−6.0 nM, respectively. Their relative stereochemistry and connectivity was described based on spectroscopic techniques, although absolute stereochemistry remains unknown. Unusual structural features of these natural products are the C(8−18) tricyclic core, based on [6,5] spiroketal and *trans*-bridged tetrahydropyran rings. In addition, they possess an exocyclic dienamide moiety (Figure 38). Robertson[148] worked on the synthesis of these complex compounds, achieving partial synthesis of the proposed structures. Smith III[149,150] achieved the total synthesis of the proposed structures of lituarines B and C and upon comparison of synthetic, and isolated compounds stated that the proposed stereochemistry was erroneous.

3.11.1. Smith III's Synthesis of Proposed Lituarines B and C.[149,150] The retrosynthetic analysis of lituarines B and C gave three building blocks: the most challenging tetracyclic core fragment **293**, dithiane fragment **294**, and iodoenamide **295** (Figure 39).

Fragment **293** was synthesized from aldehyde **296** and phosphonate **297**.[149a] Epoxide **298** was converted to alcohol **299** through the following reaction sequence: copper catalyzed allylmagnesium bromide addition, protection of the resulting alcohol, terminal double bond oxidative cleavage, Wittig olefination, and reduction. Asymmetric Sharpless epoxidation and oxidation of the alcohol resulted in aldehyde **296** (Scheme 61).

Phosphonate **297** was obtained by alkylation of (*S*,*S*)-pseudoephedrine amide with epoxide **300**[151] and acid mediated cyclization, followed by treatment with the lithium anion of dimethyl methanephosphonate and in situ protection as a TES ether (Scheme 62).

HWE olefination between **296** and **297** produced **301** with exclusive *E*-selectivity. Luche reduction and treatment with TBAF afforded self-cyclized product **302**. Oxidation of **302** to give a conjugated ketone, followed by double bond reduction and acetalization with *p*-toluensulfonic acid, afforded tricyclic core **303** in high yield and stereocontrol.[149a] Transformation of **303** into unsaturated ester **305** was performed via oxidative cleavage of the PMB protecting group, oxidation to the aldehyde, HWE olefination with phosphonate **304**, and equilibration with iodine of the obtained mixture of trienes. Epoxide **306** was obtained by Shi's protocol using **307** as a catalyst. Asymmetric dihydroxylation of **306** and protection of the less hindered hydroxyl afforded **308**.[149b] Removal of PMB protecting group and iodine substitution gave fragment **293** (Scheme 63).

Dithiane building block **294** was obtained from known lactone **309**,[152] upon reduction, removal the benzyl ether, oxidation to aldehyde, and addition of vinyl zinc to obtain alcohol **310** (Scheme 64). Subsequent protection, hydroboration, TMSOTf mediated dithiane formation, and orthogonal protection of the free hydroxyl groups gave fragment **294**.

Reaction of lithium derivative of **294** and iodide **293** was achieved in a reasonable good yield (Scheme 65). Removal of the TBS ether protecting group, oxidation to the aldehyde, and Takai olefination led to vinyl iodide **311**. The next steps included the removal or interchange of protecting groups, oxidation, and cyclization under Yamaguchi conditions to give macrolactone

312. Removal of the dithiane, installation of the stannane, Stille coupling with iodoenamide **295**,[150] and subsequent removal of silicon protecting groups afforded proposed lituarine C. Selective acetylation of proposed lituarine C led to proposed lituarine B.

With both synthetic targets in hand, the authors realize that neither of them matched the described natural products.

4. BIOACTIVITY

During the past few years, bioguided isolation of marine organisms furnished macrolides with important biological activities. Most of them are cytotoxic compounds; however, other interesting activities, most significantly antimicrobial and antibacterial activities, have been found as well.

Oscillariolide,[26] phormidolide,[27] and the family of the lytophilippines[133] showed potential antitumoral activity, although more assays should be done to assess their value as anticancer leads. Formosalides,[31] amphidinolides,[39] haterumalides,[110,111,113,114,116,119b] amphidinolactone B,[29] and leiodelide B[141] showed moderate to good antitumoral activity against a variety of cancer cell lines such as murine leukemia cells, human epidermoid carcinoma cells, human colon cancer cells, or human breast cancer cells. However, the more active compounds among the ones described in this review were caribenolide I,[97] amphidinolide C,[39j] and the lituarines,[147] which showed high antitumoral activity against HCT 116 cells (caribenolide I), L1210 cells (amphidinolide C1), and KB cells (lituarines). As mentioned before, antimicrobial and antibacterial activities are also found in some THF-containing macrolides, such as in lytophilippines, haterumalides, and their related family compounds.[115a,116a]

A rational comparison of bioactivity among the families described in this review would be ineffective due to the diversity of biological tests and the different experimental conditions published until now for their evaluation.

5. CONCLUSIONS

Our knowledge and tools to synthesize natural products are far from nature's ability to create these same complex compounds with high efficiency and selectivity, through the combination of evolution and thermodynamics. Marine macrolides are only an example of these elaborate natural products which have high pharmacological potential. Nevertheless, isolation from the natural sources often furnishes small amounts of the product, which makes the determination of the structure and the preparation of enough sample of compounds for clinical trials a dead end for their development. In this context, the total synthesis of natural products is the more reasonable and useful tool. Furthermore, synthesis of compounds such as those described in this work, with complex structures and a high number of stereocenters, requires the development of new reagents as well as full synthetic strategies, which are being further applied to the synthesis of other complex compounds. Thus, the continued efforts that several groups are putting into marine research sciences should fuel the identification of new chemical entities as new active pharmaceutical ingredients and the discovery of new synthetic tools, which will be applied to the synthesis of a broad range of molecules. All these advances should translate into new drug families in the near future, which will face unmet therapeutic indications and needs.

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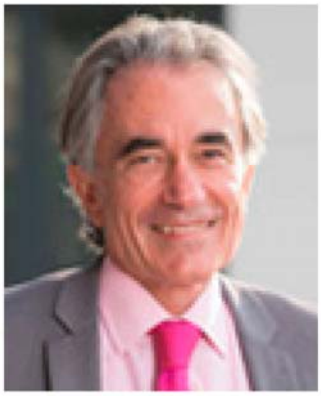
Notes

The authors declare no competing financial interest.

Biographies

Adriana Lorente was born in Barcelona in 1985. She studied chemistry at the University of Barcelona, where she received her B.S. degree in 2008, and her M.S. degree in 2009 under the supervision of Dr. Fèlix Urpí and Dr. Pedro Romea. Adriana is currently a doctoral student at the Institute for Research in Biomedicine at the Barcelona Science Park under the supervision of Dr. Mercedes Álvarez and Dr. Fernando Albericio. Her research interests include the development of new methodologies for synthesis of natural products as well as its structure determination.

Janire Lamariano-Merketegi was born in 1985 in Antzuola. In 2008, she got her B.S. degree in chemistry at the University of Basque Country (UPV/EHU). After, she moved to Complutense University of Madrid (UCM) where she received her M.S. degree under the supervision of Dr. Carmen Avendaño. In 2010, she joined for one year the Janssen-Cilag pharmaceutical division in Toledo. At this time, she is a doctoral student at the Institute for Research in Biomedicine at the Barcelona Science Park under the supervision of Dr. Mercedes Álvarez and Dr. Fernando Albericio. Her research interests are focused on stereoselective synthesis of polyketide chains present in marine natural products.



Professor Fernando Albericio received his Ph.D. in Chemistry at the University of Barcelona, in 1981. Following postdoctoral work at Tufts University (Boston), at the Université d'Aix-Marseille (France), and at the University of Minnesota (1981−1984), he returned to Barcelona as Associate Professor. During the 1992−1994 period, he was Director of Peptide Research with Millipore/Waters at Boston. He rejoined the University of Barcelona, where he was promoted to Professor in 1995. He participated in the foundation of the Barcelona Science Park, taking on different responsibilities, and served as General Director of the park (2005−2012). Nowadays, he is holding various appointments: Professor at the University of Barcelona, Research Professor at the University of KwaZulu-Natal (Durban, South Africa), and Group Leader at the Institute for Research in Biomedicine. Professor Albericio is deeply involved in the development of the third mission of the University, the transference of knowledge and technology to the society. He has founded several biotech companies and is acting on the board of directors of several foundations and companies. Furthermore, he is a consultant for several companies in the chemical and pharmaceutical areas. Professor Albericio's major research interests cover practically all aspects of peptide synthesis and combinatorial chemistry methodologies, as well as synthesis of peptides and small molecules with therapeutic activities. He has published over 600 papers, several review articles, more than 40 patents, and co-author of three books. He is editor of several scientific journals and acting on the editorial board of several others. Recently, Professor Albericio was honored with a Doctorate Honoris Causa by the Universidad de Buenos Aires (Argentina) and the Vincent du Vigneaud Award (American Peptide Society).

Professor Mercedes Álvarez received her Ph.D. in chemistry at the University of Barcelona under the supervision of Prof. Ricardo Granados. She has a permanent position in the Faculty of Pharmacy of the University of Barcelona, as Associate Professor first and later as full Professor. In 1990 she spent a sabbatical year in The Manchester University working with Prof. John A. Joule. After that period a long collaboration began between Manchester and Barcelona Universities for developing new procedures for the synthesis of marine natural products with polyheterocyclic structure and biological activities. 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. Currently, she holds a double appointment as Professor at the University of Barcelona and Researcher at the Institute for Research in Biomedicine in the Barcelona Science Park (IRB). 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.

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ABBREVIATIONS

Ac	acetyl
ACP	acyl carrier protein
AIBN	azobis(isobutyro)nitrile
AMO	alkene mono-oxigenase
AT	acyl transferase
BAIB	bis(acetate)phenyliodine
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
BOM	benzoyloxymethyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cat	catalytic
CM	cross metathesis
CoA	coenzyme A
Cp	cyclopentyl
CPBA	3-chloroperoxybenzoic acid
CSA	camphorsulfonic acid or (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-methanesulfonic acid
Cy	cyclohexyl
dba	di(benzylidene)acetone
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEBS	6-deoxyerythronolide B synthase
DET	diethyl tartrate
DH	dehydratase
DHF	dihydrofuran
DHP	dihydropyran
$(DHQ)_2PHAL$	1,4-bis(9-*o*-dihydroquininyl)phthalazine
$(DHQD)_2AQN$	1,4-bis(dihydroquinidine)anthraquinone
$(DHQD)_2Pyr$	1,4-bis(9-*o*-dihydroquininyl)pyridine
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide

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DMP	Dess Martin periodinane or 1,1,1-tris-(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
DMPM	3,4-dimethoxybenzyl
DMPS	dimethylphenylsilyl
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dpephos	bis[2-(diphenylphosphino)phenyl] ether
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
dr	diastereomeric ratio
EE	ethoxyethyl
ER	enoyl reductase
Grubbs II	[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(phenylmethylene)-(tricyclohexylphosphine)ruthenium
Grubbs I	bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride
GT	glycosyltransferase
HCT 116 VM/46	human colon carcinoma resistant cell line
HCT 116	human colon carcinoma cell line
HFIP	hexafluoroisopropanol
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HWE	Horner−Wadsworth−Emmons
IBX	1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide
Im	imidazole
Ipc	isopinocamphenyl
KB	epidermoid carcinoma
KHMDS	hexamethyldisilazane potassium salt
KR	ketoreductase
KS	ketosynthase
K-selectride	potassium tri-*sec*-butylhydroborate
L1210	murine leukemia cell line
LDA	lithium diisopropylamide
LHMDS	hexamethyldisilazane lithium salt
LTMSA	lithium trimethylsilylacetylide
MDA MB 435	melanoma cell line
MNBA	2-methyl-6-nitrobenzoic acid anhydride
MOM	methoxymethyl
MPM	4-methoxybenzyl
MS	molecular sieve
Ms	mesyl or methanesulfonyl
MT	methyl transferases
NCS	*N*-chlorosuccinimide
NHK	Nozaki−Hiyama−Kishi
NIS	*N*-iodosuccinimide
NME	*N*-methylephedrine
NMI	*N*-methylimidazole
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine oxide
NMR	nuclear magmetic resonance
NRPS	non-ribosomal peptide synthtase
OX	oxygenase
PAB	*p*-aminobenzoyl
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PKS	polyketide synthases
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PNBA	*p*-nitrobenzoic acid
PPTS	pyridinium *p*-toluenesulfonate
PTSH	1-phenyltetrazole-5-sulfonic acid
Pyr	pyridine
RCM	ring closing metathesis
SAE	Sharpless asymmetric epoxidation
Sia	siamyl or 1,2-dimethylpropyl
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	tetrabutyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TC	thiophenecarboxylic acid
TCAI	trichloroacetimidate
TE	thioesterase
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	triflate or trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine
TMS	trimethylsilyl
TMSA	trimethylsilyl acetilene
tol	toluene
TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethyl or trityl
TRITON B	*N*,*N*,*N*-trimethyl-benzenemethanaminium hydroxide
Ts	tosyl or *p*-toluensulfonyl

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4 Synthetic strategies towards the macrocyclic core of phormidolodes B-D

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SYNTHETIC STRATEGIES TOWARDS THE MACROCYCLIC CORE

1. Retrosynthetic analysis

The choice of the best synthetic strategy to attain the synthesis of the macrocyclic core of phormidolides B-D is the objective of this chapter. The retrosynthetic analysis for the macrocyclic core of pormidolides B-D (**1**) divides the target in two fragments, to be bonded by the ester bond and by the C4-C5 alkene (Figure 1). The study of the best synthetic conditions was done with a model synthesis using a mixture of diastereomers.

Two main strategies were tested for the formation of the trisubstituted alkene, the most challenging step of the synthesis. A strategy based on an olefin metathesis was the first approach, the formation of the C4-C5 alkene was planned from olefins **2a** and **3a**. A longer strategy based on a Julia-Kocienski olefination, depicted the formation of the alkene from sulfone **4** and aldehyde **5**, or from ketone **6** and sulfone **7a** with a homologous strategy switching functionalization. Both strategies planned the same disconnections, differing only in the functionalization of the fragments and the assembling methodology. Macrolactonization was depicted as the other key step of the synthesis along with double bond formation and could be performed before or after the entitled process.

Olefin **2a**, sulfone **4** and ketone **6** are the more complex fragments of the synthesis. They have 3 hdroxyl groups that need to be protected orthogonally and 5 out of the 6 stereocenters of the macrocycle. Their formation was depicted from common intermediate **8**; employing either an organometallic addition or an aldol condensation, olefin **2a** or sulfone **4** and ketone **6** can be accessed, respectively. The formation of the tetrahydrofuran (THF) ring was planned from the commercially available sugar 2-deoxy-D-ribose because it has chirality itself, which will be useful for the future stereoselective development, and it furnishes the desired trisubstituted THF ring in two steps.[1] Besides, it offers a platform to start the growing of the alkyl chain.

Olefin **3a**, aldehyde **5** and sulfone **7a** are small fragments that can be useful as platform to adjust reactivity or perform test experiments; they are readily available structures affordable in 3 to 5 steps and have a tunable hydroxyl motif near the C4-C5 targeted double bond.

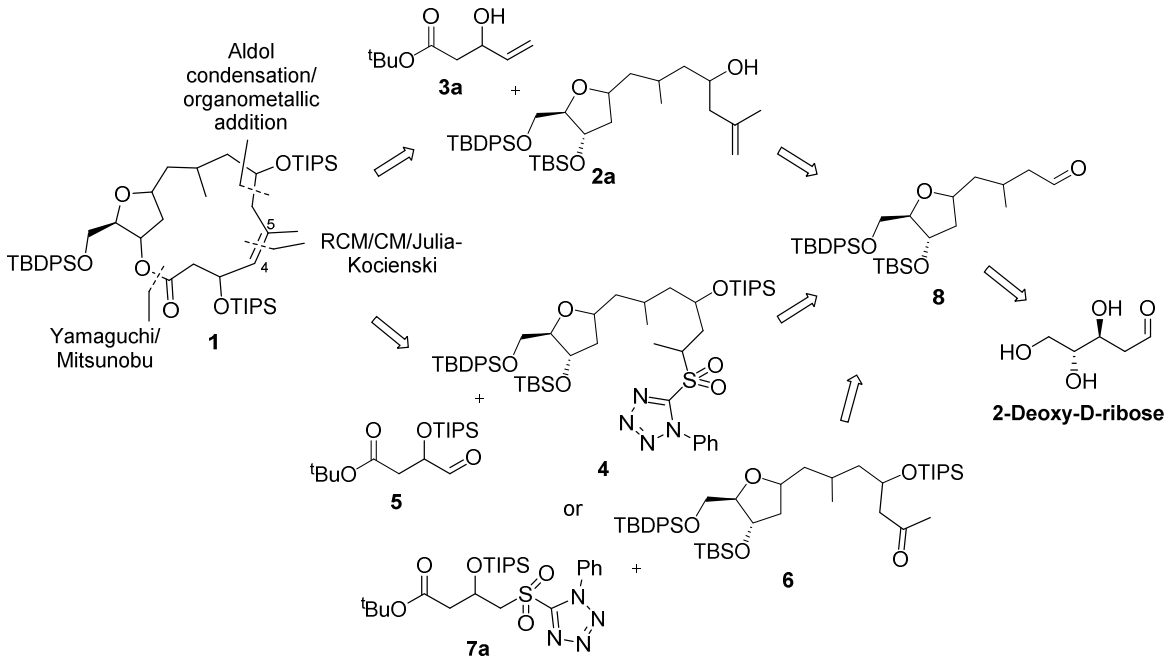


Figure 1. Retrosynthetic analysis, main tested routes.

In this chapter we will describe our efforts towards the metathesis approach, describing conditions, catalysts and changes on the olefin starting materials. Next, the Julia-Kocienski approach will be disclosed.

2. Metathesis approach for the synthesis of the macrocyclic core

It is known that *gem*-disubstituted olefins are bad substrates for metathesis reactions. Nevertheless they can react with the appropriate olefin partner if this is reactive enough to react with less reactive olefins, but not too reactive to avoid self-dimerization prior the formation of the desired trisubstituted double bond. A commonly used strategy is the modification of the olefins to adjust reactivity, combined with the appropriate choice of the catalyst, so that olefins become compatible.[2]

Our metathesis strategy for the synthesis of the macrocycle was based on this statements; while we tried to enhance the reactivity of the *gem*-disubstituted olefin by not protecting the β-hydroxyl or using a small protecting group, we also tried to lower the reactivity of the monosubstituted olefin partner by protecting the α-hydroxyl with a large protecting group, or by introducing an extra methyl at the terminal carbon of the alkene.

Such changes were combined with testing of different catalysts (Figure 2). Second generation Grubbs' (G-II),[3] second generation Hoveyda-Grubbs' (HG-II),[4] and Schrock's[5] catalyst are the more reactive available catalysts in the market.[6] Moreover, it is described that an aminocarbonyl or carbamate extra functionalization in second generation Hoveyda-Grubbs' catalyst (HG-II-CF_3 and HG-II-O^{t}Bu) adds extra stability and increases initiation rates which means also higher reactivity.[7] These were the catalysts selected for our metathesis reactions.[8]

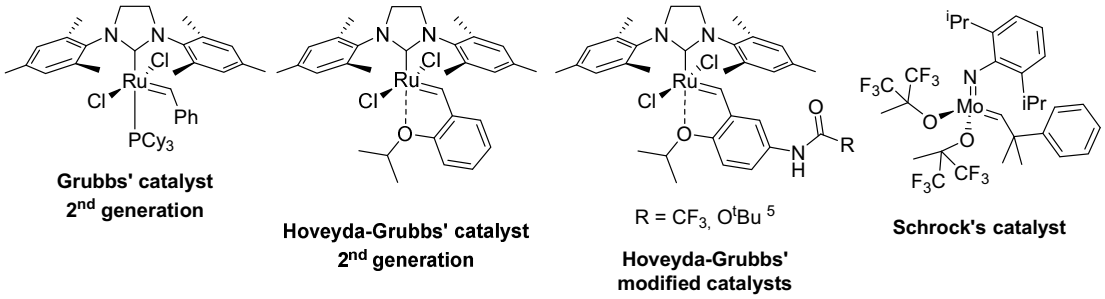
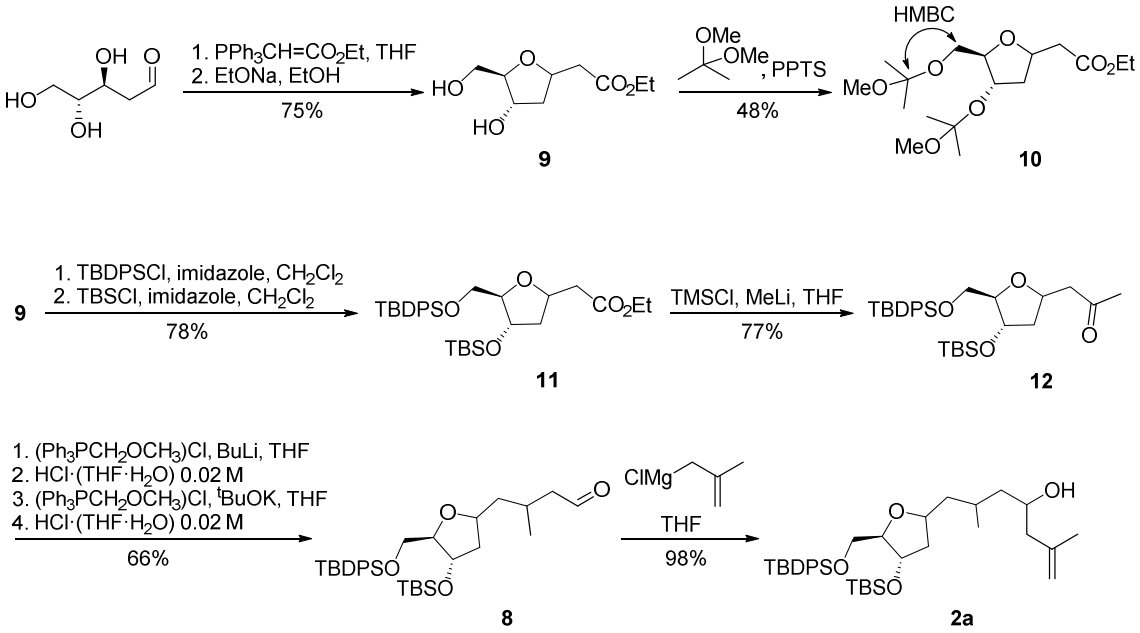


Figure 2. Structures of catalysts used for the metathesis experiments.

With these considerations in mind, the testing of a diverse set of conditions was planned either for cross metathesis experiments (CM) or for ring closing metathesis experiments. (RCM) Thus, we envisioned the synthesis of a set of *gem*-disubstituted olefins (**2a-c**) and a set of olefin partners (**3a-h**) for the metathesis reactions.

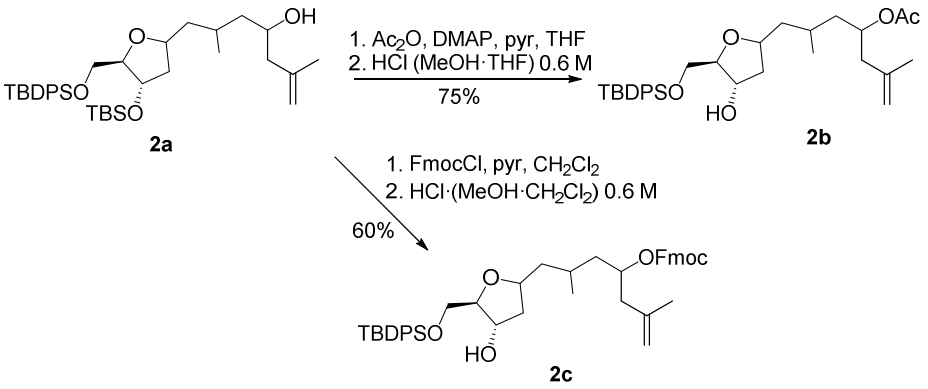
The synthesis of *gem*-disubstituted olefin **2a** started from the commercially available sugar 2-deoxy-D-ribose (Scheme 1), that furnishes the desired trisubstituted THF ring **9** in two steps by Wittig olefination and oxa-Michael addition.[1] Confirmation of the 5-membered ring formation instead of the 6-membered ring was performed by gHMBC correlations of protected adduct **10**, which was formed upon reaction of diol **9** with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate (PPTS). Protection of diol **9** with two orthogonal silyl ethers afforded ester **11**. The *tert*-butyldiphenylsilyl (TBDPS) ether was selected for the primary hydroxyl group, the steric hindrance provided by the two phenyl and *tert*-butyl groups afforded monoprotection with good selectivity. On the other hand, the more acid labile *tert*-butyldimethylsilyl (TBS) ether was selected for the secondary alcohol, because this hydroxyl

will need to be deprotected for lactone formation. Protected adduct **11** was converted to methyl ketone **12** in a one-step procedure with MeLi in the presence of chlorotrimethylsilane (TMSCl),[9] and two consecutive Wittig-enol ether hydrolysis procedures led to aldehyde **8**, common intermediate for the metathesis and Julia-Kocienski olefination routes. Reaction of aldehyde **8** with methyl allyl magnesium chloride yielded *gem*-disubstituted olefin **2a**.



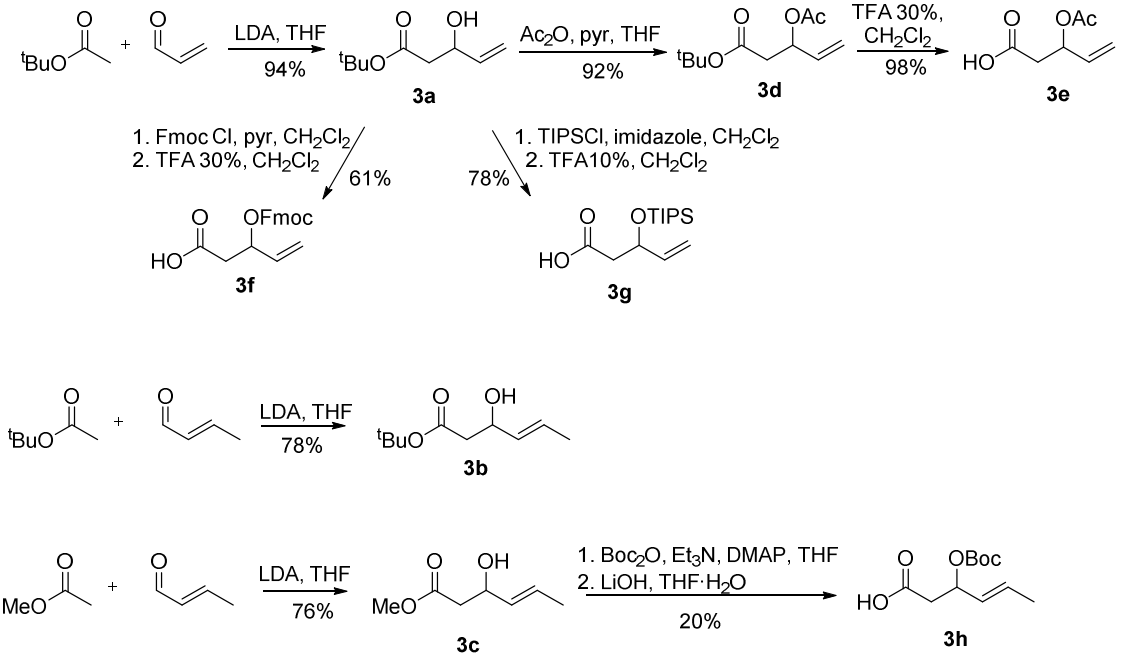
Scheme 1. Synthesis of *gem*-disubstituted olefin **2a**.

From **2a**, a small set of *gem*-disubstituted olefins was prepared (Scheme 2). Olefin **2b** was obtained as result of acetyl protection followed by removal of the TBS ether. Olefin **2c** was obtained in a similar fashion with the 9-fluorenylmethoxycarbonyl (Fmoc) protecting group. Olefins **2a** and **2b** were mainly synthesized for CM experiments, while olefin **2c** was accessed in order to condense with a set of acids bearing the terminal olefin partner motif, and then remove the Fmoc carbonate for the RCM experiments. Thus, they can be performed with the free hydroxyl motif which provides the less impeded steric effect in the *gem*-disubstituted olefin fragment.



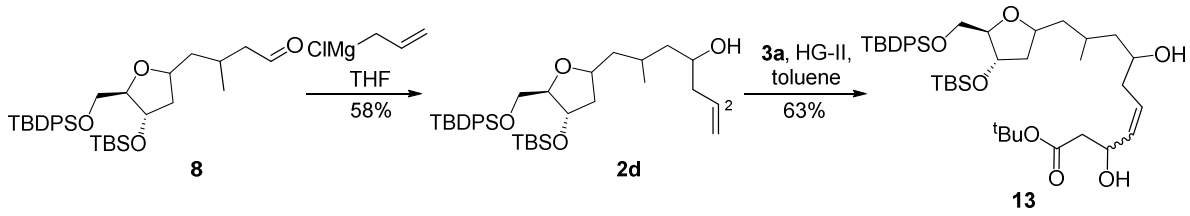
Scheme 2. Synthesis of *gem*-disubstituted olefins **2b-c**.

A series of olefins were prepared by reaction of the lithium enolate of *tert*-butyl or methyl acetate with acrolein or crotonaldehyde obtaining alcohols **3a-c** (Scheme 3). Alcohol **3a** was acetylated to obtain **3d**, and acid deprotection of the *tert*-butyl ester afforded acid **3e**. In an analogous manner, acids **3f** and **3g** were obtained protected as Fmoc and triisopropylsilyl (TIPS) ethers respectively. In a similar fashion, acid **3h** was obtained protected as *tert*-butoxycarbonyl (Boc) carbonate from alcohol **3c**. Olefins **3a-d** were obtained in order to perform CM experiments, while olefins **3e-h** were obtained for ester bond formation, as explained above, to perform RCM experiments.



Scheme 3. Synthesis of olefins **3a-h**.

Before the optimization process was performed, a model experiment showed the viability of our synthetic route. Monosubstituted olefin **2d** was obtained from aldehyde **8** and reacted with olefin **3a** in the presence of HG-II catalyst to obtain metathesis product **13** with a 63% yield (Scheme 4). Olefin **2d** differs only in the extra methyl at the C2 position from *gem*-disubstituted olefin **2a**.



Scheme 4. Synthesis of olefin **13**.

Thus, cross metathesis experiments were performed using a combination of olefins and catalysts as shown in Table 1. Note that the first experimental procedure uses the same conditions that led to olefin **13**. Nevertheless, in our hands, neither increasing the temperature nor using more hindered monosubstituted olefins afforded the target trisubstituted olefin from either olefin **2a** or **2b**. All reactions were performed with large excesses of

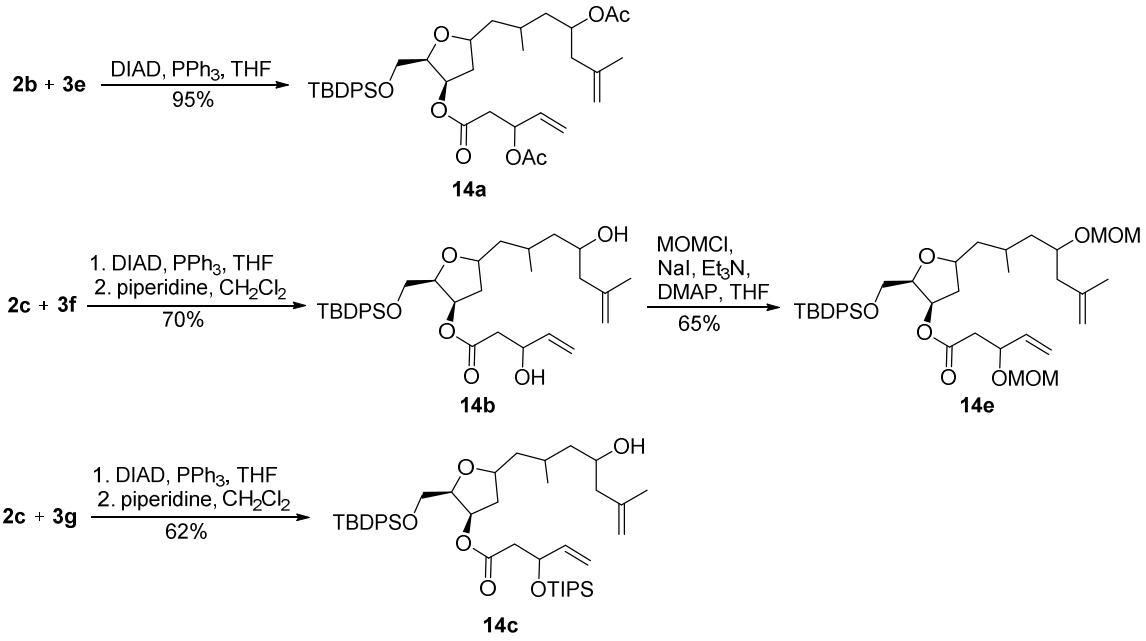
monosubstituted olefin **3** (10 to 30 equivalents) and big loadings of catalyst (30 to 40%). In all cases the *gem*-disubstituted olefin could be recovered, along with monosubstituted olefin and its homodimer.

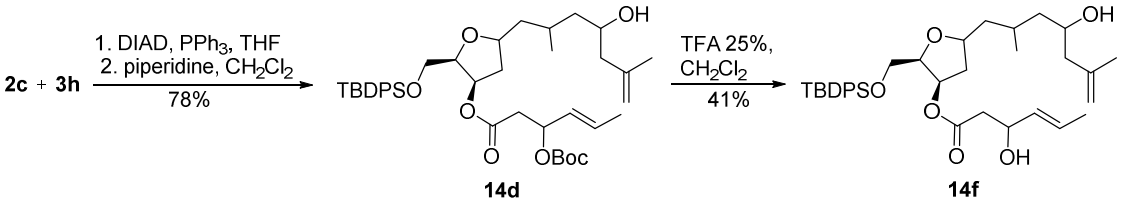
Table 1. Cross Metathesis experiments.

Olefin 2	Olefin 3	Catalyst	Solvent	Temperature
2a	**3a**	HG-II	Toluene	r.t.
2a	**3a**	HG-II-CF_3	Toluene	r.t.
2a	**3a**	HG-II	Toluene	110 °C
2a	**3b**	HG-II	Toluene	55 °C
2b	**3d**	HG-II	CH_2Cl_2	40 °C
2b	**3d**	HG-II	Toluene	110 °C
2b	**3d**	G-II	Toluene	110 °C

The other tested metathesis methodology was the RCM; this approach has the disadvantatge that no excess of one olefin can be added over the other. Nevertheless, the formation of a cyclic product may have a beneficial effect on the formation of the trisubstituted olefin.

Several precursors were synthesized, this were obtained by Mitsunobu esterification, and sometimes deprotection or protection steps were performed (Scheme 5). Condensation of alcohol **2b** and acid **3e** furnished ester **14a**. Alcohol **2c** was reacted with acids **3f**, **3g** and **3h**, and further deprotection of the Fmoc carbonate afforded esters **14b**, **14c** and **14d**, respectively. Protection of ester **14b** as its methoxymethyl (MOM) derivative was performed in order to get substrate **14e** to test the performance of Schrock's catalyst, provided that this is less prone to functional group tolerance.[10] The fully deprotected adduct **14f** with an extra methyl was obtained from deprotection of the hydroxyl group of **14d** in acidic media; the low yield obtained for this process can be explained because elimination of the β-hydroxycarbonyl motif is possible rendering the conjugated system and consequently leads to a decrease on yield.





Scheme 5. Synthesis of precursors for RCM **14a-f**.

Several RCM experiments with different catalysts, solvents and temperatures shown in Table 2 have been performed. In all assays the starting material was recovered, sometimes along with the dimeric product resulting from intermolecular metathesis. Only **14d** provided access to traces amount of product, detected by ^{1}H-NMR. Although the product was indeed detected, the quantity was not sufficient to consider this an efficient methodology.

Table 2. Ring Closing Metathesis experiments.

Precursor	catalyst	Solvent	Temperature
14a	G-II	CH_2Cl_2	40°C
14a	HG-II	CH_2Cl_2	40°C
14a	G-II	Toluene	110 °C
14a	HG-II	Toluene	110 °C
14b	HG-II	Toluene	r.t.
14b	HG-II-CF_3	Toluene	r.t.
14b	HG-II-O^{t}Bu	Toluene	r.t.
14c	HG-II	Toluene	80 °C
14d[a]	HG-II	Toluene	80 °C
14d[a]	HG-II	Toluene	MW 120-160°C
14d[a]	HG-II-CF_3	Toluene	MW 120-160°C
14d[a]	HG-II-O^{t}Bu	Toluene	MW 120-160°C
14e	Schrock	Benzene	80 °C
14f	HG-II	Toluene	80 °C

[a]Traces of product were detected.

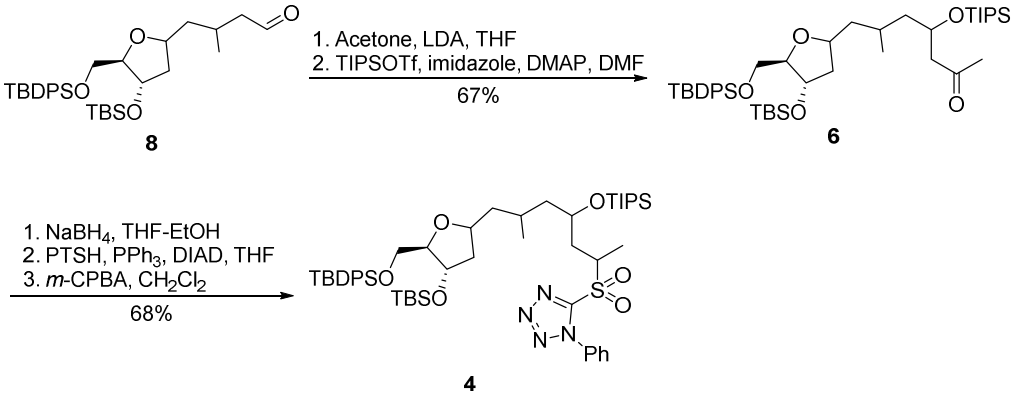
In conclusion, changing conditions, catalysts and the olefin starting materials, it was not possible to find any suitable olefination combination for the metathesis reactions and this synthetic route was finally discarded.

3. Julia-Kocienski approach for the synthesis of the macrocyclic core

The second tested synthetic pathway was based on a Julia-Kocienski olefination. Since functionalization is possible for both fragments, both possible combinations were tested and the sulfone and the carbonyl motif were placed in either side of the precursor fragments. This process is a well stablished methodology based on the addition of a α-sulfonyl carbanion to a carbonyl, followed by heterocycle transposition and sulfur dioxide extrusion to render the desired alkene.[11] It is widely used for the formation of disubstituted alkenes but this type of methodology is not commonly applied for the formation of trisubstituted double bonds.[12]

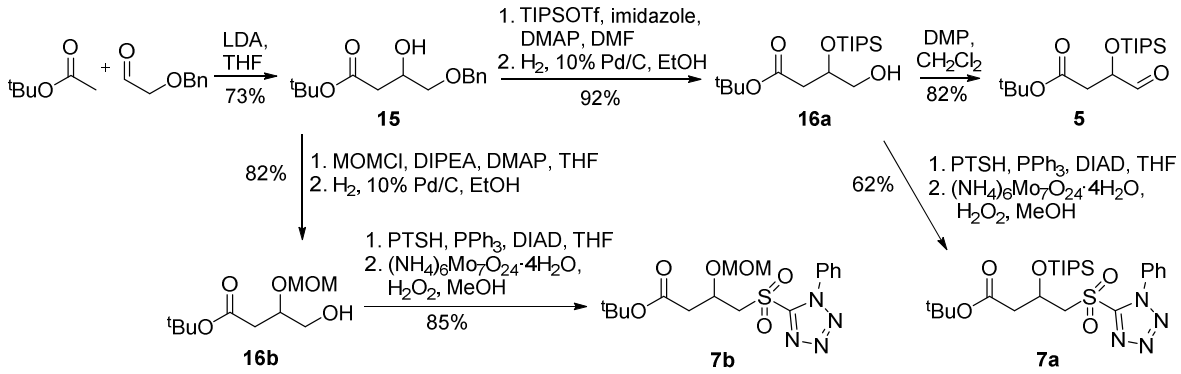
Consequently, we envisioned the synthesis of sulfone **4**, ketone **6**, aldehyde **5** and sulfones **7a** and **7b**.

Formation of ketone **6** and sulfone **4** was performed from common intermediate **8**. Addition of the lithium enolate of acetone to aldehyde **8** and protection of the obtained alcohol led to ketone **6** (Scheme 6). The carbonyl motif was transformed to sulfone **4** in a three step process based on reduction to the alcohol, introduction of 1-phenyl-1*H*-tetrazolyl-5-thiol[13] and oxidation with 3-chloroperbenzoic acid (*m*-CBPA).



Scheme 6. Synthesis of ketone **6** and sulfone **4**.

Applying the same strategy to functionalize, aldehyde **5** and sulfones **7a** and **7b** were obtained from aldol **15**. This aldol was obtained by addition of the lithium enolate of *tert*-butyl acetate to 2-(benzyloxy)acetaldehyde (Scheme 7). Aldol **15** was protected either as TIPS or MOM ethers and hydrogenated to render alcohols **16a** and **16b** respectively. Primary alcohol **16a** was oxidized with Dess-Martin periodinane (DMP) to afford aldehyde **5**. On the other hand, alcohol **16a** was also reacted with 1-phenyl-1*H*-tetrazolyl-5-thiol and oxidized to afford sufone **7a**. Sulfone **7b** was obtained is a similar fashion from alcohol **16b**.

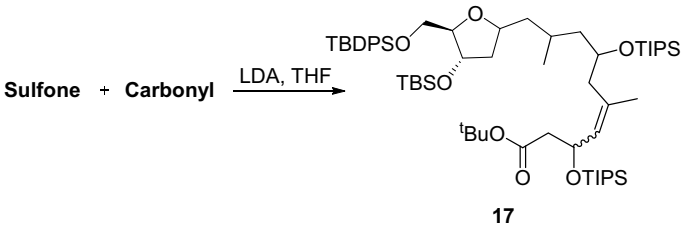


Scheme 7. Synthesis of aldehyde **5** and sulfones **7a-b**.

Julia-Kocienski experiments were performed using LDA as base employing premetalation conditions. The lithium α-sulfonyl anions of sulfones **7a** and **7b** were not reactive in front of ketone **6**, and addition to the carbonyl was not observed, neither with the less hindered sulfone **7b** (Table 3). The reverse functionalization based on the addition of the anion of sulfone **4** to aldehyde **5** afforded finally double bond formation with moderate yield.

A characteristic multiplet signal at 5.20-5.33 ppm corresponding to the vinyl proton of the trisubstituted alkene appeared on the ^{1}H-NMR.

Table 3. Julia-Kocienski olefination experiments.

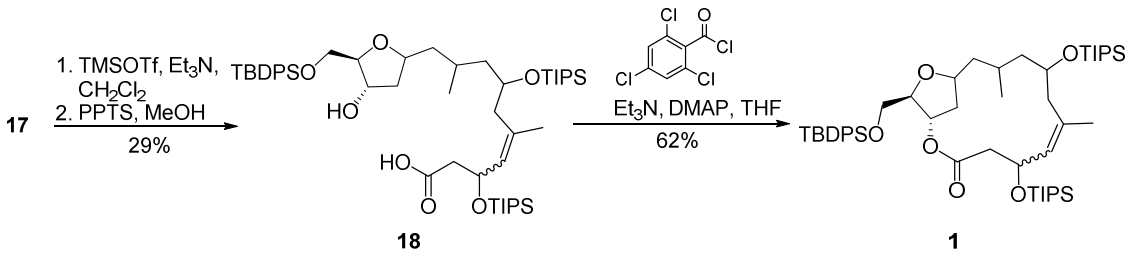


17

Sulfone	Carbonyl	Yield
7a	**6**	0%
7b	**6**	0%
4	**5**	46%

From trisubstituted olefin **17**, next step was deprotection of the alcohol and the acid. Mild conditions were mandatory in order to avoid decomposition of the starting material. Thus, deprotection of the acid and the alcohol was achieved using TMSOTf and Et_3N in CH_2Cl_2 and PPTS in MeOH, respectively, and *seco*-acid **18** was obtained (Scheme 8).

Several reaction conditions were tested for the macrolactonization step; under Mitsunobu esterification no macrocyle was formed, probably due to the more restricted access of the acid approaching the alcohol. The use of carbodiimides provided access only to dimeric macrocycle, even when performing the reaction under high dilution conditions (0.2 mM). Finally, the formation of the macrolactone was achieved under Yamaguchi[14] macrolactonization conditions, which afforded monomeric macrocycle **1** with good yield; partial formation of the dimer was observed, but the monomer could be easily isolated independently.



18 **1**

Scheme 8. Synthesis of macrocycle **1**.

Finally, double bond formation and macrolactonization were achieved, the synthetic pathway towards the macrocyclic core of phormidolides B-D was clear and steroselective development of the more successful synthetic route was then possible. The selected strategy was that based on a Julia-Kocienski olefination and Yamaguchi macrolactonization as key transformation steps.

4. Conclusions

The study of the best conditions for double bond formation and macrocyclization was performed. Disclosed are our efforts towards the metathesis approach, describing conditions, catalysts and changes on the olefin starting materials that failed to obtain the trisubstituted double bond. Finally, the Julia-Kocienski approach afforded the construction of the desired C4-C5 double bond, the synthesis was finished with the macrolactonization step and was selected for development as stereoselective version. This short resume not only explains the failed process that we carried out for the metathesis route, but shows how complicated the synthesis of trisubstituted alkenes can originate.

5. General Procedures and Experimental Section

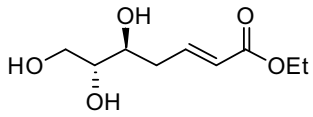
General information

Tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF) were dried using a PureSolv solvent purification system. Solvents for metathesis reactions were degassed using a freeze-pump-thaw procedure, and catalysts were handled under nitrogen atmosphere. All other solvents and reagents were used as purchased without further purification, unless otherwise 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. 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. 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. The same abbreviations were also used for the multiplicity of signals in ^{1}H-NMR. High Resolution Mass Spectroscopy (HRMS) was performed on either a LTQ-FT Ultra (Thermo scientific) or LCT-Premier (Waters) high resolution mass spectrometer by the IRB mass spectrometry service, or on an Agilent LC/MSD-TOF 2006 mass spectrometer by the UB technic support service.

Experimental procedures and characterization

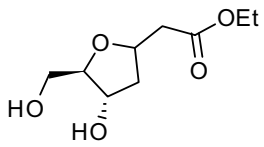
Since these routes were used as test to select the best synthetic pathway, and employed not-stereoselective procedures, substrates and products were mixtures of diastereomers, and characterization was based on ^{1}H-NMR analysis in the majority of analyzed compounds, sometimes combined with HRMS.

Ethyl (5*S*,6*R*,*E*)-5,6,7-trihydroxyhept-2-enoate (S1).[1]



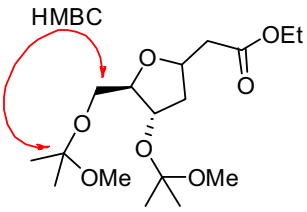
Ethyl (triphenylphosphoranylidene)acetate (9.74 g, 28.0 mmol) was added to a solution of 2-deoxy-D-ribose (3.40 g, 25.5 mmol) in THF (120 mL). The solution was stirred at reflux temperature for 5 h and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with CH_2Cl_2-MeOH (95:5 to 90:10) yielded **S1** (4.9 g, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H); 2.33–2.52 (m, 2H); 3.55–3.61 (m, 1H); 3.66–3.72 (m, 2H); 3.74–3.82 (m, 1H); 3.93–4.13 (m, 3H, OH); 4.15 (q, *J* = 7.1, 2H); 5.91 (d, *J* = 15.7, 1H); 6.98 (dt, *J* = 15.7, 7.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (q); 35.8 (t); 60.5 (t); 63.1 (t); 71.5 (d); 74.0 (d); 123.6 (d); 145.8 (d); 166.9 (s).

Ethyl 2-[(4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]acetate (9).[1]



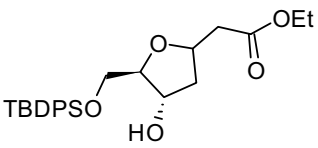
NaEtO (200 mg, 3.0 mmol) was added to a solution of **S1** (13.50 g, 64.4 mmol) in EtOH (150 mL). The reaction mixture was stirred at r.t. for 24 h. The solvent was removed under reduced pressure and the residue was filtered through a pad of silica with CH_2Cl_2-MeOH (90:10) to yield **9** (10.56 g, 80%) as a mixture of diastereomers A:B (60:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, $3H_{A+B}$); 1.80 and 1.92 (ddd, *J* = 13.1, 6.5, 5.4 Hz and ddd, *J* = 13.1, 9.4, 6.4 Hz, $1H_{A+B}$); 2.04 and 2.44 (ddd, *J* = 13.1, 5.8, 2.6 Hz and dt, *J* = 13.1, 7.1 Hz, $1H_{B+A}$); 2.59–2.66 and 2.71–2.78 (2m, $2H_{A+B}$); 3.58–3.57(m, $2H_{A+B}$); 3.85–3.96 (m, $1H_{A+B}$); 4.16 (q, *J* = 7.1 Hz, $2H_{A+B}$); 4.31–4.40 (m, $1H_{A+B}$); 4.45–4.57 (m, $1H_{A+B}$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (q_{A+B}); 39.9 (t_B); 40.0 (t_A); 40.6 (t_B); 40.8 (t_A); 60.7 (t_A); 60.8 (t_B); 62.3 (t_A); 62.9 (t_B); 72.6 (d_A); 73.1 (d_B); 74.4 (d_A); 74.5 (d_B); 85.4 (d_A); 87.1 (d_B); 171.3 (s_B); 171.6 (s_A). HRMS (+ESI): *m/z* calcd. for $C_9H_{17}O_5$ (M+H) 205.1076, found 205.1065.

Ethyl 2-[(4*S*,5*R*)-4-(2-methoxypropan-2-yloxy)-5-(2-methoxypropan-2-yloxymethyl) tetrahydrofuran-2-yl]acetate (10).



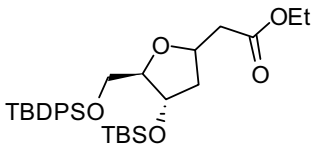
PPTS (15 mg, 0.06 mmol) was added to a solution of **9** (150 mg, 0.73 mmol) in 2,2-dimethoxypropane (1 mL). The reaction mixture was stirred at 80 °C for 24 h. The solvent was removed under reduced pressure and the residue was poured into EtOAc and was washed with $NaHCO_3$, water and brine. The organic 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) yielded **10** (117 mg, 48%) as a mixture of diastereomers A:B (60:40). IR (KBr film) ν 2989, 2942, 1737, 1463, 1380, 1211 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, $3H_{A+B}$); 1.31 (s, $6H_{A+B}$); 1.32 (s, $6H_{A+B}$); 1.65–1.76 (m, $1H_{A+B}$); 2.03 and 2.34 (ddd, *J* = 12.8, 5.4, 1.9 Hz and dt, *J* = 13.4, 6.9 Hz, $1H_{B+A}$); 2.44 and 2.55 (dd, *J* = 15.3, 6.5 Hz and dd, *J* = 15.4, 6.9 Hz, $1H_{B+A}$); 2.65 and 2.75 (dd, *J* = 15.3, 6.6 Hz and dd, *J* = 15.4, 6.8 Hz, $1H_{B+A}$); 3.18 (3s, $6H_{A+B}$); 3.32–3.41 (m, $2H_{A+B}$); 3.96 and 4.05 (td, *J* = 5.1, 2.6 Hz and td, *J* = 5.0, 3.2 Hz, $1H_{B+A}$); 4.12 (q, *J* = 7.1 Hz, $1H_{A+B}$); 4.24–4.28 and 4.30–4.34 (2m, $1H_{B+A}$); 4.41–4.50 (m, $1H_{A+B}$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (q_{A+B}); 24.3 ($3q_{A+B}$); 25.0 ($2q_{A+B}$); 25.4 ($2q_{A+B}$); 39.5 (t_A); 39.8 (t_B); 40.7 (t_B); 41.1 (t_A); 48.4 (q_{A+B}); 48.5 (q_{A+B}); 48.7 ($2q_{A+B}$) 60.3 (t_A); 60.4 (t_B); 61.5 (t_A); 61.8 (t_B); 72.4 (d_A); 72.6 (d_B); 74.9 (d_B); 75.9 (d_A); 84.0 (d_A); 84.8 (d_B); 99.2 ($2s_{A+B}$); 100.6 ($2s_{A+B}$); 171.0 (s_B); 171.3 (s_A).

Ethyl 2-[(4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxymethyl)-4-hydroxytetrahydrofuran-2-yl]-acetate (S2).



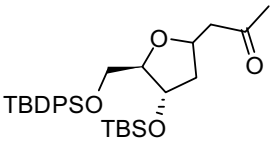
TBDPSCl (2.48 mL, 9.5 mmol) was added to a solution of diol **9** (1.95 g, 9.5 mmol) and imidazole (1.30 g, 19.1 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred at r.t. for 16 h. After this time, the reaction mixture was washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (80:20 to 70:30) yielded **S2** (3.71 g, 87%) as a mixture of diastereomers A:B (60:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, $9H_{A+B}$); 1.22–1.28 (m, $3H_{A+B}$); 1.80 and 1.83–1.87 (ddd, *J* = 13.1, 6.3, 4.7 Hz and m, $1H_{A+B}$); 2.04–2.10 and 2.44–2.54 (2m, $1H_{B+A}$); 2.44–2.75 (m, $2H_{A+B}$); 3.55–3.64 and 3.73–3.79 (2m, $2H_{A+B}$); 3.86–3.90 and 3.95–3.98 (2m, $1H_{B+A}$); 4.09–4.18 (m, $2H_{A+B}$); 4.41–4.49 (m, $1H_{A+B}$); 4.51–4.58 (m, $1H_{A+B}$); 7.35–7.45 (m, $6H_{A+B}$); 7.63–7.69 (m, $4H_{A+B}$).

Ethyl 2-[(4*S*,5*R*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]acetate (11).



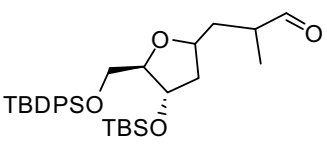
TBSCl (3.92 g, 26.0 mmol) was added to a solution of alcohol **S2** (8.80 g, 20.0 mmol) and imidazole (2.72 g, 40.0 mmol) in CH_2Cl_2 (180 mL). The reaction mixture was stirred at r.t. for 6 h. After this time, the reaction mixture was washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded **11** (9.99 g, 90%) as a mixture of diastereomers A:B (60:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, $3H_{A+B}$); 0.06 (s, $3H_{A+B}$); 0.88 (s, $9H_{A+B}$); 1.05 (s, $9H_{A+B}$); 1.05 (s, $9H_{A+B}$); 1.24 (t, *J* = 7.1 Hz, $3H_{A+B}$); 1.65–1.75 (m, $1H_{A+B}$); 1.96 and 2.29 (ddd, *J* = 12.6, 5.3, 1.9 Hz and ddd, *J* = 13.2, 7.3, 6.1 Hz, $1H_{B+A}$); 2.46 and 2.77 (dd, *J* = 15.3, 6.0 Hz and dd, *J* = 15.4, 7.1 Hz, $1H_{B+A}$); 2.55–2.66 (m, $1H_{A+B}$); 3.51–3.60 and 3.62–3.68 (2m, $2H_{A+B}$); 3.85–3.91 and 3.94–3.98 (2m, $1H_{B+A}$); 4.11–4.18 (m, $2H_{A+B}$); 4.40–4.44 and 4.45–4.50 (2m, $1H_{B+A}$); 4.51–4.58 (m, $1H_{A+B}$); 7.34–7.45 (m, $6H_{A+B}$); 7.64–7.69 (m, $4H_{A+B}$). HRMS (+ESI): *m/z* calcd. for $C_{31}H_{48}O_5NaSi_2$ (M+Na) 579.2938, found 579.2922.

1-[(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)-tetrahydro-furan-2-yl]propan-2-one (12).



MeLi (2.90 mL, 4.6 mmol) was added to a solution of TMSCl (1.18 mL, 9.3 mmol) and ester **11** (1.04 g, 1.9 mmol) in THF (25 mL) at –78 °C. The reaction mixture was stirred 15 min at –78 °C and 3 h at 0 °C and after this time, sat. NH_4Cl was added. The solvent was removed under reduced pressure and the residue was dissolved in sat. NH_4Cl and 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 CH_2Cl_2 yielded **12** (755 mg, 77%) as a colorless oil. IR (KBr film) ν 2930, 2857, 1716, 1471, 1428, 1254, 1112 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, $3H_{A+B}$); 0.06 (s, $3H_{A+B}$); 0.88 (s, $9H_{A+B}$); 1.05 (s, $9H_{A+B}$); 1.59–1.65 (m, $1H_{A+B}$); 1.95 and 2.25–2.34 (ddd, *J* = 12.6, 5.2, 1.8 Hz and m, $1H_{A+B}$); 2.17 (s, $3H_{A+B}$); 2.54 and 2.67 (dd, *J* = 15.8, 5.2 Hz and dd, *J* = 16.2, 6.1 Hz, $1H_{A+B}$); 2.73 and 2.93 (dd, *J* = 15.8, 7.5 Hz and dd, *J* = 16.2, 7.2 Hz, $1H_{A+B}$); 3.48–3.64 (m, $2H_{A+B}$); 3.78–3.83 and 3.85–3.90 (2m, $1H_{A+B}$); 4.33–4.37 and 4.39–4.43 (2m, $1H_{A+B}$); 4.43–4.51 (m, $1H_{A+B}$); 7.29–7.41 (m, $6H_{A+B}$); 7.57–7.65 (m, $4H_{A+B}$). HRMS (+ESI): *m/z* calcd. for $C_{30}H_{46}O_4NaSi_2$ (M+Na) 549.2832, found 549.2816.

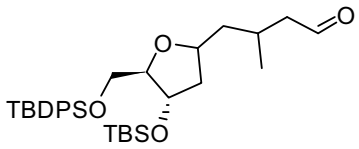
3-[(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)-tetrahydro-furan-2-yl]-2-methylpropanal (S3).



A 1.6 M solution of BuLi in hexane (10.90 mL, 17.5 mmol) was added to a solution of (methoxymethyl)(triphenyl)phosphonium chloride (5.99 g, 17.5 mmol) in THF (130 mL). The reaction mixture was stirred for 10 min and ketone **12** was added (4.61 g, 8.7 mmol). The reaction was stirred for additional 1 h and sat. NH_4Cl was added. The solvent was removed under reduced pressure, the residue was dissolved in Et_2O and was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was dissolved in EtOAc (100mL) and 2M aq. HCl (2 mL) was added, the solution was stirred for 16 h. After this time, sat. $NaHCO_3$ was added, and the solution was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **S3** (4.04 g, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04, 0.05 and 0.06 (3s, 6H); 0.87 and 0.88 (2s, 9H); 1.04 and 1.05 (2s, 9H); 1.10–1.15 (m, 3H); 1.40–1.67 (m, 2H);

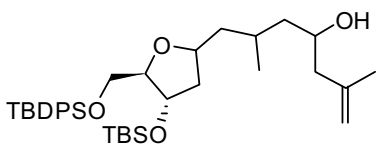
1.80–1.98 and 2.15–2.30 (2m, 2H); 2.52–2.64 (m, 1H); 3.53–3.59 and 3.61–3.67 (2m, 2H); 3.81–3.86 (m, 1H); 4.15–4.25 (m, 1H); 4.36–4.43 and 4.45–4.51 (2m, 1H); 7.35–7.45 (m, 6H); 7.65–7.73 (m, 4H); 9.61–9.63 and 9.64–9.66 (2m, 1H).

4-[(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)-tetrahydro-furan-2-yl]-3-methylbutanal (8).



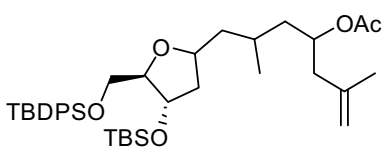
K^tBuO (790 mg, 7.0 mmol) was added to a solution of (methoxymethyl)(triphenyl)phosphonium chloride (2.41 g, 7.0 mmol) in THF (50 mL). The reaction mixture was stirred for 10 min and aldehyde **S3** was added (1.91 g, 3.5 mmol). The reaction was stirred for additional 1 h and sat. NH_4Cl was added. The solvent was removed under reduced pressure, the residue was dissolved in Et_2O and was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was dissolved in EtOAc (50 mL) and 2M aq. HCl (1 mL) was added, the solution was stirred for 3 h. After this time, sat. $NaHCO_3$ was added, and the solution was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **8** (1.52 g, 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04, 0.05 and 0.06 (3s, 6H); 0.87 and 0.88 (2s, 9H); 0.97–1.02 (m, 3H); 1.05 (bs, 9H); 1.34–1.65 (m, 3H); 1.68–1.80 and 1.81–1.89 (2m, 1H); 2.17–2.35 (m, 2H); 2.46–2.55 (m, 1H); 3.53–3.59 and 3.63–3.68 (2m, 2H); 3.81–3.86 (m, 1H); 4.12–4.23 (m, 1H); 4.36–4.40 and 4.46–4.51 (2m, 1H); 7.35–7.45 (m, 6H); 7.66–7.73 (m, 4H); 9.71–9.76 (m, 1H). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{50}O_4NaSi_2$ (M+Na) 577.3140, found 577.3142

7-[(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)-tetrahydro-furan-2-yl]-2,6-dimethylhept-1-en-4-ol (2a).



A 0.5 M solution of methyl allyl magnesium chloride solution in THF (10.80 mL, 5.4 mmol) was added to a solution of aldehyde **10** (1.00 g, 1.8 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred for 30 min and sat. NH_4Cl was added. The solvent was removed under reduced presure, the residue was dissolved in CH_2Cl_2 and was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **2a** (1.07 g, 98%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02–0.06 (m, 6H); 0.87 and 0.88 (2s, 9H); 0.95–0.99 (m, 3H); 1.05 (bs, 9H); 1.20–1.28 (m, 1H); 1.38–1.48 (m, 1H); 1.48–1.69 (m, 3H); 1.74 and 1.75 (2s, 3H); 1.79–1.87 (m, 1H); 2.01–2.28 (m, 3H); 3.52–3.58 and 3.62–3.72 (2m, 2H); 3.78–3.88 (m, 2H); 4.16–4.27 (m, 1H); 4.35–4.40 and 4.45–4.51 (m, 1H); 4.75–4.80 (m, 1H); 4.84–4.89 (m, 1H); 7.34–7.45 (m, 6H); 7.65–7.73 (m, 4H). HRMS (+ESI): *m/z* calcd. for $C_{36}H_{59}O_4Si_2$ (M+H) 611.3952, found 611.3954.

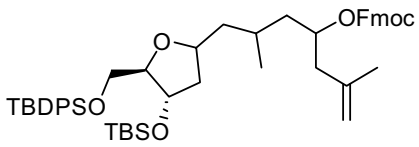
7-[(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)-tetrahydro-furan-2-yl]-2,6-dimethylhept-1-en-4-yl acetate (S4).



Acetic anhydride (0.21 mL, 2.3 mmol) was added to a solution of alcohol **2a** (1.07 g, 1.8 mmol), pyridine (0.4 mL, 32 mmol) and 4-(dimethylamino)pyridine (DMAP) (30 mg, 0.24 mmol) in THF (50 mL). The reaction mixture was stirred for 7 h and sat. NH_4Cl was added. The solvent was removed under reduced presure, the residue was dissolved in EtOAc and was washed with NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel

column chromatography with hexane-EtOAc (95:5) yielded **S4** (1.09 g, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02–0.07 (m, 6H); 0.87 and 0.88 (2s, 9H); 0.92–0.98 (m, 3H); 1.05 (bs, 9H); 1.24–1.34 (m, 2H); 1.44–1.65 (m, 3H); 1.72 and 1.74 (2s, 3H); 1.78–1.79 (m, 1H); 1.97–2.01 (m, 3H); 2.11–2.32 (m, 3H); 3.50–3.57 and 3.61–3.73 (2m, 2H); 3.79–3.88 (m, 1H); 4.09–4.22 (m, 1H); 4.35–4.40 and 4.44–4.52 (m, 1H); 4.67–4.73 (m, 1H); 4.74–4.79 (m, 1H); 5.08–5.21 (m, 1H); 7.34–7.45 (m, 6H); 7.65–7.73 (m, 4H).

(9*H*-Fluoren-9-yl)methyl [7-((4*S*,5*R*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenyl-silyloxymethyl)tetrahydrofuran-2-yl)-2,6-dimethylhept-1-en-4-yl] carbonate (S5).

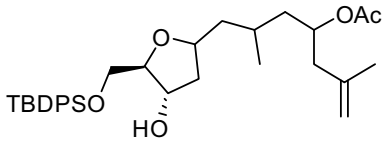


FmocCl (450 mg, 0.87 mmol) was added to a solution of alcohol **2a** (530 mg, 0.87 mmol) and pyridine (0.14 mL, 1.74 mmol) in THF (15 mL). The reaction mixture was stirred for 1 h and sat. NH_4Cl was added. The residue was dissolved in Et_2O and was washed with NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **S5** (704 mg, quant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01–0.08 (m, 6H); 0.86–0.90 (m, 9H); 0.95–1.01 (m, 3H); 1.05 (bs, 9H); 1.25–1.38 (m, 1H); 1.48–1.68 (m, 4H); 1.70–1.88 (m, 5H); 2.19–2.42 (m, 2H); 3.50–3.57 and 3.62–3.70 (2m, 2H); 3.79–3.87 (m, 1H); 4.13–4.28 (m, 2H); 4.29–4.54 (m, 3H); 4.74–4.81 (m, 2H); 4.95–5.09 (m, 1H); 7.27–7.33 (m, 2H); 7.34–7.44 (m, 8H); 7.57–7.63 (m, 2H); 7.66–7.73 (m, 4H); 7.74–7.79 (m, 2H).

General procedure for TBS deprotection:

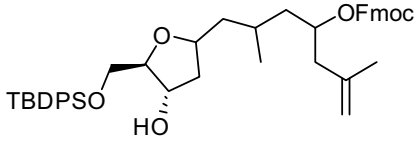
A 1.25 M solution of HCl in MeOH (10 mL, 12.5 mmol) was added to a solution of protected adduct **S4** or **S5** in THF (12 mL), and the resulting mixture was stirred for 3 h. After this time, sat. $NaHCO_3$ was added, and the solution was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (80:20) yielded the corresponding alcohol **2b** or **2c** as a colorless oil.

7-[(4*S*,5*R*)-4-(Hydroxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl]-2,6-dimethylhept-1-en-4-yl acetate (2b).



Protected **S4** (1.08 g, 1.7 mmol) led to alcohol **2b** (712 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.98 (m, 3H); 1.05 (bs, 9H); 1.21–1.32 (m, 1H); 1.38–1.70 (m, 5H); 1.72 and 1.74 (2s, 3H); 1.97–2.03 (m, 3H); 2.10–2.42 (m, 3H); 3.53–3.68 (m, 1H); 3.74–3.94 (m, 2H); 4.10–4.25 (m, 1H); 4.38–4.46 (m, 1H); 4.67–4.71 (m, 1H); 4.74–4.78 (m, 1H); 5.10–5.22 (m, 1H); 7.35–7.47 (m, 6H); 7.64–7.72 (m, 4H).

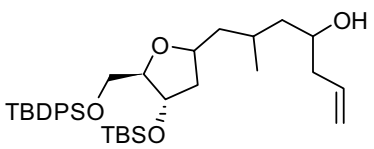
(9*H*-fluoren-9-yl)methyl [7-((4*S*,5*R*)-4-(hydroxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl)-2,6-dimethylhept-1-en-4-yl] carbonate (2c).



Protected **S5** (704 mg, 0.87 mmol) led to alcohol **2c** (356 mg, 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93–1.01 (m, 3H); 1.04–1.06 (m, 9H); 1.30–1.38 (m, 1H); 1.47–1.71 (m, 4H); 1.72–1.97 (m, 5H); 2.19–2.43 (m, 2H); 3.53–3.67 (m, 1H); 3.70–3.91 (m, 2H); 4.11–4.28 (m, 2H);

4.30–4.46 (m, 3H); 4.74–4.81 (m, 2H); 4.95–5.06 (m, 1H); 7.26–7.33 (m, 2H); 7.34–7.44 (m, 8H); 7.56–7.63 (m, 2H); 7.63–7.71 (m, 4H); 7.73–7.79 (m, 2H).

7-[(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl]-6-methylhept-1-en-4-ol (2d).

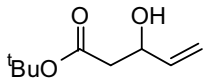


A 1 M solution of allyl magnesium chloride solution in Et_2O (1.14 mL, 0.76 mmol) was added to a solution of aldehyde **10** (422 mg, 0.76 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 1 h and sat. NH_4Cl was added. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 and was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **2d** (263 mg, 58%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01–0.07 (m, 6H); 0.87 (s, 9H); 0.92–0.98 (m, 3H); 1.05 (bs, 9H); 1.17–1.93 (m, 6H); 2.07–2.33 (m, 3H); 3.51–3.59 and 3.62–3.70 (2m, 2H); 3.71–3.80 (m, 1H); 3.82–3.89 (m, 1H); 4.15–4.28 (m, 1H); 4.33–4.40 and 4.45–4.53 (2m, 1H); 5.04–5.15 (m, 2H); 5.74–5.91 (m, 1H); 7.34–7.46 (m, 6H); 7.64–7.73 (m, 4H).

General procedure for the synthesis of aldols 3a-c:

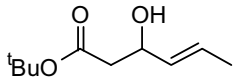
tert-Butyl or methyl acetate (1 eq.) was added to a solution of LDA (1 eq.) in THF at –78 °C. The solution was stirred for 10 min and acrolein or crotonaldehyde (2 eq.) was added. The reaction mixture was stirred for additional 30 min at –78 °C and was then quenched with sat. NH_4Cl. The solvent was removed under reduced pressure and the residue 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 (90:10) yielded the corresponding aldol **3a-c** as colorless oils.

***tert*-Butyl 3-hydroxypent-4-enoate (3a).**



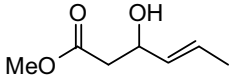
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H); 2.43 (dd, *J* = 16.2, 8.3 Hz, 1H); 2.51 (dd, *J* = 16.2, 4.0 Hz, 1H); 3.11 (bs, OH); 4.45–4.52 (m, 1H); 5.14 (dt, *J* = 10.5, 1.4 Hz, 1H); 5.30 (dt, *J* = 17.2, 1.4 Hz, 1H); 5.87 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H).

***tert*-Butyl 3-hydroxyhex-4-enoate (3b).**



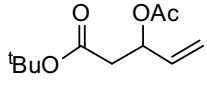
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H); 1.69 (ddd, *J* = 6.5, 1.6, 1.0 Hz, 3H); 2.42 (dd, *J* = 16.1, 7,5 Hz, 1H); 2.46 (dd, *J* = 16.1, 4.7 Hz, 1H); 4.39–4.46 (m, 1H); 5.49 (ddq, *J* = 15.4, 6.5, 1.6 Hz, 1H); 5.73 (dqd, *J* = 15.4, 6.5, 1.0 Hz, 1H).

Methyl 3-hydroxyhex-4-enoate (3c).



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (dd, *J* = 6.5, 1.6 Hz, 3H); 2.54–2.55 (m, 2H); 3.71 (s, 3H); 4.48 (q, *J* = 6.5 Hz, 1H); 5.51 (ddq, *J* = 15.3, 6.5, 1.6 Hz, 1H); 5.74 (dqd, *J* = 15.3, 6.5, 1.1 Hz, 1H).

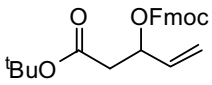
***tert*-Butyl 3-acetoxypent-4-enoate (3d).**



Acetic anhydride (0.81 mL, 8.5 mmol) was added to a solution of alcohol **3a** (1.23 g, 7.1 mmol), pyridine (1.7 mL, 21.3 mmol) and DMAP (60 mg, 0.48

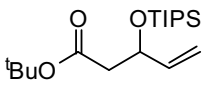
mmol) in THF (50 mL). The reaction mixture was stirred for 4 h and sat. NH_4Cl was added. The solvent was removed under reduced presure, the residue was dissolved in EtOAc and was washed with NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **3d** (1.41 g, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H); 2.06 (s, 3H); 2.52 (dd, *J* = 15.3, 6.0 Hz, 1H); 2.60 (dd, *J* = 15.3, 8.2 Hz, 1H); 5.20 (dt, *J* = 10.5, 1.2 Hz, 1H); 5.30 (dt, *J* = 17.1, 1.2 Hz, 1H); 5.60 (dtt, *J* = 8.2, 6.0, 1.2 Hz, 1H); 5.83 (ddd, *J* = 17.1, 10.5, 6.0 Hz, 1H).

tert-Butyl 3-[(9*H*-fluoren-9-yl)methoxycarbonyloxy]pent-4-enoate (S6).



FmocCl (631 mg, 2.4 mmol) was added to a solution of alcohol **3a** (350 mg, 2.0 mmol) and pyridine (0.19 mL, 2.4 mmol) in CH_2Cl_2 (10 mL) and the solution was stirred for 1 h. The reaction mixture was washed with NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded **S6** (643 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H); 2.58 (dd, *J* = 15.7, 5.6 Hz, 1H); 2.72 (dd, *J* = 15.7, 8.1 Hz, 1H); 4.24–4.32 (m, 1H); 4.39–4.47 (m, 2H); 5.27 (dt, *J* = 10.5, 1.2 Hz, 1H); 5.38 (dt, *J* = 17.2, 1.2 Hz, 1H); 5.51 (dddt, *J* = 8.1, 6.6, 5.6, 1.2 Hz, 1H); 5.88 (ddd, *J* = 17.2, 10.5, 6.6 Hz, 1H); 7.28–7.36 (m, 2H); 7.38–7.45 (m, 2H); 7.59–7.66 (m, 2H); 7.75–7.81 (m, 2H).

tert-Butyl 3-(triisopropylsilyloxy)pent-4-enoate (S7).

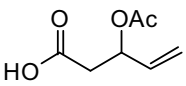


TIPSCl (0.55 mL, 2.6 mmol) was added to a solution of alcohol **3a** (344 mg, 2.0 mmol) and imidazole (272 mg, 4.0 mmol) in CH_2Cl_2 (10 mL) and the solution was stirred for 16 h. The reaction mixture was washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded **S7** (663 mg, quant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (bs, 21H); 1.43 (s, 9H); 2.38 (dd, *J* = 14.5, 7.4 Hz, 1H); 2.56 (dd, *J* = 14.5, 5.8 Hz, 1H); 4.59–4.66 (m, 1H); 5.06 (d, *J* = 10.4 Hz, 1H); 5.21 (d, *J* = 17.2 Hz, 1H); 5.87 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H).

General procedure for ^{t}Bu ester hydrolysis:

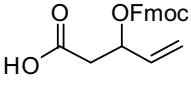
A solution of ^{t}Bu ester **3d**, **S6** or **S7** in CH_2Cl_2-trifluoroacetic acid (10:1 or 7:3) was stirred for 1 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-EtOAc (80:20) to yield the corresponding acid **3e-g** as a colorless oil.

3-Acetoxypent-4-enoic acid (3e).



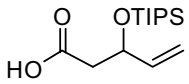
Ester **3d** (1.58 g, 7.4 mmol) led to acid **3e** (1.14 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H); 2.67 (dd, *J* = 16.1, 5.6 Hz, 1H); 2.76 (dd, *J* = 16.1, 7.8 Hz, 1H); 5.24 (dt, *J* = 10.5, 1.2 Hz, 1H); 5.34 (dt, *J* = 17.1, 1.2 Hz, 1H); 5.63 (dddt, *J* = 7.8, 6.4, 5.6, 1.2 Hz, 1H); 5.85 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1H).

3-[(9*H*-Fluoren-9-yl)methoxycarbonyloxy]pent-4-enoic acid (3f).



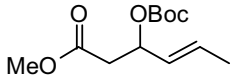
Ester **S6** (600 mg, 1.5 mmol) led to acid **3f** (1.21 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (dd, *J* = 16.4, 5.3 Hz, 1H); 2.86 (dd, *J* = 16.4, 8.0 Hz, 1H); 4.26 (t, *J* = 7.4 Hz, 1H); 4.40 (dd, *J* = 10.5, 7.4 Hz, 1H); 4.45 (dd, *J* = 10.5, 7.4 Hz, 1H); 5.29 (dt, *J* = 10.6, 1.0 Hz, 1H); 5.40 (dt, *J* = 17.2, 1.0 Hz, 1H); 5.52 (dddt, *J* = 8.0, 6.5, 5.3, 1.0 Hz, 1H); 5.89 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H); 7.31 (t, *J* = 7.4 Hz, 2H); 7.41 (t, *J* = 7.4 Hz, 2H); 7.58–7.62 (m, 2H); 7.76 (d, *J* = 7.4 Hz, 2H).

3-(Triisopropylsilyloxy)pent-4-enoic acid (3g).



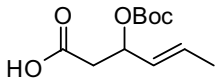
Ester **S7** (200 mg, 0.61 mmol) in led to acid **3g** (130 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (bs, 21H); 2.63–2.66 (m, 2H); 4.68 (dtt, *J* = 6.6, 5.7, 1.2 Hz, 1H); 5.16 (dt, *J* = 10.4, 1.2 Hz, 1H); 5.28 (dt, *J* = 17.2, 1.2 Hz, 1H); 5.90 (ddd, *J* = 17.2, 10.4, 6.6 Hz, 1H).

Methyl 3-(*tert*-butoxycarbonyloxy)hex-4-enoate (S8).



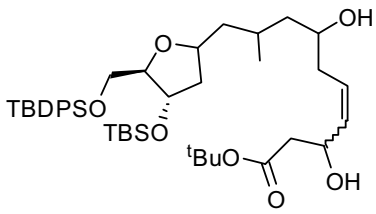
Di-*tert*-butyl dicarbonate (1.49 g, 6.8 mmol) was added to a solution of alcohol **3c** (822 mg, 5.7 mmol), Et_3N (0.19 mL, 2.4 mmol) and DMAP (60 mg, 0.48 mmol) in CH_2Cl_2 (20 mL) and the solution was stirred for 16 h. After this time, the reaction mixture was washed with NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5 to 92:8) yielded **S8** (954 mg, 69%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H); 1.70 (dd, *J* = 6.5, 1.6 Hz, 3H); 2.58 (dd, *J* = 15.6, 5.9 Hz, 1H); 2.75 (dd, *J* = 15.6, 7.7 Hz, 1H); 3.68 (s, 3H); 5.35–5.42 (m, 1H); 5.48 (ddq, *J* = 15.1, 7.4, 1.6 Hz, 1H); 5.83 (dq, *J* = 15.1, 6.5 Hz, 1H).

3-(*tert*-Butoxycarbonyloxy)hex-4-enoic acid (3h).



$LiOH·H_2O$ (670 mg, 16.0 mmol) was added to a solution of ester **S8** (734 mg, 3.0 mmol) in THF-H_2O (2:1) (15 mL) and the solution was stirred for 3 h. The reaction mixture was acidified with 2M aq. HCl until pH=3–4 and the residue was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (80:20) yielded **3h** (203 mg, 29%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H); 1.71 (dd, *J* = 6.6, 1.6 Hz, 3H); 2.62 (dd, *J* = 16.1, 5.8 Hz, 1H); 2.79 (dd, *J* = 16.1, 7.7 Hz, 1H); 5.35–5.42 (m, 1H); 5.49 (ddq, *J* = 15.2, 7.6, 1.6 Hz, 1H); 5.85 (dqd, *J* = 15.2, 6.6, 0.8 Hz, 1H).

***tert*-Butyl 10-[(4*S*,5*R*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-3,7-dihydroxy-9-methyldec-4-enoate (13).**

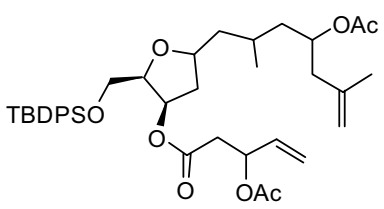


Hoveyda-Grubbs catalyst 2nd generation (20 mg, 0.03 mmol) was added to a solution of olefins **2d** (60 mg, 0.1 mmol) and **3a** (172 mg, 1 mmol) in toluene (5 mL). The reaction mixture was stirred for 5 h and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded **13** (47 mg, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02–0.07 (m, 6H); 0.84–0.90 (m, 9H); 0.92–0.98 (m, 3H); 1.05 (bs, 9H); 1.19–1.38 (m, 2H); 1.45 (bs, 9H); 1.52–1.67 (m, 2H); 1.66–1.92 (m, 3H); 2.07–2.29 (m, 2H); 2.38–2.54 (m, 2H); 3.51–3.59 and 3.61–3.69 (2m, 2H); 3.69–3.79 (m, 1H); 3.80–3.88 (m, 1H); 4.14–4.26 (m, 1H); 4.33–4.40 and 4.41–4.52 (2m, 2H); 5.50–5.62 (m, 1H); 5.67–5.80 (m, 1H); 7.34–7.45 (m, 6H); 7.65–7.73 (m, 4H).

General Procedure for ester bond formation by Mitsunobu esterification:

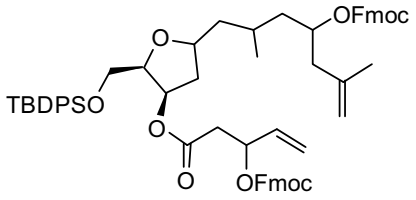
Diisopropyl azodicarboxylate (DIAD) (1.8 eq.) was added to a solution of alcohol (1 eq.), acid (1.4–2 eq.) and PPh_3 (2 eq.) in THF. The reaction mixture was stirred at r.t. for 30 min. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-EtOAc (95:5) to yield the corresponding ester as a colorless oil.

(2*R*,3*R*)-5-(4-Acetoxy-2,6-dimethylhept-6-en-1-yl)-2-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-3-yl 3-acetoxypent-4-enoate (14a).



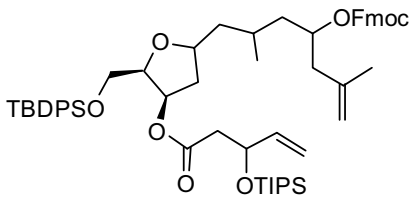
Alcohol **2b** (300 mg, 0.55 mmol) and acid **3e** (174 mg, 1.1 mmol) led to ester **14a** (354 mg, 95%).^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.98 (m, 3H); 1.03 (bs, 9H); 1.21–1.32 (m, 2H); 1.41–1.67 (m, 4H); 1.72 and 1.74 (2s, 3H); 1.75–1.84 (m, 1H); 1.91–2.06 (m, 6H); 2.06–2.33 (m, 2H); 2.41–2.65 (m, 2H); 3.74–3.98 and 4.15–4.25 (2m, 4H); 4.67–4.72 (m, 1H); 4.73–4.78 (m, 1H); 4.97–5.06 and 5.10–5.21 (2m, 2H); 5.22–5.29 (m, 1H); 5.32–5.39 and 5.45–5.49 (2m, 1H); 5.51–5.62 (m, 1H); 5.71–5.85 (m, 1H); 7.33–7.45 (m, 6H); 7.62–7.69 (m, 4H).

(2*R*,3*R*)-5-[4-((9H-Fluoren-9-yl)methoxycarbonyloxy)-2,6-dimethylhept-6-en-1-yl]-2-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-3-yl 3-[(9*H*-fluoren-9-yl)methoxycarbonyl-oxy]pent-4-enoate (S9).



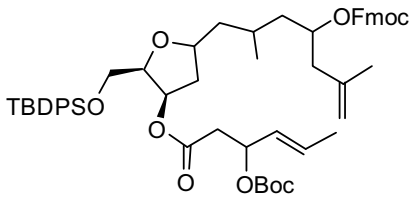
Alcohol **2c** (320 mg, 0.44 mmol) and acid **3f** (408 mg, 1.2 mmol) led to ester **S9** (423 mg, 93%).^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.97 (m, 3H); 1.03 (bs, 9H); 1.20–1.36 (m, 2H); 1.46–1.66 (m, 2H); 1.72 and 1.74 (2s, 3H); 1.76–1.83 (m, 1H); 2.04–2.42 (m, 3H); 2.43–2.61 (m, 2H); 2.62–2.76 (m, 1H); 3.72–4.01 and 4.12–4.27 (2m, 7H); 4.28–4.44 (m, 3H); 4.72–4.81 (m, 2H); 4.92–5.04 (m, 1H); 5.16–5.26 (m, 1H); 5.31–5.64 (m, 3H); 5.75–5.89 (m, 1H); 7.26–7.32 (m, 4H); 7.32–7.44 (m, 10H); 7.54–7.61 (m, 4H); 7.62–7.69 (m, 4H); 7.72–7.79 (m, 4H).

(2*R*,3*R*)-5-[4-((9*H*-Fluoren-9-yl)methoxycarbonyloxy)-2,6-dimethylhept-6-en-1-yl]-2-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-3-yl 3-[(triisopropylsilyloxy)carbonyloxy]-pent-4-enoate (S10).



Alcohol **2c** (250 mg, 0.35 mmol) and acid **3g** (190 mg, 0.70 mmol) led to ester **S10** (quant.).^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93–0.99 (m, 3H); 1.03 (bs, 30H); 1.19–1.40 (m, 2H); 1.47–1.68 (m, 3H); 1.74 and 1.75 (2s, 3H); 1.76–1.94 (m, 2H); 2.16–2.50 (m, 3H); 2.52–2.62 (m, 1H); 3.73–3.97 (m, 3H); 4.09–4.46 (m, 4H); 4.54–4.70 (m, 1H); 4.74–4.81 (m, 2H); 4.93–5.06 (m, 2H); 5.10–5.21 (m, 1H); 5.30–5.35 and 5.39–5.44 (2m, 1H); 5.73–5.93 (m, 1H); 7.28–7.44 (m, 10H); 7.55–7.69 (m, 6H); 7.74–7.79 (m, 2H).

(2*R*,3*R*)-5-[4-((9*H*-Fluoren-9-yl)methoxycarbonyloxy)-2,6-dimethylhept-6-en-1-yl]-2-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-3-yl-3-(*tert*-butoxycarbonyloxy)hex-4-enoate (S11).

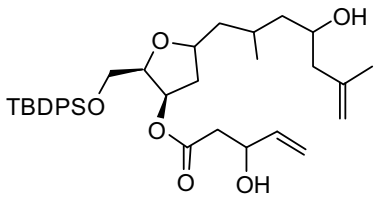


Alcohol **2c** (429 mg, 0.59 mmol) and acid **3h** (197 mg, 0.85 mmol) led to ester **S11** (quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93–0.98 (m, 3H); 1.02 (bs, 9H); 1.21–1.37 (m, 2H); 1.46 (bs, 9H); 1.47–1.83 (m, 8H); 1.74 and 1.75 (2s, 3H); 2.17–2.52 (m, 3H); 2.56–2.70 (m, 1H); 3.74–3.97 (m, 3H); 4.10–4.47 (m, 4H); 4.73–4.81 (m, 2H); 4.94–5.04 (m, 1H); 5.30–5.50 (m, 3H); 5.72–5.84 (m, 1H); 7.27–7.44 (m, 10H); 7.55–7.68 (m, 6H); 7.72–7.78 (m, 2H).

General procedure for Fmoc deprotection:

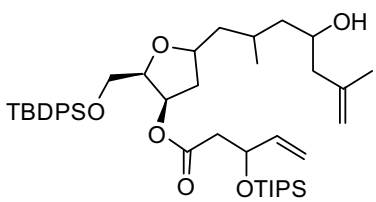
A solution of Fmoc protected adduct **S9-11** (1 eq.) in CH_2Cl_2-piperidine (10:1) was stirred for 1 h. The reaction mixture was quenched with sat. NH_4Cl and the residue was extracted with Et_2O. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10 to 80:20) yielded the corresponding alcohol **14b-d** as a colorless oil.

(2*R*,3*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-5-(4-hydroxy-2,6-dimethylhept-6-en-1-yl) tetrahydrofuran-3-yl 3-hydroxypent-4-enoate (14b).



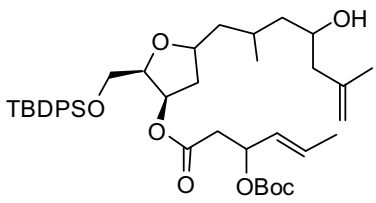
Carbonate **S9** (382 mg, 0.36 mmol) led to alcohol **14b** (160 mg, 75%).^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93–0.98 (m, 3H); 1.03 (bs, 9H); 1.17–1.70 (m, 4H); 1.73 and 1.74 (2s, 3H); 1.78–1.88 (m, 1H); 2.06–2.22 (m, 3H); 2.36–2.55 (m, 3H); 3.75–3.88 (m, 3H); 3.89–4.08 (m, 1H); 4.14–4.28 (m, 1H); 4.40–5.48 (m, 1H); 4.75–4.80 (m, 1H); 4.84–4.89 (m, 1H); 5.08–5.15 (m, 1H); 5.22–5.31 (m, 1H); 5.38–5.44 and 5.49–5.55 (2m, 1H); 5.76–5.87 (m, 1H); 7.34–7.45 (m, 6H); 7.62–7.69 (m, 4H).

(2*R*,3*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-5-(4-hydroxy-2,6-dimethylhept-6-en-1-yl) tetrahydrofuran-3-yl 3-(triisopropylsilyloxy)pent-4-enoate (14c).



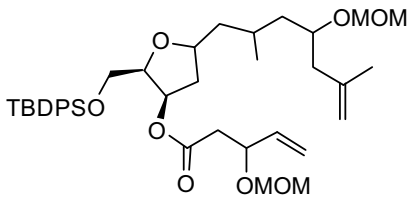
Carbonate **S10** (0.35 mmol) led to alcohol **14c** (163 mg, 62%, 2 steps).^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93–0.99 (m, 3H); 1.03 (bs, 30H); 1.19–1.40 (m, 1H); 1.47–1.68 (m, 3H); 1.74 (s, 3H); 1.78–1.95 (m, 2H); 2.00–2.21 (m, 3H); 2.32–2.61 (m, 2H); 3.75–3.85 (m, 3H); 3.87–4.00 (m, 1H); 4.11–4.27 (m, 1H); 4.55–4.65 (m, 1H); 4.75–4.81 (m, 1H); 4.84–4.88 (m, 1H); 4.93–5.04 (m, 1H); 5.11–5.20 (m, 1H); 5.27–5.35 and 5.39–5.45 (2m, 1H); 5.72–5.90 (m, 1H); 7.33–7.44 (m, 6H); 7.62–7.70 (m, 4H).

(2*R*,3*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-5-(4-hydroxy-2,6-dimethylhept-6-en-1-yl) tetrahydrofuran-3-yl (*E*)-3-(*tert*-butoxycarbonyloxy)hex-4-enoate (14d).



Carbonate **S11** (0.59 mmol) led to alcohol **14d** (326 mg, 78%, 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92–0.99 (m, 3H); 1.03 (bs, 9H); 1.11–1.44 (m, 3H); 1.45 and 1.46 (2s, 9H); 1.48–1.63 (m 3H); 1.65 and 1.66 (3s, 3H); 1.73 and 1.74 (2s, 3H); 1.77-1.93 (m, 1H); 2.04–2.19 (m, 2H); 2.34–2.51 (m, 1H); 2.56–2.70 (m, 1H); 3.73–3.87 (m, 3H); 3.87–4.01 (m, 1H); 4.10–4.31 (m, 1H); 4.72–4.80 (m, 1H); 4.83–4.87 (m, 1H); 5.25–5.48 (m, 3H); 5.70–5.83 (m, 1H); 7.34–7.45 (m, 6H); 7.61–7.68 (m, 4H).

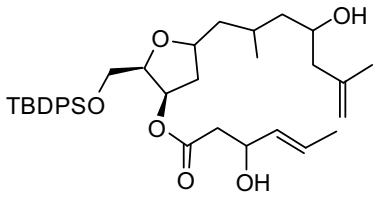
(2*R*,3*R*)-2-(*tert*-butyldiphenylsilyloxymethyl)-5-[4-(methoxymethoxy)-2,6-dimethylhept-6-en-1-yl]tetrahydrofuran-3-yl 3-(methoxymethoxy)pent-4-enoate (14e).



MOMCl (0.13 mL, 1.7 mmol) was added to a solution of **14b** (125 mg, 0.21 mmol), diisopropylethylamine (DIPEA) (0.3 mL, 1.7 mmol), NaI (30 mg, 0.20 mmol) and DMAP (15 mg, 0.25 mmol) in THF (50 mL) and the solution was stirred for 3 days at 50 °C. The solvent was removed under reduced presure, the residue was dissolved in Et_2O

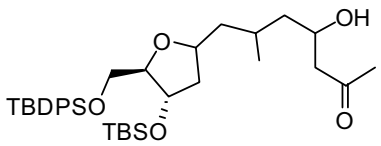
and was washed with sat. NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **14e** (93 mg, 65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90–0.97 (m, 3H); 1.03 (bs, 9H); 1.17–1.29 (m, 1H); 1.36–1.68 (m, 4H); 1.73 and 1.74 (2s, 3H); 1.75–1.88 (m, 1H); 2.08–2.19 (m, 2H); 2.22–2.61 (m, 3H); 3.26–3.37 (m, 6H); 3.74–3.99 (m, 3H); 4.13–4.26 (m, 2H); 4.37–5.46 (m, 1H); 4.46–4.54 (m, 1H); 4.56–4.70 (m, 3H); 4.70–4.79 (m, 2H); 5.13–5.30 (m, 2H); 5.33–5.40 and 5.44–5.50 (2m, 1H); 5.61–5.77 (m, 1H); 7.33–7.45 (m, 6H); 7.62–7.70 (m, 4H).

(2*R*,3*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-5-(4-hydroxy-2,6-dimethylhept-6-en-1-yl) tetrahydrofuran-3-yl (*E*)-3-hydroxyhex-4-enoate (14f).



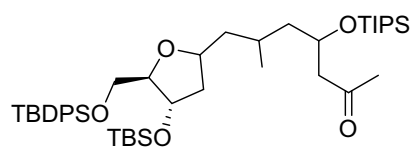
Trifluoroacetic acid (1 mL) was added to a solution of olefin **14e** (103 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) at 0 °C and the solution was stirred for 15 min. The reaction mixture was poured into CH_2Cl_2 and was washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (80:20) yielded **14f** (37 mg, 41%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93–0.99 (m, 3H); 1.03 (bs, 9H); 1.11–1.42 (m, 3H); 1.44–2.00 (m, 11H); 2.01–2.17 (m, 1H); 2.35–2.53 (m, 2H); 3.77–3.88 (m, 3H); 3.87–4.05 (m, 1H); 4.11–4.29 (m, 1H); 4.33–4.45 (m, 1H); 4.74–4.81 (m, 1H); 4.85–4.90 (m, 1H); 5.35–5.53 (m, 2H); 5.61–5.74 (m, 1H); 7.33–7.45 (m, 6H); 7.62–7.68 (m, 4H).

7-[(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydro-furan-2-yl]-4-hydroxy-6-methylheptan-2-one (S12).



Acetone (0.16 mL, 2.2 mmol) was added to a solution of LDA 2M (1.1 mL, 2.2 mmol) in THF (10 mL) at –78 °C. The solution was stirred for 10 min and a solution of aldehyde **8** (1.02 g, 1.8 mmol) in THF (4 mL) was added. The reaction mixture was stirred for additional 30 min at –78 °C and sat. NH_4Cl was added. The solvent was removed under reduced pressure and the residue was dissolved in sat. NH_4Cl and 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 (90:10) yielded **S12** (1.043 g, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02-0.06 (m, 6H); 0.87 and 0.88 (2s, 9H); 0.93–0.99 (m, 3H); 1.05 (s, 9H); 1.12–1.85 (m, 6H); 2.11–2.17 (m, 3H); 2.18–2.28 (m, 1H); 2.44–2.60 (m, 2H); 3.50–3.69 (m, 2H); 3.81–3.87 (m, 1H); 4.10–4.25 (m, 2H); 4.34–4.40 and 4.45–4.51 (2m, 1H); 7.34–7.43 (m, 6H); 7.65–7.72 (m, 4H).

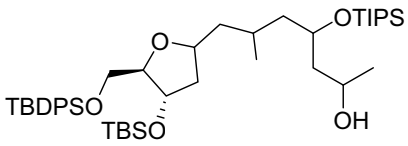
7-[(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5- (*tert*-butyldiphenylsilyloxymethyl)tetrahydro-furan-2-yl]-6-methyl-4-(triisopropylsilyloxy)heptan-2-one (6).



Triisopropylsilyl trifluoromethanesulfonate (1.60 mL, 5.9 mmol) was added to a solution of **S12** (3.05 g, 4.97 mmol), imidazole (1.02 g, 15.0 mmol) and DMAP (20 mg) in DMF (40 mL), and the reaction mixture was stirred at 95 °C for 5 h. Te solvent was removed under reduced pressure and the residue was dissolved in Et_2O and washed with water, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (96:4) yielded **6** (2.56 g, 72%) as a colorless oil. ^{1}H NMR

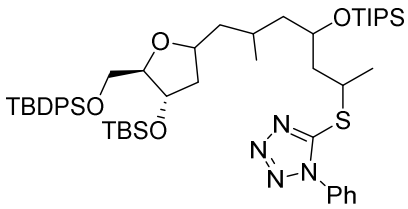
(400 MHz, $CDCl_3$) δ 0.02–0.08 (m, 6H); 0.87, 0.88 and 0.89 (3s, 9H); 0.90–0.97 (m, 3H); 1.04 and 1.05 (2s, 30H); 1.15–1.63 (m, 7H); 2.08–2.18 (m, 3H); 2.51–2.63 (m, 2H); 3.46–3.54 and 3.60–3.69 (2m, 2H); 3.78–3.84 (m, 1H); 4.10–4.23 (m, 1H); 4.33–4.52 (m, 2H); 7.34–7.45 (m, 6H); 7.65–7.71 (m, 4H).

7-[(4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl]-6-methyl-4-(triisopropylsilyloxy)heptan-2-ol (S13).



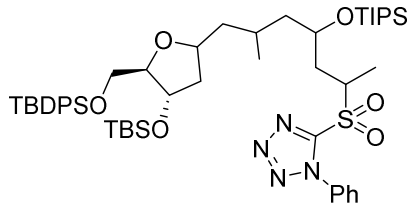
A solution of $NaBH_4$ (74 mg, 1.9 mmol) and ketone **6** (378 mg, 0.49 mmol) in THF-EtOH 2:1 (6 mL) was stirred for 6 h. After this time, sat. NH_4Cl was added and the residue was extracted with CH_2Cl_2 the organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **S13** (372 mg, 98%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03–0.07 (m, 6H); 0.87 and 0.88 (2s, 9H); 0.92–0.98 (m, 3H); 1.01–1.09 (m, 30H); 1.13–1.19 (m, 3H); 1.35–1.85 and 2.17–2.27 (2m, 9H); 3.47–3.56 and 3.60–3.68 (2m, 2H); 3.80–3.86 (m, 1H); 3.94–4.06 and 4.10–4.26 (2m, 3H); 4.36–4.41 and 4.45–4.50 (2m, 1H); 7.34–7.44 (m, 6H); 7.64–7.72 (m, 4H).

5-[7-((4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-ylthio]-1-phenyl-1*H*-tetrazole (S14).



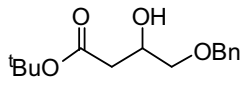
Diisopropyl azodicarboxylate (0.19 mL, 0.96 mmol) was added to a solution of alcohol **S13** (372 mg, 0.48 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (171 mg, 0.96 mmol) and PPh_3 (250 mg, 0.96 mmol) in THF (5 mL). The reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-EtOAc (98:2 to 95:5) to yield **S14** (337 mg, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02–0.07 (m, 6H); 0.85–0.89 (m, 9H); 0.90–0.95 (m, 3H); 0.98–1.07 (m, 30H); 1.32–1.45 (m, 2H); 1.46–1.64 (m, 6H); 1.65–1.75 (m, 1H); 1.78–2.04 and 2.19–2.25 (2m, 3H); 3.45–3.55 and 3.60–3.70 (2m, 2H); 3.75–3.86 (m, 1H); 4.02–4.24 (m, 3H); 4.35–4.41 and 4.44–4.53 (2m, 1H); 7.32–7.44 (m, 6H); 7.50–7.56 (m, 5H); 7.64–7.72 (m, 4H).

5-[7-((4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-ylsulfonyl]-1-phenyl-1*H*-tetrazole (4).



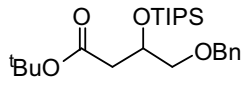
A solution of 70% *m*-CPBA (466 mg, 2.7 mmol) and **S14** (840 mg, 0.9 mmol) in CH_2Cl_2 (10 mL) was stirred for 16 h. The reaction mixture was dissolved with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ and the residue was extracted with CH_2Cl_2, the organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **4** (800 mg, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02–0.07 (m, 6H); 0.85–0.89 (m, 9H); 0.90–0.96 (m, 3H); 1.02–1.08 (m, 30H); 1.22–1.46 (m, 3H); 1.45–1.53 (m, 3H); 1.59–1.42 (m, 4H); 2.08–2.47 (2m, 2H); 3.45–3.55 and 3.61–3.69 (2m, 2H); 3.78–3.86 (m, 1H); 3.95–4.30 (m, 3H); 4.36–4.42 and 4.47–4.53 (2m, 1H); 7.31–7.44 (m, 6H); 7.54–7.72 (m, 9H).

***tert*-Butyl 4-(benzyloxy)-3-hydroxybutanoate (15).**



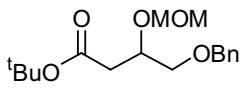
^{t}BuOAc (5.35 mL, 40.0 mmol) was added to a solution of LDA 2M (20.0 mL, 40.0 mmol) in THF (150 mL) at −78 °C. The solution was stirred for 10 min and 2-(benzyloxy)acetaldehyde (2.8 mL, 20 mmol) was added. The reaction mixture was stirred for additional 3 h at −78 °C and was then quenched with sat. NH_4Cl. The solvent was removed under reduced pressure and the residue was dissolved in sat. NH_4Cl and 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 (85:15) yielded **15** (3.86 g, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H); 2.46 (d, *J* = 6.2 Hz, 2H); 3.04 (d, *J* = 4.2 Hz, OH); 3.46 (dd, *J* = 9.1, 5.4 Hz, 1H); 3.50 (dd, *J* = 9.1, 4.2 Hz, 1H); 4.15–4.24 (m, 1H); 4.56 (s, 2H); 7.27–7.39 (m, 5H).

***tert*-Butyl 4-(benzyloxy)-3-(triisopropylsilyloxy)butanoate (S15).**



Triisopropylsilyl trifluoromethanesulfonate (5.0 mL, 18.8 mmol) was added to a solution of aldol **15** (3.90 g, 14.5 mmol), imidazole (2.90 g, 43.5 mmol) and DMAP (50 mg, 0.41 mmol) in DMF (80 mL), and the reaction mixture was stirred at 95 °C for 4 h. The solvent was removed under reduced pressure and the residue was dissolved in Et_2O and washed with water, the organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **S15** (6.11 g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.09 (m, 21H); 1.42 (s, 9H); 2.47 (dd, *J* = 15.2, 5.6 Hz, 1H); 2.58 (dd, *J* = 15.2, 6.3 Hz, 1H); 3.45 (dd, *J* = 9.5, 6.2 Hz, 1H); 3.53 (dd, *J* = 9.5, 5.0 Hz, 1H); 4.36–4.40 (m, 1H); 4.53 (s, 2H); 7.27–7.34 (m, 5H).

***tert*-Butyl 4-(benzyloxy)-3-(methoxymethoxy)butanoate (S16)**

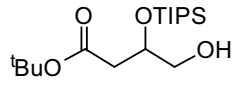


MOMCl (0.15 mL, 2.0 mmol) was added to a solution of aldol **15** (240 mg, 0.9 mmol), DIPEA (0.46 mL, 2.7 mmol) and DMAP (20 mg 0.16 mmol) in THF (10 mL), and the reaction mixture was stirred at reflux temperature for 16 h. The residue was dissolved in Et_2O and washed with sat. NH_4Cl, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **S16** (241 mg, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H); 2.50–2.58 (m, 2H); 3.36 (s, 3H); 3.52 (dd, *J* = 10.0, 5.1 Hz, 1H); 3.58 (dd, *J* = 10.0, 5.1 Hz, 1H); 4.16 (dq, *J* = 7.1, 5.1 Hz, 1H); 4.54–4.56 (m, 2H); 4.71 (d, *J* = 6.8 Hz, 1H); 4.74 (d, *J* = 6.8 Hz, 1H); 7.28–7.37 (m, 5H).

General procedure for hydrogenation:

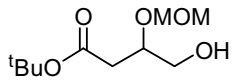
A solution of benzyloxy alcohol **S15-16** and 10% Pd/C (10% w/w) in EtOH was stirred under H_2 atmosphere for 24 h. Argon was then passed, and the reation mixture was filtered through Celite® 545 to yield the corresponding alcohol **16** as a colorless oil.

***tert*-Butyl 4-hydroxy-3-(triisopropylsilyloxy)butanoate (16a).**



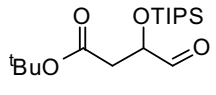
Benzyloxy alcohol **S15** (6.11 g, 14.4 mol) led to alcohol **16a** (4.00 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04–1.10 (m, 21H); 1.44 (s, 9H); 2.08–2.13 (m, OH); 2.50 (dd, *J* = 15.3, 4.5 Hz, 1H); 2.61 (dd, *J* = 15.3, 8.0 Hz, 1H); 3.55–3.70 (m, 2H); 4.24–4.30 (m, 1H).

***tert*-Butyl 4-hydroxy-3-(methoxymethoxy)butanoate (16b).**



Benzyloxy alcohol **S16** (241 mg, 0.77 mmol) led to alcohol **16b** (141 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H); 2.42 (dd, *J* = 15.6, 5.5 Hz, 1H); 2.50 (dd, *J* = 15.6, 7.7 Hz, 1H); 3.42 (s, 3H); 3.52–3.67 (m, 2H); 4.01 (dddd, *J* = 7.7, 6.6, 5.5, 3.1 Hz, 1H); 4.71 (d, *J* = 6.9 Hz, 1H); 4.74 (d, *J* = 6.9 Hz, 1H).

***tert*-Butyl 4-oxo-3-(triisopropylsilyloxy)butanoate (5)**

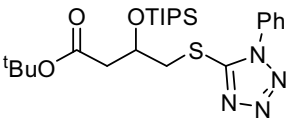


A solution of alcohol **16a** (4.04 g, 12.0 mmol) and DMP (6.61 g, 15.6 mmol) in CH_2Cl_2 (60 mL) was stirred at r.t. for 1 h. The reation mixture was filtered through silica to yield **5** (3.25 g, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04–1.14 (m, 21H); 1.44 (s, 9H); 2.66 (dd, *J* = 15.7, 5.8 Hz, 1H); 2.79 (dd, *J* = 15.7, 4.0 Hz, 1H); 4.32 (dd, *J* = 5.8, 4.0 Hz, 1H); 9.80 (s, 1H).

General procedure for thioester formation:

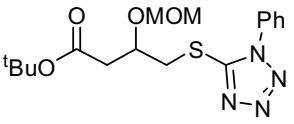
Diisopropyl azodicarboxylate (1.1 eq.) was added to a solution of alcohol **16** (1 eq.), 1-phenyl-1*H*-tetrazole-5-thiol (1.1 eq.) and PPh_3 (1.1 eq.) in THF. The reaction mixture was stirred for 30 min. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-EtOAc (95:5) to yield the corresponding thioester **S17** or **S18** as a colorless oil.

***tert*-Butyl 3-(triisopropylsilyloxy)-4-[(1-phenyl-1*H*-tetrazol-5-yl)thio]butanoate (S17).**



Alcohol **16a** (95 mg, 0.28 mmol) led to thioester **S17** (119 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 and 1.06 (2bs, 21H); 1.44 (s, 9H); 2.61 (d, *J* = 5.8 Hz, 2H); 3.69 (dd, *J* = 13.3, 5.7 Hz, 1H); 3.74 (dd, *J* = 13.3, 4.9 Hz, 1H); 4.61–4.69 (m, 1H); 7.51–7.63 (m, 5H).

***tert*-Butyl 3-(methoxymethoxy)-4-[(1-phenyl-1*H*-tetrazol-5-yl)thio]butanoate (S18).**

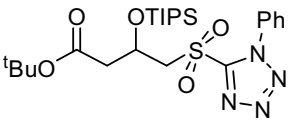


Alcohol **16b** (159 mg, 0.72 mmol) led to thioester **S18** (240 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H); 2.60 (dd, *J* = 15.7, 5.8 Hz, 1H); 2.65 (dd, *J* = 15.7, 6.8 Hz, 1H); 3.36 (s, 3H); 3.70 (dd, *J* = 13.6, 5.6 Hz, 1H); 3.76 (dd, *J* = 13.6, 4.9 Hz, 1H); 4.33–4.40 (m, 1H); 4.69 (d, *J* = 7.0 Hz, 1H); 4.73 (d, *J* = 7.0 Hz, 1H); 7.51–7.61 (m, 5H).

General procedure for thioester oxidation:

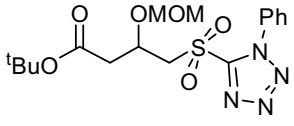
$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1 eq.) was added to a solution of thioester (1 eq.) in H_2O_2-MeOH (1:9). The reaction mixture was stirred for 24 h and was dissolved with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$. The residue was extracted with Et_2O, the organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded the corresponding sulfone **7** as a colorless oil.

***tert*-Butyl 3-(triisopropylsilyloxy)-4-[(1-phenyl-1*H*-tetrazol-5-yl)sulfonyl]butanoate (7a).**



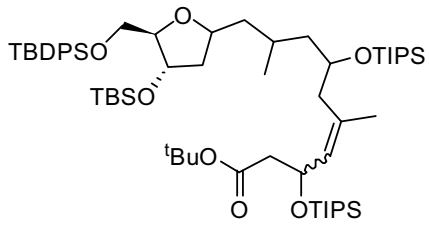
Thioester **S17** (103 mg, 0.21 mmol) led to sulfone **7a** (88 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 and 1.06 (2bs, 21H); 1.43 (s, 9H); 2.66–2.80 (m, 2H); 4.07 (dd, *J* = 14.6, 4.6 Hz, 1H); 4.39 (dd, *J* = 14.6, 6.7 Hz, 1H); 4.83–4.89 (m, 1H); 7.56–7.71 (m, 5H).

***tert*-Butyl 3-(methoxymethoxy)-4-[(1-phenyl-1*H*-tetrazol-5-yl)sulfonyl]butanoate (7b).**



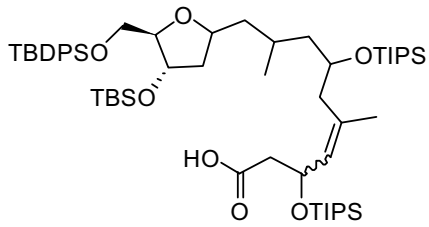
Thioester **S18** (240 mg, 0.63 mmol) led to sufone **7b** (243 mg, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H); 2.67 (dd, *J* = 16.1, 6.4 Hz, 1H); 2.72 (dd, *J* = 16.1, 5.4 Hz, 1H); 3.32 (s, 3H); 4.04 (dd, *J* = 15.1, 4.5 Hz, 1H); 4.10 (dd, *J* = 15.1, 7.2 Hz, 1H); 4.51–4.58 (m, 1H); 4.54 (d, *J* = 7.0 Hz, 1H); 4.64 (d, *J* = 7.0 Hz, 1H); 7.58–7.67 (m, 5H).

***tert*-Butyl 10-[(4S,5R)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoate (17).**



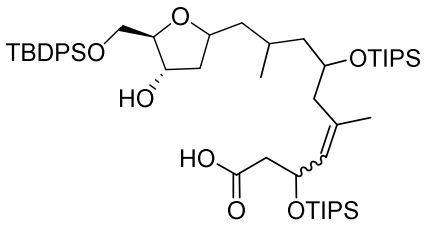
LDA (0.16 mL, 0.33 mmol) was added to a solution of sulfone **4** (110 mg, 0.11 mmol) in THF (3 mL) at –78 °C, and the solution was stirred for 30 min. After this time, a solution of aldehyde **5** (73 mg, 0.22 mmol) in THF (1mL) was added and the solution was stirred for additional 2 h at –78 °C and 15 min at r.t. The reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2, the organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in EtOH (5 mL) and 40% $NaHSO_3$ (1mL), the white solid was removed by filtration and the solvent was concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-Et_2O (95:5) yielded **17** (54 mg, 46%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02–0.08 (m, 6H); 0.84–0.90 (m, 9H); 0.90–0.94 (m, 3H); 0.99–1.08 (m, 51H); 1.19–1.33 (m, 2H); 1.38–1.47 (m, 9H); 1.49–1.60 (m, 3H); 1.60–1.70 (m, 3H); 1.71–2.00 (m, 1H); 2.07–2.54 (m, 5H); 3.35–3.56 and 3.60–3.69 (2m, 2H); 3.77–3.87 (m, 1H); 3.96–4.22 (m, 2H); 4.35–4.42 and 4.45–4.55 (2m, 1H); 4.85–5.00 (m, 1H); 5.20–5.33 (m, 1H); 7.34–7.45 (m, 6H); 7.64–7.72 (m, 4H).

10-[(4S,5R)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydro-furan-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoic acid (S19).



TMSOTf (72 µL, 0.40 mmol) was added to a solution of **17** (110 mg, 0.10 mmol) and Et_3N (112 µL, 0.80 mmol) in CH_2Cl_2 (3 mL) and the reaction was stirred for 15 min. The solution was dissolved in CH_2Cl_2 and was washed with sat. $NaHCO_3$ and sat. NH_4Cl; the organic residue was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded **S19** (88 mg, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02–0.08 (m, 6H); 0.83–0.88 (m, 9H); 0.89–0.94 (m, 3H); 0.99–1.11 (m, 51H); 1.18–1.39 (m, 2H); 1.39–1.92 (m, 7H); 2.07–2.69 (m, 5H); 3.60–3.75 (m, 2H); 3.76–3.94 (m, 1H); 3.96–4.26 (m, 2H); 4.32–4.54 (m, 1H); 4.85–4.95 (m, 1H); 5.23–5.37 (m, 1H); 7.34–7.43 (m, 6H); 7.64–7.72 (m, 4H).

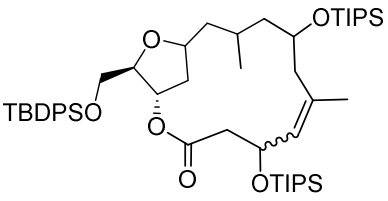
10-[(4S,5R)-5- (*tert*-Butyldiphenylsilyloxymethyl)-4-hydroxytetrahydrofuran-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoic acid (18).



PPTS (980 mg, 3.9 mmol) was added to a solution of **S19** (393 mg, 0.39 mmol) in MeOH (5 mL) and the reaction was stirred for 16 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-EtOAc (90:10 to 80:20) to yield **18** (121 mg, 33%) as a colorless oil. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 0.84–0.96 (m, 3H); 0.99–1.08 (m, 51H); 1.18–1.52 (m, 4H); 1.55–1.77 (m, 5); 1.89–2.22 (m, 2H); 2.28–2.71 (m 3H); 3.45–3.96 (m, 3H); 3.96–4.32 (m, 2H); 4.35–4.45 (m, 1H); 4.82–4.98 (m, 1H); 5.18–5.35 (m, 1H); 7.34–7.45 (m, 6H); 7.64–7.71 (m, 4H). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{92}NO_7Si_3$ ($M+NH_4$) 914.6282, found 914.6267.

(1S,15R)-15-(*tert*-Butyldiphenylsilyloxymethyl)-7,11-dimethyl-5,9-bis(triisopropylsilyloxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (19).



2,4,6-Trichlorobenzoyl chloride was added to a solution of **18** (62 mg, 0.07 mmol) and Et_3N (30 µL, 0.14 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h before being added *via* syringe pump to a stirred solution of DMAP (17 mg, 0.14 mmol) in PhMe (280 mL) over 3 h and the reaction mixture was stirred for further 1 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-EtOAc (95:5) to yield **19** (38 mg, 62%) as a colorless oil. IR (KBr film) ν 2942, 2866, 1740, 1463, 1113, 1063 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.86–0.96 (m, 3H); 0.96–1.08 (m, 51H); 1.13–1.84 (m, 9H); 1.86–2.25 (m, 2H); 2.27–2.70 (m, 3H); 3.53–3.85 (m, 2H); 3.86–4.40 (m, 3H); 4.89–5.05 (m, 1H); 5.17–5.43 (m, 2H); 7.33–7.45 (m, 6H); 7.64–7.74 (m, 4H). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{90}NO_6Si_3$ ($M+NH_4$) 896.6070, found 896.6060.

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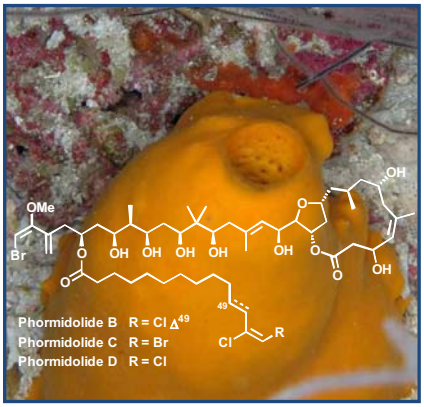
5 Enantioselective synthesis of the macrocyclic core of phormidolides B-D

Thouarella antarctica

PHORMIDOLIDES B-D, NEW CYTOTOXIC AGENTS FROM THE SEA. SYNTHESIS AND STRUCTURE DETERMINATION



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RESUME

The enantioselective total synthesis of the macrocyclic core of phormidolides B-D is described in this chapter. The Julia-Kocienski strategy selected in chapter 4 is adapted to stereoselective procedures and this methodology is used for the synthesis of enantiopure macrocycles (Figure 1).

Enantiopure trisubstituted THF with three stereocenters is achieved by separation of the diastereomers obtained from oxa-Michael cyclization starting from commercially available 2-deoxy-sugars; depending on the targeted stereochemistry the choice of the sugar and the formed diastereomer upon cyclization leads to any of the desired stereochemical possibilities on the C11 and C14 of the macrocycle. Inversion steps can be further applied to fix the C13 stereochemistry opposite to that provided by the sugar.

The introduction of the methyl branch is performed by a 1,4-asymmetric addition of a methyl cuprate to an α,β-insaturated carbonyl condensed with a chiral oxazolindinone, and formation of the C7 stereocenter is obtained by addition of a chiral boron enolate to the corresponding enantiopure aldehyde. The choice of the C3 stereochemistry is available from picking the desired enantiomer from the enzymatic kinetic resolution of racemic *tert*-butyl 3-hydroxypent-4-enoate. Finally, the *Z*-selective formation of the trisubstituted alkene was extremely challenging but conditions were optimized to reach the objective; although is applied on this synthesis, this optimization is explained in detail in the next chapter.

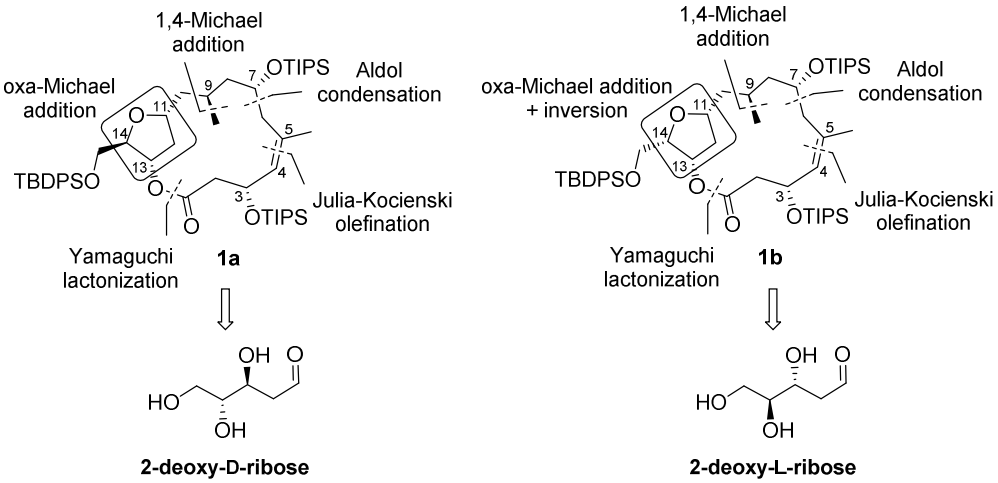

Figure 1. Retrosynthesis of macrolides **1a-b**.

The development of an efficient and selective methodology for the synthesis of the macrocyclic core of phormidolides B-D has achieved the construction of a set of macrocyclic compounds **1a-c** that has been compared with the chemical shifts of the natural compound, leading to a proposal for the relative stereochemistry of the macrocycle. This methodology serves as platform for the synthesis of other macrocycles with other stereochemistry, provided that a well established strategy is available.

Phormidolides B-D, new cytotoxic agents from the sea. Synthesis and structure determination

Adriana Lorente, Alejandro Gil, Rogelio Fernández, Carmen Cuevas, Fernando Albericio and Mercedes Álvarez*

Abstract: New cytotoxic polyketide macrolides named phormidolides B-D were isolated from a marine sponge of the Petrosiidae family collected off the coast of Pemba (Tanzania). The isolation, structure elucidation and enantioselective synthesis of three diastereomers of the macrolide core is described herein. The versatility of the synthetic methodology may provide access to other enantiopure macrocycles by making changes in the starting materials or chiral inductors. Moreover, the synthetic results provide structural information about the possible relative stereochemistry of the macrocycle and a proposal is made towards this direction.

Natural products isolated from marine sources suppose a giant impact on the antitumor drug discovery scenario of the present day.[1] Every year, novel and potent structures are discovered due to the exploration of new unknown environments.[2] During the last years, the isolation of polyketide macrolides with the occurrence of oxygen-containing heterocycles has opened a challenging field on structure determination as well as on chemical synthesis of these potent compounds.[3]

Sponges of the Petrosiidae family are rich in several classes of compounds such as polyacetylenes, sterols, alkaloids and heterocyclic compounds.[2] We isolated three new cytotoxic macrolides named phormidolides B-D, related to oscillariolide[4] (Figure 1) and phormidolide A[5] from an active organic extract of a sponge of the Petrosiidae family collected off the coast of Pemba (Tanzania). The cytotoxic activity of phormodolides B-D was tested against three human tumor cell lines: lung (A-549), colon (HT-29), and breast (MDA-MB-231). All three tumor cell lines exhibited growth inhibition at micromolar concentrations.

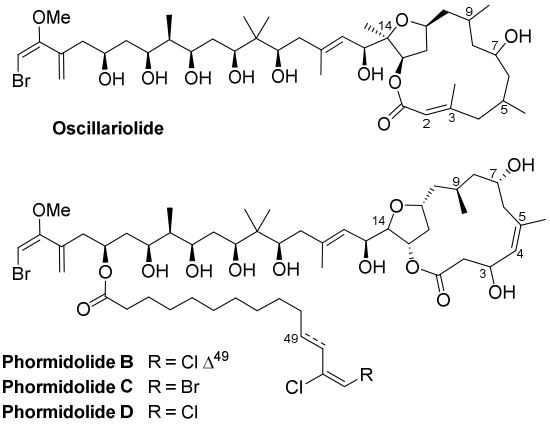

Figure 1. Structures of oscillariolide and phormidolides B-D.

The structures of phormidolides B-D were elucidated by a combination of spectroscopic techniques, including MS, ^{1}H, ^{13}C, and 2D NMR spectroscopy. Phormidolides B-D exhibit a common structure based on a THF-containing macrolide, bonded to a polyhydroxylated chain and a fatty acid linked by an ester bond to the polyol; they only differ in the substitution and insaturations of the fatty acid. Interesting similarities were found between the macrolide core of oscillariolide and the core of phormidolides B-D, both are 14-membered lactones, have methyl groups at positions C5 and C9 and a hydroxyl group at C7. They differ in the position of the insaturation, at C2 or C4, and in the presence of an extra methyl group at the C14 position of oscillariolide. The rarest feature of phormidolides B-D is the terminal haloalkenes present on the fatty acid, and the bromoenol ether present at the end of the polhydroxy chain. Since halogenated compounds are mostly known to be isolated from marine cyanobacteria,[6] and phormidolide A[5] and oscillariolide[4] were indeed isolated from cyanobacteria, it is feasible to think that these natural compounds are of a bacterial origin as well, and that the sponge may not be the producer itself, but a symbiotic organism.

The stereochemistry of the linear polyols was determined by comparison of the chemical shifts and coupling constants with the literature values of phormidolide A.[5] The relative stereochemistry of substituents on the tetrahydrofuran ring was determined by ROESY experiments. Although it was clear that H11 and H13 were in a *cis* arrangement, the relative disposition of H14 was not determined. Relative stereochemistry from C9 and from C7 to C11 stereocenter was determined by *J*-based configuration analysis (see supporting information). The endocyclic double bond was found to have the *Z*-stereochemistry based on ROESY correlations. However the configuration of the C3 hydroxylated methylene was not determined.

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Supporting information for this article is given via a link at the end of the document.

We envisioned the development of a flexible enantioselective methodology that would: synthesize enantiopure macrolactones of plausible stereochemistry; assign the relative stereochemistry at C3 and C14 and establish a route to attain the macrocyclic core for the future total synthesis.

The retrosynthetic analysis of **1a** shows the construction of the endocyclic *Z*-alkene by a Julia-Kocienski olefination while the macrolactonization was depicted as the final step of the synthesis (Figure 2). This strategy requires the synthesis of two main fragments, sulfone **2a** and aldehyde **3**. The choice of the appropriate sulfone is crucial, provided that stereoselective formation of trisubstituted alkenes is extremely complex, and they usually end up acquiring the *E*-configuration, typical for this type of methodology.[7] The formation of the C7 stereocenter was depicted to be formed by an asymmetric aldol condensation, and the introduction of the C9 methyl by an asymmetric Michael addition.

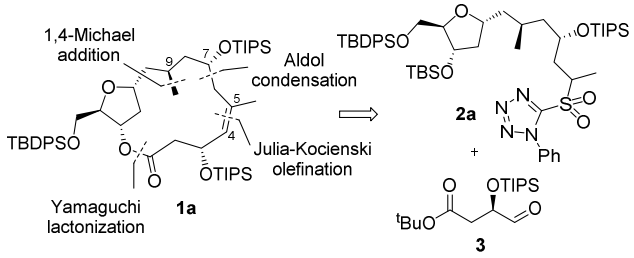
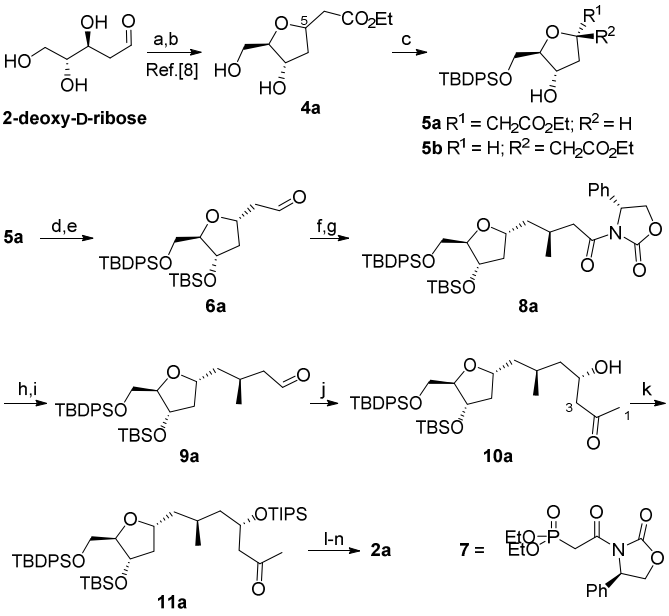


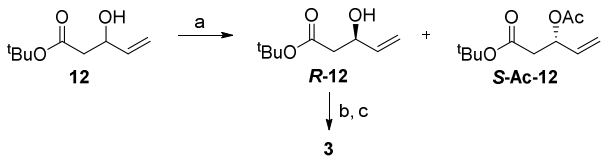
Figure 2. Retrosynthesis of macrocycle 1a.

The formation of the enantiopure THF ring started from 2-deoxy-D-ribose, which constitutes the first source of chirality in this strategy (Scheme 1). Wittig olefination of the sugar and further oxa-Michael cyclization[8] furnished the desired THF **4a** as a C5 diastereomer mixture (60:40).Once the primary hydroxyl group was protected giving **5a** and **5b**, it was possible to isolate each diastereomer independently by means of silica gel column chromatography.[9] Transformation of **5a** into aldehyde **6a** was performed with excellent yield by protection of the secondary alcohol as a TBS ether and reduction with DIBALH. Aldehyde **6a** was elongated with the enantiopure phosphonate **7**[10] and methylated to adduct **8a** in an excellent diastereomeric ratio (d.r. 97:3) under Williams conditions.[11] Aldehyde **9a** was obtained after removal of the chiral auxiliary group and oxidation of the resulting alcohol. This aldehyde was then subjected to asymmetric aldol addition of the chiral boron enolate of acetone to obtain aldol **10a** (d.r. 88:12). The configuration of the new stereocenter was determined by formation of the Mosher ester and ^{1}H-NMR analysis (see supporting information).[12,13] Aldol adduct **10a** was protected as the triisopropylsilyl ether **11a** and then converted to sulfone **2a** by reduction of the carbonyl, followed by Mitsunobu reaction with1-phenyl-1*H*-tetrazolyl-5-thiol[14] and subsequent oxidation.



Scheme 1. Synthesis of sulfone **2a**. Reagents and conditions: a) $Ph_3P{=}CHCO_2Et$, THF, 66 ºC, 6 h, 94%; b) NaEtO, EtOH, RT, 24 h, 80%; c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, RT, 48 h, **5a** 45%, **5b** 28%; d) TBSCl, imidazole, DMAP, CH_2Cl_2, RT, 3 h, 90%; e) DIBALH, CH_2Cl_2, –78 ºC, 15 min, 94%; f) **7**, NaHMDS, THF, RT, 2 h, 78%; g) MeMgBr, CuBr·DMS, $BF_3{\cdot}Et_2O$, THF, –78 ºC to RT, 4 h, 84%; h) $LiBH_4$, Et_2O, 0 ºC, 1 h, 79%; i) DMP, CH_2Cl_2, RT, 1 h, 92%; j) acetone, (–)-DIPCl, Et_3N, Et_2O, –78 ºC to –20 ºC, 16 h, then H_2O_2, MeOH, RT, 1h, 67%; k) TIPSOTf, imidazole, DMAP, DMF, 90 ºC, 16 h, 93%; l) $NaBH_4$, THF, EtOH, RT, 1 h, 89%; m) 1-phenyl-1*H*-tetrazolyl-5-thiol, DIAD, PPh_3, THF, RT, 6 h, 71%; n) *m*-CPBA, CH_2Cl_2, RT, 16 h, 89%. *m*-CPBA = 3-chloroperoxybenzoic acid; DIAD = diisopropylazodicarboxylate; DIBALH = diisobutylaluminium hydride; (–)-DIP = (–)-diisopinocampheylborane; DMAP = 4-(dimethylamino)pyridine; DMP = Dess-Martin periodinane; DMS = dimethylsulfide; HMDS = bis(trimethylsilyl)amide; TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonate; TIPS = triisopropylsilyl.

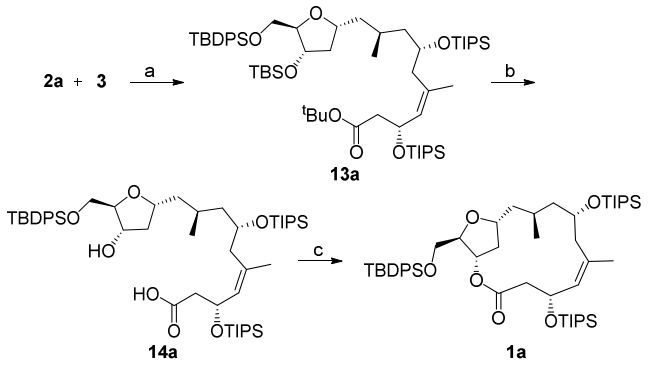
Enantioselective synthesis of aldehyde **3** was performed by kinetic resolution of racemic β-hydroxy ester **12** with lipase PS-30, which produces ***R*-12** and ***S*-Ac-12** with excellent enantiopurity (Scheme 2).[15] Protection of alcohol ***R*-12** as a TIPS ether, followed by reductive ozonolysis, led to aldehyde **3**.



Scheme 2. Synthesis of aldehyde **3**. Reagents and conditions: a) Lipase PS-30, vinyl acetate, pentane, 37 ºC, 48 h, ***R*-12** 49%, ***S*-Ac-12** 48%;b) TIPSOTf, imidazole, DMAP, THF, 66 ºC, 16 h, 89%; c) O_3, MeOH, CH_2Cl_2, –78 ºC, 30 min, then PPh_3, RT, 16 h, 93%.

Treatment of **2a** with LDA as base in the presence of HMPA, before the addition of aldehyde **3**, gave **13a** with moderate diastereoselectivity (d.r. 70:30). The major *Z*-diastereomer was isolated in a 38% yield (Scheme 3).[16] Removal of the protecting groups required extremely mild

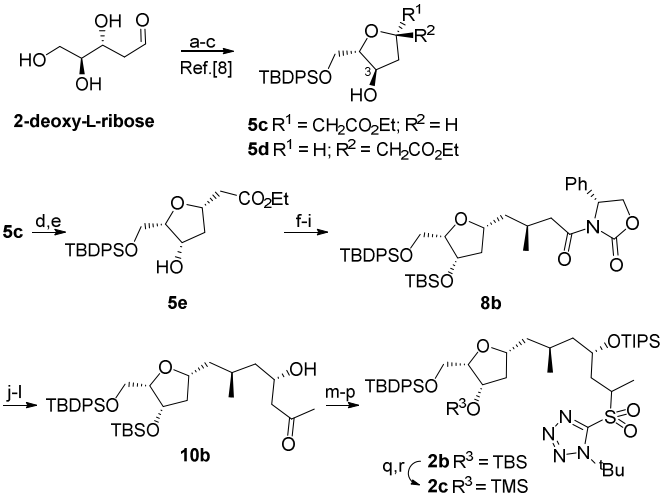
conditions to avoid partial decomposition of the starting material. Thus, TMSOTf and Et_3N in CH_2Cl_2, and PPTS in MeOH were used to deprotect the acid and the alcohol, respectively, giving the desired *seco*-acid **14a** in good yield. Yamaguchi conditions were used to perform macrolactonization in high dilution to avoid formation of the dimer. Nevertheless, cyclization of **14a** provided the desired macrocycle **1a** and its dimer in a 2:1 ratio respectively. Purification enabled isolation of the sole monomer.



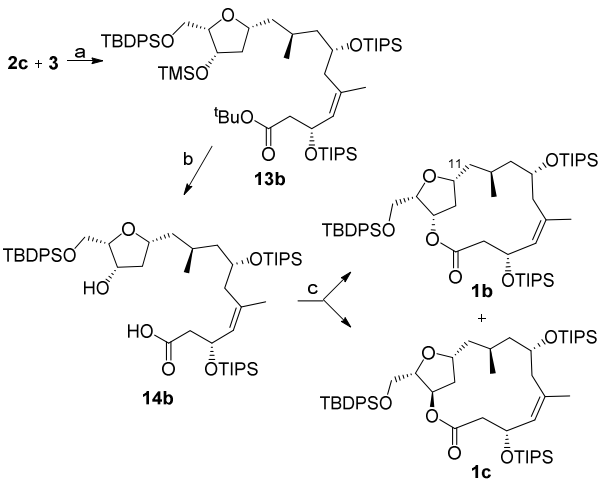
Scheme 3. Total synthesis of **1a**. Reagents and conditions: a) LDA, HMPA, 4Å MS, THF, RT, 1 min, then **3**, RT, 2 h, 38%; b) TMSOTf, Et_3N, CH_2Cl_2, RT, 15 min, then PPTS, MeOH, RT, 30 min, 68%; c) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, RT, 16 h, 39%. HMPA = hexamethylphosphoramide; LDA = lithium diisopropylamide; PPTS = pyridinium *p*-toluenesulfonate; TMS = trimethylsilyl.

The synthesis of an all *cis*-substituted THF lactone **1b** (Scheme 5) was the next target in order to get another possible macrocycle and to prove the versatility of our methodology. For this purpose, sulfone **2c** was obtained in an analogous manner to sulfone **2a** using slight strategy modifications (Scheme 4). Starting from 2-deoxy-L-ribose, **5c** and **5d** were obtained. Two-step configuration inversion at C3 on **5c** was required prior to protection as TBS ether. Inversion was performed by an oxidation-reduction procedure that furnished the all *cis*-trisubstituted THF derivative **5e** with good stereocontrol (d.r. 93:7).[9] Introduction of the methyl branch to obtain **8b,** followed by its transformation into alcohol **10b** gave good yields and diastereoselectivites (d.r. 97:3 and 85:15 respectively).[12,13] At this point, the 1-(*tert*-butyl)tetrazolylsulfone[17] was tested for the Julia-Kocienski olefination to improve the stereoselectivity of the process, provided that sulfone **2a** showed only moderate *Z*-selectivity. Thus, 1-(*tert*-butyl)-1*H*-tetrazolyl-5-thiol[18] was used instead of 1-phenyl-1*H*-tetrazolyl-5-thiol in the reaction sequence that led to **2b**. Deprotection assays of the TBS ether for lactone formation in further steps showed that this was not a suitable protecting group for the all *cis*-THF adducts, as it was too stable in acidic conditions compared to the instability of the starting material. Thus, a deprotection-protection sequence completed the preparation of the appropriate sulfone as that of **2c**.

The formation of the trisubstituted double bond with the 1-(*tert*-butyl)tetrazolyl sulfone proved to be highly selective, affording **13b** with moderate yield (42%) but excellent diastereoselectivity (d.r. 97:3) (Scheme 5).[16] The same deprotection sequence as before led to *seco*-acid **14b**. Surprisingly, macrocyclization produced two monomers: the desired macrocycle **1b** and its C13 epimer **1c,** in a 4:1 ratio respectively. Both monomers were isolated independently.[19]



Scheme 4. Synthesis of sulfone **2c**. Reagents and conditions: a) PPh_3CHCO_2Et, THF, 66 ºC, 6 h, 92%; b) NaEtO, EtOH, RT, 24 h, 89%; c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, RT, 48 h, **5c** 28%, **5d** 48%; d) DMP, CH_2Cl_2, RT, 2 h, 90%; e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, –20 ºC, 40 min, 86%; f) TBSCl, imidazole, DMAP, CH_2Cl_2, RT, 48 h, 94%; g) DIBALH, CH_2Cl_2, –78 ºC, 15 min, 99%; h) **7**, NaHMDS, THF, RT, 2 h, 95%; i) MeMgBr, CuBr·DMS, $BF_3{\cdot}Et_2O$, THF, –78 ºC to RT, 4 h, 81%;j) $LiBH_4$, Et_2O, 0 ºC, 1 h, 84%; k) DMP, CH_2Cl_2, RT, 1 h, 92%; l) acetone, (–)-DIPCl, Et_3N, Et_2O, –78 ºC to –20 ºC, 16 h, then H_2O_2, MeOH, RT, 1h, 80%; m) TIPSOTf, imidazole, DMAP, DMF, 90 ºC, 16 h, 77%; n) $NaBH_4$, THF, EtOH, RT, 1 h, 92%; o) 1-(*tert*-butyl)-1*H*-tetrazolyl-5-thiol, DIAD, PPh_3, THF, RT, 6 h, 92%; p) *m*-CPBA, CH_2Cl_2, RT, 16 h, 80%; q) PPTS, MeOH, 65 ºC, 5 h, 95%; r) TBDPSCl, imidazole, CH_2Cl_2, RT, 1h, then TMSCl, RT, 15 min, 73%.

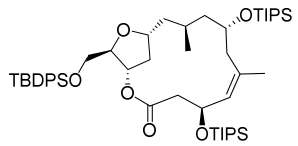


Scheme 5. Total synthesis of **1b** and **1c**. Reagents and conditions: a) LDA, HMPA, 4Å MS, THF, RT, 1 min, then **3**, RT, 2 h, 42%; b) TMSOTf, Et_3N, CH_2Cl_2, RT, 15 min, then PPTS, MeOH, RT, 30 min, 58%; c) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, RT, 16 h, **1b** 29%,**1c** 6%.

Formation of macrolactone **1c** under Yamaguchi conditions may be explained by competitive reaction of free alcohol with 2,4,6-trichlorobenzoyl chloride followed by intramolecular nucleophilic substitution of the resulting benzoate by the carboxylate with inversion of configuration.

With the three synthetic macrolides, enough data were obtained to understand that changes on the stereochemistry of a

single stereocenter produce tremendous differences on the chemical shifts of the macrocycle (see supporting information). Nevertheless, the most diverse set of chemical shifts of the synthetic macrocycles to convert to phormidolides was observed in the C2-C6 region for ^{1}H-NMR and ^{13}C-NMR, suggesting that the C3 stereocenter has a configuration that on the natural product is the opposite of that synthesized on the three macrocycles. On the other hand, regarding the THF region, the compound that is most similar to the phormidolides B-D macrocyclic core appears to be that of **1a.** Therefore, our proposal for the relative stereochemistry of the macrocyclic core of phormidolides B-D is that of **1d**. This proposal must be confirmed by synthesis, which will be considered in due course.



1d

Figure 3. Proposed relative stereochemistry for the macrocyclic core of phormidolides B-D (**1d**).

In conclusion, three new cytotoxic marine polyketide macrolides named phormidolides B-D have been isolated and characterized. Structural determination has been achieved by spectroscopic techniques but the stereochemical assignment needs to be completed. A robust methodology for the enantioselective synthesis of the macrolide core of phormidolides B-D has been achieved. The enantioselective synthesis of macrolactones **1a**, **1b** and **1c**, starting from 2-deoxy-D-ribose or 2-deoxy-L-ribose, has been afforded with good total yield and high enantiomeric purity. The key step of the synthesis is the formation of the *Z*-trisubstituted double bond using a Julia-Kocienski olefination. Our synthetic strategy can be used for the preparation of the different diastereomers of the macrolactone, making the appropriate changes in the starting materials and chiral inductors. The synthetic macrolides have been compared with the natural compound and a proposal for the relative stereochemistry of phormidolides B-D has been performed.

Acknowledgements

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Keywords: marine natural products • enantioselective synthesis • polyketides • anticancer agent

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[16] Determination of the configuration of the alkene was performed by 1D-NOE experiments. Irradiation over the vinyl proton at 5.30 and 5.29 ppm of **13a** and **13b**, respectively, produced a clear nOe on the vinylic CH_3 singlet signal at 1.67 and 1.66 ppm, respectively (see supporting information).

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[19] Confirmation of the obtained C9 sterochemistry during the synthesis was possible because a clear nOe could be observed between the methyl branch at C9 and the proton at C11 for macrocycles **1b** and **1c**. As the stereochemistry at C7, C11, and C13 is fixed in our system and is the same relative stereochemsitry as that of the natural macrocycle, the observation of this nOe signal, also observed in the natural compound, confirms the stereochemistry of the C9 stereocenter.

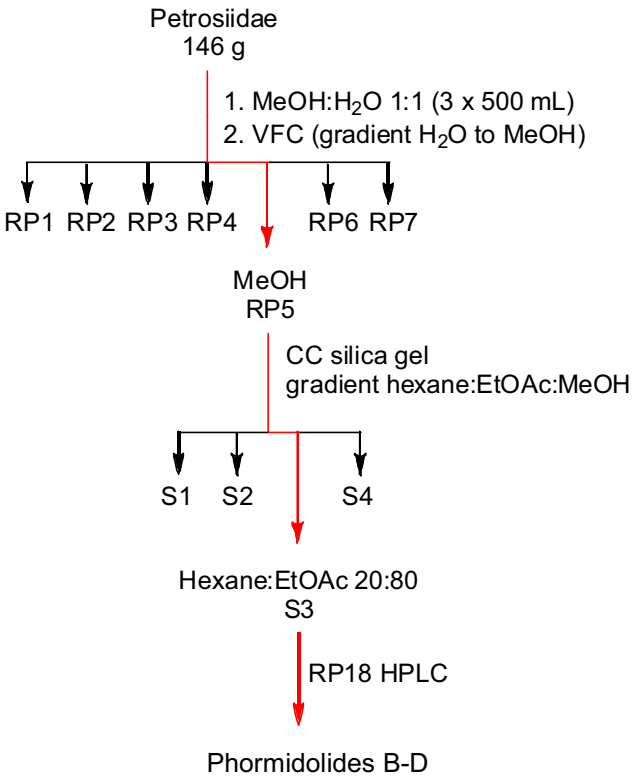
Supporting Information

TABLE OF CONTENTS

1. 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 SDS 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 Thermo Nicolet FT-IR Nexus spectrometer. For the isolation ^{1}H-NMR and ^{13}C-NMR were recorded on a Varian Unity 300MHz or a Varian Unity 500MHz; for the synthesis 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.

2. Isolation of Phormidolides B-D



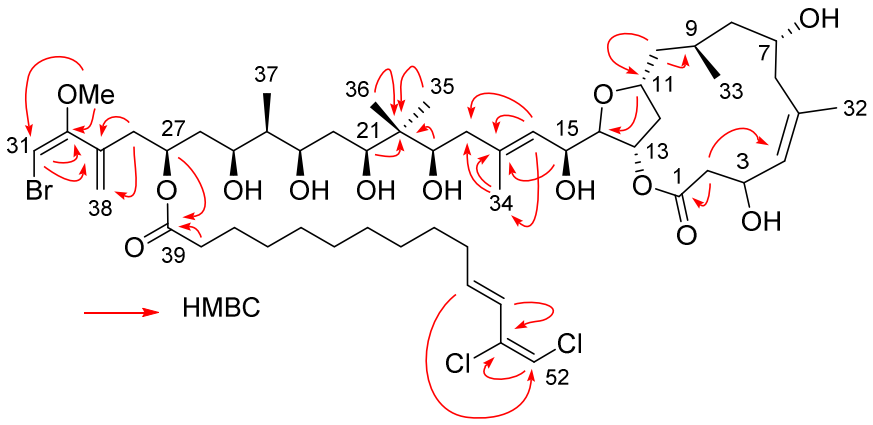
Scheme 1. Isolation of phormidolides B-D.

The frozen sponge (146 g, ORMA 41004) was triturated and extracted with a mixture of MeOH-CH_2Cl_2 (50:50, 3 × 500 mL) at 23 ºC (Scheme 1). The organic extract was evaporated under reduced pressure to yield a crude of 6.7 g. This material was chromatographed (VLC) on Lichroprep RP-18 with a stepped gradient from H_2O to MeOH and then to CH_2Cl_2. The fraction eluted with MeOH (340 mg) was subjected to flash Silica gel CC eluting with a gradient of hexane:EtOAc:MeOH to yield 4 fractions (S1 to S4). Fraction S3 (hexane:EtOAc 20:80) was subjected to semipreparative reversed phase HPLC (SunFire, 10 ×150 mm, 100% of CH_3CN in 30 min, UV detection, flow 3.8 mL/min) to yield phormidolide B (34.7 mg) and phormidolide C (8.3 mg) and a mixture of compounds (6.8 mg). This mixture was further purified by semipreparative HPLC (SunFire, 10 ×150 mm, gradient H_2O:MeOH from 90 to 100% of MeOH in 30 min, UV detection, flow 3.8 mL/min) to yield phormidolide D (1.5 mg).

Table 1. GI_{50} values for Phormidolides B-D.

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

3. NMR data table of phormidolides B-D. Spectra recorded in $CDCl_3$ (500MHz)



	Phormidolide B		Phormidolide C		Phormidolide D
	δ_H, mult, J (Hz)	δ_C, mult	δ_H, mult, J (Hz)	δ_C, mult	δ_H, mult, J (Hz)
1	-	171.1, s	-	171.1, s	-
2	2.72, dd, 13.5, 11.9 2.34, dd 13.5, 3.0	39.5, t	2.73, dd, 13.5, 12.2 2.36, dd, 13.5, 3.0	39.5, t	2.73, dd, 13.3, 12.8 2.36, dd, 13.3, 2.9
3	4.74, brd, 11.8	71.9, d	4.75, brd, 12.2	71.9, d	4.76, brd, 12.8
4	5.36, brs	121.6, d	5.37, brs	121.5, d	5.38, brs
5	-	133.1, s	-	133.2, s	-
6	1.91, dd, 16.8, 10.9 1.76, dd, 16.8, 2.5	36.4, t	1.90, brd, 16.1, 11.2 1.78, dd, 16.1, 2.9	36.4, t	1.93, dd, 16.2, 10.4 1.78, m
7	3.86, m	63.3, d	3.85, m	63.3, d	3.87, m
8	1.45, ddd, 13.2, 13.2, 3.6 1.30, ddd, 13.2, 13.2, 3.5	43.2, t	1.46, dd, 13.5, 13.5 1.31, dd, 13.5, 13.5	43.2, t	1.46, m 1.31, m
9	1.71, m	24.9, d	1.72, m	24.9, d	1.74, m
10	1.94, dd, 12.4, 12.4 1.15, ddd, 12.4, 12.4, 4.9	39.6, t	1.95, dd, 12.4, 12.4 1.17, ddd, 12.4, 12.4, 4.9	39.6, t	1.95, dd, 12.3, 12.3 1.18, ddd, 12.3, 12.3, 4.9
11	4.34, ddd, 12.4, 8.4, 4.9	77.6, d	4.36, ddd, 12.4, 8.3, 4.9	77.6, d	4.36, ddd, 12.8, 8.4, 4.9
12	2.41, d, 14.4 2.09, ddd 13.4, 8.0, 4.0	34.3, t	2.43, d, 14.4 2.11, ddd 13.7, 7.8, 3.9	34.3, t	2.44, d, 14.7 2.10, m
13	5.22, dd, 3.4, 3.4	75.2, d	5.24, dd, 3.9, 3.9	75.3, d	5.25, dd, 3.0, 3.0
14	3.81,dd, 8.6, 3.4	83.9, d	3.84, dd, 8.3, 3.4	83.8, d	3.84, m
15	4.59, dd, 8.6, 8.6	66.6, d	4.64, dd, 8.3, 8.3	66.8, d	4.68, dd, 7.8, 7.8
16	5.36, d, 8.6	129.0, d	5.37, d, 8.3	128.9, d	5.38, m
17	-	137.6, s	-	137.8, s	-

18	2.30, brd, 13.4 2.05, dd, 13.4, 11.4	42.0, t	2.32, d, 13.2 2.06, dd, 13.2, 10.8	41.9, t	2.35, d, 13.5 2.06, dd, 13.5, 11.8
19	3.67, 10.9, 2.0	77.3, d	3.68, brd, 10.8	77.2, d	3.67, d, 9.9
20	-	40.3, s	-	40.4, s	-
21	3.83, brd, 10.9	81.6, d	3.83, d, 10.7	81.6, d	3.83, m
22	1.63, m 1.44, m	35.1, t	1.62, m 1.43, m	35.1, t	1.62, m 1.44, m
23	4.06, brd, 10.4	77.8, d	4.07, brd, 9.8	77.8, d	4.06, d, 9.8
24	1.47, m	41.5, d	1.44, m	41.5, d	1.45, m
25	3.95, ddd, 6.5, 6.5, 1.0	74.0, d	3.97, dd, 8.5, 8.5	74.0, d	3.98, dd, 7.5, 7.5
26	1.80, m 1.74, m	39.3, t	1.80, m 1.74, m	39.4, t	1.83, m 1.65, m
27	4.95, dddd, 6.8, 6.8, 6.8, 6.8	70.6, d	4.96, dddd, 6.8, 6.8, 6.8, 6.8	70.6, t	5.03, m
28	2.57, dd, 14.4, 6.8 2.53, dd, 14.4, 6.8	39.3, t	2.58, dd, 14.2, 7.3 2.53, dd, 14.2, 5.9	39.4, t	2.78, dd, 14.2, 3.9 2.44, dd, 14.2, 8.7
29	-	138.2, s	-	138.2, s	-
30	-	158.3, s	-	158.3, s	-
31	5.33, s	78.9, d	5.33, s	78.6, d	4.27, d, 12.3 4.18, d, 12.3
32	1.69, s	23.0, q	1.70, s	23.0, q	1.70, s
33	0.83, d, 6.4	20.6, q	0.84, d, 6.9	20.6, q	0.85, d, 6.4
34	1.77, s	17.0, q	1.79, s	17.2, q	1.80, s
35	0.73, s	21.7, q	0.74, s	21.6, q	
36	0.88, s	13.8, q	0.90, s	13.8, q	0.91, s
37	0.91, d, 7.0	5.0, q	0.93, d, 7.5	4.9, q	0.94, d, 6.9
38	5.41, d, 1.0 5.36, d, 1.0	122.1, d	5.42, d, 0.9 5.37, d, 0.9	122.2, t	6.09, s 5.94, s
39	-	173.7, s	-	173.8, s	
40	2.27, t, 7.0	34.6, t	2.27, dd, 7.8, 7.3	34.6, t	2.24, ddd, 7.4, 7.4, 2.9
41	1.58, m	24.8, t	1.58, m	24.9, t	1.56, m
42	1.27, m	28.5, t	1.27, m	28.6, t	1.27, m
43-47	1.27, m	29.1- 29.0, t	1.27, m	29.4- 28.4, t	1.27, m
48	2.14, ddd, 6.7, 6.7, 6.7	33.0, t	1.39, m	28.4, t	1.39, m
49	6.01, ddd, 15.4, 6.7, 6.7	140.4, d	1.62, m	29.5, t	1.60, m

50	6.06, d, 15.4	116.7, d	2.91, dd, 7.8, 6.8	33.3, t	2.90, t, 7.4
51	-	129.7, s	-	131.3, s	-
52	6.36, s	116.5, d	6.53, s	105.7, d	6.43, s
OMe	3.58, s	55.6, q	3.59, s	55.6, q	3.58, s

4. *J*-based configuration analysis

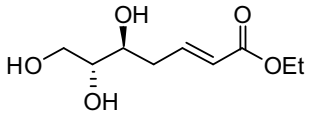
Please refer to the introduction chapter section: phormidolides B-D; structure determination (Page 11).

5. Experimental procedures and characterization

General procedure for the preparation of triol S1: [2]

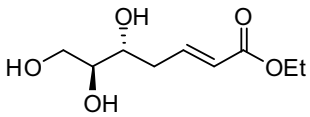
Ethyl (triphenylphosphoranylidene)acetate (1.1 eq.) was added to a solution of sugar (1 eq.) in THF. The solution was stirred at reflux temperature for 5 h and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with CH_2Cl_2-MeOH (95:5 to 90:10) yielded the corresponding triol **S1** as a colorless oil.

Ethyl (5*S*,6*R*,*E*)-5,6,7-trihydroxyhept-2-enoate (S1a).



2-Deoxy-D-ribose (3.40 g, 25.5 mmol) led to triol **S1a** (4.9 g, 94%). IR (KBr film) ν 3380, 2981, 2936, 1701, 1654, 1370, 1270, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H); 2.33–2.52 (m, 2H); 3.55–3.61 (m, 1H); 3.66–3.72 (m, 2H); 3.74–3.82 (m, 1H); 3.93–4.13 (m, 3H, OH); 4.15 (q, *J* = 7.1, 2H); 5.91 (d, *J* = 15.7, 1H); 6.98 (dt, *J* = 15.7, 7.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (q); 35.8 (t); 60.5 (t); 63.1 (t); 71.5 (d); 74.0 (d); 123.6 (d); 145.8 (d); 166.9 (s). HRMS (+ESI): *m/z* calcd. for $C_9H_{17}O_5$ (M+H) 205.1076, found 205.1068.

Ethyl (5*R*,6*S*,*E*)-5,6,7-trihydroxyhept-2-enoate (S1b).

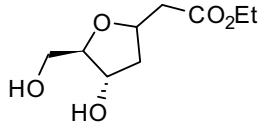


2-Deoxy-L-ribose (627 mg, 4.7 mmol) led to triol **1b** (875 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H); 2.33–2.52 (m, 2H); 3.55–3.61 (m, 1H); 3.66–3.72 (m, 2H); 3.74–3.82 (m, 1H); 3.93–4.13(m, 3H, OH); 4.15 (q, *J* = 7.1, 2H); 5.91 (d, *J* = 15.7, 1H); 6.98 (dt, *J* = 15.7, 7.5 Hz, 1H).

General procedure for the preparation of the tetrahydrofuran ring: [2]

NaEtO (0.1 eq.) was added to a solution of **S1** (1 eq.) in EtOH. The reaction mixture was stirred at r.t. for 24 h. The solvent was removed under reduced pressure and the residue was filtered through a pad of silica with CH_2Cl_2-MeOH (90:10) to yield the corresponding tetrahydrofuran **4** as a mixture of diastereomers A:B (60:40).

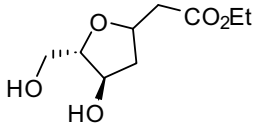
Ethyl 2-[(2*RS*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]acetate (4a).



Triol **S1a** (13.50 g, 64.4 mmol) led to tetrahydrofuran **4a** (10.56 g, 80%) as a mixture of diastereomers A:B (60:40). IR (KBr film) ν 3409, 2981, 2935, 1731, 1370, 1303, 1197 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)

δ 1.26 (t, J = 7.1 Hz, $3H_{A+B}$); 1.80 and 1.92 (ddd, J = 13.1, 6.5, 5.4 Hz and ddd, J = 13.1, 9.4, 6.4 Hz, $1H_{A+B}$); 2.04 and 2.44 (ddd, J = 13.1, 5.8, 2.6 Hz and dt, J = 13.1, 7.1 Hz, $1H_{B+A}$); 2.59–2.66 and 2.71–2.78 (2m, $2H_{A+B}$); 3.58–3.57 (m, $2H_{A+B}$); 3.85–3.96 (m, $1H_{A+B}$); 4.16 (q, J = 7.1 Hz, $2H_{A+B}$); 4.31–4.40 (m, $1H_{A+B}$); 4.45–4.57 (m, $1H_{A+B}$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (q_A+q_B); 39.9 (t_B); 40.0 (t_A); 40.6(t_B); 40.8 (t_A); 60.7 (t_A); 60.8 (t_B); 62.3 (t_A); 62.9 (t_B); 72.6 (d_A); 73.1 (d_B); 74.4 (d_A); 74.5(d_B); 85.4 (d_A); 87.1 (d_B); 171.3 (s_B); 171.6 (s_A). HRMS (+ESI): *m/z* calcd. for $C_9H_{17}O_5$ (M+H) 205.1076, found 205.1065.

Ethyl 2-[(2*RS*,4*R*,5*S*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]acetate (4b).

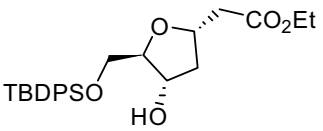


Triol **S1b** (280 mg, 2.8 mmol) led to tetrahydrofuran **4b** (517 mg, 89%) as a mixture of diastereomers A:B (60:40). IR (KBr film) ν 3340 (bs), 2980, 2935, 1730, 1304, 1094 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, $3H_{A+B}$); 1.80 and 1.92 (ddd, J = 13.1, 6.5, 5.4 Hz and ddd, J = 13.1, 9.4, 6.4 Hz, $1H_{A+B}$); 2.04 and 2.44 (ddd, J = 13.1, 5.8, 2.6 Hz and dt, J = 13.1, 7.1 Hz, $1H_{B+A}$); 2.59–2.66 and 2.71–2.78 (2m, $2H_{A+B}$); 3.58–3.67 (m, $2H_{A+B}$); 3.85–3.96 (m, $1H_{A+B}$); 4.16 (q, J = 7.1 Hz, $2H_{A+B}$); 4.31–4.40 (m, $1H_{A+B}$); 4.45–4.57 (m, $1H_{A+B}$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (q_A+q_B); 40.0 (t_B); 40.2 (t_A); 40.7 (t_B); 40.9 (t_A); 60.8 (t_A+t_B); 62.4 (t_A); 63.0 (t_B); 72.7 (d_A); 73.2 (d_B); 74.5 (d_A); 74.6 (d_B); 85.5 (d_A); 87.2 (d_B); 171.4 (s_B); 171.7 (s_A). HRMS (+ESI): *m/z* calcd. for $C_9H_{17}O_5$ (M+H) 205.1076, found 205.1065.

General procedure for TBDPS protection:

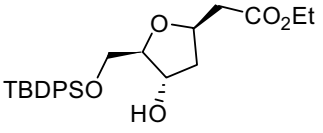
TBDPSCl (0.95 eq) was added to a solution of diol **4a** or **4b** (1 eq.), Et_3N (2 eq.) and DMAP (0.1 eq.) in CH_2Cl_2. The reaction mixture was stirred at r.t. for 48 h. After this time, the reaction mixture was washed with 1M aqueous HCl, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-CH_2Cl_2-Et_2O (50:30:20) yielded **5a** (45%) and **5b** (28%) or **5c** (28%) and **5d** (48%) respectively as colorless oils.

Ethyl 2-[(2*S*,4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxymethyl)-4-hydroxytetrahydrofuran-2-yl] acetate (5a).



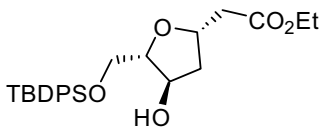
$[\alpha]_D$ = +14.0 (c 1.0, $CHCl_3$). IR (KBr film) ν 3450, 2931, 2857, 1735, 1427, 1112, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H); 1.25 (t, J = 7.1 Hz, 3H); 1.79 (ddd, J = 13.2, 6.3, 4.6 Hz, 1H); 2.47 (dt, J = 13.2, 7.2 Hz, 1H); 2.63 (dd, J = 15.7, 6.0 Hz, 1H); 2.72 (dd, J = 15.7, 6.4 Hz, 1H); 3.62 (dd, J = 10.6, 6.0 Hz, 1H); 3.75 (dd, J = 10.6, 3.9 Hz, 1H); 3.98 (dt, J = 6.0, 3.9 Hz, 1H); 4.15 (q, J = 7.1 Hz, 2H); 4.42–4.53 (m, 2H); 7.35–7.45 (m, 6H); 7.63–7.69 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (q); 19.2 (s); 26.8 (q); 39.9 (t); 40.9 (t); 60.5 (t); 64.8 (t); 74.5 (d); 75.0 (d); 85.7 (d); 127.7 (d); 129.8 (d); 133.1 (s); 135.5 (d); 171.4 (s). HRMS (+ESI): *m/z* calcd. for $C_{25}H_{34}O_5NaSi$ (M+Na) 465.2073, found 465.2083.

Ethyl 2-[(2*R*,4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxymethyl)-4-hydroxytetrahydrofuran-2-yl] acetate (5b).



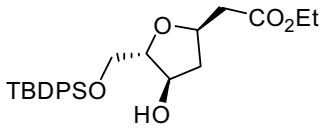
$[\alpha]_D$ = +12.1 (c 1.0, $CHCl_3$). IR (KBr film) ν 3450, 2931, 2857, 1735, 1427, 1112, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H); 1.25 (t, J = 7.1 Hz, 3H); 1.84 (ddd, J = 13.1, 9.6, 6.2 Hz, 1H); 2.06 (ddd, J = 13.1, 5.7, 2.3 Hz, 1H); 2.48 (dd, J = 15.4, 6.0 Hz, 1H); 2.64 (dd, J = 15.4, 7.1 Hz, 1H); 3.58 (dd, J = 10.6, 6.0 Hz, 1H); 3.76 (dd, J = 10.6, 3.9 Hz, 1H); 3.86–3.90 (m, 1H); 4.14 (q, J = 7.1 Hz, 2H); 4.43-4.48 (m, 1H); 4.51–4.60 (m, 1H); 7.35–7.45 (m, 6H); 7.63–7.69 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (q); 19.2 (s); 26.8 (q); 40.5 (t); 40.6 (t); 60.5 (t); 64.6 (t); 74.3 (d); 74.6 (d); 86.9 (d); 127.7 (d); 129.7 (d); 133.1 (s); 135.5 (d); 171.0 (s). HRMS (+ESI): *m/z* calcd. for $C_{25}H_{34}O_5NaSi$ (M+Na) 465.2073, found 465.2083.

Ethyl 2-[(2*S*,4*R*,5*S*)-5-(*tert*-butyldiphenylsilyloxymethyl)-4-hydroxytetrahydrofuran-2-yl] acetate (5c).



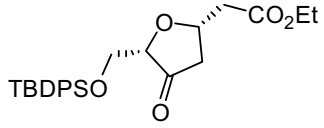
$[\alpha]_D$ = –11.2 (c 1.0, $CHCl_3$). IR (KBr film) ν 3449 (br), 2931, 2857, 1736, 1428, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H); 1.25 (t, *J* = 7.1 Hz, 3H); 1.84 (ddd, *J* = 13.1, 9.6, 6.2 Hz, 1H); 2.07 (ddd, *J* = 13.1, 5.8, 2.3 Hz, 1H); 2.48 (dd, *J* = 15.4, 5.8 Hz, 1H); 2.64 (dd, *J* = 15.4, 7.1 Hz, 1H); 3.59 (dd, *J* = 10.6, 6.0 Hz, 1H); 3.76 (dd, *J* = 10.6, 3.8 Hz, 1H); 3.86–3.90 (m, 1H); 4.14 (q, *J* = 7.1 Hz, 2H); 4.43–4.47 (m, 1H); 4.55 (ddt, *J* = 9.6, 7.1, 5.8 Hz, 1H); 7.35–7.45 (m, 6H); 7.63–7.69 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (q); 19.2 (s); 26.8 (q); 40.6 (t); 40.6 (t); 60.5 (t); 64.6 (t); 74.3 (d); 74.6 (d); 86.9 (d); 127.7 (d); 129.7 (d); 133.1 (s); 133.2 (s); 135.5 (d); 135.6 (d); 171.0 (s). HRMS (+ESI): *m/z* calcd. for $C_{25}H_{34}O_5NaSi$ (M+Na) 465.2073, found 465.2067.

Ethyl 2-[(2*R*,4*R*,5*S*)-5-(*tert*-butyldiphenylsilyloxymethyl)-4-hydroxytetrahydrofuran-2-yl] acetate (5d).



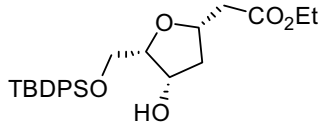
$[\alpha]_D$ = –15.1 (c 1.0, CH_2Cl_2). IR (KBr film) ν 3449 (br), 2931, 2857, 1736, 1428, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H); 1.25 (t, *J* = 7.1, 3H); 1.70 (ddd, *J* = 13.5, 6.2, 4.7 Hz, 1H); 2.48 (dt, *J* = 13.5, 7.2 Hz, 1H); 2.55 (dd, *J* = 15.6, 6.0 Hz, 1H); 2.75 (dd, *J* = 15.6, 7.6 Hz, 1H); 3.62 (dd, *J* = 10.5, 6.1 Hz, 1H); 3.76 (dd, *J* = 10.5, 4.1 Hz, 1H); 3.97 (m, 1H); 4.15 (q, *J* = 7.1 Hz, 2H); 4.45–4.52 (m, 2H); 7.35–7.45 (m, 6H); 7.63–7.69 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.3 (q); 19.3 (s); 27.0 (q); 40.0 (t); 41.0 (t); 60.7 (t); 65.0 (t); 74.8 (d); 75.1 (d); 85.9 (d); 127.9 (d); 129.9 (d); 133.2 (s); 135.7 (d); 171.6 (s). HRMS (+ESI): *m/z* calcd. for $C_{25}H_{38}NO_5Si$ (M+NH_4) 460.2514, found 460.2511.

Ethyl 2-[(2*S*,5*S*)-5-(*tert*-butyldiphenylsilyloxymethyl)-4-oxotetrahydrofuran-2-yl]acetate (S2).



DMP (10.4 g, 24.5 mmol) was added to a solution of alcohol **5c** (8.35 g, 18.8 mmol) in CH_2Cl_2 (100 mL) and was stirred for 2 h. The reaction mixture was dissolved with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ and the residue 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 (80:20) yielded **S2** (7.45 g, 90%) as a colorless oil. $[\alpha]_D$ = –94.4 (c 1.0, $CHCl_3$). IR (KBr film) ν 2931, 2858, 1762, 1737, 1472, 1428, 1194, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 9H); 1.29 (t, *J* = 7.1 Hz, 3H); 2.32 (dd, *J* = 17.7, 10.3 Hz, 1H); 2.69–2.77 (m, 2H); 2.94 (dd, *J* = 15.8, 6.7 Hz, 1H); 3.87 (dd, *J* = 11.6, 2.8 Hz, 1H); 3.90–3.94 (m, 2H); 4.21 (qd, *J* = 7.1, 1.8 Hz, 2H); 4.65 (dtd, *J* = 10.3, 6.7, 5.8 Hz, 1H); 7.36–7.45 (m, 6H); 7.65–7.74 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (q); 19.2 (s); 26.7 (q); 40.9 (t); 43.5 (t); 60.8 (t); 63.0 (t); 72.2 (d); 82.2 (d); 127.7 (d); 129.7 (d); 132.7 (s); 132.9 (s); 135.6 (d); 170.3 (s); 213.7 (s). HRMS (+ESI): *m/z* calcd. for $C_{25}H_{32}O_5NaSi$ (M+Na) 463.1911, found 463.1910.

Ethyl 2-[(2*S*,4*S*,5*S*)-5-(*tert*-butyldiphenylsilyloxymethyl)-4-hydroxytetrahydrofuran-2-yl] acetate (5e).



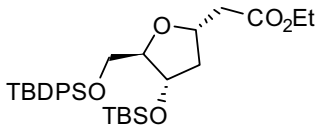
$NaBH_4$ (953 mg, 25.2 mmol) was added to a solution of ketone **S2** (5.56 g, 12.6 mmol) and $CeCl_3 \cdot 7H_2O$ (5.16 g, 13.9 mmol) in EtOH (200 mL) at –20 ºC. The reaction mixture was stirred at this temperature for 40 min. After this time, NH_4Cl was added and the solvent was removed under reduced pressure. The residue was extracted with EtOAc, 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 (80:20) yielded **5e** (4.8 g, 86%) as a colorless oil. $[\alpha]_D$ = –5.0 (c 1.0, $CHCl_3$). IR (KBr film) ν 3469, 2932, 2858,

1735, 1472, 1428, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H); 1.24 (t, *J* = 7.1 Hz, 3H); 1.80 (ddd, *J* = 13.4, 6.0, 3.1 Hz, 1H); 2.42 (ddd, *J* = 13.4, 7.9, 6.2 Hz, 1H); 2.65 (dd, *J* = 16.0, 6.0 Hz, 1H); 2.77 (dd, *J* = 16.0, 6.9 Hz, 1H); 3.81 (dt, *J* = 5.7, 4.2 Hz, 1H); 3.96 (dd, *J* = 10.9, 4.2 Hz, 1H); 4.00 (dd, *J* = 10.9, 5.7 Hz, 1H); 4.14 (q, *J* = 7.1 Hz, 2H); 4.34 (ddt, *J* = 7.9, 6.9, 6.0 Hz, 1H); 4.48–4.53 (m, 1H); 7.36–7.45 (m, 6H); 7.65–7.73 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (q); 19.1 (s); 26.8 (q); 40.5 (t); 40.8 (t); 60.5 (t); 63.1 (t); 73.6 (d); 74.0 (d); 81.5 (d); 127.8 (d); 129.9 (d); 133.5 (s); 133.8 (s); 135.5 (d); 135.6 (d); 171.4 (s). HRMS (+ESI): *m/z* calcd. for $C_{25}H_{35}O_5Si$ (M+H) 443.2248, found 443.2251.

General procedure for TBS protection:

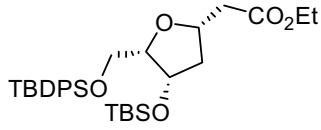
TBSCl (1.2 eq.) was added to a solution of alcohol **5** (1 eq.) and imidazole (1 eq.) in CH_2Cl_2 (180 mL). The reaction mixture was stirred at r.t. for 6 or 48 h. After this time, the mixture was washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded the corresponding protected adduct **S3** as a colorless oil.

Ethyl 2-[(2*S*,4*S*,5*R*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]acetate (S3a).



Alcohol **5a** (8.8 g, 20 mmol) led to **S3a** (9.99 g, 90%). $[\alpha]_D$ = +26.0 (c 1.0, $CHCl_3$). IR (KBr film) ν 2955, 2930, 2857, 1737, 1471, 1428, 1256, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H); 0.06 (s, 3H); 0.88 (s, 9H); 1.05 (s, 9H); 1.25 (t, *J* = 7.1 Hz, 3H); 1.71 (dt, *J* = 13.0, 4.4 Hz, 1H); 2.29 (dt, *J* = 13.0, 6.7 Hz, 1H); 2.60 (dd, *J* = 15.3, 6.7 Hz, 1H); 2.78 (dd, *J* = 15.3, 7.1 Hz, 1H); 3.57 (dd, *J* = 11.0, 5.2 Hz, 1H); 3.64 (dd, *J* = 11.0, 3.8 Hz, 1H); 3.94–3.98 (m, 1H); 4.15 (q, *J* = 7.1 Hz, 2H); 4.45–4.49 (m, 1H); 4.57–4.50 (m, 1H); 7.34–7.45 (m, 6H); 7.64–7.69 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –4.7 (q); –4.8 (q); 14.2 (q); 17.9 (s); 19.2 (s); 25.7 (q); 26.8 (q); 40.2 (t); 41.6 (t); 60.3 (t); 64.2 (t); 73.6 (d); 75.4 (d); 86.8 (d); 127.7 (d); 129.6 (d); 129.7 (d); 133.2 (s); 133.4 (s); 135.6 (d); 171.5 (s). HRMS (+ESI): *m/z* calcd. for $C_{31}H_{48}O_5NaSi_2$ (M+Na) 579.2938, found 579.2922.

Ethyl 2-[(2*S*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]acetate (S3b).



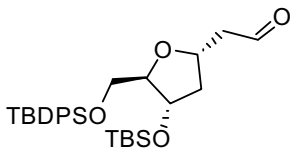
Alcohol **5e** (9.14 g, 20.6 mmol) led to **S3b** (10.7 g, 94%). $[\alpha]_D$ = +17.2 (c 1.0, $CHCl_3$). IR (KBr film) ν 2950, 2931, 2857, 1735, 1471, 1428, 1255, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.01 (s, 3H); 0.04 (s, 3H); 0.83 (s, 9H); 1.07 (s, 9H); 1.24 (t, *J* = 7.1 Hz, 3H); 1.73 (ddd, *J* = 13.2, 4.7, 2.7 Hz, 1H); 2.28 (ddd, *J* = 13.2, 8.0, 5.4 Hz, 1H); 2.58 (dd, *J* = 15.5, 7.4 Hz, 1H); 2.77 (dd, *J* = 15.5, 6.6 Hz, 1H); 3.73–3.81 (m, 1H); 3.83–3.90 (m, 2H); 4.09–4.17 (m, 2H); 4.33–4.52 (m, 2H); 7.34–7.45 (m, 6H); 7.64–7.69 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.2 (q); –4.7 (q); 14.2 (q); 17.9 (s); 19.2 (s); 25.7 (q); 26.9 (q); 40.1 (t); 41.8 (t); 60.2 (t); 63.3 (t); 72.4 (d); 74.1 (d); 83.9 (d); 127.6 (d); 129.5 (d); 133.6 (s); 133.8 (s); 135.6 (d); 135.7 (d); 171.5 (s). HRMS (+ESI): *m/z* calcd. for $C_{31}H_{48}O_5NaSi_2$ (M+Na) 579.2938, found 579.2932.

General procedure for ester reduction:

A 1 M solution of DIBALH in heptane (1 eq.) was added to a solution of ester **S3** (1 eq.) in CH_2Cl_2 at −78 ºC. The reaction mixture was stirred at this temperature for 15 min and MeOH and a saturated solution of NaK tartrate were added, the mixture was stirred at r.t. for further 2 h. After this time, water was added and the residue was extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$, filtered and the solvent was removed under reduced

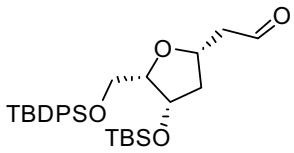
pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded the corresponding aldehyde **6** as a colorless oil.

2-[(2*S*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]acetaldehyde (6a).



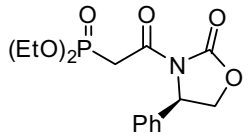
Ester **S3a** (1.65 g, 2.96 mmol) led to aldehyde **6a** (1.43 g, 94%). $[\alpha]_D$ = +28.9 (c 1.0, $CHCl_3$). IR (KBr film) ν 2955, 2930, 2857, 1726, 1471, 1428, 1256, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H); 0.07 (s, 3H); 0.89 (s, 9H); 1.07 (s, 9H); 1.69 (ddd, *J* = 13.0, 5.3, 4.0 Hz, 1H); 2.34 (ddd, *J* = 13.0, 7.4, 6.2 Hz, 1H); 2.66 (ddd, *J* = 16.7, 5.3, 2.0 Hz, 1H); 2.90 (ddd, *J* = 16.7, 7.4, 2.0 Hz, 1H); 3.61 (dd, *J* = 11.0, 5.0 Hz, 1H); 3.66 (dd, *J* = 11.0, 3.8 Hz, 1H); 3.95–3.99 (m, 1H); 4.48–4.52 (m, 1H); 4.60 (tt, *J* = 7.4, 5.3 Hz, 1H); 7.36–7.46 (m, 6H); 7.66–7.70 (m, 4H); 9.82 (t, *J* = 2.0, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –4.7 (q); –4.8 (q); 17.9 (s); 19.2 (s); 25.7 (q); 26.8 (q); 40.5 (t); 50.5 (t); 64.1 (t); 73.5 (d); 73.9 (d); 86.8 (d); 127.7 (d); 129.7 (d); 133.2 (s); 133.3 (s); 135.6 (d); 201.6 (s). HRMS (+ESI): *m/z* calcd. for $C_{29}H_{44}O_4NaSi_2$ (M+Na) 535.2670, found 535.2672.

2-[(2*S*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]acetaldehyde (6b).



Ester **S3b** (7.0 g, 12.6 mmol) led to aldehyde **6b** (6.43 g, 99%). $[\alpha]_D$ = +22.9 (c 1.0, $CHCl_3$). IR (KBr film) ν 2955, 2930, 2857, 1726, 1472, 1428, 1256, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.02 (s, 3H); 0.02 (s, 3H); 0.81 (s, 9H); 1.07 (s, 9H); 1.66 (ddd, *J* = 13.4, 4.9, 2.5 Hz, 1H); 2.33 (ddd, *J* = 13.4, 8.2, 5.5 Hz, 1H); 2.63 (ddd, *J* = 16.8, 5.6, 1.8 Hz, 1H); 2.85 (ddd, *J* = 16.8, 7.1, 2.1 Hz, 1H); 3.74–3.82 (m, 1H); 3.83–3.90 (m, 2H); 4.33–4.37 (m, 1H); 4.38–4.47 (m, 1H); 7.36–7.46 (m, 6H); 7.66–7.70 (m, 4H); 9.78 (t, *J* = 1.9 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.2 (q); –4.7 (q); 17.9 (s); 19.2 (s); 25.7 (q); 26.9 (q); 41.0 (t); 50.7 (t); 63.4 (t); 72.4 (d); 72.6 (d); 84.1(d); 127.6 (d); 129.5 (d); 129.6 (d); 133.5 (s); 133.8 (s); 135.6 (d); 135.7 (d); 201.7 (s). HRMS (+ESI): *m/z* calcd. for $C_{29}H_{44}O_4NaSi_2$ (M+Na) 535.2670, found 535.2673.

Diethyl (*R*)-2-oxo-2-(2-oxo-4-phenyloxazolidin-3-yl)ethylphosphonate (7).[3]



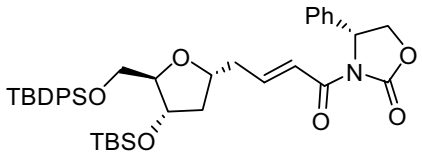
A 50% solution of T3P in EtOAc (13 mL, 21.8 mmol) was added to a solution of (*R*)-4-phenyl-2-oxazolidinone (2.45 g, 15 mmol) and diethylphosphonoacetic acid (2.65 mL, 16.5 mmol) in EtOAc (100 mL) and the mixture was stirred at reflux temperature for 48 h. After this time, water was added, and the solution was treated with a 20% solution of NaOH until pH = 6. The organic phase 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 (50:50 to 30:70) yielded **7** (4.78 g, 94%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (dt, *J* = 10.3, 7.0 Hz, 6H); 3.76 (dd, *J* = 22.2, 13.9 Hz, 1H); 3.81 (dd, *J* = 22.6, 13.9 Hz, 1H); 3.71–3.86 (m, 4H); 4.11 (m, 2H); 4.28 (dd, *J* = 8.8, 3.9 Hz, 1H); 4.70 (t, *J* = 8.8 Hz, 1H); 5.46 (dd, *J* = 8.8, 3.9 Hz, 1H); 7.30–7.41 (m, 5H).

General procedure for HWE reaction:

A 1 M solution of NaHMDS in THF (1.3 eq.) was added to a solution of phosphonate 7 (1.4 eq.) in THF. After 10 min, a solution of aldehyde **6** (1 eq.) in THF was added dropwise, and the mixture was stirred at r.t. for 2 h. 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

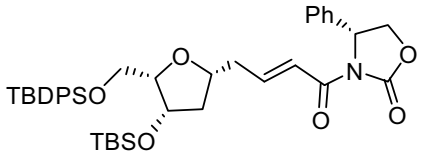
removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10 to 80:20) yielded the corresponding olefin **S3** as a colorless oil.

(*R*)-3-[(*E*)-4-((2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl)but-2-enoyl]-4-phenyloxazolidin-2-one (S4a).



Aldehyde **6a** (4.18g, 8.15 mmol) led to olefin **S4a** (4.46 g, 78%). $[\alpha]_D$ = −14.1 (c 1.0, $CHCl_3$). IR (KBr film) ν 2954, 2929, 2857, 1781, 1689, 1636, 1383, 1347, 1196, 1256, 1252, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H); 0.05 (s, 3H); 0.87 (s, 9H); 1.04 (s, 9H); 1.66 (ddd, *J* = 12.8, 5.9, 4.7 Hz, 1H); 2.21 (dt, *J* = 12.8, 6.4 Hz, 1H); 2.49–2.59 (m, 1H); 2.64–2.73 (m, 1H); 3.59 (dd, *J* = 11.0, 4.3 Hz, 1H); 3.63 (dd, *J* = 11.0, 3.8 Hz, 1H); 3.91 (dt, *J* = 4.3, 3.8 Hz, 1H); 4.14–4.20 (m, 1H); 4.28 (dd, *J* = 8.8, 3.9 Hz, 1H); 4.46 (ddd, *J* = 6.4, 4.7, 3.8 Hz, 1H); 4.69 (t, *J* = 8.8 Hz, 1H); 5.49 (dd, *J* = 8.8, 3.9 Hz, 1H); 7.09 (dt, *J* = 15.4, 7.3, 1H); 7.30–7.45 (m, 12H); 7.64–7.68 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.8 (q); 17.9 (s); 19.2 (s); 25.8 (q); 26.8 (q); 39.7 (t); 40.2 (t); 57.7 (d); 64.1 (t); 69.9 (t); 73.3 (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); 133.2 (s); 133.4 (s); 135.6 (d); 139.0 (s); 148.2 (d); 153.6 (s); 164.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{40}H_{53}O_6NNaSi_2$ (M+Na) 722.3304, found 722.3309.

(*R*)-3-[(*E*)-4-((2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl)but-2-enoyl]-4-phenyloxazolidin-2-one (S4b).

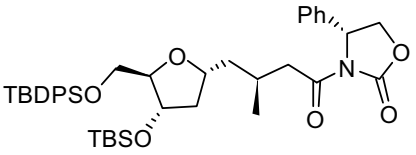


Aldehyde **6b** (5.0 g, 9.8 mmol) led to **S4b** (6.66 g, 95%). $[\alpha]_D$ = −14.8 (c 1.0, $CHCl_3$). IR (KBr film) ν 2954, 2930, 2857, 1781, 1689, 1637, 1384, 1346, 1197, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 3H); 0.02 (s, 3H); 0.81 (s, 9H); 1.07 (s, 9H); 1.65 (ddd, *J* = 13.2, 5.1, 2.7 Hz, 1H); 2.20 (ddd, *J* = 13.2, 7.9, 5.6 Hz, 1H); 2.47–2.56 (m, 1H); 2.64–2.73 (m, 1H); 3.77 (dd, *J* = 9.8, 5.6 Hz, 1H); 3.80–3.84 (m, 1H); 3.88 (dd, *J* = 9.8, 4.4 Hz, 1H); 4.04 (dtd, *J* = 7.9, 6.6, 5.1 Hz, 1H); 4.28 (dd, *J* = 8.8, 3.9 Hz, 1H); 4.33 (ddd, *J* = 5.6, 3.9, 2.7 Hz, 1H); 4.68 (t, *J* = 8.8 Hz, 1H); 5.48 (dd, *J* = 8.7, 3.9 Hz, 1H); 7.08 (ddd, *J* = 15.4, 7.7, 6.6 Hz, 1H); 7.30–7.45 (m, 12H); 7.64–7.68 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.3 (q); −4.7 (q); 17.9 (s); 19.2 (s); 25.7 (q); 26.9 (q); 39.9 (t); 40.5 (t); 57.7 (d); 63.4 (t); 69.9 (t); 73.4 (d); 76.4 (d); 83.9 (d); 121.8 (d); 126.0 (d); 127.5 (d); 128.6 (d); 129.1 (d); 129.5 (d); 133.6 (s); 133.9 (s); 135.6 (d); 139.0 (s); 148.2 (d); 153.6 (s); 164.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{40}H_{53}O_6NNaSi_2$ (M+Na) 722.3304, found 722.3300.

General procedure for 1,4-addition:

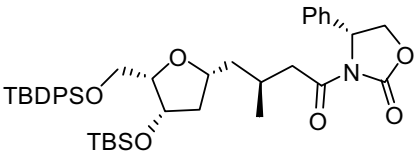
A 1.4 M solution of MeMgBr in THF (1.1 eq.) was added to a solution of $CuBr{\cdot}Me_2S$ (1.1 eq.) in THF at −40 ºC, and the mixture was stirred at −40 ºC for 1 h. The solution was cooled to −78 ºC and $BF_3{\cdot}Et_2O$ (1.1 eq.) was added, followed by a solution of oxazolidinone **S4** (1 eq.) in THF. 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 further 1 hour. 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 the corresponding methylated **8a** as a colorless oil.

(*R*)-3-[(*S*)-4-((2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl)-3-methylbutanoyl]-4-phenyloxazolidin-2-one (8a).



Olefin **S4a** (4.27 g, 6.1 mmol) led to methylated **8a** (3.67 g, 84%). $[\alpha]_D$ = −40.0 (c 1.0, $CHCl_3$). IR (KBr film) ν 2956, 2930, 2857, 1784, 1707, 1471, 1428, 1384, 1322, 1252, 1196, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H); 0.06 (s, 3H); 0.88 (s, 9H); 0.94 (d, *J* = 6.7 Hz, 3H); 1.05 (s, 9H); 1.46–1.69 (m, 3H); 2.09–2.25 (m, 2H); 2.85 (dd, *J* = 16.7, 7.4 Hz, 1H); 2.96 (dd, *J* = 16.7, 6.2 Hz, 1H); 3.64 (dd, *J* = 11.0, 3.9 Hz, 1H); 3.69 (dd, *J* = 11.0, 3.9 Hz, 1H); 3.81 (dt, *J* = 4.5, 3.9 Hz, 1H); 4.07–4.16 (m, 1H); 4.24 (dd, *J* = 8.8, 3.6 Hz, 1H); 4.47 (td, *J* = 6.4, 4.5 Hz, 1H); 4.62 (t, *J* = 8.8 Hz, 1H); 5.40 (dd, *J* = 8.8, 3.6 Hz, 1H); 7.27–7.45 (m, 11H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.8 (q); −4.6 (q); 17.9 (s); 19.2 (s); 20.1 (q); 25.8 (q); 26.8 (q); 27.5 (d); 41.4 (t); 42.3 (t); 42.9 (t); 57.6 (d); 64.0 (t); 69.8 (t); 72.9 (d); 76.8 (d); 85.5 (d); 125.8 (d); 127.6 (d); 129.1 (d); 128.6 (d); 129.1 (d); 129.5 (d); 129.6 (d); 133.4 (s); 133.5 (s); 135.6 (d); 139.3 (s); 153.6 (s); 171.9 (s). HRMS (+ESI): *m/z* calcd. for $C_{41}H_{57}O_6NNaSi_2$ (M+Na) 738.3617, found 738.3614.

(*R*)-3-[(*S*)-4-((2*R*,4*S*,5*S*)-4-(tert-Butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl)-3-methylbutanoyl]-4-phenyloxazolidin-2-one (8b).

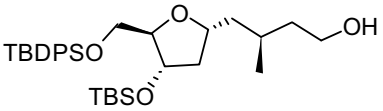


Olefin **S4b** (8.0 g, 11.4 mmol) led to methylated **8b** (7.73 g, 81%). $[\alpha]_D$ = −11.1 (c 1.0, $CHCl_3$). IR (KBr film) ν 2956, 2930, 2857, 1783, 1707, 1471, 1428, 1384, 1325, 1252, 1198, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ −0.04 (s, 3H); 0.01 (s, 3H); 0.80 (s, 9H); 0.92 (d, *J* = 6.7 Hz, 3H); 1.06 (s, 9H); 1.49 (dt, *J* = 13.6, 5.9 Hz, 1H); 1.53 (ddd, *J* = 16.6, 6.3, 3.8 Hz, 1H); 1.67 (dt, *J* = 13.6, 7.5 Hz, 1H); 2.10–2.22 (m, 2H); 2.80 (dd, *J* = 16.7, 7.6 Hz, 1H); 2.96 (dd, *J* = 16.7, 6.1 Hz, 1H); 3.71–3.79 (m, 2H); 3.81–3.94 (m, 2H); 4.23 (dd, *J* = 8.8, 3.6 Hz, 1H); 4.31 (dt, *J* = 6.0, 3.8 Hz, 1H); 4.61 (t, *J* = 8.8 Hz, 1H) 5.39 (dd, *J* = 8.8, 3.6 Hz, 1H); 7.27–7.46 (m, 11H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.6 (q); 18.0 (s); 19.2 (s); 20.2 (q); 25.8 (q); 26.9 (q); 27.4 (d); 41.5 (t); 42.2 (t); 43.2 (t); 57.6 (d); 63.6 (t); 69.8 (t); 72.5 (d); 75.8 (d); 83.3 (d); 125.9 (d); 127.5 (d); 128.6 (d); 129.1 (d); 129.4 (d); 133.7 (s); 134.0 (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 738.3612.

General procedure for oxazolidinone removal:

A 2 M solution of $LiBH_4$ in THF (2 eq.) was added to a solution of olefin **8** (1 eq.) in Et_2O 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 the corresponding alcohol **S5** as a colorless oil.

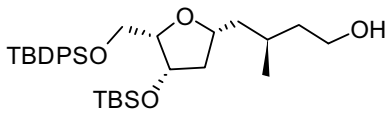
(*R*)-4-[(2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-3-methylbutan-1-ol (S5a).



Oxazolidinone **8a** (3.67 g, 5.12 mmol) led to alcohol **S5a** (2.25 g, 79%). $[\alpha]_D$ = +25.8 (c 1.0, $CHCl_3$). IR (KBr film) ν 3395 (br) 2955, 2929, 2857, 1472, 1428, 1252, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H); 0.05 (s, 3H); 0.87 (s, 9H); 0.95 (d, *J* = 6.6 Hz, 3H); 1.05 (s, 9H); 1.38–1.69 (m, 5H); 1.70–1.78 (m, 1H); 2.19–2.26 (m, 1H); 3.61–3.73 (m, 4H); 3.85 (dt, *J* = 4.2, 4.0 Hz, 1H); 4.16–4.23 (m, 1H); 4.49 (td, *J* = 6.3, 4.4 Hz, 1H); 7.34–7.44 (m, 6H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.8 (q);

–4.7 (q); 17.9 (s); 19.2 (s); 20.4 (q); 25.8 (q); 26.8 (q); 27.2 (d); 39.7 (t); 41.3 (t); 43.3 (t); 61.0 (t); 64.1 (t); 73.0 (d); 76.8 (d); 85.7 (d); 127.6 (d); 129.6 (d); 133.4 (s); 133.5 (s); 135.6 (d). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{52}O_4NaSi_2$ (M+Na) 579.3296, found 579.3296.

(*R*)-4-[(2*R*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-3-methylbutan-1-ol (S5b).

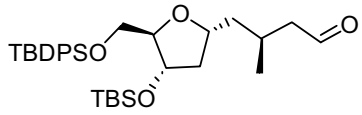


Oxazolidinone **8b** (2.3 g, 3.21 mmol) led to alcohol **S5b** (1.50 g, 84%). $[\alpha]_D$ = +12.8 (c 1.0, $CHCl_3$). IR (KBr film) ν 3408 (br), 2955, 2930, 2857, 1471, 1428, 1254, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.04 (s, 3H); 0.01 (s, 3H); 0.80 (s, 9H); 0.93 (d, *J* = 6.6 Hz, 3H); 1.06 (s, 9H); 1.41 (td, *J* = 13.6, 6.8 Hz, 1H); 1.46–1.57 (m, 2H); 1.61–1.69 (m, 2H); 1.72–1.80 (m, 1H); 2.21 (ddd, *J* = 12.7, 7.2, 6.2 Hz, 1H); 3.60–3.73 (m, 2H); 3.74–3.80 (m, 2H); 3.83–3.89 (m, 1H); 3.94–4.02 (m, 1H); 4.33 (dt, *J* = 6.2, 3.9 Hz, 1H); 7.33–7.43 (m, 6H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.2 (q); –4.6 (q); 18.0 (s); 19.2 (s); 20.6 (q); 25.7 (q); 26.9 (q); 27.0 (d); 39.8 (t); 41.5 (t); 43.5 (t); 61.1 (t); 63.6 (t); 72.6 (d); 75.9 (d); 83.3 (d); 127.5 (d); 129.4 (d); 129.5 (d); 133.7 (s); 133.9 (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 579.3272.

General procedure for alcohol oxidation:

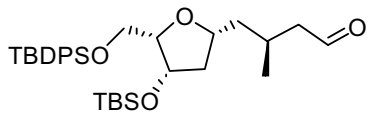
Dess-Martin Periodinane (DMP**,** 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one) (1.2 eq.) was added to a solution of alcohol **S5** (1 eq.) in CH_2Cl_2 and was stirred for 2 h. The reaction mixture was diluted with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ and the residue was extracted with 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 (95:5) yielded the corresponding aldehyde **9** as a colorless oil.

(*S*)-4-[(2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-3-methylbutanal (9a).



Alcohol **S5a** (2.25 g, 4 mmol) led to aldehyde **9a** (2.04 g, 92%). $[\alpha]_D$ = +22.2 (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 0.05 (s, 3H); 0.06 (s, 3H); 0.88 (s, 9H); 1.01 (d, *J* = 6.5 Hz, 3H); 1.06 (s, 9H); 1.50 (ddd, *J* = 14.1, 6.6, 5.1 Hz, 1H); 1.61 (ddd, *J* = 12.8, 7.3, 5.8 Hz, 1H); 1.73 (ddd, *J* = 14.1, 8.3, 6.4 Hz, 1H); 2.18–2.29 (m, 3H); 2.45–2.55 (m, 1H); 3.66 (dd, *J* = 11.1, 3.9 Hz, 1H); 3.70 (dd, *J* = 11.1, 4.1 Hz, 1H); 3.85 (dt, *J* = 4.1, 3.9 Hz, 1H); 4.11–4.19 (m, 1H); 4.47–4.53 (m, 1H); 7.34–7.44 (m, 6H); 7.66–7.72 (m, 4H); 9.74 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –4.8 (q); –4.7 (q); 17.9 (s); 19.2 (s); 20.5 (q); 25.8 (q); 25.8 (d); 26.8 (q); 41.4 (t); 43.2 (t); 50.6 (t); 64.1 (t); 73.0 (d); 76.4 (d); 85.8 (d); 127.6 (d); 129.6 (d); 133.4 (s); 133.5 (s); 135.6 (d); 202.9 (d). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{50}O_4NaSi_2$ (M+Na) 577.3140, found 577.3142.

(*S*)-4-[(2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-3-methylbutanal (9b)



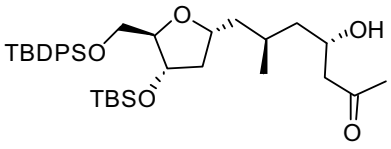
Alcohol **S5b** (5.70 g, 10.24 mmol) led to aldehyde **9b** (5.2 g, 92%). $[\alpha]_D$ = +11.9 (c 1.0, $CHCl_3$). IR (KBr film) ν 2955, 2930, 2857, 1726, 1472, 1428, 1255, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.04 (s, 3H); 0.01 (s, 3H); 0.80 (s, 9H); 0.99 (d, *J* = 6.5 Hz, 3H); 1.06 (s, 9H); 1.48 (ddd, *J* = 13.9, 6.7, 5.3 Hz, 1H); 1.56 (ddd, *J* = 12.9, 6.4, 3.4 Hz, 1H); 1.73 (ddd, *J* = 13.9, 8.0, 6.3 Hz, 1H); 2.15–2.30 (m, 3H); 2.42–2.53 (m, 1H); 3.74–3.82 (m, 2H); 3.83–3.88 (m, 1H); 3.91–3.98 (m, 1H); 4.30–4.35 (m, 1H); 7.34–7.44 (m,

6H); 7.66–7.72 (m, 4H); 9.73 (t, *J* = 2.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.6 (q); 18.0 (s); 19.2 (s); 20.6 (q); 25.7 (q); 25.8 (d); 26.9 (q); 41.6 (t); 43.4 (t); 50.6 (t); 63.7 (t); 72.5 (d); 75.4 (d); 83.5 (d); 127.5 (d); 129.5 (d); 133.7 (s); 133.9 (s); 135.6 (d); 135.7 (d); 203.1 (d). HRMS (+ESI): *m/z* calcd. for $C_{32}H_{50}O_4NaSi_2$ (M+Na) 577.3140, found 577.3147.

General procedure for stereoselective aldol addition:

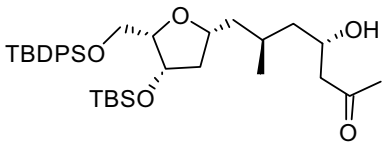
Acetone (5.5 eq.) and Et_3N (5 eq.) were added to a solution of (–)-B-chlorodiisopinocampheylborane (5 eq.) in Et_2O at 0 ºC and the solution was stirred at 0 ºC for 45 min. The solution was cooled to −78 ºC, a solution of aldehyde **9** (1 eq.) was added and the reaction mixture was stirred at −78 ºC for 1 h and at −20 ºC for 16 h. After this time, H_2O_2, KH_2PO_4-NaOH pH = 7 buffer and MeOH were added and stirring continued for further 1 h. The reaction mixture was diluted with water and extracted with Et_2O and EtOAc. The organic extracts were 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 the corresponding aldol **10** as a colorless oil.

(4*S*,6*R*)-7-[(2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-4-hydroxy-6-methylheptan-2-one (10a).



Aldehyde **9a** (2.04 g, 3.7 mmol) led to aldol **10a** (1.51 g, 67%) (dr = 8:1). $[\alpha]_D$ = +36.1 (c 1.0, $CHCl_3$). IR (KBr film) ν 3454 (br), 2955, 2929, 2857, 1711, 1478, 1428, 1361, 1257, 1113 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H); 0.05 (s, 3H); 0.87 (s, 9H); 0.95 (d, *J* = 6.7 Hz, 3H); 1.05 (s, 9H); 1.36–1.41 (m, 2H); 1.50–1.64 (m, 3H); 1.71–1.81 (m, 1H); 2.12 (s, 3H); 2.19–2.26 (m, 1H); 2.46 (dd, *J* = 17.6, 9.0 Hz, 1H); 2.56 (dd, *J* = 17.6, 2.7 Hz, 1H); 3.64 (dd, *J* = 10.9, 3.9 Hz, 1H); 3.69 (dd, *J* = 10.9, 3.9 Hz, 1H); 3.83–3.87 (m, 1H); 4.10–4.22 (m, 2H); 4.43–4.49 (m, 1H); 7.34–7.44 (m, 6H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.8 (q); −4.6 (q); 17.9 (s); 19.2 (s); 21.0 (q); 25.8 (q); 26.8 (q); 26.9 (d); 30.7 (q); 41.2 (t); 42.8 (t); 43.6 (t); 50.2 (t); 64.1 (t); 65.6 (d); 73.0 (d); 76.9 (d); 85.8 (d); 127.6 (d); 129.6 (d); 133.4 (s); 133.5 (s); 135.6 (d); 210.0 (s). HRMS (+ESI): *m/z* calcd. for $C_{35}H_{57}O_5Si_2$ (M+H) 613.3739, found 613.3743.

(4*S*,6*R*)-7-[(2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-4-hydroxy-6-methylheptan-2-one (10b).



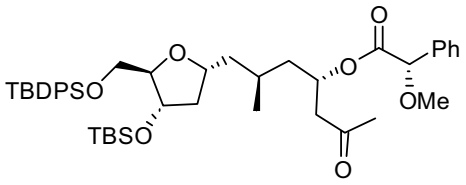
Aldehyde **9b** (1.2 g, 2.16 mmol) led to aldol **10b** (1.06 g, 80%) (dr = 6:1). $[\alpha]_D$ = 19.8 (c 1.0, $CHCl_3$). IR (KBr film) ν 3462 (br), 2955, 2930, 2857, 1711, 1472, 1428, 1361, 1255, 1112 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.05 (s, 3H); 0.01 (s, 3H); 0.80 (s, 9H); 0.94 (d, *J* = 6.7 Hz, 3H); 1.06 (s, 9H); 1.38 (t, *J* = 6.8 Hz, 2H); 1.50–1.70 (m, 3H); 1.78 (h, *J* = 6.7 Hz, 1H); 2.12 (s, 3H); 2.21 (ddd, *J* = 13.2, 7.5, 6.1 Hz, 1H); 2.48 (dd, *J* = 17.5, 8.9 Hz, 1H); 2.58 (dd, *J* = 17.5, 3.0 Hz, 1H); 3.16 (bs, 1H); 3.73–3.80 (m, 2H); 3.82–3.88 (m, 1H); 3.94–4.01 (m, 1H); 4.10–4.18 (m, 1H); 4.32 (dt, *J* = 6.1, 3.6 Hz, 1H); 7.33–7.43 (m, 6H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.6 (q); 18.0 (s); 19.2 (s); 21.2 (q); 25.7 (q); 26.6 (d); 26.9 (q); 30.8 (q); 41.6 (t); 43.0 (t); 43.6 (t); 50.1 (t); 64.6 (t); 65.6 (d); 72.5 (d); 75.8 (d); 83.4 (d); 127.5 (d); 129.5 (d); 133.7 (s); 133.9 (s); 135.6 (d); 135.7 (d); 210.1 (s). HRMS (+ESI): *m/z* calcd. for $C_{35}H_{57}O_5Si_2$ (M+H) 613.3739, found 613.3729.

General procedure for MPA derivatization:

α-Methoxyphenylacetic acid (3 or 6 eq.) and DCC (3 or 6 eq.) were added to a solution of alcohol **10** (1 eq.) in THF, then DMAP (0.1 eq.) was added and the solution was stirred for 30

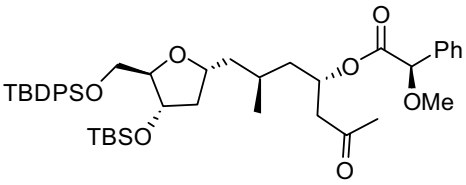
min. The solution was filtered, poured into Et_2O and washed with 0.2 M aqueous HCl and sat. $NaHCO_3$. The organic residue was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded the corresponding ester **S6** as a colorless oil.

(2*S*,4*S*)-1-[(2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-2-methyl-6-oxoheptan-4-yl (*S*)-2-methoxy-2-phenylacetate (S6a).



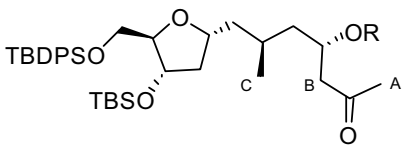
S-α-Methoxyphenylacetic acid (25 mg, 0.15 mmol) and alcohol **10a** (30 mg, 0.05 mmol) led to ester **S6a** (30 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H); 0.05 (s, 3H); 0.87 (s, 9H); 0.94 (d, *J* = 5.6 Hz, 3H); 1.05 (s, 9H); 1.45–1.60 (m, 6H); 1.81 (s, 3H); 2.17 (dt, *J* = 12.6, 6.4 Hz, 1H); 2.45 (dd, *J* = 16.1, 4.9 Hz, 1H); 2.52 (dd, *J* = 16.1, 7.6 Hz, 1H); 3.37 (s, 3H); 3.64 (dd, *J* = 11.0, 3.9 Hz, 1H); 3.68 (dd, *J* = 11.0, 3.9 Hz, 1H); 3.81 (q, *J* = 3.9 Hz, 1H); 4.03–4.11 (m, 1H); 4.42–4.47 (m, 1H); 4.68 (s, 1H); 5.33–5.41 (m, 1H); 7.30–7.47 (m, 11H); 7.65–7.72 (m, 4H).

(2*S*,4*S*)-1-[(2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-2-methyl-6-oxoheptan-4-yl (*R*)-2-methoxy-2-phenyl-acetate (S6b).



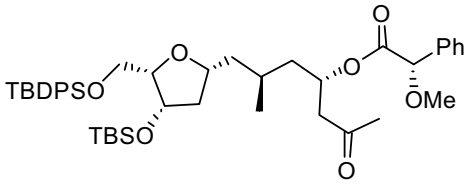
R-α-Methoxyphenylacetic acid (25 mg, 0.15 mmol) and alcohol **10a** (30 mg, 0.05 mmol) led to ester **S6b** (26 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H); 0.05 (s, 3H); 0.78 (d, *J* = 6.5 Hz, 3H); 0.87 (s, 9H); 1.04 (s, 9H); 1.54–1.98 (m, 6H); 2.05 (s, 3H); 2.06–2.10 (m, 1H); 2.56 (dd, *J* = 16.1, 5.0 Hz, 1H); 2.63 (dd, *J* = 16.1, 7.5 Hz, 1H); 3.41 (s, 3H); 3.55–3.70 (m, 2H); 3.75–3.81 (m, 1H); 3.90–4.01 (m, 1H); 4.39–4.44 (m, 1H); 4.68 (s, 1H); 5.30–5.37 (m, 1H); 7.28–7.44 (m, 11H); 7.65–7.72 (m, 4H).

Absolute configuration determination:



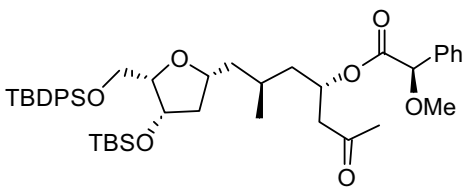
	δ H_A	δ H_B	δ H_C
R=*R*-MPA	2.05	2.59	0.78
R=*S*-MPA	1.81	2.48	0.94
Δ^{RS}	0.24	0.11	–0.16

(2*S*,4*S*)-1-[(2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-2-methyl-6-oxoheptan-4-yl (*S*)-2-methoxy-2-phenylacetate (S6c).



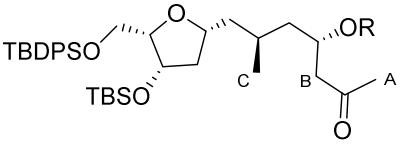
S-Methoxyphenylacetic acid (50 mg, 0.3 mmol) and alcohol **10b** (32 mg, 0.05 mmol) led to ester **S6c** (22 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.05 (s, 3H); 0.00 (s, 3H); 0.79 (s, 9H); 0.94 (d, *J* = 5.9 Hz, 3H); 1.05 (s, 9H); 1.40–1.65 (m, 6H); 1.81 (s, 3H); 2.12–2.19 (m, 1H); 2.47 (dd, *J* = 16.2, 4.8 Hz, 1H); 2.55 (dd, *J* = 16.2, 7.7 Hz, 1H); 3.38 (s, 3H); 3.72–3.78 (m, 2H); 3.81–3.88 (m, 2H); 4.30 (dt, *J* = 6.1, 3.8 Hz, 1H); 4.69 (s, 1H); 5.30–5.37 (m, 1H); 7.30–7.42 (m, 11H); 7.66–7.72 (m, 4H). HRMS (+ESI): *m/z* calcd. for $C_{44}H_{64}O_7NaSi_2$ (M+Na) 783.4083, found 783.4070.

(2*S*,4*S*)-1-[(2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-2-methyl-6-oxoheptan-4-yl (*R*)-2-methoxy-2-phenylacetate (S6d).



R-Methoxyphenylacetic acid (50 mg, 0.3 mmol) and alcohol **10b** (32 mg, 0.05 mmol) led to ester **S6d** (30 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H); 0.00 (s, 3H); 0.79 (s, 9H); 0.80 (d, *J* = 5.9 Hz, 3H); 1.05 (s, 9H); 1.25−1.53 (m, 6H); 2.05 (s, 3H); 2.05−2.12 (m, 1H); 2.59 (dd, *J* = 16.2, 5.1 Hz, 1H); 2.65 (dd, *J* = 16.2, 7.5 Hz, 1H); 3.40 (s, 3H); 3.67−3.75 (m, 3H); 3.80−3.86 (m, 1H); 4.27 (dt, *J* = 6.2, 3.8 Hz, 1H); 4.68 (s, 1H); 5.28−5.36 (m, 1H); 7.28−7.42 (m, 11H); 7.66−7.72 (m, 4H). HRMS (+ESI): *m/z* calcd. for $C_{44}H_{64}O_7NaSi_2$ (M+Na) 783.4083, found 783.4075.

Absolute configuration determination:

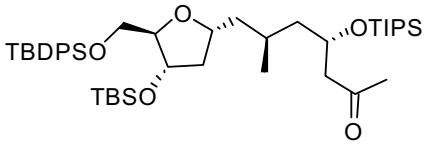


	δ H_A	δ H_B	δ H_C
R = *R*-MPA	2.11	2.68	0.86
R = *S*-MPA	1.86	2.57	0.99
Δ^{RS}	0.25	0.11	−0.13

General procedure for TIPS protection:

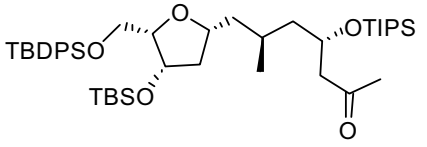
Triisopropylsilyl trifluoromethanesulfonate (1.2 eq.) was added to a solution of **10** (1 eq.), imidazole (2 eq.) and DMAP (0.1 eq.) in DMF, and the reaction mixture was stirred at 95 ºC for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in water and extracted with Et_2O. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-Et_2O (95:5) yielded the corresponding protected aldol **11** as a colorless oil.

(4*S*,6*S*)-7-[(2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-6-methyl-4-(triisopropylsilyloxy)heptan-2-one (11a).



Alcohol **10a** (1.5 g, 2.45 mmol) led to protected **11a** (1.79 g, 93%). $[\alpha]_D$ = +27.6 (c 1.0, $CHCl_3$). IR (KBr film) ν 2956, 2930, 2864, 1719, 1476, 1427, 1251, 1112 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H); 0.05 (s, 3H); 0.87 (s, 9H); 0.93 (d, *J* = 6.3 Hz, 3H); 1.05−1.06 (3bs, 30H); 1.25−1.65 (m, 6H); 2.11 (s, 3H); 2.23 (dt, *J* = 12.6, 6.5 Hz, 1H); 2.54 (d, *J* = 5.7 Hz, 2H); 3.65 (dd, *J* = 11.0, 3.9 Hz, 1H); 3.70 (dd, *J* = 11.0, 3.9 Hz, 1H); 3.83 (dt, *J* = 4.4, 3.9 Hz, 1H); 4.11−4.19 (m, 1H); 4.36−4.43 (m, 1H); 4.47 (td, *J* = 6.2, 4.4 Hz, 1H); 7.34−7.44 (m, 6H); 7.66−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.8 (q); −4.6 (q); 12.7 (d); 17.9 (s); 18.2 (q); 19.2 (s); 21.0 (q); 25.8 (q); 26.8 (q); 27.5 (d); 31.7 (q); 41.6 (t); 44.7 (t); 45.4 (t); 50.9 (t); 64.1 (t); 67.7 (d); 73.1 (d); 76.7 (d); 85.6 (d); 127.6 (d); 129.6 (d); 133.4 (s); 133.5 (s); 135.6 (d); 207.9 (s). HRMS (+ESI): *m/z* calcd. for $C_{44}H_{80}O_5NSi_3$ ($M+NH_4$) 786.5339, found 786.5365.

(4*S*,6*S*)-7-[(2*R*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl) tetrahydrofuran-2-yl]-6-methyl-4-(triisopropylsilyloxy)heptan-2-one (11b).



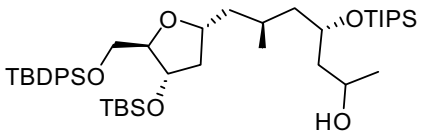
Alcohol **10b** (0.97 g, 1.58 mmol) led to protected **11b** (0.96 g, 77%). $[\alpha]_D$ = 25.6 (c 1.0, $CHCl_3$). IR (KBr film) ν 2931, 2864, 1719, 1463, 1428, 1254, 1113 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H); 0.00 (s, 3H); 0.80 (s, 9H); 0.91 (d, *J* = 6.3 Hz, 3H); 1.04 and 1.05 (2bs, 30H); 1.30−1.66 (m, 7H); 2.12 (s, 3H); 2.23 (dt, *J* = 13.2, 6.7 Hz, 1H); 2.55 (d, *J* = 5.7 Hz, 1H);

3.72–3.80 (m, 2H); 3.81–3.88 (m, 1H); 3.90–3.97 (m, 1H); 4.32 (dt, *J* = 6.0, 3.7 Hz, 1H); 4.35–4.44 (m, 1H); 7.34–7.44 (m, 6H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.6 (q); 12.6 (d); 17.8 (s); 18.2 (q); 19.2 (s); 20.1 (q); 25.7 (q); 26.9 (q); 27.4 (d); 31.7 (q); 41.9 (t); 44.9 (t); 45.2 (t); 50.8 (t); 63.7 (t); 67.8 (d); 72.6 (d); 75.6 (d); 83.3 (d); 127.5 (d); 129.5 (d); 133.7 (s); 134.0 (s); 135.6 (d); 135.7 (d); 208.0 (s). HRMS (+ESI): *m/z* calcd. for $C_{44}H_{80}O_5NSi_3$ (M+NH4) 786.5339, found 786.5316.

General procedre for ketone reduction:

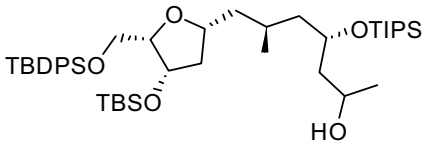
A solution of $NaBH_4$ (1.2 eq.) and ketone **11** (1 eq.) in THF-EtOH 2:1 was stirred at r.t. for 16 h. After this time, aqueous sat. NH_4Cl was added and the residue was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded a 6:4 mixture of the corresponding alcohol **S7** as a colorless oil.

(2*RS*,4*S*,6*S*)-7-[(2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl]-6-methyl-4-(triisopropylsilyloxy)heptan-2-ol (S7a).



Ketone **11a** (5.56 g, 7.2 mmol) led to a 6:4 mixture of alcohol **S7a** (4.79 g, 89%). IR (KBr film) ν 3506, 2955, 2931, 2865, 1463, 1428, 1252, 1113 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H); 0.05 (s, 3H); 0.87 (s, 9H); 0.91 (d, *J* = 6.1 Hz, 3H); 1.06–1.09 (3bs, 30H); 1.11 and 1.15 (2d, *J* = 6.2 Hz, 3H); 1.30–1.75 (m, 8H); 2.24 (dt, *J* = 12.8, 6.6 Hz, 1H); 3.62–3.96 (m, 2H); 3.84–3.88 (m, 1H); 3.98–4.06 (m, 1H); 4.12–4.26 (m, 2H); 4.42–4.50 (m, 1H); 7.34–7.44 (m, 6H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.8 (q); −4.6 (q); 12.4 (d); 13.1(d); 17.7 (s); 17.9 (s); 18.1 (q); 18.2 (q); 19.2 (s); 19.6 (q); 19.7 (q); 23.8 (q); 23.9 (q); 25.8 (q); 26.8 (q); 27.4 (d); 27.7 (d); 41.2 (t); 41.4 (t); 41.6 (t); 42.6 (t); 44.6 (t); 44.7 (t); 45.1 (t); 45.2 (t); 64.1 (t); 64.2 (d); 66.9 (d); 70.7 (d); 72.1 (d); 73.1 (d); 73.3 (d); 76.9 (d); 85.9 (d); 127.6 (d); 129.6 (d); 133.4 (s); 133.5 (s); 135.6 (d). HRMS (+ESI): *m/z* calcd. for $C_{44}H_{78}O_5NaSi_3$ (M+Na) 793.5049, found 793.5068.

(2*RS*,4*S*,6*S*)-7-[(2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl]-6-methyl-4-(triisopropylsilyloxy)heptan-2-ol (S7b).



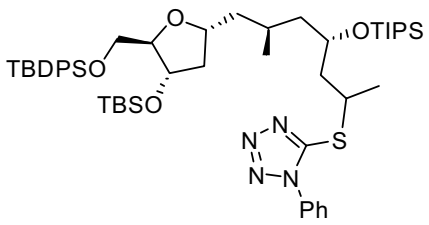
Ketone **11b** (1.81 g, 2.36 mmol) led to a 6:4 mixture of alcohol **S7b** (1.69 g, 92%). IR (KBr film) ν 3456 (br), 2955, 2931, 2863, 1463, 1428, 1255, 1113 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.04 (2s, 3H); 0.01 (s, 3H); 0.81 (2s, 9H); 0.89 (d, *J* = 6.3 Hz, 3H); 1.05 and 1.09 (2s, 9H); 1.08 (bs, 21H); 1.09 and 1.15 (2d, *J* = 6.2 Hz, 3H); 1.30–1.75 (m, 8H); 2.15–2.25 (m, 1H); 3.72–3.80 (m, 2H); 3.83–3.88 (m, 1H); 3.91–4.00 (m, 1H); 4.01–4.07 and 4.11–4.25 (2m, 2H); 4.30–4.35 (m, 1H); 7.34–7.45 (m, 6H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.6 (q); 12.3 (d); 13.1 (d); 17.7 (s); 18.0 (s); 18.1 (q); 18.2 (q); 19.2 (s); 19.7 (q); 19.8 (q); 23.8 (q); 25.7 (q); 26.9 (q); 27.4 (d); 27.5 (d); 40.9 (t); 41.7 (t); 41.9 (t); 42.0 (t); 44.3 (t); 45.2 (t); 45.3 (t); 63.5 (t); 63.6 (t); 64.3 (d); 67.0 (d); 70.9 (d); 72.4 (d); 72.5 (d); 72.6 (d); 75.4 (d); 75.5 (d); 83.3 (d); 127.5 (d); 129.4 (d); 129.5 (d); 133.8 (s); 133.9 (s); 135.6 (d); 135.7 (d). HRMS (+ESI): *m/z* calcd. for $C_{44}H_{79}O_5Si_3$ (M+H) 771.5230, found 771.5217.

General procedure for thioester formation by Mitsunobu reaction:

Diisopropyl azodicarboxylate (1.5 eq.) was added to a solution of alcohol **S7a** (1 eq.), 1-R-1*H*-tetrazole-5-thiol (1.5 eq.) and PPh_3 (1.5 eq.) in THF. The reaction mixture was stirred at r.t. for 5 h. The solvent was removed under reduced pressure and the residue was purified by

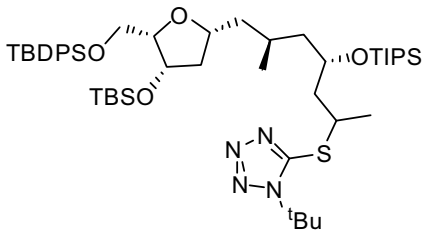
silica gel column chromatography with hexane-EtOAc (98:2 to 95:5) to yield the corresponding thioester **S8** as a colorless oil.

5-[(2*RS*,4*S*,6*S*)-7-((2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-thio]-1-phenyl-1*H*-tetrazole (S8a).



Alcohol **S7a** (4.9 g, 6.35 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (1.69 g, 9.5 mmol) led to thioester **S8a** (4.19 g, 71%). IR (KBr film) ν 2930, 2864, 1598, 1500, 1462, 1428, 1388, 1251, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (2s, 3H); 0.04 and 0.05 (2s, 3H); 0.86 and 0.87 (2s, 9H); 0.92 (d, *J* = 6.3 Hz, 3H); 1.01 (s, 13H); 1.04, 1.05 and 1.06 (3s, 17H); 1.35–1.50 (m, 2H); 1.56 and 1.58 (2d, *J* = 6.7 Hz, 3H); 1.54–1.68 (m, 5H); 1.85–2.02 (m, 1H); 2.20–2.27 (m, 1H); 3.61–3.71 (m, 2H); 3.80–3.85 (m, 1H); 4.04–4.22 (m, 3H); 4.43–4.50 (m, 1H); 7.34–7.44 (m, 6H); 7.52–7.56 (m, 5H); 7.65–7.71 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –4.8 (q); –4.6 (q); 12.9 (d); 17.8 (s); 17.9 (s); 18.2 (q); 18.3 (q); 19.2 (s); 19.8 (q); 21.8 (q); 23.1 (q); 25.8 (q); 26.8 (q); 27.4 (d); 41.3 (t); 41.6 (t); 42.0 (d); 43.2 (t); 44.7 (t); 44.9 (t); 45.1 (t); 64.1 (t); 68.6 (d); 68.7 (d); 73.1 (d); 76.9 (d); 85.6 (d); 85.7 (d); 124.0 (d); 127.6 (d); 129.6 (d); 129.9 (d); 130.0 (d); 133.4 (s); 133.5 (s); 133.8 (s); 135.6 (d); 153.8 (s). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{82}O_4N_4NaSSi_3$ (M+Na) 953.5257, found 953.5268.

5-[(2*RS*,4*S*,6*S*)-7-((2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-thio]-1-*tert*-butyl-1*H*-tetrazole (S8b).

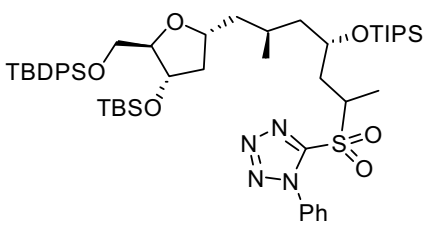


Alcohol **S7b** (490 mg, 0.63 mmol), and 1-(*tert*-butyl)-1*H*-tetrazole-5-thiol[4] (140 mg, 0.89 mmol) led to **S8b** (529 mg, 92%). IR (KBr film) ν 2931, 2864, 1463, 1390, 1253, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.05 and –0.04 (2s, 3H); –0.00 and 0.00 (2s, 3H); 0.79 and 0.80 (2s, 9H); 0.91 (2d, *J* = 6.2 Hz, 3H); 1.03 (s, 10H); 1.05, 1.06 and 1.07 (3s 20H); 1.36–1.48 (m, 3H); 1.53 and 1.54 (2d, *J* = 6.6 Hz, 3H); 1.57–1.67 (m, 4H); 1.68 and 1.70 (2s, 9H); 1.84–2.02 (m, 1H); 2.19–2.26 (m, 1H); 3.72–3.80 (m, 2H); 3.82–3.86 (m, 1H); 3.87–3.96 (m, 1H); 4.07–4.26 (m, 2H); 4.30–4.36 (m, 1H); 7.32–7.42 (m, 6H); 7.67–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.2 (q); –4.7(q); –4.6 (q); 12.9 (d); 17.9 (s); 18.2 (q); 18.3 (q); 19.2 (s); 19.9 (q); 21.8 (q); 23.2 (q); 25.7 (q); 26.9 (q); 27.4 (d); 28.7 (q); 41.7 (t); 41.8 (t); 41.9 (d); 42.3 (d); 43.1 (t); 43.2 (t); 44.9 (t); 45.0 (t); 45.1 (t); 60.8 (s); 63.7 (t); 68.8 (d); 72.6 (d); 75.6 (d); 75.9 (d); 83.2 (d); 83.3 (d); 127.5 (d); 129.4 (d); 132.2 (s); 133.7 (s); 135.6 (d); 135.7 (d); 152.1 (s). HRMS (+ESI): *m/z* calcd. for $C_{49}H_{87}N_4O_4SSi_3$ (M+H) 911.5750, found 911.5740.

General procedure for oxidation to the sulfone:

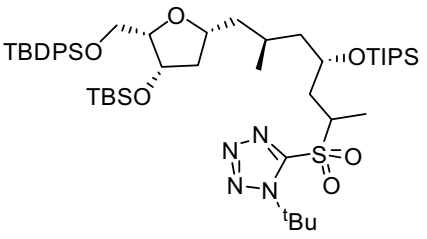
A solution of 70% m-CPBA (2.2 eq) and thioester **S8** (1 eq.) in CH_2Cl_2 was stirred for 16 h. The reaction mixture was diluted with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ and the residue was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded the corresponding sulfone **2** as a colorless oil.

5-[(2*RS*,4*S*,6*S*)-7-((2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-sulfonyl]-1-phenyl-1*H*-tetrazole (2a).



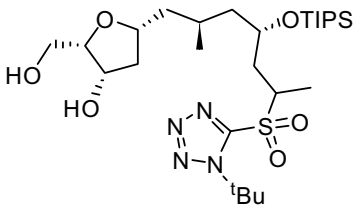
Thioester **S8a** (4.19 g, 4.5 mmol) led to sulfone **2a** (3.85 g, 89%). IR (KBr film) ν 2930, 2865, 1498, 1463, 1338, 1252, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.03, 0.04, 0.05 and 0.06 (4s, 6H); 0.88 and 0.89 (2s, 9H); 0.89 and 0.92 (2d, *J* = 6.0 Hz, 3H); 1.06, 1.07 and 1.08 (3s, 30H); 1.38–1.70 and 1.83–1.91 (2m, 7H); 1.49 and 1.56 (2d, *J* = 6.8 Hz, 3H); 2.12–2.28 and 2.42–2.50 (2m, 2H); 3.62–3.71 (m, 2H); 3.77–3.85 (m, 1H); 4.07–4.21 and 4.24–4.31 (2m, 3H); 4.40–4.51 (m, 1H); 7.34–7.43 (m, 6H); 7.55–7.62 (m, 3H); 7.64–7.71 (m, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –4.8 (q); –4.7 (q); 12.9 (d); 13.5 (q); 15.9 (q); 17.7 (s); 17.9 (s); 18.2 (q); 18.3 (q); 19.0 (s); 19.2 (q); 19.7 (q); 25.8 (q); 26.8 (q); 27.3 (d); 27.4 (d); 34.1 (t); 35.7 (t); 41.4 (t); 41.6 (t); 44.6 (t); 45.0 (t); 45.1 (t); 58.6 (d); 58.8 (d); 64.1 (t); 64.3 (t); 67.5 (d); 69.3 (d); 73.1 (d); 73.3 (d); 76.5 (d); 76.9 (d); 85.8 (d); 85.9 (d); 125.3 (d); 125.4 (d); 127.6 (d); 129.5 (d); 129.6 (d); 131.3 (d); 133.2 (s); 133.4 (s); 133.5 (s); 135.6 (d); 152.6 (s); 152.7 (s). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{83}O_6N_4SSi_3$ (M+H) 963.5336, found 963.5351.

5-[(2*RS*,4*S*,6*S*)-7-((2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-sulfonyl]-1-*tert*-butyl-1*H*-tetrazole (2b).



Thiotetrazole **S8b** (2.56 g, 2.8 mmol) led to sulfone **2b** (2.10 g, 80%). IR (KBr film) ν 2941, 2865, 1463, 1332, 1158, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.04 (s, 3H); 0.00 and 0.01 (2s, 3H); 0.80 (2s, 9H); 0.91 (d, *J* = 6.2 Hz, 3H); 1.05 (2s, 9H); 1.06 and 1.07 (2s, 21H); 1.37–1.70 (m, 7H); 1.50 and 1.56 (2d, *J* = 6.9 Hz, 3H); 1.84 (s, 9H); 2.12–2.26 and 2.42–2.49 (2m, 2H); 3.71–3.78 (m, 2H); 3.82–3.96 (m, 2H); 4.07–4.16 and 4.24–4.43 (2m, 3H); 7.32–7.42 (m, 6H); 7.67–7.71 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.2 (q); –4.6 (q); 12.9 (d); 13.9 (q); 16.3 (q); 18.0 (s); 18.2 (q); 18.3 (q); 19.1 (q); 19.2 (s); 19.6 (q); 25.7 (q); 26.9 (q); 27.4 (d); 27.5 (d); 29.6 (q); 29.7 (q); 34.2 (t); 35.9 (t); 41.7 (t); 41.9 (t); 45.0 (t); 45.2 (t); 45.3 (t); 58.8 (d); 59.3 (d); 63.5 (t); 65.3 (s); 65.4 (s); 67.6 (d); 69.5 (d); 72.5 (d); 75.6 (d); 75.9 (d); 83.2 (d); 83.3 (d); 127.5 (d); 129.5 (d); 133.7 (s); 133.8 (s); 134.0 (s); 135.6 (d); 135.7 (d); 153.2 (s); 153.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{49}H_{90}N_5O_6SSi_3$ (M+NH_4) 960.5914, found 960.5907.

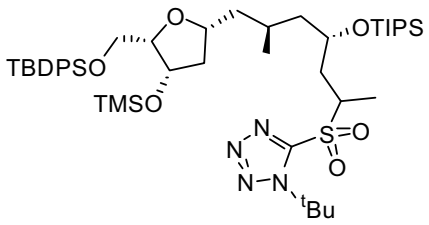
(2*S*,3*S*,5*R*)-5-[(2*S*,4*S*,6*RS*)-6-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl-sulfonyl)-2-methyl-4-(triisopropylsilyloxy)heptyl]-2-(hydroxymethyl)tetrahydrofuran-3-ol (S9).



PPTS (666 mg, 2.6 mmol) was added to a solution of sulfone **2b** (250 mg, 0.26 mmol) in MeOH (10 mL) and the reaction was stirred at 65 ºC for 5 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-EtOAc (80:20 to 50:50) to yield **S9** (114 mg, 95%) as a colorless oil. IR (KBr film) ν 3419 (br), 2943, 2867, 1464, 1377, 1332, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 and 0.94 (2d, *J* = 6.3 Hz, 3H); 1.08 (bs, 21H); 1.41–1.78 and 1.94–2.03 (m, 6H); 1.55 and 1.61 (2d, *J* = 6.8 Hz, 3H); 1.86 (2s, 9H); 2.20–2.27 and 2.36–2.50 (2m, 3H); 3.73–3.80 (m, 1H); 3.86–4.01 (m, 3H); 4.16–4.30 (m, 1H); 4.33–4.41 (m, 1H); 4.43–4.51 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.7 (d); 12.9 (d); 14.4 (q); 16.0 (q); 18.2 (q); 19.8 (q); 20.1 (q); 26.9 (d); 27.4 (d); 29.7 (q); 33.7 (t); 36.4 (t); 42.7 (t); 42.9 (t); 43.1 (t); 44.0 (t); 44.5 (t); 45.0 (t); 59.2 (d); 59.3 (d); 61.7 (t); 61.8 (t); 65.5 (s); 65.6 (s); 68.1 (d); 69.6

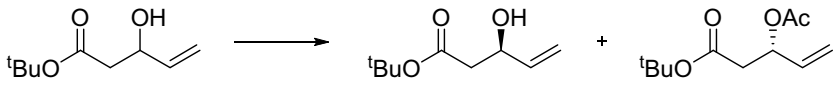
(d); 73.9 (d); 74.1 (d); 75.2 (d); 75.3 (d); 80.6 (d); 80.7 (d); 153.1 (s); 153.2 (s). HRMS (+ESI): *m/z* calcd. for $C_{27}H_{55}N_4O_6SSi$ (M+H) 591.3606, found 591.3608.

1-(*tert*-Butyl)-5-[(2*RS*,4*S*,6*S*)-7-((2*R*,4*S*,5*S*)-5-(*tert*-butyldiphenylsilyloxymethyl)-4-(trimethylsilyloxy) tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-sulfonyl]-1*H*-tetrazole (2c).



TBDPSCl (71 µL, 0.27 mmol) was added to a solution of diol **S9** (150 mg, 0.25 mmol) and imidazole (68 mg, 1 mmol) in CH_2Cl_2 (10 mL) and the reaction was stirred for 1 h. After this time, TMSCl (48 µL, 0.37 mmol) was added and the reaction was stirred for further 15 min. Finally, the resulting 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 (97:3) yielded **2c** (165 mg, 73%) as a colorless oil. IR (KBr film) ν 2943, 2866, 1463, 1333, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 and 0.06 (2s, 9H); 0.91 (d, *J* = 5.9 Hz, 3H); 1.04 (s, 9H); 1.07 (2bs, 21H); 1.38–1.68 (m, 7H); 1.50 and 1.56 (2d, *J* = 6.8 Hz, 3H); 1.84 (s, 9H); 1.89–1.94, 2.13–2.30 and 2.41–2.49 (3m, 2H); 3.70–3.77 (m, 2H); 3.83–3.93 (m, 2H); 4.07–4.16 and 4.23–4.31 (2m, 1H); 4.32–4.44 (m, 2H); 7.32–7.43 (m, 6H); 7.66–7.74 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 0.0 (q); 12.9 (d); 14.0 (q); 16.2 (q); 18.2 (q); 18.3 (q); 19.2 (s); 19.2 (q); 19.7 (q); 26.9 (q); 27.4 (d); 27.5 (d); 29.6 (q); 29.7 (q); 34.2 (t); 35.9 (t); 41.8 (t); 41.9 (t); 44.7 (t); 45.0 (t); 45.1 (t); 58.9 (d); 59.2 (d); 62.8 (t); 65.3 (s); 65.4 (s); 67.7 (d); 69.4 (d); 72.1 (d); 75.5 (d); 75.9 (d); 82.8 (d); 83.0 (d); 127.5 (d); 129.5 (d); 133.7 (s); 133.8 (s); 134.0 (s); 135.6 (d); 135.7 (d); 153.2 (s); 153.3 (s). HRMS (+ESI): *m/z* calcd. For $C_{46}H_{84}N_5O_6Ssi_3$ ($M+NH_4$) 918.5445, found 918.5443.

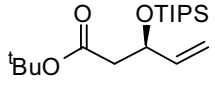
Kinetic resolution of **12**:[5]



12 ***R*-12** ***S*-Ac-12**

Lipase PS-30 (4.32 g) was added to a solution of **(±)-12** (2.15 g, 12.5 mmol) in vinyl acetate (10 mL) and pentane (25 mL), and the suspension was stirred for 48 h at 37 ºC. The residue was filtered through Celite® 545, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded ***R*-12** (1.05 g, 49%) and ***S*-Ac-12** (1.28 g, 48%) as colorless oils. ***R*-12**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H); 2.43 (dd, *J* = 16.2, 8.3 Hz, 1H); 2.51 (dd, *J* = 16.2, 4.0 Hz, 1H); 3.11 (bs, OH); 4.45–4.52 (m, 1H); 5.14 (dt, *J* = 10.5, 1.4 Hz, 1H); 5.30 (dt, *J* = 17.2, 1.4 Hz, 1H); 5.87 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H). ***S*-Ac-12**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H); 2.05 (s, 3H); 2.52 (dd, *J* = 15.3, 5.8 Hz, 1H); 2.60 (dd, *J* = 15.3, 8.0 Hz, 1H); 5.20 (dd, *J* = 10.5, 1.0 Hz, 1H); 5.30 (dd, *J* = 17.2, 1.0 Hz, 1H); 5.57–5.63 (m, 1H); 5.83 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H).

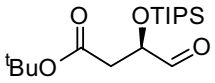
***tert*-Butyl (*R*)-3-(triisopropylsilyloxy)pent-4-enoate (S10).**



Triisopropylsilyl trifluoromethanesulfonate (1.98 mL, 7.34 mmol) was added to a solution of aldol **(*R*)-12** (1.05 g, 6.1 mmol), imidazole (830 mg, 12.2 mmol) and DMAP (20 mg) in THF (60 mL), and the reaction mixture was stirred for 16 h at reflux temperature. The solvent was removed under reduced pressure and the residue was dissolved in water and 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 (97:3) yielded **S10** (1.78 g, 89%) as a colorless oil. $[\alpha]_D$ = −3.8 (c 1.0, $CHCl_3$). IR (KBr film) ν 2944, 2867, 1732, 1464, 1367, 1256, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04–1.07 (m, 21H); 1.43 (s, 9H); 2.37 (dd, *J* = 14.4, 7.5 Hz, 1H); 2.56

(dd, *J* = 14.4, 5.8 Hz, 1H); 4.59–4.65 (m, 1H); 5.06 (ddd, *J* = 10.4, 1.7, 1.1 Hz, 1H); 5.20 (ddd, *J* = 17.2, 1.7, 1.1 Hz, 1H); 5.87 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.3 (d); 18.0 (q); 18.1 (q); 28.1 (q); 45.2 (t); 71.3 (d); 80.4 (s); 114.5 (t); 140.6 (d); 170.1 (s). HRMS (+ESI): *m/z* calcd. for $C_{18}H_{37}O_3Si$ (M+H) 329.2507, found 329.2506.

***tert*-Butyl (*R*)-4-oxo-3-(triisopropylsilyloxy)butanoate (3).**

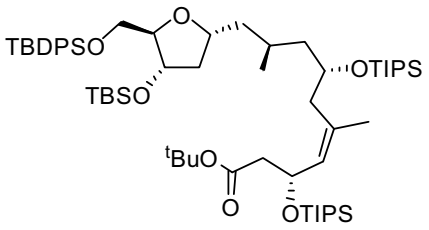


Ozone gas was bubbled into a solution of olefin **S10** (1.45 g, 4.41 mmol) in a 4:1 mixture of CH_2Cl_2-MeOH (100 mL) at −78ºC until the blue color persisted. Argon was passed through the solution for 10 min at −78ºC to remove any excess ozone. Then, PPh_3 (1.5 g, 5.73 mmol) was added and the solution was stirred at r.t. for 16 h. The reation mixture was concentrated under reduced pressure and filtered through silica to yield **3** (1.35 g, 93%) as a colorless oil. $[\alpha]_D$ = +11.5 (c 1.0, $CHCl_3$). IR (KBr film) ν 2944, 2868, 1736, 1464, 1367, 1256, 1157 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04–1.07 (m, 21H); 1.44 (s, 9H); 2.66 (ddd, *J* = 15.7, 5.8, 0.8 Hz, 1H); 2.78 (dd, *J* = 15.7, 4.0 Hz, 1H); 4.32 (ddd, *J* = 5.8, 4.0, 0.8 Hz, 1H); 9.80 (t, *J* = 0.8, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.1 (d); 17.8 (q); 28.0 (q); 41.22 (t); 74.2 (d); 81.4 (s); 169.0 (s); 204.2 (d). HRMS (+ESI): *m/z* calcd. for $C_{17}H_{35}O_4Si$ (M+H) 331.2299, found 331.2297.

General Procedure for Julia-Kocienski olefination:

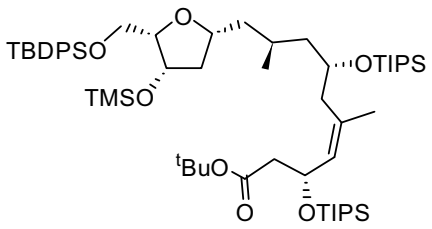
A 2M solution of LDA in THF/heptane/ethylbenzene (2 eq.) was added to a solution of sulfone **2** (1 eq.) and HMPA (2 eq.) in THF with 4Å molecular sieves, and the solution was stirred for 1 min. After this time, a solution of aldehyde **3** (2 eq.) in THF was added and the solution was stirred for an additional 2 h. The reaction mixture was quenched with sat. NH_4Cl and was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in EtOH and 40% $NaHSO_3$, the white precipitate was removed by filtration and the solvent was concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-Et_2O (97:3) yielded the corresponding olefin **13** as a colorless oil.

***tert*-Butyl (3*R*,7*S*,9*S*,*Z*)-10-[(2*R*,4*S*,5*R*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenyl silyloxymethyl)tetrahydrofuran-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoate (13a).**



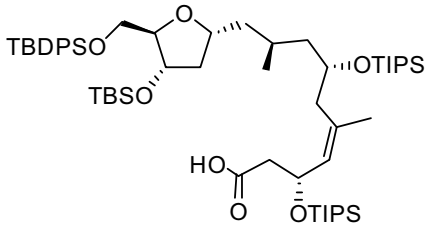
Sulfone **2a** (670 mg, 0.69 mmol) and aldehyde **3** (460 mg, 1.39 mmol) led to olefin **13a** as a *Z*:*E* (7:3) mixture of diastereomers. The major diastereomer could be isolated independently (283 mg, 38%). $[\alpha]_D$ = +14.3 (c 1.0, $CHCl_3$). IR (KBr film) ν 2930, 2865, 1733, 1463, 1367, 1256, 1112 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H); 0.05 (s, 3H); 0.87 (s, 9H); 0.93 (d, *J* = 6.6 Hz, 3H); 1.06 (bs, 51H); 1.26–1.38 (m, 2H); 1.42 (s, 9H); 1.50–1.61 (m, 3H); 1.66–1.69 (m, 1H); 1.67 (s, 3H); 2.19–2.28 (m, 3H); 2.38–2.41 (m, 2H); 3.66 (dd, *J* = 11.0, 3.9 Hz, 1H); 3.71 (dd, *J* = 11.0, 3.9 Hz, 1H); 3.83 (q, *J* = 3.9 Hz, 1H); 4.08–4.17 (m, 2H); 4.46–4.42 (m, 1H); 4.91–4.80 (m, 1H); 5.30 (d, *J* = 7.5 Hz, 1H); 7.34–7.45 (m, 6H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.8 (q); −4.6 (q); 12.5 (d); 13.0 (d); 17.9 (s); 18.1 (q); 18.2 (q); 18.3 (q); 18.4 (q); 19.2 (s); 20.5 (q); 23.2 (q); 25.8 (q); 26.8 (q); 27.7 (d); 28.1 (q); 40.8 (t); 41.8 (t); 43.6 (t); 45.7 (t); 46.2 (t); 64.2 (t); 67.0 (d); 68.7 (d); 73.0 (d); 77.5 (d); 79.9 (s); 85.5 (d); 127.6 (d); 129.6 (d); 131.8 (s); 132.0 (d); 133.4 (s); 133.6 (s); 135.6 (d); 135.7 (d); 170.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{61}H_{114}NO_7Si4$ (M+NH_4) 1084.7667, found 1084.7664.

***tert*-Butyl (3*R*,7*S*,9*S*,*Z*)-10-[(2*R*,4*S*,5*S*)-4-(trimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoate (13b).**



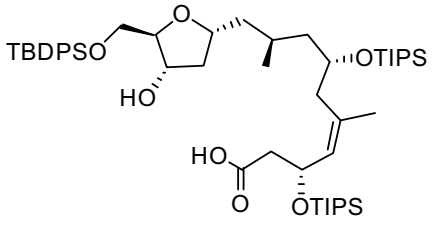
Sulfone **2c** (165 mg, 0.18 mmol) and aldehyde **3** (165 mg, 0.5 mmol) led to olefin **13b** as a *Z*:*E* (97:3) mixture of diastereomers (76 mg, 42%). $[\alpha]_D$ = +5.0 (c 0.5, CH_2Cl_2). IR (KBr film) ν 2943, 2866, 1732, 1464, 1367, 1252, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.06 (s, 9H); 0.93 (d, *J* = 6.6 Hz, 3H); 1.02 and 1.04 (2bs, 51H); 1.28–1.34 (m, 2H); 1.42 (s, 9H); 1.45–1.57 (m, 3H); 1.63–1.65 (m, 1H); 1.66 (d, *J* = 1.4 Hz, 3H); 2.12–2.29 (m, 3H); 2.39 (d, *J* = 6.1 Hz, 2H); 3.70–3.78 (m, 2H); 3.80–3.92 (m, 2H); 4.05–4.11 (m, 1H); 4.37 (dt, *J* = 6.6, 4.1 Hz, 1H); 4.91–4.98 (m, 1H); 5.29 (d, *J* = 8.6 Hz, 1H); 7.32–7.42 (m, 6H); 7.66–7.74 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 0.0 (q); 12.5 (d); 13.0 (d); 18.1 (q); 18.3 (q); 19.2 (s); 20.5 (q); 23.1 (q); 26.9 (q); 27.8 (d); 28.1 (q); 40.6 (t); 42.2 (t); 43.7 (t); 45.7 (t); 46.0 (t); 62.8 (t); 67.0 (d); 68.8 (d); 72.1 (d); 76.3 (d); 79.9 (s); 83.0 (d); 127.5 (d); 129.4 (d); 131.9 (d); 133.8 (s); 134.0 (s); 135.6 (d); 135.7 (d); 170.4 (s). HRMS (+ESI): *m/z* calcd. For $C_{58}H_{104}NaO_7Si4$ (M+Na) 1047.6751, found 1047.6776.

(3*R*,7*S*,9*S*,*Z*)-10-[(2*R*,4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy methyl)tetrahydrofuran-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoic acid (S11).



Trimethylsilyl trifluoromethanesulfonate (0.1 mL, 0.55 mmol) was added to a solution of **13a** (120 mg, 0.11 mmol) and Et_3N (0.15 mL, 1.1 mmol) in CH_2Cl_2 (5 mL) and the reaction mixture was stirred for 15 min. The solution was diluted with CH_2Cl_2 and was washed with sat. $NaHCO_3$ and sat. NH_4Cl. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded **S11a** (106 mg, 96%) as a colorless oil. $[\alpha]_D$ = +10.6 (c 1.0, $CHCl_3$). IR (KBr film) ν 2930, 2865, 1712, 1463 , 1256, 1106 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H); 0.03 (s, 3H); 0.86 (s, 9H); 0.94 (d, *J* = 6.6 Hz, 3H); 1.05 and 1.06 (2bs, 51H); 1.22–1.28 (m, 1H); 1.38–1.46 (m, 1H); 1.50–1.62 (m, 3H); 1.67–1.73 (m, 1H); 1.72 (s, 3H); 2.02–2.10 (m, 1H); 2.25 (dt, *J* = 12.6, 6.5 Hz, 1H); 2.34 (dd, *J* = 13.3, 5.8 Hz, 1H); 2.53 (dd, *J* = 14.8, 5.2 Hz, 1H); 2.61 (dd, *J* = 14.8, 5.6 Hz, 1H); 3.63–3.71 (m, 2H); 3.85 (q, *J* = 4.2 Hz, 1H); 4.06–4.14 (m, 1H); 4.17 (p, *J* = 6.9 Hz, 1H); 4.39–4.45 (m, 1H); 4.86–4.92 (m, 1H); 5.33 (d, *J* = 8.0 Hz, 1H); 7.34–7.45 (m, 6H); 7.65–7.71 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –4.9 (q); –4.7 (q); 12.2 (d); 13.0 (d); 17.9 (q); 18.0 (q); 18.3 (q); 19.2 (s); 20.9 (q); 23.9 (q); 25.8 (q); 26.8 (q); 27.5 (d); 41.0 (t); 41.6 (t); 43.3 (t); 43.5 (t); 45.2 (t); 64.2 (t); 66.9 (d); 69.4 (d); 73.1 (d); 77.1 (d); 85.7 (d); 127.6 (d); 129.5 (d); 129.6 (d); 133.4 (s); 133.5 (s); 135.6 (d); 135.7 (d); 172.0 (s). HRMS (+ESI): *m/z* calcd. for $C_{57}H_{106}NO_7Si4$ (M+NH_4) 1028.7041, found 1028.7022.

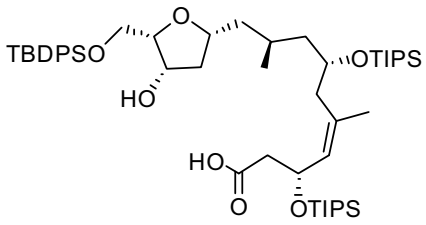
(3*R*,7*S*,9*S*,*Z*)-10-[(2*R*,4*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-4-hydroxytetrahydro furan-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoic acid (14a).



Pyridinium *p*-toluenesulfonate (251 mg, 1 mmol) was added to a solution of **S11a** (106 mg, 0.1 mmol) in MeOH (5 mL) and the reaction mixture was stirred for 16 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-EtOAc (95:5 to 80:20) to yield **14a** (64 mg, 71%) as a colorless oil. $[\alpha]_D$ = +0.1 (c 1.0, $CHCl_3$). IR (KBr film) ν 2943, 2866, 1712, 1463, 1105 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ

0.92 (d, *J* = 6.6 Hz, 3H); 1.06 (bs, 51H); 1.24–1.30 (m, 1H); 1.39–1.47 (m, 1H); 1.51–1.57 (m, 2H); 1.59–1.71 (m, 2H); 1.71 (d, *J* = 1.3 Hz, 3H); 2.00–2.07 (m, 1H); 2.32–2.41 (m, 2H); 2.52 (dd, *J* = 14.8, 5.3 Hz, 1H); 2.61 (dd, *J* = 14.8, 5.5 Hz, 1H); 3.63 (dd, *J* = 10.4, 6.4 Hz, 1H); 3.78 (dd, *J* = 10.4, 4.4 Hz, 1H); 3.87 (dt, *J* = 6.4, 4.4 Hz, 1H); 4.01–4.10 (m, 1H); 4.11–4.18 (m, 1H); 4.38–4.44 (m, 1H); 4.84-4.91 (m, 1H); 5.31 (d, *J* = 8.3 Hz, 1H); 7.35–7.46 (m, 6H); 7.64–7.69 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.3 (d); 13.0 (d); 17.8 (q); 17.9 (q); 18.3 (q); 19.2 (s); 20.8 (q); 24.3 (q); 26.9 (q); 27.5 (d); 40.8 (t); 41.0 (t); 43.3 (t); 43.5 (t); 45.2 (t); 65.0 (t); 66.9 (d); 69.6 (d); 74.7 (d); 76.9 (d); 84.2 (d); 127.8 (d); 129.5 (d); 129.8 (d); 133.1 (s); 134.6 (s); 135.5 (d); 135.6 (d); 172.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{92}NO_7Si_3$ (M+NH_4) 914.6176, found 914.6165.

(3*R*,7*S*,9*S*,*Z*)-10-((2*R*,4*S*,5*S*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-4-hydroxytetrahydro furan-2-yl)-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoic acid (14b).

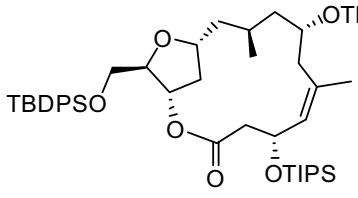


TMSOTf (58 µL, 0.32 mmol) was added to a solution of **13b** (65 mg, 0.06 mmol) and Et_3N (88 µL, 1.5 mmol) in CH_2Cl_2 (5 mL) and the reaction was stirred for 10 min. The solution was washed with sat. $NaHCO_3$ and sat. NH_4Cl; the organic residue was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude product was dissolved in MeOH (5 mL) and pyridinium *p*-toluenesulfonate (80 mg, 0.31 mmol) was added; the reaction was stirred for further 15 min. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-EtOAc (95:5 to 80:20) to yield **14b** (33 mg, 58%) as a colorless oil. $[\alpha]_D$ = −3.4 (c 1.0, CH_2Cl_2). IR (KBr film) ν 2942, 2866, 1712, 1463, 1105 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.7 Hz, 3H); 1.05 (2bs, 51H); 1.18–1.24 (m, 1H); 1.42–1.49 (m, 1H); 1.51–1.59 (m, 1H); 1.60–1.69 (m, 2H); 1.73 (d, *J* = 1.4 Hz, 3H); 1.74–1.80 (m, 1H); 2.02 (dd, *J* = 13.3, 7.5 Hz, 1H); 2.39 (dt, *J* = 13.3, 6.9 Hz, 1H); 2.41–2.46 (m, 1H); 2.54 (dd, *J* = 14.4, 6.1 Hz, 1H); 2.59 (dd, *J* = 14.4, 5.4 Hz, 1H); 3.83–3.87 (m, 1H); 3.89–3.98 (m, 3H); 4.04–4.12 (m, 1H); 4.53 (dt, *J* = 6.7, 4.4 Hz, 1H) 4.82–4.89 (m, 1H); 5.31 (d, *J* = 8.9 Hz, 1H); 7.34–7.47 (m, 6H); 7.64–7.74 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.3 (d); 13.1 (d); 17.9 (q); 18.0 (q); 18.3 (q); 19.1 (s); 21.2 (q); 24.7 (q); 26.8 (q); 27.6 (d); 41.0 (t); 41.9 (t); 43.4 (t); 43.5 (t); 44.3 (t); 63.2 (t); 66.7 (d); 67.0 (d); 73.7 (d); 75.9 (d); 80.4 (d); 127.8 (d); 129.5 (d); 129.9 (d); 133.4 (s); 132.7 (s); 134.7 (s); 135.5 (d); 135.6 (d); 171.9 (s). HRMS (-ESI): *m/z* calcd. For $C_{51}H_{87}O_7Si_3$ (M-H) 895.5765, found 895.5793.

General procedure for Yamaguchi lactonization:

A solution of 2,4,6-trichlorobenzoyl chloride (2 eq.) in THF was added to a solution of seco-acid **14** (1 eq.) and Et_3N (3 eq.) in THF. The reaction mixture was stirred for 5 min and DMAP (1 eq.) was added. The reaction mixture was stirred for further 5 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-Et_2O (98:2) to yield the corresponding macrocycle/s **1** as colorless oil/s.

(1*S*,5*R*,9*S*,11*S*,13*R*,15*R*,*Z*)-15-(*tert*-Butyldiphenylsilyloxymethyl)-7,11-dimethyl-5,9-bis (triisopropylsilyloxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (1a).

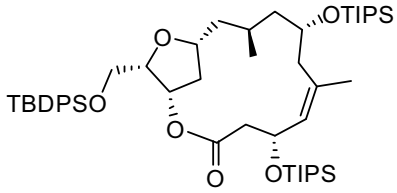


Seco-acid **14a** (40 mg, 0.044 mmol) led to macrocycle **1a** (15 mg, 39%). $[\alpha]_D$ = +2.1 (c 0.5, $CHCl_3$). IR (KBr film) ν 2943, 2865, 1745, 1463, 1273, 1117 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.3 Hz, 3H); 1.06 (bs, 51H); 1.37–1.48 (m, 2H); 1.52–1.58 (m, 1H); 1.63–1.71 (m, 1H); 1.78 (s, 3H); 1.98–2.07 (m, 2H); 2.18–2.25 (m, 1H); 2.29 (dd, *J* = 14.0, 4.1 Hz, 1H); 2.48 (dd, *J* = 14.0, 6.9 Hz, 1H); 2.65 (d, *J* = 5.3 Hz, 2H); 3.66 (dd, *J*

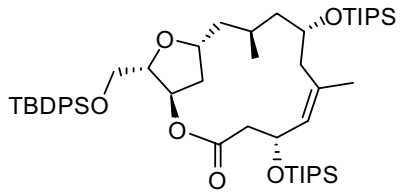
= 10.9, 4.0 Hz, 1H), 3.80 (dd, *J* = 10.9, 3.3 Hz, 1H); 4.06–4.14 (m, 2H); 4.43–4.50 (m, 1H); 4.94–5.01 (m, 1H); 5.27 (d, *J* = 5.6 Hz, 1H); 5.41 (d, *J* = 7.7 Hz, 1H); 7.35–7.46 (m, 6H); 7.65–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.4 (d); 12.8 (d); 18.0 (q); 18.2 (q); 19.2 (s); 20.2 (q); 24.4 (q); 26.8 (q); 27.1 (d); 34.1 (t); 39.9 (t); 41.8 (t); 46.5 (t); 47.1 (t); 64.9 (t); 67.7 (d); 70.8 (d); 77.5 (d); 78.3 (d); 84.2 (d); 127.7 (d); 129.6 (d); 129.7 (d); 131.4 (d); 133.2 (s); 133.3 (s); 134.7 (s); 135.6 (d); 170.7 (s). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{90}NO_6Si_3$ (M+NH_4) 896.6070, found 896.6062.

(1*S*,5*R*,9*S*,11*S*,13*R*,15*RS*,*Z*)-15-(*tert*-Butyldiphenylsilyloxymethyl)-7,11-dimethyl-5,9-bis (triisopropylsilyloxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (1b and 1c).

Seco-acid **14b** (32 mg, 0.035 mmol) led to macrocycles **1b** (9 mg, 29%) and **1c** (2 mg, 6%).

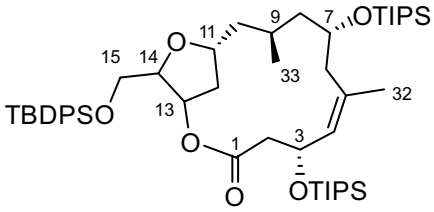


(15*S*)-1b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 and 0.97 (2s, 20H); 1.00 (d, *J* = 6.6 Hz, 3H); 1.03 and 1.04 (2s, 31H); 1.31–1.47 (m, 4H); 1.53–1.66 (m, 2H); 1.72 (d, *J* = 1.2 Hz, 3H); 2.03 (dd, *J* = 13.6, 6.0 Hz, 1H); 2.30 (dd, *J* = 15.1, 4.0 Hz, 1H); 2.36 (dd, *J* = 13.6, 6.7 Hz, 1H); 2.42 (dd, *J* = 15.1, 8.4 Hz, 1H); 2.48 (dt, *J* = 13.7, 7.0 Hz, 1H); 3.75–3.82 (m, 1H); 3.83–3.89 (m, 3H); 4.04 (p, *J* = 10.9 Hz, 1H); 4.86 (td, *J* = 8.4, 4.0 Hz, 1H); 5.16–5.20 (m, 1H); 5.21 (d, *J* = 8.4 Hz, 1H); 7.33–7.42 (m, 6H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.6 (d); 13.1 (d); 18.1 (q); 18.2 (q); 18.5 (q); 19.4 (s); 20.5 (q); 25.5 (q); 27.0 (q); 28.8 (d); 40.2 (t); 40.8 (t); 43.3 (t); 44.3 (t); 45.9 (t); 62.8 (t); 66.8 (d); 70.1 (d); 74.3 (d); 77.5 (d); 81.4 (d); 127.7 (d); 127.8 (d); 129.7 (d); 131.3 (d); 133.4 (s); 133.7 (s); 134.0 (s); 135.7 (d); 135.8 (d); 170.6 (s). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{90}NO_6Si_3$ (M+NH_4) 896.6070, found 896.6053.



(15*R*)-1c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 5.2 Hz, 3H); 1.02 and 1.05 (2s, 51H); 1.25–1.44 (m, 3H); 1.58–1.71 (m, 2H); 1.74 (d, *J* = 1.4 Hz, 3H); 1.99 (dd, *J* = 14.2, 2.1 Hz, 1H); 2.14–2.21 (m, 1H); 2.31 (dd, *J* = 14.3, 5.0 Hz, 1H); 2.42 (dd, *J* = 14.3, 5.8 Hz, 1H); 2.47 (dd, *J* = 15.1, 6.2 Hz, 1H); 2.62 (dt, *J* = 15.1, 5.3 Hz, 1H); 3.80–3.84 (m, 2H); 3.92–3.97 (m, 1H); 4.04 (td, *J* = 6.6, 3.4 Hz, 1H); 4.19–4.26 (m, 1H); 4.75 (dt, *J* = 7.8, 5.8 Hz, 1H); 5.31–5.35 (m, 2H); 7.33–7.44 (m, 6H); 7.61–7.68 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.5 (d); 12.9 (d); 18.2 (q); 18.4 (q); 19.4 (s); 20.5 (q); 25.3 (q); 26.9 (q); 27.0 (d); 35.1 (t); 40.3 (t); 43.6 (t); 46.1 (t); 47.1 (t); 62.3 (t); 67.0 (d); 71.1 (d); 74.6 (d); 76.9 (d); 82.2 (d); 127.8 (d); 129.8 (d); 131.5 (d); 133.6 (s); 133.7 (s); 135.0 (s); 135.7 (d); 170.8 (s). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{90}NO_6Si_3$ (M+NH_4) 896.6070, found 896.6057.

6. NMR data table of macrocycles 1a-c. Spectra recorded in $CDCl_3$



	1a		1b		1c	
	δ_H, mult, J (Hz)	**δ_C, mult**	**δ_H, mult, J (Hz)**	**δ_C, mult**	**δ_H, mult, J (Hz)**	**δ_C, mult**
1	-	170.9, s	-	170.6, s	-	170.8, s
2	2.65, d, 5.3	46.6, t	2.42, dd, 15.1, 8.4 2.30, dd, 15.1, 4.0	44.3, t	2.62, dd, 15.1, 5.3 2.47 dd, 15.1, 6.2	46.1, t
3	4.97, m	67.8, d	4.86, td, 8.4, 4.0	66.8, d	4.75 dt, 7.8, 5.8	67.0, d
4	5.41, d, 7.7	131.6, d	5.21, d, 8.4	131.3, d	5.33, m	131.5, d
5	-	134.8, s	-	133.4, s	-	135.0, s
6	2.48, dd, 14.0, 6.9 2.29 dd, 14.0, 4.4	40.0, t	2.36, dd, 13.6, 6.7 2.03, dd, 13.6, 6.0	40.2, t	2.42, dd, 14.3, 5.8 2.31 dd, 14.3, 5.0	40.3, t
7	4.11, m	71.0, d	4.04, p, 6.3	70.1, d	3.95, m	71.1, d
8	1.69, dt, 13.5, 6.6 1.42, m	47.2, t	1.34, m	45.9, t	1.60, m 1.33, m	47.1, t
9	1.56, m	27.2, d	1.63, m	28.8, d	1.34 m	27.0, d
10	2.05, m 1.42, m	42.0, t	1.57, m 1.44, m	43.3, t	1.66, m 1.38, m	43.6, t
11	4.46, m	78.5, d	3.78, m	77.5, d	4.22, m	77.0, d
12	2.22, ddd, 13.8, 7.8, 5.8 2.01, d, 13.8	34.3, t	2.48, dt, 13.7, 7.0 1.36, m	40.8, t	2.17, m 1.99, dd, 14.2, 2.1	35.1 t
13	5.27, d, 5.6	77.7, d	5.18, m	74.3, d	5.33, m	74.6, d
14	4.10, m	84.4, d	3.84, m	81.4, d	4.04, td, 6.6, 3.4	82.2, d
15	3.66, dd, 10.9, 4.0 3.80, dd, 10.9, 3.3	64.9 t	3.86, m	62.8 t	3.82, m	62.3 t
32	1.78, s	24.6, q	1.72, d, 1.2	25.5, q	1.74, d, 1.4	25.3, q
33	0.94, d, 6.3	20.4, q	1.00, d, 6.6	20.5, q	0.88 d, 5.2	20.5, q

7. NMR spectra

NMR spectra images are available in the supporting information in electronic format.

8. References

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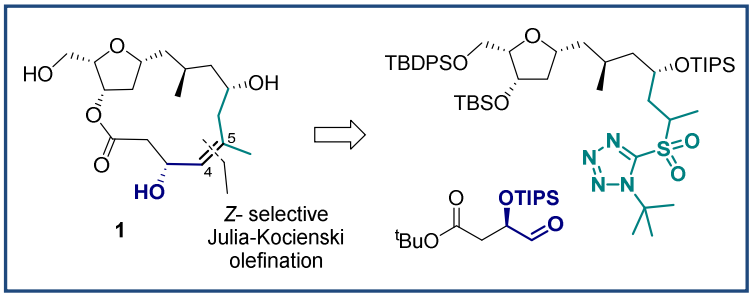
6 Formation of the endocyclic *Z*-trisubstituted double bond of phormidolides B-D

Tritonia odhneri

HIGHLY SELECTIVE FOMRATION OF A Z-TRISUBSTITUTED DOUBLE BOND USING A *tert*-BUTYL TETRAZOLYL SUFLONE



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RESUME

The formation of the *Z*-trisubstituted alkene present in the macrocyclic core of phormidolides B-D is the objective of the work presented in this chapter. We carried out an optimization process based on the testing of two different sulfones differing on the functionalization of the tetrazole moiety with a set of aldehydes with different protecting groups on the α-hydroxyl to the carbonyl (Figure 1). Changes on temperature and addition of HMPA completed the optimization on the reaction conditions.

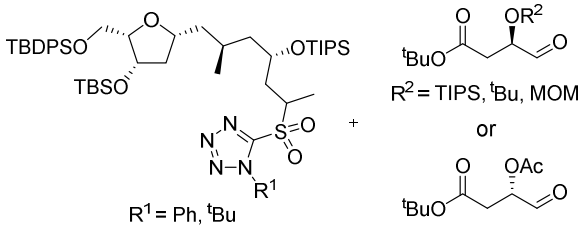

Figure 1. Substrates selected for optimization.

After the optimization process, we concluded that the best results were obtained with the *tert*-butyl tetrazolyl sulfone giving good to excellent *Z*-selectivities for all the tested aldehydes, at room temperature and with the addition of HMPA as additive. Moreover, a mechanistic explanation to our results is provided.

Highly selective formation of a *Z*-trisubstituted double bond using a 1-(*tert*-butyl)tetrazolyl sulfone

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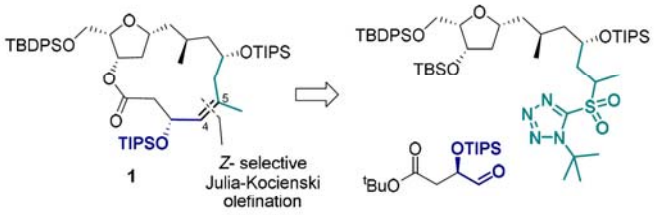
Supporting Information Placeholder



ABSTRACT: In our effort to gain further insight into the enantioselective synthesis of the structural core of phormidolides B-D, we have come across the formation of a *Z*-trisubstituted double bond. Here, we describe a highly selective process for application to our target, following a strategy based on a Julia-Kocienski olefination. The use of the 1-(*tert*-butyl)tetrazolyl sulfone affords the construction of the *Z*-trisubstituted alkene with high efficiency and stereoselectivity.

In the total synthesis of natural products, the design of efficient and stereoselective transformations is key to the success of a specific synthetic plan. Stereodefined alkenes are part of the structure of many natural products, and serve as foundation for a wide range of chemical transformations to introduce diversity in the carbon skeleton of a targeted compound.

Among the synthetic tactics employed in the formation of C-C double bonds, the most generally applicable are those involving olefination of carbonyl compounds, including the Wittig reaction,[1,2] Horner-Wittig,[2,3] Horner-Wadsworth-Emmons,[2,4] Peterson,[5] Johnson,[6] Still-Gennari[7]and the Julia-Kocienski olefination.[8] Other useful synthetic methods are alkenylation processes,[9] olefin metathesis,[10] and cycloaddition or sigmatropic reactions.[11] Nevertheless, despite the variety of available methods, the stereoselective formation of tri- and tetra-substituted double bonds is still a challenge for organic chemists.[12]

The lack of efficient and stereoselective methods to construct tri- and tetra-substituted double bonds lies on the fact that the congestion of the starting materials make it difficult for reagents to approach and the eclipsing interactions between the substituents destabilize both the products and the transition states leading to them. Moreover, the stereochemistry of the resulting products depends on a variety of parameters that are, in the majority of scenarios, difficult to control.

The modified Julia olefination has emerged as a useful tool for the construction of disubstituted alkenes in natural products synthesis,[13] because of the easy preparation of the starting materials, the mild reaction conditions needed and the variety of tunable parameters that can control stereoselectivity. Nevertheless, only few examples of stereoselective formation of tri- and tetrasubstituted double bonds using this methodology have been reported. Some good results have been achieved with the use of 3,5-bis(trifluoromethyl)phenylsulfones[14] and sulfoxides,[15] but in the majority of cases, selectivity is directed towards the *E*-isomer.[14-16]

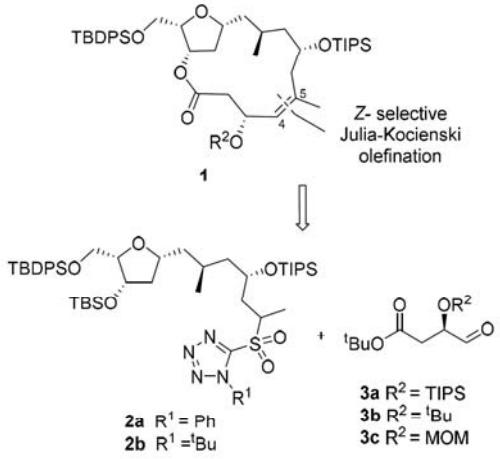
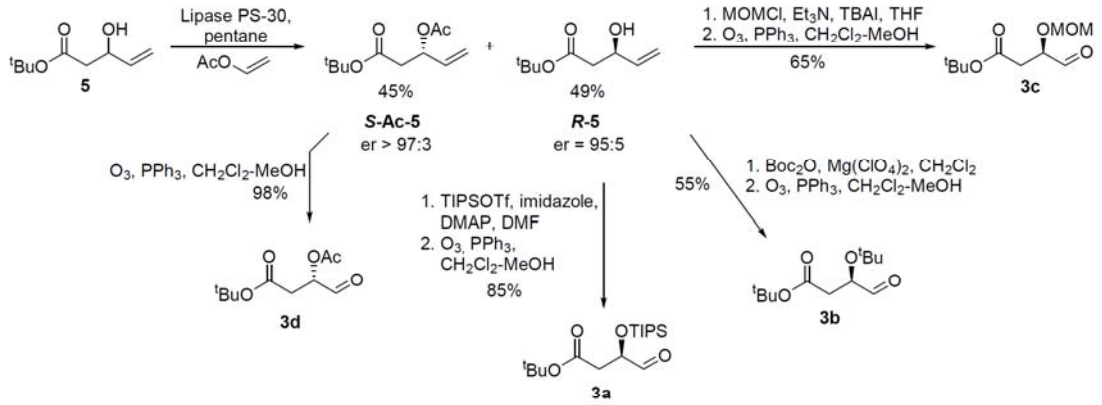


Figure 1. Retrosynthetic analysis of macrolactone **1**.

The use of 1-(tert-butyl)tetrazolyl sulfones for *Z*-selective olefinations was described in 2000 to obtain disubstituted olefins.[17] Some work has been conducted on methylenation

Scheme 2. Enantioselective synthesis of aldehydes 3a-d.



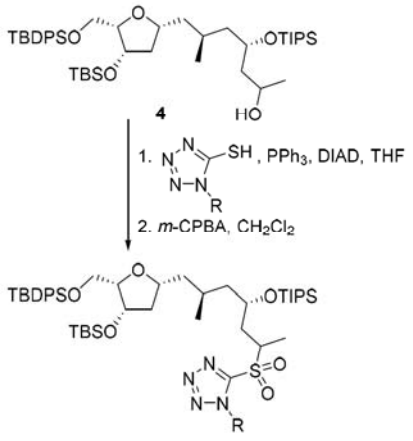
and cyclopropanation processes,[18] and also on the preparation of fluorinated[19] and trifluoromethylated[20] alkenes, but its applicability has only been reported in a few examples for the total synthesis of natural products.[21]

In further work towards the synthesis of the macrocyclic core **1,** common to phormidolides B-D, we have come across the formation of a *Z*-trisubstituted double bond, and our strategy depicted its formation by means of a Julia-Kocienski olefination (Figure 1).With the outlined background in mind, our strategy lied on the comparison of the 1-(*tert*-butyl)tetrazolyl sulfone with the widely used 1-phenyltetrazolyl sulfone, and its possible application to our total synthesis.

Here, we describe the optimization of the reaction conditions, the testing of these two different sulfones **2a** and **2b**, and the effect of the steric bulk on the aldehyde partner (**3a-d**), by protection of the available α-hydroxyl, for this type of olefinations.

Two sulfones, **2a** and **2b**, were prepared starting from known alcohol **4**,[22] by Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol or 1-(*tert*-butyl)-1*H*-tetrazole-5-thiol[23] and subsequent oxidation with 3-chloroperoxybenzoic acid (*m*-CPBA (Scheme 1).

Scheme 1. Synthesis of sulfones 2a-b.

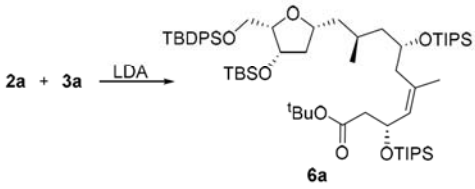


Enantioselective synthesis of aldehydes **3a-d** (Scheme 2) was performed by kinetic resolution of racemic β-hydroxy ester **5** with lipase PS-30, which produces ***R*-5** and ***S*-Ac-5** with excellent enantiopurity.[24] Aldehydes **3a-c** were prepared by protection of the free alcohol under mild conditions as triisopropylsilyl (TIPS), ^{t}Bu[25] or methoxymethyl (MOM) ethers, followed by reductive ozonolysis of the terminal olefins. Since we already had the acetylated ***S*-Ac-5**, this enantiomer was directly subjected to reductive ozonolysis to render aldehyde **3d**.

Several strategies were tested for the formation of the double bond motif. Neither Barbier conditions[26] nor intramolecular olefination[27] provided good results. Thus, premetallation of the sulfone was needed before the addition of the aldehyde. In our experience, the most appropriate base to perform the olefinations was lithium diisopropylamide (LDA). The use of BuLi, ^{t}BuLi and K^{t}BuO only led to decomposition of the starting materials. Lithium bis(timethylsilyl)amide (LiHMDS) gave slightly lower yields, although it can also be used for olefinations.

We studied the optimal temperature with sulfone **2a** and aldehyde **3a** to obtain olefin **6a** as a model (Table 1). Our experiments led to the conclusion that temperature had an effect on the diastereoselectivity of the reactions; while lower temperatures favoured *E*-selectivity and higher temperatures favoured *Z*-selectivity. Interestingly, when performing the reaction at reflux temperature, the yield decreased dramatically, most likely due to decomposition of the starting materials. An intermediate temperature appeared to be the best option between yield and diastereoselectivity (entry 2).

Table 1. Temperature optimization.



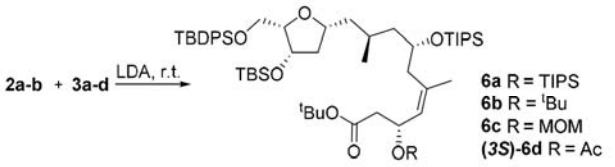
	T	yield	d.r. (*E*:*Z*)*
1	-78 ºC	31%	62:38
2	r.t.	42%	35:65
3	66 ºC	13%	30:70

*d.r. determined by ^{1}H-NMR

Reaction parameters were optimized at a fixed temperature (Table 2). The use of hexamethylphosphoramide (HMPA) as additive increased the diastereoselectivity of the reactions towards the *Z*-configuration (see entries 3 and 4). In general, the use of the 1-phenyltetrazolyl sulfone led to the desired

trisubstituted double bond with moderate yields and low selectivities (entries 1, 3 and 4). On the other hand, the use of the 1-(*tert*-butyl)tetrazolyl sulfone afforded good to excellent *Z*-selectivities (entries 2, 5, 6, and 7). Considering the effect of the steric bulk on the aldehyde, lower *Z*-selectivities were observed when a smaller protecting group was used (entries 6 and 7). The low yield observed to afford olefin **6d** (entry 7) might be due to the low stability of aldehyde **3d**, which can easily undergo an elimination process in the basic conditions of the reaction.

Table 2. Formation of *Z*-trisubstituted double bonds.



	Sulfone	Aldehyde	Additive	Product (yield)	d.r. (*E*:*Z*)*
1	**2a**	**3a**	-	**6a** (42%)	35:65
2	**2b**	**3a**	HMPA	**6a** (61%)	3:97
3	**2a**	**3b**	-	**6b** (30%)	50:50
4	**2a**	**3b**	HMPA	**6b** (42%)	33:67
5	**2b**	**3b**	HMPA	**6b** (47%)	3:97
6	**2b**	**3c**	HMPA	**6c** (59%)	12:88
7	**2b**	**3d**	HMPA	**(3*S*)-6d** (20%)	13:87

*d.r. determined by ^{1}H-NMR

The configuration of the formed double bonds was determined by NOESY experiments for **6a** and **6b** (see supporting information). Irradiation over the vinyl proton at 5.30 and 5.24 ppm of ***Z*-6a** and ***Z*-6b**, respectively, produced a clear nOe on the vinylic CH_3 singlet signal at 1.67 and 1.65 ppm, respectively. On the other hand, for ***E*-6a** and ***E*-6b**, this effect was not observed when the vinyl proton was irradiated. However, it was observed when irradiation was performed at the signal of around 4.95 and 4.69 respectively, which corresponded to the C3 hydroxylated methyne hydrogen. Thus, the relative disposition of the methyl group of the double bond was determined in each case. In addition, the ^{13}C-NMR chemical shift of the methyl at C5 can be used as an indicator to deduce stereochemistry. While the chemical shift for alkenes ***E*-6a** and ***E*-6b** is 17.7 and 17.6 ppm respectively, the chemical shift for alkenes ***Z*-6a** and ***Z*-6b** is 23.1 and 23.2 ppm respectively. The chemical shift of the same signal for major alkenes **6c** and **6d** is 23.9 and 24.6 ppm respectively, indicating they have the *Z*-configuration, which is consistent with our results. This fact may be explained by the effects that steric compression exerts on carbon nuclei causing a shielding effect.[28] In our case, the *E*-diastereomer has the methyl residue in a more compressed state, and therefore, the chemical shift on the ^{13}C-NMR chemical shift is decreased. Thus, in our system, a chemical shift below 20 on ^{13}C-NMR suggest the formation of the *E*-alkene, whereas a chemical shift over 20 suggests the formation of the *Z*-alkene.

The commonly accepted manifold mechanism of the Julia olefination[29] describes the formation of either the *E* or *Z* isomer based on the major species formed upon addition of the sulfone to the aldehyde *si* or *re* face. On a quelated transition state (addition to the *si* face), the aldehyde approach would lead to a *cis*-disposed intermediate, which has the right conformation for Smiles rearrangement. On the other hand, a less constricted open transition state (addition to the *re* face) would lead to the *trans*-intermediate, which needs equilibration to the conformation that undergoes Smiles rearrangement. Next, antiperiplanar β–elimination *via* extrusion of sulfur dioxide provides *Z* or *E* olefins in each case (Figure 2).

It is postulated that aliphatic α-sulfonyl carbanions may exist on a conformation where the electron pair of the carbanion is in a gauche conformation to both oxygen atoms of the sulfone,[30] and this may be true for aliphatic 1-phenyl and 1-(*tert*-butyl)tetrazolyl sulfones as well.[31] In our system, this fact may enable simultaneous quelation of the aldehyde and the sulfone, minimising the steric repulsion between R^1 and R^2 (A1). The addition to the aldehyde may lead to conformation A2 and Smiles rearrangement followed by sulfur dioxide extrusion would explain the formation of the *Z*-olefin (Figure 2).

On the other hand, the conformation that results from a *re* face addition and equilibrates to undergo Smiles rearrangement (B3) is extremely unfavoured by the steric repulsions of substituents R^1 and R^2, and the extra steric bulk provided by the phenyl or *tert*-butyl group on the tetrazole. As the equilibration process is slow, and the addition of the sulfonyl anion to the aldehyde is reversible, we postulate that pathway A is predominant.

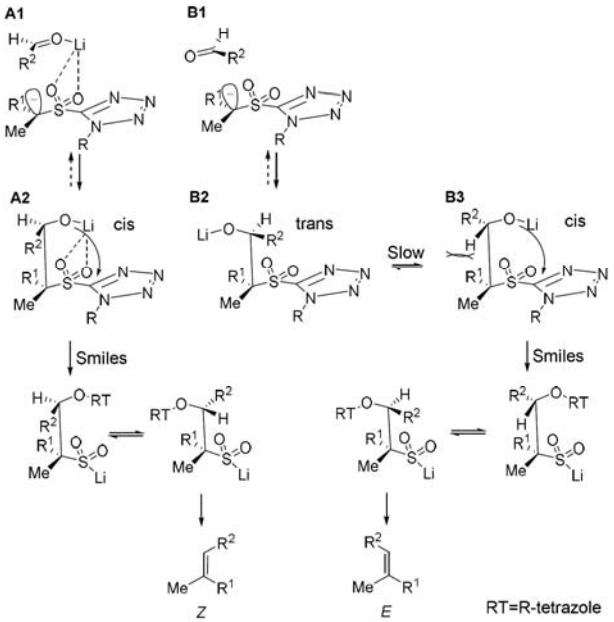


Figure 2. Putative structure of metallated tetrazolyl sulfones and mechanistic explanation.

This scenario explains why decreasing the steric bulk on the aldehyde and the use of the less bulky phenyl substituent on the tetrazole motif leads to lower stereoselectivities, and it also explains why the addition of HMPA, a disruptor of lithium oligomers, favours the formation of the *Z*-stereoisomer.

In summary, in our effort to attain the total synthesis of a natural product, we have come across the formation of a *Z*-trisubstituted double bond, which, despite the variety of me-

thods available to obtain C-C double bonds, is still a difficult motif to afford in an efficient and stereoselective manner. We have described the optimization process towards our target, and have provided a mechanistic explanation to our results. We have shown that the use of the 1-(*tert*-butyl)tetrazolyl sulfone provided higher yield and was more selective than the use of the 1-phenyltetrazolyl sulfone. Our reactions were performed at room temperature in the presence of HMPA, premetallating before the addition of the aldehyde, with a bulky protecting group on the α-hydroxyl. With this result in hand, the most challenging point of the synthesis was solved and we were able to effectively complete the total synthesis of the macrolide core of phormidolides B-D, **1**.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest

ACKNOWLEDGMENTS

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(22) The epimeric alcohol is used provided that this stereocenter is lost when the α-sulfonyl anion is formed.

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(26) A 2M solution of LDA in THF/heptane/ethylbenzene (2 eq.) was added to a solution of sulfone (1 eq.) and aldehyde (2 eq.) in THF with 4Å molecular sieves, and the solution was stirred for 2 h. After this time, sat. NH_4Cl was added and the residue was extracted with CH_2Cl_2.

(27) The TBS ether of sulfone **2a** was removed and the resulting alcohol was reacted with the acid resulting from protection of ***R*-5** with TIPSCl and imidazole and hydrolysis of the ^{t}Bu ester with TMSOTf and Et_3N. The resulting ester was then oxidized at the terminal olefin. The aldehyde-sulfone adduct was disolvedin THF with 4Å molecular sieves and a 2M solution of LDA in THF/heptane/ethylbenzene (2 eq.) was added. The solution was stirred for 2 h. After this time, sat. NH_4Cl was added and the residue was extracted with CH_2Cl_2.

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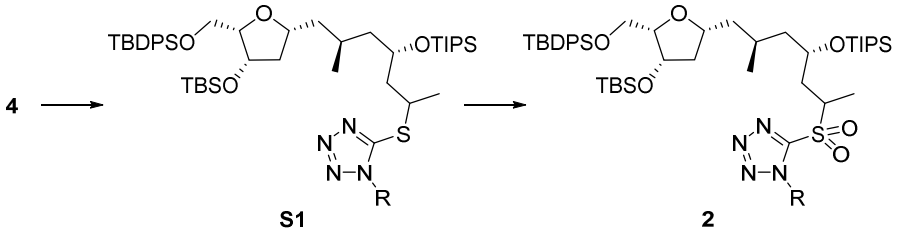
Supporting Information

TABLE OF CONTENTS

1. 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 SDS 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 Thermo Nicolet FT-IR Nexus spectrometer. ^{1}H-NMR and ^{13}C-NMR were recorded on a Varian Mercury 400MHz. 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. The same abbreviations were also used for the multiplicity of signals in ^{1}H-NMR, along with bs = broad singlet, m = multiplet. High Resolution Mass Spectroscopy (HRMS) was performed on an Agilent LC/MSD-TOF 2006 system using the ESI-MS technique.

2. Experimental procedures and characterization

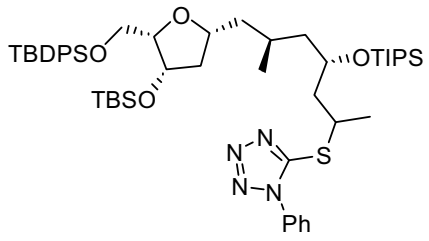


General Procedure for the preparation of sulfones 2a and 2b:

Diisopropyl azodicarboxylate (DIAD) (2.5 eq.) was added to a solution of known alcohol **4** (1 eq.), 1-phenyl-1*H*-tetrazole-5-thiol or 1-(*tert*-butyl)-1*H*-tetrazole- 5-thiol[2] (2.5 eq. or 1.4 eq. respectively) and PPh_3 (2.5 eq.) in THF. The reaction mixture was stirred for 6 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with hexane-Et_2O (95:5 to 80:20) to yield the corresponding thiotetrazole **S1** as a mixture of diastereomers.

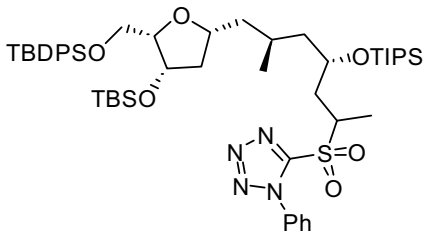
A solution of 70% 3-chloroperoxybenzoic acid (*m*-CPBA) (1 eq.) and S**1** (2.3 eq.) in CH_2Cl_2 (50 mL) was stirred for 16 h. The reaction mixture was dissolved with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ and the residue was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (95:5) yielded the corresponding sulfone **2** as a mixture of diastereomers.

5-[(2*RS*,4*S*,6*S*)-7-((2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy-methyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-thio]-1-phenyl-1*H*-tetrazole (S1a).



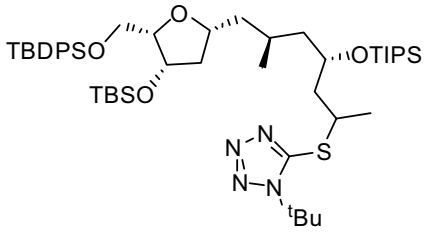
Alcohol **4** (1.60 g, 1.08 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (463 mg, 2.60 mmol) led to **S1a** (1.36 g, 70%). IR (KBr film) ν 2930, 2864, 1598, 1500, 1462, 1388, 1251, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.05 (2s, 3H); 0.00 and 0.01 (2s, 3H); 0.79 and 0.80 (2s, 9H); 0.86 and 0.91 (2d, *J* = 6.0 Hz, 3H); 1.01 (s, 13H); 1.04, 1.05 and 1.06 (3s 17H); 1.35–1.45 (m, 2H); 1.57 (d, *J* = 6. Hz, 3H); 1.46–1.72 (m, 5H); 1.87–2.02 (m, 1H); 2.18–2.26 (m, 1H); 3.72–3.79 (m, 2H); 3.83–3.88 (m, 1H); 3.89–3.96 (m, 1H); 4.03–4.14 (m, 1H); 4.15–4.24 (m, 1H); 4.29–4.36 (m, 1H); 7.31–7.42 (m, 6H); 7.49–7.56 (m, 5H); 7.66–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.2 (q); –4.7 (2q); 12.9 (2d); 17.7 (s); 17.9 (s); 18.2 (2q); 18.3 (2q); 19.2 (s); 19.8 (q); 19.9 (q); 21.7 (q); 23.2 (q); 25.7 (q); 26.9 (q); 27.4 (2d); 41.3 (d); 41.7 (d); 41.9 (t); 43.0 (t); 44.8 (t); 44.9 (t); 45.0 (t); 45.1 (t); 63.7 (t); 68.7 (d); 68.8 (d); 72.6 (d); 75.6 (d); 75.9 (d); 83.2 (d); 83.3 (d); 124.0 (2d); 127.5 (2d); 129.5 (d); 129.6 (d); 129.9 (d); 133.7 (s); 133.8 (s); 134.0 (s); 135.6 (d); 135.7 (d); 153.8 (s); 153.9 (s). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{82}O_4N_4NaSSi_3$ (M+Na) 953.5257, found 953.5240.

5-[(2*RS*,4*S*,6*S*)-7-((2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy-methyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-sulfonyl]-1-phenyl-1*H*-tetrazole (2a).



Thiotetrazole S**1a** (1.30 g, 1.40 mmol) led to sulfone **2a** (1.22 g, 91%). IR (KBr film) ν 2931, 2864, 1498, 1463, 1338, 1254, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.04 (2s, 3H); 0.00 (2s, 3H); 0.80 (s, 9H); 0.88 and 0.90 (2d, *J* = 6.2 Hz, 3H); 1.04, 1.06 and 1.07 (3s, 30H); 1.35–1.70 and 1.81–1.89 (2m, 7H); 1.49 and 1.55 (2d, *J* = 6.9 Hz, 3H); 2.08–2.25 and 2.42–2.50 (2m, 2H); 3.70–3.78 (m, 2H); 3.82–3.95 (m, 2H); 4.05–4.31 (m, 2H); 4.32–4.36 (m, 1H); 7.30–7.42 (m, 6H); 7.54–7.62 (m, 3H); 7.64–7.70 (m, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.2 (q); –4.2 (q); 12.9 (d); 13.5 (q); 16.1 (q); 18.0 (s); 18.2 (4q); 19.1 (q); 19.2 (s); 19.6 (q); 25.7 (q); 26.9 (q); 27.4 (d); 27.5 (d); 34.1 (t); 35.5 (t); 41.7 (t); 41.9 (t); 44.9 (t); 45.0 (2t); 45.3 (t); 58.5 (d); 58.8 (d); 63.5 (t); 67.5 (d); 69.3 (d); 72.5 (2d); 75.5 (d); 75.8 (d); 83.2 (d); 83.3 (d); 125.4 (2d); 127.5 (2d); 129.5 (4d); 131.3 (d); 133.2 (s); 133.7 (2s); 134.0 (2s); 135.6 (d); 135.7 (d); 152.6 (s); 152.7 (s). HRMS (+ESI): *m/z* calcd. for $C_{51}H_{86}O_6N_5SSi_3$ ($M+NH_4$) 980.5601, found 980.5587.

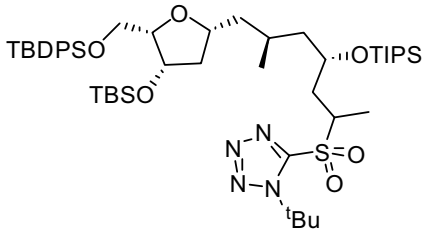
5-[(2*RS*,4*S*,6*S*)-7-((2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy-methyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-thio]-1-*tert*-butyl -1*H*-tetrazole (S1b).



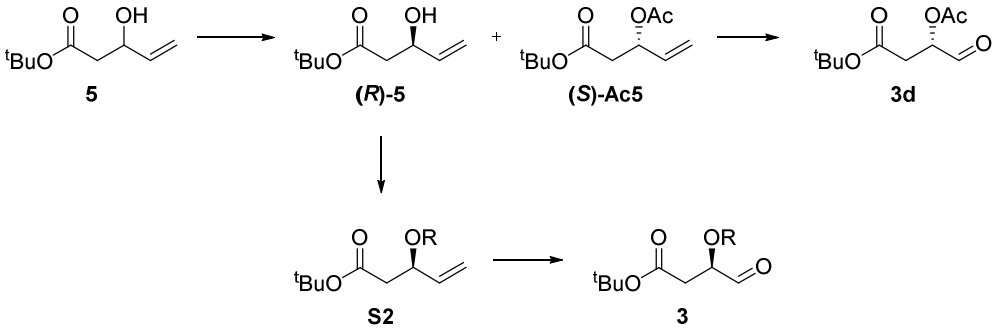
Alcohol **4** (490 mg, 0.63 mmol), and 1-(*tert*-butyl)-1*H*-tetrazole-5-thiol[1] (140 mg, 0.89 mmol) led to **S1b** (529 mg, 92%). IR (KBr film) ν 2931, 2864, 1463, 1390, 1253, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.05 and –0.04 (2s, 3H); –0.00 and 0.00 (2s, 3H); 0.79 and 0.80 (2s, 9H); 0.91 (2d, *J* = 6.2 Hz, 3H); 1.03 (s, 10H); 1.05, 1.06 and 1.07 (3s 20H); 1.36–1.48 (m, 3H); 1.53 and 1.54 (2d, *J* = 6.6 Hz, 3H); 1.57–1.67 (m, 4H); 1.68 and 1.70 (2s, 9H); 1.84–2.02 (m, 1H); 2.19–2.26 (m, 1H); 3.72–3.80 (m, 2H); 3.82–3.86 (m, 1H); 3.87–3.96 (m, 1H); 4.07–4.26 (m, 2H); 4.30–4.36 (m, 1H); 7.32–7.42 (m, 6H); 7.67–7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ

–5.2 (q); –4.7(q); –4.6 (q); 12.9 (2d); 17.9 (s); 18.2 (2q); 18.3 (2q); 19.2 (s); 19.9 (q); 21.8 (q); 23.2 (q); 25.7 (q); 26.9 (q); 27.4 (d); 28.7 (2q); 41.7 (t); 41.8 (t); 41.9 (d); 42.3 (d); 43.1 (t); 43.2 (t); 44.9 (t); 45.0 (t); 45.1 (t); 60.8 (s); 63.7 (t); 68.8 (2d); 72.6 (d); 75.6 (d); 75.9 (d); 83.2 (d); 83.3 (d); 127.5 (2d); 129.4 (d); 132.2 (s); 132.3(s); 133.7 (s); 134.0 (s); 135.6 (d); 135.7 (d); 152.1 (s); 152.2 (s). HRMS (+ESI): *m/z* calcd. for $C_{49}H_{87}N_4O_4SSi_3$ (M+H) 911.5750, found 911.5740.

5-[(2*RS*,4*S*,6*S*)-7-((2*R*,4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-sulfonyl]-1-*tert*-butyl-1*H*-tetrazole (2b).



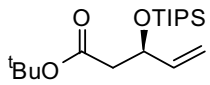
Thiotetrazole **S1b** (2.56 g, 2.80 mmol) led to sulfone **2b** (2.10 g, 80%). IR (KBr film) ν 2941, 2865, 1463, 1332, 1158, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ –0.04 (s, 3H); 0.00 and 0.01 (2s, 3H); 0.80 (2s, 9H); 0.91 (d, *J* = 6.2 Hz, 3H); 1.05 (2s, 9H); 1.06 and 1.07 (2s, 21H); 1.37–1.70 (m, 7H); 1.50 and 1.56 (2d, *J* = 6.9 Hz, 3H); 1.84 (s, 9H); 2.12–2.26 and 2.42–2.49 (2m, 2H); 3.71–3.78 (m, 2H); 3.82–3.96 (m, 2H); 4.07–4.16 and 4.24–4.43 (2m, 3H); 7.32–7.42 (m, 6H); 7.67–7.71 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.2 (q); –4.6 (q); 12.9 (2d); 13.9 (q); 16.3 (q); 18.0 (s); 18.2 (2q); 18.3 (q); 19.1 (q); 19.2 (s); 19.6 (q); 25.7 (q); 26.9 (q); 27.4 (d); 27.5 (d); 29.6 (q); 29.7 (q); 34.2 (t); 35.9 (t); 41.7 (t); 41.9 (t); 45.0 (t); 45.2 (t); 45.3 (t); 58.8 (d); 59.3 (d); 63.5 (2t); 65.3 (s); 65.4 (s); 67.6 (d); 69.5 (d); 72.5 (2d); 75.6 (d); 75.9 (d); 83.2 (d); 83.3 (d); 127.5 (d); 129.5 (d); 133.7 (s); 133.8 (s); 134.0 (s); 135.6 (d); 135.7 (d); 153.2 (s); 153.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{49}H_{90}N_5O_6SSi_3$ ($M+NH_4$) 960.5914, found 960.5907.



Kinetic resolution of **5**:[2]

Lipase PS-30 (4.32 g) was added to a solution of racemic **5** (2.15 g, 12.50 mmol) in vinyl acetate (10 mL) and pentane (25 mL), and the suspension was stirred for 48 h at 37 ºC. The residue was filtered through Celite® 545, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded (*R*)-**5** (1.05 g, 49%) and (*S*)-Ac-**5** (1.28 g, 48%) as colorless oils. **(*R*)-5**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H); 2.43 (dd, *J* = 16.2, 8.3 Hz, 1H); 2.51 (dd, *J* = 16.2, 4.0 Hz, 1H); 3.11 (bs, OH); 4.45–4.52 (m, 1H); 5.14 (dt, *J* = 10.5, 1.4 Hz, 1H); 5.30 (dt, *J* = 17.2, 1.4 Hz, 1H); 5.87 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H). **(*S*)-Ac-5**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H); 2.05 (s, 3H); 2.52 (dd, *J* = 15.3, 5.8 Hz, 1H); 2.60 (dd, *J* = 15.3, 8.0 Hz, 1H); 5.20 (dd, *J* = 10.5, 1.0 Hz, 1H); 5.30 (dd, *J* = 17.2, 1.0 Hz, 1H); 5.57–5.63 (m, 1H); 5.83 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H).

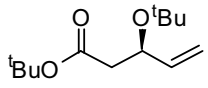
***tert*-Butyl (*R*)-3-(triisopropylsilyloxy)pent-4-enoate (S2a).**



Triisopropylsilyl trifluoromethanesulfonate (1.98 mL, 7.34 mmol) was added to a solution of aldol **(*R*)-5** (1.05 g, 6.10 mmol), imidazole (830 mg, 12.20 mmol) and 4-dimethylaminopyridine (20 mg) in THF (60 mL), and

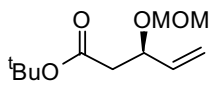
the reaction mixture was stirred for 16 h at reflux temperature. The solvent was removed under reduced pressure and the residue was dissolved in water and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (97:3) yielded **S2a** (1.78 g, 89%) as a colorless oil. $[\alpha]_D$ = −3.8 (c 1.0, $CHCl_3$). IR (KBr film) ν 2944, 2867, 1732, 1464, 1367, 1256, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04–1.07 (m, 21H); 1.43 (s, 9H); 2.37 (dd, *J* = 14.4, 7.5 Hz, 1H); 2.56 (dd, *J* = 14.4, 5.8 Hz, 1H); 4.59–4.65 (m, 1H); 5.06 (ddd, *J* = 10.4, 1.7, 1.1 Hz, 1H); 5.20 (ddd, *J* = 17.2, 1.7, 1.1 Hz, 1H); 5.87 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.3 (d); 18.0 (q); 18.1 (q); 28.1 (q); 45.2 (t); 71.3 (d); 80.4 (s); 114.5 (t); 140.6 (d); 170.1 (s). HRMS (+ESI): *m/z* calcd. for $C_{18}H_{37}O_3Si$ (M+H) 329.2507, found 329.2506.

***tert*-Butyl (*R*)-3-(*tert*-butoxy)pent-4-enoate (S2b).**



Di-*tert*-butyl dicarbonate (10.60 mL, 46.50 mmol) was added in portions to a mixture of aldol **(*R*)-5** (1.60 g, 9.30 mmol), and $Mg(ClO_4)_2$ (207 mg, 0.93 mmol) in CH_2Cl_2 (100 mL), and the reaction was stirred for 16 h at reflux temperature. The resulting mixture was dissolved in water and 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 (96:4) yielded **S2b** (1.33 g, 63%) as a colorless oil. $[\alpha]_D$ = +11.2 (c 1.0, $CHCl_3$). IR (KBr film) ν 2977, 2933, 1732, 1367, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H); 1.44 (s, 9H); 2.30 (dd, *J* = 14.5, 6.4 Hz, 1H); 2.43 (dd, *J* = 14.5, 7.4 Hz, 1H); 4.37–4.43 (m, 1H); 5.04 (ddd, *J* = 10.5, 1.6, 1.1 Hz, 1H); 5.20 (ddd, *J* = 17.3, 1.6, 1.1 Hz, 1H); 5.85 (ddd, *J* = 17.3, 10.5, 6.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.1 (q); 28.6 (q); 44.1 (t); 70.3 (d); 74.4 (s); 80.4 (s); 114.3 (t); 141.3 (d); 170.5 (s). HRMS (+ESI): *m/z* calcd. for $C_{13}H_{24}NaO_3$ (M+Na) 251.1618, found 251.1618.

***tert*-Butyl (*R*)-3-(methoxymethoxy)pent-4-enoate (S2c).**

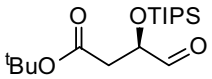


Et_3N (2.62 mL, 18.80 mmol) was added to a solution of aldol **(*R*)-5** (540 mg, 3.10 mmol), MOMCl (0.71 mL, 9.4 mmol) and tetrabutylammonium iodide (347 mg, 0.9 mmol) in THF (20 mL), and the reaction mixture was stirred for 16 h at reflux temperature. The resulting mixture was dissolved in NH_4Cl and extracted with EtOAc, the organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-EtOAc (90:10) yielded **S2c** (494 mg, 73%) as a colorless oil. $[\alpha]_D$ = +64.3 (c 1.0, $CHCl_3$). IR (KBr film) ν 2980, 1733, 1368, 1152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H); 2.41 (dd, *J* = 15.0, 5.6 Hz, 1H); 2.55 (dd, *J* = 15.0, 8.1 Hz, 1H); 3.37 (s, 3H); 4.41–4.48 (m, 1H); 4.57 (d, *J* = 6.7 Hz, 1H); 4.69 (d, *J* = 6.7 Hz, 1H); 5.21 (ddd, *J* = 10.3, 1.6, 0.8 Hz, 1H); 5.29 (ddd, *J* = 17.2, 1.6, 1.0 Hz, 1H); 5.73 (ddd, *J* = 17.2, 10.3, 7.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.1 (q); 42.1 (t); 55.6 (q); 74.2 (d); 80.7 (s); 94.1 (t); 117.8 (t); 137.0 (d); 169.9 (s). HRMS (+ESI): *m/z* calcd. for $C_{11}H_{24}NO_4$ (M+NH_4) 234.1700, found 234.1700.

General Procedure for reductive ozonolysis reactions:

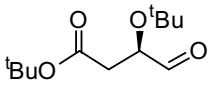
Ozone gas was bubbled into a solution of olefin **S2** (1 eq.) in a 4:1 mixture of CH_2Cl_2-MeOH (100 mL) at −78ºC until the blue color persisted. Argon was then passed through the solution for 10 min at −78ºC to remove any excess ozone. Then, PPh_3 (1.3 eq.) was added and the solution was stirred at r.t. for 16 h. The reation mixture was concentrated under reduced pressure and filtered through silica with hexane-EtOAc (95:5) to yield the corresponding aldehyde **3** as a colorless oil.

***tert*-Butyl (*R*)-4-oxo-3-(triisopropylsilyloxy)butanoate (3a).**



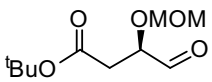
Olefin **S2a** (1.45 g, 4.41 mmol) led to aldehyde **3a** (1.35 g, 93%). $[\alpha]_D$ = +11.5 (c 1.0, $CHCl_3$). IR (KBr film) ν 2944, 2868, 1736, 1464, 1367, 1256, 1157 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04–1.07 (m, 21H); 1.44 (s, 9H); 2.66 (ddd, *J* = 15.7, 5.8, 0.8 Hz, 1H); 2.78 (dd, *J* = 15.7, 4.0 Hz, 1H); 4.32 (ddd, *J* = 5.8, 4.0, 0.8 Hz, 1H); 9.80 (t, *J* = 0.8, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.1 (d); 17.8 (q); 28.0 (q); 41.22 (t); 74.2 (d); 81.4 (s); 169.0 (s); 204.2 (d). HRMS (+ESI): *m/z* calcd. for $C_{17}H_{35}O_4Si$ (M+H) 331.2299, found 331.2297.

***tert*-Butyl (*R*)-4-oxo-3-(*tert*-butoxy)butanoate (3b).**



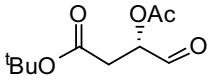
Olefin **S2b** (1.30 g, 5.68 mmol) led to aldehyde **3b** (1.09 g, 83%). $[\alpha]_D$ = +45.9 (c 1.0, $CHCl_3$). IR (KBr film) ν 2977, 1733, 1368, 1156 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H); 1.44 (s, 9H); 2.52 (dd, *J* = 15.4, 5.7 Hz, 1H); 2.56 (dd, *J* = 15.4, 6.2 Hz, 1H); 4.18 (ddd, *J* = 6.2, 5.7, 1.5 Hz, 1H); 9.70 (d, *J* = 1.5, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.0 (q); 28.2 (q); 39.1 (t); 73.7 (d); 75.3 (s); 81.3 (s); 169.4 (s); 204.6 (d). HRMS (+ESI): *m/z* calcd. for $C_{12}H_{22}NaO_4$ (M+Na) 253.1410, found 253.1412.

***tert*-Butyl (*R*)-4-oxo-3-(methoxymethoxy)butanoate (3c).**



Olefin **S2c** (460 mg, 2.13 mmol) led to aldehyde **3c** (418 mg, 90%). $[\alpha]_D$ = +10.8 (c 1.0, $CHCl_3$). IR (KBr film) ν 2979, 1731, 1368, 1154 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H); 2.66 (dd, *J* = 16.3, 6.7 Hz, 1H); 2.73 (ddd, *J* = 16.3, 4.8, 0.4 Hz, 1H); 3.42 (s, 3H); 4.24 (ddd, *J* = 6.7, 4.8, 0.8 Hz, 1H); 4.76 (d, *J* = 6.9 Hz, 1H); 4.79 (d, *J* = 6.9 Hz, 1H); 9.76 (dd, *J* = 0.8, 0.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.0 (q); 37.5 (t); 56.0 (q); 79.0 (d); 81.6 (s); 97.2 (t); 169.1 (s); 201.8 (d). HRMS (+ESI): *m/z* calcd. for $C_{10}H_{19}O_5$ (M+H) 219.1227, found 219.1230.

***tert*-Butyl (*S*)-3-acetoxy-4-oxobutanoate (3d).**

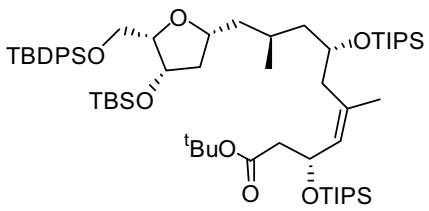


Olefin **(*S*)-Ac-5** (1.00 g, 4.60 mmol) led to aldehyde **3d** (0. 99 g, 98%). $[\alpha]_D$ = –15.0 (c 1.0, CH_2Cl_2). IR (KBr film) ν 2980, 2935, 1733, 1370, 1158 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H); 2.16 (s, 3H); 2.78–2.81 (m, 2H); 5.24 (dd, *J* = 5.9, 5.4 Hz, 1H); 9.60 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.6 (q); 28.0 (q); 36.3 (t); 74.5 (d); 82.1 (s); 168.3 (s); 170.3 (s); 197.8 (d). HRMS (+ESI): *m/z* calcd. for $C_{10}H_{17}O_5$ (M+H) 217.1071, found 217.076.

General Procedure for Julia-Kocienski olefinations:

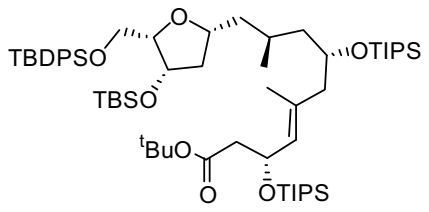
A 2M solution of LDA in THF/heptane/ethylbenzene (2 eq.) was added to a solution of sulfone **2** (1 eq.) and HMPA (2 eq.) in THF with 4Å molecular sieves, and the solution was stirred for 1 min. After this time, a solution of aldehyde **3** (2 eq.) in THF was added and the solution was stirred for an additional 2 h. The reaction mixture was quenched with sat. NH_4Cl and then extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in EtOH and 40% $NaHSO_3$, the white precipitate was removed by filtration and the solvent was concentrated under reduced pressure. Purification by silica gel column chromatography with hexane-Et_2O (97:3) yielded the corresponding olefin **6** as a colorless oil. For yields and diastereomeric ratios, please refer to Table 2 in the journal article.

***tert*-Butyl (3*R*,7*S*,9*S*,*Z*)-10-[(2*R*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenyl silyloxymethyl)tetrahydrofuran-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoate (*Z*-6a).**



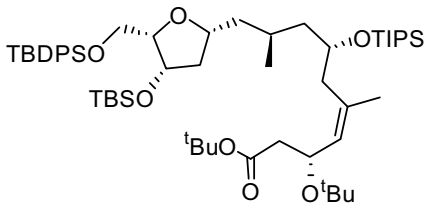
$[\alpha]_D$ = +9.9 (c 1.3, CH_2Cl_2). IR (KBr film) ν 2943, 2865, 1732, 1463, 1367, 1255, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ −0.04 (s, 3H); 0.00 (s, 3H); 0.80 (s, 9H); 0.93 (d, *J* = 6.4 Hz, 3H); 1.04 and 1.06 (2bs, 51H); 1.28−1.34 (m, 1H); 1.42 (s, 9H); 1.43−1.58 (m, 4H); 1.63−1.66 (m, 1H); 1.67 (s, 3H); 2.12−2.26 (m, 3H); 2.34−2.42 (m, 2H); 3.72−3.79 (m, 2H); 3.82−3.89 (m, 2H); 4.05−4.14 (m, 1H); 4.30−4.36 (m, 1H); 4.93−4.98 (m, 1H); 5.30 (d, *J* = 7.6 Hz, 1H); 7.33−7.43 (m, 6H); 7.64−7.73 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.6 (q); 12.5 (d); 13.0 (d); 17.9 (s); 18.1 (q); 18.2 (q); 18.3 (2q); 19.2 (s); 20.5 (q); 23.1 (q); 25.7 (q); 26.9 (q); 27.9 (d); 28.1 (q); 40.6 (t); 42.2 (t); 44.0 (t); 45.7 (t); 46.1 (t); 63.6 (t); 67.0 (d); 68.8 (d); 72.5 (d); 76.3 (d); 79.9 (s); 83.2 (d); 127.5 (2d); 129.5 (2d); 131.9 (d); 133.7 (s); 133.4 (s); 134.0 (s); 135.6 (d); 135.7 (d); 170.4 (s). HRMS (+ESI): *m/z* calcd. for $C_{61}H_{114}NO_7Si4$ ($M+NH_4$) 1084.7667, found 1084.7654.

***tert*-Butyl (3*R*,7*S*,9*S*,*E*)-10-[(2*R*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenyl silyloxymethyl)tetrahydrofuran-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoate (*E*-6a).**



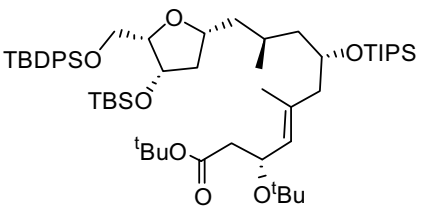
IR (KBr film) ν 2943, 2865, 1732, 1463, 1367, 1255, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H); −0.01 (s, 3H); 0.79 (s, 9H); 0.93 (d, *J* = 6.7 Hz, 3H); 1.03 and 1.06 (2bs, 51H); 1.19−1.28 (m, 1H); 1.42 (s, 9H); 1.44−1.56 (m, 4H); 1.65 (s, 3H); 1.68−1.76 (m, 1H); 2.11−2.25 (m, 3H); 2.27 (dd, *J* = 14.5, 5.6 Hz, 1H); 2.47 (dd, *J* = 14.5, 7.0 Hz, 1H); 3.72−3.79 (m, 2H); 3.81−3.89 (m, 2H); 3.99−4.07 (m, 1H); 4.32 (dt, *J* = 6.3, 4.1 Hz, 1H); 4.91 (ddd, *J* = 8.7, 7.0, 5.6 Hz, 1H); 5.25 (d, *J* = 8.7 Hz, 1H); 7.32−7.43 (m, 6H); 7.66−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.7 (q); 12.4 (d); 12.9 (d); 17.7 (q); 20.0 (s); 18.0 (q); 18.1 (q); 18.3 (q); 19.2 (s); 20.9 (q); 25.7 (q); 26.9 (q); 27.7 (d); 28.1 (q); 42.3 (t); 43.7 (t); 44.7 (t); 45.4 (t); 47.7 (t); 63.7 (t); 66.9 (d); 69.8 (d); 72.6 (d); 76.5 (d); 80.1 (s); 83.2 (d); 127.5 (d); 129.4 (d); 131.1 (d); 133.6 (s); 133.8 (s); 134.1 (s); 135.6 (d); 135.7 (d); 170.3 (s). HRMS (+ESI): *m/z* calcd. for $C_{61}H_{114}NO_7Si4$ ($M+NH_4$) 1084.7667, found 1084.7654.

***tert*-Butyl (3*R*,7*S*,9*S*,*Z*)-3-(*tert*-butoxy)-10-[(2*R*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl]-5,9-dimethyl-7-(triisopropylsilyloxy)-dec-4-enoate (*Z*-6b).**



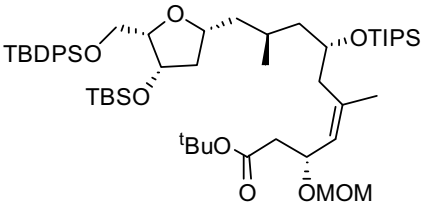
$[\alpha]_D$ = +5.2 (c 1.0, $CHCl_3$). IR (KBr film) ν 2931, 2864, 1732, 1463, 1365, 1256, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H); 0.00 (s, 3H); 0.80 (s, 9H); 0.95 (d, *J* = 6.4 Hz, 3H); 1.04 (bs, 21H); 1.05 (s, 9H); 1.15 (s, 9H); 1.30−1.39 (m, 1H); 1.44 (s, 9H); 1.46−1.63 (m, 3H); 1.64−1.70 (m, 1H); 1.65 (s, 3H); 2.16−2.28 (m, 4H); 2.30−2.34 (m, 2H); 3.72−3.79 (m, 2H); 3.82−3.92 (m, 2H); 4.07−4.16 (m, 1H); 4.33 (dt, *J* = 6.4, 4.1 Hz, 1H); 4.64−4.72 (m, 1H); 5.24 (d, *J* = 6.8 Hz, 1H); 7.32−7.43 (m, 6H); 7.66−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.7 (q); 13.0 (d); 18.0 (s); 18.2 (q); 18.3 (q); 19.2 (s); 20.4 (q); 23.2 (q); 25.7 (q); 26.9 (q); 28.0 (d); 28.1 (q); 28.9 (q); 40.5 (t); 42.1 (t); 44.2 (t); 44.3 (t); 46.3 (t); 63.7 (t); 66.6 (d); 68.9 (d); 72.6 (d); 73.7 (s); 76.3 (d); 79.8 (s); 83.2 (d); 127.5 (2d); 129.4 (d); 131.4 (s); 132.5 (d); 133.8 (s); 134.0 (s); 135.6 (d); 135.7 (d); 170.6 (s). HRMS (+ESI): *m/z* calcd. for $C_{56}H_{98}NaO_7Si3$ (M+Na) 989.6513, found 989.6517.

***tert*-Butyl (3*R*,7*S*,9*S*,*E*)-3-(*tert*-butoxy)-10-[(2*R*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl]-5,9-dimethyl-7-(triisopropylsilyloxy)-dec-4-enoate (*E*-6b).**



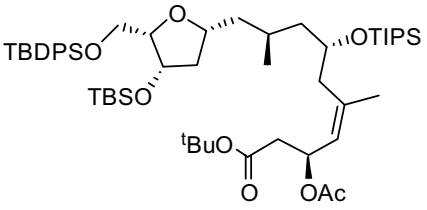
IR (KBr film) ν 2931, 2864, 1732, 1463, 1365, 1256, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H); −0.01 (s, 3H); 0.79 (s, 9H); 0.92 (d, *J* = 6.6 Hz, 3H); 1.05 (bs, 30H); 1.15 (s, 9H); 1.20−1.28 (m, 1H); 1.44 (s, 9H); 1.45−1.68 (m, 3H); 1.63−1.68 (m, 1H); 1.69 (s, 3H); 2.09−2.26 (m, 5H); 2.38 (dd, *J* = 14.4, 8.8 Hz, 1H); 3.72−3.78 (m, 2H); 3.81−3.89 (m, 2H); 3.99−4.05 (m, 1H); 4.32 (dt, *J* = 6.2, 4.2 Hz, 1H); 4.64 (td, *J* = 8.8, 4.7 Hz, 1H); 5.20 (d, *J* = 8.8 Hz, 1H); 7.32−7.42 (m, 6H); 7.67−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.7 (q); 12.9 (d); 17.6 (q); 18.0 (s); 18.3 (2q); 19.2 (s); 20.8 (q); 25.7 (q); 26.9 (q); 27.7 (d); 28.2 (q); 28.8 (q); 42.3 (t); 43.9 (2t); 44.8 (t); 47.4 (t); 63.8 (t); 66.5 (d); 70.0 (d); 72.6 (d); 73.7 (s); 76.4 (d); 80.1 (s); 83.1 (d); 127.5 (2d); 129.4 (2d); 131.7 (d); 131.8 (s); 133.8 (s); 135.6 (d); 135.7 (d); 170.6 (s). HRMS (+ESI): *m/z* calcd. for $C_{56}H_{98}NaO_7Si3$ (M+Na) 989.6513, found 989.6517.

***tert*-Butyl (3*R*,7*S*,9*S*,*Z*)-10-[(2*R*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenyl silyloxymethyl)tetrahydrofuran-2-yl]-3-(methoxymethoxy)-5,9-dimethyl-7-(triisopropyl-silyloxy)dec-4-enoate (*Z*-6c).**



$[\alpha]_D$ = +22.2 (c 1.0, $CHCl_3$). IR (KBr film) ν 2930, 2863, 1730, 1462, 1367, 1255, 1151 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H); 0.00 (s, 3H); 0.80 (s, 9H); 0.94 (d, *J* = 6.3 Hz, 3H); 1.05 (2bs, 30H); 1.31−1.41 (m, 1H); 1.44 (s, 9H); 1.45−1.68 (m, 5H); 1.73 (d, *J* = 1.4 Hz, 3H); 2.19−2.28 (m, 3H); 2.39 (dd, *J* = 15.0, 4.6 Hz, 1H); 2.45 (dd, *J* = 15.0, 8.7 Hz, 1H); 3.33 (s, 3H); 3.72−3.78 (m, 2H); 3.82−3.90 (m, 2H); 4.06−4.14 (m, 1H); 4.33 (dt, *J* = 6.2, 4.0 Hz, 1H); 4.48 (d, *J* = 6.7 Hz, 1H); 4.65 (d, *J* = 6.7 Hz, 1H); 4.73−4.80 (m, 1H); 5.11 (d, *J* = 9.2 Hz, 1H): 7.32−7.43 (m, 6H); 7.66−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.6 (q); 13.0 (d); 18.0 (s); 18.3 (2q); 19.2 (s); 20.1 (q); 23.9 (q); 25.7 (q); 26.9 (q); 27.9 (d); 28.1 (q); 40.2 (t); 42.2 (t); 42.6 (t); 44.3 (t); 45.8 (t); 55.4 (q); 63.6 (t); 69.0 (d); 69.1 (d); 72.6 (d); 76.2 (d); 80.2 (s); 83.2 (d); 93.5 (t); 126.7 (d); 127.5 (2d); 129.4 (d); 133.8 (s); 134.0 (s); 135.6 (d); 135.7 (d); 137.9 (s); 170.2 (s). HRMS (+ESI): *m/z* calcd. for $C_{54}H_{98}NO_8Si_3$ (M+NH_4) 972.6595, found 972.6586.

***tert*-Butyl (3*S*,7*S*,9*S*,*Z*)-3-acetoxy-10-[(2*R*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyl-diphenylsilyloxymethyl)tetrahydrofuran-2-yl]-5,9-dimethyl-7-(triisopropylsilyloxy)-dec-4-enoate (*Z*-6d).**



$[\alpha]_D$ = +11.0 (c 1.0, $CHCl_3$). IR (KBr film) ν 2931, 2864, 1739, 1463, 1368, 1251, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H); 0.00 (s, 3H); 0.80 (s, 9H); 0.95 (d, *J* = 6.6 Hz, 3H); 1.05 (2bs, 30H); 1.28−1.39 (m, 2H); 1.42 (s, 9H); 1.45−1.61 (m, 3H); 1.66−1.72 (m, 1H); 1.73 (d, *J* = 1.4 Hz, 3H); 1.98 (s, 3H); 2.12−2.27 (m, 2H); 2.42 (dd, *J* = 15.1, 4.4 Hz, 1H); 2.54 (dd, *J* = 15.1, 9.0 Hz, 1H); 2.64 (dd, *J* = 13.6, 6.7 Hz, 1H); 3.71−3.78 (m, 2H); 3.82−3.90 (m, 2H); 4.03−4.11 (m, 1H); 4.29−4.35 (m, 1H); 5.18 (d, *J* = 9.0 Hz, 1H); 5.83 (td, *J* = 9.0, 4.4 Hz, 1H); 7.32−7.43 (m, 6H); 7.67−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2 (q); −4.6 (q); 13.0 (d); 18.0 (s); 18.3 (q); 19.2 (s); 20.5 (q); 21.1 (q); 24.6 (q); 25.7 (q); 26.9 (q); 27.8 (d); 28.0 (q); 40.6 (t); 41.5 (t); 42.2 (t); 44.0 (t); 47.0 (t); 63.6 (t); 67.7 (d); 69.9 (d); 72.6 (d); 76.2 (d); 80.7 (s); 83.2 (d); 124.2 (d); 127.5 (d); 129.4 (d); 133.8 (s);

135.6 (d); 135.7 (d); 169.1 (s); 169.7 (s). HRMS (+ESI): *m/z* calcd. for $C_{54}H_{96}NO_8Si_3$ ($M+NH_4$) 970.6438, found 970.6429.

3. NMR spectra

NMR spectra images are available in the supporting information in electronic format

4. References

(1) Quast, H; Bieber, L. *Chem. Ber.* **1981**, *114*, 3253–3272.

(2) Vrielynck, S.; Vandewalle, M. *Tetrahedron Lett.* **1995**, *36*, 9023–9026.

Conclusions

Porania antarctica

CONCLUSIONS

Chemistry attempts both to understand the structures and characteristics of compounds and to create new compounds with desirable properties and functions. The work carried out in this thesis has intended to fulfill the area of the understanding and move on to the production of natural products isolated from marine habitat.

In our case, synthesis proved to be a useful tool for our drug development programs, since the scarce amount of product isolated from their marine source does not permit the whole structure elucidation of barmumycin and phormidolides B-D. Our strategy lied on the identification of the target by comparison of the available data from the natural product with data of our synthetic compounds. Moreover, overcoming the challenges faced during the synthesis has permitted the detailed study of processes, their optimization and comprehension until finally reaching the objective. From a general overview and focusing into detail, this work can be resumed into several conclusions:

Total Synthesis and structure confirmation of barmumycin.

- A synthetic plan has been developed for the synthesis of the proposed structure of barmumycin. The completion of the synthesis has drawn to the conclusion that the structure was misassigned and needed revision.

- The structure of barmumycin has been revised and confirmed upon enantioselective total synthesis.

Overview of bioactive marine macrolides with the characteristic presence of THF motifs in their structure.

- A general overview of THF-containing macrolactones has been compiled. A class of compounds with interesting structures and high potential as drug candidates. Described are isolation, structure determination and the described synthesis up to 2012.

Synthesis and structure determination of the macrocyclic core of phormidolides B-D.

- The best synthetic pathway to the synthesis of the macrolide core of phormidolides B-D has been selected with a not-stereoselective synthetic study. A strategy based on an olefin metathesis has been discarded. On the other hand a strategy based on a Julia-Kocienski olefination has been selected. Therein is shown the suitability of the protecting groups for the three hydroxyl and the acid motifs, present in the macrolactone precussor, testing its orthogonality and its resistance to the applied reaction conditions.

- A methodologic study has reached the selective synthesis of the *Z*-trisubstituted double bond present on the macrocyclic core of phormidolides B-D. The use of a 1-(*tert*-butyl)tetrazolyl sulfone succesfully afforded the formation of the endocyclic alkene with excellent stereoselectivity.

- A robust and efficient methodology for the enantioselective synthesis of the macrolide core of phormidolides B-D has been developed. The strategy is versatile and can be used for the synthesis of the different diastereomers of the macrocycle making the appropriate changes in the starting materials and chiral inductors.

- The synthesis of three enantiopure macrocycles and its comparison with the natural product has led to a proposal of the relative stereochemistry of the macrocyclic core of phormidolides B-D; this needs to be confirmed by synthesis.

It is a fact that the discovery of New Molecular Entities (NME) requires innovation and a refocus of mentality with new ideas and processes. Scientists have learned over the years how to overcome the problems often associated with marine derived natural products development. Nevertheless, we should not forget that there is indeed a symbiotic relationship between chemistry and drug development; chemistry takes profit of the new challenges provided by these complex structures, because need stimulates ideas and these are converted into innovative technology.

Contribution to publications

CONTRIBUTION TO PUBLICATIONS

- *Isolation, structural assignment, and total synthesis of barmumycin***.** A. Lorente, D. Pla, L. M. Cañedo, F. Albericio, M. Álvarez. *J. Org. Chem.*, **2010**, *75*, 8508.

  Design of the synthetic plan. Development of the nucleophilic substitution route to the synthesis of the proposed structure and development of the synthesis of the revised structure. Characterization of compounds. Writing of the manuscript.

- *Tetrahydrofuran containing macrolides: a fascinating gift from the deep sea*. A. Lorente, J. Lamariano-Merketegi, F. Albericio, M. Álvarez. *Chem. Rev.* **2013**, *113*, 4567.

  Choosing of the topic. Writing of the review.

- *Phormidolides B-D, new cytotoxic agents from the sea. Synthesis and structure determination*. A. Lorente, A. Gil, R. Fernández, C. Cuevas, F. Albericio, M. Álvarez. **2014**, Submitted.

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

- *Highly selective formation of a Z-trisubstituted double bond using a 1-(tert-butyl) tetrazolyl sulfone*. A. Lorente, F. Albericio, M. Álvarez. **2014**, Submitted.

  Design of the methodology. Development of the experimental method. Characterization of compounds. Writing of the manuscript.

Resum en català

RESUM EN CATALÀ

1. Introducció

Els productes naturals han estat durant molts anys font d'inspiració per a la creació de fàrmacs per curar malalties.[1] Extractes de plantes i organismes terrestres han donat lloc a processos de desenvolupament que han portat a nous fàrmacs, per contra el medi marí no ha rebut tanta atenció. La química dels productes naturals marins ha hagut d'esperar que les tecnologies es modernitzessin per facilitar la recol·lecció de mostres i la determinació estructural dels productes extrets, ja que se n'acostuma a extreure poca quantitat i presenten molta més complexitat estructural que els productes naturals extrets de fonts terrestres.

En els últims 50 anys, aquest camp ha estat objecte de gran interès. L'aigua cobreix al voltant d'un 70% de la superfície de la terra i presenta una biodiversitat molt més extensa que la del medi terrestre, això representa una font de molècules bioactives noves, amb diferents estructures i mecanismes d'acció, que ja han començat a donar els primers resultats en forma de fàrmacs prometedors.[2]

Els productes bioactius extrets d'organismes marins acostumen a ser metabòlits secundaris,[3] que no tenen una funció essencial en la vida de l'organisme però que ofereixen una funció complementària en la defensa contra amenaces en la competició per la supervivència a la que estan sotmesos els organismes vius en l'hàbitat marí. Com a conseqüència, aquests productes presenten estructures i estereoquímiques complexes i activitats biològiques molt potents, ja que són el resultat de rutes biosintètiques sofisticades creades a partir de l'evolució de l'espècie dins d'un medi molt competitiu.

En la Taula 1 i la Figura 1 es recullen els productes naturals d'orígen marí que han estat aprovats per a ús mèdic fins ara.[4] Pocs productes extrets d'organismes marins han arribat fins al mercat, però molts estan en fase d'assajos clínics i preclínics.[5]

Taula 1. Fins a Febrer del 2014. Productes extrets de l'hàbitat marí aprovats per la Food and Drug Adminstration (FDA) i per la European Medicines Agency (EMEA).

Producte natural	Nom comercial	Organisme d'orígen	Estructura	Diana	Aplicació mèdica
Cytarabina	Cytosar-U® Depocyte®	Esponja	Nucleòsid	Polimerasa d'ADN	Càncer
Ziconotida	Prialt®	Cargol cònic	Pèptid	Canal de calci tipus N	Dolor
Trabectedina (només EMEA)	Yondelis®	Tunicat	Alcaloide	Solc menor de l'ADN	Càncer
Eribulina	Halaven®	Esponja	Macròlid	Microtúbuls	Càncer
Brentuximab vedotina (conjugat de MMAE)	Adcetris®	Mol·lusc	Conjugat Droga-Anticos	CD30 i microtúbuls	Càncer
Esters etílics d'àcids omega-3 (EPA i DHA) (només FDA)	Lovaza®	Peix	Àcids grassos Omega-3	Enzims sintetitzadors de triglicèrids	Hipertrigli-ceridèmia

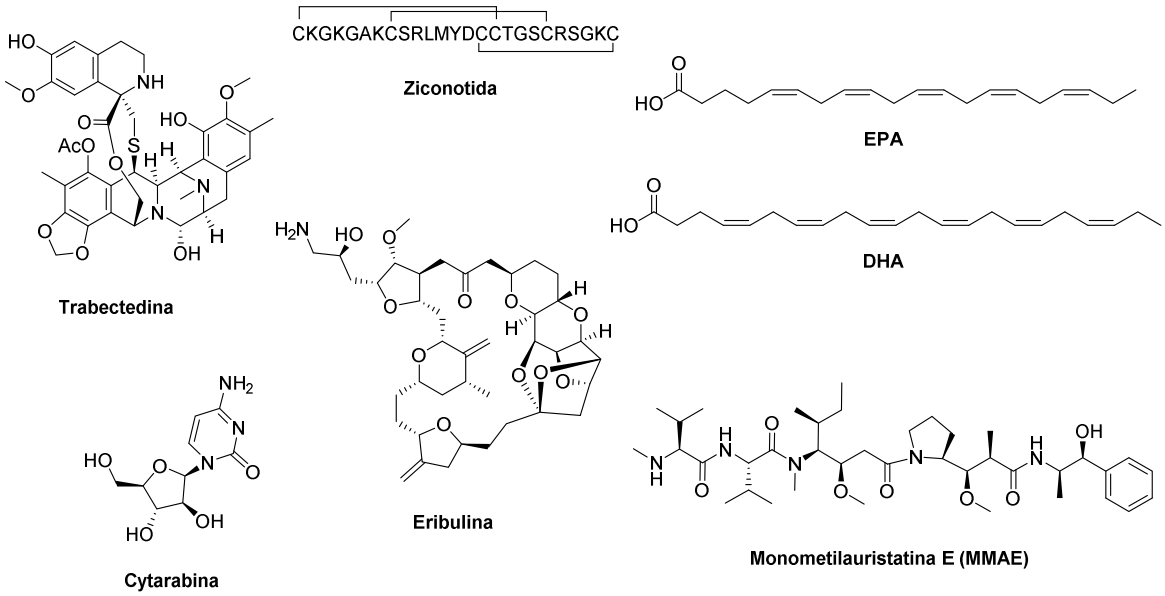


Figura 1. Estructures de fàrmacs procedents d'organismes marins.

Com es pot veure, només uns quants d'aquests productes han estat aprovats pels organismes corresponents a Europa i als Estats Units per a ser utilitzats com a medicaments. El principal problema per al desenvolupament clínic d'aquests compostos és la poca quantitat de producte que se n'obté en l'extracció de les fonts naturals, que en dificulta l'assignació estructural i els assajos biològics. En aquest context, la síntesi química és de vital importància per ajudar en la determinació de l'estructura i resoldre els problemes de subministrament.

Cal afegir que, en l'escenari actual, pocs fàrmacs presenten realment un avanç sobre els que ja estan en el mercat doncs habitualment les dianes són repetitives o les activitats són tan sols una mica millors.[6] Per això cal buscar en llocs nous, com els oceans i oferir innovació en idees i processos per a obrir noves vies de desenvolupament que realment suposin un avanç.

2. Objectius

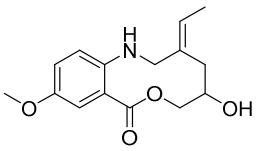
En l'investigació per a obtenir productes naturals d'orígen marí amb activitat citotòxica i continuant la nostra col·laboració amb els laboratoris Biomar S.A. i Pharmamar S.A., aquesta tesi té com a objectiu el desenvolupament de dos projectes:

- Síntesi i determinació estructural de la barmumicina.
- Síntesi i determinació estructural del macrocicle de les phromidolides B-D.

3. Síntesi i determinació estructural de la barmumicina

3.1. Objectiu sintètic

La barmumicina es va aïllar d'un extracte de l'actinomicet marí *Streptomyces sp.* BOSC-022A de la costa d'Escòcia i va presentar activitat antitumoral davant de diverses línies cel·lulars (Taula 2). La seva estructura es va determinar per una combinació de tècniques espectroscòpiques i per la formació d'un derivat diacetilat, d'on se'n va deduir la presència d'un hidroxil i un grup amino lliures però la síntesi era necessària per confirmar-ne l'estructura. La lactona **1** va ser l'estructura proposada per la barmumicina (Figura 2), aquesta es basa en una macrolactona amb un doble enllaç exocíclic amb la configuració *E*, que està fusionada amb un anell aromàtic.



1

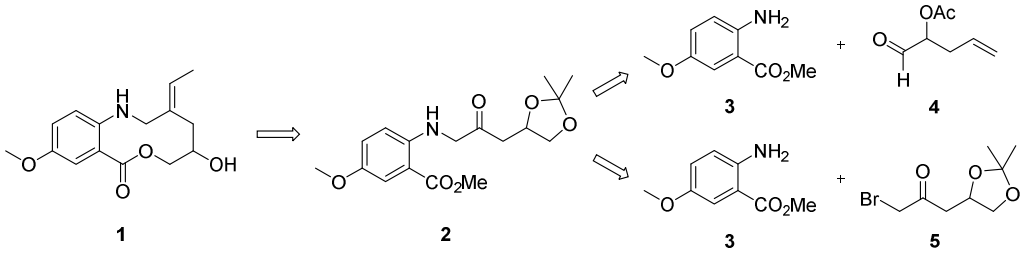
Figura 2. Estructura proposada per la barmumicina.

Taula 2. Valors d'inhibició del creixement al 50% (GI_{50}) per la barmumicina i el seu derivat acetilat.

Compost	IGROV (ovari)	K-562 (leucèmia)	LOVO-DOX (colon)	PANC-1 (pancreas)
Barmumicina	0.8 µM	0.8 µM	0.6 µM	0.9 µM
Ac-barmumicina	5.9 µM	5.0 µM	6.5 µM	5.5 µM

3.2. Síntesi i determinació estructural de la barmumicina

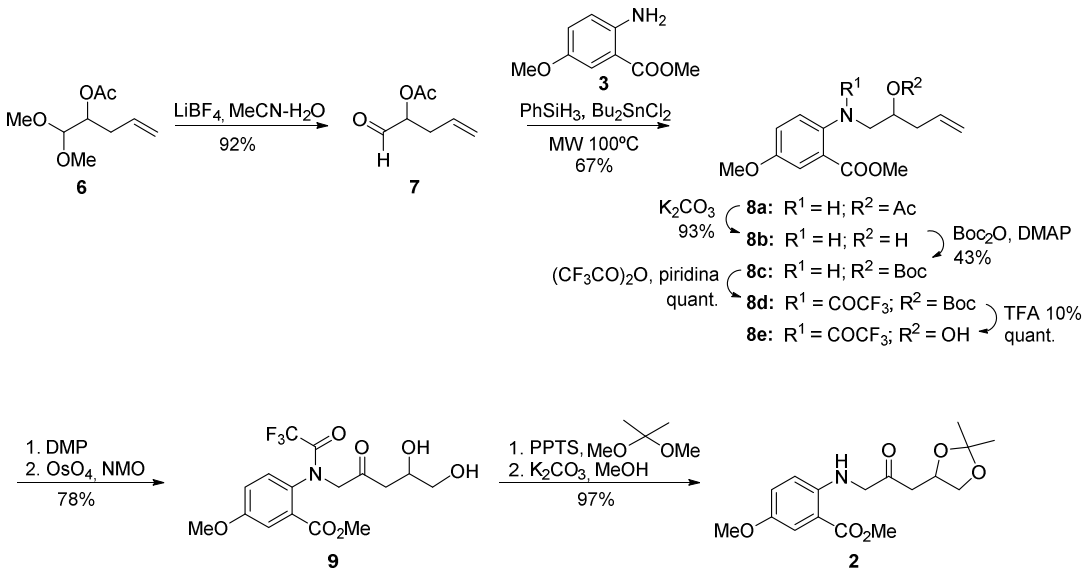
Es van dissenyar dues rutes per a la síntesi de la macrolactona proposada com a estructura de la barmumicina (Figura 3). Les dues conflueixen en l'intermedi **2**, i es basen en la *N*-alquilació de l'anilina **3**, *via* aminació reductiva o substitució nucleòfila fent servir l'aldehid **4** o la bromocetona **5** respectivament, posterior formació del doble enllaç exocíclic i macrolactonització. Les dues estratègies es van dur a terme en paral·lel.



1 **2** **3** **4** **3** **5**

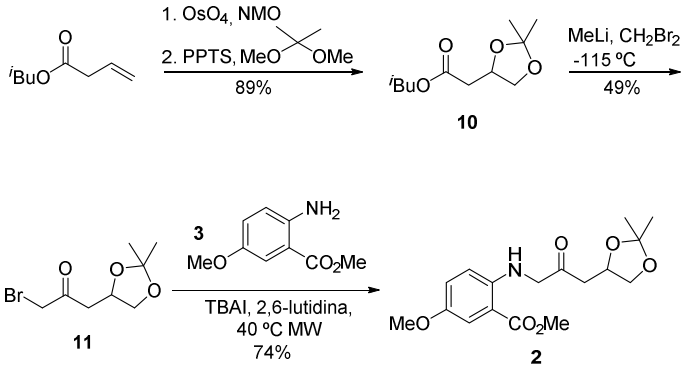
Figura 3. Esquema retrosintètic per la síntesi de la lactona **1**.

La ruta basada en una aminació reductiva començà amb la desprotecció del dimetil acetal conegut **6**[7] per donar l'aldehid **7**, que es va fer reaccionar amb l'anilina **3**[8] sota les condicions desenvolupades per Kangasmetsä[9] per a obtenir l'anilina alquilada **8a** (Esquema 1). Es van haver de fer successius canvis en els grups protectors per oxidar l'alcohol a la corresponent cetona, ja que no es va poder dur a terme amb l'amina lliure, observant descomposició del material de partida i l'anilina va resultar ser molt poc reactiva davant la protecció amb Boc. Finalment, es va obtenir l'alcohol **8e**, protegit com a *N*-trifluoroacetil que es va convertir en el diol **9** per oxidació de l'alcohol i dihidroxilació del doble enllaç terminal. El diol **9** es va protegir en forma d'acetal i la hidròlisi de la trifluoroacetil amida va portar a l'intermedi **2**, comú per a les dues vies.



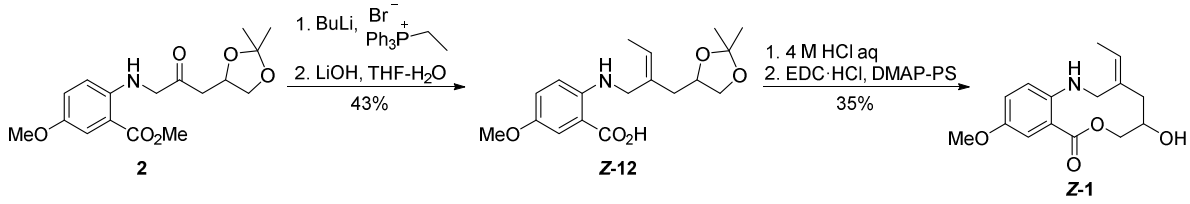
Esquema 1. Síntesi de l'intermedi **2** *via* aminació reductiva.

Paral·lelament, es va desenvolupar una ruta sintètica que va arribar al mateix intermedi de manera més eficaç, en menys passos i amb un rendiment global més alt. Començant pel but-3-enoat d'isobutil, aquest es va dihidroxilar i protegir per obtenir l'ester **10**, que al reaccionar amb bromometil liti preparat *in situ*, proporcionà la bromocetona **11** (Esquema 2). L'alquilació de l'anilina **3** sota condicions d'irradiació per microones en presència de 2,6-lutidina amb iodur de tetrabutilamoni com a catalitzador va fornir directament l'intermedi **2**.



Esquema 2. Síntesi de l'intermedi **2** *via* substitució nucleòfila.

A partir de la cetona **2**, la formació del doble enllaç exocíclic,amb una relació *Z*/*E* (7:3), es va dur a terme per olefinació de Wittig, la posterior hidròlisi de l'ester va permetre la separació de diastereòmers (Esquema 3). A partir de l'àcid ***Z*-12**, l'eliminació de l'acetal i macrolactonització portà a ***Z*-1**, que tot i presentar esteroquímica inversa en el doble enllaç, es va fer servir per comparar-lo amb el producte natural.



Esquema 3. Síntesi de la lactona ***Z*-1** a partir de l'intermedi **2**.

Malauradament, les diferències en els desplaçaments químics del producte sintètic amb les del producte natural eren massa grans com per ser atribuïdes tan sols a la diferència en l'estereoquímica del doble enllaç, per tant, l'estructura proposada per la barmumicina havia de ser revisada. Arribats a aquest punt, es va reassignar l'estructura de la barmumicina com a **13** (Figura 4). La nostra retrosíntesi es va basar en la desconexió per l'enllaç amida, format a partir de l'àcid **14** i l'amina **15**.

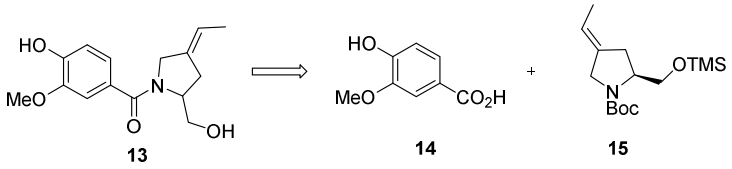
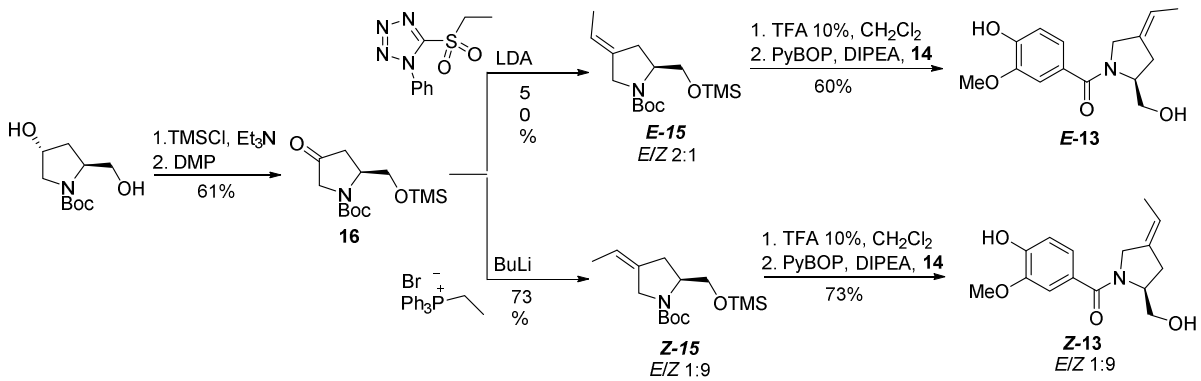


Figura 4. Estructura revisada i retrosíntesi proposada.

La síntesi de ***E*/*Z*-13** es va aconseguir fàcilment a partir del *N*-Boc-*trans*-4-hidroxi-L-prolinol. Protecció de l'alcohol primari i oxidació del secundari dugueren a la cetona **16**, que es va sotmetre a condicions d'olefinació de Julia o de Wittig per a obtenir les corresponents olefines **15** amb una relació *E*/*Z* 2:1 i 1:9 respectivament (Esquema 4). Desprotecció de l'amina i l'alcohol i formació de l'enllaç amida van portar a la mescla de diastereòmers en ambdós casos. La mescla *E*/*Z* 2:1 es va purificar per HPLC semipreparatiu per obtenir ***E*-13** com a únic diastereòmer. Aquest es va comparar amb l'estructura del producte natural i es va confirmar com a estructura de la barmumicina.



Esquema 4. Síntesi de ***E*/*Z*-13**.

En resum, s'ha identificat un producte natural amb activitat biològica utilitzant la síntesi de les estructures proposades per confirmar-ne l'estructura. En una primera assignació, es va proposar l'estructura de tipus macrolactona **1**, però la síntesi va determinar que aquesta

no era l'estructura del producte natural. La reassignació com a estructura **13** i la posterior síntesi en van confirmar la identitat. Aquest treball és un exemple més de la importància de la síntesi orgànica per la confirmació de l'estructura assignada als productes naturals quan s'ha determinat sols per tècniques espectroscòpiques,[10] a més de ser una eina imprescindible pel subministrament de productes per assajos clínics i en cas favorable per la seva comercialització

4. Síntesi i determinació estructural del macrocicle de les phormidolides B-D

4.1. Objectiu sintètic

Les phormidolides B-D es van aïllar de l'extracte d'una esponja de la família Petrosiidae de la costa de Pemba (Tanzania). Aquests compostos tenen certa semblança amb la oscillariolida[11] i la phormidolida A,[12] presentant una estructura i estereoquímica complexes (Figura 5) i van mostrar activitat antitumoral davant de diverses línies cel·lulars (Taula 3).

De l'estructura general de les phormidolides B-D s'en poden diferenciar tres fragments: un macrocicle, una cadena polihidroxilada i un àcid gras. El macrocicle és comú a les tres phormidolides, presenta 6 estereocentres i un doble enllaç *Z*-trisubstituït. La cadena polihidroxilada també és comú a les tres phormidolides i té 7 estereocentres i 3 dobles enllaços dels que el terminal és un metil èter de bromoenol. L'àcid gras és la part diferenciativa de les phormidolides està unit per un enllaç ester a la mateixa posició de la cadena polihidroxílica de les phormidolides. Cada àcid gras es diferencia per la constitució de l'haloalquè terminal, un fragment rar per aquest tipus de productes.

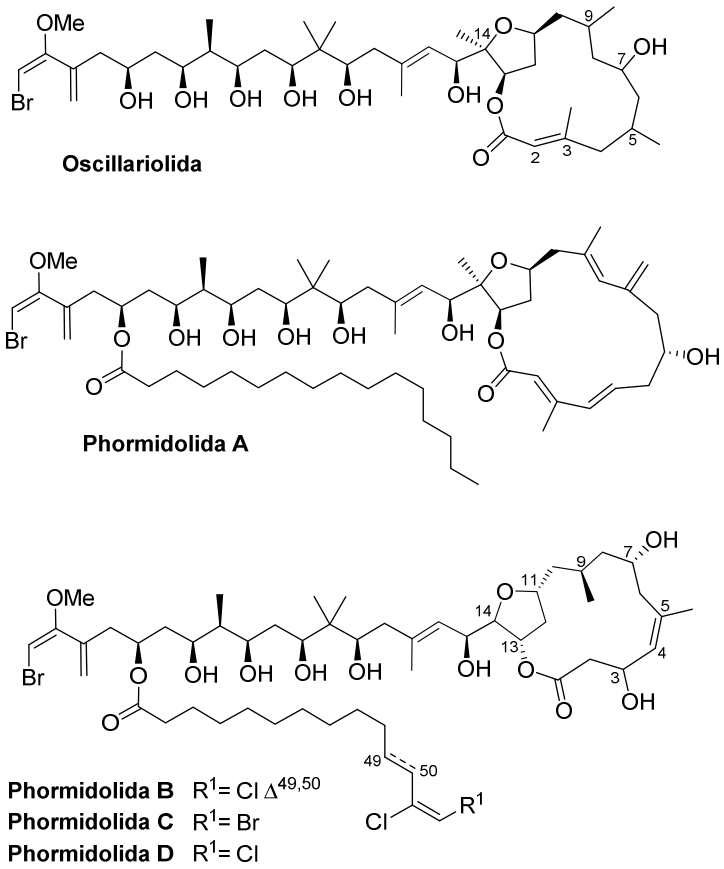


Figura 5. Estructures de l'oscillariolida i les phormidolides A-D.

Taula 3. Valors d'inhibició del creixement al 50% (GI_{50}) per les phormidolides B-D.

Compost	A-549 (pulmó)	HT-29 (colon)	MDA-MB-231 (mama)
Phormidolida B	1.4 µM	1.3 µM	1.0 µM
Phormidolida C	1.3 µM	0.8 µM	0.5 µM
Phormidolida D	1.2 µM	0.3 µM	1.4 µM

L'estructura i connectivitat de les phormidolides es va determinar per l'estudi d'experiments de RMN de ^{1}H, ^{13}C, 1D-TOCSY, gCOSY, gHSQC, i gHMBC. L'estereoquímica de la cadena polihidroxilada es va determinar per comparació amb els valors dels desplaçaments químics i constants d'acoblament de la phormidolida A,[12] però la configuració dels alquens presents en l'àcid gras només es va poder determinar per la phormidolida B, deduint que era *E-E*.

L'esteroquímica relativa dels substituents de l'anell de tetrahidrofurà (THF) es va determinar per experiments ROESY. Es veia clar que H11 i H13 estaven en una relació *cis*, mentre la disposició d'H14 no quedava clara. D'altra banda la configuració relativa de C9 i C7 a C11 es va deduir per l'anàlisi de les constants d'acoblament combinat amb els resultats dels experiments ROESY. La configuració del doble enllaç endocíclic es va determinar com a *Z*, en canvi no es va poder deduir la configuració relativa de l'estereocentre a C3.

Les tres phormidolides tenen en comú la part del macrocicle (**17**) i la cadena polihidroxilada (**18**) i són diferents només en la constitució de l'àcid gras (**19a-c**). La retrosíntesi general per les phormidolides B-D divideix cada molècula en aquests tres fragments, determinant-ne les desconexions per l'enllaç ester que uneix l'àcid gras al poliol i per l'enllaç C14-C15 que es pot aconseguir per diversos processos d'alquenilació (Figura 6).

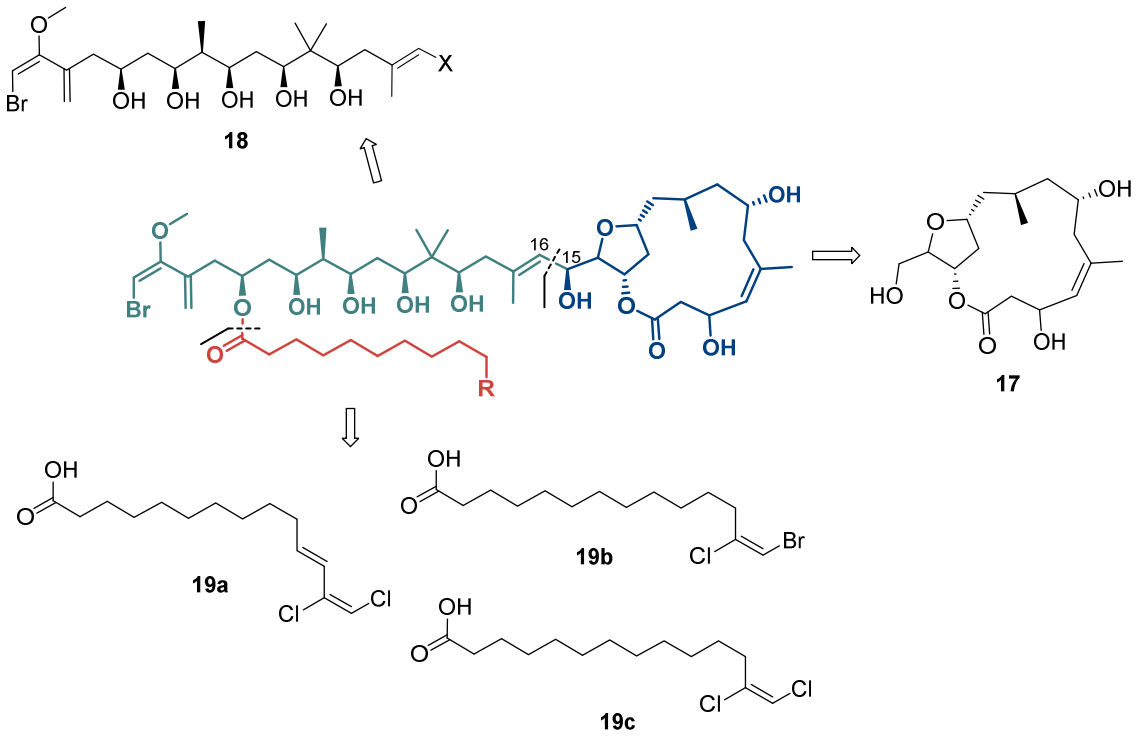


Figura 6. Retrosíntesi general per les phormidolides B-D.

L'objectiu d'aquesta part és la síntesi del macrocicle present en les phormidolides B-D. Això en facilitarà la seva determinació estructural i obrirà el camí a obtenir-ne prou quantitat per completar la síntesi total en un futur.

4.2. Estudi del camí sintètic per l'obtenció del macrocicle de les phormidolides B-D

La síntesi del fragment macrocíclic de les phormidolides B-D va començar per l'estudi de les millors condicions per a obtenir el doble enllaç, ja que aquest és el punt més complicat de la síntesi. Per això es va començar per la síntesi de manera no estereoselectiva i després es va adaptar la millor ruta a procediments estereoselectius.

S'assajaren dues estratègies, una basada en una metàtesi d'olefines i una altra en una olefinació de Julia-Kocienski (Figura 7). Les dues rutes determinaven les desconexions per l'enllaç ester i per l'alquè C4–C5 i l'única diferència pràctica era la metodologia i funcionalització per a la formació del doble enllaç. Per a la primera ruta es necessitava de l'obtenció de les olefines **20a** i **21a**, que també es podien derivatitzar per donar lloc a altres olefines per fer diferents proves de metàtesi. Per la segona ruta es va planejar la síntesi a partir de la sulfona **22** i l'aldehid **23**, o de manera anàloga a partir de la sulfona **24** i la cetona **25**, segons en quin fragment s'introdueix cada funcionalització.

L'olefina **2a**, la sulfona **22** i la cetona **25** són els fragments més complexos, contenen 5 dels 6 estereocentres del macrocicle i l'anell de tetrahidrofurà. La síntesi d'aquest fragments es va plantejar a partir de l'aldehid **25**, com a intermedi comú a les dues rutes i la síntesi es va planejar a partir del sucre comercial 2-desoxi-D-ribosa ja que ja conté dos estereocentres definits i això ens podia ser útil per a la futura síntesi enantioselectiva.

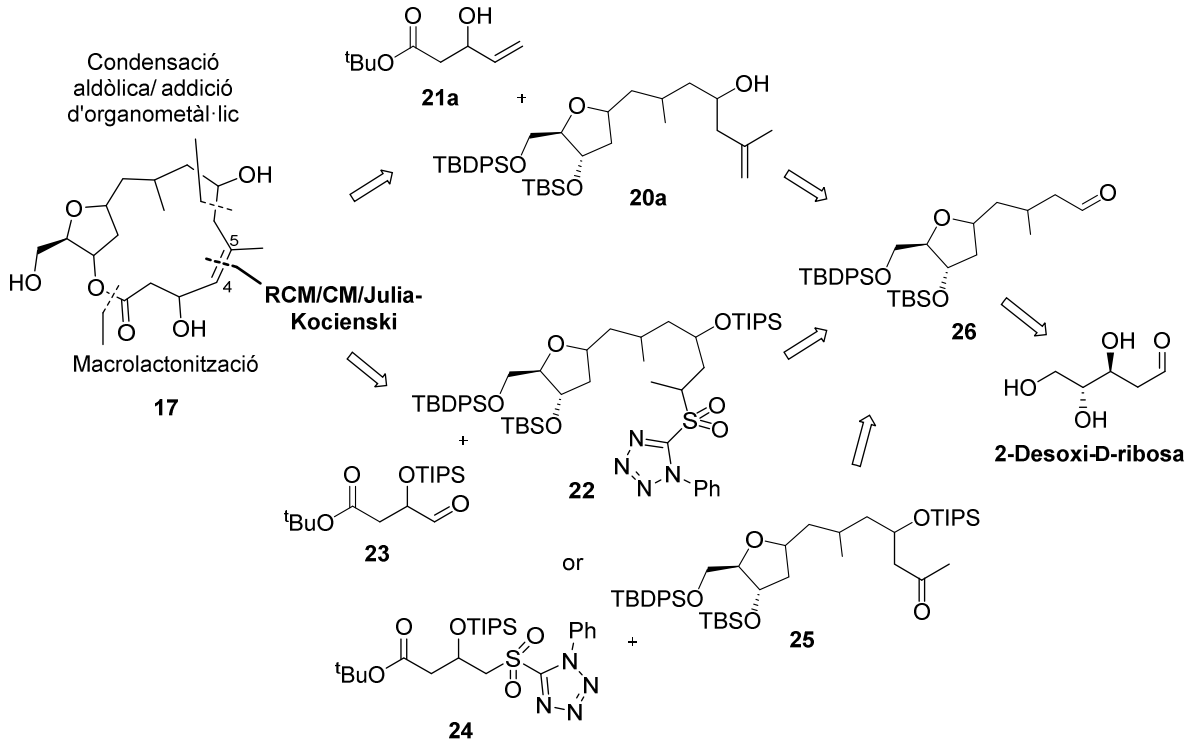


Figura 7. Anàlisi retrosintètic per a l'elecció de la millor ruta.

4.2.1. Estratègia basada en metàtesi d'olefines

És conegut que les olefines *gem*-disubstituides són mals substrats per a reaccions de metàtesi d'olefines, però es poden utilitzar si es troba una olefina compatible amb el catalitzador i la metodologia adients.[13] Com a primera estratègia es van sintetitzar les olefines **20a-c** i **21a-h** que es diferencien en els grups protectors i es van sotmetre a diferents combinacions i condicions de reacció canviant temperatura i catalitzador.

Els catalitzadors es van seleccionar fent servir aquells que destaquen per la seva alta reactivitat.[15] Així, els catalitzadors seleccionats van ser els catalitzadors de Grubbs[15] i Hoveyda-Grubbs[16] de segona generació,el catalitzador de Schrock[17] i uns catalitzadors de Hoveyda-Grubbs de segona generació modificats que presenten una funcionalització extra que aporta estabilitat al catalitzador i majors velocitats d'iniciació (Figura 8).[18]

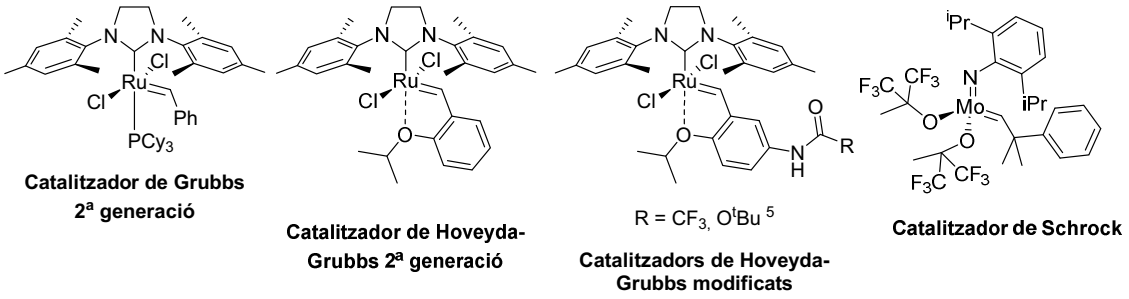
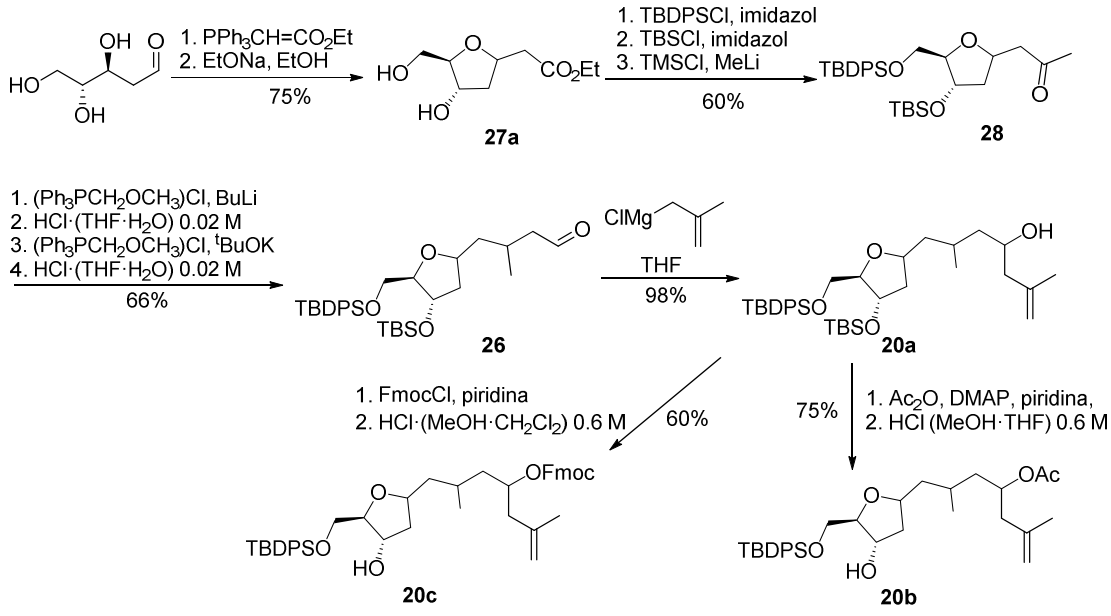


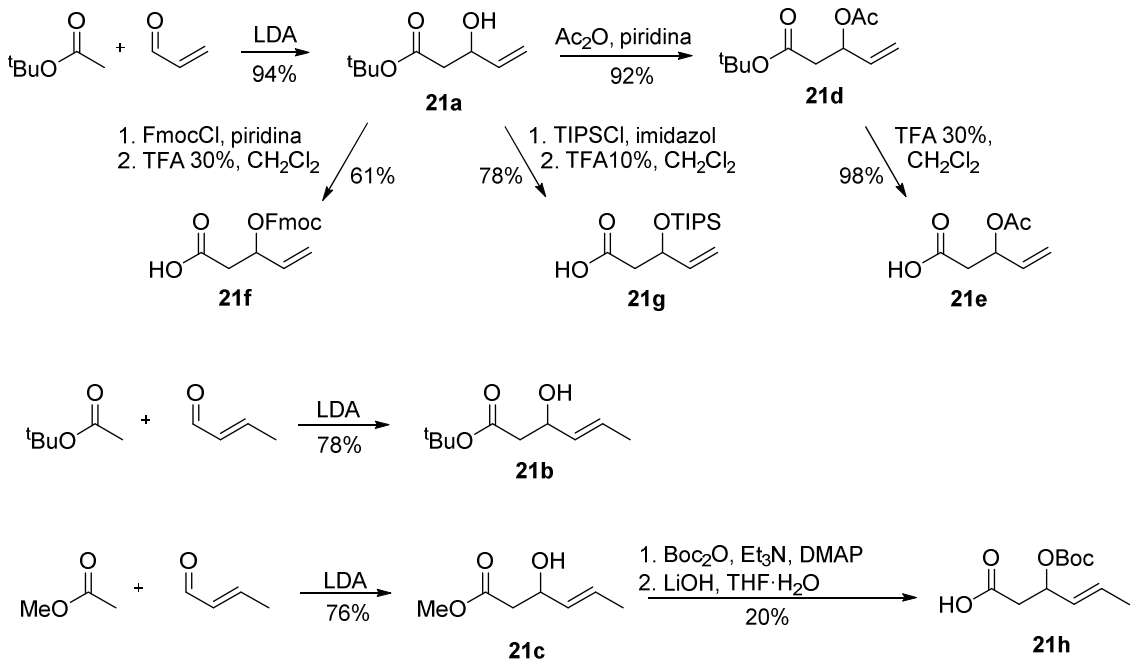
Figura 8. Catalitzadors seleccionats per a les reaccions de metàtesi d'olefines.

A partir de la 2-desoxi-D-ribosa, el THF **27a** es va obtenir per procediments ja descrits,[19] els dos hidroxils de **27a** es van protegir amb eters de silici ortogonals i es va transformar directament a la corresponent metil cetona **28** (Esquema 5). Dues reaccions de Wittig-hidròlisi consecutives dugueren a l'aldehid **26**, intermedi de les dues vie i introducció de clorur de metil al·lil magnesi ens va portar a l'olefina **20a**. A partir de **20a**, es van preparar via protecció i desprotecció adients les olefines **20b** i **20c**.



Esquema 5. Síntesi de les olefines **20a-c**.

Les olefines monosubstituides **21a-c** es van obtenir per la reacció d'acetat de metil o de *tert*-butil amb acroleïna o crotonaldehid (Esquema 6). L'alcohol **21a** fou transformat en el derivat acetilat **21d** i la posterior hidròlisi donà **21e**. De manera anàloga, es van sintetitzar els àcids **21f** i **21g** protegits amb 9-fluorenilmetoxicarbonil (Fmoc) i amb triisopropilsilil (TIPS) respectivament a partir de l'alcohol **21a** i l'àcid **21h** protegit amb *tert*-butoxicarbonil (Boc) a partir de l'alcohol **21c**.



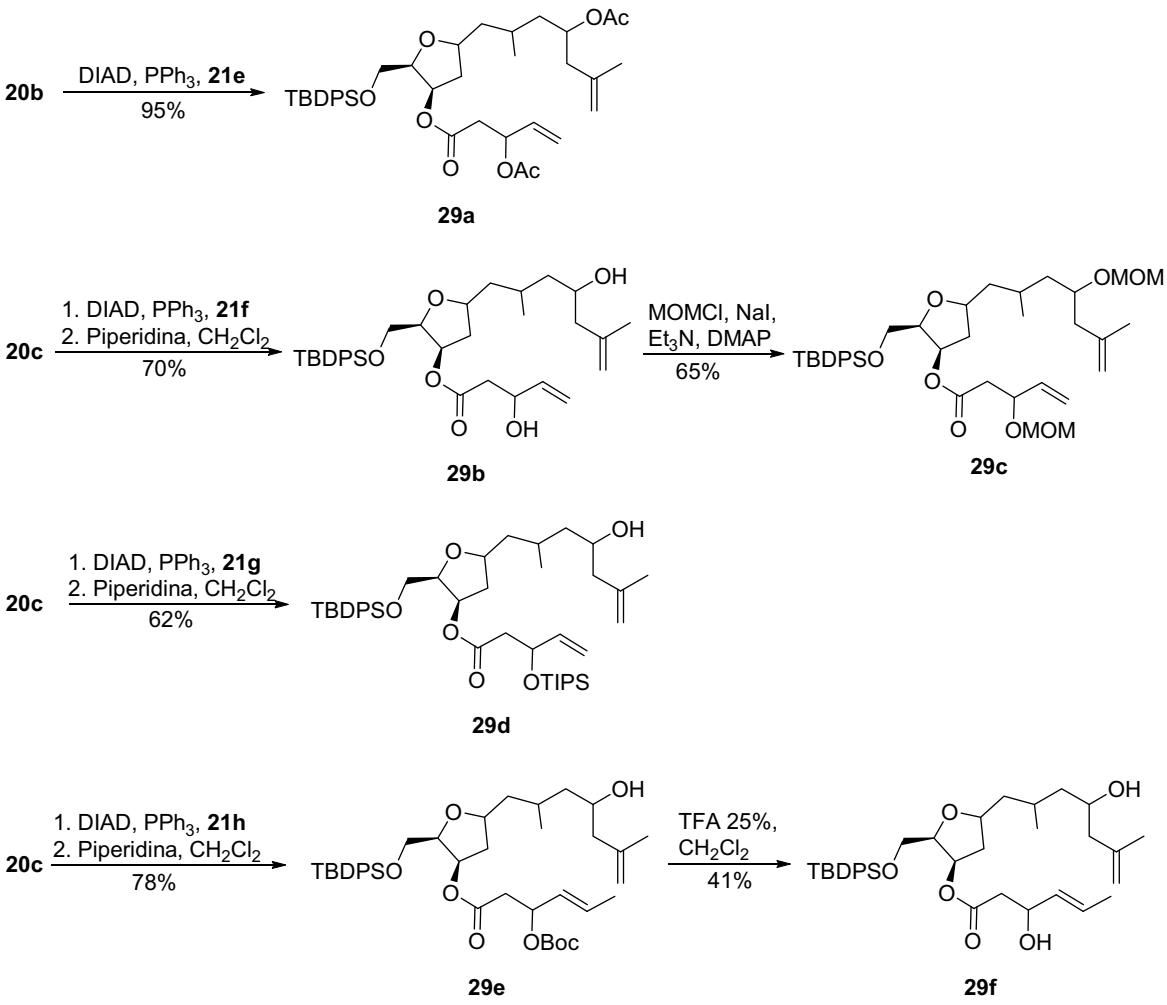
Esquema 6. Síntesi de les olefines **21a-h**.

Els experiments de metàtesi creuada es van dur a terme fent servir combinacions d'olefines i catalitzadors en diferents condicions de reacció (Taula 4). Les reaccions es van dur a terme amb excessos d'olefina monosubstituida (de 10 a 30 equivalents) i amb quantitats de catalitzador abundants (30-40%). Cap de les reaccions assajades va portar al producte esperat.

Taula 4. Experiments de metàtesi creuades.

Olefina 20	Olefina 21	Catalitzador	Dissolvent	Temperatura
20a	**21a**	HG-II	Toluè	t.a.
20a	**21a**	HG-II-CF_3	Toluè	t.a.
20a	**21a**	HG-II	Toluè	110 °C
20a	**21b**	HG-II	Toluè	55 °C
20b	**21d**	HG-II	CH_2Cl_2	40 °C
20b	**21d**	HG-II	Toluè	110 °C
20b	**21d**	G-II	Toluè	110 °C

Es van sintetitzar també una sèrie d'esters **29a-f** per sotmetre a reaccions de metàtesi amb el factor a favor que es produïa un tancament de l'anell amb la formació de l'alquè (RCM) i també s'hi van provar diferents condicions de reacció i diferents catalitzadors. La formació de l'ester es va dur a terme per esterificació de Mitsunobu i després es van dur a terme els passos de desprotecció o protecció corresponents (Esquema 7).



Esquema 7. Síntesi dels esters **29a-f**.

Es van provar diferents condicions i catalitzadors per obtenir el macrocicle (Taula 5). Si bé en algun cas es van detectar traces de producte, en cap cas es va poder obtenir prou quantitat com per a que el procés es pogués considerar adient per finalitzar la síntesi.

Taula 5. Experiments de RCM.

Precursor	Catalitzador	Dissolvent	Temperatura
14a	G-II	CH_2Cl_2	40°C
14a	HG-II	CH_2Cl_2	40°C
14a	G-II	Toluè	110 °C
14a	HG-II	Toluè	110 °C
14b	HG-II	Toluè	t.a.
14b	HG-II-CF_3	Toluè	t.a.
14b	HG-II-O^{t}Bu	Toluè	t.a.
14c	Schrock	Benzè	80 °C
14d	HG-II	Toluè	80 °C
14e[a]	HG-II	Toluè	80 °C
14e[a]	HG-II	Toluè	MW 120-160°C
14e[a]	HG-II-CF_3	Toluè	MW 120-160°C
14e[a]	HG-II-O^{t}Bu	Toluè	MW 120-160°C
14f	HG-II	Toluè	80 °C

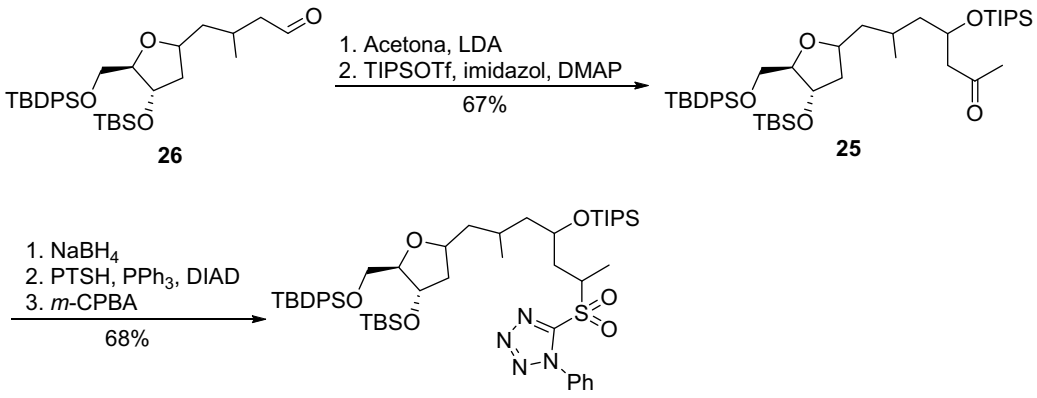
[a]Es van detectar traces de producte.

Finalment, ni els experiments de metàtesi creuada ni els experiments de metàtesi amb el factor a favor del tancament de l'anell van produir un rendiment de producte suficient per seguir amb la síntesi i aquesta estratègia va haver de ser abandonada.

4.2.2. Estratègia basada en l'olefinació de Julia-Kocienski

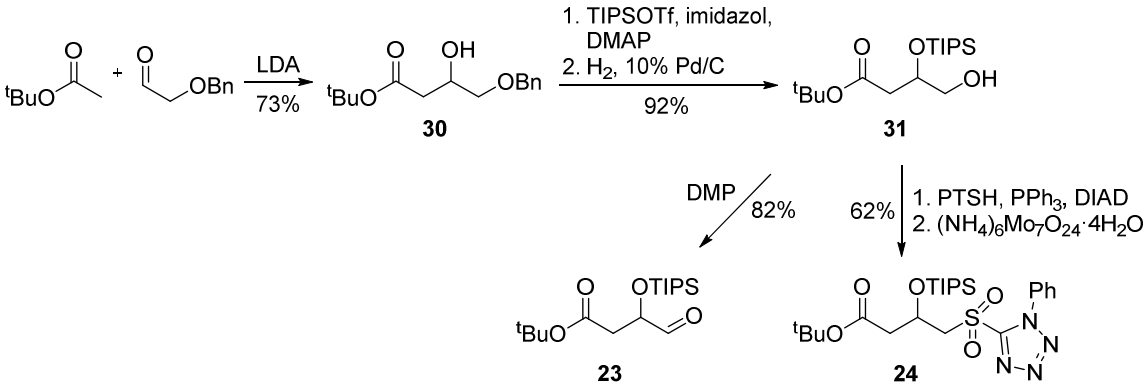
La segona estratègia es va basar en la formació de l'alquè trisubstituit per olefinació de Julia-Kocienski[20] fent reaccionar la sulfona adequada amb el corresponent grup carbonil. Cada una de les funcionalitzacions es va provar per cada un dels fragments.

La sulfona **22** fou preparada amb un rendiment moderat a partir de l'aldehid **26** per una serie de reaccions basades en la condensació aldòlica amb acetona seguida de protecció de l'hidroxil per donar la cetona **25**, reducció del carbonil, introducció de 1-phenil-1*H*-tetrazol-5-tiol[21] per reacció de Mitsunobu i finalment oxidació (Esquema 8).



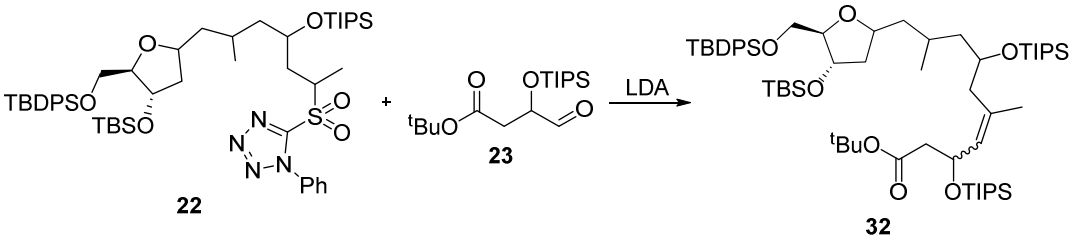
Esquema 8. Síntesi de la cetona **25** i la sulfona**22**.

D'altra banda, la reacció de l'enolat de liti de l'acetat de *tert*-butil amb 2-benziloxiacetaldehid va donar l'aldol **30**, que mitjançant protecció i hidrogenació forní l'alcohol **31**. A partir de **31** es va obtenir l'aldehid **23** per oxidació de l'alcohol, o la sulfona **24** de la mateixa manera descrita que per la sulfona **22** (Esquema 9).



Esquema 9. Síntesi de l'aldehid **23** i la sulfona **24**.

L'estratègia basada en la reacció de Julia-Kocienski no va permetre la unió entre la sulfona **24** i la cetona **25**, però sí entre la sulfona **22** i l'aldehid **23**. L'addició del carbanió de la sulfona **22** sobre l'aldehid **23**, transposició de l'heterocicle i l'eliminació de diòxid de sofre va fornir el producte amb el doble enllaç trisubstituit **32** (Esquema 10).



Esquema 10. Síntesi de l'alquè **32**.

Amb l'obtenció del doble enllaç C4-C5, l'optimització per aconseguir el pas clau de la síntesi es va donar per acabada i es va seleccionar la ruta basada en l'olefinació de Julia-Kocienski per adaptar-la a procediments enantioselectius. La síntesi enantioslectiva del fragment macrocíclic de les phormidolides B-D està explicada en global i amb més detall en el següent apartat.

4.3. Síntesi enantioselectiva del fragment macrocíclic de les phormidolides B-D

Un cop clara la ruta sintètica a seguir, es va adaptar aquesta síntesi a procediments estereoselectius. L'objectiu va ser la construcció de macrocicles amb la mateixa constitució i diferent estereoquímica que poguéssin ser útils en l'assignació estructural. L'esteroquímica relativa dels esterocentres a C7, C9, C11 i C13 quedava fixada en base a la determinació estructural. Així, es va definir com a objectiu el macrocicle **33a**, que en l'anàlisi retrosintètic prové de la sulfona **22a** i l'aldehid **23a** (Figura 9).

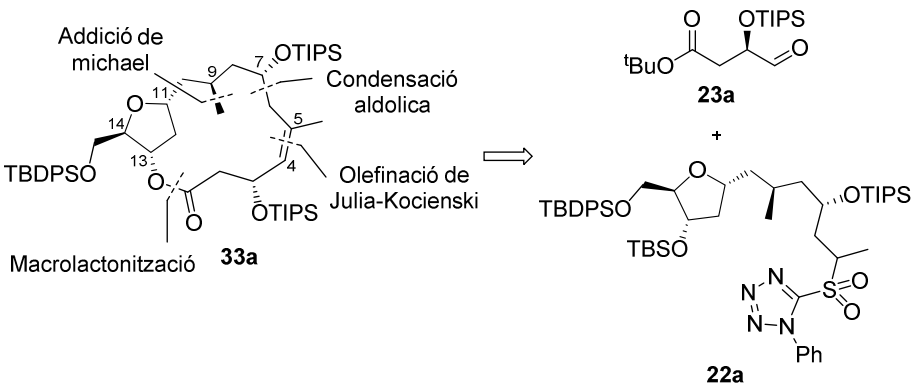
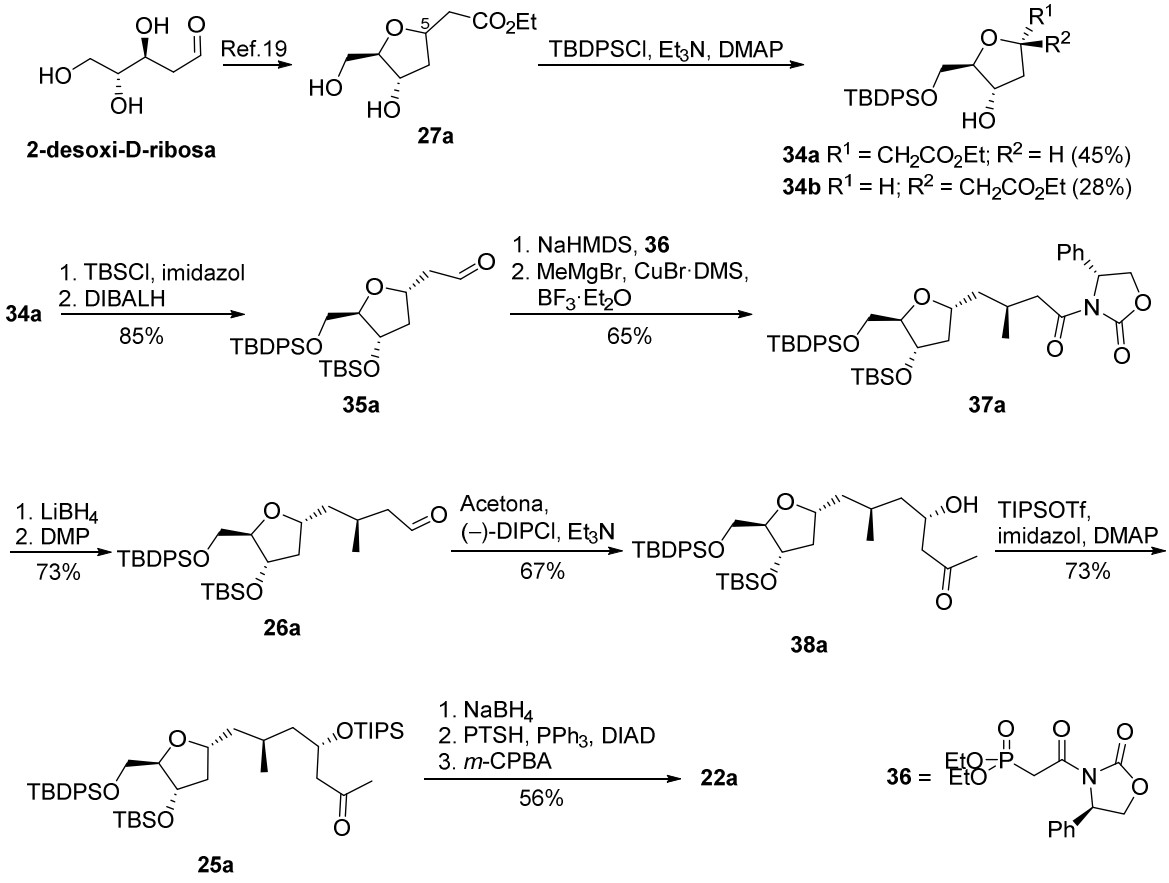


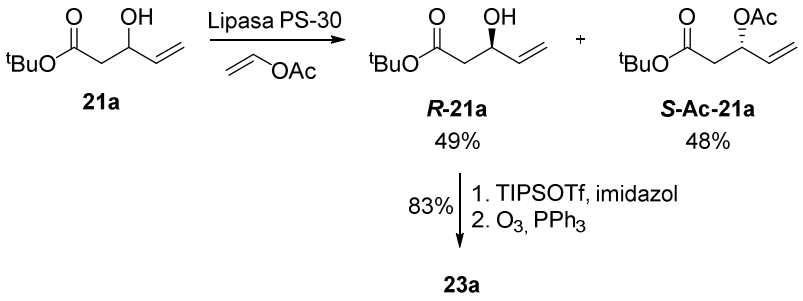
***Figura 9*.** Anàlisi retrosintètic per la síntesi del macrocicle **33a**.

La síntesi enantioselectiva de la sulfona **22a** va començar a partir de la 2-desoxi-D-ribosa que es va convertir a la mescla d'epímers a C5 **27a** (60:40) (Esquema 11).[19] La protecció de l'alcohol primari en va permetre la separació i així es va obtenir l'anell de THF **34a** com a únic diastereòmer. La protecció de l'alcohol secundari, reducció de l'ester a l'aldehid **35a** i posterior reacció amb el fosfonat **36**[22] en les condicions de reacció desenvolupades per Williams,[23] forní l'adducte metilat **37a** amb una relació diastereomèrica excel·lent (r.d. 97:3). A continuació s'eliminà l'auxiliar quiral per obtenir l'aldehid **26a** per un procés de reducció-oxidació. L'aldehid **26a** es va fer reaccionar amb un enolat de bor quiral que va donar el cetol **38a** amb l'estereoquímica desitjada amb bona relació diastereomèrica (r.d. 88:12). La configuració del nou estereocentre es va determinar pel mètode de Mosher; per formació de l'ester amb àcid (*R*)-MPA i (*S*)-MPA i anàlisi dels desplaçaments químics.[24] El cetol **38a** es va protegir en forma d'eter de silici **25a** i es va funcionalitzar el carbonil fins a la corresponent sulfona **22a** per reducció, introducció de 1-phenil-1*H*-tetrazol-5-tiol per esterificació de Mitsunobu i oxidació amb àcid 3-cloroperbenzoic (*m*-CPBA).



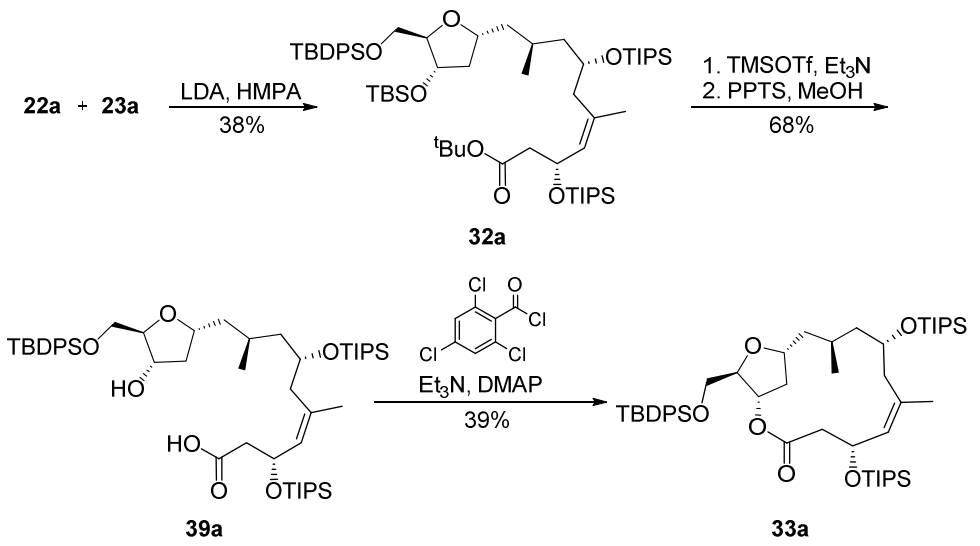
Esquema 11. Síntesi de la sulfona **22a.**

L'aldehid **23a** enantiomericament pur es va preparar per ozonòlisi reductiva de l'alcohol al.lílic ***R*-21a** prèvia protecció. ***R*-21a** es va obtenir per resolució cinètica de la mescla racèmica de l'aldol **21a** amb lipasa PS-30[25] (Esquema 12).



***Esquema 12*.** Síntesi de l'aldehid **23a**.

L'assemblatge dels dos fragments **22a** i **23a** es va dur a terme amb diisopropilamida de liti (LDA) en presència d'hexametilfosforamida (HMPA), que va dur al doble enllaç trisubstituit ***Z*-32a** amb rendiment moderat i selectivitat baixa (r.d. 70:30) (Esquema 13). El distereòmer *Z* es va poder aïllar i la desprotecció quimioselectiva de l'hidroxil a C13 i l'àcid es va dur a terme en condicions extremadament suaus per evitar descomposició del material de partida portant al *seco*-acid **39a**. Finalment, **39a** es va ciclar en condicions de Yamaguchi per obtenir **33a**, juntament amb el seu dímer del qual va poder ser separat.



***Esquema 13*.** Síntesi del macrocicle **33a**.

Seguidament, es va plantejar la síntesi d'un macrocicle amb una estereoquímica diferent del THF amb tots els substituents en *cis*. Així, es demostra la versatilitat de l'estratègia sintètica desenvolupada i es dóna accés a un altre dels possibles macrocicles per l'estructura de les phormidolides B-D.

La ruta per obtenir la macrolactona amb l'anell de THF amb els substituents en *cis* va necessitar algunes modificacions, però l'anàlisi retrosintètic es basava en les mateixes desconexions (Figura 10). A més, es va dur a terme una optimització de les condicions de l'olefinació per millorar la selectivitat *Z* de la reacció en aquest substrat. Així, es va plantejar la síntesi de les sulfones **22b-c** i dels aldehids **23a-d**.

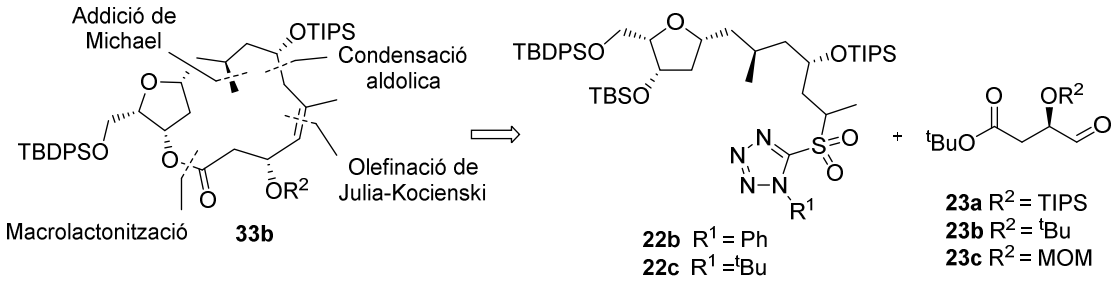
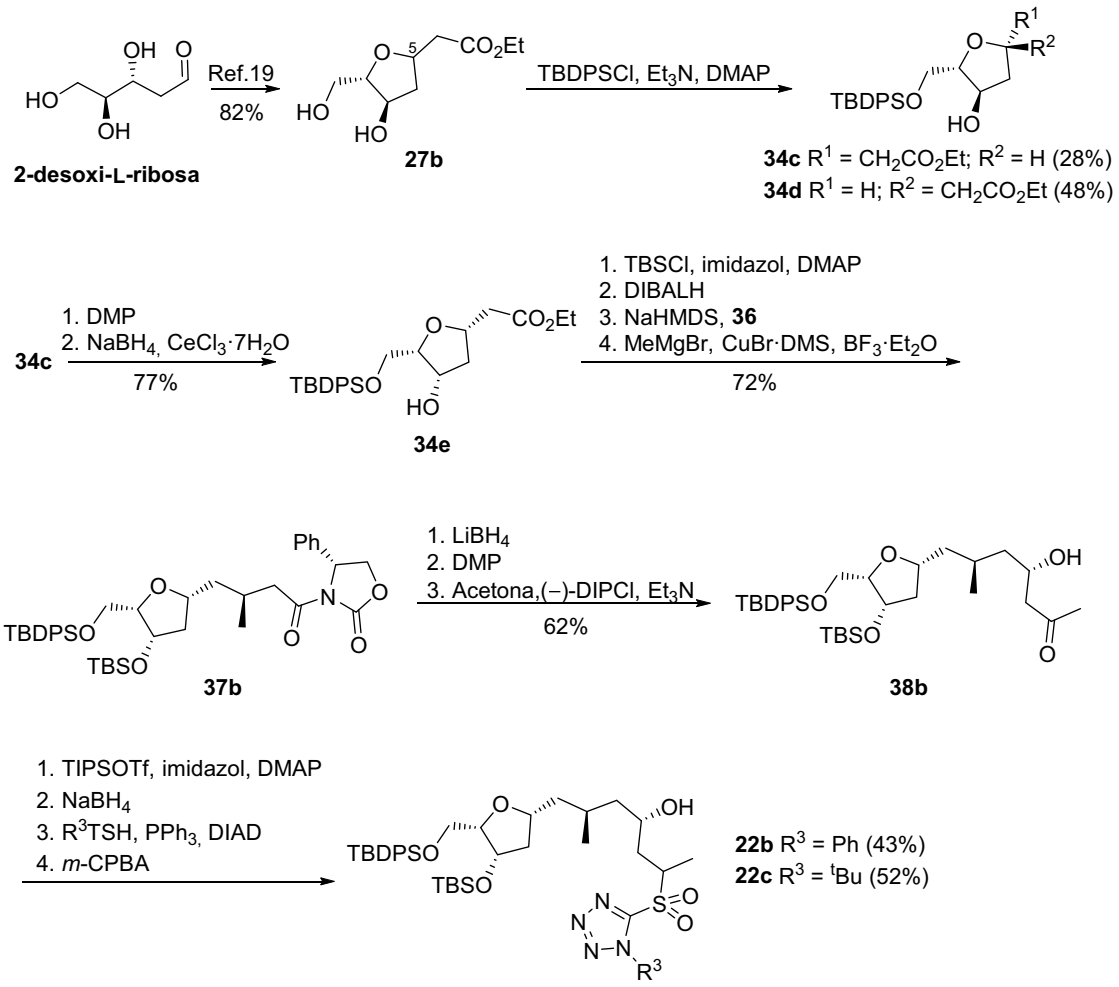


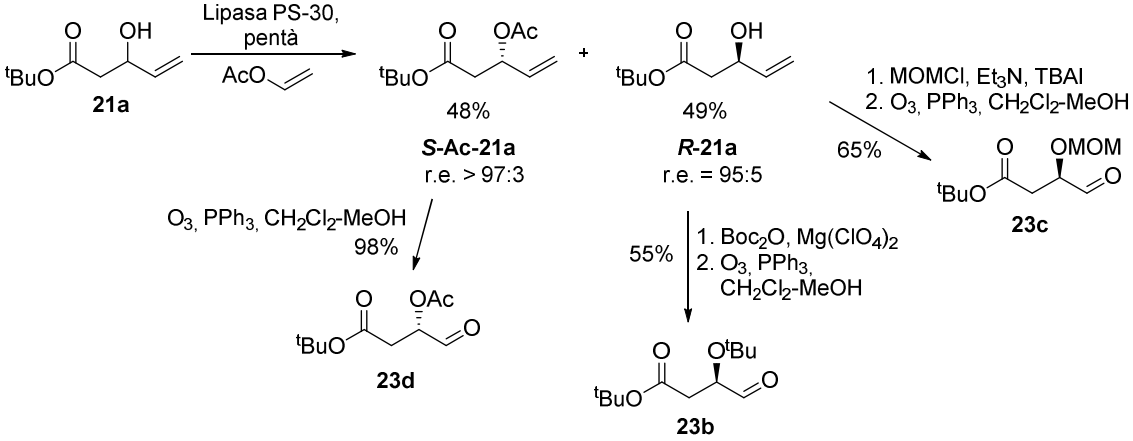
***Figura 10*.** Anàlisi retrosintètic per la síntesi del macrocicle **33b**.

El primer canvi va ser en el sucre de partida, ja que es va començar la síntesi per la 2-desoxi-L-ribosa. En aquest cas les mateixes condicions aplicades anteriorment, van portar a la mescla d'epímers a C5 **27b** (40:60), que en protegir-los amb TBDPSCl es van poder separar (Esquema 14). La configuració de C3 del THF **34c** es va invertir per oxidació seguida de reducció estereoselectiva per arribar al sistema *cis*-THF **34e** amb bona selectivitat (r.d. 93:7). Una seqüència de reaccions anàloga a l'anterior ens va dur a la introducció estereoselectiva del metil per obtenir **37b**, també amb una relació diastereomèrica excel·lent (r.d. 97:3) i a la aldòlica amb l'enolat de bor quiral que ens va donar **38b** (r.d. 85:15). Arribats a aquest punt, per optimitzar les condicions de l'olefinació, es van sintetitzar dues sulfones, **22b** i **22c** diferents en la substitució del tetrazol, per un procediment anàleg al de la síntesi anterior.



Esquema 14. Síntesi de les sulfones **22b-c.**

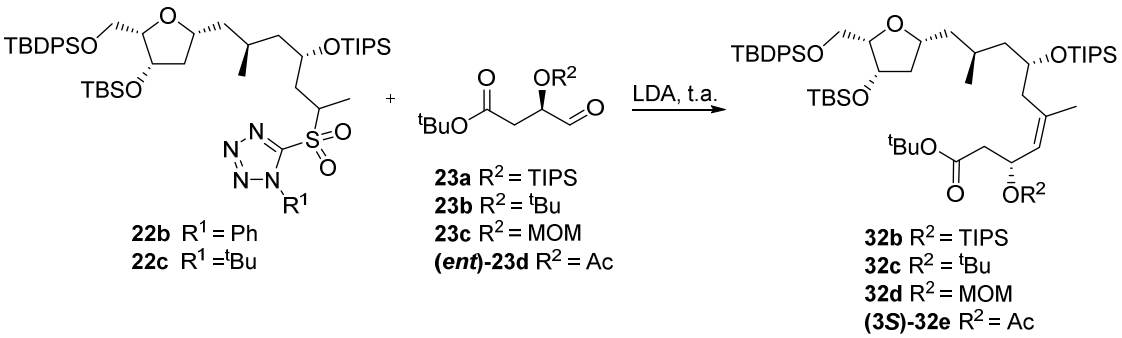
Els aldehids **23b-d** es van sintetitzar de manera anàloga a **23a**, per ozonòlisi reductiva dels alcohols protegits procedents de la resolució cinètica de l'aldol **21a**. (Esquema 15). Així, es van obtenir els aldehids **23b**, **23c** i **23d** protegits amb ^{t}Bu, metoximetil (MOM) i Ac respectivament.



***Esquema 15*.** Síntesi dels aldehids **23b-d**.

Els rendiments i l'estereoselectivitat de la reacció de les dues sulfones amb els diferents aldehids estan resumits a la Taula 6. Es va veure clarament que l'ús de la 1-(*tert*-butil)tetrazolil sulfona[26] donava millors selectivitats *Z* que el de la 1-pheniltetrazolil sulfona i que grups protectors petits, no només no oferien millors rendiments per estar menys impedits, sinó que disminuïen la selectivitat *Z* de la reacció (Taula 6). Les millors condicions es van obtenir amb la sulfona **22b** en presència de HMPA amb un aldehid amb un grup protector voluminós tal com **23a** o **23b**.

Taula 6. Optimització per la formació de l'alquè trisubstituït *Z*.

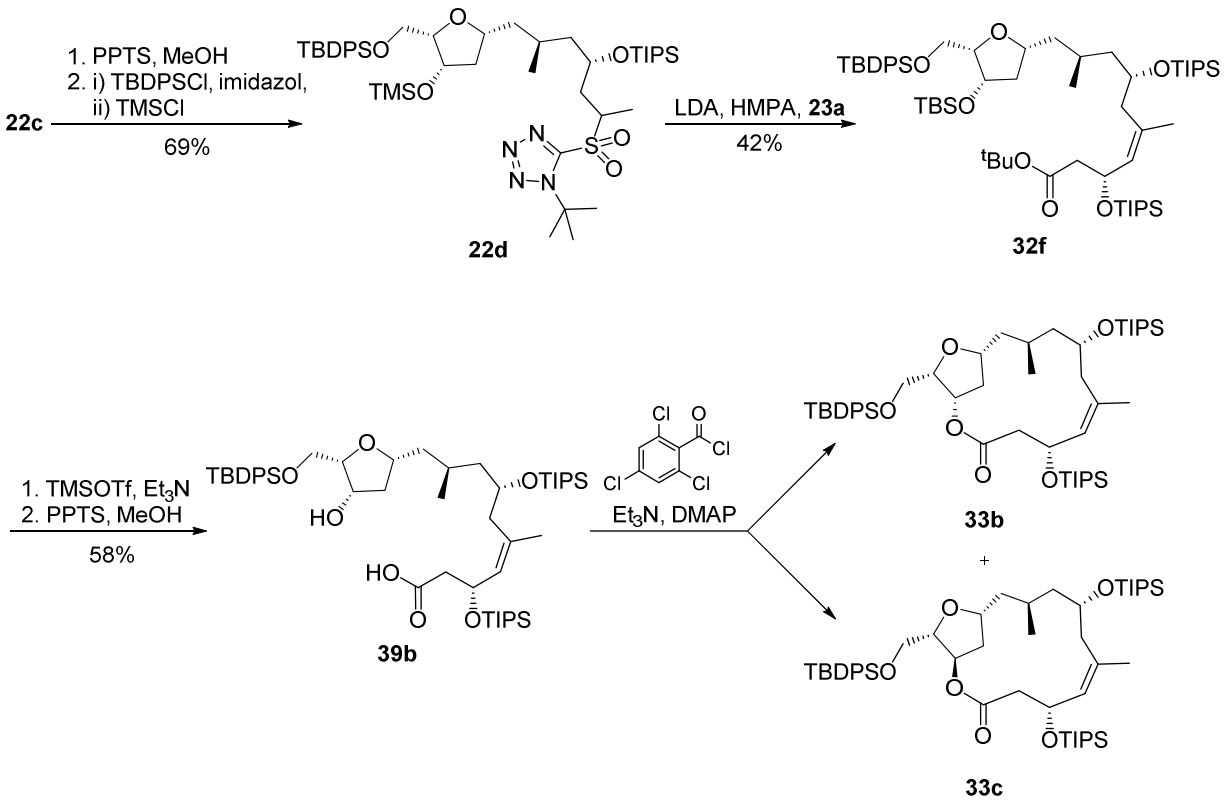


	Sulfona	Aldehid	Additiu	Producte (rendiment)	r.d. (*E*:*Z*)*
1	**22b**	**23a**	-	**32b** (42%)	35:65
2	**22c**	**23a**	HMPA	**32b** (61%)	3:97
3	**22b**	**23b**	-	**32c** (30%)	50:50
4	**22b**	**23b**	HMPA	**32c** (42%)	33:67
5	**22c**	**23b**	HMPA	**32c** (47%)	3:97
6	**22c**	**23c**	HMPA	**32d** (59%)	12:88
7	**22c**	**23d**	HMPA	**32e** (20%)	13:87

*Determinat per ^{1}H-RMN

Finalment, els millors resultats es van aconseguir amb la 1-(tert-butil)tetrazolil sulfona **22c** i aquesta es va fer servir per continuar la síntesi amb l'aldehid **23a**. Malauradament, estudis de desprotecció de l'hidroxil protegit amb TBS van demostrar que aquest no era un grup protector adient per la sèrie de compostos on el THF té tots els substituents en *cis*.

Arribat a aquest punt, es va convertir la sulfona **22c** en la sulfona **22d**, per facilitar la desprotecció en els passos següents (Esquema 16). Per la olefinació de Julia-Kocienski es van fer servir les condicions optimitzades, que dugueren a l'aquè trisubstituit **32f** amb molt bona estereoselectivitat (r.d. 97:3). La desprotecció es va aconseguir amb bon rendiment amb el grup protector de silici més làbil i el seco-àcid **39b** es va sotmetre a condicions de ciclació. Sorprenentment, aquest cop la ciclació va donar lloc a dos diasteròmers del macrocicle **33b** i **33c**.



Esquema 16. Síntesi dels macrocicle **33b** i **33c**.

Amb els tres macrocicles enantiopurs en mà, ja es pot fer una comparació amb el producte natural que en permeti una aproximació a l'estereoquímica. En general, els desplaçaments químics de ^{1}H-RMN i ^{13}C-RMN per la zona C2-C6 són molt diferents entre els macrocicles sintètics i el macrocicle del producte natural, el que fa pensar que la configuració del C3 del producte natural és l'oposada de la sintetitzada. D'altra banda, el macrocicle en què la zona de l'anell de tetrahidrofurà té més similituds amb el macrocicle natural és **33a**. Per tant, la proposta que fem per a l'esteroquímica relativa del macrocicle de les phormidolides B-D és la del macrocicle **33d**, que haurà de ser sintetitzat en el futur per la seva validació (Figura 11).

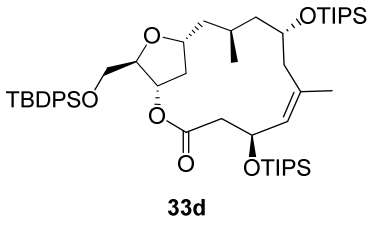


Figura 11. Macrocicle amb l'estereoquímica proposada per les phormidolides B-D (**33d**).

En resum, per aquest segon projecte, s'ha desenvolupat una metodologia que permet sintetitzar eficaçment i de forma enantioselectiva el macrocicle de les phormidolides B-D. La síntesi dels nostres compostos ha donat una idea sobre la possible configuració de l'anell de THF i del C3 dels macrocicles i permet la síntesi d'altres diastereòmers ja que és una estratègia versàtil, on només canviant els materials de partida o els inductors de quiralitat es pot dirigir la síntesi cap al diastereòmer desitjat.

5. Conclucions

En aquesta tesi s'ha treballat en dos projectes que han estat focalitzats en l'estudi de molècules d'origen marí com a fàrmacs, utilitzant la síntesi com a eina en els primers estadis de desenvolupament ja que la quantitat extreta de les fonts naturals només serveix per fer una primera aproximació a estructura i activitat.

La barmumicina és un producte natural amb activitat biològica del que s'ha confirmat l'estructura gràcies a la síntesi. L'estructura proposada es va obtenir per síntesi i es va comparar amb el producte natural duent a la conclusió que no era la correcta. La síntesi de l'estructura revisada ha confirmat la identitat d'aquest producte natural.

Les phormidolides B-D són productes naturals d'alta complexitat estructural dels quals encara no es té clara l'estereoquímica al complet. El treball sintètic ha estat focalitzat a la consecució de diversos objectius.

S'ha desenvolupat la síntesi del fragment macrocíclic de les phormidolides B-D, abordant dues aproximacions per a la formació de l'alquè trisubstituit; una basada en una metàtesi d'olefines i l'altra en una olefinació de Julia-Kocienski. La poca reactivitat de les olefines *gem*-disubstituides va portar a l'abandonament de la primera estratègia. En canvi, la segona va aconseguir arribar a l'alquè trisubstituït i es va seleccionar com a ruta per adaptar a procediments estereoselectius.

Adaptant l'estratègia seleccionada, s'ha desenvolupat una metodologia que permet sintetitzar eficaçment i de forma enantioselectiva el macrocicle de les phormidolides B-D; l'estratègia és versàtil, ja que canviant els materials de partida o els auxiliars quirals dels reactius es pot dirigir la síntesi cap al diastereòmer desitjat. El punt clau de la síntesi ha estat la formació del doble enllaç trisubstituit *Z* amb bon rendiment i selectivitat, pel qual s'ha dut a terme una optimització del procés.

La síntesi de tres macrocicles enantiopurs ha donat una idea sobre la possible configuració de l'anell i s'ha fet una proposta sobre l'estereoquímica relativa del producte natural. Aquesta haurà de ser confirmada per síntesi, clarament accessible utilitzant l'estratègia desenvolupada.

Els resultats presentats demostren la utilitat de la síntesi en el desenvolupament de productes naturals, ja sigui en la determinació d'estructura, estereoquímica o en la producció en sí. Cal recordar però, que aquesta és una relació simbiòtica, perquè és en la síntesi de productes naturals complexos on es produeix l'aprofundiment i la innovació en els processos, ja que són les necessitats les que estimulen l'enginy.

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