DOCTOR OF SCIENCES

Towards the total synthesis of L-783,277

Hoang, Thanh Vy

Award date:
2016

Awarding institution:
University of Namur

TOWARDS THE TOTAL SYNTHESIS OF L-783,277

A dissertation presented for the degree of Doctor of Philosophy
of the Faculty of Science, University of Namur

2015

Hoàng Thanh Vy

Thesis supervisor:	Pr. Steve Lanners
Thesis jury:	Pr. Daniel Vercauteren
	Dr. Gilles Hanquet
	Pr. Stéphane Vincent
	Pr. Christoph Tzschucke

« If one way be better than another, that you may be sure is nature's way. »
Aristotle (384 – 322 BC)

Table of Contents

Université de Namur

Faculté des Sciences

Rue de Bruxelles 61 – 5000 Namur

Towards the total synthesis of L-783,277

Hoàng Thanh Vy

Resorcylic Acid Lactones (RALs) are a family of mycotoxins which share the same structural skeleton composed of a β-resorcylic acid core fused with a 12- or 14-membered macrolactone. Despite their small strutural variations, these macrolides display an astonishingly large spectrum of biological activities, spanning from being Hsp90 inhibitors to antimalarial and antifouling. Three metabolites of the cis-enone containing subfamily have been recently recognised as a structurally unique class of kinase inhibitors. Their inhibition of kinases with a Cys residue properly located in their ATP binding pocket (*ca* 10% of the kinome), result from the 1,4-adddition of the abovementioned protein thiol to the *cis*-enone. One of them, L-783,277 has been recently disclosed to owe an anti-angiogenetic potential.

This project aimed for an elegant and modular synthetic pathway towards L-783,277, extracted from the fruitbody of *Helvella acetabulum*. This thesis outlines the construction of a dialkyne precursor, as the pivotal stage for a ring-closing alkyne metathesis, followed by Lindlar reduction to incorporate the delicate *cis*-enone.

The first chapter portrays a succinct biological profile of RALs over the period 1968-2014, which have been the target of a myriad of total syntheses. The syntheses of some chosen resorcylides are detailed to illustrate how early studies on structurally simple macrolides built the solid basement for innovative strategies and methodologies. The syntheses targeting cis-enone containing RALs, *e.g*. L-783,277, elucidate our inspirations and strategies towards the latter.

The second chapter exposed the pre*para*tion and tactical assembly of three fragments resulting from the retrosynthetic disconnection of L-783,277: an aromatic core and two straight-chained segments containing both a terminal substituted propyne. The synthesis of one of the latter led to the development of a new method for the opening one-carbon homologation and opening of lactones *via* the corresponding phosphine oxide. The key step resides in the direct alkylation at the benzylic position of the aromatic core as the first assembly. Finally, the crucial dialkyne precursor has been obtained on multigram scale, based on robust procedures with simple purification. The first series of assays devoted to RCAM are also discussed at the end of this chapter.

The third chapter depicts the application of our synthetic blueprint to other RALs, namely two natural resorcylides (zeranol and *(R)*-(+)-lasiodiplodin) and two synthetic ones: *(S)*-lasiodiplodin and neolasiodiplodin. Their accomplishment illustrates our elegant and concise strategy, promising further synthetic avenues leading to more complex resorcylides with a 12- or 14-membered ring.

« The roots of education are bitter, but the fruit is sweet”

Aristotle

To Pr. Steve Lanners: Thank you for helping me to overcome my occasional existential crisis and teaching me how to cope with stressful situations. Especially, I would like to thank you for believing in my competence.

I would like to thank Pr. Daniel Vercauteren, Pr. Stéphane Vincent, Dr. Gilles Hanquet and Pr. Christoph Tzschucke for the assessment of my work, presented in this thesis. I am honored by your presence at my thesis presentation and your judgment.

To the first generation of COS: “COS un jour, COS toujours”

To all the chemists on the third floor: Thank you for accompanying me through this seemingly endless but colourful journey. Without your glowing soul of love and kindness, suffering and pedantry, your anxiety and euphoria, obsessions and fairness, *para*noia and workaholism, patience and carefreeness, generosity and egocentrism, etc.. all these years would have been a mere theatre of human imagination. Grateful thanks to my dear United Nations.

To my last colleague next-fume hood: you have transformed my last thesis years into a refreshing glimpse of life. Thank you for tolerating my aberrant theories and compulsive behaviors, and for introducing me to the person who has made “Le Maigre” a legend…

Gởi Ba, Má và Mén. Đây là bài luận án cuối cùng của Cọp lùn. 15 năm lưu lạc xa xứ người. 15 năm gia đình mình sống xa nhau. Ba và Má tạo ra con một lúc, lo lắng cho con một đời. Lời thì vô nghĩa, lòng Cha Mẹ vô tận. "Cảm ơn" là lời, ơn thì trĩu tâm.

Dangeschä an all die Pälzer wu iwwer die hadde Johr for mich do waren un an mich geglabd hän. Vorneo kumm´ do erschdemol de π un dodenoch die Umu un de Uhu, awwer a de Rescht vun denne Deisemer Grischer.

Last but not least, I would like to thank YOU, the person who is reading this page…

BBN (9-BBN)	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	tert-butoxycarbonyl
Bz	benzoyl
Bu	butyl
ca	circa
CAN	cerium(IV) ammonium nitrate (cericammoniumnitrate) $Ce(NH_4)_2(NO_3)_6$
CBS reduction	Corey–Bakshi–Shibata reduction
CDI	carbonyl diimidazole
COD	1,5-cyclooctadiene
CSA	camphorsulfonic acid
Cy	cyclohexane
Cp	cyclopentadiyl
DCC	dicyclohexylcarbodiimide
DMB	3,4-dimethoxybenzyl
3,5-DMP	3,5-dimethylpyrazine
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	disopropylazodicarboxylate
DCM	dichloromethane
DIBAL(DIBAL-H)	diisobutylaluminum hydride
DIPEA (Hünig's base)	diisopropylethylamine
DMAP	N,N-4-dimethylaminopyridine
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DIPA	diisopropylamine
e.g.	exempligratia
EtOAc	ethylacetate
EOM	ethoxymethyl
F-oct3SnH	tris (1H, 1H, 2H, 2H-perfluorooctyl)tin hydride
HBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoric acid triamide (hexamethylphosphoramide)
HOBt	1-hydroxybenzotriazole
HPLC	high-pressure liquid chromatography
IBX	*o*-iodoxybenzoic acid
Im	imidazole
KHMDS	potassium bis(trimethylsilyl)amide

LAH	lithium aluminum hydride (LiAlH4)
LDA	lithium diisopropylamide
LHMDS (LiHMDS)	lithium bis(trimethylsilyl)amide
LG	leaving group
LTMP	lithium tetramethylpiperidide
L-selectride	lithium tri-sec-butylborohydride
m	*meta*
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MOM	methoxymethyl
m.p.	melting point
MPM or PMB	*para*-methoxybenzyl
MSA	methanesulfonic acid
NBS	N-bromosuccinimide
o	*ortho*
Oxone	potassium peroxymonosulfate
p	*para*
PG	protecting group
PCC	pyridiniumchlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Piv	pivaloyl
PMB or MPM	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	pyridinium p-toluenesulfonate
PTSA (TsOH)	*para*-toluenesulfonic acid
Py (pyr)	pyridine
RaNi	Raney nickel
RCAM	ring-closing alkyne metathesis
RCM	ring-closing metathesis
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerization
RT or r.t.	Room temperature
Salen	N,N'-ethylenebis(salicylideneiminato)bis(salicylidene)ethylenediamine
sec	secondary
SEM	2-(trimethylsilyl)ethoxymethyl

SET	single electron transfer
SIMES	N,N’-disubstituted 2,3-dihydro-1H-imidazol-2-ylidene
TASF	tris(diethylamino)sulfoniumdifluorotrimethylsilicate
TBAF	tetra-n-butylammonium fluoride
TBAI	tetra-n-butylammonium iodide
TBHP	tert-butyl hydroperoxide
TBDMS (TBS)	tert-butyldimethylsilyl
TBDPS (BPS)	tert-butyldiphenylsilyl
TCCA	trichloroisocyanuric acid
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFP	tri-2-furylphosphine
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	*para*-tolyl
Ts (Tos)	*para*-toluenesulfonyl
vs	versus

It would be erroneous to believe that Total Synthesis is either a mere copy of Mother Nature or an arrogant human game of creation in the name of our conceptual God and Faith. To scheme out the structure and an efficient approach of natural products is intrinsic to this discipline, as this would provide access to a multitude of analogues, in view of a better understanding of their biological activities. But this does not mean that all the chemically modified or laboratory-made substances have never existed at any moment in the world, or the naturally occurring products cannot meet human expectations. As there must be a constant union between cause and effect[1], all natural substances have their inherent role in existence, whereas Total Synthesis chemists wish to modify these compounds to suit some expected biological activities, solely for the sake of humankind. Giving that human beings are also part of the Cosmos, chemical substances that are believed to be acquired through human imagination and accomplishment should be consequently fruits of the universe, either are they the exact reproduction of Nature or a target-oriented modification. Hence synthetic chemists do not pretend to surpass the efficiency or essence of Nature. We simply follow Nature's evolution.

Chapter 1

INTRODUCTION

1 INTRODUCTION

1.1 Resorcylic acid lactones (RALs)

Little is known of the real biodiversity of the fungus kingdom which has a worldwide distribution, inhabiting even the extreme environments ranging from very high salt concentration areas to deserts or ionising radiation regions. Some of these organisms, commonly known as moulds, grow in the form of multicellular filaments and produce toxic secondary metabolites called mycotoxins. The production of mycotoxin is not indispensable for the intrinsic growth or development of the fungus, but may facilitate its proliferation into colonies, in particular by weakening the receiving host which provides organic matter. However, from a human point of view, these compounds have revealed a valuable research avenue for drug discovery. Among them are a family of mycotoxins produced *via* a unique polyketide biosynthetic pathway,[2] which are named resorcylic acid lactones (RALs).

One common characteristic of these natural products is the macrolactone ($\geq$ 12), which are in general referred to as “macrolides”. In particular, resorcylic acid lactones (RALs) are a family of benzannulated macrolides.[3] Their name originates from the structure containing a partially substituted β-resorcylic acid scaffold accolated with a 12- or 14-membered lactone. These naturally occurring compounds present a similar squeletal structure which differs by the arrangement of a limited number of functional groups, and despite only small structural variations, they display an astonishingly and unexpectedly wide spectrum of biological activities.Some examples of RALs are presented in **Figure 1**.

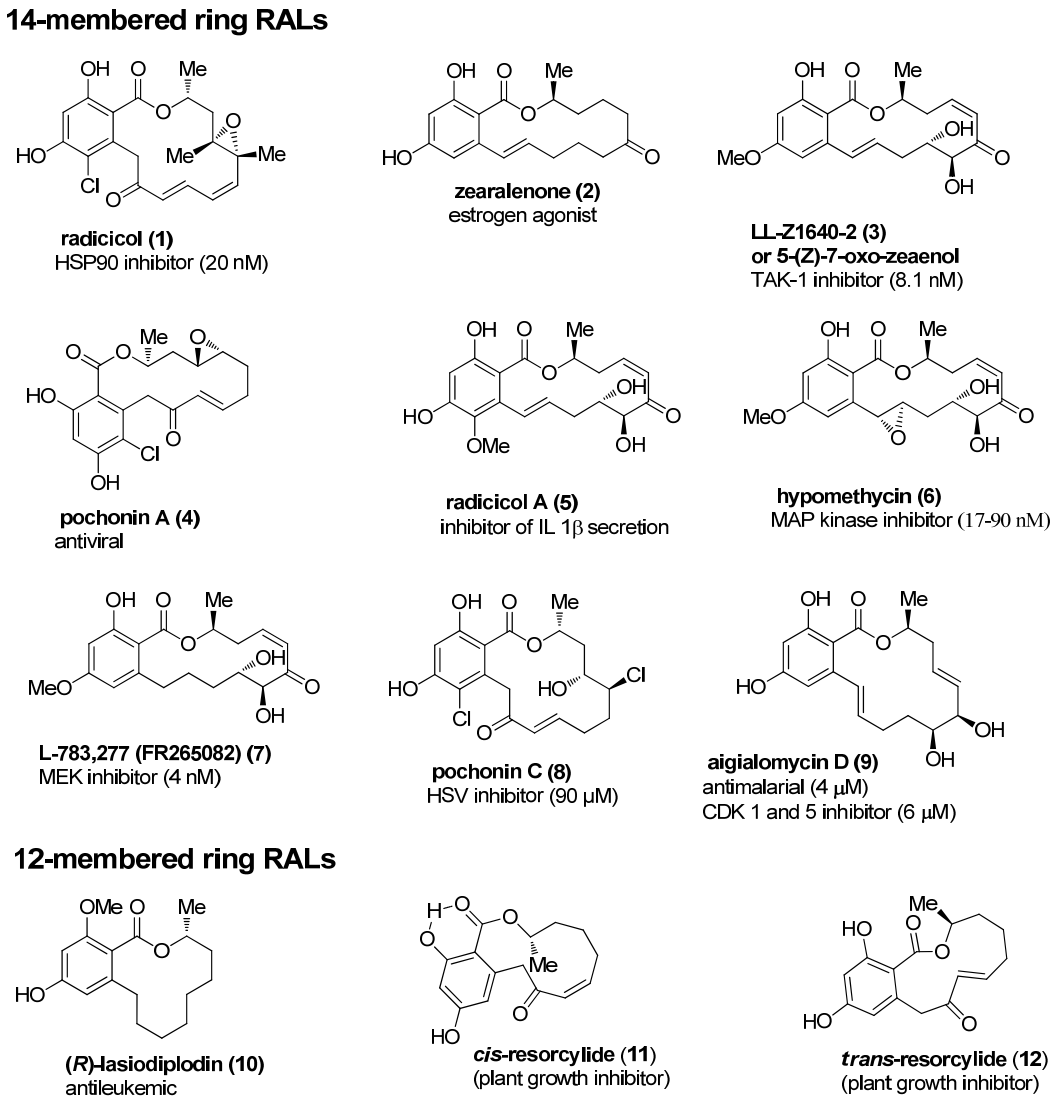


Figure 1: Representative members of the resorcylic acid marolactones

The first isolated macrocycle of this family is radicicol (**1**) (monorden) in 1953 from *Monocillium nordinii*[4]then *Nectria radicicola*.[5] It is at the beginning known to be an antifungal and a potent tranquilizer of low toxicity.[6]In 1962, the anabolic, uterotrophic metabolite zearalenone (**2**) was extracted from corn infected with *Gibberella zeae* (which was fed to swine)[7], followed by the isolation from unidentified fungus of LL-Z1640-2 (**3**) in 1978, whose biological activities except anabolic and estrogen-like one didn't raise any particular interest at that time.[8] α-zearalenol (produced by *Fusarium roseum* growing in cereals), which is the reduced form of zearalenone (**2**) and three to four times as estrogenically active, was initially identified around 1979[9], while hypothemycin(**6**) (isolated from a strain of *Hypomyces trichothecoides*) was closely reported to be an antibiotic metabolite of *Pyrenomycetes* in 1980.[10] However it was only in the early 1990s that these naturally occurring compounds started to earn awareness of organic chemistry community, who was intrigued by radicicol (**1**)'s reversal of Src-transformed morphology of fibroblasts and attribution to the inhibition of the oncogenic kinase Src.[11] The potent and selective inhibitor effect of radicicol (**1**) on the HSP90 (heat shock protein 90)[12] responsible for the maturation and stability of several oncogenic proteins (*e.g.* Src) and the belief Hsp90 be in an activated form in cancer cells

(clients of Hsp90 rather involve in the tumor genesis than tumour suppression)[13] propelled radicicol to the front stage of chemotherapeutic treatment.

Meanwhile, the targeted therapy entered the long-lasting cancer fights as it works by influencing the processes that control growth, division, and spread of cancer cells, as well as the signals that cause cancer cells to die naturally (the way normal cells do when they are damaged or old). Yet the MAP kinases, discovered approximately 27 years ago, together with their immediate upstream regulator,[14] collaborate in transmitting various extracellular signals and thus control a large number of various and even opposing cellular processes such as proliferation, differentiation, development, stress response, survival and apoptosis.[15] Four MAPK cascades have been identified in the last 24 years and those are usually named according to the MAPK components that are the central building blocks of each of the cascades[16]. In a general way, a stimulus switches on the activator which phosphorylates the first kinase (MAPKKK), which in turn phosporylates the second kinase (MAPKK), which repeats the same process on the third kinase (MAPK), that decisively activates a cytosolic protein or transcription factor.[17] To date, three classes of mitogene activated protein kinases have been identified: the ERKs (extracellular signal-regulated kinases), the JNKs (c-Jun N-terminal kinases) and the p38 MAP kinases. While unregulated activation of these MAP kinases can result in oncogenesis, their tight control and specific inhibition, on the other hand, may open a potential therapeutic pathway against cancer.

For these reasons, since 1998, when Williams *et al.* discovered the microbial compound RO 09-2210 inhibits activated biochemically purified MEK *in vitro* (IC_{50}= 0.06 μM),[18] followed by the report from the Merck group of Zhao, in 1999, about the noticeably irreversible inhibition of MEK of L-783,277 (**7**) and hypothemycin (**6**),[19] the RALs have resuscitated interest from organic chemists. In particular, various RALs and RALs analogues containing a *cis*-enone moiety are reported to be more effective (in comparison to the *trans* isomers (**14**))[19] ATP-competitive irreversible inhibitors of MAP kinases, which led to the hypothesis of a covalent interaction between the α,β-unsaturated ketone within the macrolactones and the active site of the kinases.

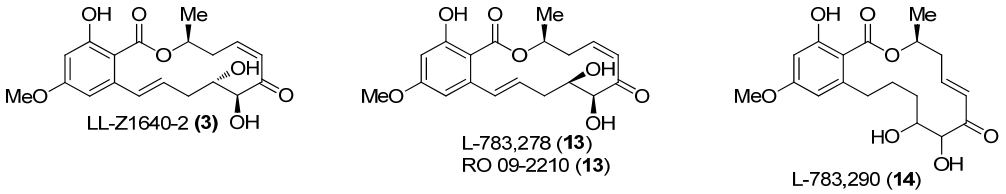


Figure 2: L-Z1640-2 (**8**), L-783,277 (**7**) and its *E*-isomer

Radicicol A (**5**), another *cis*-enone containing RAL was first disclosed in 1996 by the Sandoz group of Kastelic *et al.* to inhibit interleukin (IL-1β), a major mediator of inflammation, as well as tumour necrosis factor (TNF-α) secretion from THP-1 cells.[20] This fungal metabolite, if added to cells activated by interferon gamma and lipopolysaccharide, also induced an extremely rapid degradation of IL-1β, IL-6 and TNF-α mRNA to undetectable levels within 5-8 h. However no further study has identified its molecular target until 2007, when Winssinger's group confirmed the necessity of the *cis*-enone moiety in the inhibition activity (low nanomolar range) against VEGF-R2, VEGF-R3, FLT3, and PDGFR-β. In this same report, none of

the products lacking the *cis*-enone showed significant activity against a panel of 24 therapeutically relevant kinases.[21]

Anterior to this work, in 2003, the LL-Z1640-2 (FR148083) (**3**), isolated from an unidentified fungus Lederle Culture Z1640,[8] was proven to block pro-inflammatory signaling by selectively inhibiting TAK1 (IC_{50} = 8.1 nM) in an ATP-competitive way[22]. In agreement with Zhao *et al.'s* 1999 publication[19], among the seven RALs submitted to the inhibition tests, the structurally related compounds but devoid of *cis*-enone moiety (*e.g.* radicicol (**1**)) had little inhibitory activity with an IC_{50}> 10 µM. The *in vivo* test was carried out on picryl chloride (PC)-induced ear swelling undergone by mice as a model. Besides, LL-Z1640-2 (**3**) showed an inhibition against MEK1 (IC_{50} = 411 nM) which is 50-fold lower than that of TAK1, a MAPKKK involved in the p38 MAP kinase signaling cascade of pro-inflammatory signals. At the end of 2006, Ohori *et al.* published the X-ray crystal structure of the ERK2/LL-Z1640-2 (**3**) adduct revealed that the compound binds to the ATP-binding site of ERK2, involving a covalent bond of ERK2 Cys166 and the C8' of the *Z*-ketone.[23] This appealing basis for future inhibitor design was shortly preceded by an attractive modeling study focusing on another *cis*-enone RAL: hypothemycin (**6**).[24]

Indeed, in March 2006, Schirmer *et al.* published a bioinformatic study, where hymothemycin (**6**) was screened against a panel of 124 kinases and 18 out of 19 putative Cys-containing RAL targets were inhibited.[24] A structural-bioinformatics analysisidentified a Cys residue that is conserved in the ATP site of Ser/Thr/Tyr protein kinases reported to be inhibited by *cis*-enone RALs but absent from those that are not. This same approach also revealed that only a subset of 46 protein kinases (out of 510 identified from the human kinome sequence database) possess the Cys residue, which shed light on the specificity of the inhibitors. Additionally, kinetic analyses showed time-dependent inhibition, a hallmark of covalent inactivation, which was in line with the biochemical studies of the interaction of ERK2 with hypothemycin (**6**). This publication confirmed the hypothesis concerning the irreversible inhibition of MEK by L-783,277 (**7**) earlier submitted by Zhao.[19] Two years later, Rastelli *et al.* solidly supported the previous molecular modeling with the determination of the 2.5 Å resolution crystal structure of ERK2 covalently bound to hypothemycin (**6**).[25] The most recent investigation by Winssinger *et al.* revealed that both LL-Z1640-2 (**3**) and hypothemycin (**6**) are competitive ligands for the ATP-binding pocket.[26]

Aigialomycins A (**15**), B (**16**), C (**17**), D (**9**), E (**18**) and dihydrohypothemycin (**19**) (**scheme 3**) were first isolated in 2002, together with the known hypothemycin (**6**), from the mangrove fungus *Aigialus parvus* BCC 5311 by the Thailandese team of Isaka.[27] They found out that both aigialomycin D (**9**) and hypothemycin (**6**) were moderate antimalarial (respectively, IC_{50} = 6.6 µg/mL and 2.2 µg/mL against *Plasmodium falciparum* K1) while other structurally close aigiaglomycins inactive in the same assays. Recently, Winssinger *et al.* disclosed that aigiaglomycin D (**9**) inhibits CDK1/cyclin B and CDK5/p25 at 5.7 and 5.8 µm, respectively, as well as GSK-3 at 14 µm but much less PfGSK-3, the *Plasmodium* homologue of GSK-3.[28] This discovery further supports the hypothesis that the RALs constitute a promising scaffold for ATP antagonism/kinase inhibition.

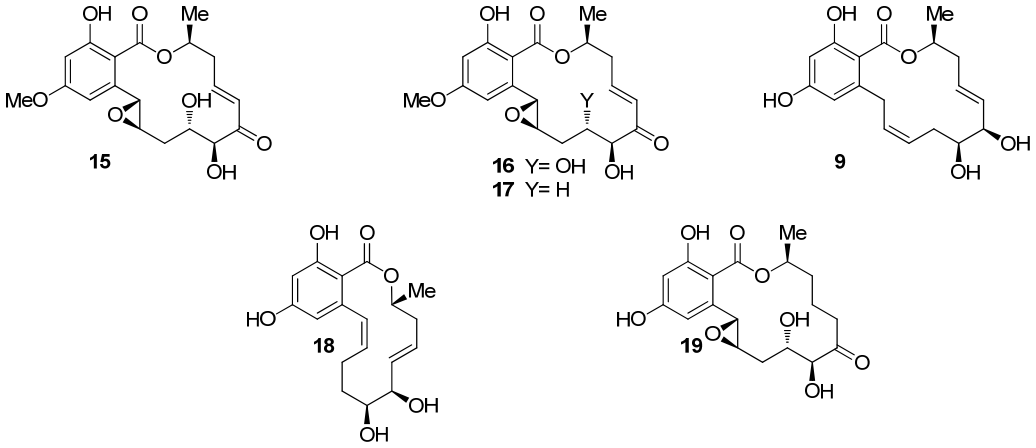


Figure 3: Aigialomycins A (**15**), B (**16**), C (**17**), D (**9**), E (**18**) and dihydrohypothemycin (**19**)

Pochonins and in particular pochocin C(**8**) were isolated from cultures of the mould *Pochonia chlamydosporia* var. *catenulata* strain P 0297.[29] Unexpectedly,pochonin C (**8**) which is closely related to radicicol (**1**) was found to be poor Hsp90 inhibitor, contrary to radicicol (**1**),[12] whereas it inhibits Herpes Simplex Virus (HSV) replication with a significant therapeutic window.[29] This divergence could be rationalised by their different conformations in solution.[30] Interestingly, pochonin A (**4**), structurally closer to radicicol (**1**), was proven to be a competitive antagonist of ATP for Hsp90 (90 nM).[31]

Recently, two new subgroups of RALs were unraveled, namely paecilomycins A-F isolated from *Paecilomyces* species SC0924 by Xu *et al.* in 2010 [32] (**scheme 4**) and cochliomycins A-C (**26-28**) from the culture broth of *Cochliobolus lunatus*, a fungus obtained from the gorgonian *Dichotella gemmacea* collected in the South China Sea by the team of Shao in 2011 (together with the *E*-isomer of LL-Z1640-2 (**3**),and paecilomycin F (**7**)).[33] Among these, paecilomycin E (**24**)exhibited antiplasmodial activity against *Plasmodium falciparum* line 3D7 with IC_{50} values of 20.0 nM, and paecilmycins E (**24**)and F (**25**)showed moderate activity against the *P.falciparum* line Dd2.[32] As cochliomycin A (**26**), possessing the acetonide moiety, exhibited moderate antibacterial activity against *S. aureus*, with an inhibition zone of 11 mm in diameter at a concentration of 50 µg/mL, the authors suggested it be useful as environmentally benign antifouling agent.[33]

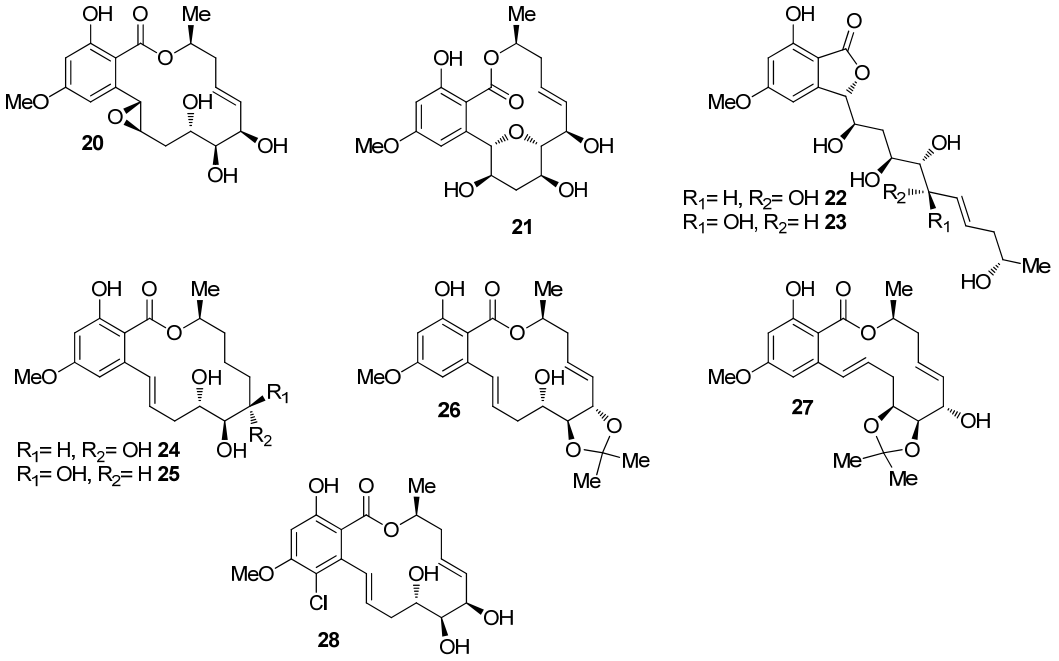


Figure 4: Paecilomycins A-F (**20-25**) and cochliomycins A-C (**26-28**)

In 2013, bioassay-guided fractionation of an unidentified fungal species *Neocosmospora* allowed the isolation of three new RALs, neocosmosins A-C (**29**–**31**)[34]; among these, neocosmosin C (**31**) exhibited potent and full agonistic activity against the human *δ*-opioid receptor. From the same extraction also radicicol (**1**) was isolated and interestingly, this first-discovered compound of the RALs family also showed potent binding affinities at the *μ*-opioid receptor. Consequently, the longstanding interest for radicicol (**1**) from the organic chemist community will contribute to the structure and activity relationship study of this class of compound.

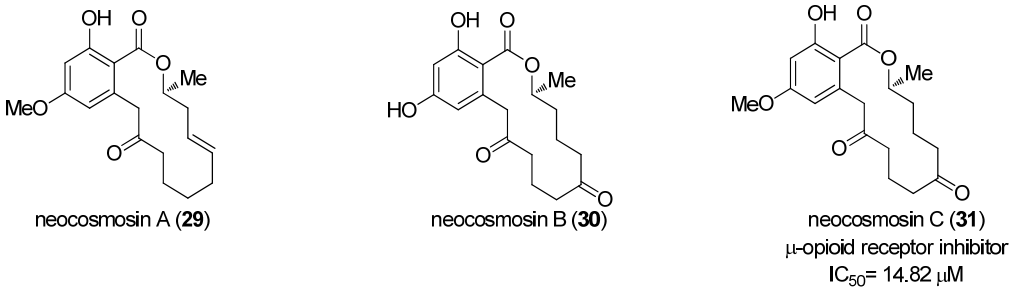


Figure 5: Neocosmosin A-C (**29-31**)

To date, several bioactive natural RALs have been the targets of total syntheses, designing the general synthetic strategies that usually involve olefin metathesis catalysed by Grubbs catalyst or alkyne metathesis as the key step, together with some other classical chemical reactions (*e.g.* the Suzuki coupling reaction, the Stille coupling reaction, the Wittig reaction, the Mitsunobu reaction, *etc*). As an overview of the growing synthesis field, only some selected examples are described in details in this chapter to highlight the diverse chemical

approacheswhich imitate and confront the boundaries of human creativity with the diversity of natural products.

The examples highlighted hereafter begin with the syntheses of zearalenone (**2**), the earliest synthetic target of the family. They illustrate a brief historical perspective of total synthesis of RALs and shed light on the competitive development of visionary synthetic strategies, at first applied to the "ancestral member" of the natural RALs, e.g. zearalenone (**2**).

The second representative molecule of our choice is aigialomycin D (**9**), one of the RALs discovered in the 21st century. The syntheses of this metabolite give an overview of our modern synthetic mindset and instruments, especially the most popular among the chemists community. These methods emphasise how early investigations of the "simplest" natural products can build a solid basement for innovative concepts.

The general numbering of the atoms composing the structural frame of RALs is illustrated in **Figure 6** below.

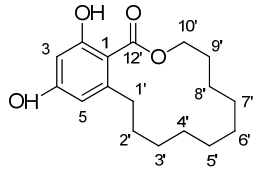


Figure 6: General number assignment for RALs' structural frame

1.1.1 Synthesis of zearalenone (2)

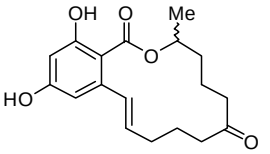
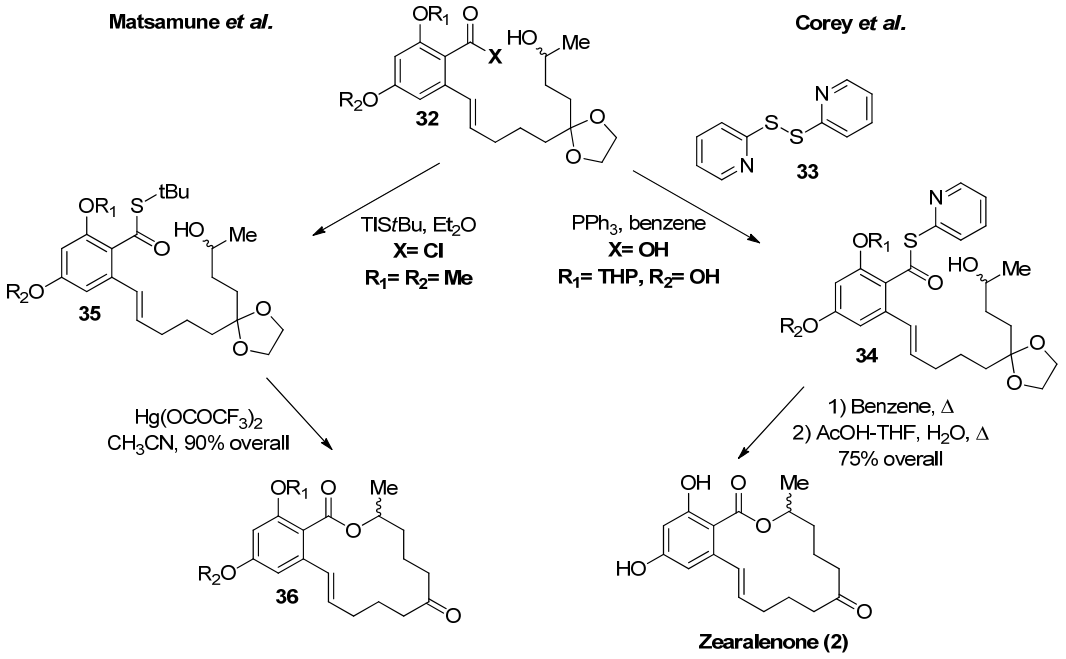


Figure 7: zearalenone (**2)**

Produced mainly by fungi belonging to the genus *Fusarium* in foods and feeds, zearalenone (**2**) has been frequently involved in reproductive disorders observed in farm animals, especially in swine, since the first report of its toxicity of the abovementioned agricultural damaging fungus.[35]

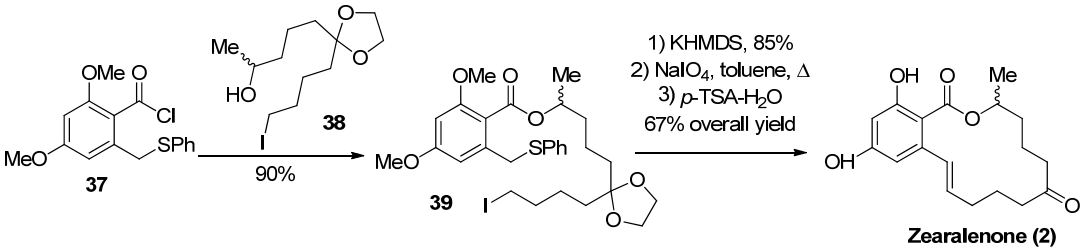
With the structural identification of zearalenone (**2**) in 1966, the late 1960s witnessed several total syntheses as a response to the widespread interest in the anabolic and oestrogenic properties of this metabolite implicated in hyperoestrogenic syndromes in humans. .

Between the first total synthesis of **2**, published in 1967[36] and the latest one in 2013,[37] more than 11 syntheses have been accomplished. Generally, the limiting step was the formation of the 14-membered ring which relied on an intramolecular ring-closure, especially the cyclisation of the seco-acid. Several approaches have been developed, setting the stage for the application of conceptually innovative methodologies, namely the remarkable progresses made by Corey and Nicolaou [38] and independently in the same year as Masamune's group.[39]



Scheme 1: Macrolactonisation methods by Corey and Nicolaou,[38] and Masamune *et al.*[39]

The first total syntheses of **2** accomplished by the Merck and Syntex groups were disadvantaged by a low yield for the late-stage lactonisation of the related 14-membered seco-acid (less than 31%).[36] In order to illustrate the efficiency of their newly developed methodology, Corey and Nicolaou preactivated the benzoic acid function of **32** as a 2-pyridinethiol ester 3**4** before closing the macrocycle in refluxing benzene (**scheme 1**). The overall yield was 75% after the ultimate deprotection to release the target **2**.[38] Meanwhile, the group of Masamune also proposed a similar method transformed the corresponding acid chloride of **32** into *tert*-butyl thiol ester 3**5** in the presence of mercuric acetate at room temperature to yield the zearalenone methyl ether **36** in 90%.[39]



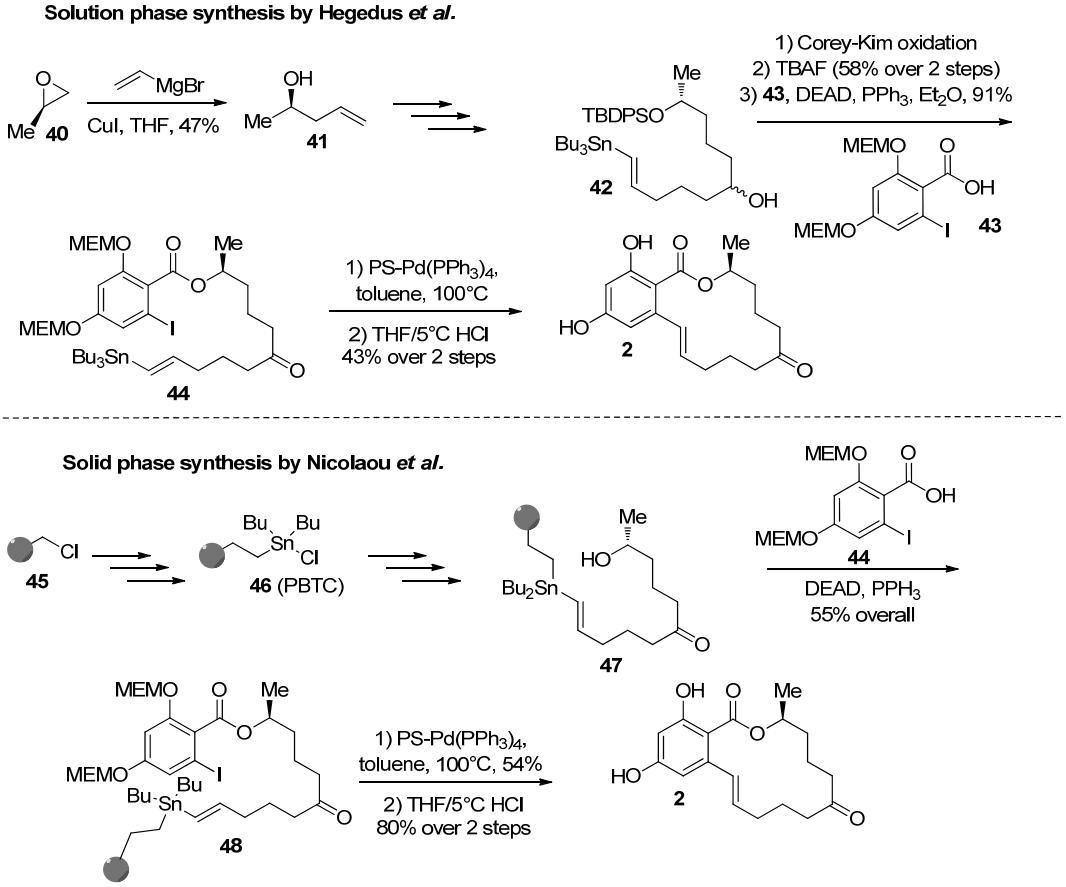
Scheme 2: Macrocyclisation protocol based on olefination *via* ω-iodoalkyl 2-phenylthiomethyl-4,6-dimithoxybenzoate (**39**) by Tsuji *et al.*

Four years later, the research group of Tsuji reversed the synthetic sequence by synthesising the intermediate **39** *via* the addition of the 2-phenylthiomethyl-4,6-dimethoxybenzoyl chloride **37** to the hydroxyl iodide **38** (**scheme 2**). This intermolecular ester formation proved to be much more efficient than the related intramolecular macrolactonisation. The 14-membered ring was accomplished upon treatment of the iodoalkyl phenylthioacetate **39** with KHMDS

(85%), followed by an oxidation/ elimination to yield the corresponding macrocyclic *E*-alkene. The success of this strategy marked the first of a series of syntheses which include a late-stage ring-closure at either C1'-C2' or C2'-C3' bond as a direct application of the newly developed methodologies, as well as the growing concern in asymmetric synthesis.

While the first syntheses resorted to a subsequent chiral resolution to procure the naturally occurring *(S)*-zearalenone (**2**), the first total syntheses of the optically active metabolite were reported in the early 1990s, to begin with that by Pattenden and Hitchcock.[40] Their ring-closing strategy was based on a *14-endo-trig* macrolactonisation from a cinnamyl radical intermediate. In the same year, the group of Solladié published their synthesis which induced the configuration of the C10' by a chiral β-keto sulfoxide.[41]

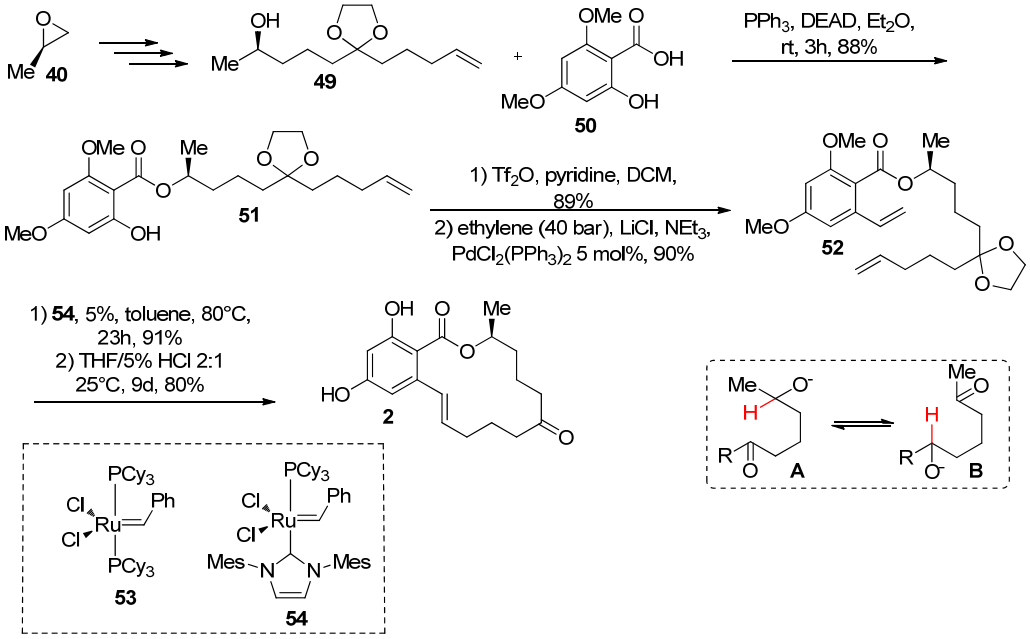
One year later, Stille and Hedgedus successfully applied the intramolecular Stille coupling between a vinylstannane and an iodide, as part of a series of carbon-carbon bond formation towards the cyclisation of 10- to 15-membered β-resorcylic macrolides.[42] The synthetic approach implicated a Mitsunobu based esterification of 2-halo- or 2-trifloxybenzoic acids (*e.g.* 2-iodobenzoic acid) with (*E*)-vinylstannyl alcohols, followed by the intramolecular coupling of the vinylstannane with the aryl electrophile. The *(R)*-propylene oxide **40** was opened by vinylmagnesium bromide in the presence of CuI to provide the optically pure secondary alcohol **41**, which was subjected to the next 6 transformations leading to the obtainment the hydroxy vinylstannane **42** (**scheme 3**).



Scheme 3: Stille coupling applied to the macrocyclisation in solution-phase and solid-phase syntheses

Being at the heart of the emergence of combinatorial chemistry and solid-phase synthesis in the late 1980s and early 1990s, Nicolaou *et al.* reported a novel solid-phase synthetic tool for the macrocyclisation that employs the Stille coupling cyclorelease (**scheme 3**). The *E*-vinyltin polymer **47** was prepared from the Merrifield resin **45**, which was first transformed into the polymer-supported tin chloride (PBTC) **46**. Esterification under Mitsunobu conditions between **47** and carboxylic acid **46** gave the desired precursor **48**, setting the stage for the cyclorelease which smoothly took place in the presence of the polymer-supported [$Pd(PPh_3)_4$] catalyst and an ultimate acidic deprotection completed the total synthesis of optically pure *(S)*-zearalenone (**2**). As expected, the ring-closing Stille coupling did not give place to any *Z*-isomer of **2**.

In 2000, the group of Fürstner published, as part of their program on the ring-closing metathesis (RCM) as a general and *via*ble tool for syntheses of natural products (since 1997), another synthesis of (*S*)-zearalenone (**2**) as illustrated in **scheme 4** beneath.[43]

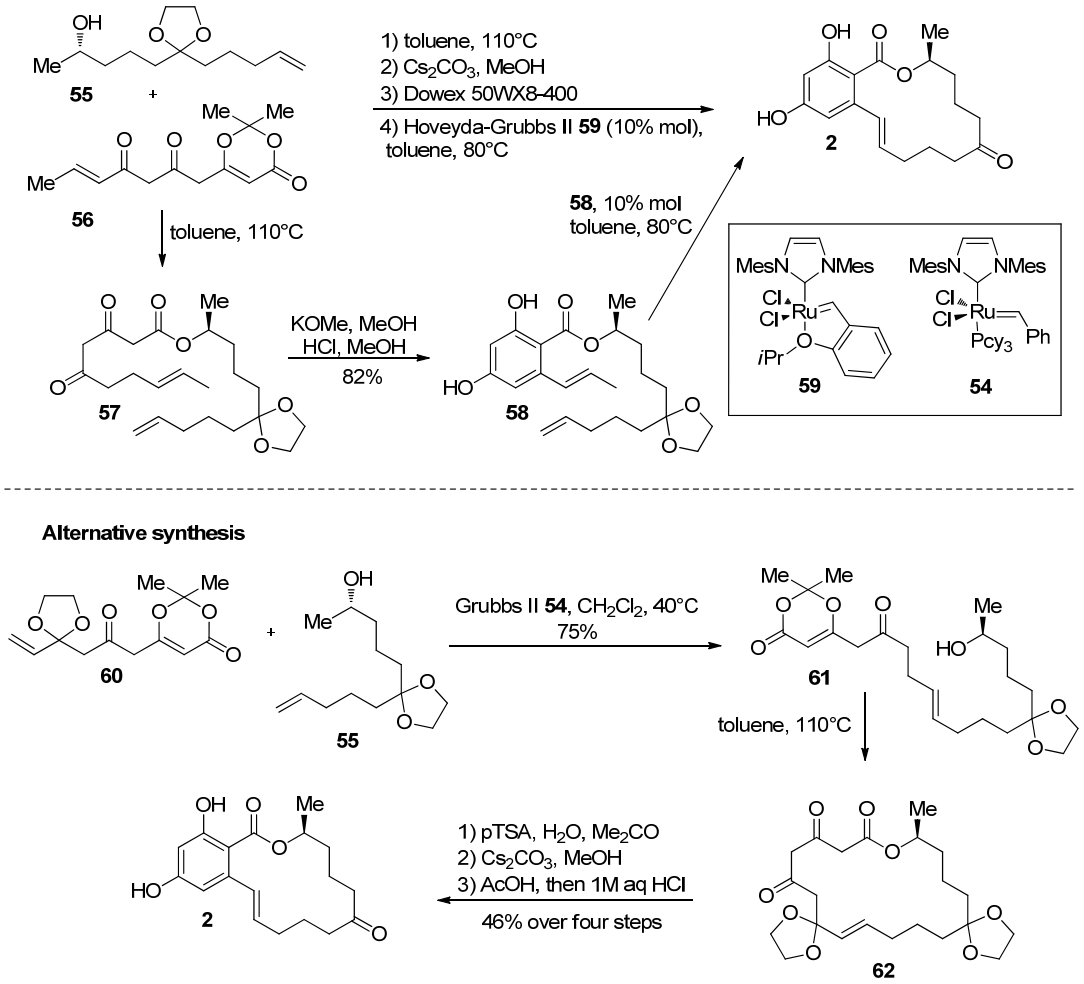


Scheme 4: Ring-closing metathesis applied to the synthesis of (*S*)-zearalenone (**2**) by Fürstner *et al.*[43]

The penultimate step consists in a strategically pioneer RCM to introduce the double bond at the benzylic position followed by the demethylation under acidic conditions. Their synthetic scheme included a Stille coupling to install the benzylic double-bond, which was also prepared by a Heck coupling for practical convenience. The diene precursor **52** was prepared from the commercial *(R)*-(+)-propylene oxide **40** which was first opened in the presence of catalytic CuCl(COD) and vinylmagnesium bromide. It is worth mentioning that even though the planified Mitsunobu based esterification to join fragment **49** with the readily prepared phloroglucinol acid derivative **50**, as well as the subsequent Heck coupling to build the benzylic alkene and the crucial RCM would not interfere with the ketone function, as proven by the racemic synthesis of zearalenone.[43] The loss of optical activity of the alcohol would have been caused by a reversible intramolecular hydride shift (**scheme 4**).[44] Nonetheless, the release of the ketone

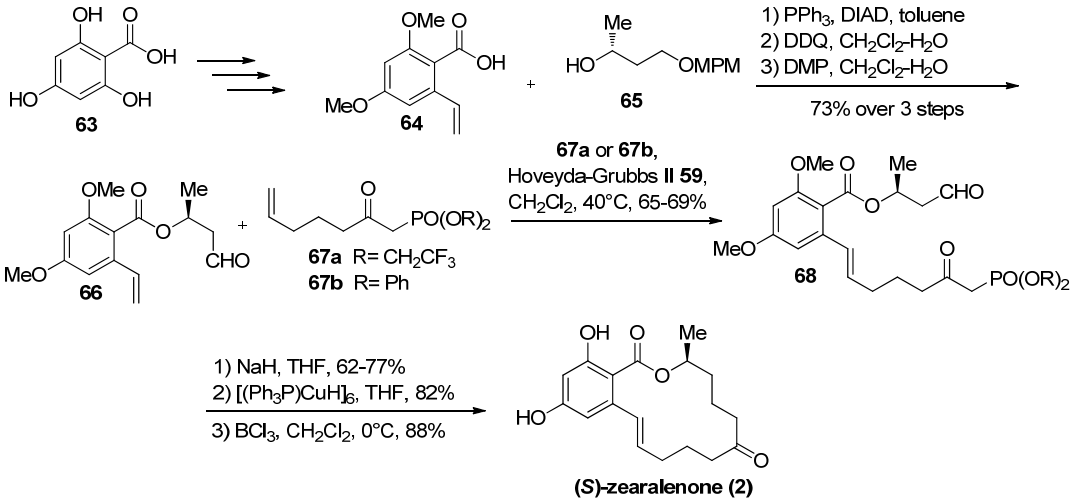
could be carried out by the final deprotection under acidic conditions to afford the target compound **7**. They reported a superior reactivity of the 2nd generation Grubbs' catalyst **54** (91% of yield) in contrast to the complete failure in case the 1st generation Grubbs's catalyst **53**. Moreover, the RCM catalysed by **54** provided exclusively *E*-isomer.

The same ring-closing metathesis to build the *E*-alkene at C1'-C2' featured in the biomimetic synthesis of *(S)*-zearalenone (**2**), among other resorcylate natural products, that was issued in 2008 by Barrett *et al.* [45] Their synthetic scheme involves a late-stage aromatisation of triketo-ester **57** which consisted in an aldol condensation under strongly basic conditions (KOMe in methanol) with subsequent dehydration and aromatisation assisted by strong acid (HCl in methanol) (**scheme 5**). The triketo-ester **57** resulted from the thermolysis of the dioxinone **56** (at 110°C in toluene) to release the ketene which was then trapped *in situ* by alcohol **55**. The unmasked ketone function, under acidic conditions, would not interfere with the scheduled RCM as described by Fürstner *et al.* in their racemic synthesis of zearalenone. Indeed, the RCM smoothly proceeded in the catalytic presence of 2nd generation Hoveyda-Grubbs catalyst **59** to provide the desired final product (E/Z: 8/1). Interestingly, the four-step synthetic sequence could also be carried out without intermediate purification, or in some cases a simple but yield-increasing filtration of Dowex resin, and subtle modification of the reaction conditions to lead to the same result. Besides, attempts of RCM with the 2nd generation Grubbs catalyst **54** only gave unyielding mixtures containing (*S*)-zearalenone (**2**). Noteworthily, the late-stage aromatisation method proved to be highly compatible with fragile functions and hence promising for syntheses towards more complex biologically active targets.



Scheme 5: Biomimetic syntheses proposed by Barrett *et al.*[45-46]

Two years later, the same research group proposed an alternative approach to the same mycotoxin, which exploited their previously developed "transannular aromatisation", followed *in situ* by a total deprotection, as the finalising steps to achieve the target molecule **2**, avoiding a RCM.[46] The macrocycle **62** was prepared by a retro-Diels-Alder fragmentation, on heating, resulting in a ketene which was intramolecularly trapped by the intramolecular secondary alcohol. The intermediate **61** was obtained, with good *E*/*Z* selectivity (> 20:1) by a cross-metathesis (CM) between the alcohol **55** and keto-dioxinone **60**. Though their first total synthesis featuring an aromatisation from a tri-ester was closely inspired from the biosynthesis, the very late-stage transannular aromatisation of the second approach remarkably mimics Nature's pathway leading to resorcylate natural products.

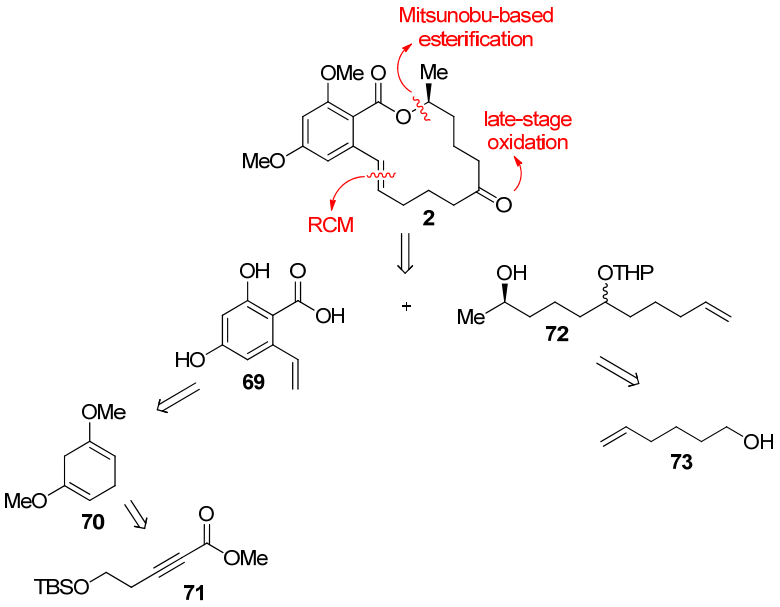


Scheme 6: Synthesis of (*S*)-zearalenone (**2**) proposed by Murphy *et al.*[47]

In the same year, Napolitano and Murphy described a synthetic sequence that involved a modified Horner-Wadsworth-Emmons (HWE) olefination for the macrocyclic formation, resulting in the enone intermediate **66** (**scheme 6**).[47] The applicability of this novel synthetic strategy was first proven by the successful total synthesis of *(S)*-zearalenone (**2**), which was retrosynthetically disconnected at the C7'-C8' bond, necessitating the pre*para*tion of **67a** and **67b**.

Indeed, the latter derived from a Hoveyda-Grubbs II-assisted cross metathesis with the resorcylate intermediate **64** to implant the C1'-C2' double bond as single *E*-isomers of the phosphonate. The resorcylate ester **64** resulted from a Mitsunobu based esterification between the optically pure alcohol 6**4** and resorcylate **64**, obtained from 2,4,6-trihydroxybenzoic acid **63**. According to the authors, the choice of **67a** (Still-Gennari phosphonate) and **67b** (Ando phosphonate) was based on usual reporting of *cis*-enones when these reactants were used, which would extend the strategy to the pre*para*tion of other *cis*-resorcylides, *e.g.* LL-Z1640-2 (**3**). Unfortunately, the intramolecular olefination, promoted by NaH in THF at 0°C, only gave *E*-isomer **68** in 77% and 62%, respectively. The subsequent chemoselective reduction of C7'-C8' double bond was successfuly carried out with the copper(I) hydride cluster $[(Ph_3P)CuH]_6$ in THF in 82% of yield. Conceptually, as the order of coupling **64**-**67** was possible in all permutations, intermolecular olefination would prepare the testing field for novel ring-closing strategies.

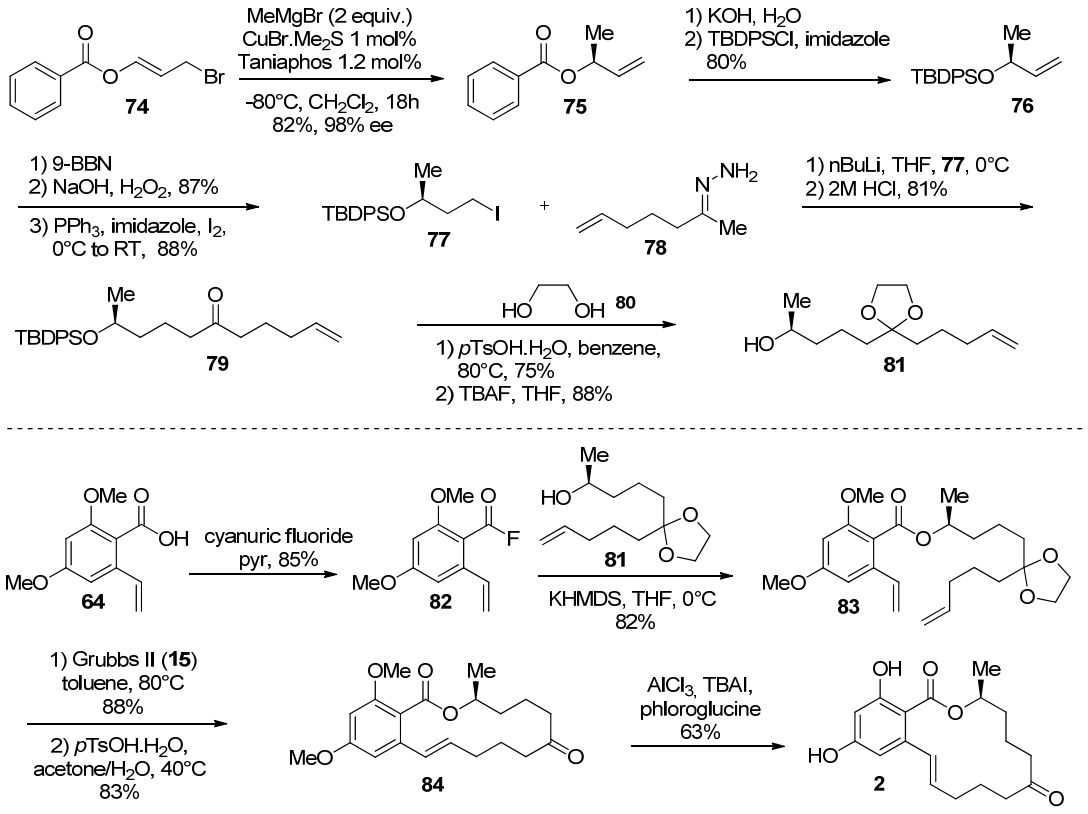
In 2011, Yadav and Murthy reported another convergent total synthesis of *(S)*-zearalenone (**2**), together with its unse*para*ted congeners α-zeranol and β-zeranol, a powerful oestrogen and animal growth- promoting agent,[48] as both proceeded *via* same C6'-alcohol precursor. Their synthetic strategy involves a Diels-Alder reaction to construct the resorcylate moiety **69**, which was fused with the functionalised polyol alkene **72** *via* a Mitsunobu-based esterification, followed by a 2nd generation Grubbs catalysed RCM (**scheme 7**). The styrene **69** was prepared by a Diels-Alder reaction between the diene **70** and the dienophile **71**. The open chain of the macrocyclic backbone **72** was synthesised from 5-hexen-1-ol **73**. A more detailed synthesis will be exposed in section *3.3.2*.



Scheme 7: Retrosynthesis of *(S)*-zearalenone (**2**) by Yadav *et al.*[48]

The latest synthesis of *(S)*-zearalenone (**2**) was reported by Baggerlaar and Minnaard in 2013.[37] Their synthetic strategy also consisted in a late-stage RCM to install the 14-membered macrocycle, preceded by an ester formation (**scheme 8**). The macrocyclic chain was prepared in 9 steps, starting with a copper/Taniaphos asymmetric allylic methylation by MeMgBr onto the commercial **74** to afford intermediate **75** in remarkable enantioselectivity (98% ee). Hydrolysis of **75** and protection of the released alcohol afforded **76** which underwent a hydroboration to give the corresponding alcohol selectively, followed by an iodination. The lithiation of the readily prepared dimethylhydrazone **78** allowed a regioselective addition onto the iodide **77** in high yield. The authors decided to protect the ketone before unmasking the secondary alcohol, in order to preserve the optical purity of the secondary alcohol, as it was described by Wendler *et al.* in their first total synthesis of zearalenone.[44]

The starting aromatic moiety remained the same (**64**) as described by Napolitano and Murphy (**scheme 6**),[47] however their esterification method relied on the formation of acyl fluoride in the presence of cyanuric fluoride, prior to the addition of potassium alkoxide derived from fragment **81**. Due to the severely steric hindrance of the acid function, the authors have also noticed a fruitless esterification by means of Yamaguchi reagent or carbodiimide-based coupling reagents. These results had been previously mentioned by Fürstner *et al.* in their attempts towards the total synthesis of cruentaren A.[49] To overcome the bulky resorcylate, they found out that fluoride would be the appropriate leaving group thanks to its very small size. The subsequent RCM smoothly provided a protected resorcylate macrolactone, which was first unmasked at the ketone function under acidic condition to furnish **84**. Demethylation was based on the procedure described by Maier and co-workers in their efforts to elucidate the effect of an allylic methyl group in zearalenone analogues.[50]



Scheme 8: Synthesis of *(S)*-zearalenone (**2**) proposed by Baggerlaar *et al.*[37]

Since the first racemic synthesis of zearalenone (**2**)[36] until its latest catalytic asymmetric synthesis in 2013,[37] many of the syntheses relied on either the racemate, or kinetic resolution, or natural chiral pool, or on chiral auxiliaries, or enzymatic approach leading to the chiral building blocks, or enantioselective catalytic allylic alkylation. The macrocylic closure has also witnessed remarkable progresses, either based on various macrolactonisation methods or olefination approaches (*e.g.* Julia-Kocienski olefination, Stille coupling or ring-closing metathesis).

Another member of the RALs family which also contains a *trans* C1'-C2' double bond is aigialomycin D (**9**), which bears an additional *trans*-olefin at C7'-C8'. Through various structure-activitie studies, it was found that the C7'-C8' *trans*-configured RAL, such as radicicol (**1**) (containing a *trans*-epoxide) and pochonin D (containing an *E*-alkene), inhibit HSP90 by a competitive binding at the ATP-binding site.[51] Behaving like an outlier among the reported RALs, aigialomycin D (**9**) does not inbibit Hsp90, in spite of its *trans* C7'-C8' double bond, and exhibits instead moderate inhibition of kinase similar *cis*-enone bearing RALs.[52]

The unsusual activities of aigialomycin D (**9**) and its intriguing structure have led to a series of novel synthetic routes towards this metabolite, as well as its analogues.

1.1.2 Synthesis of aigialomycin D (9)

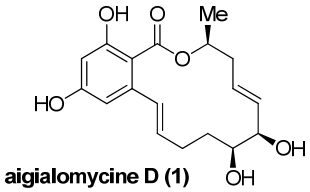
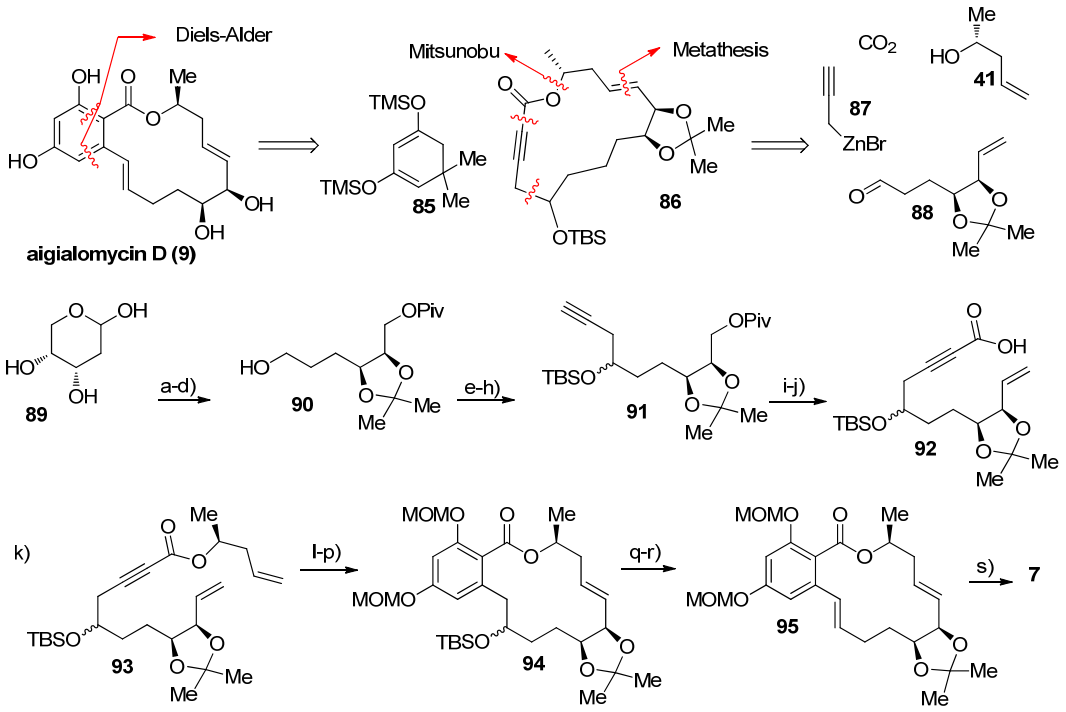


Figure 8: aigialomycin D (**9**)

Isolated in 2002 from a mangrove fungus *Aigialus parvus* BCC 5311 by Thailandese researchers,[27] the first total synthesis of this bioactive secondary metabolite was realised 2 years later,[53] and the latest total synthesis was published in 2009.[54] Most of the syntheses developed for aigialomycin D (**9**) feature a RCM.

The first total synthesis of aigialomycin D (**9**) was reported by Danishefsky *et al.* in 2004.[53] The key steps feature a Diels-Alder reaction using a disiloxydiene **85** and a 14-membered "ynolide" **86** as the dienophile, a RCM to introduce the *E* double bond C7'-C8'and a Martin's sulfurane conditions to construct the benzylic alkene (**scheme 9**).

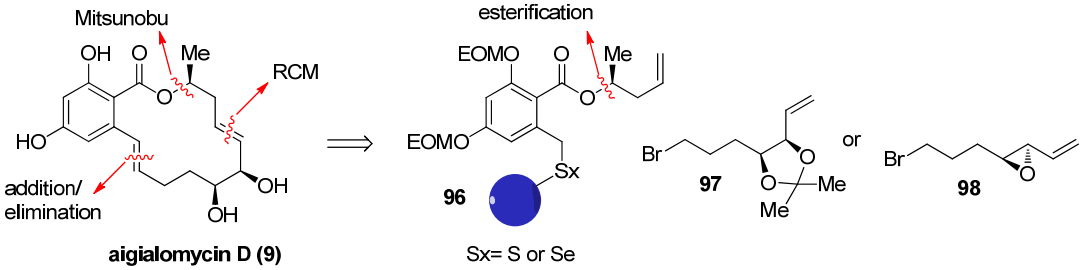


Scheme 9: Synthesis of aigialomycin D (9) by Danishefsky *et al.* Reagents and conditions : a) 2-methoxypropene, *p*-TSA, DMF, 3 h, 62%; b) KHMDS, $Ph_3P^+CH_3I^-$, THF, -78°C to RT, 10 h, 68%; c) PivCl, Et_3N, DMAP, DCM, 10 h, 90%; d) 9-BBN, THF, 0°C to RT, 4 h, then NaOH, H_2O_2, H_2O, 2.5 h, 88% ; e) SO_3.Pyr, DMSO, DCM, Et_3N, 0°C, 1 h; f) propargyl bromide, Zn, THF, 0°C, 2 h; g) TBSOTf, 2,6-lutidine, DCM, 10 h, 89% over 3 steps; h) NaOMe/MeOH, 10 h, 88% ; i) SO_3.Pyr, DMSO, DCM, Et_3N, 0°C, 2 h then KHMDS, $Ph_3P^+CH_3I^-$, THF, -78°C to RT, 10 h, 86% over 2 steps; j)

BuLi, dry ice, -78°C to rt, 2 h; k) **41**, DIAD, PPH_3, toluene, 10 h, 85% for 2 steps ; l) $Co_2(CO)_8$, toluene, 30 min, 94% ; m) 2nd generation Grubbs catatlyst **54** (25 mol %), DCM, 10 h; n) CAN, acetone, -10°C, 15 min, 95%; o) **85**, neat, 140°C, 36 h, 84% ; p) MOMCl, DIPEA, DCM, 10 h, 83%; q) HF-pyr, pyr, THF, 10h, 87%; r) $[PhC(CF_3)_2O]_2SPh_2$, DCM, 0°C to RT, 2 h, 84%; s) 0.5 N HCl, H_2O/MeOH, 2 days, 69%.

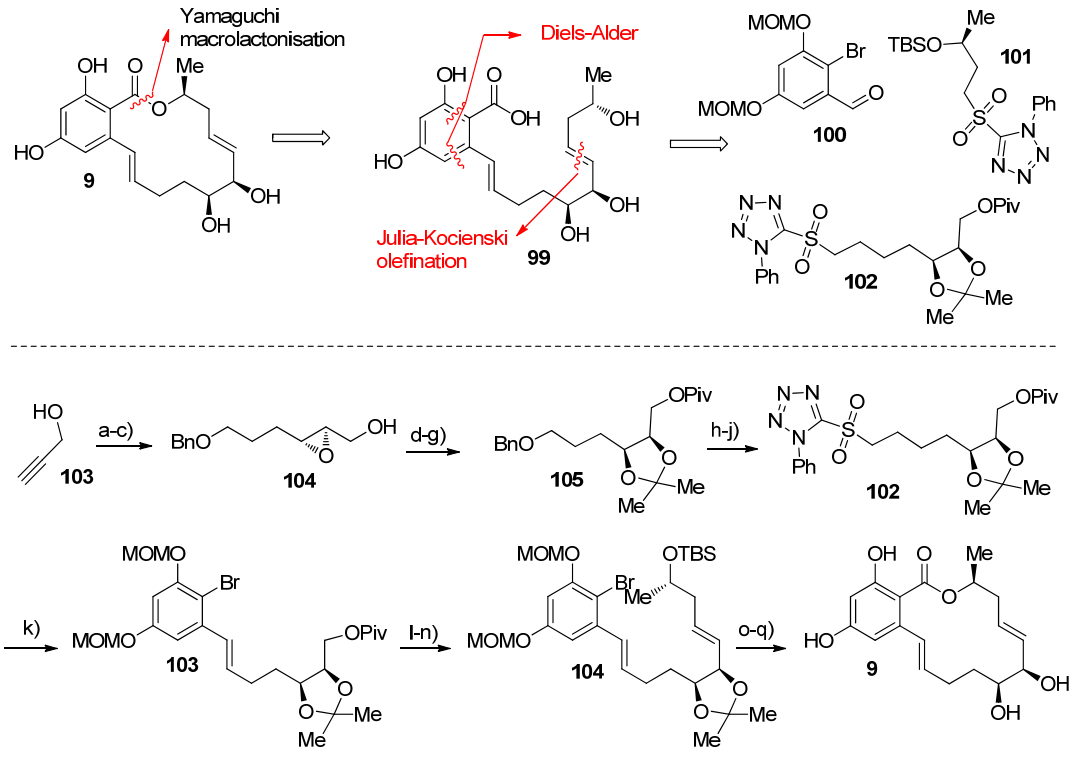
The "ynolide" **86** was obtained in 15 steps from 2-deoxy-D-ribose (**89**) which provided the C5'-C6' *anti*-diol in the right configurations. The pentose was submitted to a sequence of protection, Wittig olefination, hydroboration, oxidation, propargylation then protection to provide the intermediate **91** bearing the much triple bond and one terminal alkene. The other olefin extension was built through addition of the derived alkynyl lithium of **92** onto carbon dioxide, followed by Mitsunobu reaction with the alcohol **4**, giving rise to the *R* ester **93**. It is worth noting that previous to the RCM, it was necessary to mask the ethynyl linkage as its dicobalt hexacarbonyl complex, which would be easily removed under oxidative reaction. This protection of the alkyne avoided the diversion to an ene-yne metathesis while distorting the alkyne geometry to favour the metathesis by bringing the carbons C7' and C8' closer in space. RCM was easily accomplished, using 2nd generation Grubbs catalyst **54**. Only the *E*-configured double bond was obtained, and their decomplexation revealed the "ynolide" **86**, which was subjected to the pivotal Diels-Alder reaction with **85**. The cycloaddition turned out to be successful for both stereoisomers. The dehydration of C1' alcohol under Martin's conditions[55] smoothly proceeded to install the styrene like double bond, proving especially the useful MOM protection of the phenol groups. The final deprotection under acidic condition released aigialomycin D (**9**), completing the 18-step synthesis in an overall yield of approximately 8%.

In 2006, two other total syntheses of aigialomycin D (**9**) were disclosed by Winssinger *et al.*[28] In hope of enlarging the diversity of RAL beyond the naturally available RAL analogues, the group of Winssinger became interested in the aigialomycins. As described previously, the general synthetic blueprint was a direct alkylation at benzylic position by means of the stabilised anion derived from a thio- or selenoether at the benzylic position (**scheme 10**). The macrolactonisation was carried out through RCM. The trans diol was obtained through Sharpless asymmetric epoxidation/$Sc(OTf)_3$-catalysed opening.



Scheme 10: **Retrosynthesis of aigialomycin D (9) by the group of Winssinger**

In the same year, the third total synthesis was published by Pan *et al.*[56] The key features are the use of Julia-Kocienski olefination to create both *E* olefins and a Yamaguchi based macrolactonisation (**scheme 11**). The polyketide fragment **87** was obtained in 10 steps from prop-2-yn-1-ol (**103**). The *anti*-diol was formed *via* Sharpless asymmetric epoxidation and a titanium-assisted regioselective opening. The first Julia-Kocienski coupling afforded the benzylic olefin **103**, prior to the second one which furnished the precursor **104** containing all the needed functionalities. Operated under thermal conditions (refluxing during three day), the Yamaguchi based macrolactonisation gave rise to the macrocycle in 51% yield. This step fulfilled the formal synthesis of aigialomycin D (**9**), as the fully protected metabolite was identical to that reported by Danishefsky.



Scheme 11: Synthesis of aigialomycin D (9) by Pan *et al.*[56] Reagents and conditions : a) $BnOCH_2CH_2CH_2I$, BuLi, HMPA, -78°C, 8 h, 70%; b) $LiAlH_4$, THF, reflux, 1 h, 96%; c) $Ti(O\text{-}iPr)_4$, TBHP, (-)-DIPT, cat. CaH_2, DCM, -25°C, 12 h, 89%; (d) $Ti(OiPr)_4$, $PhCO_2H$, DCM, rt, 15 min, 75%; e) EtMgBr, ether, RT, 1 h, 95%; f) PivCl, Et_3N, DMAP, DCM, RT, 10 h, 88%; g) 2-methoxypropene, PPTS, DCM, RT, 5 h, 95%; h) 10% Pd/C, H_2, EtOH, RT, 4 h, 95%; i) 1-phenyl-

1H-tetrazole-5-thiol, DIAD, PPh_3, THF, 0 °C to rRT, 1 h; j) m-CPBA, $NaHCO_3$, RT, DCM, 12 h, 81% for two steps; k) KHMDS, DME, -60°C to RT, 3 h, 68%; l) DIBAL-H, DCM, -78 °C, 1 h, 96%; m) Dess–Martin periodinane, DCM, rt, 2 h, 85%; m) **100**, KHDMS, DME, -60°C to RT, 3 h, 58%, n) TBAF, THF, RT, 8 h, 95%, o) BuLi, CO_2, THF, -78 °C to RT, 2 h, 83%; p) 2,4,6-trichlorobenzoylchloride, Et_3N, THF, RT, 2 h, then DMAP, toluene, reflux, 36 h, 51%; q) 0.5M HCl, H_2O/MeOH, RT, 2 d, 70%.

From the first isolated macrolide radicicol (**1**) in 1953[4] to the polyketides cochliomycins in 2011,[33] more than 30 naturally occurring RALs have been isolated, characterised and have undergone extensive bioactivity screening and therefore revealed powerful biological activities with respect to estrogenic, antifungal, antimalarial, antiviral, cytotoxic effects and nematicidal properties.

Historically, the high-throughput screening approach has efficiently led to the discovery of many type 1 ATP-competitive inhibitors out of compound libraries. Until now, most of the scaffolds able to serve as ATP-competitive ligands have been successfully identified, which leaves this method to be restrictively of use when a kinase with an unusual active site is screened or when allosteric inhibitors are specifically being sought.[57] At the dawn of computational philosophy of science, combination of methods evolving analogue synthesis, structure-informed design and fragment-based assembly strategies, have become the prevailing *para*digm.

The next chapter deals with a specific subset of RALs composed of 4 metabolites which contain a *cis*-enone and have been the subject of several total syntheses. An overview of some significant retrosynthetic strategies for LL-Z1640-2 (**3**), as well as 2 detailed pathways towards hypothemycin (**6**) will precede the development of our efforts targeting the naturally occurring L-783,277 (**7**).

1.2 *cis*-enone containing RALs

Among the most extensively investigated natural polyketides is a subset of *cis*-enone containing RALs, which exhibit inhibitory activities against ATPases and kinases. The mechanism of inhibition is tightly linked to the Michael acceptor nature of the *cis*-enone moiety, which enables covalent binding to the cysteine residue in the ATP-binding pocket existing in barely 10% of kinases encoded in the human genome.[58] The high potential to find new ATPase or kinase inhibitors among this class of natural products, paired with the interest of reducing their potential for toxicity as a result of rationalising of anticipated targets, has intrigued and challenged the synthetic chemists' creativity.

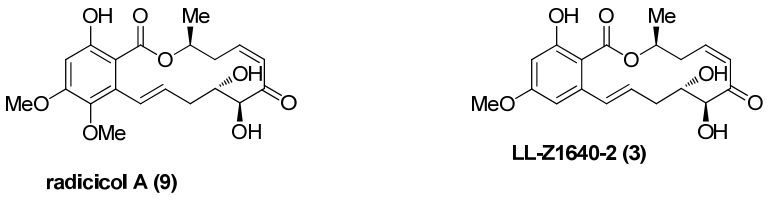


Figure 9: RALs with *cis*-enone

LL-Z1640-2 (**3**) was the first isolated RAL member of the *cis*-enone bearing subfamily (1978),[8] followed by hypothemycin (**6**) (1980),[59] radicicol A (**1**) (1996)[20] and a few years later L-783,277 (**7**) and its related lactones (1999).[19] Since the report about the inhibition of IL1β activity by radicicol A (**5**), preceded by its identification in the same paper,[20] and later the discovery of *cis*-enone-containing RALs as kinase inbibitors, total syntheses of all the four naturally occurring resorcylides of this family (**scheme 17**) have been developed over the past decade.

Structurally similar, with the only difference at C1'-C2'as distinctive feature (in addition to the *meta*-methoxy for radicicol A (**5**)), yet all the four metabolites have been the stage for conceptually diverse synthetic routes. Giving the eager isomerisation of the *cis*-enone to the more stable *trans*-isomer, all the published syntheses of RALs containing a *cis*-enone featured a late-stage oxidation of the vinylic alcohol to reveal the characteristic enone function.

1.2.1 Synthesis of LL-Z1640-2 (3)

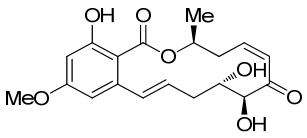
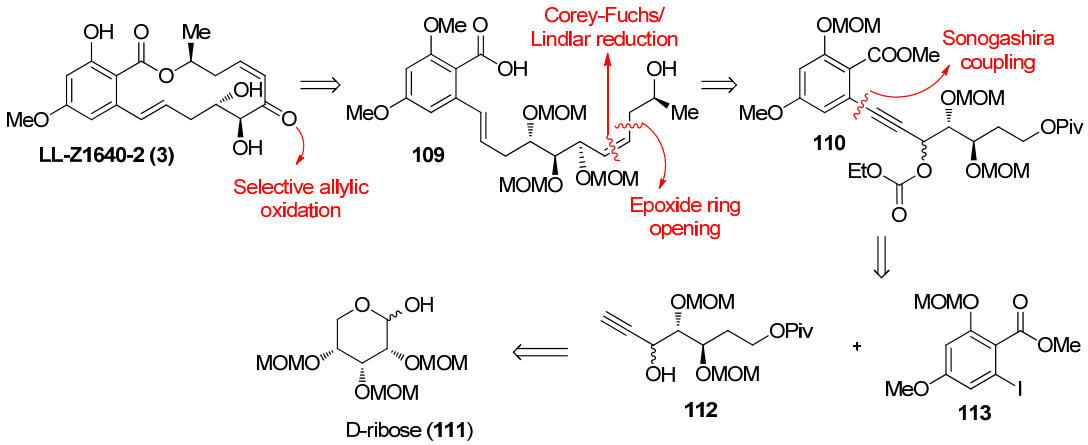


Figure 10: LL-Z1640-2 (**3**)

In 2001, Tatsuta *et al.* reported the first synthesis of LL-Z1640-2 (**3**), featuring a Mukaiyama lactonisation to generate the macrocycle (**scheme 12**).[60] At first, the *Z*-alkene C1'-C2' came from a Lindlar reduction of the C1'-C2' triple bond, which resulted from a Sonogashira coupling between iodoresorcylate **113** and the polyol segment **112**. Following the Tsuji's reduction to cleave the ethyl carbonate at C3', the *Z*-alkene isomerised into its corresponding isomer *E*. The configuration at the C4' and C5' was established by D-ribose **111**, the starting material for the pre*para*tion of **112**, which included a Corey-Fuchs reaction, closely followed by a Lindlar reduction to construct the *cis* double bond precursor of *cis*-enone. Selective oxidation of the allylic alcohol, the last step to LL-Z1640-2 (**3**), was proven effective only by use of the Dess-Martin periodinane reagent (62%), while other methods gave either very poor yield (*e.g.* DDQ gave 20% of yield) or no expected product at all.

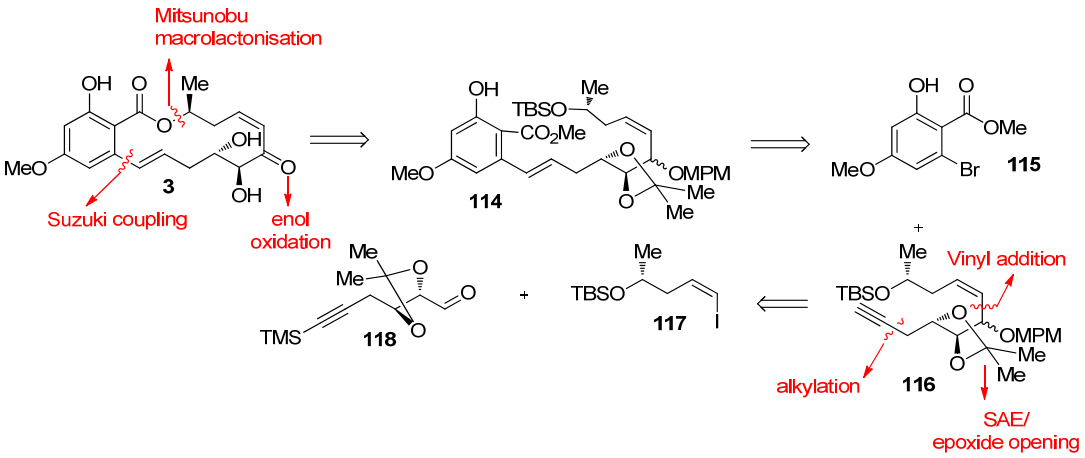


Scheme 12: Retrosynthesis of LL-Z1640-2 (**3**) by Tatsuta *et al.*

One year later, Sellès and Lett accomplished the second total synthesis of LL-Z1640-2 (**3**), which suitably led to the first total synthesis of hypothemycin (**6**) by a tactical epoxidation of C1'-C2' double bond.[61] The retrosynthetic scheme ofLL-Z1640-2 (**3**) is illustrated hereafter (**scheme 13**), and the synthesis of hypothemycin (**6**) will be detailed in the *para*graph *1.2.1*.

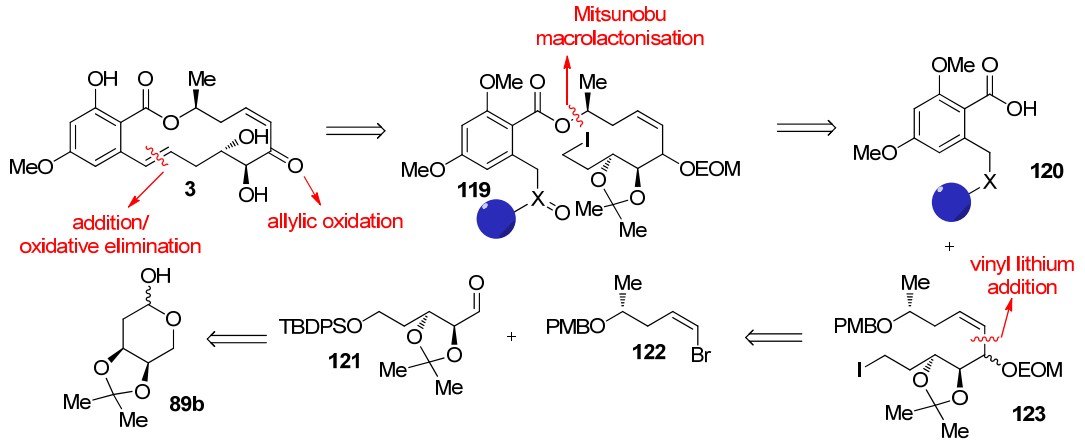
The authors performed a Mitsunobu-based esterification to achieve the 14-membered ring and a Suzuki coupling for the C1'-C2' double bond. Conceptually, the order of these 2 steps would be permutable, yet it turned out that a Suzuki-based ring closing was far too unproductive. The alkene at C7' was formed by a vinyl addition onto an aldehyde, determining the precursor *cis*-enol. It is worth mentioning that after deprotection of the allylic alcohol, only one diastereoisomer could be oxidised under mild conditions (PCC, 2,5-DMP in CH_2Cl_2),

whereas the other required harsher method (Jones oxidation) to be transformed into ketone. The anti-diol was constructed *via* a Sharpless asymmetric epoxidation combined with a carbamate-assisted opening of the epoxide.



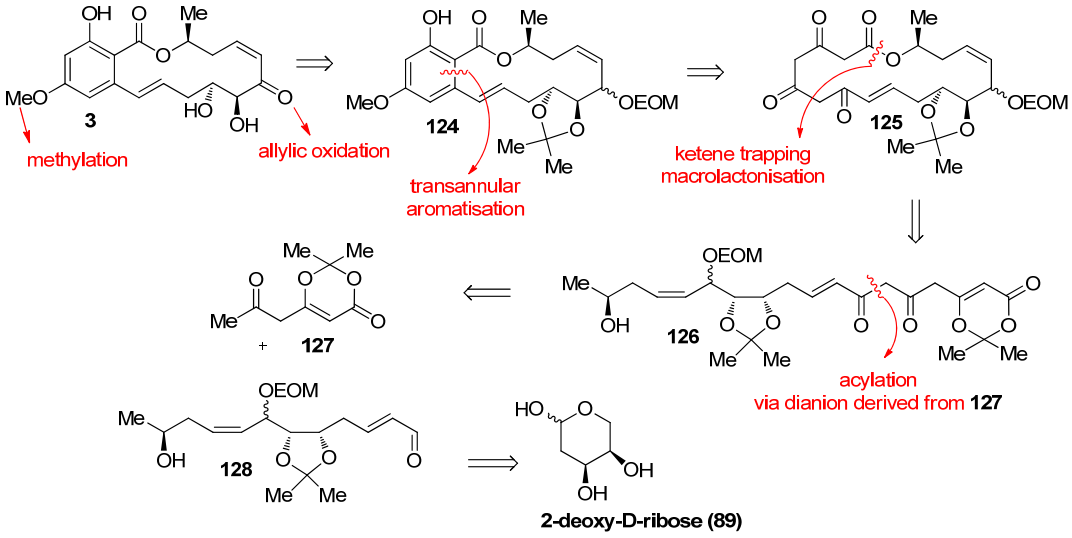
Scheme 13: Retrosynthesis of LL-Z1640-2(**3**) by Sellès and Lett

Another total synthesis of LL-Z1640-2 (**3**), and consequently the second one of hypothemycin (**6**) (**scheme 14**), together with the second total synthesis of L-783,277 (**7**), were disclosed by the group of Winssinger in 2009.[62] Their synthetic route relied on a macrocyclisation through a Mitsunobu-based esterification in the presence of fluorous-tagged triphenylphosphine and diazodicarboxylate, and a vinyl addition to introduce the *cis* allylic alcohol. In an ulterior step of the synthetic strategy, the polymer-supported IBX oxidation of the allylic acohol led to very interesting outcome. While one isomer cleanly gave the desired macrolactone **3**, the other afforded a different monooxidation product, supposedly with a ketone at C5' postion. The same issue was independently observed by Altmann *et al.* in their efforts to synthesise L-783,277 (**7**). The requisite C1'-C2' styryl bond was installed by exploiting a sequence of alkylation-oxidation-elimination. This methodology could be extended to other RALs by substituting the selenide with a benzyl sulfide, such as L-783,277 (**7**) which will be detailed in chapter *1.2.3*.



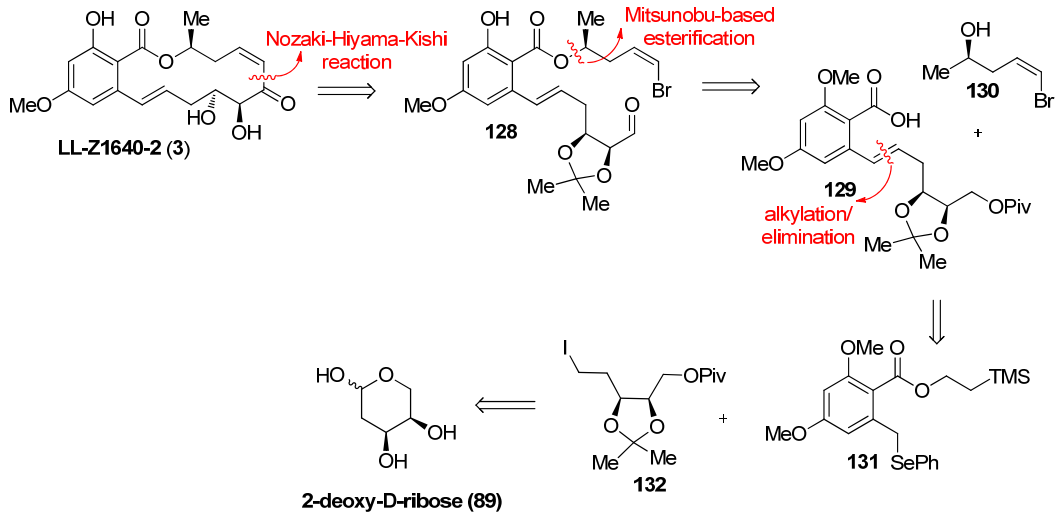
Scheme 14: Retrosynthesis of LL-Z1640-2 (**3**) by Winssinger *et al.*

In 2010, Barrett's group reported the biomimetic total synthesis of **6** without protection of phenol, a common point to all the reported syntheses to date.[63] Instead, their approach features an intermolecular ketene trapping and late-stage transannular aromatisation applied to macrocyclic diketo-ester **125** (**scheme 15**), a strategy which had successfully laid foundation for the synthesis of (*S*)-zearalenone (**2**) (**scheme 15**).[46] The efficacy of this methodology has made it a reliable alternative to the widespread RCM for macrocyclisation. The configuration of the anti-diol was also derived from 2-deoxy-D-ribose (**89**), as described by Winssinger's group within their synthetic pathway.



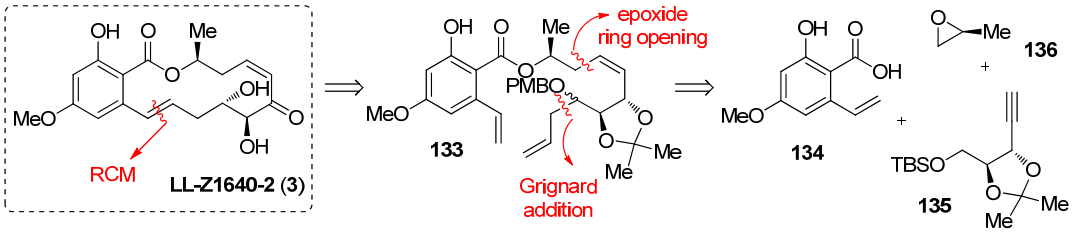
Scheme 15: Retrosynthesis of LL-Z1640-2(**3**) by Barrett *et al.*

In the same year, Thomas and collaborators published a synthetic approach to LL-Z1640-2 (**3**) which is conceptually similar to that by Winssinger's group.[64] Their synthetic route notably made use of an intramolecular Nozaki-Hiyama-Kishi coupling with vinyl iodide for the ring-closure (**scheme 16**). Like Winssinger's group, the authors employed the same selenide precursor **129** to construct the benzylic double bond, as well as a Mitsunobu-based esterification to complete the carbon framework of **128**, setting the stage for the macrocyclisation.



Scheme 16: Retrosynthesis of LL-Z1640-2 (**3**) by Thomas *et al.*

In summary, among all the tactical approaches employed by the aforementioned syntheses of LL-Z1640-2 (**3**), macrolactonisation appears to be the most effective method to implant the core ring structure. Intriguingly, the use of RCM as ring-closure to introduce the *E*-alkene has not been reported so far. In 2007, Marquez *et al.* have detailed the fast and efficient synthesis of the triene **133** as the stage for a RCM as an alternative mode to achieve the macrocycle (**scheme 17**).[65] However, no attempts of RCM on this precursor have been described so far, leaving this proposition an unproven method to access the ring structure of this *cis*-enone RAL.



Scheme 17: RCM-based strategy towards LL-Z1640-2(**3**) proposed by Marquez *et al.*

1.2.2 Synthesis of hypothemycin (6)

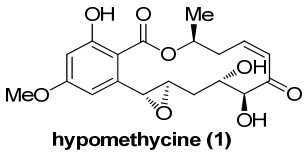
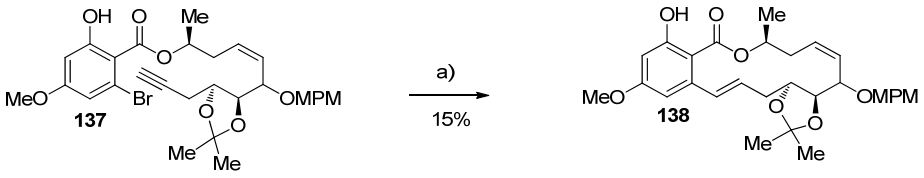


Figure 10: hypothemycin (**6**)

Isolated from the fermentation broth of *Hypomyces trichothecoides* in 1980[10a], hypothemycin's structure was first attributed to the 14-membered RALs **2**. More than a decade later, a

Japanese group discovered a cytotoxic substance from the crude extract of *Coriolus versicolor* whose physico-chemical properties were identical with those from zeralenone (**2**).[66] A thorough reinvestigation lead to the reassignment of hypothemycin's structure which is the *cis*-enone RAL hypothemycin (**4**), an epoxide of LL-Z1640-2 (**3**)- discovered in 1978.[8] Initially, the metabolite LL-Z1640-2 (**3**) was synthesised from D-ribose in 2001,[60] yet the first total synthesis of hypothemycin (**6**) was only disclosed in 2002 by Sellès and Lett, as an epoxidised product of the convergently synthesised LL-Z1640-2 (**3**).[61, 67]

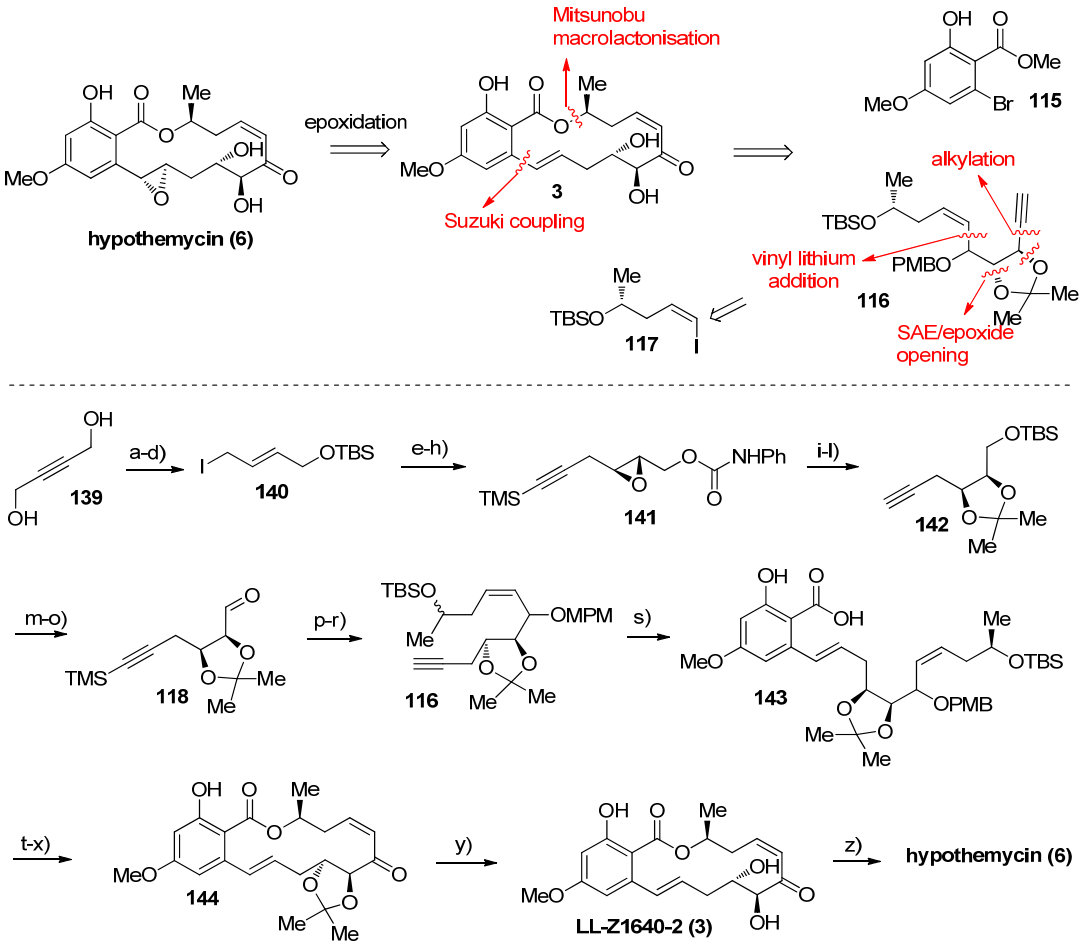
The key features of the synthesis are a Suzuki coupling to form the benzylic olefin, a Mitsunobu based macrolactonisation and a selective epoxidation. The *Z*-alkene was implanted through a vinyl lithium derived from the vinyl iodide **117** containing readily the adapted absolute configuration for the methyl at C10'. The terminal alkyne **116** needed for the Suzuki coupling at benzylic position was prepared from but-2-yne-1,4-diol **139** which intermediately underwent a Sharpless epoxidation followed by a selective epoxide opening to introduce the *anti*-diol at C4' and C5'. The first attempts to form the 14-membered macrolide *via* an intramolecular Suzuki coupling of vinyldisiamylborane derived from **137** turned out to be ineffective (**scheme 17**). According to the authors, the major difficulty was to get a good turn-over of the catalyst, at the minimal dilution (0.03-0.04 M) required for minimising intermolecular reactions and kinetically compatible with the time scale necessary to adopt the appropriate conformations allowing the formation of the palladamacrocycle.



Scheme 17: *Intramolecular Suzuki coupling by Selles and Lett:*[61, 67] a) Sia_2BH (3.9 equiv.), THF, −20°C to RT, 2 h, then addition of acetone (3 equiv.) and afterwards 2 M aq. K_3PO_4 (2 equiv.) at −10°C to RT, further addition of that mixture *via* cannula to a solution of 4 mol% [$Pd(OAc)_2$ + 4 TFP] in DME, *i.e.* substrate 0.034 M in DME/H_2O (30/1), reflux, 6 h.

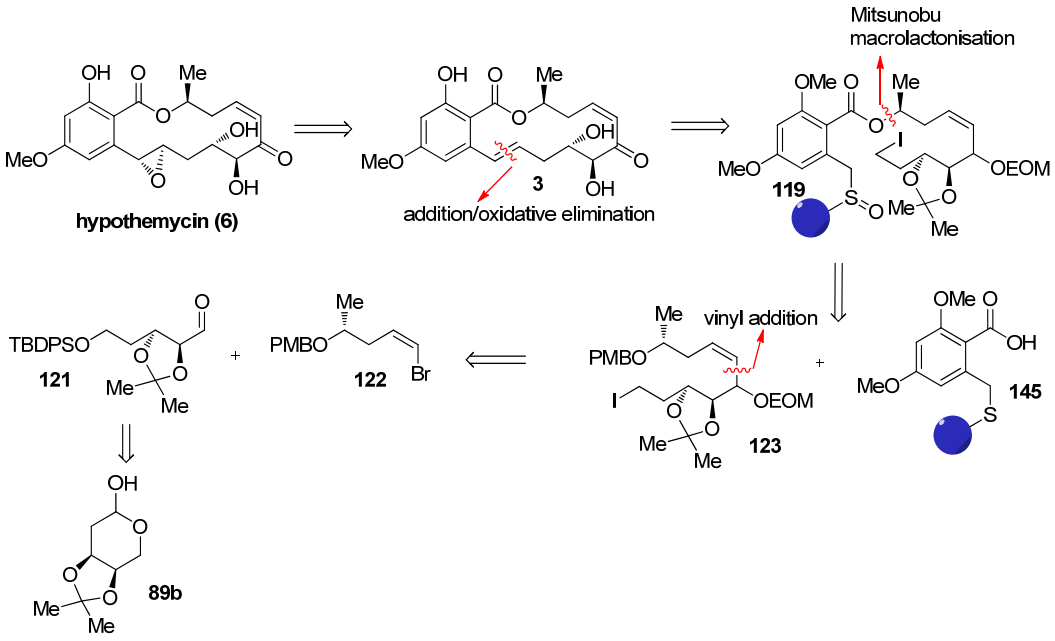
The strategy was therefore changed into a Suzuki coupling between **116** and the aromatic part **116** (**scheme 18**). This reaction provided the intermediate **143** in satisfactory yield, which underwent an orthogonal cleavage of the TBS group to set the stage for the Mitsunobu macrolactonisation. This step completed the 14-membered macrocyclic framework in 67% yield. The (*Z*)-allylic alcohol was selectively deprotected then oxidised to release the characteristic *cis*-enone and the acetonide was smoothly cleaved into the *anti*-diol, completing the total synthesis of LL-Z1604-2 (**2**). Giving the *cis*-olefin readily epimerises to the more stable *trans* isomer, finding an appropriate oxidising reagent was indispensable. In the synthesis of LL-Z1604-2 by Tatsuta *et al.,* the best condition was found to be Dess-Martin periodinane reagent.[60] The group of Lett opted for PCC in the presence of 2,5-dimethylpyrazole (Parish conditions) which afforded the ketone in excellent yield, though only one of the diastereoisomers reacted under these conditions.

The final key step was a selective oxidation of the benzylic olefin. As expected, the oxidation proved to be arduous, due to an unusually unreactive benzylic double bond and lability of the product. The best result was observed for *m*CPBA/$NaHCO_3$ with 17% yield, increased to 24% after recovering 30% of LL-Z1604-2. Gratifyingly, no other epoxides were observed in this case.



Scheme 18: Synthesis of hypothemycin (6) by Sellès and Lett[61, 67] *Reagents and conditions*: a) Red-Al® (1.5 equiv.)/toluene, THF, 0°C to rt, overnight, 81%; b) NaH (1.03 equiv.), THF, RT, 1 h, then −78°C, TBSCl (1.03 equiv.), 36 h, 74%; c) MsCl (1.1 equiv.), NEt_3 (1.1 equiv.), DCM, −10°C to RT, 30 min; d) NaI(1.5 equiv.), acetone, RT, 1 h; e) ethynyltrimethylsilane(1.5 equiv.), THF, BuLi (1.5 equiv.), −78°C, 30 min, then **140** and HMPA (THF/HMPA=10/1), RT, 4 h; f) DDQ (5 mol%), MeCN/H_2O (9/1), RT, 2 h; g) $Ti(OiPr)_4$ (1 equiv.), (+)-DET (1.24 equiv.), anhydr. DCM, *t*BuOOH (3 M in isooctane) (2.1 equiv.), −25°C, overnight; h) PhNCO (2.5 equiv.), DCM/pyridine, RT, 1 h; i) $BF_3{\cdot}Et_2O$ (1.1 equiv.), Et_2O, −20°C, 2 h, then 1N H_2SO_4, RT, overnight; j) MeONa (0.35 equiv.), MeOH, RT, 8 h, then Dowex 50 WX8 column eluted by MeOH; k) TBSCl (1.05 equiv.), imidazole (1.05 equiv.), DMF, RT, 1 h; l) 2-methoxypropene (2 equiv.), TsOH cat., DCM, RT, 1 h; m) BuLi/hexane (1.1 equiv.), Et_2O, −30°C, 30 min, then TMSCl (1.1 equiv.), −30 to −10°C, 98%; n) DDQ (8 mol%), MeCN/H_2O (9/1), RT, 2 h, 73%; o) oxalyl chloride (1.1 equiv.), DMSO (2.2 equiv.), DCM, −78°C, 30 min, then alcohol, 30 min and NEt_3 (5.0 equiv.), −78 to 0°C; p) **118** (*n* equiv.), Et_2O, −78°C, then *t*BuLi/pentane (2*n* equiv.), 15 min, and further addition of **142** in pentane, −78 to 0°C; q) K_2CO_3 (1.4 equiv.), MeOH, RT, 5 h; r) $CH_3OC_6H_4CH_3OC(NH)CCl_3$(2 equiv.), Et_2O, CF_3SO_3H (0.004 equiv.), RT, 4 h; s) Sia_2BH (2 equiv.), THF, −25°C to RT, 2 h and then aq. 2 M K_3PO_4 (2 equiv.), further addition of that mixture *via* cannula at RT to a solution of **116**(1.2 equiv.) and 15 mol% [$Pd(OAc)_2$ + 4 TFP] in DME; DME/H_2O: 7/1, reflux, 8 h; t) TBAF 1 M/THF (3.5 equiv.), RT, 6 h, 93%; u) 2M aq. NaOH (13 equiv.)/MeOH (1/3), reflux, overnight, 71%; v) hydroxy-acid 0.007 M in anhydr. toluene, PPh_3 (2 equiv.), DEAD (2 equiv.), RT, 15 min; w) DDQ (1 equiv.), DCM/pH 7 buffer (9/1), RT, 30 min; x) PCC (3 equiv.), 2,5-DMP (10 equiv.), DCM, 0°C, 6 h; y) *p*TsOH (0.5 equiv.), DCM/MeOH (1/1), RT, 3 h 30 min; z) *m*CPBA/$NaHCO_3$ (3 equiv.), −20°C to 0°C, 4 h, then pH 7 work-up, 17% (24% based on recovered starting material).

The most recent total synthesis of hypothemycin (**6**) was accomplished by the group of Winssinger as part of their effort to broaden the diversity of the RALs family beyond naturally occurring products, especially those containing a *cis*-enone moiety.[62] The synthetic route relies also on a late-stage epoxidation, a Mitsunobu macrolactonisation as well as a vinyl lithium addition onto an aldehyde to induce the *Z*-enol prior to the construction of the *cis*-enone (**scheme 19**). Interestingly, the benzylic functionalisation was addressed by using a stabilised anion derived from the resorcylic ester **145** bearing a sulfoxide at the benzylic position, which allowed a direct alkylation onto the iodide fragment **123**, followed by an oxidative elimination to reveal the 1',2'-alkene. The epoxidation was carried out by using DMDO (5.0 equiv.) which afforded hypothemycin (**6**) in 25% isolated yield at 50% conversion. It was mentioned that all attempts to drive the reaction to completion resulted in decomposition, as the epoxide was quite sensitive to acid and partial degradation of the final product was also observed upon isolation.

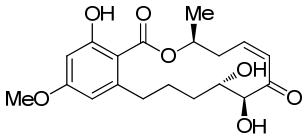


Scheme 19: Retrosynthesis of hypothemycin (**6**) by Winssinger *et al.*

Our interest, as synthetic chemists, was directed towards the metabolite L-783,277 (**7**), which is the latest synthetic target among all the other *cis*-enone RALs of this family.[68] Carrying a saturated bond at C1'-C2', while the other members contain an unsaturated bond at this position, **7** has been subject of efficiently concise and conceptually heterologous synthetic pathways.

The coming chapter will give a summary of the intriguing biological activities of this secondary metabolite, followed by descriptions of different synthetic approaches realised to date.

1.2.3 Syntheses of L-783,277 (7)



L-783277 (FR265082) (7)

Figure 11: L-783,277 (**7**)

The metabolite L-783,277 (**7**) was purified from fermentations of *Phoma sp*. (ATC 74403) which came from the fruitbody of *Helvella acetabulum*, together with its *trans*-isomer L-783,290. Its structure was established on the basis of NMR and MS analysis by the Merck group of Zhao in 1999.[19] The identification and fermentation of the culture that produced L-783,277 (**7**) and other related lactones, represented in **figure 12**, were reported by Dombrowski *et al.* in the same year.[69] Anterior to this work, RO 09-2210, or L-783,278 (**13**) had been isolated from the mycelial cake of *Curvularia* species by Ms. K. Ilida (Nippon Roche Research Centre).[18]

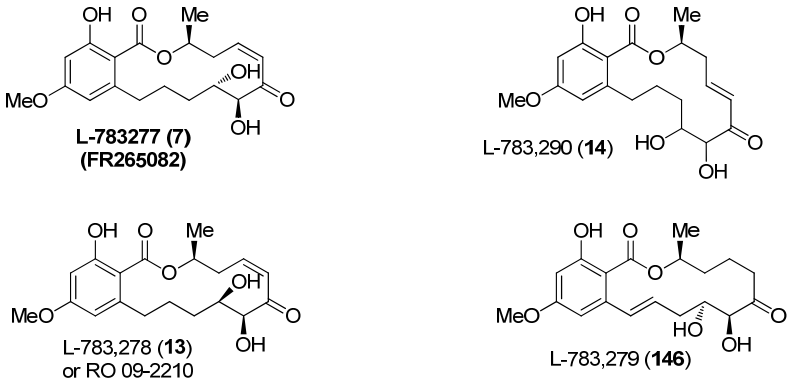


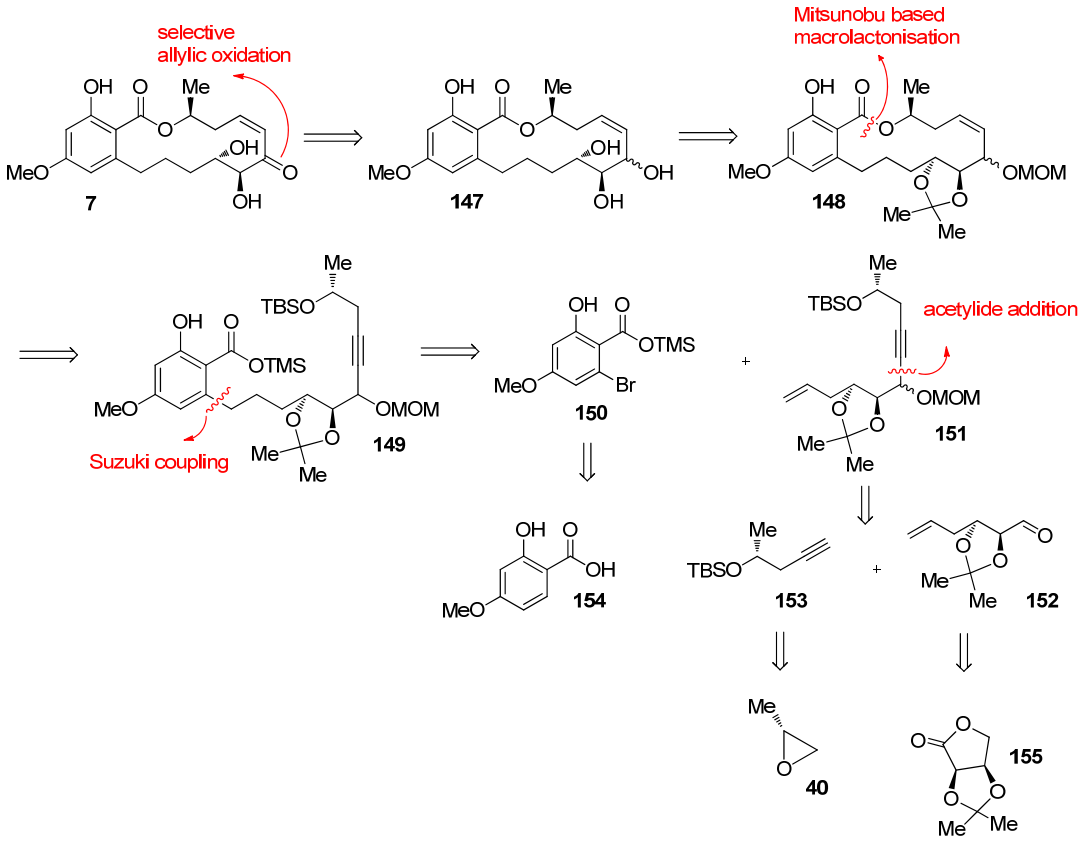
Figure 12: L-783,277 (**7**) and other RALs isolated and characterized in 1999 [19,69]

In great agreement with the discovery by Zhao *et al.* of the potent and irreversible inhibition of MEK1 (4 nM) by the natural product L-783,277 (**7**),[19] Altmann and collaborators have also reported this metabolite as a time-dependent, ATP-competitive irreversible inhibitor of MEK2 (IC_{50}= 15 nM), VEGFR2 (IC_{50}= 2 nM), and PDGFRα (IC_{50}= 2.4 nM).[70] Interestingly, the same research group mentioned that L-783,277 (**7**) inhibits the formation of tube during investigations in human umbilical vein endothelial cells (HUVEC), a common test to assess angiogenesis *in vitro*.[71] Their study disclosed that **7**, when added at the time of seeding, effectively inhibited the formation of tubes, but had no significant effect on readily formed capillary-like networks. Consequently, **7** is also an inhibitor of VEGF-induced tube formation, at the condition of being incubated with the cells at day 0.

- **Synthesis by Altmann *et al.***

The first total synthesis of L-783,277 (**7**) was disclosed by Hofmann and Altmann in 2008.[68] One of the key features of their strategy is the ultimate introduction of the ketone moiety at C6'

through a selective oxidation of allylic alcohol applied to the triol precursor **147** (**scheme 20**). The 14-membered ring was formed *via* Mitsunobu-based macrolactonisation, following a Suzuki coupling at *ortho* position of the aromatic part **150** and the borane resulting from hydroboration of the substructure **151**, a strategy which was previously employed by Sellès and Lett in their synthesis of LL-Z1640-2 (**3**).[67] Prior to the macrocyclic ring-closing, the *Z*-alkene was formed by Lindlar reduction of the previously inserted triple bond through an acetylide addition of the deprotonated homopropargylic TBS-protected alcohol **153** onto the aldehyde fragment **152**.

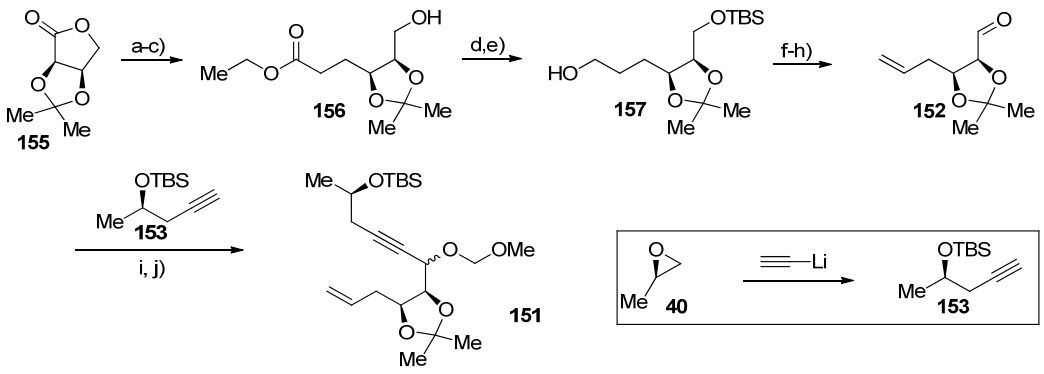


Scheme 20: Retrosynthesis of L-783,277 (**7**) by Hofmann and Altmann

The *R* configuration of C10' was determined by the configuration of the epoxide **40** which underwent a regioselective attack of lithium acetylide. The released secondary alcohol was subsequently protected as TBS ether and provided O-TBS-protected *(R)*-1-pentyn-4-ol **153**. Keeping in mind that the very same stereogenic carbon was to be subjected to a configurational inversion as a consequence of the late-stage Mitsunobu-based macrolactonisation, the resulting C10' would have the desired *S* configuration for the target metabolite L-783,277 (**7**).

On the other hand, the *anti*-diol configuration at C4' and C5' was induced by the commercially available chiral pool erythronolactone **155** which was submitted to a well established sequence of reduction, Wittig olefination and hydrogenation to provide the ester **156** (**scheme 21**). The primary alcohol was silylated before the ester was reduced to primary alcohol **157**, which underwent Grieco-Sharpless olefination, TBS removal and Swern oxidation to give aldehyde **152**. The nucleophilic attack of the anion derived from the readily prepared O-TBS-

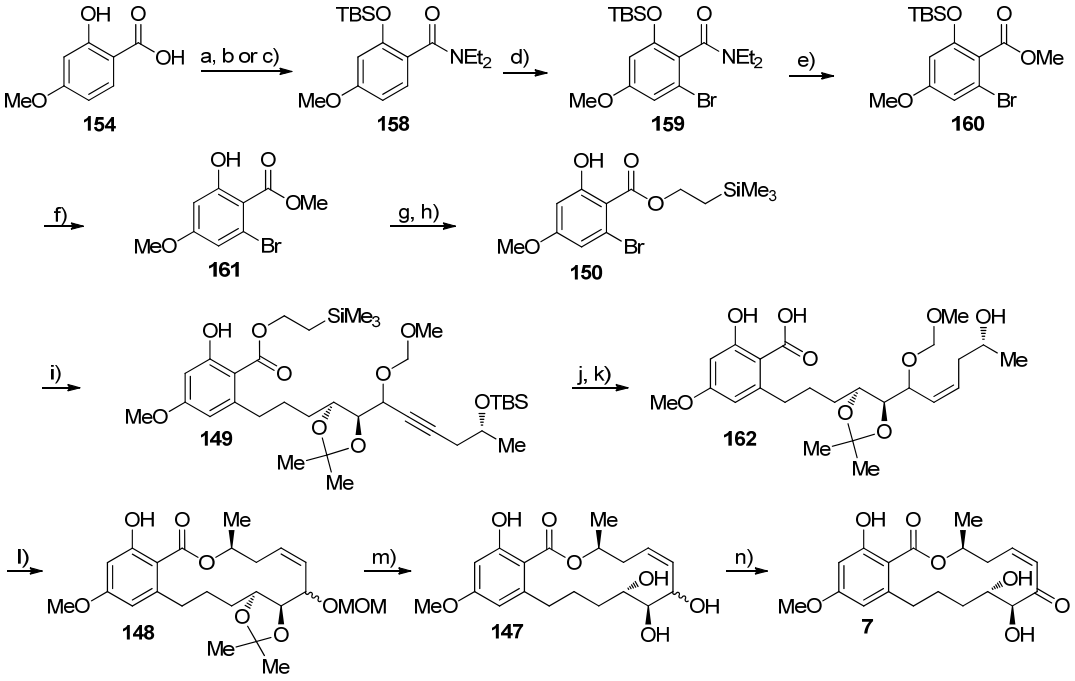
protected (*R*)-1-pentyn-4-ol **153** onto the aldehyde led to a mixture of diastereomeric alcohol **151**.



Scheme 21 *Reagents and conditions:* a) DIBAL-H, Et_2O, -78°C, 2 h, 95%; b) $Ph_3PCHCOOEt$, dioxane, reflux, 7 h, 91% (*E/Z* = 1.1/1); c) H_2, Pd/C, EtOH, 4 h, quant.; d) TBSOTf, CH_2Cl_2, 93%; e) DIBAL-H, toluene, 2 h, 85%; f) i. 2-$O_2NC_6H_4SeCN$, Bu_3P; ii. $NaHCO_3$, 30% H_2O_2, 19 h, 81%; g) TBAF, THF, 0°C to RT, 0.5 h, 90%; h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C, 1 h, 74%; i) **153**, BuLi, -78°C, 1.5 h, 87%; j) MOMCl, iPr_2NEt, Bu_4NI, DMF, 19 h, 87% (1:9:1 mixture of isomers)

The aromatic core **160** was obtained from 4-methoxysalicylic acid **154** following ester cleavage with TMSOK under microwave conditions and DCC/DMAP-mediated protection of the released acid with 2-TMS-ethanol (**scheme 22**). The Suzuki coupling between **150** and **151** provided in high yield the precursor **149** whose triple bond was partially reduced into *Z*-olefin. At this stage, the isomers derived from **149** were se*para*ted before being submitted to the remaining transformations, respectively. The TMS ester and TBS ether were removed concurrently, leading to the precursor **162**. The Mitsunobu macrolactonisation proceeded smoothly, followed by the deprotection with sulfonic acid resin to give the fully deprotected macrolactones **147** which were both submitted to oxidation with polymer-bound IBX.

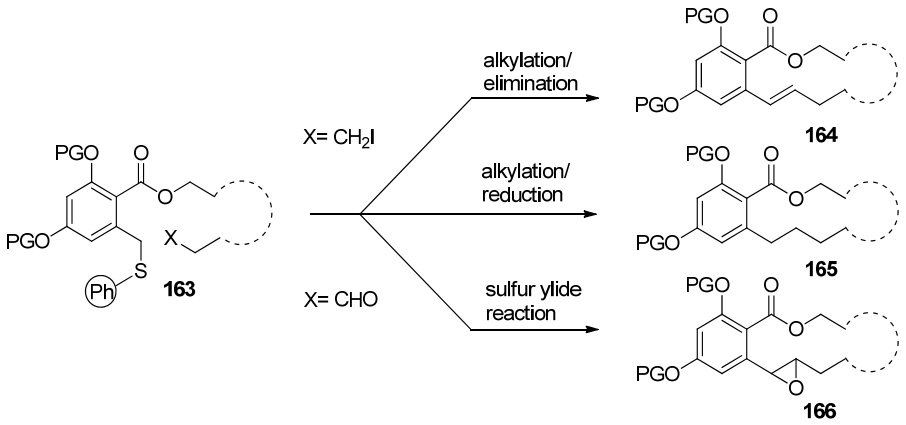
The oxidation of the major C6'-isomer of **147** gave a 1:4 mixture of L-783,277 and an unknown mono-oxidised product whereas the minor isomer afforded L-783,277 in 93% yield, along with 8% of inse*para*ble mono-oxidised product.



Scheme 22 *Reagents and conditions:* a) TBSCl (2.5 equiv.), iPr_2NEt (3.6 equiv.), DMF, RT, 2 h; b) oxalyl chloride (1.1 equiv.), DMF cat., CH_2Cl_2, −10°C to RT, overnight, then Et_2NH (2.0 equiv.), 1 h, RT; c) Et_2NAlMe_2 from Me_3Al (4 equiv.) and Et_2NH (4 equiv.), toluene, −6°C to RT, 45 min, then reflux, overnight; d) *t*BuLi/pentane (1.08 equiv.), Et_2O, −78°C, 10 min, then Br_2 (1.06 equiv.); e) Me_3O^+, BF_4^- (1.3 equiv.), CH_2Cl_2, RT, overnight, then evaporation; f) aq. sat. Na_2CO_3/MeOH (1/1), RT, 6 h; g) TMSOK, DME, µwave, 110°C, 2 h, acidic workup, 85%; h) $Me_3SiCH_2CH_2OH$, DCC, DMAP, CH_2Cl_2, 15h, 88%; i) i. 9-BBN, THF, r.t., 2 h; ii. 2 M K_3PO_4, [Pd(OAc)2+4 TFP], DME, reflux, 5.5 h, 81%; j) i. H_2, Lindlar catalyst, EtOAc, 3 h, 94%; k) se*para*tion of isomers (1.6:1); f) TBAF, THF, RT, 15 h, quant. (major isomer); quant. (minor isomer); l) DIAD, Ph_3P, toluene, 25 min, 59% (major isomer), 74% (minor isomer); m) sulfonic acid resin, MeOH, reflux, 6 h, 78% (major isomer), 46% (minor isomer); n) IBX (polymer-supported), CH_2Cl_2, RT, 6 h; from major isomer of **7**: 1:4 product mixture of L-783,277 and a second mono-oxidised species (major product), 82% (total yield); from minor isomer of **147** : 93% of **7** (91% purity)

- **Synthesis by Winssinger *et al.***

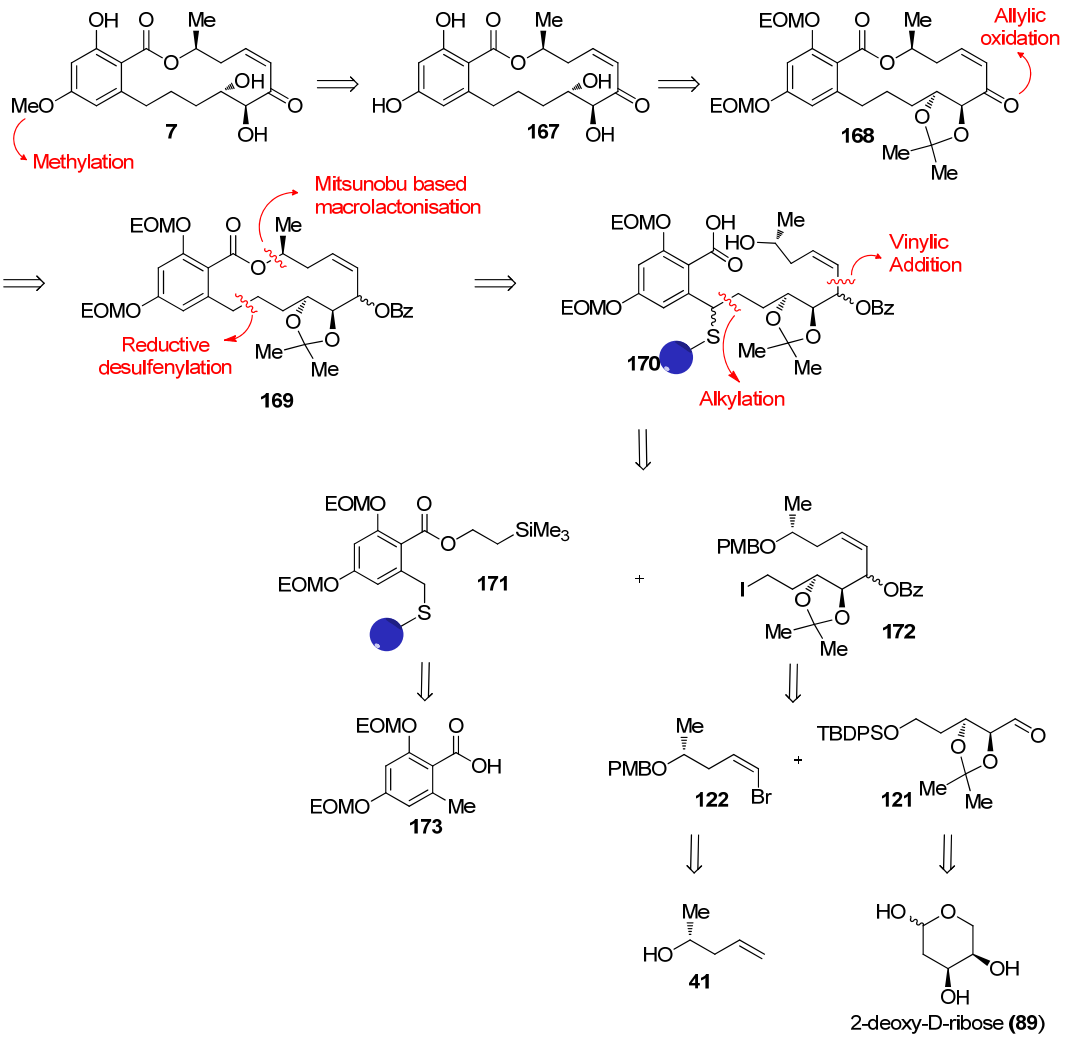
The second total synthesis of L-783,277 (**7**) was published in 2009 by the group of Winssinger, as a result of their efforts in broadening the diversity of the RALs family beyond naturally occurring compounds.[62] In the first place, Winssinger and co-workers tried to address, through a general synthetic map, the largest spectrum of readily existing metabolites of the family bearing either an alkane, or an alkene, or even an epoxide at the benzylic position. Indeed, their major tactical step comprises a sulfide at the benzylic position of the resorcylic ester as a common pattern, which allows the direct attachment of another fragment (**scheme 23**).



Scheme 23: Formation of benzylic alkene **154**, alkane **165** and epoxide **166** from common intermediate **163** by Winssinger *et al.*

The total synthesis of L-783,277 (**7**), an instance of RAL whose structure is fully saturated at the benzylic position, embodied the tactical use of the resorcylic ester **171** bearing a benzylic sulfide. As illustrated above, the C1-C2 alkane bond would be built through a direct alkylation

Retrosynthetically, the metabolite **7** was dismantled into two major parts (**scheme 24**): the aromatic core **171** and the iodide substructure **172**, which was aimed to build the characteristic 14-membered macrocycle. Prior to the benzylic alkylation, the *Z* configuration of the alkene would be induced by the appropriate and enantiomerically pure *cis*-vinyl bromide **122** which was to be lithiated in the presence of tert-butyllithium.The aldehyde fragment **121** containing the right *anti*-diol configuration was synthesised from the naturally-occurring D-form of deoxyribose (**89**). While the late-stage Mitsunobu macrolactonisation leading to the 14-membered ring joined the strategy employed by Altmann and Hofmann,[68] an earlier orthogonal deprotection combined with the oxidation of the released allylic alcohol was aimed to provide the *cis*-enone more selectively.

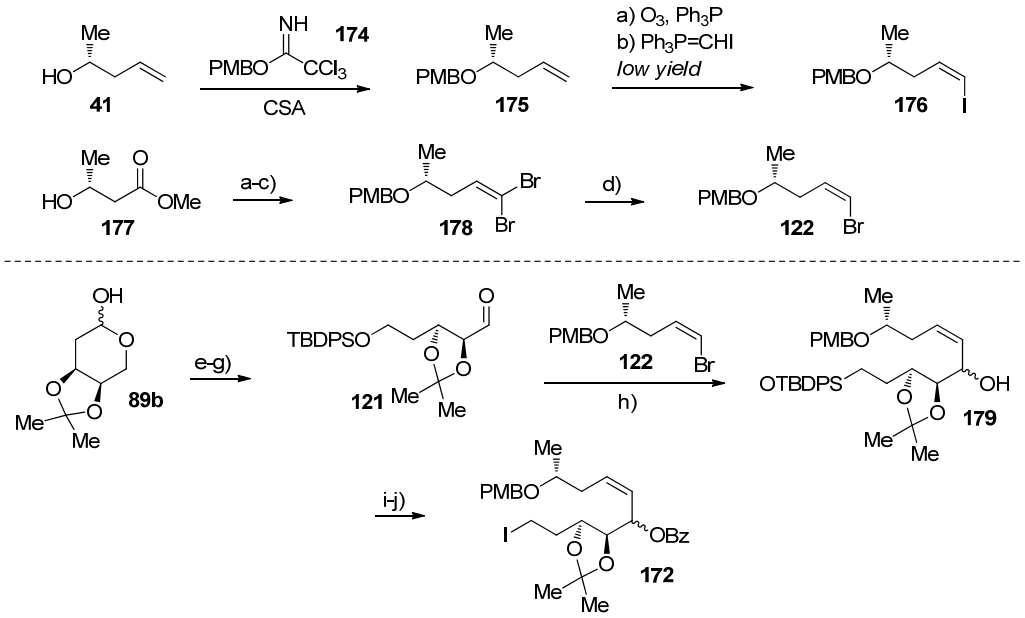


Scheme 24: Retrosynthesis of L-783,277 by Winssinger and co-workers

The pre*para*tion of *cis*-vinyl bromide **122** was achieved in four steps from methyl 3-hydroxybutyrate **177**, using well-established procedures (**scheme 25**). The initial attempts of synthesising the corresponding *cis*-vinyl iodide **176** by means of a final Wittig reaction ended up with unpleasingly low yields (<30%), despite the appealing existence of all the involved reagents under immobilised versions. Alternatively, the sequence starting with the less expensive methyl 3-hydroxybutyrate **177**, introducing compound vinyl *gem*-dibromide **178** was undertaken. The supposingly more reactive *trans*-isomer underwent the tributyltin hydride reduction catalysed by tetrakis(triphenylphosphine)palladium and afforded the desired *cis*-vinyl bromide **122** in excellent yield.

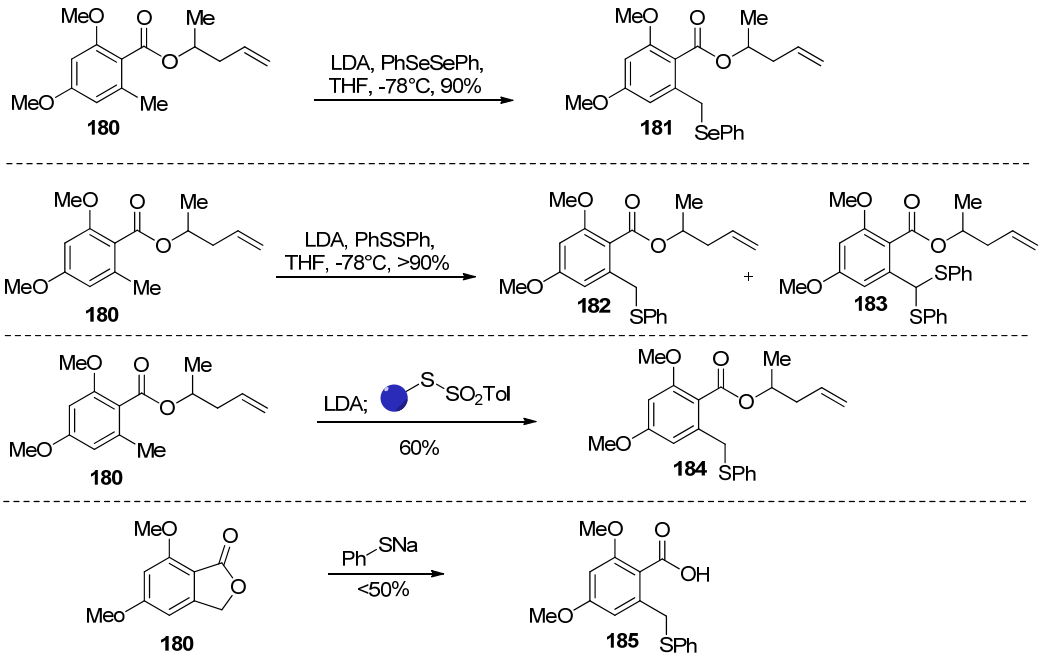
The aldehyde **121** was, as previously reported by the same research group (**scheme 14**),[21] prepared in three steps: LAH mediated reduction of the corresponding hydroxyaldehyde of 2-deoxy-D-ribose **89**, mono-protection of the obtained diol and a mild oxidation of the unprotected alcohol. The resulting aldehyde was then submitted to an addition of the lithiated derived of *cis*-vinyl bromide **122** to provide the *cis* allylic alcohol **179**. Benzyl protection of the unse*para*te diastereomeric mixture of **179**, TBAF mediated deprotection and iodination of the released primary alcohol completed the synthesis of intermediate **172**. As outlined in the

retrosynthesis, this subunit was to be bound to the aromatic core by means of the corresponding polymer-bound linker **171**.



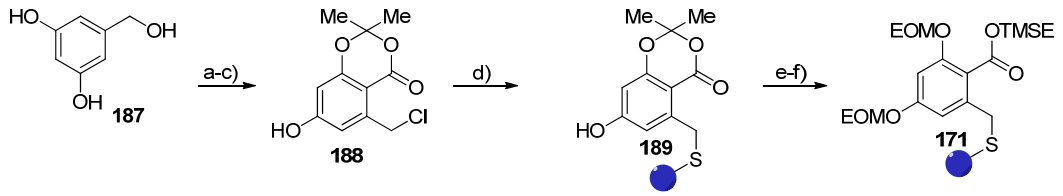
Scheme 25: *Reagents and conditions*: a) $PMBOCNHCCl_3$ (1.0 equiv), CSA (0.1 equiv), CH_2Cl_2, 23°C, 12 h, 92%; b) DIBAL-H, (1.1 equiv), toluene, 78°C, 2 h, 89%; c) CBr_4 (4.0 equiv), Ph_3P (8.0 equiv), CH_2Cl_2, 0°C, 45 min, 90%; d) $[Pd(PPh3)_4]$ (0.2 equiv), *n*Bu_3SnH (5.1 equiv), benzene, 23°C, 1.5 h, 95%; e) $LiAlH_4$ (1.4 equiv), THF, 0 to 23°C, 2 h, 95%; f) TBDPSCl (1.0 equiv), imidazole (1.5 equiv), DMF, 23°C, 2 h, 66%; g) PS-IBX (3.0 equiv), CH_2Cl_2, 23°C, 2 h, quantitative; h) **122** (1.0 equiv), *t*BuLi (2.0 equiv), Et_2O, -100 °C, 30 min, 88%; i) BzCl (2.5 equiv), pyridine (2.5 equiv), TBAI (cat), CH_2CH_2, 0 to 23°C, 6 h, 90% ; j) TBAF (2.0 equiv), THF, 23°C, 6 h, quantitative; then I_2 (1.5 equiv), Ph_3P (1.5 equiv), imidazole (2.5 equiv), THF, 0°C, 30 min, 91%.

The introduction of a selenide or sulfur at the benzylic position is compelling in spite of the tricky pre*para*tion of the required selenide or sulfide, in particular the compound **171**. Commonly, if the sulfur or selenium sources are envisioned as electrophiles, the toluate position of the aromatic substrated can be easily deprotonated by LDA, though the reaction is not always reliable as for the sulfur, *e.g*. diphenyl disulfide, which inevitably gave the unwanted disubstituted compound **183** (**scheme 26**).[62] Even solid-phase processes gave very modest yields. On the other hand, reactions with nucleophilic selenols or thiols revealed to be high yielding, with the exception of the opening of phtalide ring **186** with sodium thioxide. Even this least efficient transformation failed to provide passable results, access to benzyl halide in the presence of appropriate protecting groups (*e.g*. EOM phenol ether or TMSE ester) was undoubtedly much more tedious.



Scheme 26: Selenide formation through electrophilic selenium

According to the authors, it was most convenient to access the polymer bound resorcylate **171** from an acetonide protection of the acid and *ortho*-phenol **188**, which is obtained in three steps from the commercially available 3,5-dihydroxybenzyl alcohol **187** (**scheme 27**). Treatment of the benzyl chloride **188** with a thiophenol resin afforded quantitatively the sulfide **189** which was doubly protected into the polymer bound resorcylate **171** in 93% overall yield.

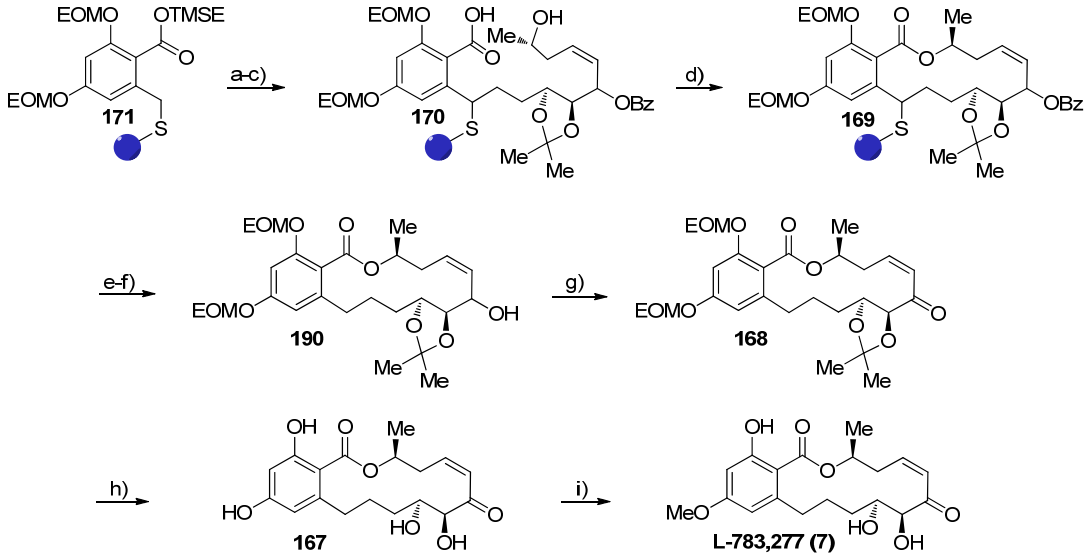


Scheme 27: *Reagents and conditions*: a) $POCl_3$, DMF; b) $NaClO_2$; c) acetone, TFA, TFAA; d) in solution: Ph-SH (1.0 equiv), **188** (1.0 equiv), iPr_2NEt (1.0 equiv), DMF, 60°C, 12 h, 98%; on solid phase: PS-SH (1.0 equiv, 0.8 $mmol.g^{-1}$), **188** (1.5 equiv), iPr_2NEt (1.0 equiv), DMF, 60°C, 12 h, quantitative; e) in solution: EOM-Cl (2.0 equiv), iPr_2NEt (2.0 equiv), TBAI (cat.), CH_2Cl_2, 23°C, 12 h, 97%; on solid phase: EOMCl (2.0 equiv), DBU (2.0 equiv), TBAI (cat), DMF, 23°C, 12 h. quantitative; f) in solution: TMSEOH (1.1 equiv), NaHMDS (1.1 equiv), THF, 0°C, 2 h, 95%; on solid phase: TMSEOH (4.2 equiv), NaHMDS (1.1 equiv), THF, 0 to 23°C, 12 h.

The resin **171** was deprotonated prior to its alkylation with **172** then submitted to DDQ and TBAF deprotections to release the precursor **170** required for the Mitsunobu-based macrolactonisation (**scheme 28**). The polymer-bound macrocycle **190** was released under reductive conditions followed by a benzoate hydrolysis. The allylic alcohol was mildly oxidised into *cis*-enone **168** by Dess-Martin periodinane. Though the group had previously

accomplished the total synthesis of radicicol A (**5**) using a selective oxidation of the triol precursor to introduce the desired *Z*-enone successfully, this method was supposedly unsuitable for macrolides lacking a substituent on the aromatic ring which should be *ortho* to the alkene. As for the attainment of LL-Z1640-2 (**3**) through the same selective oxidation strategy, the less polar triol isomer was cleanly transformed into enone in 86% yield, while the other isomer only led to the *γ*-enone. Interestingly, the group of Altmann also mentioned, in their article concerning the first total synthesis of L-783,277 (**7**), the same issue during their attempts to oxidize the precursor triol of this metabolite. Noteworthily, L-783,277 (**7**) is totally saturated at the benzylic position.

As a consequence, in contrast with the synthetic sequence by Hofmann and Altmann, Winssinger and colleagues opted for an early and selective oxidation of allylic alcohol, followed by total deprotection of alcohol and phenol moieties upon treatment with HF. Then a diazomethane mediated methylation leading to a selective alkylation of the *para*-phenol in relatively high yield (63-74%), ended the total synthesis of L-783,277 (**7**) (**scheme 36**).



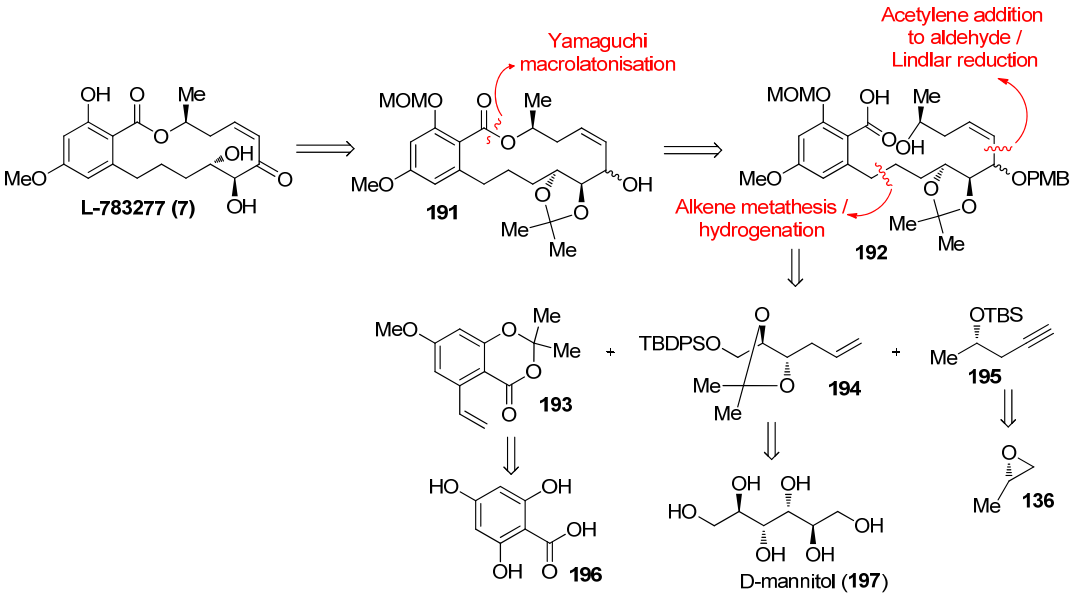
Scheme 28 *Reagents and conditions:* a) **172** (3.0 equiv), LDA (6.0 equiv), THF/HMPA (10:1), -78°C, 20 min; b) DDQ (2.4 equiv), CH_2Cl_2/H_2O (2:1), 23°C, 4 h; c) TBAF (10 equiv), THF, 23°C, 6 h; d) DIAD (3.0 equiv), Ph_3P (3.0 equiv), toluene, 23°C, 12 h; e) F-OctSnH (5.0 equiv), AIBN (cat), toluene, 150°C, µwave, 10 min, 52% over 5 steps; f)NaOH/MeOH, 23°C, 12 h, 76-80%; g) DMP (3.0 equiv), CH_2Cl_2, 65°C, 6 h, 85-87%; h) 40% HF in CH_3CN (1:10), 23°C, 7 h, 50%; i) CH_2N_2 (5.0-10 equiv), Et_2O, 23°C, 6 h, 63-74%.

This strategy allowed an apparently more selective and reliable oxidation of allylic alcohol, hence higher overall yield even with an additional step (methylation of the *para*-phenol) to accomplish the total synthesis. Conceived amid the library of RAL products, the use of a sulfide linker followed by reductive cleavage led to a strategically concise benzylic extension of the macrocyclic precursor. Though the choice of benzoyl as the protecting group for the *cis* allylic alcohol was suitably orthogonal, to find the appropriate conditions to deprotect both EOM ethers and the acetonide revealed to be troublesome, because of the eagerly isomerisable *cis*-enone into its related *trans*-isomer. According to Winssinger *et al.*, the *para*-EOM exhibited the most resistance to acidic cleavage, which constrained the reaction to be stopped before its completion (*e.g.* within 7h) in order to avoid the isomerisation of the *cis*-enone, affording the

expected L-783,277 in merely 50% yield. The other half amount was composed of the *ortho*-EOM protected analogue which was once again submitted to the same acidic deprotection, followed by a selective *para*-protection in the presence of diazomethane. In accordance with the preceding results published by the group of Hofmann,[68] the final product was, upon the isolation by HPLC, usually tainted with more than 5% of the supposed *trans*-isomer.

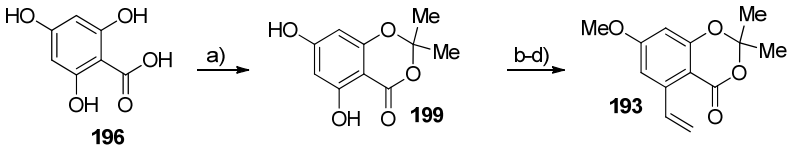
- **Synthesis by Sim *et al.***

The most recent total synthesis of L-783,277 (**7**) was published by Sim *et al.* in 2010.[72] The synthetic strategy relies on the introduction of the *anti*-diol configuration *via* the chiral pool *D*-mannitol, the Yamaguchi-based macrolactonisation and the built-in triple bond which would be later partially reduced into *Z*-alkene.



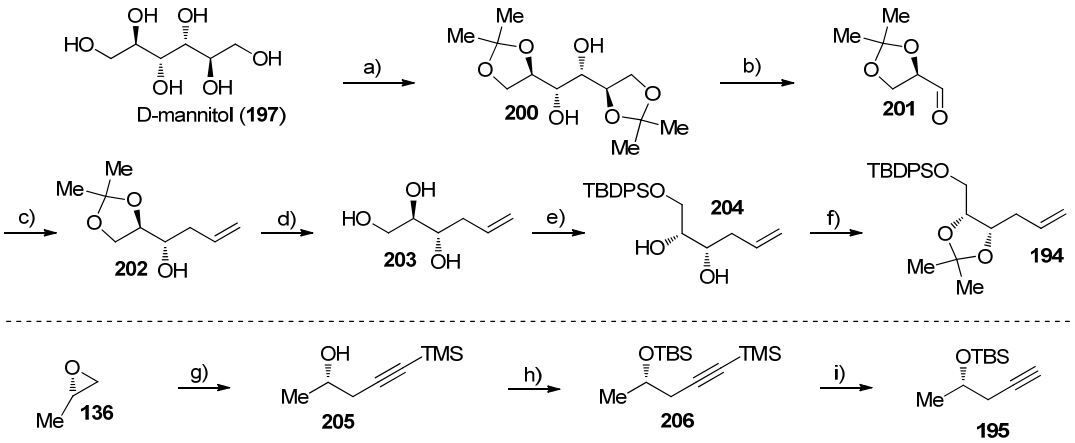
Scheme 29: Retrosynthesis of L-783,277 by Sim *et al.*

The resorcylic fragment **6** was prepared from commercially available 2,4,6-trihydroxybenzoic acid **196**, which was submitted to Danishefsky-based method to afford acetonide **3**, followed by a regioselective methylation and the formation of the corresponding triflate in order to carry out a Stille coupling reaction to provide styrene **193** (**scheme 29**).



Scheme 30 *Reagents and conditions:* a) TFAA, TFA, acetone, 45°C, 2d, 57%; b) MeOH, PPh_3, DIAD, THF, 0°C to RT, 82%; c) Tf_2O, pyridine, 0°C, 12h, 68%; d) $Pd(PPh_3)_4$, LiCl, (vinyl)$SnBu_3$, dioxane, 110°C, 2h, 75%

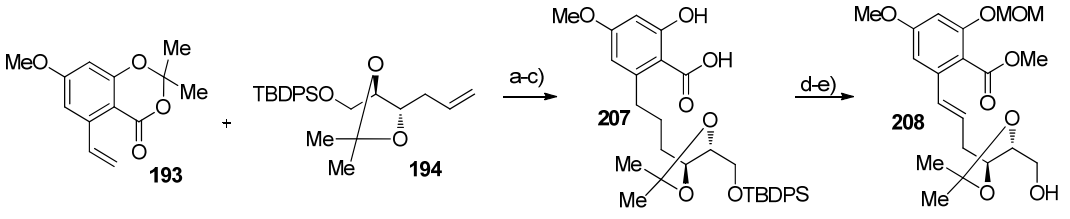
The vinyl fragment **194** containing the *anti*-diol was synthesised in 6 steps starting with D-mannitol (**197**) which gave according to well-known procedures enantiomerically pure D-*(R)*-glyceraldehyde acetonide **201** (**scheme 31**). The latter was subjected to an asymmetric Brown allylation, acetonide deprotection, TBDPSCl protection of the released primary alcohol to give **204**, which was then subjected to the re-protection of the *anti*-diol to provide the intermediate **194**.



Scheme 31 *Reagents and conditions:* a) 2,2-dimethoxypropane, $SnCl_2$, DME, reflux, 3 h, 36%; b) $NaIO_4$, DCM, H_2O, 20°C, 2 h, 94%; c) (-)-Ipc_2BOMe, allylMgBr, Et_2O, -78°C to r.t., 12 h; d) $AcOH/H_2O$ (4/1), r.t., 12 h, 56% over two steps; e) TBDPSCl, imidazole, DMF, r.t., 2 h, 74%; f) 2,2-dimethoxypropane, PPTS, DCM, r.t., 12 h, 93%

Reagents and conditions: g) TMS acetylene, BuLi, $BF_3.Et_2O$, THF, -78°C, 3 h, 50%; h) TBSCl, imidazole, DMF, r.t., 1 h; i) K_2CO_3, MeOH, r.t., 4 h, 93% over two steps

The enatiomerically pure **195** was prepared in 3 steps from the commercial (*S*)-propylene oxide **136** (**scheme 31**). The sequence commenced with the selective opening of **136** by lithium TMS acetylene in presence of $BF_3.Et_2O$, followed by TBS protection of **205** and selective demethylation to provide **195**.

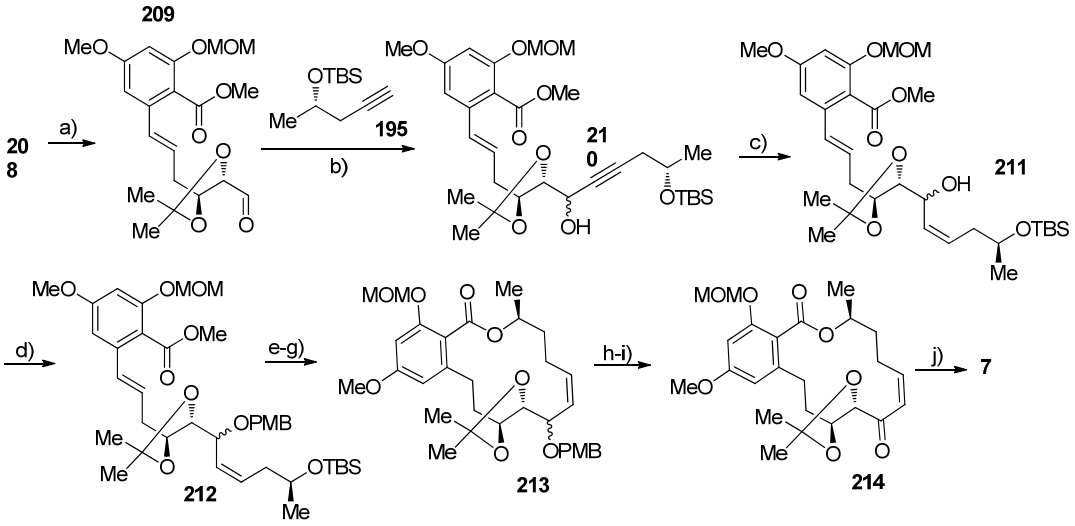


Scheme 32 *Reagents and conditions:* a) Grubbs II (**54**), toluene, 80°C, 1.5 days, 55%; b) Pd/C, H_2, EtOAc, r.t., 3.5 h, 60%; c) NaOMe, THF, 0°C to r.t., 15 min; d) MOMCl, DIPEA, DMF, r.t., 14 h, 59% over two steps; e) TBAF, THF, r.t., 2 h, 92%

Fragments **193** and **194** were connected by Grubbs II (**54**) catalyst cross olefin metathesis, followed by hydrogenation and exposure to sodium methoxide to furnish compound **207**

(**scheme 32**)**.** MOM protection of the phenol moiety and TBAF deprotection released the primary alcohol **208** in 59% over 2 steps.

The intermediate **208** was exposed to a Dess-Martin oxidation to smoothly provide aldehyde **209**, which reacted with the lithium acetylide derived from **195**, furnishing a 2:1 ratio diastereomeric mixture of compound **210**. Without further se*para*tion, both diastereomers of **210** was partially reduced into *Z*-olefin. The resulting allylic alcohol **211** was transformed in PMB ether **212**, before submission to TBAF to release the C10' alcohol. Subsequent saponification released the benzoic acid required for the macrolactonisation under Yamaguchi conditions (23% yield over 2 steps), completing the carbon frame **213** of the target molecule. It is worth mentioning that the similar strategy employed by Altmann, a Mitsunobu-based macrolactonisation gave a relatively better yield (59%).

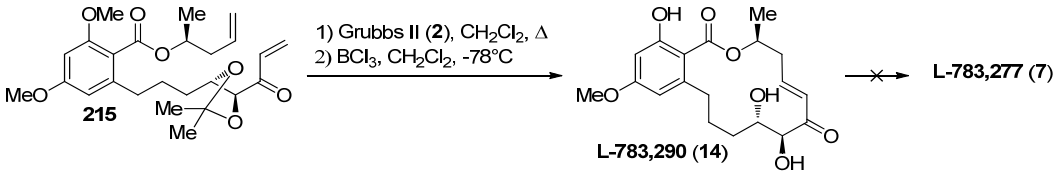


Scheme 33 *Reagents and conditions:* a) DMP, $NaHCO_3$, DCM, r.t., 3 h; b)BuLi, THF, -78°C, 2 h, 42% over two steps; c) Lindlar catalyst, quinoline, H_2, EtOAc, 1.5 h, 99%; d) PMB-Cl, NaI, NaH, DMF, 50°C, 5 h, 96%; e) TBAF, THF, r.t., 3 h, 86%; f) NaOH, EtOH/H_2O, 120°C, 8 h; g) 2,4,6-trichlorobenzoyl chloride, TEA, THF, r.t., 3 h then DMAP, toluene, reflux, 24 h, 23% over two steps; h) DDQ, DCM/H_2O, 5 h, 93%; i) DMP, $NaHCO_3$, DCM, r.t., 2 h, 72%; j) THF:H_2O:TFA (2:1:2), 2 h, 93%

The oxidative deprotection revealed the cis allylic enol which was successfully oxided by Dess-Martin periodinane into the corresponding *Z*-enone precursor **214**. Upon exposure of **214** to TFA, simultaneous cleavage of the acetonide and the MOM protecting groups (93% of yield) accomplished the third total synthesis of L-783,277 (**7**). Furthermore, the authors reported for the first time the optical rotation value of L-783,277 (**7**): $[\alpha]_D^{24,5}$ = +8.8° (*c* 0.5, $CHCl_3$).

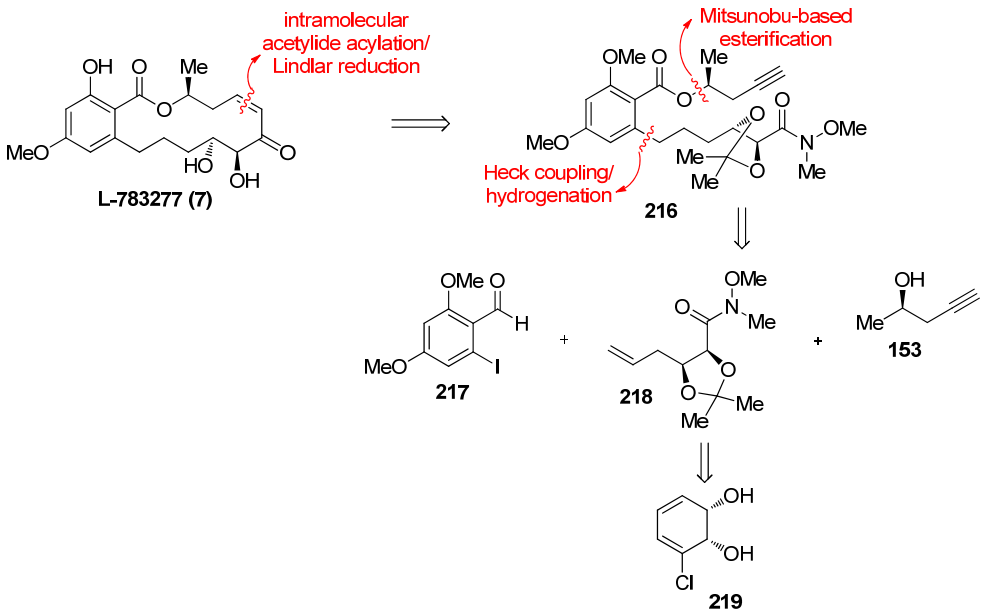
- **Synthesis by Banwell *et al.***

The latest synthesis targeting L-783,277 (**7**) has been disclosed by Banwell and collaborators.[73] Initially, the authors had succeeded in synthesising the co-metabolite L-783,290 (**14**) which contains a *trans*-enone instead of *cis*-enone like L-783,277 (**7**).[74] However, after fruitless attempts to photoisomerise **14** into **7** (**scheme 34**), the synthetic framework has been slightly modified in order to install the desired *Z*-alkene in a direct way.



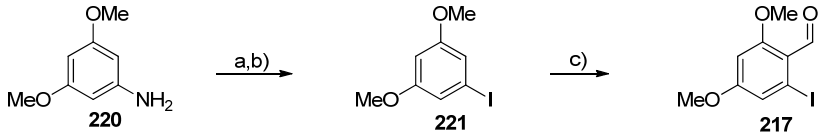
Scheme 34: Banwell's effort to photoisomerise the *trans*-isomer L-783,290 (**9**) into L-783,277 (**7**)

As illustrated in **scheme 35**, their synthesis is a modular one that combines three fragments corresponding to C1-C6 + C12 aromatic structure, C1'-C6' and C7'-O11' of L-783,277 (**7**). The C4'-C'5 diol configuration was induced by *cis*-1,2-dihydrocatechol **219** . The benzaldehyde **217** was connected to terminal alkene **218** *via* a Heck coupling, followed by hydrogenation of the C1'-C2' double bond. A Mitsunobu-based esterification, involving homopropargylic alcohol **153**, completed the pre*para*tion of precursor **216**. The ring-closure was performed by an intramolecular acetylide acylation and the subsequent Lindlar reduction revealed the desired *cis*-enone.



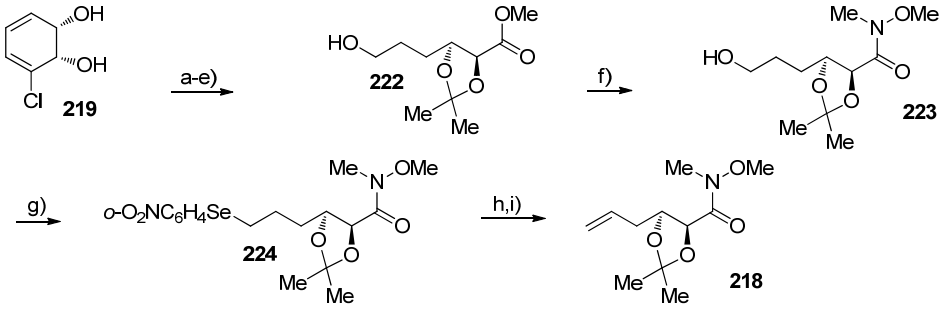
Scheme 35: Retrosynthesis of L-783,277 (**7**) by Banwell *et al.*

The benzaldehyde **217** was synthesised from the commercially available dimethoxyaniline **220**, which was first subjected to a Sandmeyer reaction, using potassium iodide as nucleophile to give **221** in 71% yield (**scheme 36**). The resulting iodide was engaged in a Vilsmeier-Haack reaction to give **217** (63%).



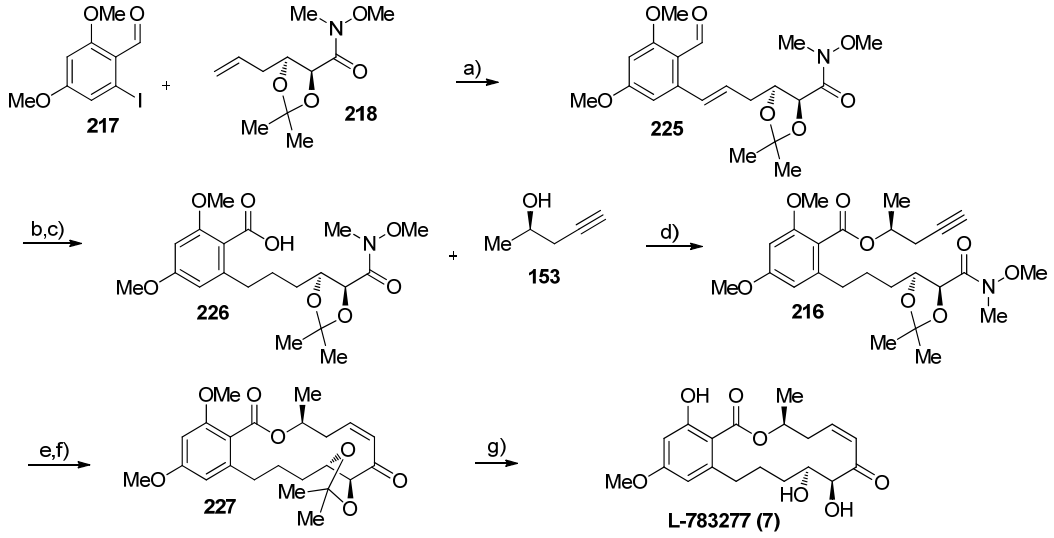
Scheme 36: **Synthesis of the aromatic core.***Reagents and conditions*: a) $NaNO_2$, H_2SO_4, -15°C, 3h; b) KI, H_2O, -15°C, 3h; c) DMF, $POCl_3$, 100°C, 5h

The C1'-C6' fragment was prepared from the enantiomerically pure catechol **219** (**scheme 37**). The non-chlorinated double bond was selectively hydrogenated in the presence of rhodium on alumina and the diol protected by dimethoxypropane. Reductive ozonolysis, followed by *in situ* sodium borohydride reduction and subjection to (MeO)MeNH.HCl in the presence of *i*-PrMgCl delivered the Weinreb amide **223**, which was directly converted to o-nitrophenylselenide **224** (89%). Oxidative elimination to reveal terminal alkene **218** was carried out in two steps, upon treatment of **224** with *m*-CPBA then O_2 in diethylamine.



Scheme 37: **Synthesis of C7'-O11' fragment.***Reagents and conditions:* a) H_2, Rh on Al_2O_3, MeOH, 18°C, 25min; e) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, 0°C, 0.5 h; f) O_3, pyr., MeOH, -78°C, 12 min; g) dimethylsulfur, 0°C, 2h; h) $NaBH_4$, 0°C, 1h; i) *i*-PrMgCl, (MeO)MeNH.HCl, THF, -15°C, 0.5h; j) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, 18°C, 1h; k) *m*-CPBA, CH_2Cl_2, -78°C, 0.25h; l) O_2, Et_2NH, 18°C, 3h.

The Heck coupling between **217** and **218** was achieved by heating a DMF solution of the substrates in the presence of $Pd(AcO)_2$, K_2CO_3, and TBAB at 80°C for 40h, providing a 8:1 mixture of product **225** and its *Z*-isomer in 56% combined yield (**scheme 38**). Pinnick oxidation and 10% palladium on charcoal assisted hydrogenation led to the saturated system **226**. Subjection of acid **226** to a Mitsunobu-based esterification with homopropargylic alcohol **153** gave the ester/amide **216** required for the pivotal ring-closure strategy. Intramolecular acetylide alkylation took place upon exposure of **216** to LiHMDS in THF at -35%, and a subsequent Lindlar reduction afforded the *Z*-enone. Protecting group removal with boron trichloride at -78°C, a method previously described by Winssinger's group for the same target,[62] accomplished the total synthesis of L-783,277 (**7**). However, the acid-sensitive *Z*-enone was partially isomerised into the more stable *E*-isomer, resulting in a *ca*. 4:1 mixture of L-783,277 (**7**) and L-783,290 (**14**).



Scheme 38: Assembly of three fragments and completion of L-783,277 (**7**). *Reagents and conditions*: a) $Pd(OAc)_2$, TBAB, K_2CO3, DMF, water, 80°C, 19h; b) $NaClO_2$, t-BuOH, NaH_2PO_4, 2,3-dimethylbutene; c) 10% Pd/C, H_2, 18°C, 48 h; d) DIAD, Ph_3P, PhMe, 0°C, 1h; e) LHMDS, THF, -35°C; f) $Pd/CaCO_3(Pb)$, H_2, py., toluene; g) BCl_3, CH_2Cl_2, -78°C.

1.3 Conclusion

Within 3 years, 4 accomplished syntheses have been disclosed for L-732,277 (**7**) as a consequence of extensive efforts to develop economical and adjustable routes to this *cis*-containing RAL and its analogues for further assessment of their biological activities.

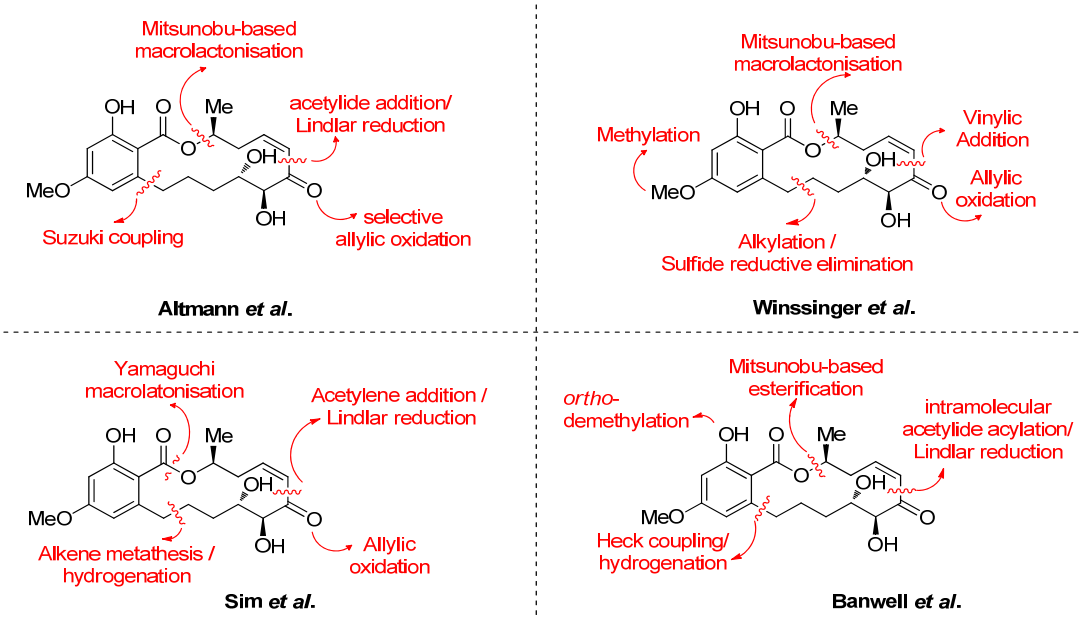


Figure 13: Retrosynthetic disconnections wielded on L-783,277 (**7**) in the literature

All the 4 routes opted for the connection of the target metabolite into 3 keys fragments: an aromatic core, a straight-chained fragment containing the anti-diol C4'-C5' and a segment bearing the appropriate configuration of C10'. With the exception of the approach by Banwell *et al.*, the other 3 syntheses bear a number of conceptually com*para*ble strategies. Macrolactonisation, either based on the classical Mitsunobu conditions or using Yamaguchi reagent, appears to be the most favored strategy to establish the ring structure (**figure 13**). Though the Winssinger's group has also proven the benzylic sulfoxide represented an effective ring-closure tool, this method precludes L-783,277 (**7**) as it leads to an unsaturated C1'-C2' bond. The same 3 groups also opted for a late-stage oxidation to restore the characteristic enone. Altmann *et al.* had attempted to selectively oxidize the enol, in competition with the C4'-C5' anti-diol, only to obtain the desired metabolite **7** from the less abundant triol isomer. Interestingly, the same observation was stated by Winssinger's group in their synthesis of LL-Z1640-2 (**8**).

The configuration of the *cis* double bond was determined by a partial reduction based on Lindlar's conditions by Altmann's, Sim's and Banwell's groups respectively. Nonetheless, Banwell and collaborators have auspiciously achieved the ring-closure *via* an intramolecular acetylide acylation followed by a Lindlar reduction, which simultaneously built the *cis*-enone. Altmann's and Winssinger's syntheses resorted to a Suzuki coupling and an alkylation/reductive elimination respectively to functionalise at the benzylic position. In a different manner, Sim's and Banwell's approaches employed an alkene metathesis and a Heck coupling, respectively to create first a C1'-C2' double bond, which was subsequently reduced.

The intrinsic *para*-methoxy had been introduced in distinct manners, taking into account the plausible interference with the *ortho*-phenol of the same target. Altmann's approach implicated an early orthogonal release of the *ortho*-phenol. Sim's synthesis opted for the final step to release the phenol, together with the *anti*-diol, while Winssinger's final target-releasing deprotection compelled a selective *ortho*-methylation. Banwell's synthesis ended with the selective mono-deprotection.

1.4 Research objectives

- **A modular and efficient synthetic route to L-783,277 (7)**

Our interest in L-783,277 (**7**) has been triggered by the anti-angiogenetic actitivity of this metabolite, originally disclosed by the group of Altmann in 2008.[71] While hypothemycin (**6**) and LL-Z1640-2 (**3**) have much earlier attracted the attention of organic chemists, at the time of our first envisaged synthesis targeting (**7**) in 2009, this metabolite appeared in only 2 total syntheses.[62, 68]

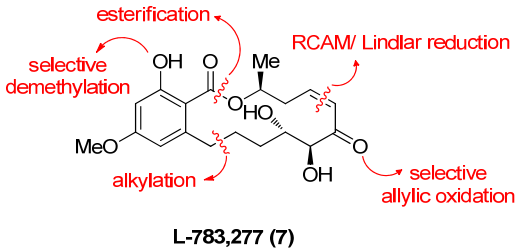
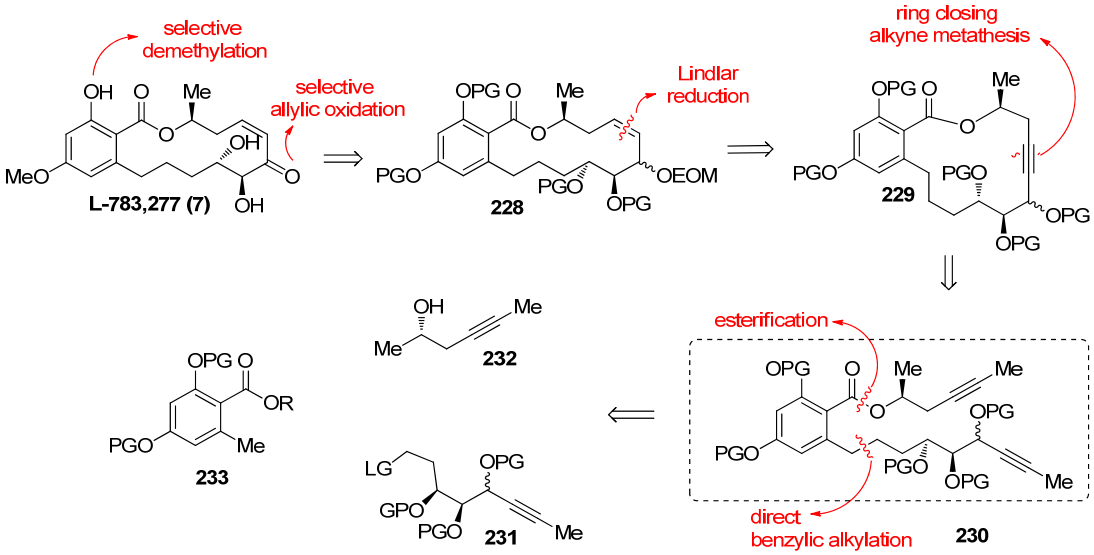


Figure 14: Our initial disconnections of L-783,277 (**7**)

Retrosynthetically, it seemed to be judicious to disconnect the target molecule **7** also into 3 fragments: one aromatic core **233**, one straight-chained segment containing the C4'-C5' anti diol **231** and another one bearing the asymmetric C10' **232** (**scheme 39**).



Scheme 39: Three synthons required for the construction of L-783,277 (**7**)

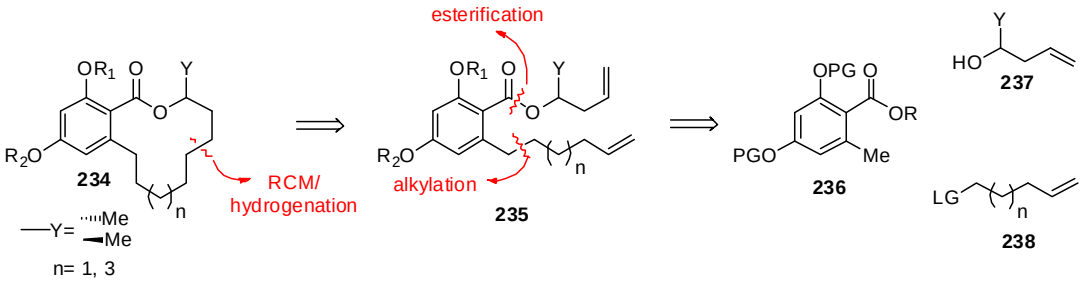
Conceptually different from Winssinger's strategy, we aspired to carry out a more direct alkylation at the benzylic position, in view of abbre*via*ting the final route. This approach was expected to be quite time-and effort-consuming to fine-tune the alkylation conditions.

Besides, an esterification was thought to link the northern fragment to the aromatic core.

Before the disclosure of the *trans*-isomer of L-783,277 (**7**) by Banwell and collaborators in 2010 which had recourse to a RCM for the ring-closure, a late-stage macrolactonisation had prevailed. Independently, we aimed to achieve the cyclisation of the 14-membered ring by a RCAM and a subsequent partial reduction to reveal the *cis* double bond. A selective oxidation of allylic alcohol would complete the construction of the well-known acid-sensitive *cis*-enone, at the most remote step as possible. And a selective demethylation would reach the end of our synthetic pathway.

As a consequence of this retrosynthetic plan, the construction of the dialkyne precursor with strategically appropriate protecting groups was pivotal, as it would lay the foundation for further study of RCAM as a novel ring-closure for *cis*-enone containing RALs.

- **Application to other natural RALs and analogues**



Scheme 40: General synthetic scheme for RALs without *cis*-enone

From a broader point of view, the abovementioned synthetic pattern could be exploited for the syntheses of other RALs, especially those bearing a saturated C1'-C2' bond (*e.g. (R)*-(+)-lasiodiplodin (**10**) as the most uncomplicated 12-membered macrolactone).

Fundamentally based on the strategies targeting the synthesis of L-783,277 (**7**), the retrosynthesis of the simplified lactone **234**, as depicted in **scheme 40**, encompasses the assembly of three se*para*te segments: an aromatic core **236** derived from orsellinic acid, and two straight-chained fragments **237** and **238** containing each a terminal alkene. The first assembly would result from the application of our strategic direct alkylation at the benzylic position of **236**, to which **238** would be anchored. An esterification between the resulting alkylation product and the last fragment **237** and a subsequent RCM would complete the carbon framework of the target macrolactone.

This synthetic approach is rather modular in various aspects, such as the insertion of either a double bond (resulting from the RCM) or simply a saturated bond instead, *via* a subsequent hydrogenation. Moreover, a *Z*-alkene would also be at reach through a RCAM followed by a Lindlar reduction of the newly formed triple bond, as described for the retrosynthesis of L-783,277 (**7**).

In case our crucial step, the direct benzylic alkylation, takes effect, the previous synthetic pathway would give straightforward access to various RALs, as well as their ananogues. And to the greatest extent, incorporating this step into a synthetic pathway would considerably shorten the number of transformations, and thus contribute to the elaboration of very concise and efficient syntheses.

1.5 List of references

1. Hertweck, C., The Biosynthetic Logic of Polyketide Diversity. *Angewandte Chemie International Edition* **2009**, *48* (26), 4688-4716.
2. Bräse, S.; Gläser, F.; Kramer, C.; Lindner, S.; Linsenmeier, A.; Masters, K.-S.; Meister, A.; Ruff, B.; Zhong, S., Resorcylic Acid Lactones. In *The Chemistry of Mycotoxins*, Springer Vienna: 2013; Vol. 97, pp 91-108.
3. Delmotte, P.; Delmotte-Plaquee, J., A new antifungal substance of fungal origin. *Nature (London, U. K.)* **1953**, *171*, 344.
4. Mirrington, R. N.; Ritchie, E.; Shoppee, C. W.; Taylor, W. C.; Sternhell, S., Constitution of radicicol. *Tetrahedron Lett.* **1964**,, 365-70.
5. McCapra, F.; Scott, A. I.; Delmotte, P.; Delmotte-Plaquee, J.; Bhacca, N. S., Constitution of monorden, an antibiotic with tranquilizing action. *Tetrahedron Lett.* **1964**,, 869-75.
6. Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G., Isolation of an anabolic, uterotrophic compound from corn infected with Gibberella zeae. *Nature (London, U. K.)* **1962**, *196*, 1318.
7. Ellestad, G. A.; Lovell, F. M.; Perkinson, N. A.; Hargreaves, R. T.; McGahren, W. J., New zearalenone related macrolides and isocoumarins from an unidentified fungus. *J. Org. Chem.* **1978**, *43*, 2339-43.
8. Mirocha, C. J.; Schauerhamer, B.; Christensen, C. M.; Niku-Paavola, M. L.; Nummi, M., Incidence of zearalenol (Fusarium mycotoxin) in animal feed. *Appl. Environ. Microbiol.* **1979**, *38*, 749-50.
9. (a) Nair, M. S. R.; Carey, S. T., Metabolites of pyrenomycetes. XIII. Structure of (+)-hypothemycin, an antibiotic macrolide from Hypomyces trichothecoides. *Tetrahedron Lett.* **1980**, *21*, 2011-12; (b) Nair, M. S. R.; Carey, S. T.; James, J. C., Metabolites of pyrenomycetes. XIV. Structure and partial stereochemistry of the antibiotic macrolides hypothemycin and dihydrohypothemycin. *Tetrahedron* **1981**, *37*, 2445-9.
10. (a) Kwon, H. J.; Yoshida, M.; Abe, K.; Horinouchi, S.; Beppu, T., Radicicol, an agent inducing the reversal of transformed phenotypes of src-transformed fibroblasts. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 538-9; (b) Kwon, H. J.; Yoshida, M.; Fukui, Y.; Horinouchi, S.; Beppu, T., Potent and specific inhibition of p60v-src protein kinase both in vivo and in vitro by radicicol. *Cancer Res* **1992**, *52*, 6926-30.
11. (a) Schulte, T. W.; Akinaga, S.; Soga, S.; Sullivan, W.; Stensgard, B.; Toft, D.; Neckers, L. M., Antibiotic radicicol binds to the N-terminal domain of Hsp90 and shares important biologic activities with geldanamycin. *Cell Stress Chaperones* **1998**, *3*, 100-108; (b) Sharma, S. V.; Agatsuma, T.; Nakano, H., Targeting of the protein chaperone, HSP90, by the transformation suppressing agent, radicicol. *Oncogene* **1998**, *16*, 2639-2645.
12. Kamal, A.; Thao, L.; Sensintaffar, J.; Zhang, L.; Boehm, M. F.; Fritz, L. C.; Burrows, F. J., A high-affinity conformation of Hsp90 confers tumor selectivity on Hsp90 inhibitors. *Nature (London, U. K.)* **2003**, *425*, 407-410.
13. Avruch, J., MAP kinase pathways: The first twenty years. *Biochim. Biophys. Acta, Mol. Cell Res.* **2007**, *1773*, 1150-1160.
14. Pearson, G.; Robinson, F.; Gibson, T. B.; Xu, B.-E.; Karandikar, M.; Berman, K.; Cobb, M. H., Mitogen-activated protein (MAP) kinase pathways: Regulation and physiological functions. *Endocr. Rev.* **2001**, *22*, 153-183.

15. Keshet, Y.; Seger, R., The MAP kinase signaling cascades: a system of hundreds of components regulates a diverse array of physiological functions. *Methods Mol. Biol. (N. Y., NY, U. S.)* **2010**, *661*, 3-38.

16. Chang, L.; Karin, M., Mammalian MAP kinase signalling cascades. *Nature (London, U. K.)* **2001**, *410*, 37-40.

17. Williams, D. H.; Wilkinson, S. E.; Purton, T.; Lamont, A.; Flotow, H.; Murray, E. J., Ro 09-2210 exhibits potent anti-proliferative effects on activated T cells by selectively blocking MKK activity. *Biochemistry* **1998**, *37*, 9579-9585.

18. Zhao, A.; Lee, S. H.; Mojena, M.; Jenkins, R. G.; Patrick, D. R.; Huber, H. E.; Goetz, M. A.; Hensens, O. D.; Zink, D. L.; Vilella, D.; Dombrowski, A. W.; Lingham, R. B.; Huang, L., Resorcylic acid lactones: Naturally occurring potent and selective inhibitors of MEK. *Journal of Antibiotics* **1999**, *52* (12), 1086-1094.

19. Kastelic, T.; Schnyder, J.; Leutwiler, A.; Traber, R.; Streit, B.; Niggli, H.; Mackenzie, A.; Cheneval, D., Induction of rapid IL-1β mRNA degradation in THP-1 cells mediated through the Au-rich region in the 3'UTR by a radicicol analog. *Cytokine* **1996**, *8*, 751-761.

20. Dakas, P. Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winssinger, N., Modular synthesis of radicicol A and related resorcylic acid lactones, potent kinase inhibitors. *Angewandte Chemie - International Edition* **2007**, *46* (36), 6899-6902.

21. Ninomiya-Tsuji, J.; Kajino, T.; Ono, K.; Ohtomo, T.; Matsumoto, M.; Shiina, M.; Mihara, M.; Tsuchiya, M.; Matsumoto, K., A Resorcylic Acid Lactone, 5Z-7-Oxozeaenol, Prevents Inflammation by Inhibiting the Catalytic Activity of TAK1 MAPK Kinase Kinase. *J. Biol. Chem.* **2003**, *278*, 18485-18490.

22. Ohori, M.; Kinoshita, T.; Yoshimura, S.; Warizaya, M.; Nakajima, H.; Miyake, H., Role of a cysteine residue in the active site of ERK and the MAPKK family. *Biochem. Biophys. Res. Commun.* **2007**, *353*, 633-637.

23. Schirmer, A.; Kennedy, J.; Murli, S.; Reid, R.; Santi, D. V., Targeted covalent inactivation of protein kinases by resorcylic acid lactone polyketides. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 4234-4239.

24. Rastelli, G.; Rosenfeld, R.; Reid, R.; Santi, D. V., Molecular modeling and crystal structure of ERK2-hypothemycin complexes. *J. Struct. Biol.* **2008**, *164*, 18-23.

25. Jogireddy, R.; Dakas, P. Y.; Valot, G.; Barluenga, S.; Winssinger, N., Synthesis of a Resorcylic Acid Lactone (RAL) library using fluorous-mixture synthesis and profile of its selectivity against a panel of kinases. *Chemistry - A European Journal* **2009**, *15* (43), 11498-11506.

26. Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y., Aigialomycins A-E, new resorcylic macrolides from the marine mangrove fungus Aigialus parvus. *J. Org. Chem.* **2002**, *67*, 1561-1566.

27. Barluenga, S.; Dakas, P.-Y.; Ferandin, Y.; Meijer, L.; Winssinger, N., Modular asymmetric synthesis of aigialomycin D, a kinase-inhibitory scaffold. *Angew. Chem., Int. Ed.* **2006**, *45*, 3951-3954.

28. Hellwig, V.; Mayer-Bartschmid, A.; Mueller, H.; Greif, G.; Kleymann, G.; Zitzmann, W.; Tichy, H.-V.; Stadler, M., Pochonins A-F, new antiviral and anti*para*sitic resorcylic acid lactones from Pochonia chlamydosporia var. catenulata. *J. Nat. Prod.* **2003**, *66*, 829-837.

29. Barluenga, S.; Moulin, E.; Lopez, P.; Winssinger, N., Solution- and solid-phase synthesis of radicicol (monorden) and pochonin C. *Chem. - Eur. J.* **2005**, *11*, 4935-4952.

30. Moulin, E.; Barluenga, S.; Winssinger, N., Concise synthesis of pochonin A, an HSP90 inhibitor. *Org Lett* **2005**, *7*, 5637-9.

31. Xu, L.; He, Z.; Xue, J.; Chen, X.; Wei, X., β-Resorcylic acid lactones from a Paecilomyces fungus. *Journal of natural products* **2010**, *73* (5), 885-889.

32. Shao, C.-L.; Wu, H.-X.; Wang, C.-Y.; Liu, Q.-A.; Xu, Y.; Wei, M.-Y.; Qian, P.-Y.; Gu, Y.-C.; Zheng, C.-J.; She, Z.-G.; Lin, Y.-C., Potent Antifouling Resorcylic Acid Lactones from the Gorgonian-Derived Fungus Cochliobolus lunatus. *Journal of natural products* **2011**, *74* (4), 629-633.

33. Gao, J.; Radwan, M. M.; León, F.; Dale, O. R.; Husni, A. S.; Wu, Y.; Lupien, S.; Wang, X.; Manly, S. P.; Hill, R. A.; Dugan, F. M.; Cutler, H. G.; Cutler, S. J., Neocosmospora sp.-Derived Resorcylic Acid Lactones with in Vitro Binding Affinity for Human Opioid and Cannabinoid Receptors. *Journal of natural products* **2013**, *76* (5), 824-828.

34. Xu, J.; Jiang, C.-s.; Zhang, Z.-l.; Ma, W.-q.; Guo, Y.-w., Recent progress regarding the bioactivities, biosynthesis and synthesis of naturally occurring resorcinolic macrolides. *Acta Pharmacol. Sin.* **2014**, *35*, 316-330.

35. Girotra, N. N.; Wendler, N. L., New total synthesis of the macrolide zearalenone. *Chem. Ind. (London)* **1967**,, 1493.

36. Baggelaar, M. P.; Huang, Y.; Feringa, B. L.; Dekker, F. J.; Minnaard, A. J., Catalytic asymmetric total synthesis of (S)-(-)-zearalenone, a novel lipoxygenase inhibitor. *Bioorg. Med. Chem.* **2013**, *21*, 5271-5274.

37. Corey, E. J.; Nicolaou, K. C., Efficient and mild lactonization method for the synthesis of macrolides. *J. Am. Chem. Soc.* **1974**, *96*, 5614-16.

38. Masamune, S.; Kamata, S.; Schilling, W., Syntheses of macrolide antibiotics. III. Direct ester and lactone synthesis from S-tert-butyl thioate (thiol ester). *J. Am. Chem. Soc.* **1975**, *97*, 3515-16.

39. Hitchcock, S. A.; Pattenden, G., Synthesis of macrocycles *via* allylic radical intermediates. A total synthesis of (-)-zearalenone. *Tetrahedron Lett.* **1990**, *31*, 3641-4.

40. Solladie, G., Chiral sulfoxides and low-valent titanium in asymmetric total synthesis of natural products. *Bull. Soc. Chim. Belg.* **1990**, *99*, 837-47.

41. Kalivretenos, A.; Stille, J. K.; Hegedus, L. S., Synthesis of β-resorcylic macrolides *via* organopalladium chemistry. Application to the total synthesis of (S)-zearalenone. *J. Org. Chem.* **1991**, *56*, 2883-94.

42. Furstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B., Total syntheses of (S)-(-)-zearalenone and lasiodiplodin reveal superior metathesis activity of ruthenium carbene complexes with imidazol-2-ylidene ligands. *J Org Chem* **2000**, *65*, 7990-5.

43. Taub, D.; Girotra, N. N.; Hoffsommer, R. D., Jr.; Kuo, C.-H.; Slates, H. L.; Weber, S.; Wendler, N. L., Total synthesis of the macrolide, zearalenone. *Tetrahedron* **1968**, *24*, 2443-61.

44. Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Brackow, J.; Barrett, A. G. M., Biomimetic synthesis of resorcylate natural products utilizing late stage aromatization: Concise total syntheses of the marine antifungal agents 15G256ι and 15G256β. *J. Am. Chem. Soc.* **2008**, *130*, 10293-10298.

45. Miyatake-Ondozabal, H.; Barrett, A. G. M., A novel biomimetic synthesis of (S)-(-)-zearalenone: *via* macrocyclization and transannular aromatization. *Tetrahedron* **2010**, *66*, 6331-6334.

46. Napolitano, C.; McArdle, P.; Murphy, P. V., Access to Resorcylic Acid Lactones *via* Phosphonate Based Intramolecular Olefination. *J. Org. Chem.* **2010**, *75*, 7404-7407.
47. Yadav, J.; Murthy, P., A Concise Total Synthesis of (S)-Zearalenone and Zeranol. *Synthesis* **2011**, *2011* (13), 2117-2124.
48. Vintonyak, V. V.; Maier, M. E., Total synthesis of cruentaren A. *Angewandte Chemie - International Edition* **2007**, *46* (27), 5209-5211.
49. Rink, C.; Sasse, F.; Zubriene, A.; Matulis, D.; Maier, M. E., Probing the Influence of an Allylic Methyl Group in Zearalenone Analogs on Binding to Hsp90. *Chem. - Eur. J.* **2010**, *16*, 14469-14478, S14469/1-S14469/56.
50. Winssinger, N.; Barluenga, S., Chemistry and biology of resorcylic acid lactones. *Chem. Commun. (Cambridge, U. K.)* **2007**,, 22-36.
51. Ting, S. Z. Y.; Baird, L. J.; Dunn, E.; Hanna, R.; Leahy, D.; Chan, A.; Miller, J. H.; Teesdale-Spittle, P. H.; Harvey, J. E., Synthesis of diastereomeric, deoxy and ring-expanded sulfone analogues of aigialomycin D. *Tetrahedron* **2013**, *69*, 10581-10592.
52. Geng, X.; Danishefsky, S. J., Total Synthesis of Aigialomycin D. *Org. Lett.* **2004**, *6*, 413-416.
53. Calo, F.; Richardson, J.; Barrett, A. G. M., Total Synthesis of Aigialomycin D using a One-Pot Ketene Generation-Trapping-Aromatization Sequence. *Org. Lett.* **2009**, *11*, 4910-4913.
54. Martin, J. C.; Arhart, R. J., Sulfuranes. III. Reagent for the dehydration of alcohols. *J. Amer. Chem. Soc.* **1971**, *93*, 4327-9.
55. Lu, J.; Ma, J.; Xie, X.; Chen, B.; She, X.; Pan, X., Enantioselective total synthesis of aigialomycin D. *Tetrahedron: Asymmetry* **2006**, *17*, 1066-1073.
56. Zhang, J.; Yang, P. L.; Gray, N. S., Targeting cancer with small molecule kinase inhibitors. *Nat. Rev. Cancer* **2009**, *9*, 28-39.
57. Manning, G.; Whyte, D. B.; Martinez, R.; Hunter, T.; Sudarsanam, S., The protein kinase complement of the human genome. *Science* **2002**, *298*, 1912-34.
58. Nair, M.; Carey, S. T., Metabolites of pyrenomycetes XIII: Structure of (+)hypothemycin, an antibiotic macrolide from Hypomyces trichothecoides. *Tetrahedron Lett* **1980**, *21*, 2011-2.
59. Tatsuta, K.; Takano, S.; Sato, T.; Nakano, S., The first total synthesis of a macrocyclic anti-protozoan, LL-Z1640-2. *Chem. Lett.* **2001**,, 172-173.
60. Selles, P.; Lett, R., Convergent stereospecific synthesis of C292 (or LL-Z1640-2), and hypothemycin. Part 1. *Tetrahedron Lett.* **2002**, *43*, 4621-4625.
61. Dakas, P. Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N., Divergent syntheses of resorcylic acid lactones: L-783277, LL-Z1640-2, and hypothemycin. *Chemistry - A European Journal* **2009**, *15* (43), 11490-11497.
62. Miyatake-Ondozabal, H.; Barrett, A. G. M., Total Synthesis of TAK-Kinase Inhibitor LL-Z1640-2 *via* Consecutive Macrocyclization and Transannular Aromatization. *Org. Lett.* **2010**, *12*, 5573-5575.
63. LeClair, C. A.; Boxer, M. B.; Thomas, C. J.; Maloney, D. J., Total synthesis of LL-Z1640-2 utilizing a late-stage intramolecular Nozaki-Hiyama-Kishi reaction. *Tetrahedron Lett.* **2010**, *51*, 6852-6855.
64. Henry, N.; Robertson, M. N.; Marquez, R., Fast and efficient synthesis of the complete LL-Z1640-2 framework. *Tetrahedron Lett.* **2007**, *48*, 6088-6091.

65. Agatsuma, T.; Takahashi, A.; Kabuto, C.; Nozoe, S., Revised structure and stereochemistry of hypothemycin. *Chem. Pharm. Bull.* **1993**, *41*, 373-5.

66. Selles, P.; Lett, R., Convergent stereospecific synthesis of LL-Z1640-2 (or C292), hypothemycin and related macrolides. Part 2. *Tetrahedron Lett.* **2002**, *43*, 4627-4631.

67. Hofmann, T.; Altmann, K. H., Total synthesis of the resorcylic lactone-based kinase inhibitor L-783277. *Synlett* **2008**, (10), 1500-1504.

68. Dombrowski, A.; Jenkins, R.; Raghoobar, S.; Bills, G.; Polishook, J.; Pelaez, F.; Burgess, B.; Zhao, A.; Huang, L.; Zhang, Y.; Goetz, M., Production of a family of kinase-inhibiting lactones from fungal fermentations. *J. Antibiot.* **1999**, *52*, 1077-1088.

69. Liniger, M.; Neuhaus, C.; Hofmann, T.; Fransioli-Ignazio, L.; Jordi, M.; Drueckes, P.; Trappe, J.; Fabbro, D.; Altmann, K. H., Kinase inhibition by deoxy analogues of the resorcylic lactone L-783277. *ACS Medicinal Chemistry Letters* **2011**, *2* (1), 22-27.

70. Hofmann, T. Resorcylic Lactone L-783277 as a New Lead Structure for kinase Inhibition-Total Synthesis and SAR Studies. Dissertation, ETH Zürich, 2009.

71. Choi, H. G.; Son, J. B.; Park, D. S.; Ham, Y. J.; Hah, J. M.; Sim, T., An efficient and enantioselective total synthesis of naturally occurring L-783277. *Tetrahedron Lett.* **2010**, *51* (38), 4942-4946.

72. Lin, A.; Willis, A. C.; Banwell, M. G., An enantioselective synthesis of the resorcylic acid lactone L-783,277 *via* addition of an acetylide anion to a tethered weinreb amide. *Heterocycles* **2010**, *82* (1), 313-318.

73. Lin, A.; Willis, A. C.; Banwell, M. G., A chemoenzymatic and enantioselective total synthesis of the resorcylic acid lactone L-783,290, the trans-isomer of L-783,277. *Tetrahedron Lett.* **2010**, *51* (7), 1044-1047.

Chapter 2

TOWARDS THE TOTAL SYNTHESIS L-783,277 (7)

2 TOWARDS THE TOTAL SYNTHESIS OF L-783,277 (7)

2.1 Strategies for the synthesis of L-783,277 (7)

All the four aforementioned syntheses were flawless proofs of highly convergent and concise strategies, based on modern chemistry, and propulsed by the report of the high potential against MEK (IC_{50} =4 nM) of L-783,277 (**7**) by Zhao *et al.*,.[1] Like other members of the *cis*-enone containing subfamily, L-783,277 (**7**) owes its irreversible inhibition of kinase to the 1,4-addition of a properly located Cys residue inside the ATP-binding pocket to the inherent *cis*-enone. The presence of this functional group is not only crucial for the biological activities of these macrolides, but also stimulating from a synthetic point of view.

The biological activity due to this *cis*-enone has been supported by comprehensive studies of the mode of action of hypothemycin (**6**) by Schirmer *et al.*.[2] This is in great agreement with the weak inhibition potential of MEK 1 (IC_{50} =300 nM) by the natural *trans*-isomer of L-783,277 (**7**).[3] More recently, Altmann's group has also disclosed that the lack of C5' alcohol does not deprive **7** of its inhibition of a panel of kinases, as part of an extensive study of **7** analogues after their discovery of the anti-angiogenetic potential of L-783,277 (**7**). [4]

For these reasons, several total synthesis chemists have chosen L-783,277 (**7**) as target, in quest of an elegantly efficient synthetic pattern towards **7** and its analogues for further assessment of their promising biological profile. So have we.

Our first synthetic scheme for the metabolite L-783,277 (**7**) was devised in 2009, right after the publication of the second synthesis of **7** by Winssinger *et al.*[5]

At the time, we envisioned to tackle the formal synthesis of L-783,277 (**7**) *via* the fully protected intermediate **239** with a convergent synthetic route, which highlights a RCAM combined with subsequent Lindlar reduction as a reliable macrocyclisation method. As previously mentioned, the *cis*-enone's construction would be crucial, due to the greater stability of the *trans*-enone isomer, thus the easy isomerisation, especially by using the traditional alkene metathesis catalysts, *e.g*. 2nd generation Grubbs catalyst (**54**) within macrocycles of more than 12 members.

Though in the synthesis of cruentaren A accomplished by Kusuma, Brandt and Blagg,[6] the *cis*-olefin containing macrocycle was obtained in diastereomerically pure form (2nd generation Grubbs catalyst (**54**) 5%, CH_2Cl_2, 0°C-RT, 3h30, 78%), the use of RCM had not been depicted in the literature for 14-membered macrolactones until the advent of *Z*-selective catalysts discovered by the group of Schrock in 2011.[7] Besides, to preserve an early-stage, though masked, *cis*-enone throughout the synthetic sequence seemed to be risky and this would confine our strategies to some selectively mild conditions, due to the ready isomerisation of the double bond. Nevertheless, our research work had been far too advanced in the direction of the RCAM strategy at the time of the publication of the new *Z*-selective metathesis catalysts. Nevetheless, we considered a second way of synthesis including a selective *Z*-alkene RCM once the initial formal synthesis would have been successfully fulfilled.

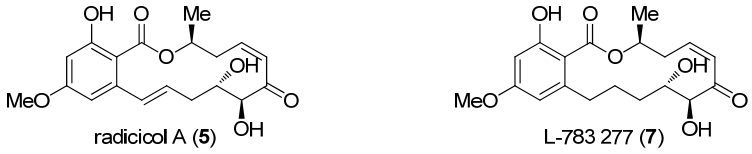
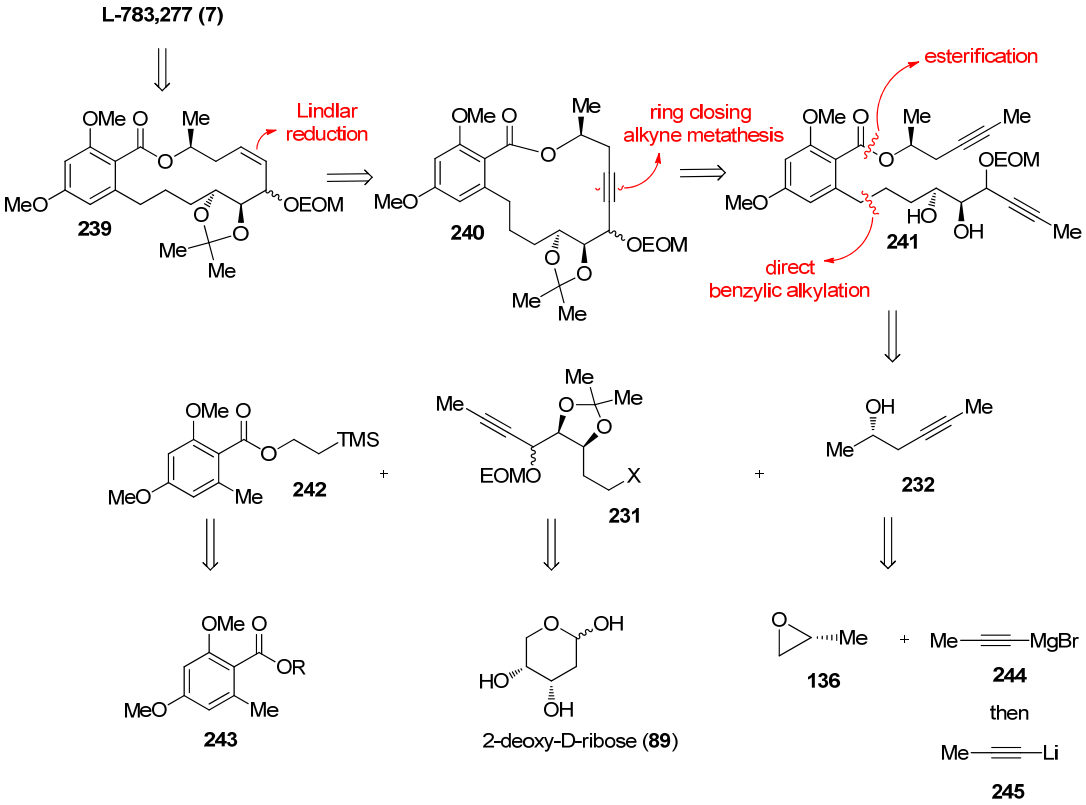


Figure 15: Structures of radicicol A (**5**) and L-783,277 (**7**)

Retrosynthetically, the macrolactone could be disconnected into 3 relatively similar sections: the aromatic core **242**, the polyol **231** and the propargylic alcohol **232 (scheme 41)**. Given the highly similar structure of L-783,277 (**7**) to that of radicicol A (**5**) (**figure 15**), and our priority in attaining in the shortest way the dialkyne precursor **241**, desired platform for our key step RCAM, the pre*para*tion of the building blocks **242** and **231** was conveniently based on some syntheses described by the group of Winssinger.[8] The protected aromatic acid **242** would derive from the commercially available methylated orsellinic acid **243**, while the assembly of intermediate **231** would start with the natural chiral pool 2-deoxy-D-ribose (**89**), containing the right configuration of the *anti*-diol.



Scheme 41: 1st generation retrosynthesis of L-783,277 (**7**)

The building block **232** was planned to result from the selective opening of the enantiomerically pure *(S)*-(-)-propylene oxide (**136**) in the presence of the commercial prop-1-yn-1-ylmagnesium bromide **245**. With all the three fragments in hand, the first connection would be worked out through a direct alkylation at benzylic position between the protected ester **242** and the polyol **231**, whose leaving group was still to be fine-tuned. It was decided to transform the methylated orsellinic acid into TMSE ester in the first place for the

deprotonation at benzylic acid, for fear of a possibly competitive nucleophilic attack from the carboxylate onto the polyol **231**. The success of this pivotal step would provide a fairly concise synthetic sequence, without additional steps to obtain a benzylic sulfide, in view of stabilising the derived anion of **242**, as in the strategy of Winssinger *et al.*[9]

The esterification was in the first place outlined to proceed, as commonly described in the literature, between the acid halide derived from the earlier funtionalised orsellinic acid as electrophile (*e.g*. in the presence of cyanuric fluoride[10]), and the secondary alcohol **232** as nucleophile. This seemingly easy step then turned out to be unexpectedly troublesome, a point that would be discussed in more details in the next chapter.

Since the RCAM was introduced as a pivotal step towards the total synthesis of sophorolipid lactone by the research group of Fürstner in 2000,[11] which has led many total syntheses projects to accomplishment, *e.g*. the total synthesis of cruentaren A,[10] it would be judicious to make use of some commercially available Fürstner's catalysts, and contingently, the commercial Schrock catalyst for alkyne metathesis. The Lindlar reduction would be either conducted under classical conditions or under continuous conditions *via* automatic *via* H-cube®, according to some readily defined conditions from our research group. For example, a standard Lindlar hydrogenation could also be conducted in the flask, using the same conditions described by the group of Fürstner for their successful reduction of cyclic alkynes into macrocyclic *Z*-alkenes, *e.g.* the last step completing the total synthesis of marine natural product (-)-prostaglandin E_2-1,15-lactone.[12]

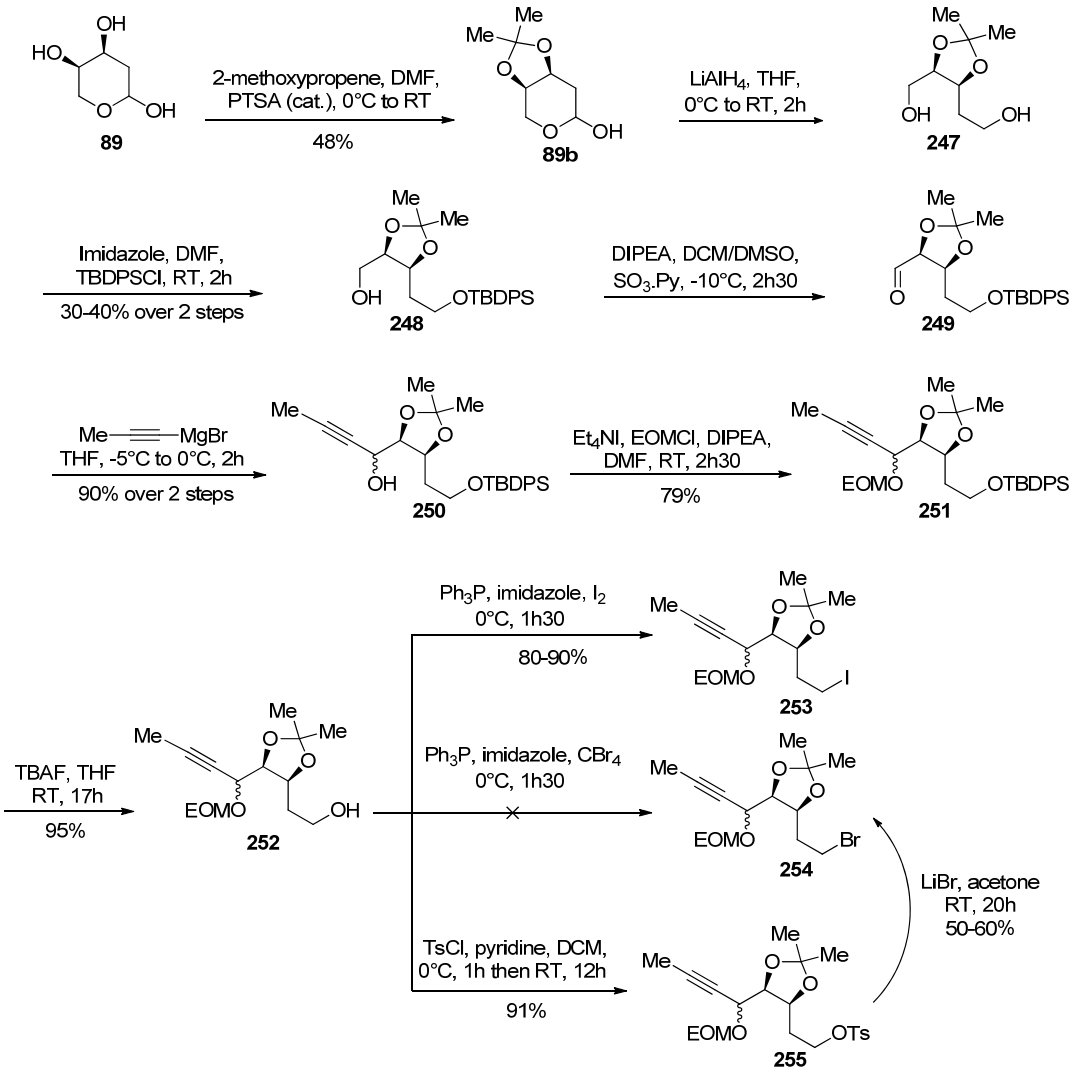
The attainment of the *Z*-selective partial reduction would lead to the formation of precursor **239**, which would be totally protected. The choice of all these protecting groups was originally based on the readily existing precursors within the total syntheses of the same natural product,[9, 13] and other resorcylides of the same family, namely radicicol A (**5**).[8] Actually, the relatively unstable *cis*-enone would naturally be introduced at the very last stage of the synthesis, a strategy which was already accomplished by Hoffmann and Altmann.[14] However, to carry out a direct benzylic alkylation in the presence of an appropriately strong base, the protection of both phenols of the aromatic core were compelling.

2.2 Construction of the building blocks

2.2.1 Polyol fragment

2.2.1.1 First generation strategy: "2-deoxy-D-ribose approach"

With the objective of attaining the first series of synthon **231** (**scheme 41**) in mind, we opted for the pre*para*tion of compound **248** as a conveniently reachable intermediate to found basement for our synthesis of alcohol **248** (**scheme 42**). Indeed, this precursor intersects our synthetic route with the one leading to the total synthesis of radicicol A (**5**) by Winssinger and collaborators in 2007.[15]



Scheme 42: Synthesis of fragment **3** from 2-deoxy-D-ribose (**89**)

The synthesis of the polyketide sector commenced with the protection of 2-deoxy-D-ribose (**89**) with 2-methoxypropene catalysed by PTSA in DMF. The purification required assiduous

labour, due to the viscous aspect of the crude product, its low miscibility with common polar solvents (CH_2Cl_2, EtOAC), and especially the inevitable formation of several undesired by-products. By using 2 equivalents of 2-methoxypropene and PPTS in catalytic amount (0.02 equivalent), the reaction gave incoherent yields on larger scales (up to 5 g of starting material) which was occasionally due to the incompletion of the reaction. Not only the sugar **89** but also the acetonide **246** were difficult to handle because of their high viscosity.

Nonetheless, we pursued our synthesis according to the procedure described by the group of Winssinger,[16] reducing the protected sugar with LAH (total conversion and NMR spectra correspond to the literature data[16]), followed by a mono-protection of the non-purified obtained diol **247** with one equivalent of TBDPSCl in the presence of imidazole at room temperature, giving the polyol intermediate **248**. The reaction was monitored by thin layer chromatography and showed the disappearance of TBDPSCl while the crude diol **247** still remained. It was quite tricky to optimise the reaction, as the formation of both mono-protected diols as well as the totally protected by-product was unavoidable, giving the structurally similar primary alcohols at both extremities. Thus the best yield obtained over 2 steps was around 45%, which was reasonable for the next oxidation step of the primary alcohol under Parikh-Doering conditions: SO_3.pyr complex, freshly distilled DCM, DMSO and DIPEA.[17]

The oxidation occurred smoothly with total conversion and quantitative yield to provide the aldehyde **249** which was immediately employed for the nucleophilic attack of commercial prop-1-yn-1-ylmagnesium bromide (**244**) to provide a 60:40 diastereomeric mixture of alcohol **250** in fairly good yield (90% over 2 steps). Neither the se*para*tion of each of the diastereoisomers nor a diastereomerically selective synthetic way were required for this step on account of a late stage oxidation of this alcohol to furnish the *cis*-enone, as described in the synthesis of the same metabolite by Altmann and Hofmann.[13]

The protection of the alcohol function with EOMCl was promoted by TEAI at RT proceeded uneventfully to give the fully protected polyol **251**. Since we pursued the same approach to a late-stage oxidation of the enol to access the *cis*-enone,[13] both EOM ether and the acetonide would be quantitatively cleaved using sulfonic acid resin in MeOH, while the *ortho*-phenol could be selectively deprotected by the Lewis acid BCl_3, or while closely monitored, all these cited protecting groups could be simultaneously cleaved by BCl_3.[16] As rightly programmed, the TBAF deprotection of the primary alcohol was unproblematic and afforded the intermediate **252** in very high yield. Despite the common use of bromide alkyls for the direct alkylation at benzylic position,[18] we decided to verify the compatibility of different leaving groups attached at the primary carbon, in view of establishing a general design motif. Therefore, with the alcohol in hands, we embarked on the pre*para*tion of halogenated intermediates derived from **252** as the first target to verify their accessibility.

The iodination took place at first according to the Appel reaction, which necessitated the use of iodine in the presence of triphenyl phosphine and a mild base (*e.g.* imidazole).[16] This reaction resulted in the iodide fragment **253** which was carefully purified by flash chromatography through neutralised silica gel (1% Et_3N), taking into account the instability of primary iodide when confronted with slightly acidic conditions. Indeed, the yield obtained after purification for the iodide was clearly inferior to 80% on non-neutralised silica gel chromatography column. Once isolated, the resulting iodide should be conserved at low temperature (-20°C) and the decomposition of the product was easily detected as the initially obtained colourless oil turned gradually pink. Encouraged by the success of the Appel reaction, we applied the same strategy for the next bromination.

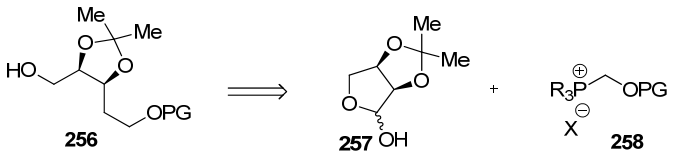
The bromination was first performed under the similar conditions,[19] using CBr_4 as the bromine donor. Unfortunately, the Appel reaction only gave a complex, uncharacterised mixture, despite the use of freshly distilled solvents and PPh_3 that was recrystallised in hot hexane and CBr_4 recrystallised in hot ethanol and dried in the dark under vacuum.[20] It was also described in the literature that NBS was also used as a brominating agent when combined with PPh_3, which led us to replace CBr_4 by NBS.[21] Disappointedly, this reaction mainly led to products with either complete or partial loss of the acetal protection, as it occurred in the initials attempts. Later, we found out in the literature that this unexpected incident was due to the unpreventable cleavage of acetonides in the presence of triphenylphosphine (2 equiv.) and CBr_4 (2 equiv.) in THF or CH_2Cl_2 at 0°C under inert atmosphere.[22] The authors proposed a mechanistic explanation by a plausible coordination of the phosphonium adduct formed by PPh_3 and CBr_4 onto one oxygen of the acetonide, while the freed bromide ion liberated the respective carbonyl compound, in addition to the triphenylphosphine oxide commonly observed. These findings condemned our initial strategy to transform alcohol **252** intobromide **254** as well as chloride derivatives. However according to the literature, other halogenation methods theoretically would not interfere with the existing acetonide, such as the use of the complex 2,4,6-trichloro[1,3,5]triazine and *N,N*-dimethyl formamide in the presence of $NaHCO_3$.[23] In the meanwhile, the sulfonation unsurprisingly proceeded to provide the intermediate **7** in relatively high yields (91% after isolation).

While the direct pre*para*tion of the corresponding bromoalkane **254** from alcohol **252** by well-known procedures, like Appel reaction, was to avoid, another method has allowed to adress this issue *via* the available tosylate **255**. To our pleasure, exposure of intermediate **255** to 10 equivalentS of LiBr in refluxing acetone has resulted in the attainment of **254** in acceptable yield (50 to 60 %).

Then we decided, after the obtainment of the tosylate compound **255**, to find out the right conditions for our key step, the direct alkylation at benzylic position, with some commercially available primary haloalkanes.

With the tosylated alcohol **255**, bromide **254** and iodide **253** in hands, we invested our efforts in benzylic alkylation which is related in detail in section *2.3.1*, starting with our first attempts in deprotonating the ester compound **242**. The series of attempts to find out the suitable electrophile for the subsequent alkylation consumed the available amount of the building blocks **253**, **254** and **255**. However, their pre*para*tion on a larger scale was time- and material-consuming, due to the lack of reproducibility of the initial sequence based on the strategy described by Winssinger *et al.,* starting with 2-deoxy-D-ribose (**89**).[8] Indeed, as mentioned above, the starting material and the resulting products were difficult to handle and purify, not to mention the very low overall yield due to the non-selective monoprotection at the beginning of the 8-step sequence. These disadvantages of the strategy revealed to be unsuitable to synthesise alcohol **252** on a multigram scale. Therefore, it was necessary to modify our strategic approach towards the desired polyol compound.

As a consequence, the new pathway required a more selective protecting group for the specific primary alcohol of diol **247**, in addition to being orthogonal to the acetonide and EOM groups. The new starting material should contain the right configuration of the vicinal diol, accessible and easily handled, unlike the viscous 2-deoxy-D-ribose (**89**). In the literature, monosaccharides have been commonly employed as chiral pools, whose equilibrium between the heterocycle ring and the straight-chain form is commonly put to profit. One of these tactical syntheses consists of the one-carbone homologation operated on the open-chain form, *e.g. via* a Wittig reaction of a lactol with alkoxymethylenephosphoranes,[24] directly followed by hydrogenation of the obtained enol ether. In our case, the lactol **257** would be required as substrate for this homologation method (**scheme 43**).

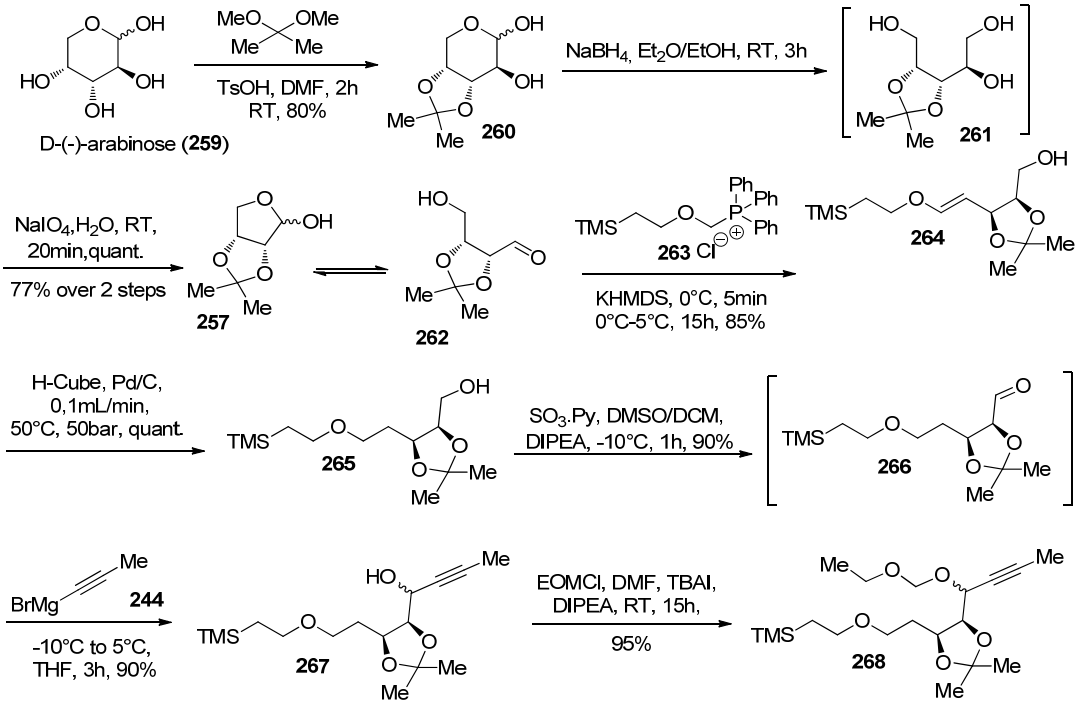


Scheme 43: Retrosynthesis of the homologation reaction

On that account, we embarked on the second synthetic sequence which involved a Wittig reaction as the decisive step. This 2nd-generation approach commenced with the pre*para*tion of lactol **257** from D-(-)-arabinose (**259**), closely following the readily described procedures.[25]

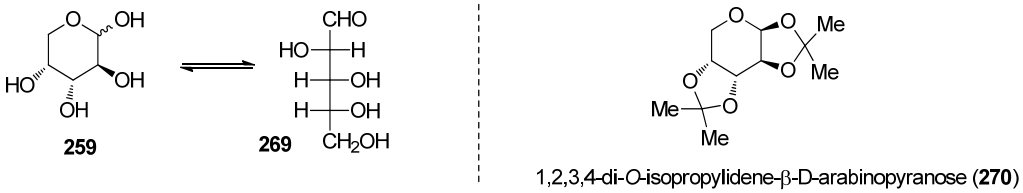
2.2.1.2 Second generation strategy: "D-arabinose approach"

The first three synthetic steps of the sequence were carried out according to the literature that begins with the selective monoprotection of D-(-)-arabinose (**259**) by 2,2-dimethoxy propane catalysed by *p*-toluensulfonic acid monohydrate in DMF (**scheme 44**).[25b]



Scheme 44: Synthesis of TMS-protected alcohol **268** from D-(-)-arabinose (**259**)

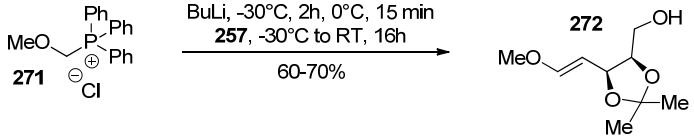
This is known to be a unique acetonating reagent for the pre*para*tion of a variety of isopropylidene derivatives, especially when reacting with some pentoses to give various products that reflect the pyranose-furanose equilibria in the reaction solution. Indeed, the reaction was carried out at room temperature (*ca* 20°C) and its completion was closely monitored by TLC in order to avoid the over-protection leading to the thermodynamically stable product **270** (**scheme 45**). This phenomenon is well known in the literature, especially when the reaction was performed at high temperature (*e.g*. 80°C) which gave the diacetonide **270** almost exclusively.[26]



Scheme 45: D-(-)-arabinose (**259**) equilibrium. The diacetonide byproduct (**270**)

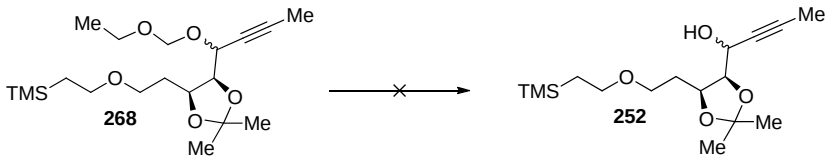
The isolated 3,4-*O*-isopropylidene-β-D-arabinopyranose **260** was then added to a solution of sodium borohydride in ethanol, followed by treatment with sodium periodate to afford the lactol **257** in satisfactory yield. The choice of the protecting group originally depended upon the commercial availability of the alkoxymethylenephosphoranes, as well as its potential cleavage at a later stage. Therefore we opted for the commercialised triphenyl((2-(trimethylsilyl)ethoxy)methyl)phosphonium chloride **263** to engage in the previously planified Wittig reaction onto lactol **257**.

As a preliminary test, the lactol **257** had been first submitted to the homologation with the ylide resulting from the BuLi deprotonation of methoxymethyltriphenyl phosphonium chloride **271**, affording the corresponding homologated compound **272** (**scheme 46**).



Scheme 46: Wittig reaction involving **257** and methoxymethyltriphenylphosphonium chloride (**271**)

Confident of the positive outcome of the previous reaction, we subjected triphenyl((2-(trimethylsilyl)ethoxy)methyl)phosphonium chloride **263** to the same procedure. But instead of remaining deep red as in the case of methoxymethyltriphenylphosphonium ylide at 0°C, the solution mixture gradually faded into bright yellow after 2h at -30°C. Suspecting the butyllithium being unappropriate for the deprotonation, we tried out potassium terbutoxide to deprotonate the phosphonium chloride at 0°C as described by Treu and Jordis.[27] Once again, the solution mixture's colour changed from orange to deep yellow, blurred by a white precipitate. Discouraged by the transient ylide generated by tBuOK, we carried on the deprotonation with KHMDS, a base that was first used by Schoenauer and Zbiral to generate triphenyl((2-(trimethylsilyl)ethoxy)methyl)phosphonium ylide.[28] To our great delight, by adding KHMDS to a suspension of phosphonium salt **263** in ether at 0°C and 5 minute stirring, followed by the addition of lactol **257** and further stirring overnight while the temperature was kept between 0°C and 5°C, the awaited compound **264** was finally detained. Without further delay, a solution of the purified enol ether in EtOAc was delivered to the hydrogenation using a Thalesnano H-Cube® equipped with a 30mm CatCart filled with 10% Pd/C, at a flow rate of 0.1 ml/min with a pressure setpoint of 50bar and the cartridge kept at 50°C. The quantitatively obtained primary alcohol **265** underwent the same next three steps as in the sequence starting with 2-deoxy-D-ribose (**89**), namely a Parikh-Doering oxidation successfully combined with a Grignard reaction, and an EOM protection of the resulting intermediate **268** without any incident.



Scheme 47: Unsuccessful TMSE deprotection

The next step was naturally the cleavage of the silylethyl group to achieve the same compound **252** which was earlier synthesised through the sequence based on Winssinger's strategy "2-deoxy-D-ribose approach" (*cf*. section *2.2.1.1*). It is worth noting that the choice of TMSE-ether as protecting form was mainly fuelled by our belief in an ultimate orthogonal deprotection under very mild conditions, in particular by a fluoride source. In fact, trialkylsilylethyl esters and carbamates have been deprotected by fragmentation analogous to the β-elimination, expulsing the silicate and an ethylene molecule (**scheme 16**).[29]

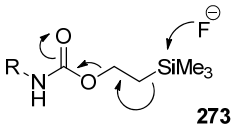


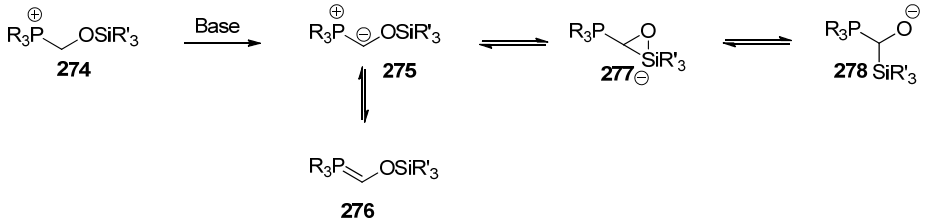
Figure 16: Example of TMSE cleavage

Given that the same principle is also behind the trimethylsilylethyl protecting group, we attempted to deprotect **268** by a fluoride source in the first place. Against all expectations, the several deprotecting trials *via* fluoride ions revealed that the collapse of the putative silicate intermediate is facilitated by expulsion of a good carboxylate leaving group for an ester, for example, while no such leaving group is available for the SEM ether, even when submitted to rather harsh conditions (**table 1**). Noting that the total synthesis of O-(methylepoxy)shikoccin by Paquette *et al.*[30] embraced a TMSE ether cleavage step involving cesium fluoride in DMF at 210°C for 6h, we carried out with high expectation the same experiment, fruitlessly. Other fluorine sources also turned out ineffective, leaving the starting material either fully recovered or totally deprotected (in acidic condition). It was also established in the literature that $BF_3.Et_2O$ was able to cleave the TMSE ether at room temperature,[31] from which we did not benefit as the acetonide was simultaneously removed, as in the case of Olah's reagent HF.pyr (70%) or in the presence of occasionally used TsOH in combination with TBAF.[32] In 2001, the group of Wu reported a novel method for the deprotection of 2-(trimethylsilyl)ethyl esters following its treatment with excess NaH (1.5 equiv.) and electrophile (2.0 equiv.) in DMF, a novel method next to the widespread deprotection by fluoride source. The authors favored a mechanism whereby the NaH reacted with adventitious moisture in the solvent to generate "anhydrous hydroxide" as the active species, which operated in the same manner as fluoride anions. However, the same method did not succeed on TMSE ether, because putative silicate intermediate is certainly facilitated by expulsion of a good carboxylate leaving group for the ester, while no such leaving group is accessible for anether. Hence also the inefficiency of LiOH was one of our many deprotecting trials.

Cleavage conditions	Conversion	Yield
CsF, DMF, 210°C, 12h [30]	0%	0%
TBAF, DMF, RT, 24h[33]	0%	0%
TEAF, DMF, RT, 24h[34]	0%	0%
TBAF, TsOH, THF, RT, 2h[35]	100%	0%
$KF.Al_2O_3$, THF, RT, 2h	0%	0%
KF, 18-crown-ether, RT, 12h	0%	0%
NaH, DMF, RT to 70°C, 12h[36]	0%	0%
$LiOH.H_2O$, THF/H_2O, RT, 12h	0%	0%
$BF_3.Et_2O$, CH_2Cl_2, 0°C to RT, 2h[31]	100%	0%
HF.pyr(70%), MeCN, 50°C, 2h	100%	0%

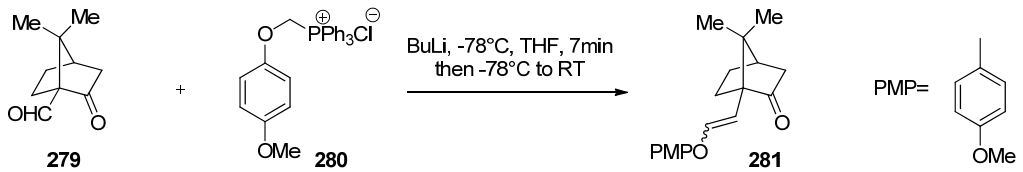
Table 1: Conditions used for TMSE ether cleavage trials

After considerable efforts, we realised that the impracticable deprotection put an end to this 2nd generation synthetic scheme. As a result, the homologation of the lactol/aldehyde imposed a customised phosphonium which would introduce a more ajustable protecting group. The idea of synthesizing an alkoxylidenephosphonium containing a silane **274** was deceivably attractive, due to the feasible retro-Brook rearrangement, once the phosphonium salt **275** was deprotonated (**scheme 48**).[37]



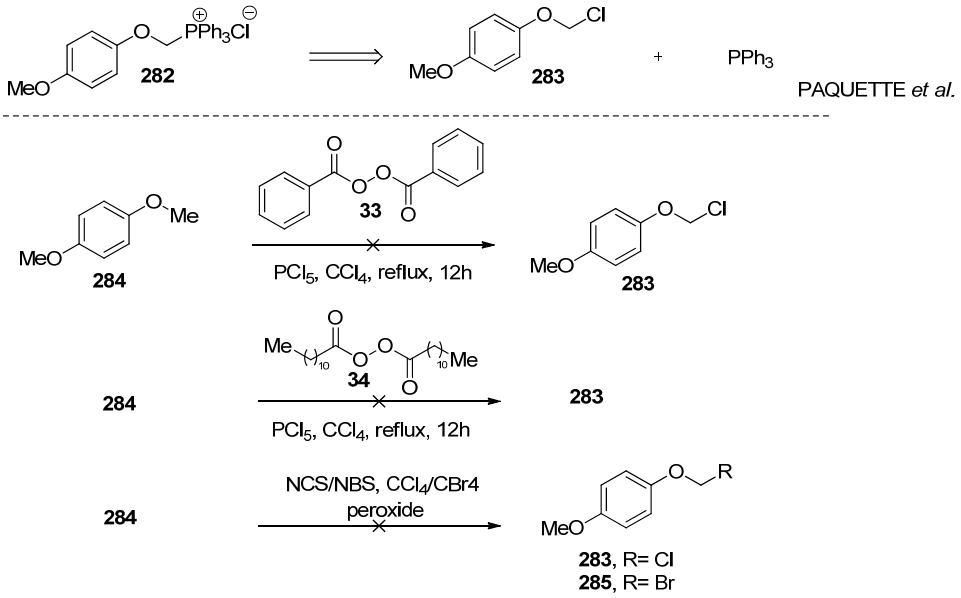
Scheme 48: Retro-Brook rearrangement

Besides the choice of fluoride-labile group (silanes) in synthetic projects, the oxidation-labile blocking groups are often employed though the choices are very limited. The 4-methoxybenzyl (PMB), 4-methoxyphenyl (PMP) and the more labile 2.4-dimethoxybenzyl (Dmpm) ethers have proved their worth as reagents in the synthesis of complex molecules. Both of these functions are easily removed under mild conditions with dichlorodicyanoquinone (DDQ) or with cerium(IV) ammonium nitrate (CAN).[32] These conditions seemed to address the difficulties previously occurring and brought us to the search for a phosphonium salt containing an oxidation-labile protecting group.



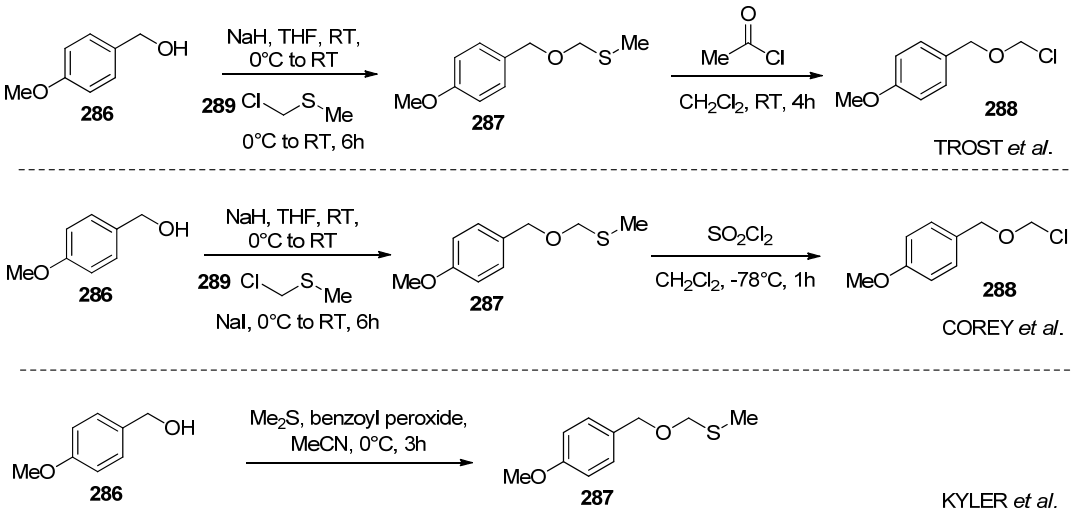
Scheme 49: Wittig reaction *via* ylide generated from phosphonium salt **280** by Paquette *et al.*

During the literature search, we came across the efficient use of phosphonium salt **280** by the group of Paquette in 1993, consequently included in their several years effort to design and develop a unique strategy for the enantiospecific synthesis of taxane diterpenes.[38] The employed Wittig reaction is depicted in **scheme 49**, illustrating the initiation by BuLi deprotonation at very low temperature (-78°C) in a brief reaction time (7min) followed closely by the addition of aldehyde **279** and the completion afforded the *cis* and *trans*-vinyl ethers **5** in a ratio of 1:2 ('H NMR analysis) with a combined efficiency of 93%.



Scheme 50: Unsuccessful attempts to synthesise PMP-Cl

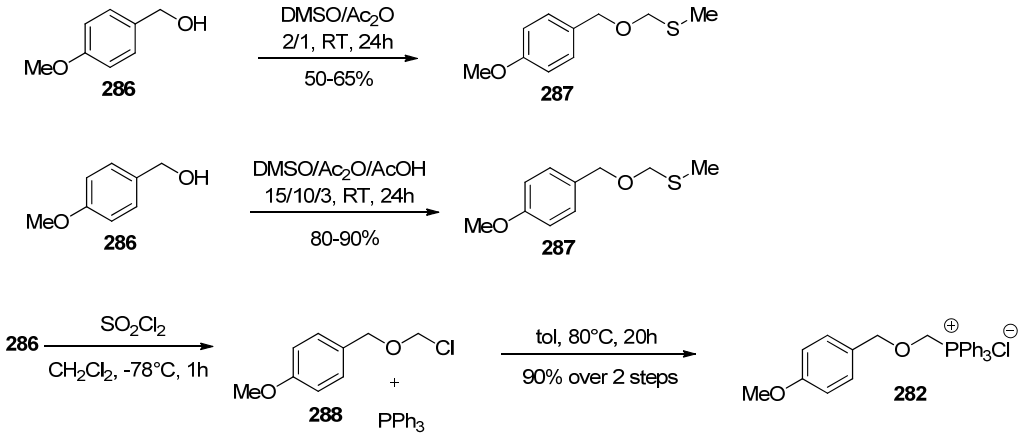
It was also documented that the pre*para*tion of the employed chloride had been inspired from an article by Masaki *et al.*,[39] which directed our attention towards the synthesis of this PMP chloride as starting material. Confident with the promising pre*para*tion of **283** which had been so far commonly cited in the literature,[39-40] our synthetic choice was first based on radical reactions to introduce the primary chloride from 1,4-dimethoxybenzene . As rightly described by Loubinoux *et al.*,[40] the pre*para*tion of chloromethyl phenyl ether demanded either lengthy, energy-consumming syntheses or drastic conditions (*e.g.* heating up to 175°C) and one of the mildest option at that time was treatment with a peroxide, PCl_5 and refluxing CCl_4 (**scheme 50**). However, all the trials realised in the same conditions did not afford us with any of the expected compound **283**, be it in the presence of the widely used PCl_5 or NCS.[41] Our attempts to synthesise instead a bromide *via* NBS in CCl_4 and benzoyl peroxide also led to no expected results. Disappointed by the outcomes, we turned out attention to an alternative for preparing aromatic chloromethyl ethers which employed the corresponding aromatic methylthiomethyl ethers, given that the PMB protecting group was as well an oxidation-labile protecting group.



Scheme 51: Access to *p*-methoxybenzyl chloromethyl **288** *via p*-methoxybenzyl methylthiomethyl ether **287**

While the terminal chlorination in the case of (*p*-methoxyphenoxy)methyl chloride (**283**) is mainly carried out in a direct way (**scheme 51**), *p*-methoxybenzyl chloromethyl (**288**)can be obtained in two steps, starting from (4-methoxyphenyl)methanol (**286**). According to several articles, it was more convenient to chlorinate the sulfide **287** into the wanted product **288** either by expposure to oxalyl chloride as described by Trost *et al.*[42], or sulfuryl chloride by Corey *et al.*[43]. The *p*-methoxybenzyl methylthiomethyl ether **287** reportedlyresulted from the smooth nucleophilic attack of the hydride-deprotonated benzyl alcohol **286** onto the chloromethyl methyl sulfane (**289**). In our hands, the same reactions did not proceed in sufficiently high yields. Another method using radical reactions by Kyler *et al.*[44] was also tested without better results. In the same printing work, the authors pointed out the major advantage of radical reactions which rested on a mild and non-acidic, and consequently widely compatible way to convert alcohols to methylthiomethyl ethers, an alternative route to Pummerer reaction. As a matter of fact, the Pummerer reaction has been established to furnish sulfides *via* sulfoxides in acidic conditions,[45] which can be seen as an expedient means to obtain **288**.

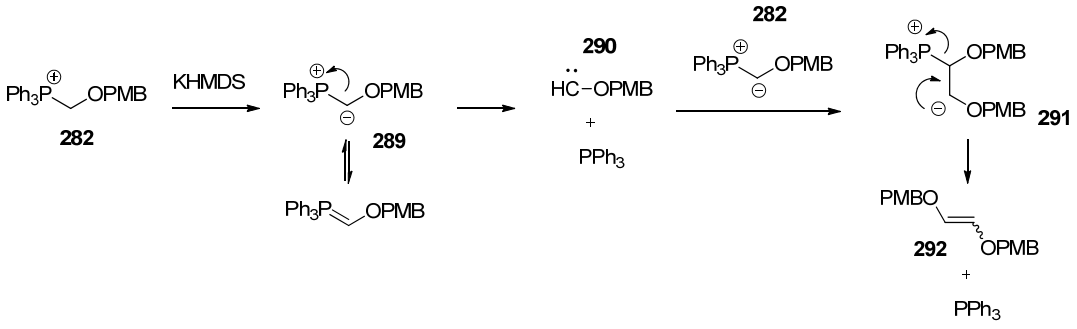
Originally, the classical Pummerer recipe, treatment of a sulfoxide with a potent acylating agent like trifluoroacetic anhydride (TFAA) in a non-participating solvent, is sufficient to generate the electrophilic thionium ion.[45] The traditional Pummerer reaction was thus performed with Ac_2O and and dimethylsulfoxide [46] in the presence of **286** to generate the anticipated sulfide **287** in approximately 60% yield. Whereas the optimisation of the reaction did not exceed 65% of yield, the simple addition of AcOH to the reaction (DMSO/Ac_2O/AcOH: 15/12/3) increased the yield up to 90%.



Scheme 52: Synthesis of (((4-methoxybenzyl)oxy)methyl)triphenylphosphonium chloride **282**

The obtained sulfide **287** was treated with sulfuryl chloride at low temperature to give the desired chloride **288**, a moisture sensitive product which was used in the next step without further purification, a decision partly due to the total conversion of the starting sulfide. The phosphonium **282** was successfully formed following treatment of the crude chloride **288** by triphenylphosphine in toluene at 80°C over 20h. With this phosphonium salt in hand, the anticipated homologation of lactol **257** based on Wittig reaction could be experimented.

Initial attempts to use KHMDS to deprotonate the freshly prepared phosphonium **282**, following the same procedure described for the successful deprotonation of the commercial phosphonium **271**, however, gave no predicted results. The reaction mixture turned deep red within 5 minutes after the addition of KHMDS at 0°C, followed by the dropwise addition of a solution of lactol **257** in THF. The mixture was vigorously stirred from 0°C to room temperature overnight. Unfortunately, no homologation product was observed and the initial lactol **257** was entirely recovered, while the phosphonium salt seemed to be decomposed. Suspecting the short-lived existence of the desired phosphonium ylide at 0°C, it was therefore evident for us to undertake the reaction temperature at an appropriately lower temperature, which indeed prolonged the deep red colour at -78°C for more than 2h right after the addition of KHMDS. The lactol was added at the same temperature and the reaction kept at -78°C to 10°C overnight. Once again, the starting material **257** was entirely recovered and the by-products coming from the decomposition of phosphonium were present in the crude product. NMR data allowed the detection of alkene, as the addition product by ylide **289** onto the resonance-stabilised carbene **292** (**scheme 53**). The same undesired decomposition was earlier studied by Wittig and Böll[24] who discovered that the higher alkoxymethylenephosphorane (*e.g.* butoxymethylene triphenylphosphorane) gave more unstable alkoxy phosphonium ylides.



Scheme 53: Decomposition of phosphonium ylide **282**

Given that the decomposition took place at 10°C for butoxymethylene triphenylphosphorane, the reaction temperature was maintained between -78°C and -15°C in several trials, without obtaining any trace of the homologated product. It was rather difficult to find out the intermediate temperature which would avoid the decomposition of the phosphorane while allowing the lactol-hydroxyaldehyde equilibrium to shift in favour of hydroxyaldehyde formation. With the purpose of favoring the hydroxyaldehyde to occur, meanwhile sparing one equivalent of the formed phosphorane, the lactol mixture was first treated with one equivalent of BuLi, before addition of the phosphorane. Nevertheless, the outcome remained unchanged.

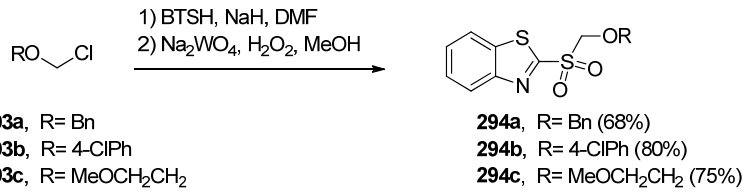
Base	Temperature	Conversion	Yield
KHMDS	-78°C, 1h, -78°C – 10°C, 12h	100%	0%
KHMDS	-30°C, 15h	100%	0%
NaHMDS	-10°C, 15 min, -10°C to 0°C, 15h	100%	0%
NaHMDS	0°C, 15 min, RT, 15h	100%	0%
Buli	-78°C, 1h, -78 to 0°C, 15h	100%	0%
Buli	-78°C, 1h, -78°C to RT, 15h	100%	0%
NaH	0°C, 15h	100%	0%

Table 2: Conditions of Wittig reaction involving phosphonium salt **282** and lactol **257**

In the literature, several alkoxymethyltriphenylphosphorane ylides are accordingly reported to be quite unstable and afford low yields of substituted vinyl ethers in case the starting ketones are easily enolisable,[24, 47] while some few have been proven to be efficient method to prepare substituted vinyl ethers. This lack of available methods stimulated our determination to synthesise and bring to application the phosphonium chloride **282**. Finally, the last trials of the series were carried out between the phosphorane and benzaldehyde at different temperature combinations, unfortunately without any success, which ended our efforts to use the phosphonium salt **282**.

- **Julia olefination**

Nonetheless, the choice for the construction of oxidation-labile substituted vinyl ethers through olefination was not abandoned. Besides the extensive use of phosphonium ylides in Wittig reactions, the construction of alkenes, in the last two decades, has also frequently been conducted *via* Julia olefination reactions.[48] The first examples of modified Julia olefination using α-alkoxyheteroaryl sulfones to yield vinyl ethers were published only a decade earlier by the Canadian group of Surprenant.[49] This convenient methodology might circumvent cases where alkoxymethyltriphenyl phosphorane ylides had failed. Their generic pre*para*tion of the required sulfones is reproduced in **scheme 54** hereafter.



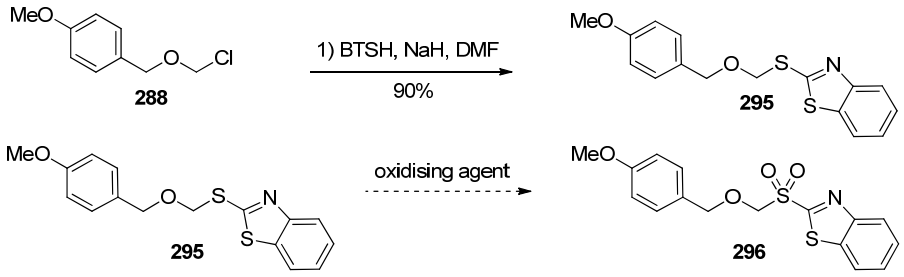
293a, R= Bn
293b, R= 4-ClPh
293c, R= $MeOCH_2CH_2$

294a, R= Bn (68%)
294b, R= 4-ClPh (80%)
294c, R= $MeOCH_2CH_2$ (75%)

Scheme 54: Synthesis of α-alkoxyheteroaryl sulfones

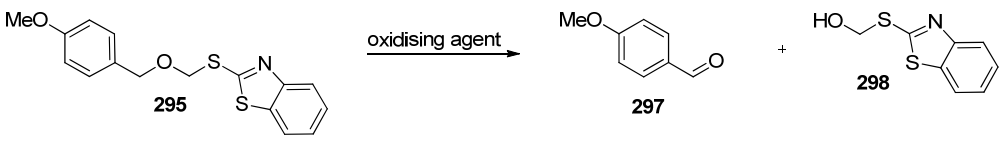
Syntheses of the sulfones with three electronically and sterically different alkylating agents were accomplished in a two-step process, namely a nucleophilic attack of the deprotonated 2-mercaptobenzothiazole (BTSH) onto the corresponding chloromethyl ethers and an oxidation of the newly formed sulfides into sulfones. If the same method was to be brought into operation, the alkoxymethyl chloride would remain the same as previously involved in the synthesis of phosphonium **282** (**scheme 52**), but the oxidation of the corresponding sulfide must be sufficiently mild to accomplish the anticipated sulfonation.

Consequently, we have in the first place synthesised the corresponding sulfur **295** from 1-((chloromethoxy)methyl)-4-methoxybenzene **288** and 2-mercaptobenzothiazole in the presence of NaH in DMF (**scheme 55**). This reaction indeed yielded the desired precursor **295** in gratifying yield (90%).



Scheme 55: Aspiring synthesis of the PMB-sulfone **296**

With the sulfide **295** in hands, we decided first to follow closely the same oxidation conditions described by Surprenant *et al.*,[49] *i.e*. sodium tungstate in catalytic amount and hydrogen peroxide at 0°C in methanol and vigorously stirred overnight between 0°C and 21°C. As a result, neither the anticipated sulfone **296** nor the corresponding sulfoxide compound was observed in the crude product, while on the contrary, 4-methoxybenzaldehyde (**297**) was mainly present. This outcome did not occur in the case of benzyl group (**293a**)[49] because of its lack of electron-donor methoxy group. According to the group of Noyori, the mechanism of the tungstate-based oxidation was explained by the rapid oxidation of Na_2WO_4 by hydrogen peroxide and aliphatic sulfides are more reactive than aromatic compounds.[50] In all likelihood, the oxidation-labile *p*-methoxybenzyl was more reactive towards the oxidising agent than the sulfide, even at low temperature (0°C to 5°C) leading only to the cleavage into 4-methoxybenzaldehyde (**297**).

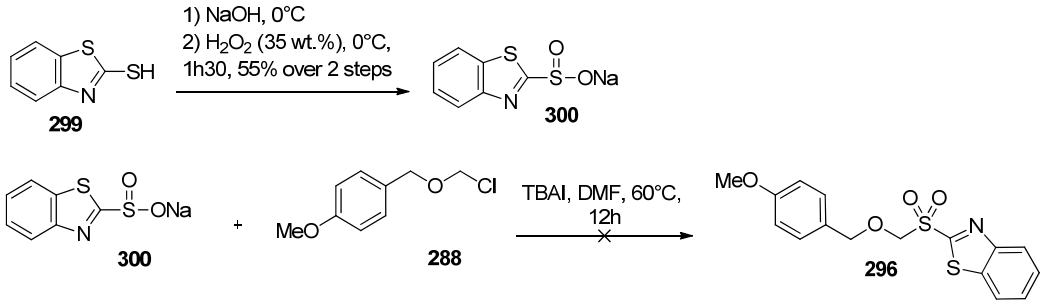


Scheme 56: Decomposition of sulfone **295** into *p*-methoxybenzaldehyde **297**

Other commonly described oxidising reagents have also been employed in hope of favouring a fast oxidation of the sulfide and hence a lower rate of decomposition into *p*-methoxybenzaldehyde **297** (**table 3**). Unfortunately, in all cases, either the formation of aldehyde was inevitable or no transformation took place.

Oxidation conditions	Conversion	Yield
$Na_2WO_4.2H_2O$, H_2O_2 (30 wt. % in H_2O), MeOH, 0°C to 21°C, 12h	100%	0%
$Na_2WO_4.2H_2O$, H_2O_2 (30 wt. % in H_2O), MeOH, 0°C, 12h	90%	0%
$Na_2WO_4.2H_2O$, H_2O_2, MeOH, 0°C to 5°C, 12h	100%	0%
H_2O_2, AcOH, 0°C to 21°C, 12h	100%	0%
mCPBA, CH_2Cl_2, 0°C, 6h	100%	0%
Oxone®, MeCN/H_2O: 2/1, 0°C, 4h	100%	0%

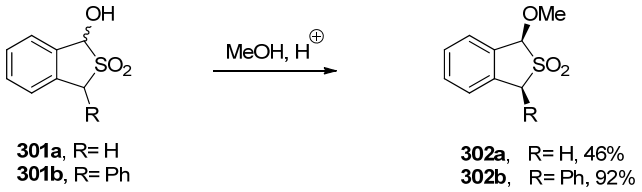
Table 3: Oxidation trials of sulphur **295** into sulfone **296**



Scheme 57: Attempts to synthesis PMB-sulfone **296**

Subdued by several unsuccessful trials, the initial synthetic scheme of sulfinate **300** was aborted and another approach based on the nucleophilic trait of sodium benzothiazole-2-sulfone **300** was undertaken. By following closely the conditions described by the group of Kouge,[51] we were able to obtain **300** in a modest yield of 55% over two steps (**scheme 14**). The freshly prepared sodium salt was immediately used in the next step, as it was speculated to attack the *in situ* chloride **288** in a nucleophilic manner to provide sulfone **296**. This reaction was first performed at 60°C in DMF and gave no trace of the expected sulfone. A higher temperature (70°C to 100°C) uniquely induced the disappearance of chloride **288** from the reaction mixture, leaving the sodium benzothiazole-2-sulfone as main compound in the final crude product. The negative outcome led to the used of ion exchange *via* TBAB and TBAI respectively, expecting a better electrophilic site. None of these expectations came true.

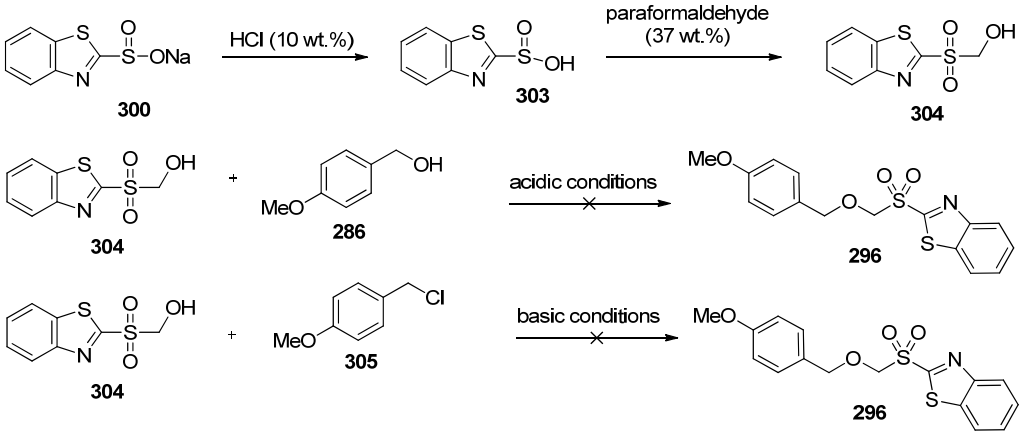
While looking for different solutions in the literature, we learnt from Charlton *et al.* a feasible way of converting hydroxyl methyl sulfone **301** to the methoxy derivative **302** by refluxing in methylene chloride solution of **301** with an equivalent of methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid (**scheme 58**).[52] Unlike the methoxy derivative **302b**, its congener **302a** was formed in roughly half amount.



Scheme 58: Charlton *et al.* methylation of sulfone **301**

Mecanistically, the methylation of sulfone **301** differs from our desired alkylation. However, the straightforward success of such a transformation was rather inspiring for our pre*para*tion of sulfone **296** which, so far, had not afforded any of the anticipated result.

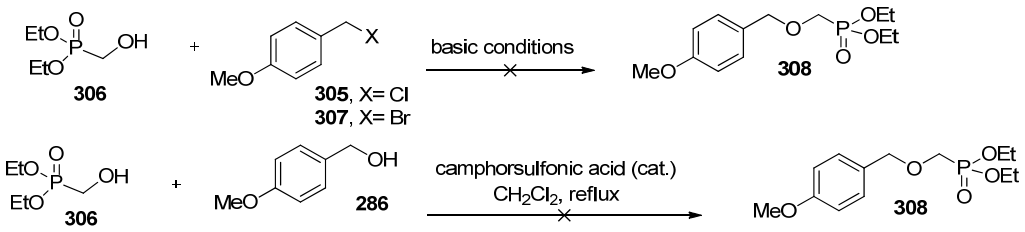
Consequently, the new sequence commenced with the synthesis of hydroxy methyl sulfone **304** in two steps from the sodium salt **300** made beforehand (**scheme 59**). The sulfinic acid **303**, previously acquired by acidification of the sodium salt **300** with HCl (10 wt. %), was submitted to an aqueous solution of *para*formaldehyde, providing hydroxy methyl sulfone **304** in 70% of yield over 2 steps.[53] With the compound **304** in hand, we applied the conditions described by Charlton *et al.*, namely the addition of (4-methoxyphenyl)methanol **286** to a solution of **304** and catalytic amount of *p*-toluenesulfonic acid in refluxing THF . As no trace of the expected sulfone was observed, other acids were used (*e.g*. camphorsulfonic acid and triflic acid) in combination with different amount of (4-methoxyphenyl) methanol (**286**) (from 1 equivalent to 10 equivalents), without formation of the desired compound. Under basic conditions (NaH or BuLi), 4-Methoxybenzyl chloride **305** was used instead of (4-methoxyphenyl)methanol while the sulfone **304** was completely consumed, contrary to the major amount of **304** recovered from the crude product under acidic conditions.



Scheme 59: Other attempts for an alternative pre*para*tion of sulfone **296**

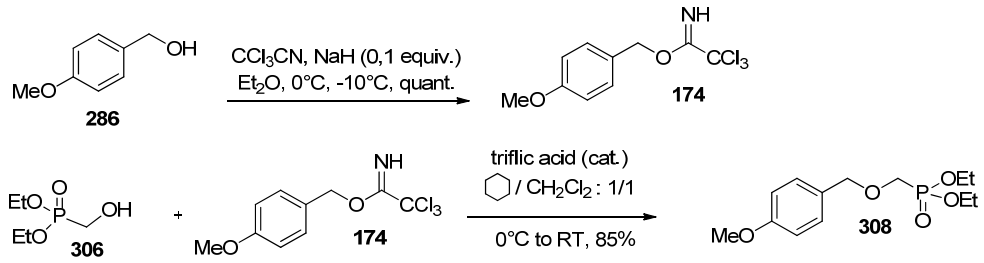
Confronted with the fruitless trials to prepare sulfone **296** as building block for a Julia based olefination, our synthetic strategy took once again another direction towards an oxidation-labile *O*-alkyl enol ether. Several years ago, Kluge *et al.* reported the pre*para*tion of some alkyl enol ethers by performing a Wadsworth-Emmons olefination with (alkoxymethyl)phosphonates,[54] and the hydroxyl protected phosphonates were obtained from the commercially available (hydroxymethyl)phosphonates (*e.g*. phosphonate **306**). Convinced by these bibliographic results, we concentrated our efforts on the preliminary synthesis of the corresponding phosphonate **308**.

- **Horner-Wadsworth-Emmons olefination**



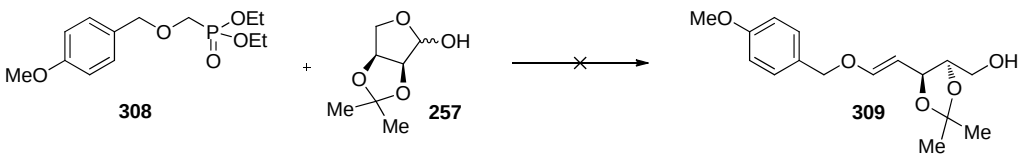
Scheme 60: Unsuccessful synthesis of phosphonate **308**

At the beginning, we tried to alkylate the commercial diethyl(hydroxymethyl) phosphonate **306** by primary deprotonation with NaH in DMF followed by addition of 4-methoxybenzyl chloride (**305**) and 4-ethoxybenzyl bromide (**307**) respectively. In the meantime, the alkylation was also conducted under acidic conditions as described previously in the case of sulfone **296**, involving (4-methoxyphenyl)methanol (**286**). One again, the results revealed only the recovery of starting materials under acidic conditions, whereas the commercial phosphonate **306** was found in an insignificant amount in the crude product following the reactions under basic conditions. This outcome was in accordance with the earlier results observed for sulfone **296**. Therefore the intended alkylation of diethyl (hydroxymethyl)phosphonate **306** seemed to be limited to acidic conditions. This observation consequently conducted to the use of 4-methoxybenzyl-2,2,2-trichloroacetimidate **147**, a benzylating agent which could be achieved by submitting (4-methoxyphenyl)methanol **286** to a solution of trichloroacetonide and NaH (0.1 equiv.) in diethylether.[55]The obtained viscous yellow oil had to be kept constantly at low temperature. The benzylation of commercial diethyl (hydroxymethyl)phosphonate **306** proceeded smoothly to yield the anticipated diethyl (((4-methoxybenzyl)oxy)methyl)phosphonate **308**.



Scheme 61: Synthesis of diethyl (((4-methoxybenzyl)oxy)methyl)phosphonate **308**

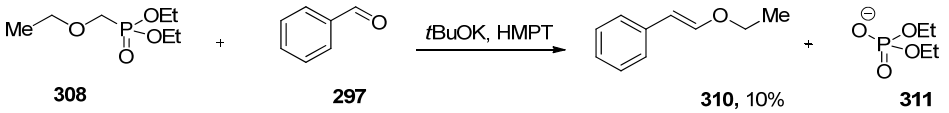
With the phosphonate in possession, a series of conditions was tried out with several bases, covering different temperature levels, as we looked forward to yielding a relatively stable corresponding phosphonate ylide (**table 4**). Indeed, it was well established that while thioalkoxymethylenephosphonates generated stabilised ylides, their homologues alkoxymethylenephosphonates were difficult to metallate.[56]



Deprotonation and addition conditions	Conversion	Yield
BuLi, -78°C to -60°C, 2h, then -78°C to RT, 12h	100%	0%
*s*BuLi, -78°C, 2h, then -78°C to RT, 12h	100%	0%
LiHMDS, Et_2O, 0°C, 5min then 0°C to RT, 12h	100%	0%
NaHMDS, Et_2O, 0°C, 5min then 0°C to RT, 12h	100%	0%
KHMDS, Et_2O, 0°C, 5min then 0°C to RT, 12h	80%	0%
KHMDS, Et_2O, -30°C to -10°C, 1h then -10°C to RT, 12h	70%	0%
*t*BuOK, HMPT, O°C to RT	100%	0%

Table 4: Unsuccessful trials *via* Horner-Woodwarth-Emmons between phosphonate **308** and lactol **257**

Attempted metallation of diethyl (((4-methoxybenzyl)oxy)methyl)phosphonate **308** with butyllithium afforded a product that was presumed to be derived from substitution on phosphorus in the manner reported by Lavielle *et al.* in 1971.[56] The authors observed indeed less than 10% of yield of the enol ether resulting from benzaldehyde and the ylide derived from diethyl (ethyloxymethyl)phosphonate **308**.



308 **297** **310**, 10% **311**

Scheme 62: Horner-Wadsworth-Emmons reaction between unstabilised ylide derived from diethyl (ethyloxymethyl)phosphonate **308** and benzaldehyde **297**

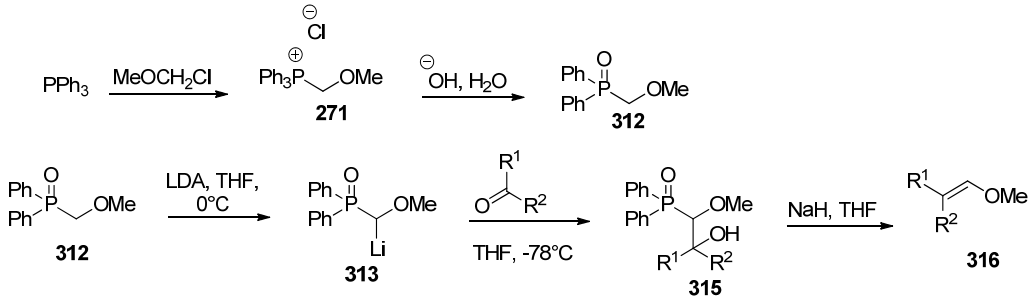
In the same report, the reaction initiated by deprotonation of **308** by butyllithium at -75°C irrefutably led to an isolated compound resulting from the substitution onto the phosphorous (30% of yield). This was attritubted to both the weakly acidic proton at the methylene position and the great electrophilicity of the phosphoryl group, an effect which would be strengthened by the electron-withdrawing effect of alcoxymethylene groups. As an example, diethyl (ethyloxymethyl) phosphonate was stated to undergo hydrolysis at a lower rate than diphenyl (chloromethoxymethyl) phosphonate.[56] Taking into account these *para*meters, our choice of bases consisted in finding the appropriate metal (among lithium, sodium and potassium), the right temperature which allowed not only the deprotonation of the phosphonate as well as the stabilisation of the newly formed ylide, but also the equilibrium shift into the corresponding hydroxyaldehyde **262** of lactol **257**. In spite of repeated efforts, the expected enol ether did not appear in the end, while the product from the substitution of onto the phosphoryl depicted by Lavielle *et al.*[56] was presumedly observed (base= BuLi). The disappointing performance of the anion coming from the phosphonate **331** and benzaldehyde in the presence of KHMDS ended our expectations of accomplishing the synthesis of enol ether **309** *via* a Horner-Wadsworth-Emmons reaction.

- **Horner-Wittig olefination**

In the literature, some reports mentioned that simultaneously Kluge *et al.* and Warren *et al.* attained the pre*para*tion of some alkyl enol ethers by performing a Horner type reaction from α-alkoxy-β-hydroxydiethylphosphonates or diphenylphosphine oxides, respectively.[57] Given that our targeted enol ether **309** remained elusive, be it *via* Wittig reaction, Julia reaction or

Horner-Wadsworth-Emmons reaction, one of the last options was to engage the recalcitrant lactol **257** into a Horner-Wittig reaction.

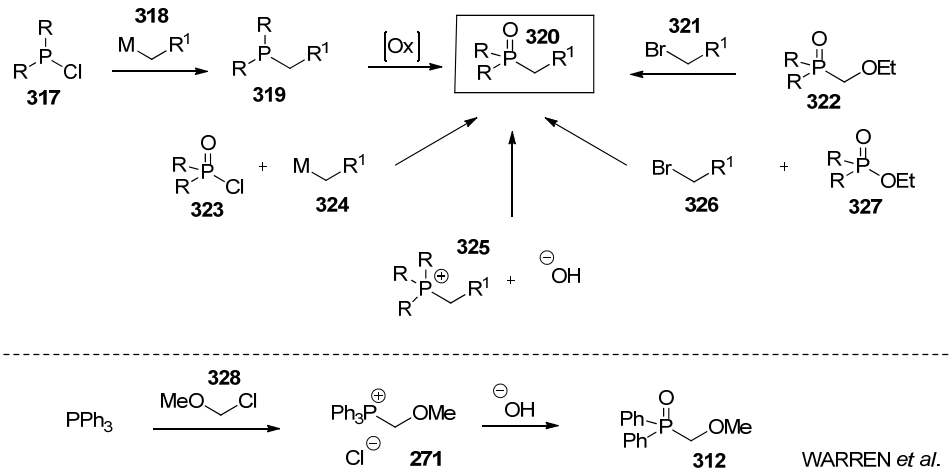
In 1959, Horner and co-workers published the first pre*para*tion of an alkene by treatment of a phosphine oxide with base followed by the addition of an aldehyde.[58] However, the reaction of a phosphorus ylide with a carbonyl, known as the so-called Wittig reaction since 1953[59] remained the most widely recognised method for carbonyl olefination. Actually, vinyl ethers can be made by the Wittig reaction using the alkoxy-ylides,[60] a convenient way to convert aldehydes and ketones into the homologous aldehydes by the alkylative carbonyle transposition.[61] This sequence worked relatively well but in some cases, the unstability of the ylides and the nucleophilic side reaction of enolisable aldehydes and ketones rendered the method unlikely reliable.[56] To overcome these hurdles, some authors used phosphonic esters[62] or amides.[56] As the first research group to employ alkoxymethylphosphine oxide in a Horner variant of Wittig reaction in 1976, Schlosser *et al.* have made the vinyl ether from cyclohexanone and the diphenyl (methoxymethyl)phosphine oxide **312** in 35% yield.[63] Three years later, the group of Warren reported the use of the same phosphine oxide (**312**) to prepare pure samples of each geometrical isomer of a vinyl ether (**scheme 63**).[61]



Scheme 63: Pre*para*tion of vinyl ethers from diphenyl (methoxymethyl)phosphine oxide **312** according to Warren *et al.*

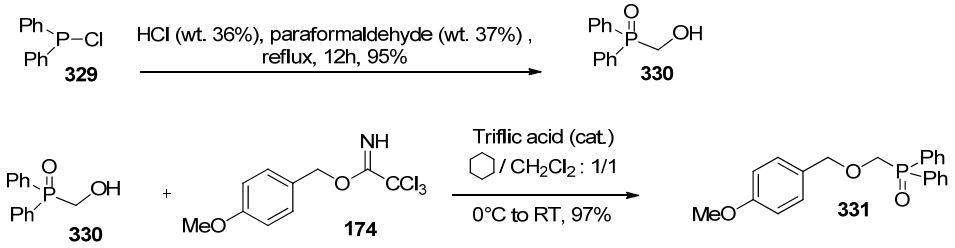
Even though phosphine oxides can be prepared by various methods (**scheme 64**), it has been proven popular to involve the reaction of organometallic reagents with halogenophosphines followed by oxidation, for the simple reason of the ready availability of halogenophosphines such as Ph_2PCl (**317**). This approach is not entirely suitable for our strategy due to the oxidation-sensitive alkoxy substituents. Another method consisted in submitting the corresponding phosphonium salt to an aqueous solution of hydroxide. As an example, the group of Warren published the formation in two steps of diphenyl(methoxymethyl)phosphine oxide **312** by oxidation of the corresponding phosphonium salt **271**, which was previously synthesised by a classic addition of triphenylphosphine onto methoxymethylchloride.[61] Though this would be a convenient way with the (((4-methoxybenzyl)oxy)methyl)triphenyl-phosphonium chloride **282** readily in our possession, the observed eager decomposition of this phosphonium salt under basic conditions made us reluctant to apply the same approach.

On the other hand, the achievement of phosphonate **322** through an acid catalysed benzylation with -methoxybenzyl-2,2,2-trichloroacetimidate **174** tempted us to follow the same pathway towards the homologous (((4- methoxybenzyl)oxy)methyl)diphenylphosphine oxide **331**.



Scheme 64: General methods to prepare phosphine oxides

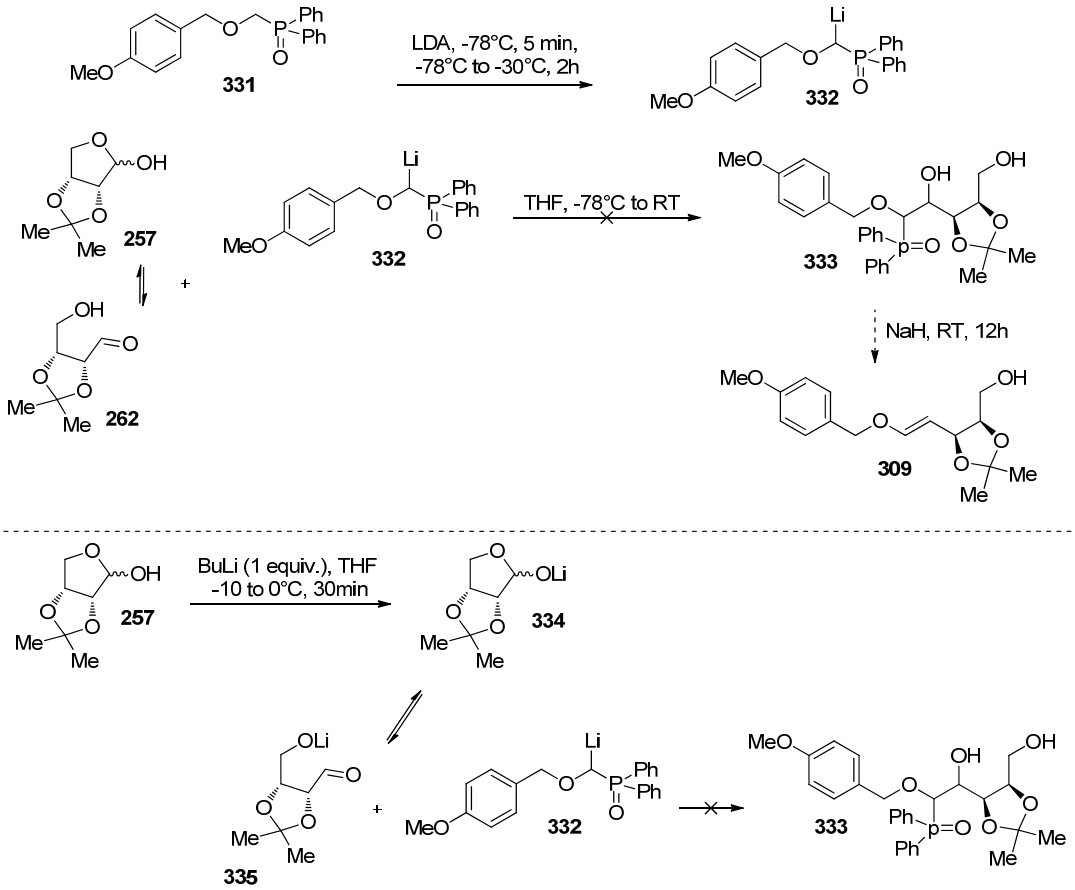
As a result, our attempts began with the pre*para*tion of (hydroxymethyl)diphenylphosphine oxide **330**,according to a short and efficient synthetic protocol described by Kiyokawa *et al.*[64] (**scheme 65**). The sole inconvenience of this method was linked to the scale-up of the reaction, as a high volume of saturated solution of $NaHCO_3$ was demanded to neutralise the excess HCl. This method has demonstrated its efficiency with a reproducible yield even at multigram scale, in addition to the easy access of the starting material. With the (hydroxymethyl)diphenyl phosphine oxide **330** in hands, the same benzylation, as for the (((4-methoxybenzyl)oxy) methyl)phosphonate **331**, was performed in the presence of trichloroacetimidate **174** and a catalytic amount of triflic acid to accomplish the synthesis of (((4- methoxybenzyl)oxy)methyl) diphenylphosphine oxide **331** as a white powder. Both triflic acid and camphorsulfonic acid proved to be suitable catalyst, though the latter, being an anhydrous powder, would be easier to handle than triflic acid which is much more sensitive to moisture.



Scheme 65: Synthesis of (((4-methoxybenzyl)oxy)methyl)diphenylphosphine oxide **331**

The Horner-Wittig olefination had to be initiated by a deprotonation leading to a metallated phosphine oxide. Initially, Horner *et al.* carried out their deprotonation in the presence of potassium *tert*-butoxide to produce the alkenes in a one-pot manner.[58] But they quickly recognised the possible splitting of the olefination into two distinct steps: the first step was composed of the addition of a lithiated phosphine oxide to a carbonyl, providing two isolated and se*para*ted diastereomers, and the second step as the elimination of a phosphinic acid to afford the corresponding alkenes with high geometrical purity. While the alkyldiphenylphosphine oxides were normally deprotonated with BuLi in THF,[65] researchers from the group of Warren referred briefly to incorporation of butyl groups upon the treatment of the (methoxymethyl)diphenylphosphine oxide **312** with BuLi at an array of temperatures (-78°C, 0°C and 25°C).[61] This observation prompted us to try lithium di-*iso*propylamide (LDA) to

deprotonate the newly formed α-methoxyalkylphosphine oxide **331**. Especially because the authors reported that LDA has not only proven to provide sufficiently stable lithiated phosphine oxide **313** (at 0°C for 10min) but also allowed the isolation of diastereoisomers of **315** (**scheme 63**).[61]



Scheme 66: Attempts to access the PMB enol ether **309** *via* the corresponding anion of (((4- methoxybenzyl)oxy)methyl)diphenylphosphine oxide **331**

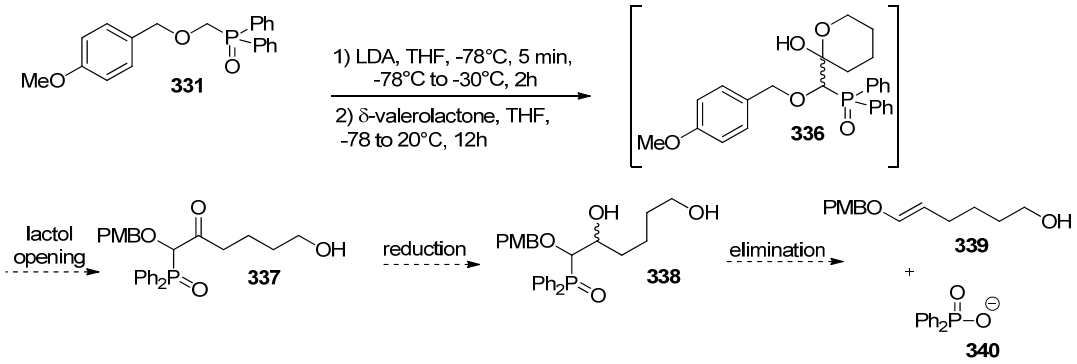
To a solution of LDA (prepared in situ by addition of BuLi to DIPA in THF at -78°C followed by vigorous stirring for at least 30 min) was added dropwise phosphine oxide **331** in THF at -78°C. The solution was kept at -78°C for 5 to 10 min, and allowed to warm up to -30°C within 2h, turning into a clear and dark red solution (as it was the case of diphenyl (methoxymethyl) phosphine oxide **312** in the presence of LDA at 0°C).[65] According to the authors, subsequent addition of the carbonyl electrophile to the corresponding lithium anions of phosphine oxides in THF gave the best results at -78°C.[61] Therefore, a solution of lactol **257** in THF was added to the burgundy solution of 2 equivalents of lithiated phosphine oxide **332** at -78°C. Alternatively, lactol was first deprotonated by Buli at -10°C, in order to avoid the use of 2 equivalents of phosphine oxide **331** (synthesised in 2 steps),then added to the solution of the corresponding anion phosphine oxide **332** at -78°C. Afterwards, the mixture was allowed to warm up to 20°C under vigorous stirring overnight. Unfortunately, no trace of the expected intermediate **333**

was observed, in both cases, within the tested array of reaction temperatures as represented in **Table 5** below.

Deprotonation of phosphine oxide 331	Conditions after addition of lactol 257 at -78°C
LDA, -78°C, 1h30 to 2h	-78°C to 0°C, 12h
LDA, -78°C, 1h30 to 2h	-78°C to 20°C, 12h
LDA, -78°C, 1h30 to 2h	-78°C to -20°C, 3h then -20°C, 12h
LDA, -78°C, 1h30 to 2h	-78°C, 1h then 0°C, 12h
LDA, -78°C, 1h30 to 2h	-78°C, 15 min, -10 to 0°C, 12h

Table 5: Horner-Wittig Reaction conditions applied to (((4- methoxybenzyl)oxy)methyl)diphenylphosphine oxide **331** and lactol **257**

Even though the group of Warren has reported reactions of lithium derivatives of alkyldiphenylphosphine oxides with aldehydes to make alcohols which rearranged to the corresponding allyl compounds,[61] to the best of our knowledge, no reactions involving lactols have been so far mentioned in the literature. The Horner-Wittig-based reaction applied to the open chain form hydroxyaldehyde **262** was trickier than expected, supposedly due to the equilibrium far in favour of the strain-free 5-membered cyclic hemiketal **257**. On the other hand, when the temperature exceeds 0°C, the lithium derivative of phosphine oxide **331** was likely to decompose into an uncharacterised PMB containing compound.



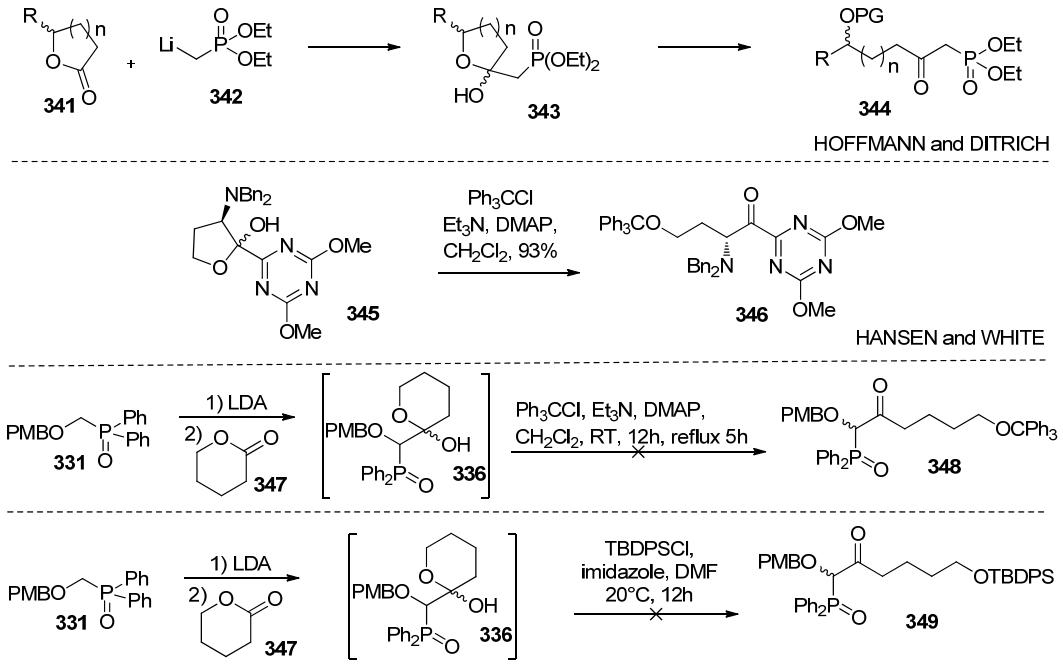
Scheme 67: Addition of lithium derivative of phosphine oxide **331** onto δ-valerolactone

In the interest of verifying the existence of the lithium derivative of phosphine oxide **331**, and in particular its nucleophile strength, δ-valerolactone was used as testing electrophile (**scheme 67**). Following closely the procedure described by Warren *et al.*,[66] to the dark red solution of deprotonated phosphine oxide **331** at -78°C was added dropwise δ-valerolactone. The solution was vigorously stirred between -78°C and 20°C overnight, providing the expected adduct **336**. Given the eager transformation of hemiacetals under acidic conditions, it was advisable to attain in the first place the hydroxyketone form of **257**. In the literature, to open a γ- or δ-lactol, one of the common methods consists in trapping the primary alcohol, which in this case would lead to compound **338**.

In 1985, Ditrich and Hoffmann have reported a reliable one pot procedure to convert 5-membered and 6-membered lactones **341** into the 5-(or 6)-silyloxy-3-keto-phosphonates **342**.[67]Their method resides in the transformation of lactones **341** into the corresponding lactols **343**, which upon treatment with LDA and silyl chlorides, *e.g*. trimethylsilyl chloride, provided the protected alcohol **344** (**scheme 68**). More recently, White and Hansen succeeded

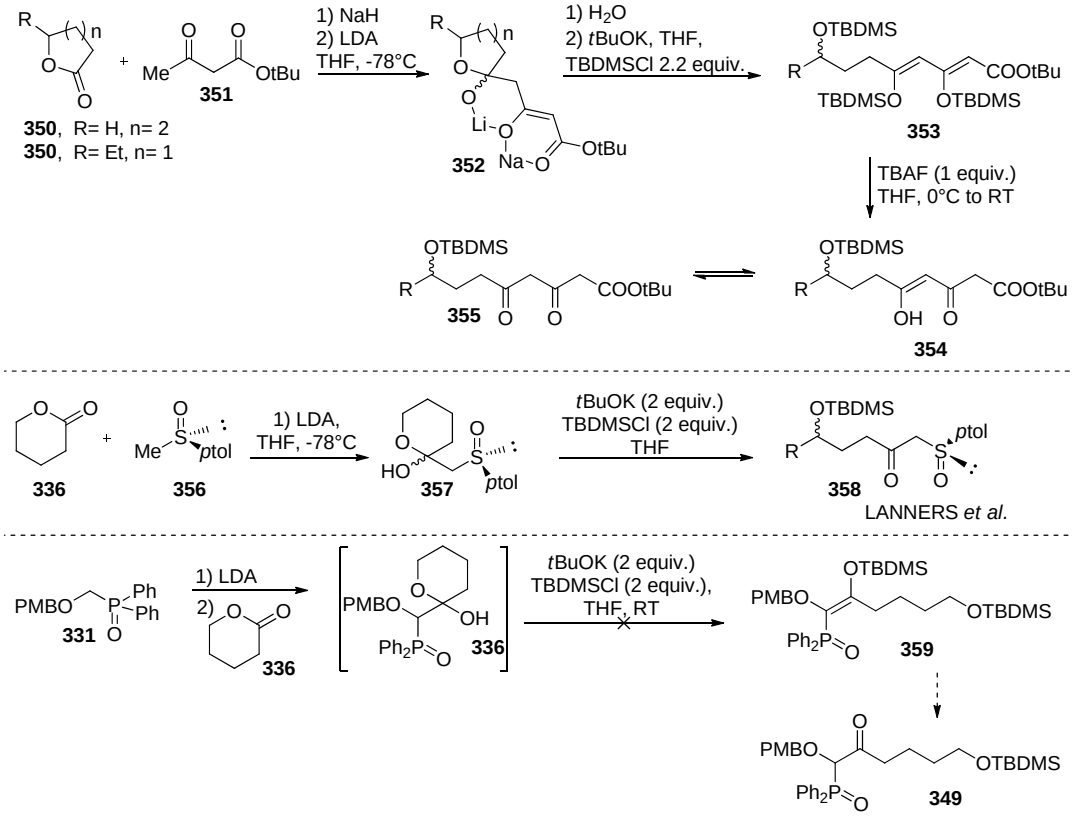
in obtaining the ring-opened isomer of adduct **345** as the corresponding compound **346**.[68] Though there was no evidence about the equilibrium between **345** and its hydroxyketone isomer, exposure of **345** to trityl chloride and triethylamine in a catalytic presence of DMAP resulted in trityl ether **346**.

The choice of a bulky protecting group, *e.g*. trityl, was to avoid protection of the lactol. In spite of the insignificant amount at equilibrium of the hydroxyketone isomer of **347** at it equilibrium, its protection would remove it from the reaction mixture, and hence shift the equilibrium into the ring-opened form. Following the same procedure described by White and Hansen,[68] our first attempts aimed to transform the primary alcohol of the ring-opened isomer of **257** as trityl ether **348** (**scheme 66**). The resulting crude mixture did not contain the desired product **348** while the adduct **336** was seemingly decomposed. Other trials using TBDPSCl or TMSCl in the presence of imidazole in DMF at room temperature did not provide the corresponding silyl ethers either.



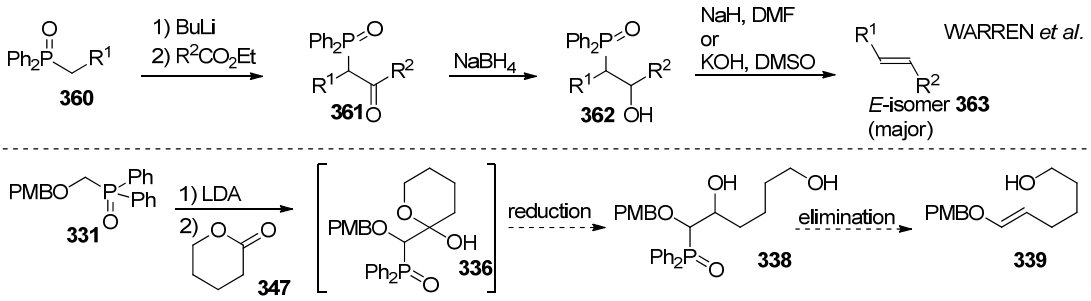
Scheme 68: Attempts to open the cyclic hemiacetal **336**

An alternative method for opening γ-, δ-, and ε-lactones was published by Lanners *et al.*, which was based on the treatment of the potassium open-chain dianion **352** (resulting from the attack of lithium enolate of ester **351** onto lactones, *e.g.*δ-valerolactone **347**) with 2 equivalents of bulky silylating reagent, giving cleanly the tri-silylated compound **353** (**scheme 69**).[69] By exposing **347** to one equivalent of TBAF, the authors obtained silyloxy-□□□-diketoesters **357** in quantitative amount. The same reaction sequence was also applicable to methylsulfoxide carbanion to afford β-ketosulfoxide **358** from the corresponding δ-valerolactone **347**. Interestingly, the addition of two equivalents of TBDMSCl, though only one equivalent would be required, to the hemiketal **357** directly led to the formation of □-ketosulfoxide **358** in good yield. Unfortunately, treatment of our phosphine oxide adduct **9** with two equivalents of *t*BuOK, followed by two equivalents of TBDPSCl under the same conditions did not give the expected disilylated intermediate **359**, or the □-ketophosphine oxide **349**.



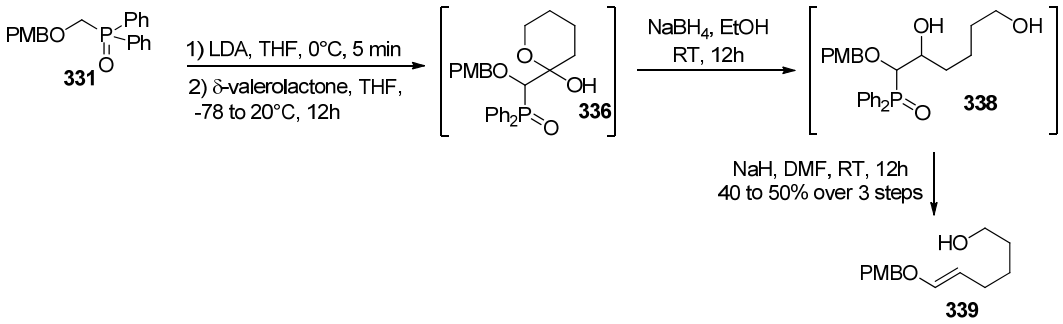
Scheme 69: Alternative method for the opening of cyclic hemiketal **336**

Subsequent to the unsuccessful trials to trap the open-chain isomer of **336** in view of reducing the resulting ?-ketone function **349** to access the intermediate **338**, we turned to another approach as presented in **scheme 70**. This was inspired by the work of Warren *et al.* who observed the formation of *E*-isomer **363** by diphenylphosphite (**340**) elimination of intermediate **362** resulting from the stereoselective reduction of β-ketophosphine oxide **361** by $NaBH_4$.[70] It was hence feasible to submit hemiketal **336** to a reduction to provide the corresponding diol **338** which would be eliminated into enol ether **339**.



Scheme 70: Lactol opening by direct reduction of phophine oxide **364**

The sequence started with the attack of the lithium anion derivative of **331** onto δ-valerolactone, followed by submission of the crude intermediate **336** to $NaBH_4$ reduction in ethanol at room temperature (**scheme 71**). After the acidic workup, the resulting mixture was exposed to 2 equivalents of NaH in DMF at 20°C overnight. To our delight, the PMB-ether enol **339** was obtained upon flash chromatography purification with an overall yield between 40 and 50% over 3 steps.

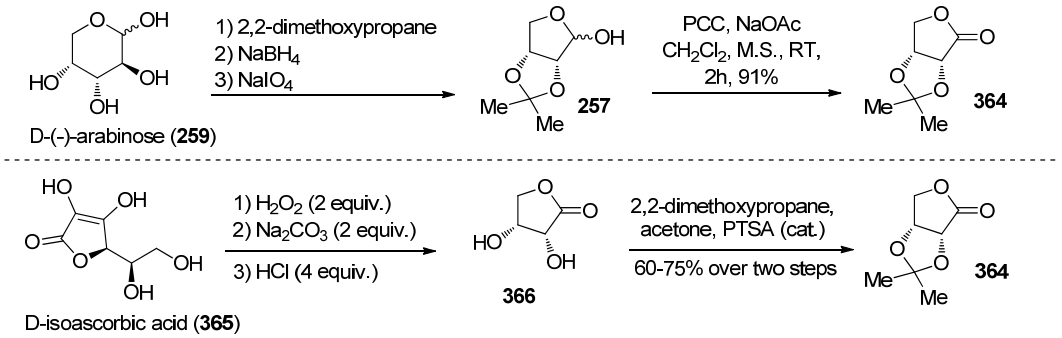


Scheme 71: Reaction sequence transforming δ-valerolactone into enol ether **339**

Encouraged by this outcome, we embarked on the synthesis of the desired PMB-enol ether **339**, which initiated with the addition of lithium anion derivative of phosphine oxide **331** onto the corresponding lactone of the readily prepared 2,3-O-isopropylidene-d-erythronolactol **257**. This required a prior pre*para*tion of the lactone **364** as presented in **scheme 72**. The first method was based on a simple oxidation of the available lactol **257**, using pyridinium chlorochromate under basic conditions (NaOAc), due to the acid-labile acetonide at room temperature. In the absence of NaOAc, the oxidation yield remained very low in spite of the total conversion of lactol **257**.

2.2.1.3 Third generation strategy: "D-isoascorbic acid approach"

Another synthetic procedure employing D-isoascorbic acid **365** as starting material was well-described by Cohen *et al.* (**scheme 72**).[71] The erythorbic acid **365** was subjected to hydrogen peroxide in the presence of sodium carbonate, and acidified by hydrochloric acid to provide D-erythronolactone **366**. Protection by 2,2-dimethoxypropane catalysed by *p*-toluenesulfonic acid furnished the wanted lactone **364** in relatively good yields. This sequence gave a more direct access to lactone **364** as it required fewer intermediate purification, cheaper starting material and allowed a more efficient scale-up procedure.

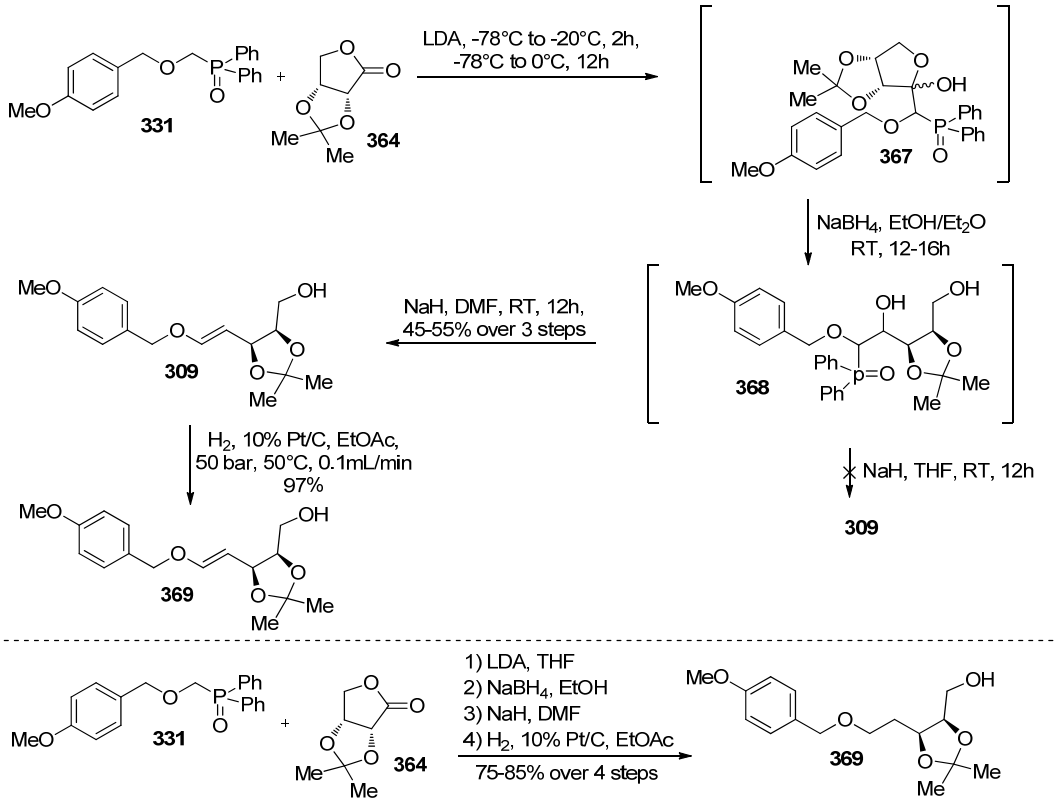


Scheme 72: Two synthetic methods towards 2,3-O-isopropylidene-D-erythronolactol **364**

With lactone **364** in hands, we applied the same reaction sequence with some subtle modifications that are featured in **scheme 73**. The first step consisted in deprotonation phosphine oxide **331** by a solution of LDA, prepared *in situ* by a solution of *Buli* and DIPA in THF at -78°C. The deep red solution was stirred between -78°C and -20°C during 2h, instead of 5 to 10 minutes at 0°C, which gave ostensibly a cleaner resulting product. A solution of lactone **364** in THF was added at -78°C and the mixture stirred between -78°C and 0°C overnight. As previously described, the reduction of **367** was carried out in the presence of $NaBH_4$ in a mixture of ethanol and ether at 20°C overnight. The resulting crude intermediate **368** had to be dried under reduced pressure until obtainment of an opaque white powder, before being subjected to a NaH-assisted elimination in anhydrous DMF. Interestingly, reactions which were carried out in THF would not lead to any desired elimination product, but a complete destruction of **368**. Isolation of **309** gave an average yield that fluctuated between 45 and 55% over 3 steps, *via* flash chromatography employing silicagel which was neturoalised by triethylamine. The subsequent hydrogenation was carried out in H-cube® through at a flow rate of 1 mL/min through a 10% Pt/C cartridge, at 50°C and 50 bar. The outcome hydrogenated solution provided without purification, up to 98% of yield the desired compound **369**. On the other hand, the same results have been obtained by means of batch hydrogenation, using 10 %-mol $PtO_2.H_2O$ in EtOAc. The 3-phased mixture was vigorously stirred at ambient temperature and pressure for 12 to 24h till completion and the catalyst was carefully filtered off through a celite pad.

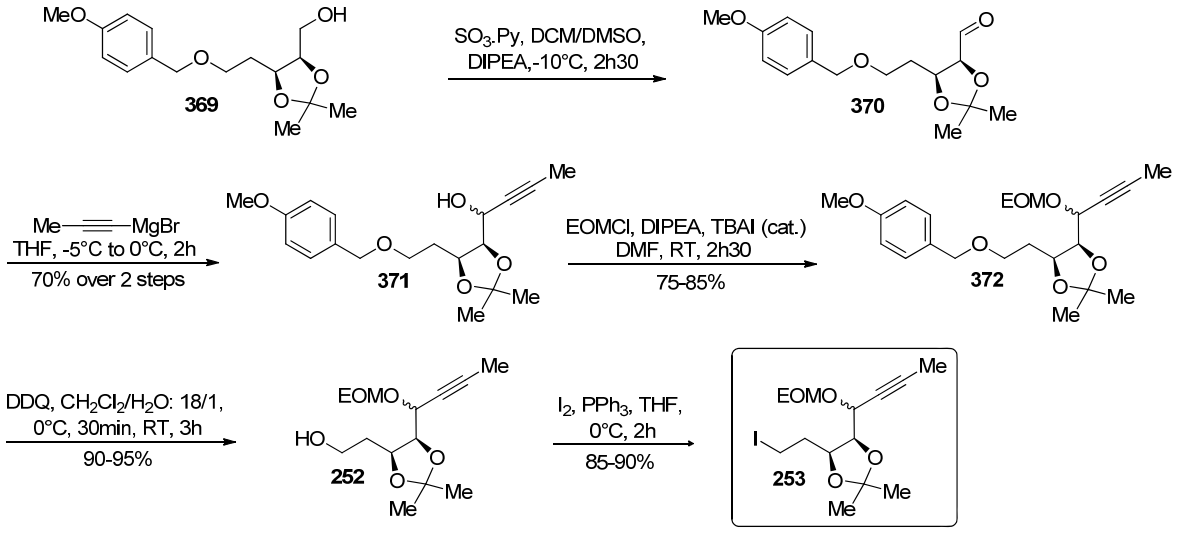
Given the generally known instability of enol ethers, it seemed to be more appropriate not to purify the intermediate **309** prior to the hydrogenation. This led to a sequence that combined all the 4 aforementioned synthetic steps without intermediate purification. To our great delight, the overall yield could reach up to 85%. However, in case the resulting ether enol was

not isolated, hydrogenation in a flask was more convenient than continuous flow hydrogenation. Indeed, the crude product from $NaBH_4$ reduction caused a more recurrent blockage of Pd/C cartridges, while it was less wasteful to add, 6h after the first addition, another 5 %-mol of $PtO_2.H_2O$ to accomplish the reaction in the flask.



Scheme 73: Reaction sequence towards PMB ether **369**

Convincingly, the one-carbon homologation, together with the introduction of the *para*-methoxy benzyl leading to the PMB enol ether was achievable by means of diphenylphosphine oxide **369**, whereas the corresponding triphenylphosphonium **282** as well as diethyl phosphonate **308** failed. Even though the Horner-Wittig reaction could not be directly conducted with lactol **257** as expected, the relatively high and reproducible yields over 4 consecutive steps have proven a novel alternative pathway to open lactones. Moreover, this method has been proven robust by an easy scale-up to afford the desired PMB protected diol in multigram amount.

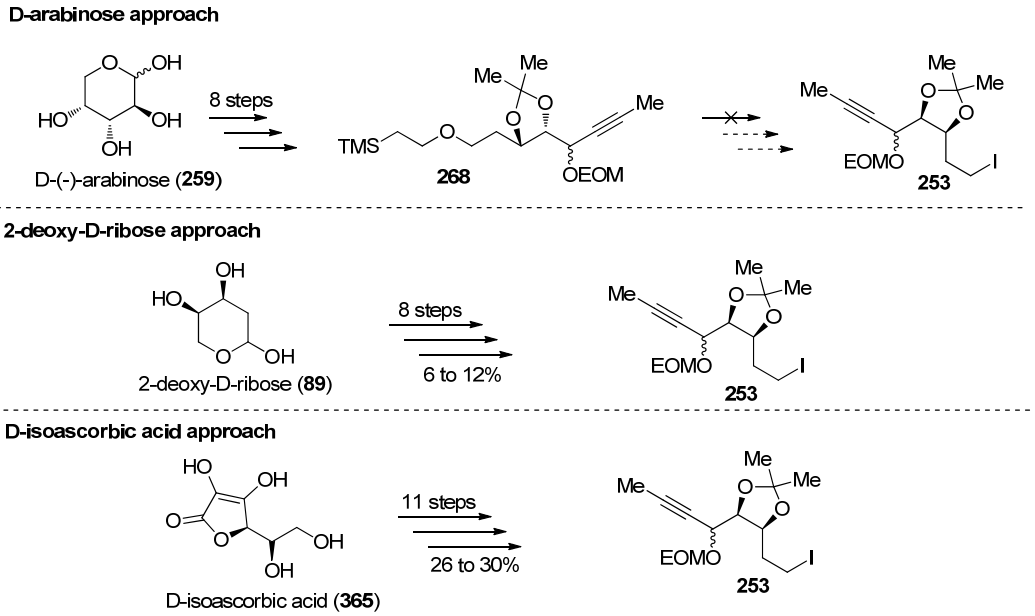


Scheme 74: Accomplishment of iodide fragment **253**

Similar to the previous route, the next step was the oxidation of the primary alcohol in the presence of complex SO_3·pyr and *N,N*-diisopropylethylamine in a mixture of DMSO and CH_2Cl_2 at low temperature (**scheme 74**). This oxidation method was mild enough to avoid the cleavage of acid-labile dioxolane, but the temperature had to be maintained under 0°C to avoid the undesired Pummerer reaction. The obtained crude mixture, containing no trace of Pummerer product according to NMR analysis, was directly subjected to Grignard addition of commercial prop-1-yn-1-ylmagnesium bromide in THF, affording intermediate **371** in adequately high yield (70% over 2 steps). Like in the first strategic approach ("2-deoxy-D-ribose approach" from section *2.2.1.1*), the newly formed alcohol was protected as ethoxymethoxy ether **372**, upon subjection of **371** to EOMCl, DIPEA and catalytic TBAI in DMF. The fully protected polyol **372** was then treated with a solution of DDQ in wet dichloromethane. When the reaction was maintained at 0°C, DDQ had to be added till total conversion, the resulting crude product was a very complex mixture, which gave less than 60% of the desired alcohol. But when stirred at 0°C for 30 minutes, then at room temperature, the reaction was completed within 2 hours. To our great pleasure, this oxidation cleaved **372** into *p*-methoxybenzaldehyde and the anticipated alcohol **252** in very high yield (90 to 95%). This synthetic sequence merged with the "2-deoxy-D-ribose approach" *via* the achievement of this polyol fragment, starting with D-isoascorbic acid (**365**) as the chiral pool for the anti-diol at C5'-C6'.

The ensuing iodination under Appel conditions (I_2 and PPh_3 in THF at 0°C) gave com*para*ble results after purification as the first synthetic approach (**scheme 42**).

- **Conclusion**

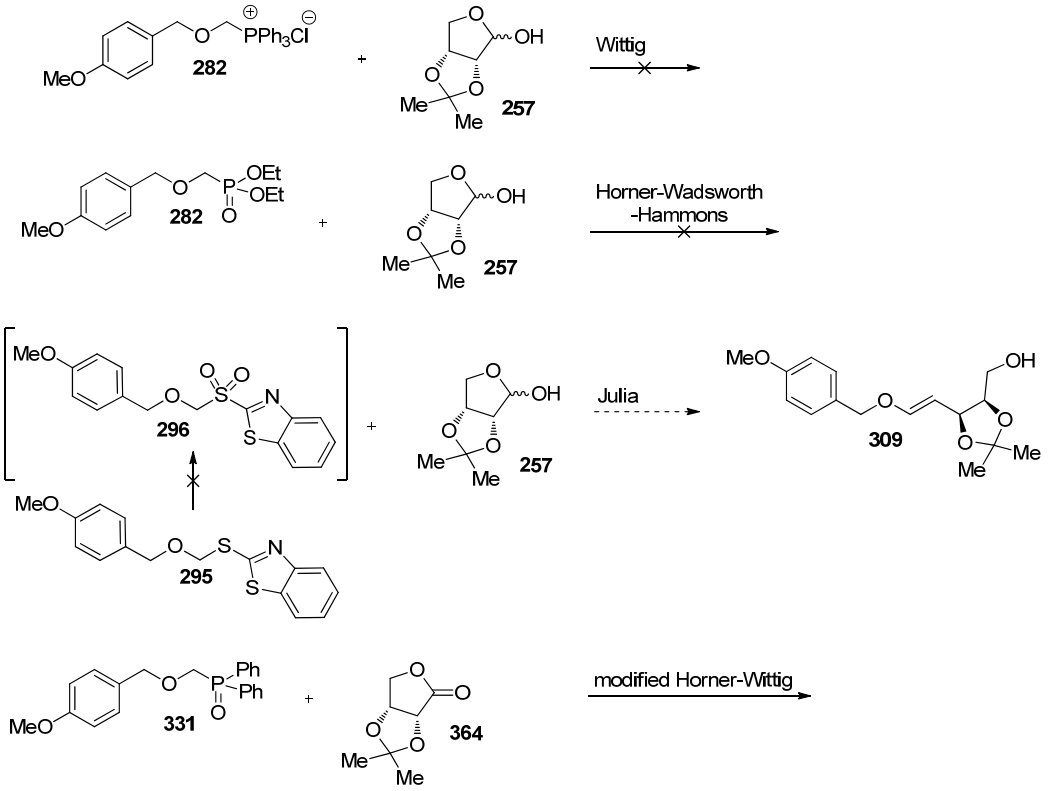


Scheme 75: 2-deoxy-D-ribose approach *versus* D-isoisoascorbic acid approach

In conclusion, we have succeeded in obtaining the iodide intermediate **253** as one of the three fragments required for convergent synthesis towards metabolite L-783,277 (**7**). Starting with D-isoascorbic acid (**365**), the last synthetic pathway was composed of 11 steps with 33% of overall yield (**scheme 75**). The very first synthetic approach starting with 2-deoxy-D-ribose (**89**) included 8 steps with 11% of overall yield. This low overall yield was due to the unselective and unrepeatable mono-protection of primary diol **247**, the third step in the sequence. In addition, the handling of some intermediates, as well as the starting material 2-deoxy-D-ribose (**89**), was difficult on a multigram scale. Despite its longer sequence, the D-isoisoascorbic acid approach provided **253** in relatively higher yield, which is also reproducible on multigram scale.

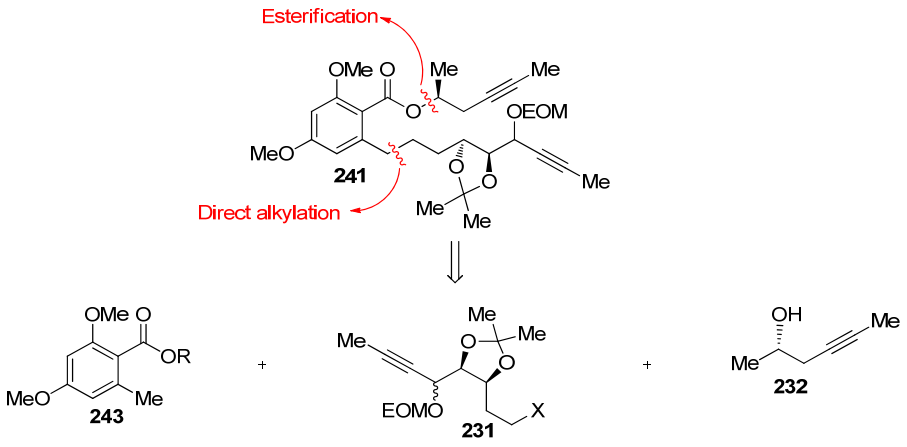
The D-arabinose approach led to compound **268**, containing a TMSE-ether which proved to be too stable to be selectively cleaved under commonly described conditions. This was the first dead end of a series of attempts to attain segment **253**, leading consequently to the pre*para*tion of PMB enol ether **309**, an intermediate which was finally obtained *via* the D-isoascorbic acid sequence.

Hereafter, **scheme 76** illustrates our various attempts to obtain the intermediate enol ether **309**. Notably, the success of the D-isoascorbic acid approach depended on the Horner-Wittig based olefination combined with intermediate reduction the pre*para*tion of PMB-enol ether **309**. Indeed, the 4 successive steps illustrated in **scheme 73**, without isolation of intermediates, have been proven to be not only concise and promising, but also very reliable method.



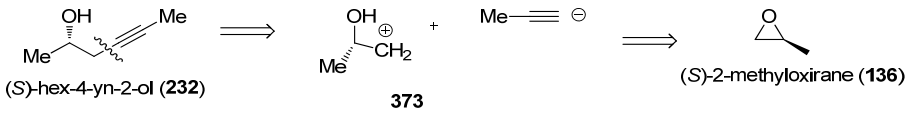
Scheme 76: Attempts to achieve PMB-enol ether **509** *via* various olefination methods

Transforming alcohol **252** into the corresponding iodide **253** instead of another corresponding haloalkanes or tosylate **255** (**scheme 42**) resulted from previous trials targeting a direct alkylation at the benzylic position of the aromatic core of L-783,277 (**7**). The next chapter will deal with this key step of our synthetic scheme towards the formal synthesis of L-783,277 (**7**), and hence our choice of the appropriate leaving group for the polyol segment **231** illustrated in **scheme 77** below.



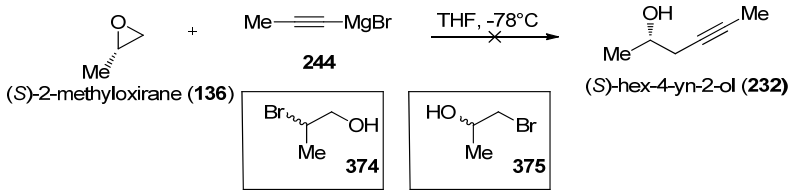
Scheme 77: Expected assembly of the three segments

2.2.2 Synthesis of *(S)*-hex-4-yn-2-ol (232)



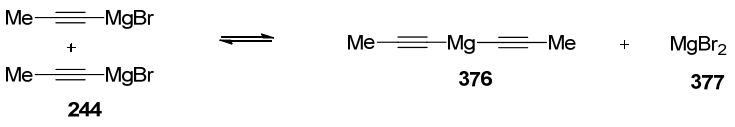
Scheme 78: First retrosynthesis of *(S)*-hex-4-yn-2-ol (**232**)

In compliance with the disconnections of dialkyne prescursor **241** (**scheme 41**), the stereochemistry of the carbon at α position to the aromatic carbonate would originate from the propargylic fraction **232**, whose retrosynthetic cleavage was illustrated in **scheme 78**. The required propargylic alcohol **232** appeared to be readily available from rather simple building blocks *via* a regioselective opening of *(S)*-2-methyloxirane(**136**) by an alkynyl anion. The latter was at first employed as the commercially available Grignard reagent **244**.



Scheme 79: Unsuccessful epoxide opening *via* Grignard reagent **244**

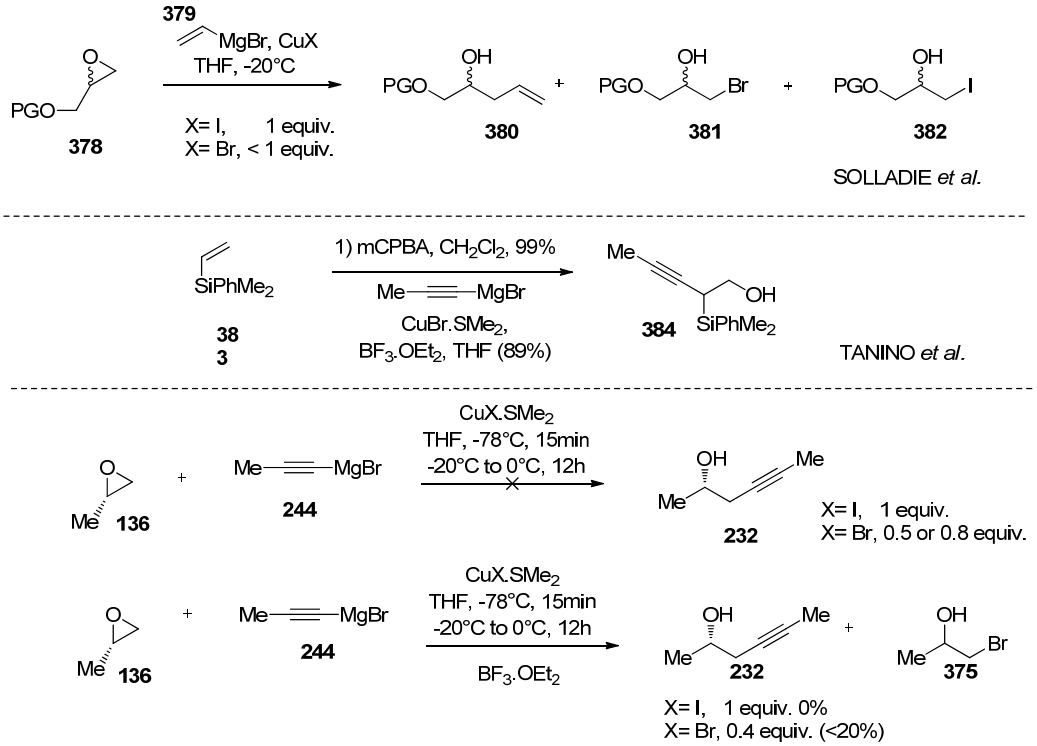
The magnesium bromide was added to a solution of *(S)*-2-methyloxirane **136** at -78°C in THF (**scheme 79**). The reaction was allowed to warm up to -20°C within 4h then stirred for further 4h at 0°C. Isolation of the main resulting product gave evidence, unfortunately, of the presence of the unintended bromohydrin **375**, and surprisingly, no trace of its isomer bromohydrin **374** was observed. Even at a constantly low temperature (-20°C) during the reaction time, the same product was still formed. Obviously, this phenomenon was induced by the Schlenk equilibrium, a well-known process which took place in the solution of Grignard reagent and led to the emergence of dibromide magnesium (**scheme 80**).



Scheme 80: Schlenk equilibrium

This degradation of the propargyl magnesium bromide was unavoidable and the ability of metal halides to open simple and functionalised epoxides has also been mentioned in the literature. This tendency of Grignard reagent to afford magnesium halide salt was interestingly tampered by the additional presence of copper halide, *e.g.* $CuI.SMe_2$ or $CuBr.SMe_2$. For instance, Solladié and co-workers had access to five-carbon functionalised homoallylic alcohols by regioselective ring opening with vinylmagnesium bromide.[72] Their careful and extensive

study on the opening reaction of protected epoxide **378** (protecting group= Bn, MPM, TBS, TBDPS, respectively). They found out that Cu(I) salts alone did not open oxiranes **378**, whereas the Grignard reagent **379** alone furnished mainly bromohydrin **381**, together with a small amount of bromohydrin **382**, but when used in combination they granted homoallylic alcohols **380** in excellent yields (**scheme 81**).[72] Some years later, Tanino *et al.* oxidised the commercially available allylsilane **384**, then exposed the resulting epoxide to an efficient ring-opening method where prop-1-yn-1-ylmagnesium bromide **245** was used, along with $CuBr.SMe_2$ in the presence of a Lewis acid, $BF_3.OEt_2$.[73]



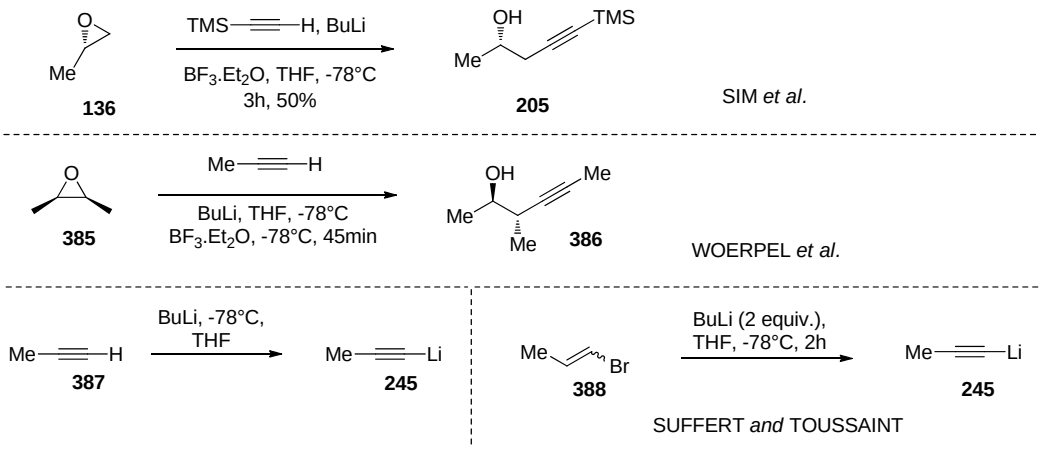
Scheme 81: Attempts to open *(S)*-2-methyloxirane (**136**) by Grignard reagent and Cu(I) salts in the manner of Solladié's group and Tanino's group

Convinced by the reasonable synergy of a Grignard reagent and a monohalide cupper, we ventured the opening of enantiomerically pure epoxide **136** with prop-1-yn-1-ylmagnesium bromide (**244**) in the presence of either CuI (1 equivalent) or CuBr (0.5 to 0.8 equivalent). The end result was only complex mixtures of several unidentified compounds, among those there was no observation of propargylic alcohol **232**. In the meantime, other trials were carried out in the same conditions, with addition of Lewis acid $BF_3.OEt_2$, as described by Tanino *et al.*,[73] which, to our discontent, did not give any better result when combined with CuI. Nevertheless, when 0.4 equivalent of $CuBr.SMe_2$ was employed, the desired product was formed, together with the bromohydrin **375** as observed when no copper salt was present, though in very low yields (less than 20%). These outcomes ended our intention to employ an organomagnesium as epoxide opening reagent and turned our attention to the corresponding organolithium.

One decade ago, Woerpel and collaborators succeeded in opening the achiral epoxide **385**, using prop-1-yn-1-yllithium **245**, in combination with $BF_3.OEt_2$ at -78°C, overmatching the steric hindrance of both tertiary carbons (**scheme 82**).[74] Typically, organolithiums have proven to be

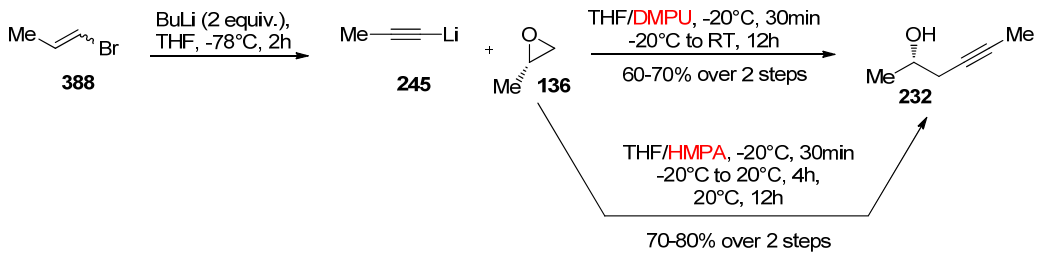
more basic than Grignard reagents, and do not create any lithium salt susceptible to induce an acid-catalysed opening of epoxides. More recently, the Korean group of Sim had recourse to ((trimethylsilyl)ethynyl)lithium formed *in situ* in the presence of $BF_3.OEt_2$ at -78°C to open regioselectively *(S)*-propylene oxide (**136**), as previously mentioned in section *1.2.3*.[75] The final yield was nevertheless only half amount of the expected amount.

For these reasons, we envisaged to resort to the corresponding prop-1-yn-1-yllithium to gain access to the enantiomerically pure homoallylic alcohol **1**.



Scheme 82: Epoxide opening by prop-1-yn-1yllithium (**244**)

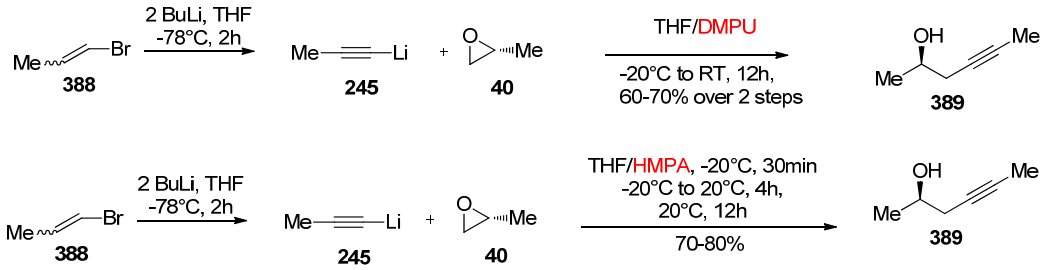
The first idea for the synthesis of the related organolithium would naturally evoke the commonly known treatment of prop-1-yne (**387**) with butyllithium at low temperature, as described by the group of Woerpel, who engaged this reaction *in situ* to open epoxide **385**.[74] Nonetheless, the use of prop-1-yne (**387**) did not appeal to us, due to its very low boiling point, hence impractical laboratory manipulation. Fortunately, Suffert and Toussaint developed a convenient method to obtain prop-1-yn-1-yllithium (**245**) from a *E/Z* mixture of bromo-1-propene (**388**) upon treatment with 2 equivalents of butyllithium.[76] This pre*para*tion step preceded the opening of oxirane **136** in the same manner detailed by Fürstner and co-workers as part of their innovative synthetic design of *(S)*-(+)-citreofuran.[77]



Scheme 83: Synthesis of *(S)*-hex-4-yn-2-ol (**136**)

Actually, the prop-1-yn-1-yllithium (**245**) was prepared *in situ* from the commercially procured bromo-1-propene (**388**) in THF at -78°C. After 2 hours, the reaction mixture was allowed to

warm up to -20°C over a period of 5 minutes before the addition of DMPU, and kept at this temperature for 30 minutes, followed by very slow addition of *(S)*-methyloxirane (**136**) in DMPU.[78] Most of the experiments were performed in the presence of DMPU as co-solvent provided the desired product at 40% to 60% yields. Some other trials which were conducted in the same conditions, in default of DMPU, would only led to very bad yields (lower than 15%). On the other hand, when the temperature exceeded -20°C right after the addition of DMPU, or the reaction temperature remained at 0°C overnight, the overall yields also shrank considerably. The use of DMPU presumably was crucial for the opening process, in the same modus operandi as HMPA in the opening of *(R)*-propylene oxide (**390**) by pentyne anion by the research group of Cho.[78] We were rather surprised to gain in yields while replacing DMPU with HMPA, which was certainly accounted as highly toxic, therefore often disfavored in comparison to the not yet listed as harmful DMPU. Considering the final high yields, we preferred though to use HMPA for the scale-up synthesis of the propargylic alcohol **3**.

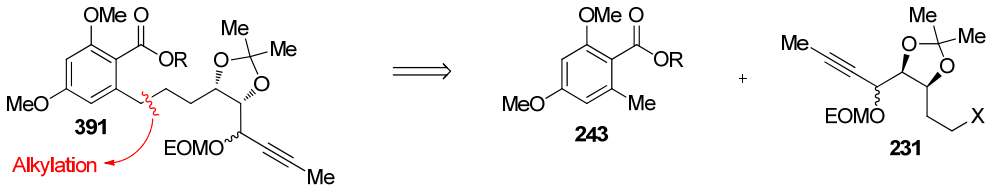


Scheme 84: Synthesis of *(R)*-hex-4-yn-2-ol (**389**)

To sum up, the alcohol fragment *(S)*-hex-4-yn-2-ol (**232**) could be achieved on multigram scale from the commercially available bromo-1-propene and *(S)*-propylene oxide (**232**), the chiral pool containing the right configuration for the C10' carbon from L-783,277 (**7**), if the upcoming connection to the aromatic section ensued from an esterification. In case the esterification did not the alternative connection induced an inversion of configuration at the carbon in question, the *R*-enantiomer (**389**) could also be obtained by the same protocol, starting this time with the corresponding *R*-propylene oxide **40** (**scheme 84**).

2.3 Assembly of the building blocks

2.3.1 Direct benzylic alkylation

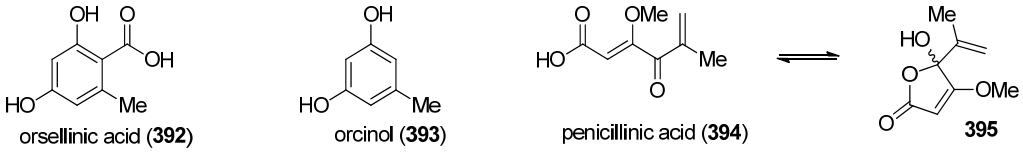


Scheme 85: Expected alkylation at benzylic position as the key step of our retrosynthesis

As indicated above, we envisioned that the synthon **231** would be appended to the aromatic moiety **243** *via* a direct S_N2 alkylation, a major improvement in atom economy of our sequence if successfully achieved. Regarding the same strategic transformation from the group of Winssinger, where the acid function of the orsellinic acid derivatives was masked as an ester prior to the deprotonation at the benzylic position,[1, 79] we decided to take the same precaution. Consequently, the pre*para*tion of the fragment **243**, both as free benzoic acid derivative and its corresponding ester took place. The subsequent step would consist in finding the right conditions to deprotonate at the benzylic position of orsellinic ester **234**, as well as the appropriate leaving group for the polyol **231**.

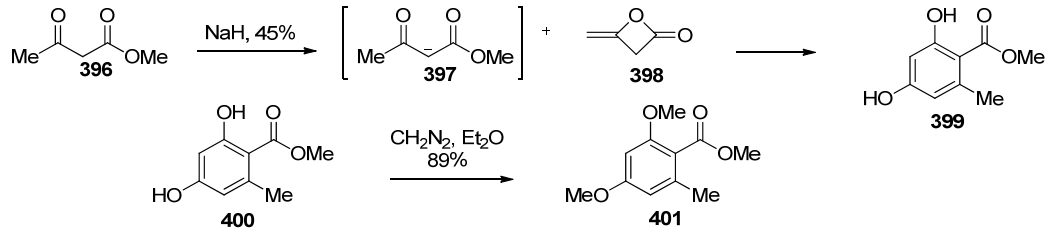
- **Pre*para*tion of orsellinic acid (401)**

Orsellinic acid (**392**), together with orcinol (**393**) and penicillinic acid (**394**), were isolated from the culture of *Penicillium fennelliae*.[80] Orsellinic acid plays an important role in the biochemistry of lichens, where the biosynthesis proceeds *via* polyketide way.



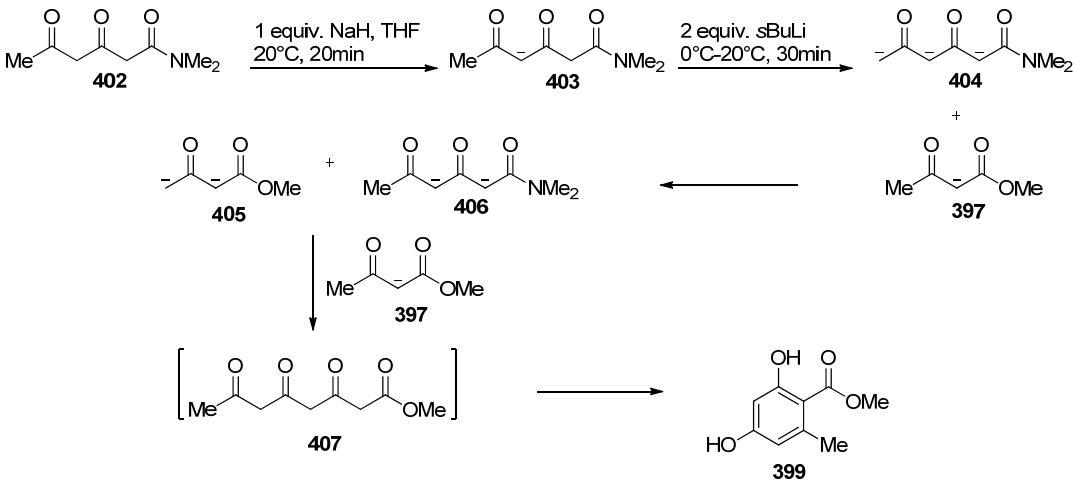
Scheme 86: Orsellinic acid (**392**), orcinol (**393**) and penicillinic acid (**394**)

The pre*para*tion of orsellinic acid **431** has been subject of several studies in the literature, involving different synthetic routes as well as various starting materials. Among these, for instance, the synthetic route taken by Kato and Hozumi in 1972 implicated the nucleophilic attack of the active methylene of β-ketoester **396** in the presence of sodium hydride onto diketene **398**, leading to the formation of methyl orsellinic ester **399** (**scheme 87**).[81] The protection of the diphenol moiety took place under the efficient treatment of **400** with diazomethane in ether, giving the totally protected orsellinic acid **401** in good yields (45% and 89%).



Scheme 87: Pre*para*tion of orsellinic acid **401** and its methylated derivative by Kato and Hozumi in 1972

Almost one decade later, Hubbard and Harris published another method yielding methyl orsellinate **399** which originated from the converting of the monoanion of methyl acetoacetate to the related dianion **405** by trianion **406**, itself came from two successive deprotonations (**scheme 88**).[82] As a consequence, the dianion **397** condensed with methyl acetoacetate monoanion to give methyl 3,5,7-trioxo-octanoate **407**, which, through an aldol cyclisation during chromatography, provided the methyl orsellinate **399**.

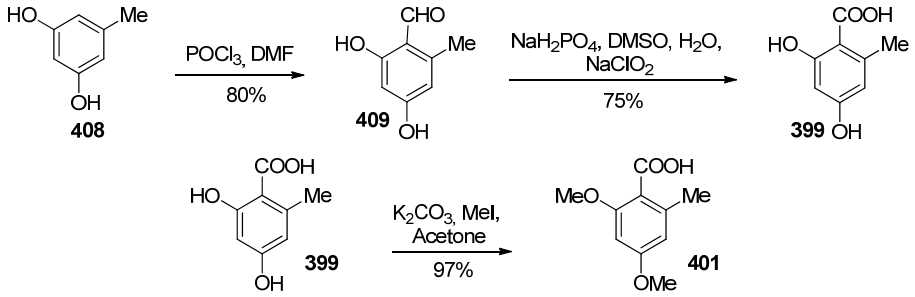


Scheme 88: Pre*para*tion of methyl orsellinoate **399** by Hubbard and Harris in 1981

Another pre*para*tive method of orsellinic acid was also reported by Nicolaou *et al.* as part of their strategic approach towards the stereocontrolled synthesis of the Everninomicin $A_1B(A)C$ ring framework.[83] Using the relatively cheap commercially available orcinol (**393**) as starting material and the convenient, classic synthetic techniques employed by the authors, this approach by Nicolaou's group seemed to be appropriate to prepare the aromatic structure of L-783,277 (**7**). Moreover, this pre*para*tive method does not result in an orsellinate derivative (*e.g.* methyl orsellinate) which necessitates a supplementary step to release the acid moiety, but directly afforded the desired orsellinic acid **401**.

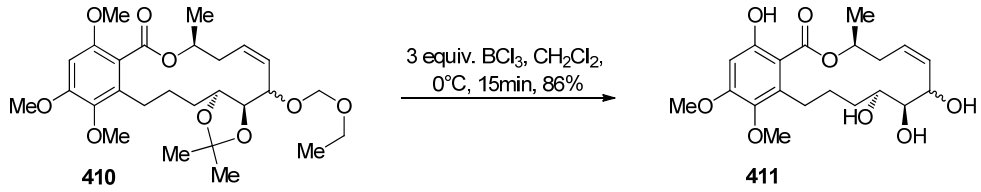
The first step consisted in a Vilsmeier-Haack formylation of orcinol **393** which gave the corresponding aromatic aldehyde **409** in rather high yield (80%) (**scheme 89**). Exposure of **409** to a mixture of sodium chlorite and in a NaH_2PO_4 buffered solution of DMSO and H_2O provided orsellinic acid **399** in an acceptable 77% yield. This Pinnick-Lindgren oxidation has the advantage of using cheap, off-the-shell reactants and can take place under atmospheric environment, in an open flask. The resulting acid can be either purified through silica

chromatography or recrystallised in dichloromethane to afford white crystals in form of needles. The diphenol was then methylated with iodomethane under the action of K_2CO_3 in acetone (97% of yield).



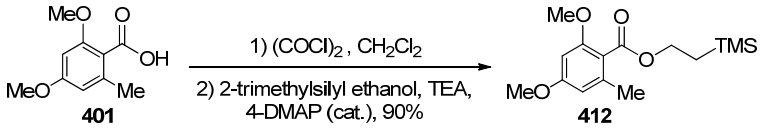
Scheme 89: Pre*para*tion of methylated orsellinic acid **401**

The choice of protecting the phenols as methyl ethers was inspired by the work of Winssinger and co-workers towards radicicol A (**2**), another member of RALs family.[16]Indeed, the *ortho* methyl ether was selectively cleaved upon treatment with boron trichloride, in the presence of other methyl ethers in *meta* and *para* positions (**scheme 90**).



Scheme 90: Final deprotection of macrolide **410** as part of the total synthesis of radicicol A by Winssinger *et al.*

- **Protection of methylated orsellinic acid**



Scheme 91: TMS protection of commercial methylated orsellinic acid (**399**)

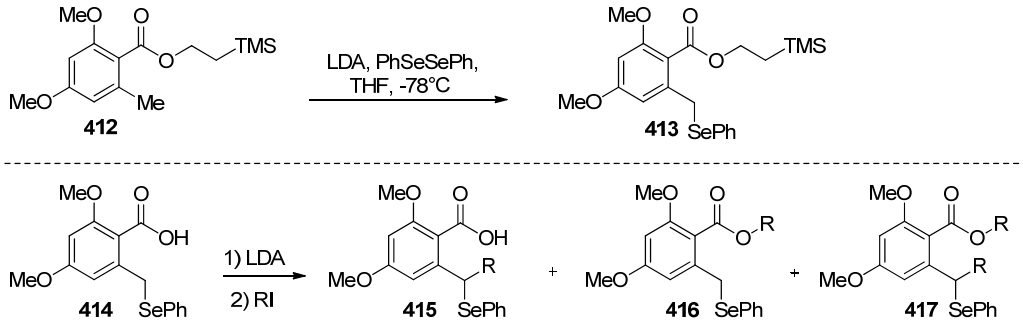
The TMSE-ester was chosen as the protecting form because it could easily undergo fragmentation reaction in the presence of TBAF in THF to give fluorotrimethylsilane, ethylene and the resulting carboxylate.[84] The TMSE-protected acid 412 has also been featured in the synthesis of radicicol A (**5**) by the group of Winssinger.[8] Its mild deprotection would theoretically not interfere with other protecting groups on the intermediate resulting from the expected alkylation between the deprotonated **401** and an appropriately electrophilic derivative of polyol section. Otherwise, the use of NaH in the presence of DMF as a mild alternative would also be compatible.[36]

The ester formation smoothly took place between the chloride acid that was formed *in situ* by submission of **401** to a solution of freshly distilled oxalyl chloride in dichloromethane, and 2-trimethylsilyl ethanol in the presence of triethylamine and a catalytic amount of 4-DMAP. The

obtained ester was to be subsequently subjected to several trials of deprotonation at the benzylic position in the conditions described by the group of Winssinger,[9] followed by addition of iodopropane and bromobutane as simple testing models.

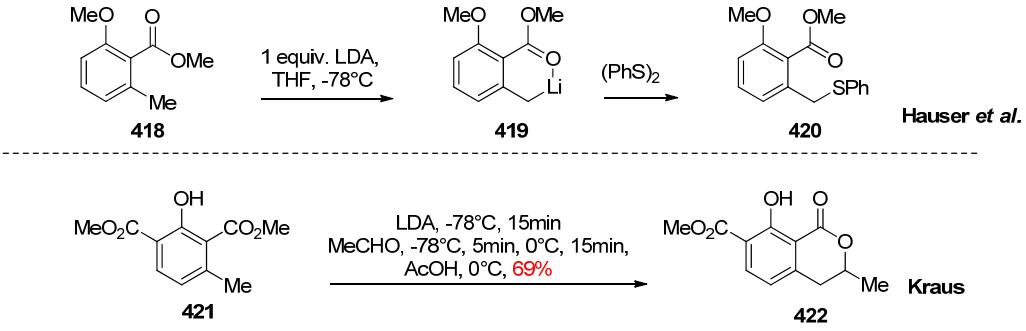
2.3.1.1 State of the art

- **Deprotonation with LDA**



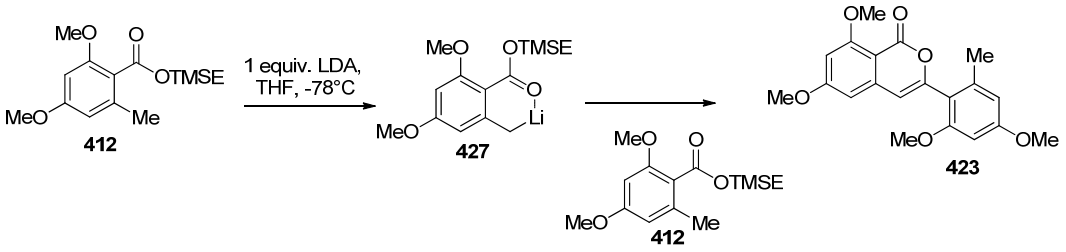
Scheme 92: Selenide formation *via* electrophilic selenium

The synthetic strategy from Winssinger *et al.* consists in the protection of the acid function prior to the functionalisation of the benzylic carbon.[79] Moreover blocking the acid function was principally meant to obtain a mono-lithiated species instead of dianion which would be much more unstable. Additionally, it would prevent the nucleophilic carboxylate from competing with the stabilised selenide anion following the addition of the electrophile alkyl iodide. For these reasons, we decided to apply the same method based on Hauser's deprotonation/selenation[85] (**scheme 93**) which used LDA (prepared *in situ* by adding one equivalent of BuLi to a stirred solution of diisopropylamine in THF at -78°C) to lithiate methyl 2-methoxy-6-methylbenzoate **419** prior to addition of diphenylselenide. This procedure was also part of the total synthesis of ochratoxin A by Kraus,[86] who deprotonated the diester **421** with two equivalents of LDA (one equivalent was to deprotonate the *o*-phenol), before its successful addition onto ethanal, followed by a lactonisation (**scheme 93**). In both reactions, the presence of the carbanion was distinctly detected by the formation of a deep red solution in place of the initial colourless reaction mixture.



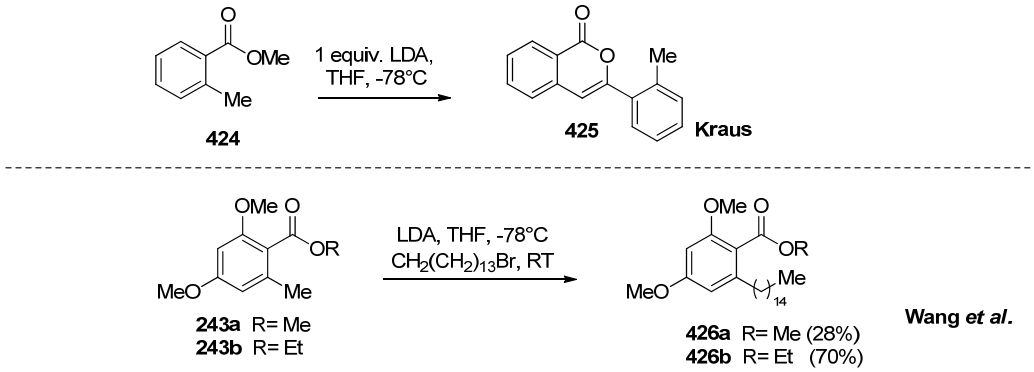
Scheme 93: LDA deprotection by Kraus and the group of Hauser

In our case, the temperature had to be constantly kept at -78°C to avoid the newly generated organolithium to add to unreacted starting material to give dimer **423**, once the temperature started to rise (**scheme 94**).[85]



Scheme 94: Inevitable self-condensation of the ester **412**

Though the dimerisation of the aromatic compound was not mentioned by the group of Winssinger throughout the systematic deprotonation/addition to prepare their library of selenide and sulfunide aromatic building blocks, this occurrence was earlier cited in the literature. Indeed, in their 1980 article, Hauser *et al.* observed the self-condensation product **425** of ethyl 2-methylbenzoate (**424**) as soon as the product organolithium formed, for it added to the undeprotonated starting material.



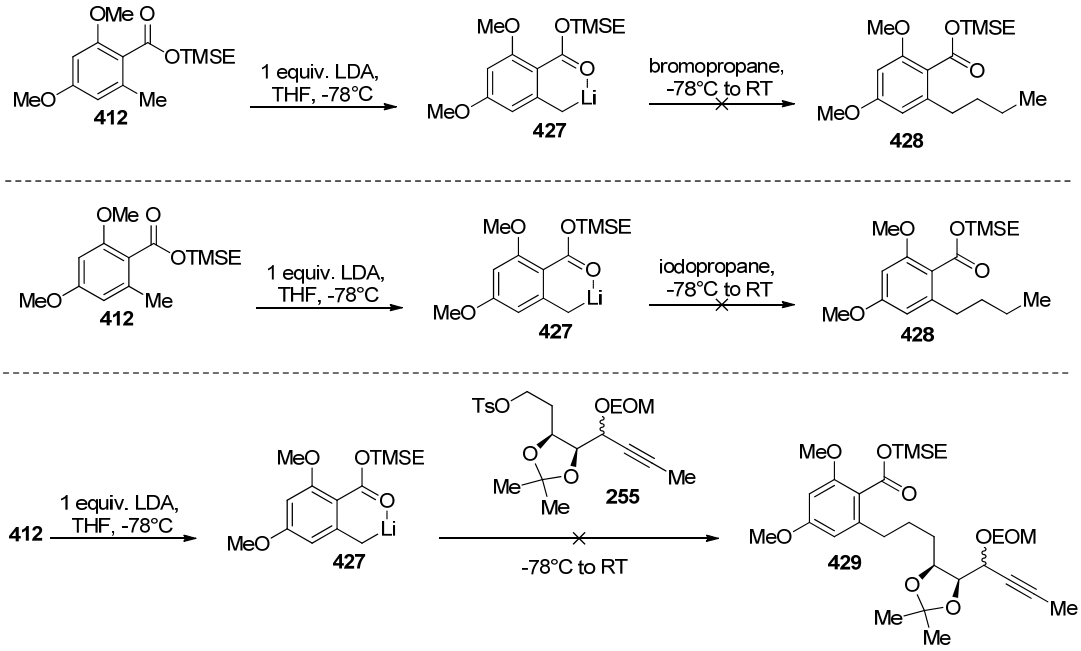
Scheme 95: Self-condensation and alkylation of alkyl 2-methylbenzoates in the literature [18, 86]

Yet a substantial factor which could slow down this undesired reaction was the substitution within the aromatic component: the addition reaction is much slower with 2,6-distubstituted esters (and phenoxides), which allowed its carbanionic lithium to react with external electrophiles (**scheme 95**).[85] Recent researches depicted the same unwanted side reaction that led to very low yield for the alkylation between 1-bromotetradecane and benzylic anion derived from ester **426a** (28%) while the ethyl ester counterpart **426b** gave a clearly higher yield under the same conditions. In comparison, it was reported that treatment of **243a** with LDA and 1-bromotetradecane in the presence of HMPA provided **426a** in only 5% yield.[87] The ethyl ester function was likely more sterically hindering than the methyl ester, which favored the benzylic alkylation to the addition onto the non-deprotonated starting compound to form dimeric products. The addition of HMPA was aimed to increase the nucleophilic effect of the anion and turned out to be ineffective as long as the acid function was blocked by a methoxy group, which conferred a greater electrophilic character to the carbonyl than ethoxy group.

2.3.1.2 First generation strategy: "TMSE-ester approach"

Following closely the protocol by Kraus,[86] the TMSE ester **424** was first deprotonated by LDA (resulting from the addition of BuLi to di*iso*propylamine) at -78°C for 1h, providing an orange red solution, then submitted to a slow dropwise addition of bromopropane at the same temperature and stirred for 4h, before the reaction was allowed to warm up to -10°C overnight. Accordingly, the compound **425** resulting from the previously mentioned self-

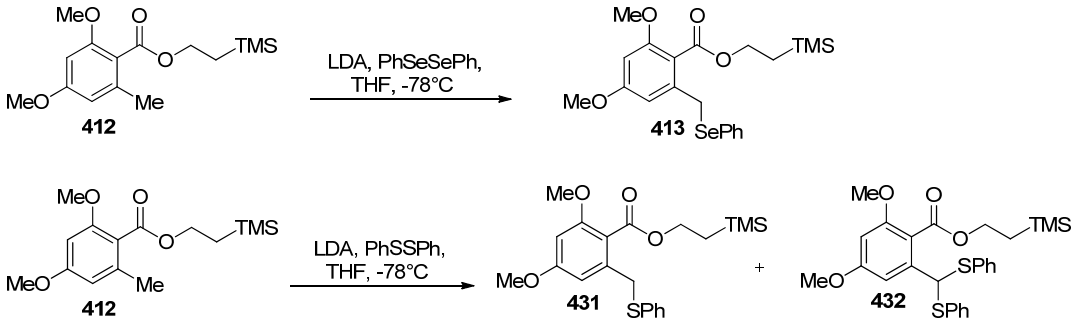
condensation was majorly present in the final reaction mixture, observed by NMR spectrum analysing, though not isolated and fully characterised (**scheme 96**). In other trials, the reaction mixture was kept at -78°C for 7h following the addition of bromopropane before warming up to room temperature overnight, which did not prevent the undesired self-condensation. It seemed to us that this phenomenon was unavoidable as long as the temperature started to rise over -78°C, which consumed the starting material before any nucleophilic attack onto the bromide.



Scheme 96: Unsuccessful alkylations with LDA

On the other hand, as long as the reaction temperature did not increase, the existing lithiated ester **427** would not react with the added bromide. The bromide leaving group was probably unsuitable at very low temperature. Hence iodopropane was substituted as it was known to be a more reactive electrophile with the better leaving group, basing on experimentally determined bond enthalpies which show a higher heterolytic bond dissociation energy for the carbone-bromide bond (72.1 kcal.mol^{-1}) compared to carbone-iodide bond (57.6 kcal mol^{-1}).[87] The lithiation was carried out as previously described at -78°C and the iodopropane was added after 1h, then the mixture was vigorously stirred at -78°C for 12h before being quenched with water at 0°C. Disappointedly, the major product was once again the dimer **423**.

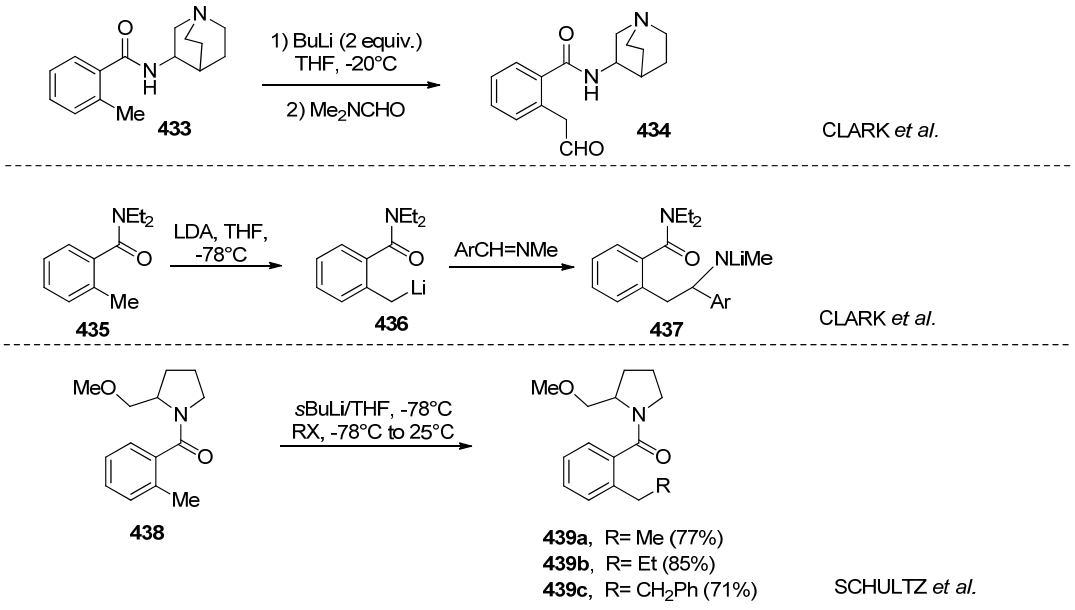
Given that the only two leaving groups that were successfully implanted onto the polyol section at that time were iodide and tosyl, we decided to test the benzylic addition directly onto the intermediate **255**. Unfortunately, no alkylation product was detected next to the previously observed dimeric by-product **423**. Finally, we had to give up on the benzylic alkylation through mono-lithiated ester **427** and find out an alternative directing group that (i) would not be prone to self-condensation, (ii) easily converted into an acid function to respect the initial retrosynthetic plan (**scheme 41**), and (iii) stabilising enough to leave out the use of benzylic selenide/sulfide like the strategy from Winssinger *et al.* The strategic method by Winssinger certainly guaranteed a well stabilised benzylic anion, the over addition of diphenyl disulfide caused however the formation of by-product **432** (**scheme 97**).



Scheme 97

Considering the self-condensation as impossible to overcome in a short time assignment, we decided to look for another directing group in the literature which would also be easily removed in mild conditions.

To this aim, amides have also been proved to be effective directing group in the literature. Even though laterally lithiation occurred in the presence of either secondary amide or tertiary amide, the latter is more prone to self-condensation like in the case of an ester, whereas the former requires two equivalents of base. As an example, the group of Clark has used the addition of both laterally lithiated secondary and tertiary amide to a Weinreb-type amide **433** and **435**[88] and imine[89] (**scheme 98**), while Schultz *et al.* employed a laterally lithiated tertiary amide **438** to add onto a series of halogenated compounds. This alternative could be attractive to replace the ester-directing benzylic metallation, but it would require additional steps to introduce the amide function then its orthogonal cleavage, in the same manner as for an ester.[90]



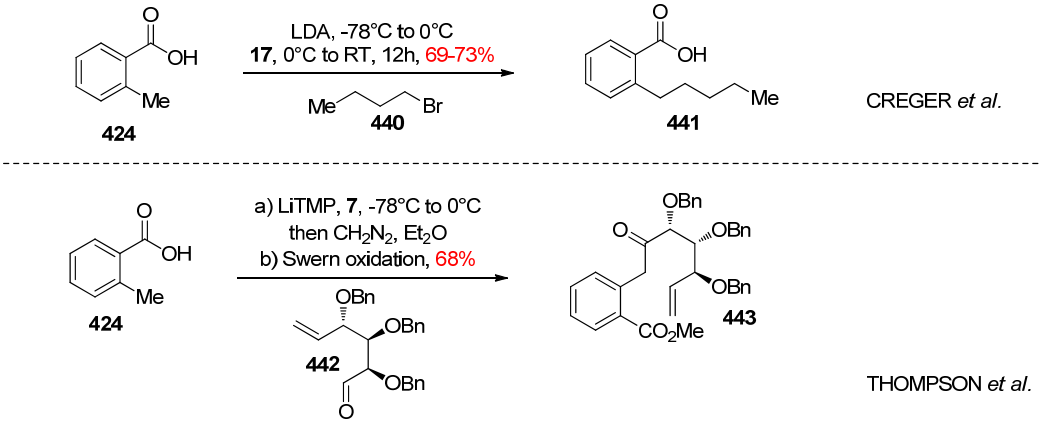
Scheme 98: Amides as directing group for lateral lithiation by Clark *et al.* and the Schultz's group

It was not unusual in the literature to use a carboxylate function as directing group in lateral lithiation. In spite of the commonly known weaker stability of a dianion compared to an anion, benzylic alkylation can also be assisted by a carboxylate instead of an ester, necessitating two

equivalents of base instead of one, but advantageously cuts down the protection/deprotection when an ester or amide is chosen as directing group. Both the ability to coordinate and the competence to acidify are important in a lateral lithiation (**scheme 98**). The presence of the carbonyle in both cases (carboxylate *vs* ester) assures a good coordination, but a carboxylate displays a weaker inductive effect. Moreover, treatment of a methyl benzoic acid with a base would greatly reduce the risk of self-condensation at higher temperature than -78°C, for an alkyloxy group is clearly better leaving group than a lithium oxide, the decisive drawback of our initial strategy *via* an ester. We embarked then on a series of attempts to carry out the benzylic alkylation through 2,4-dimethoxy-6-methylbenzoic acid (**401**), starting with the search for the most appropriate base and a fine-tuned reaction temperature.

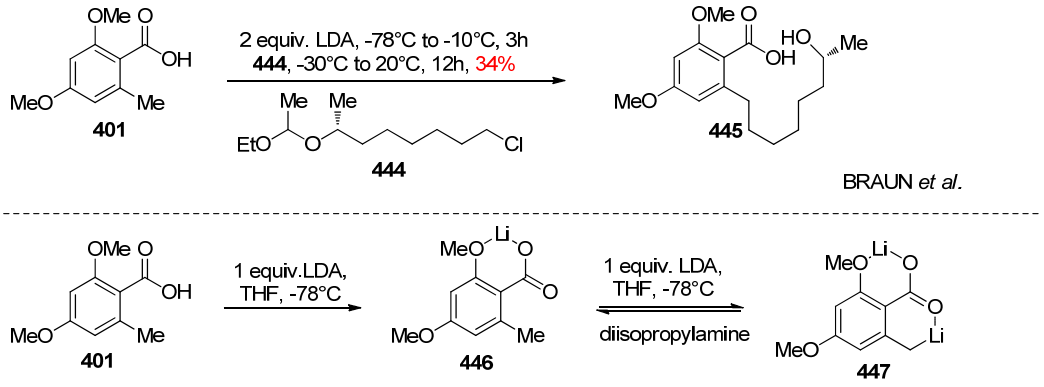
2.3.1.3 Second generation strategy: "Orsellinic acid approach"

In the literature four decades earlier, the group of Creger proved that 2-methylbenzoic acid could be laterally lithiated with two equivalents of LDA,[91] whereas the group of Thompson, twenty years later used instead LiTMP to achieve the same dilithiated species prior to successful nucleophilic addition to an aldehyde (**scheme 99**). To their great delight, the dilithio species derived from **7** was found to be stable in THF even at room temperature.[92]



Scheme 99: Literature deprotonation/addition

Taking into account the reduced stability of organolithium deriving from a functionalised 2-methylbenzoic acid, our synthetic tactics would rely on the lifespan of the dianion **447** at different temperatures. The benzylic anion would not be as stabilised as the corresponding selenide/sulfide-supported anion used by the group of Winssinger, but the alkylation would plausibly be achievable when combined with appropriate electrophiles. Furthermore, the formation of the dianion **447** would shut down the self-condensation tendency, which was observed in the case of the corresponding ester (**scheme94**).

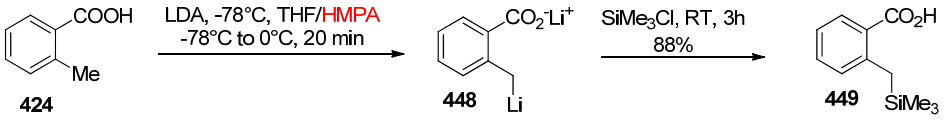


Scheme 100: Dilithiation of 2,4-dimethoxy-6-methylbenzoic acid (**401**) with LDA

Accordingly, preliminary attempts to deprotonate the 2,4-dimethoxy-6-methylbenzoic acid (**401**) were performed with two equivalents of LDA formed *in situ* at -78°C as described by Braun *et al.* in their total synthesis of *(R)*-(+)-lasiodiplodin (**10**) (**scheme 100**). Unexpectedly, these experiences turned out to be unsuccessful, which was strongly supported by experimental observations. As a matter of fact, during the slow dropwise addition of the solution of **401** in THF to LDA at -78°C, the reaction mixture turned gradually from colorless to yellow then orange red. This colour change was already documented by Braun *et al.* as being

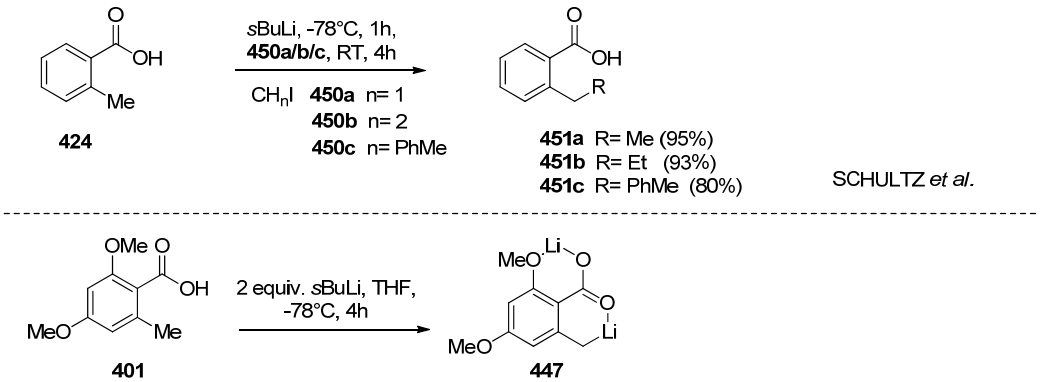
linked to the formation of benzylic anion, describing the same phenomenon when the reaction mixture was warmed up to -10°C.[93] But the red-orange colour of the mixture gradually faded away before the complete addition of acid **401**, even though the temperature was constantly maintained at -78°C. This observation could be explained either by the generation of the dianion, which was then reprotonated by the increasing amount of the di*iso*propylamine formed *in situ*. Or the deprotonation of the anion **446** was much faster than its reprotonation, which amounts to a small quantity of dianion **447** observed by its characteristic deep red color at the beginning.

Prior to the work of Braun *et al.*, Coughlin and Salomon published a synthetic methodology which allows conversion of benzylsilanes into 4-alkylidenecyclohexenes of 4-alkylidenecyclohexanones in good yields.[94] For this aim, one entry starting with 2-methylbenzylic acid involved the dilithiation in the presence of LDA and a mixture of THF and HMPA as solvent, followed by benzylic silylation and provided in rather good yield (88%) the compound **449**. Using on the same conditions, we tried to dimetallate 2,4-dimethoxy-6-methylbenzoic acid (**401**) but the reactions turned out to be fruitless, with or without HMPA as co-solvent.



Scheme 101: Benzylic sililation by Coughlin and Salomon

To overcome this insufficient basicity of LDA, we considered using an alkyllithium as proton extractor, a strong base that was often used in the literature to avoid the undesired competitive nucleophilic addition of the resulting diisopropyl amine.[95] In 1991, the group of Schultz employed *s*BuLi to dilithiate 2-methylbenzoic acid (**424**) cleanly, prior to a favorable addition onto short-chained alkyl iodides (**scheme 102**).[90] The use of *s*BuLi was meant to avoid addition to the carbonyl group if the temperature was not low enough.[96] Secondly, the proton extraction by lithium amides will release amine by-products (*e.g.* diisopropylamine) apt to react with electrophiles, and consequently compete with the dilithio species originally generated for this purpose.



Scheme 102: Dilithiation of 2,4-dimethoxy-6-methylbenzoic acid (**401**) with *s*BuLi

Our first deprotonations with *s*BuLi were maintained at -78°C for 4h after its addition to the solution of methylated orsellinic acid **401** at the same temperature. The reaction mixture's colour gradually changed from yellow to orange and did not fade back to light yellow as it

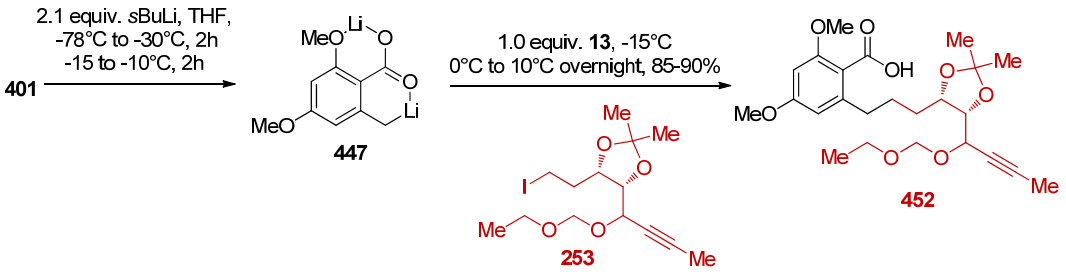
previously occurred because of reprotonation of the toluate. Noticing the prolonged lifetime of the dilithiate **447**, we added in a slow dropwise way a solution of iodopropane to the bright orange solution, obtaining a quickly fading yellow solution. The solution was stirred overnight while the temperature gradually rose from -78°C to room temperature. Despite the low yields of the resulting propylated product after an acidic workup and purification *via* flash chromatography, we were quite optimistic about the success of the addition and boldly replace iodopropane for the iodide fragment **253**, whose multi-gram synthesis was thoroughly related in the previous chapter.

Stirring temperature/time after addition of *s*BuLi	**Addition temperature of iodide 253**	**Stirring temperature/time until workup**	**Yield**
-78°C over 4h	-78°C	-78°C over 12h	X
-78°C over 4h	-78°C	-78°C to RT overnight	<10%
-78°C to -50°C over 3h	-50°C	-78°C to -20°C overnight	10-15%
-78°C to -30°C over 4h	-30°C	-30°C overnight	15-20%
-78°C to -30°C over 4h	-30°C	-30°C to -5°C overnight	35-50%
-78°C to -30°C over 3h then -15°C over 2h	-20°C	-15°C overnight	50%-60%
-78°C to -30°C over 3h then -15°C over 2h	-20°C	-20°C for 5 min then 0°C overnight	75%-85%
-78°C to -30°C over 2h then -15°C to -10°C over 2h	-15°C	-15°C for 5 min then 0°C to 10°C overnight	80%-90%

Table 6: The representative conditions of benzylic alkylation

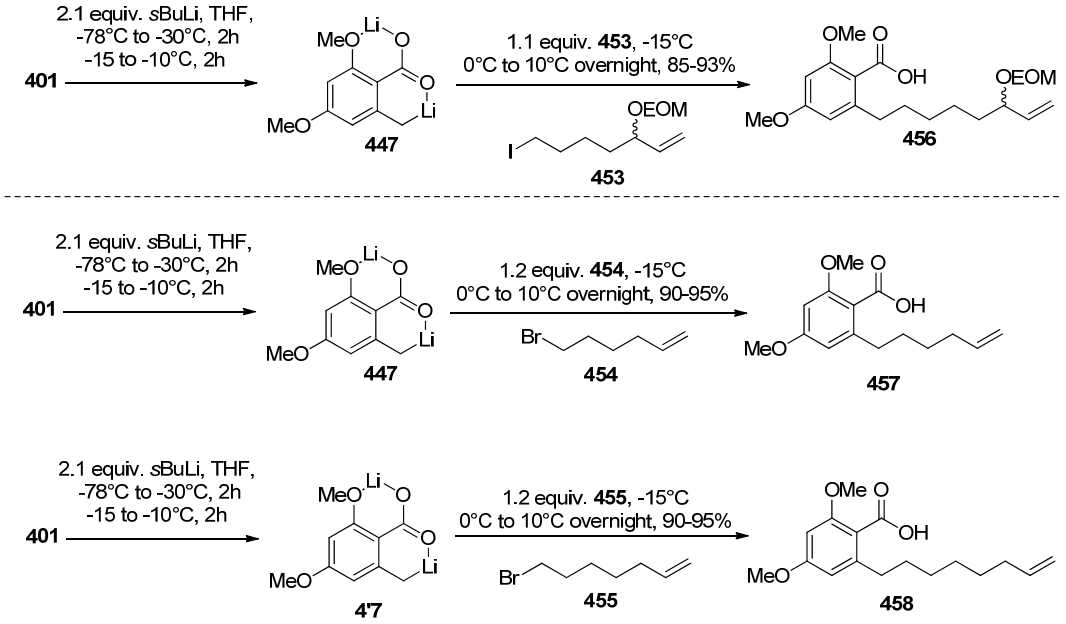
During the first experiments, by fear of causing the self-condensation reaction at higher temperature than -78°C, the dropwise addition of a solution of iodide fragment **253** in THF, as well as the subsequent stirring overnight were accomplished at the same temperature. No expected alkylated product was observed while 2,4-dimethoxy-6-methylbenzoic acid (**401**) was entirely recovered. Supposing the nucleophilic attack was inactive at such a low temperature, we allowed the reaction mixture temperature to reach room temperature overnight. The alkylation actually took place, yet the yield was far from satisfying. Indisputably, the success of the benzylic alkylation depended on the right temperature which had to be low enough to allow the total deprotonation without self-condensation, but also not below the favourable temperature for nucleophilic attack onto the iodide. Unfortunately, there was no means of controlling the consumption of 2,4-dimethoxy-6-methylbenzoic acid (**401**) during its deprotonation, other than its changing colour. Therefore, right after the addition of *s*BuLi, the temperature was allowed to steadily increase from -78°C to -15°C which caused the mixture colour to become deeper red while staying limpid for more than 2h. The subsequent addition of iodide **253** was performed between -20°C and -15°C and the alkylation gave the best results when the temperature was allowed to warm up to 0°C without further delay. Prior to this significant detail, in some experiments, the addition of iodide **253** proceeded at -20°C and the mixture temperature was maintained between -20°C and -10°C up to 2 hours before being warmed up to 0°C overnight. As a consequence, the expected adduct was yielded either in disappointing amounts (10% to 20%), or worse, none was detected. Pleasingly, when the

reaction mixture was directly warmed to 0°C following the iodide addition at -20°C or -15°C, the alkylation displayed an obvious surge in yields. Eventually the optimised yields were obtained for 12h of stirring between 0°C and 10°C (up to 90%).



Scheme 103: Successful benzylic alkylation applied to the total synthesis of L-783,277 (**7**)

The validation of direct benzylic alkylation as feasible synthetic tool, one crucial synthetic step of our strategy, was further confirmed by addition to the iodide **453** whose pre*para*tion is described in more detailed in section *3.3.2.2*. The same conditions also worked fine for commercial 7-bromohept-1-ene (**454**) and 5-bromohept-1-ene (**455**), an application of our methodology to the total syntheses of *(R)*-(+)-lasiodiplodin (**10**) and its *S* isomer which would be described in further details in section *3.2*. When the bromide was used in slightly higher excess, the yield exceeded 91% and the crude product could be used in the next step (Mitsunobu esterification) without any intermediate purification, for the remaining amount of bromide could be easily se*para*ted from the mixture by evaporation under highly reduced pressure.



Scheme 104: Application of benzylic alkylation to other halides

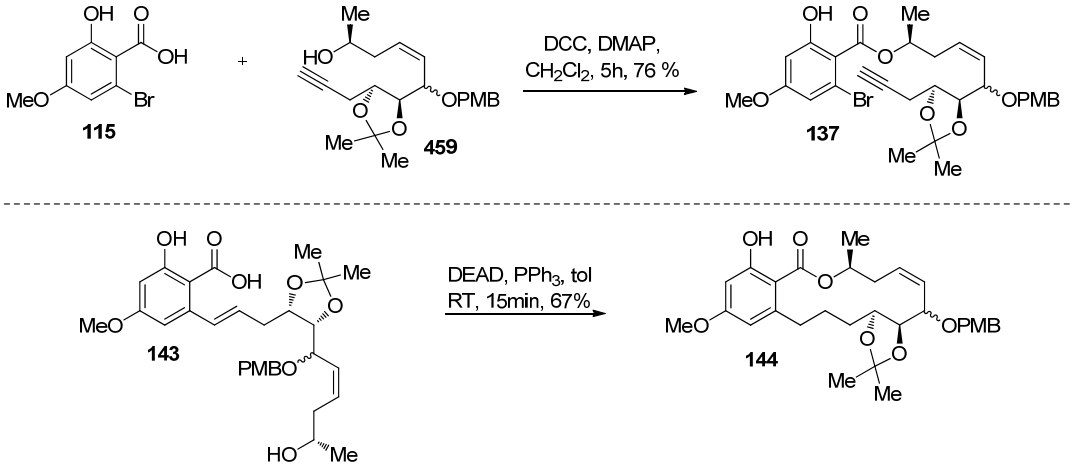
In conclusion, despite the use of two equivalents of base (to abstract the carboxylic hydrogen) instead of one as in the case of the related ester, the abstraction of the supplementary protection/deprotection steps consequentially shortened the synthetic sequence, hence affording a higher overall yield. The outstanding success of the direct alkylation *via* 2,4-dimethoxy-6-methylbenzoic acid (**401**) instead of the ester 2-(trimethylsilyl)ethyl 2,4-dimethoxy-6-methylbenzoate (**412**) undeniably renders the synthetic design more attractive without the intermediate steps of sulfenylation or selenation, followed by alkylation then elimination to form related olefins. Our strategy constitutes a *via*ble pre*para*tive entry to macrolactone analogues containing a saturated system at benzylic position, thanks to its compatibility with iodides, as well as bromides. And interestingly, this methodology has proven to be fairly mild, as it did not interfere with the different chemical functions of the precursor iodide **253**, such as ethoxymethoxy ether, alkyne or the highly acid sensitive acetonide, which restricted the conception of new synthetic design to smaller fields.

2.3.2 Esterification

2.3.2.1 State of the art

As stated in their name, the resorcylic acid lactones (RAL) consist structurally in a partially substituted β-resorcylic acid scaffold, which is linked to a 12 or 14-membered lactone. The ester moiety frequently prompted total synthesis chemists to disconnect retrosynthetically the carbon-oxygen bond, in view of either a late-stage macrolactonisation, or an intermediate connection between convergently synthesised fragments. Since the term “ester” was first referred to by Leopold Gmelin in 1848, numerous methods have been conceived, extending from the classic Fisher esterification or the commonly performed Steglich method, to cobalt (II) chloride hexahydrate as catalyst.[97] However, aromatic esterification, such as the resorcylic acid core hindered to some extent at the *ortho*-methyl, the choice of the appropriate ester formation might be pivotal. Comprised in the strategic design of RALs, the ester bond synthesis covered a wider area than the routinely used esterification between an alcohol and an acid moiety, according to the steric hindrance of the substrate or the reactivity of the involved fractions.

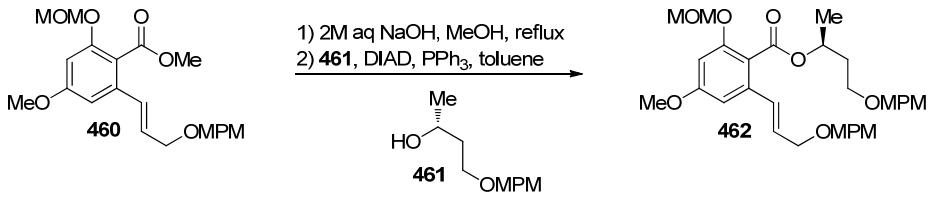
One of the convenient methods for the formation of esters is the well-known Steglich reaction which involves the use of DCC and DMAP to perform an esterification between an alcohol and a carboxylic acid. Comprised in the synthetic scheme of the total synthesis of LL-Z1640-2 (**3**) by Sellès and Lett[98] (**scheme 105**), the Steglich conditions allowed the polyol fragment **459** to be connected to the previously prepared *o*-bromo benzylic acid **115**. The macrolatonisation substrate **143** was achieved at rather high yield (76%). However, the planned intramolecular Suzuki coupling which operated onto the vinyl borane derived from **137** did not exceed 15% of yield, even under optimised conditions, urging the researchers to bring in a new approach which involved a late-staged macrolactonisation under Mitsunobu conditions.



Scheme 105: Steglich esterification *vs* Mitsunobu-based macrolactonisation by Sellès and Lett

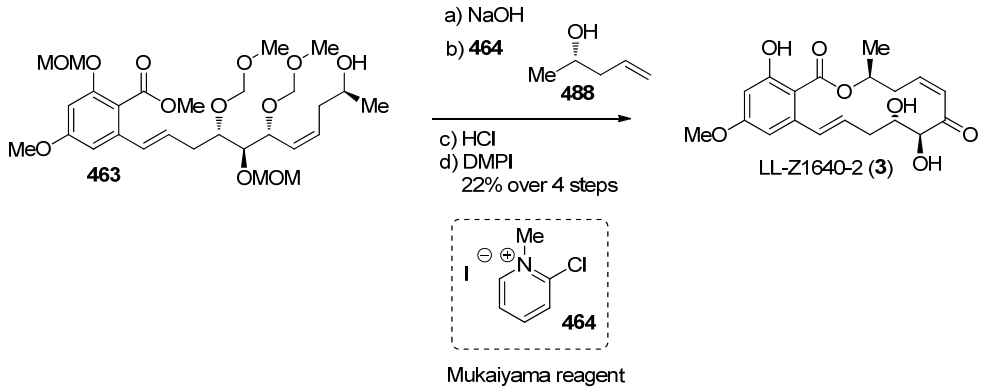
As expected, Mitsunobu esterification implied an inversion of configuration at the carbon C10' and the intramolecular Mitsunobu reaction proceeded without any incidence, providing **144** in 67% yield. This reaction required far shorter reaction time (15min) in comparison to 5h as for a classic Steglich esterification. However, this intramolecular reaction is constantly in competition against an intermolecular reaction, which remarkably reduces the final yield. As a result, the Mitsunobu conditions were also reported to perform an intermolecular esterification onto some resorcylic acid derivatives, especially those which were highly substituted at the *ortho* benzylic position.

Another application of this method for the total synthesis was reported by Murphy *et al.* as a connection step in their synthesis of a RAL incorporating a *trans*-enone and an amide in the macrocyclic ring (**scheme 106**).[99] Indeed, a sequence of hydrolysis of ester **460** closely followed by the Mitsunobu reaction of the resulting acid with alcohol **461** provided the MPM-diether **462**. The subsequent oxidative deprotection of MPM group ended the sequence in 3 steps with an overall yield of 50%, i.e. on average, each step would have reached 80% yield.



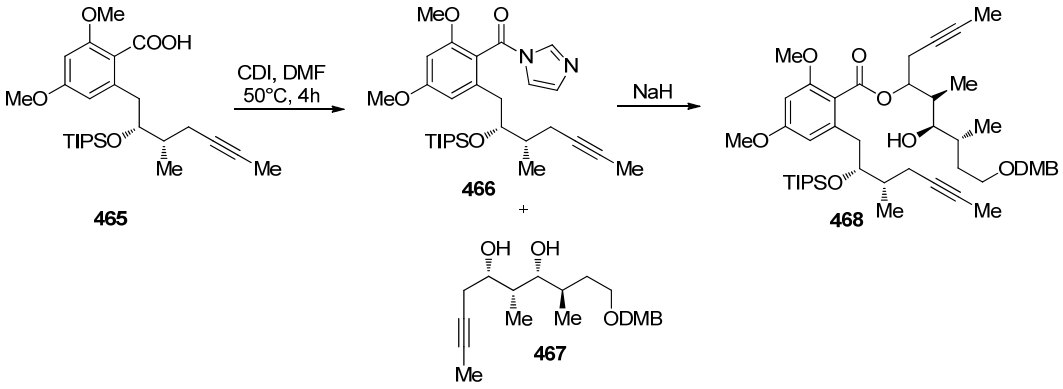
Scheme 106: Intermolecular Mitsunobu esterification by Murphy *et al.*

One year ahead of the synthesis of LL-Z1640-2 (**3**) published by Sellès and Lett, the group of Tatsuta reported their synthetic design of the same target molecule, which comprised a late-stage macrolactonisation through Mukaiyama lactonisation (**scheme 107**).[100] Considering the highly substituted benzoate at both *ortho* positions, the success of this macrolactonisation between the secondary alcohol and the benzoic acid, which came from a saponification *in situ* of the related methyl ester **463**, was greatly impressive. The yield over three successive steps (Lindlar reduction, saponification and Mukaiyama lactonisation) attained 47%, a very satisfactory result and proof of the efficiency of the tricky macrolactonisation.



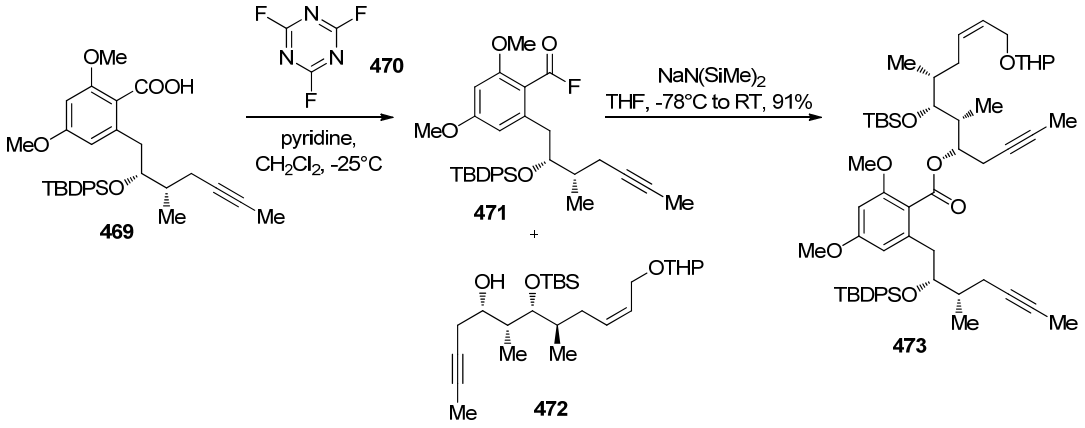
Scheme 107: Mukaiyama lactonisation as ring-closing step by Tatsuta *et al.*

Among the metabolites of the family of RALs, cruentaren A has been one of those soliciting much interest from the organic chemistry community. It was the inspiration for several innovative synthetic blueprints, and at the same time the settings for the development of competitive chemical tools. Each research group had recourse to a different esterification method, in view of an efficient and reliable ring-closing tool. The first published total synthesis belongs to Vintonyak and Maier[101] who observed no trace of ester by using standard Mitsunobu, Yamaguchi or Trost esterification. Besides, attempts to synthesise ester **468**, using the classic peptide coupling reagents like DCC/DMAP or BOP also failed. Eventually, the only satisfactory esterification relied on the reaction of the imidazolidine derivative **466**, resulting from treatment of acid **465** by carbonyldiimidazol (CDI), with the sodium alkoxide formed *in situ* (**scheme 108**). Interestingly, this reaction produced only one regioisomer of **468** as shown in the following scheme.



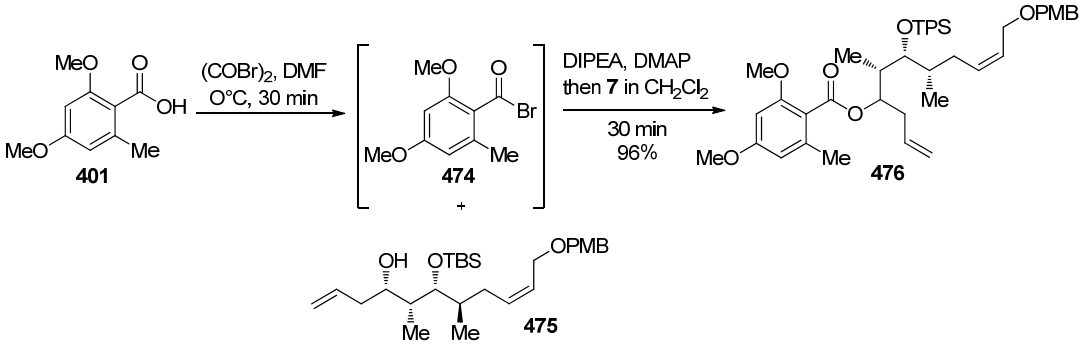
Scheme 108: Esterification *via* imidazolide by Vintonyak and Maier

One year later, in view of a concise total synthesis of the same target, the group of Fürstner envisaged carrying out an ester formation at the same strategic position.[102] In contrast to the former researchers, they were not convinced by the results yielded through the corresponded imidazolide *via* CDI. During the study, they confirmed that attempts to form the corresponding acid chloride invariably led only to the formation of a six-membered *δ*-lactone, a side reaction that Vintonyak and Maier were also confronted with while applying the same strategy. Surprisingly, to transform the acid moiety into the related acid fluoride **471** not only afforded the desired ester **473**, but also prevented the intramolecular esterification. According to the authors, the best conditions to form the acid fluoride **471** were found to be 2,4,6-trifluoro-1,3,5-triazene (**470**) in the presence of pyridine (**scheme 109**).



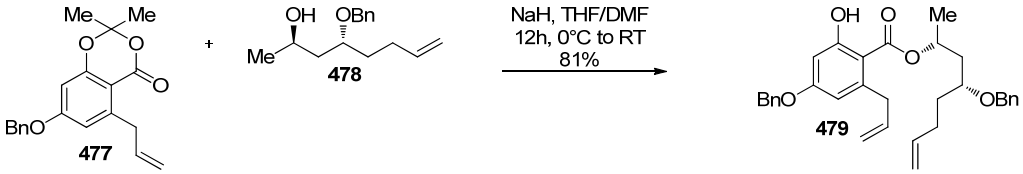
Scheme 109: Esterification *via* acid fluoride by Fürstner *et al.*

In both reports, it was not mentioned whether an acid bromide in place of acid chloride would have bettered the esterification approach. In 2012, the group of Blagg published the fifth total synthesis targeting cruentaren A, lining up a row of several successful totals syntheses and numerous approaches to fragments.[6] Comprised within their concise synthetic route was the esterification step, which was performed this time through an acid bromide (**scheme 110**), as the successfully chosen methods by Fürstner and Vintonyak for the related alkynyl derivative failed to give the wanted product. Allegedly, the acid bromide was the most appropriate intermediate, which was obtained upon treatment of the acid **401** with oxalyl bromide $(COBr)_2$, DIPEA, and catalytic DMF in CH_2Cl_2 at 0°C for 30 minutes, followed by the addition of alcohol **475** and DMAP. The ester formation proceeded within 10 minutes in excellent yield (96%).



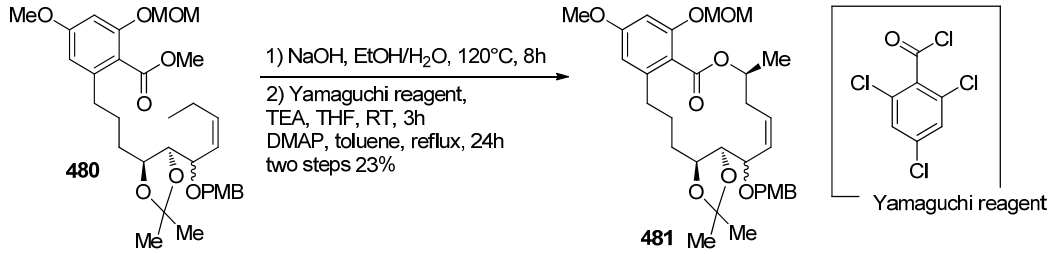
Scheme 110: Esterification *via* acid bromide by Blagg *et al.*

An alternative esterification method was employed by Yadav *et al.* within their total synthesis of analogues of *(R)*-(+)-lasiodiplodin (**10**).[103] Their strategy, like those of Fürstner and Vintonyak, consisted in an esterification, preceded by an alkylation at benzylic position *via* Stille coupling, which rendered this position much bulkier than a simple methyl, as mentioned in the esterification by Blagg and co-workers. The employed method was quite appealing, as it did not require any transformation of the acid moiety into a more reactive derivative (*e.g*. acyl imidazole, acid halide), but a previous formation of the acetonide which framed both the acid function and the *ortho* phenol. Thanks to a transesterification in the presence of the alkoxylate derived from an *in situ* deprotonation of alcohol **486**, the desired ester **479** was obtained in sufficiently high yield (**scheme 111**).



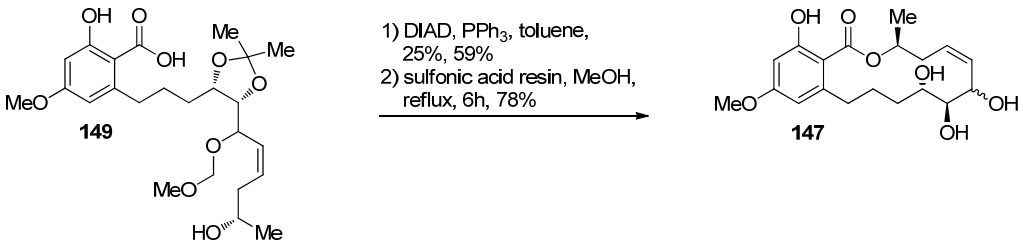
Scheme 111: Esterification *via* transesterification by Yadav *et al.*

Another representative method of esterification is illustrated by the Yamaguchi esterification realised within the total synthesis of L-782,277 (**7**) by Choi *et al* as detailed in section *1.2.3*.[104] According to the authors, this esterification was a crucial step allowing the macrolactonisation leading to the 14-membered ring. To their relief, this reaction was successfully carried out, involving a saponification of methyl ester **480** prior to the submission of the resulting acid to a modified version of Yamaguchi esterification described by Evans and collaborators (**scheme 112**). Contrary to the higher yield attained by the similar macrolactonisation at a late stage by Tatsuta *et al.* towards the total synthesis of LL-Z1640-2 (**3**),[100] where the Mukaiyama conditions met their demands, the Yamaguchi reagent obviously gave much lower yield (merely 23%) over 2 consecutive steps (saponification, esterification).



Scheme 112: Evans' modified version of Yamaguchi esterification by Choi *et al.*

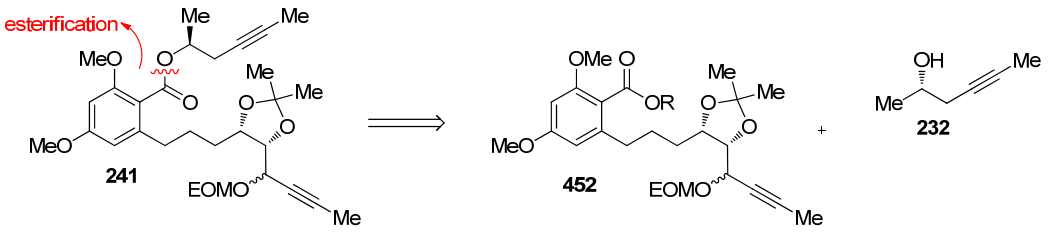
It is noteworthy that two years earlier, in the course of the synthesis of the same metabolite L-783,277 (**7**), Hofmann and Altmann achieved the macrolactonisation of their pivotal intermediate **149** *via* a Mitsunobu esterification in 59% yield (**scheme 113**).[13] In comparison to the prior example of macrolactonisation with Yamaguchi reagent, this result obviously seems to be more promising.



Scheme 113: Macrolactonisation under Mitsunobu based esterification by Hofmann and Altmann

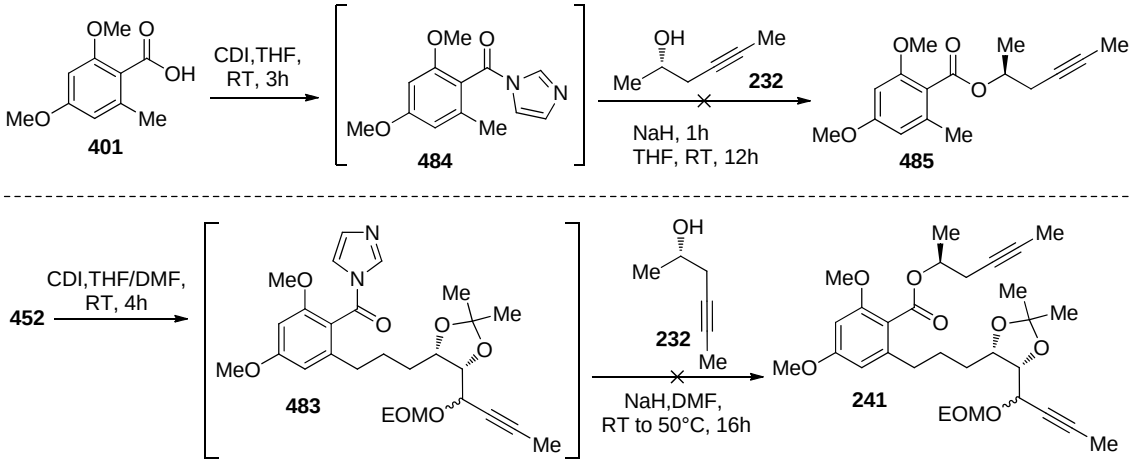
Despite all the methods mentioned so far do not constitute a comprehensive list of all the discovered esterifications by this time, they provided us, to some extent, a good overview, which would serve for the next step of our predefined synthetic scheme: attachment of the propargylic alcohol **232** tothe orsellinic acid fragment **452**. This procedure, apparently simple, turned out to be far more tricky and challenging than expected.

2.3.2.2 First generation strategy: "Orsellinic acid derivative (241) as electrophile"



Scheme 114: 1st generation retrosythetic esterification

Our first approach relied on the formation of an acyl imidazole, a classic method which has proven to be an efficient brick for Vintonyak's genuine construction of cytotoxic macrolide cruentaren A.[101]



Scheme 115: Esterification *via* carbonyldiimidazole (CDI)

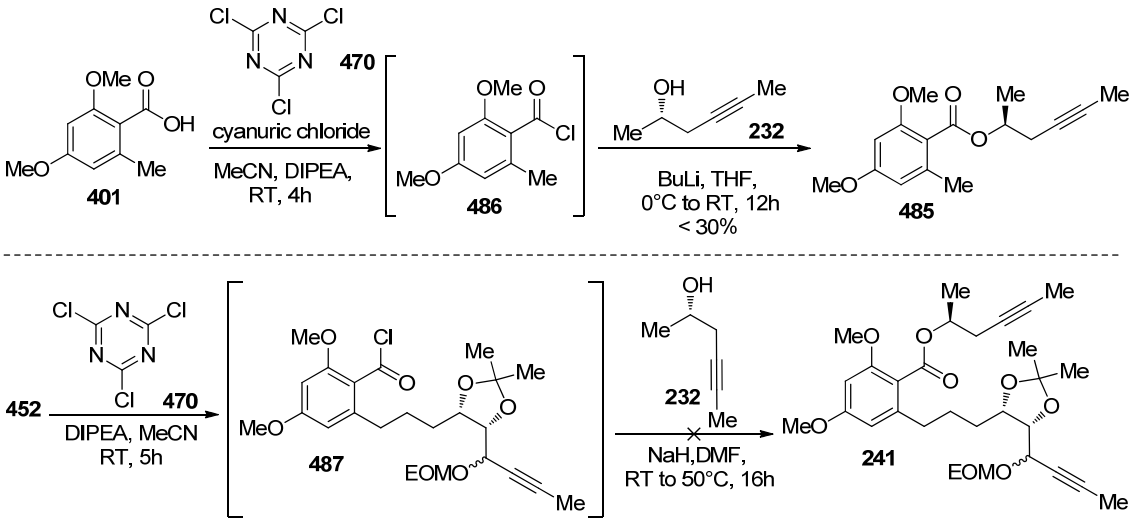
At the beginning, we tried to obtain an acyl imidazole upon treatment of the benzylic alkylated orsellinic acid derivative **483** with CDI in THF at room temperature. After 3 to 4 hour stirring, a solution of NaH deprotonated propargylic alcohol **232** was slowly added and the mixture stirred over night. The obtained crude product showed major presence of the starting material **401**, while the propargylic alcohol amount was much more reduced, probably due to its high volatility during the evaporation of the crude solution at reduced pressure. Even by increasing the reaction temperature up to 50°C right after the addition at room temperature of CDI and stirring for 4 hours before the addition of alkoxide in DMF, we did not succeed in synthesising the decisive RCAM intermediate **241**. We were rather surprised by the outcome, given the bright success of the same reaction performed on intermediates of the cruentaren A's sequence by Vintonyak and Maier, though aware of the structural difference of the alkyl chain at benzylic position in both substituted orsellinic acid intermediates. For this reason, the same procedure was tested on the simple orsellinic acid **401**, which displays less hindrance at the benzylic position. The outturn was once again very disappointing, yet in total agreement with the statement by the group of Blagg during their effort towards the esterification of the same commercially available benzoic acid **401** (**scheme 115**).[6]

According to these researchers, the synthesis of ester through the transformation of the commercial acid **401** into acyl imidazole **484** turned out to be quite challenging and only gave

unsuccessful results, in spite of its apparently unhindered structure at the benzylic position. The esterification was though successfully carried out *via* an acid bromide, we were tempted to synthesise an acid chloride from the laboratory made orsellinic acid derivative **401**.

Instead of using the Ghosez chlorinating reagent like the group of Fürstner,[10] we opted for the 2,4,6-trichloro-1,3,5-triazine (**470**), applying the procedure described by Venkatamaran and Wagle while modifying some experimental *para*meters.[105] Due to the elaborate multi-step synthesis of the aromatic fragment **452**, the esterification method was first attempted between the simple orsellinic derivative **401** and the freshly prepared propargylic alcohol **232**. The related acid chloride was prepared upon treatment of aromatic acid **401** with cyanuric chloride **470** in acetonitrile, in the presence of DIPEA. After stirring for 3 hours when the initial heterogeneous solution turned into a clear yellowish mixture, it was evaporated till total dryness before addition of THF, followed by slow introduction of a solution of alcohol **232** in THF at 0°C. Unfortunately, the resulting crude product revealed, according to NMR analysis, only trace of the more simple ester **485**, which was not worth isolating.

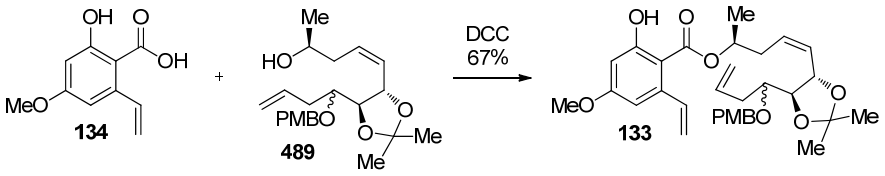
In order to optimise the reaction, we decided to put at use the lithiated alkoxide resulting from the deprotonation of **232** by butyllithium. As a result, the ester **485** was obtained in less than 30% yield, which prompted us to apply the same conditions to the esterification between the precursor **452** and the enantiomerically pure **232**. Despite our intensive efforts, the yield did not exceed 20%.



Scheme 116: Esterification *via* 2,4,6-trichloro-1,3,5-triazine (**470**)

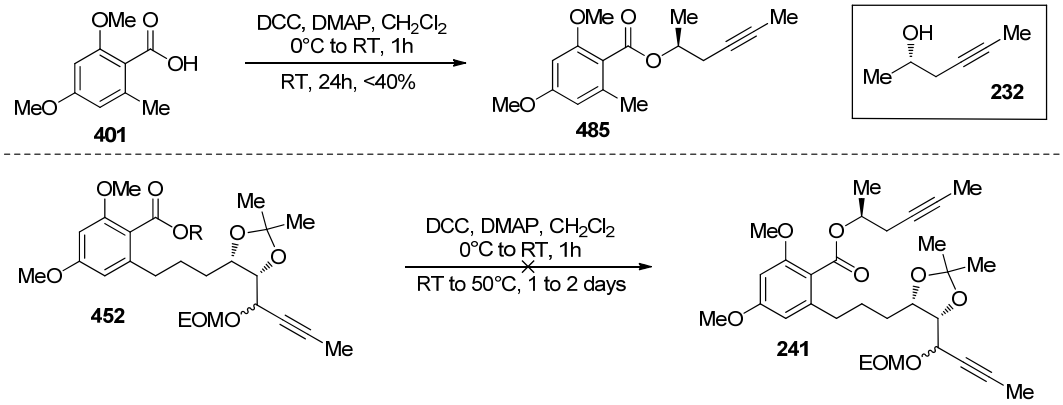
The presence of acid sensitive functions incorporated at the benzylic alkyl chain restrained the esterification conditions, preventing us from using some published methods that successfully contributed to the syntheses of some RALs, such as $(COBr)_2$ used by Blagg *et al.*, or $(COCl)_2$ introduced by Winssinger and collaborators.[16]

In the literature, a classical esterification based on DCC was successfully carried out by Marquez and collaborators as part of their concise synthesis of the complete L-Z1640-2 (**3**) framework (**scheme 117**).[106] This incited us to try out the same procedure, which unluckily ended with no significant result. However, inspired by the use of DCC, we decided to test by the same occasion the Steglich esterification, a relatively mild procedure, which allows the transformation of sterically demanding and acid labile substrates.



Scheme 117: DCC-mediated esterification by Marquez *et al.*

Once again, the Steglich esterification was first performed with methylated orsellinic acid **401**, using DCC and DMAP in DMF at 0°C for 10 minutes then at ambient temperature overnight (**scheme 118**).

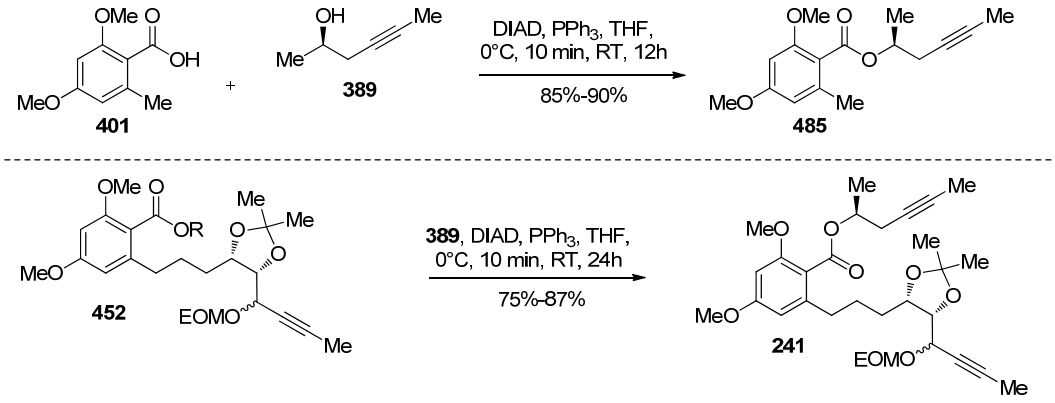


Scheme 118: Steglich esterification

We succeeded in obtaining the anticipated ester, though the yield remained low with less than 30%. By raising the reaction time up to 24 hours, and especially the use of stoichiometric (1.2 equiv.) rather than catalytic (0.1 equiv.) amount of DMAP, the yield was somehow increased to around 40%. With this moderately encouraging result, the acid fragment **452** was involved as substrate in the next Steglich based esterification trials. Unfortunately, the crude product contained no detectable amount of the desired dialkyne **241**, even after two days of stirring at a gradually increasing temperature from 20°C to around 50°C. Substituting dichloromethane by DMF did not give any better result, either.

2.3.2.3 Second generation strategy: "Orsellinic acid derivative (241) as nucleophile"

At this stage of the synthetic sequence, the achievement of the dialkyne was of great consequence, as it would allow us to test out one of the crucial steps of the strategy depiction: the ring-closing alkyne metathesis. In the end, the Mitsunobu based esterification, which was twice used as the ultimate method of esterification by both groups of Altmann[14] and Winssinger[9] respectively within their successful syntheses of our taget molecule L-783,277 (**7**) (*cf*. section *1.2.3*) was investigated the Mitsunobu reaction to determine its feasibility (**scheme 119**).



Scheme 119: Mitsunobu esterification

Nonetheless, given that a Mitsunobu-based esterification mechanistically induces inversion of stereochemistry of the involved alcohol, it was indispensable to prepare the enantiomer of *(R)*-hex-4-yn-2-ol **389**. As a consequence, as it was previously described in section *2.1.2*, the *(R)*-hex-4-yn-2-ol **232** was accordingly synthesised from the stereochemically related expoxide *(R)*-propylene oxide **40** in the same manner as its *S*-isomer **136**. As anticipated, the pre*para*tion of the alcohol **232** proceeded uneventfully. With the propargylic alcohol **232** in hand, we embarked on the following trials, which exploited the well-established Mitsunobu reaction.

In the first attempts, the simple orsellinic acid **401** was chosen as substrate to carry out the Mitsunobu reaction. By using the standard conditions described in the literature, we were very pleased to observe not only the formation of the anticipated ester **485**, but also its isolation in 85% of yield. Without further needless delay, the same procedure was applied to the precursor **452**. To our great delight, the desired dialkyne precursor **241** was smoothly attained at very gratifying yield (87%). The Mitsunobu reaction, in great accordance with the two first publications of the synthesis of L-783,277 (**7**), has proven to be a powerful and robust method to circumvent the obstacles encountered while using other standard esterification methods.

In summary, the construction of the dialkyne precursor **241**, the pivotal intermediate required for the key step RCAM, turned out to be very challenging, and hence more effort- and time-consuming than expected. Nevertheless, all the abandoned methods (*e.g*. the use of acid derivatives like acyl imidazole *via* CDI or acid chloride through cyanuric chloride, the DCC-based esterification or Steglich peptide coupling) are in agreement with the observations by other researchers during their respective studies concerning the esterification of related alkynyl derivatives.[6, 101, 107] Obviously, before tackling this synthetic step, we were aware of the relatively weak electrophilicity of aromatic acid derivatives in comparison to other acid ones, though not thoroughly prepared to be confronted to so many difficulties. Especially, the highly unpredictable conformational of the substituted orsellinic acid **452** and the counter-intuitive reactivity correlation between the latter and the structurally simple acide **401**. However, the

crucial intermediate **241** was finally achieved in rather high yield *via* a Mitsunobu esterification. With the dialkyne **241** in hands, the next step consisted in a ring-closing alkyne metathesis to complete the carbon framework of the target molecule. The coming *para*graph will give a detailed description of our efforts and extensive experimentation dedicated to this synthetic step.

2.3.3 Ring Closing Alkyne Metathesis (RCAM)

2.3.3.1 State of the art

Alkene and alkyne metatheses are among the most known and convenient tools for the synthesis of a wide range of complex, organic molecules. In accordance with the impact of such a powerful synthetic method, progress in this field is constantly growing at remarkable pace, overcoming tough challenges and giving rise to numerous breakthroughs. The contributions of Grubbs, Schrock and Chauvin to the alkene metathesis were rewarded with Nobel prize in 2005. Alongside their efforts, many research groups contributed, since decades, to the discovery of new and more efficient catalysts, in terms of activity and tolerance to different functional groups.

The most studied reaction in this context has been so far olefin metathesis. Alkene metathesis profits from an invaluable substrate basis as long as humankind relies on crude oil. Consequently, olefins are relatively common chemical functions and both terminal and disubstituted olefin metathesis catalysts are readily available. Though alkene and alkyne metatheses are mechanistically very similar, the latter has the advantage of not involving stereochemical problems, contrary to alkene metathesis due to the resulting *E/Z*-configuration of the resulting olefins. More interestingly, alkyne metathesis can be closely followed by stereoselective reduction, giving either *E* or *Z* alkenes.[11]

Investigated to a far less extent, alkyne metathesis has been, nonetheless, known almost since the advent of alkene metathesis, starting with the discovery by Mortreux and Blanchard in 1974 about the amazing reactivity of a catalytic amount of structurally unidentified species which are generated *in situ* from [$Mo(CO)_6$] or related molybdenum source combined with phenol additives.[108] This method is very attractive in use because all the involved substances are commercially available at relatively cheap prices, shelf-stable and the solvents do not need to be rigorously anhydrous. However, the required temperature often has to exceed 130°C, harsh conditions which limit its application to high temperature robust substrates. Above all, as the active species formed *in situ* have not yet been identified, the (molybdenum/phenol) system still remains ill-defined, and has been reported to be undeniably less active than other modern catalysts.[109]Succeeding the discovery of this “instant catalyst”, Schrock’s research and development of 12-electron metal-alkylidyne idyne complexes, *e.g*. the commercial neopentylidyne complex [$Me_3CC\equiv W(OCCMe_3)_3$], has popularised the alkyne metathesis among organic chemists.[110] Indeed, this prototype is able to catalyse ring-closing alkyne metathesis (RCAM) reactions under rather mild conditions and its behavior at molecular level is well understood.[111] Nevertheless, the metal alkylidyne [$Me_3CC\equiv W(OCCMe_3)_3$] and its congeners are highly air and moisture sensitive, thus requiring a strictly inert atmosphere. Moreover, though they have proven to be appreciably efficient in challenging ring-closing alkyne metathesis reactions (RCAM), and tolerate many functional groups, their tolerance towards thioethers, amines and crown ether segments has been reported to be problematic.[112]

The research group of Fürstner supposed the previously mentioned incompatibility stems from the plausible coordination of these donor sites to the high-oxidation-state tungsten center, hence rendering the catalyst inactive.[111] In order to enlarge the scope of alkyne metathesis, Fürstner and collaborators have embarked on an impressive programme searching for alternative catalysts. Recent progress in alkyne metathesis has been published by the latter, which outlined the excellent (pre)catalysts for alkyne metathesis reactions of all types. These catalysts are nitride- and alkylidyne complexes of molybdenum of the general type

[$(Ar_3SiO)_3Mo{\equiv}X$] where X= N, CR and R= aryl, alkyl and Ar= aryl, endowed with triarysilanolate ligands, which combine high activity with striking tolerance towards polar and sensitive substrates (**figure 17**).[113] According to the authors, these catalysts can become air-stable with the aid of 1,10-phenanthroline or derivatives thereof, hence clearly more user-friendly precursors than other catalysts in the literature, *e.g.* Schrock alkyne metathesis catalysts.

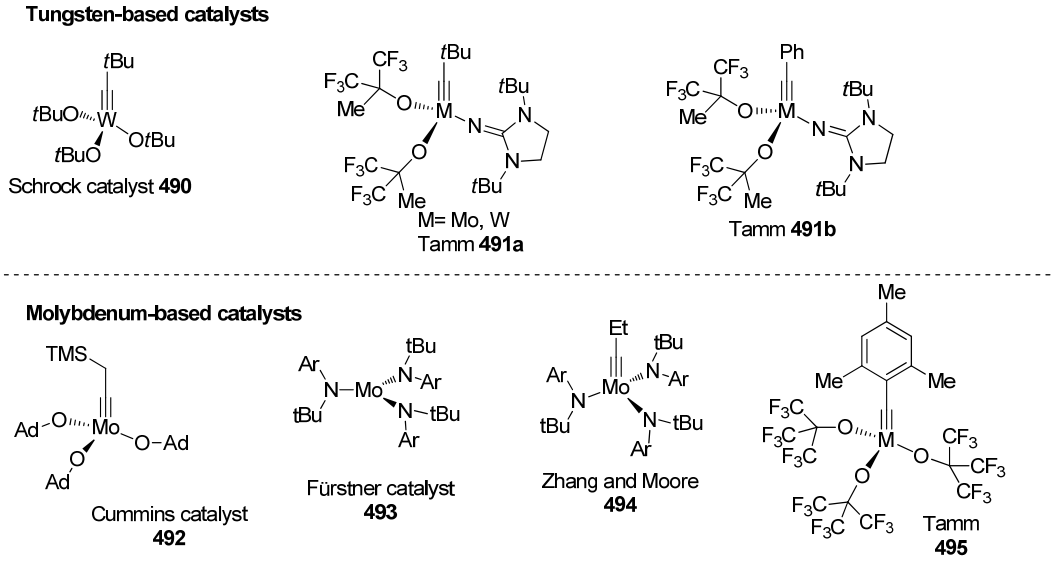


Figure 17: Catalysts for alkyne metathesis in the literature[110]

Historically, despite of the availability of well-defined tungsten-based alkyne metathesis catalysts by the group of Schrock since 1981,[114] their application was simply restricted to dimerisation or cross-metathesis of some acetylene derivatives and mainly the pre*para*tion of a few special polymers.[115]

Shortly before the turn of the millenium, the scope of ring-closing alkyne metathesis (RCAM), catalysed by Schrock's tungsten alkylidyne complex [$W({\equiv}C\mathit{t}Bu_3)(O\mathit{t}Bu)_3$], was first explored by Seidel and Fürstner, who pioneered the indirect but stereoselective approach to macrocyclic *Z* alkenes.[115] As briefly described at the beginning of this chapter, although medium-sized and macrocyclic rings could be forged by ring-closing metathesis (RCM), the resulting olefins are often obtained as mixtures of *E* and *Z* isomers with neither predictable nor controllable ratio. This inherent issue constitutes a significant drawback in many total syntheses, as it was for example reported from the epothilone case by Nicolaou and co-workers in the same year.[116]

To circumvent the stereoselectivity problem of RCM, Fürstner and collaborators disclosed an elegant and efficient way that combines ring-closing metathesis of diyne substrates with a subsequent partial reduction of the cycloalkyne molecules, using conventional methodology (*e.g*. Lindlar hydrogenation or hydroboration/protonation) to provide (*Z*) macrocyclic alkenes.

More than one decade later, a concise and stereoselective entry macrocyclic (*E*)-alkenes were developed by the group of Fürstner which was based on *trans*-selective hydrosilylation catalysed by [$Cp^*Ru(MeCN)_3$]PF_6, followed by protodesilylation with AgF in THF/MeOH.[117]

Recently, in 2011, Schrock and Hoveyda's respective groups finally succeeded collectively in synthesising the first molybdenum-based catalyst which is effective in *Z*-selective olefin cross-

metathesis (CM), which involved terminal alkenes with either allylic amides, or, for the first time in the literature known to date, terminal enol ethers.[7] These researchers not only found out the appropriate design of the complexes **496** that give rise to exceptional reactivity, in comparison to other previously described Mo- and Ru-based complexes (**498**-**500**), but also the use of reduced pressure to enhance stereoselectivity in catalytic cross-metathesis (CM). The highly *Z*-selective olefin metathesis reactions of terminal alkenes catalysed by **496** is supposed to come from the structural flexibility of the stereogenic-at-metal complexes **496a** and **496b**, and free rotation around the molybdenum-oxygen bond of these alkylidenes. Moreover, their approach took into account the relationship between efficiency and stereoselectivity, as the conversion values portray a balance struck between the highest attainable yields and maximal *Z* selectivity with minimal substrate amount, together with inevitable formation of the homocoupling side-product. Indeed, time-dependent studies carried out by both groups indicated the stereoselectivities suffered with lengthened reaction times.

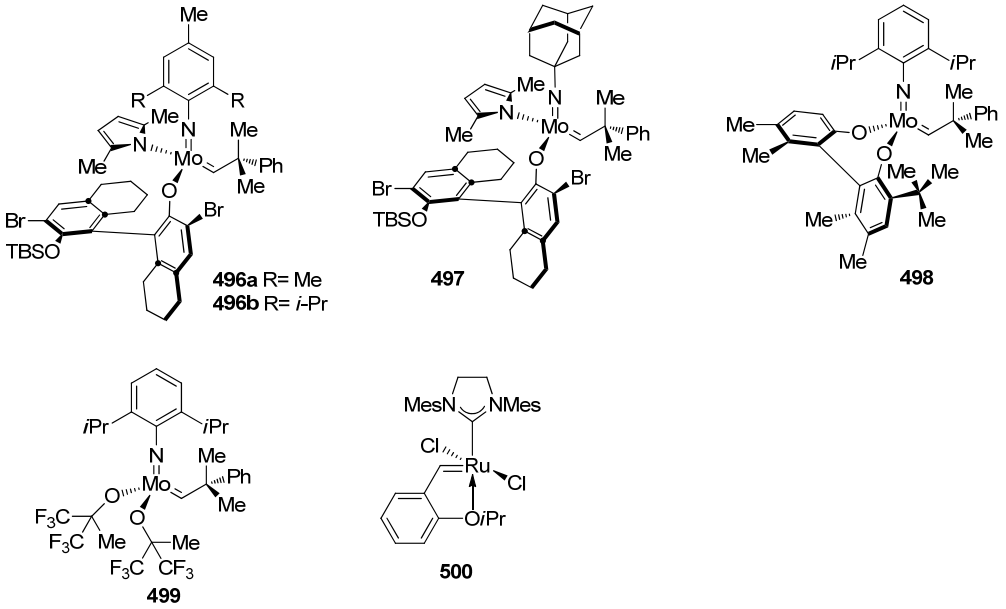
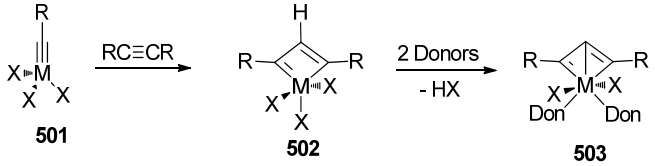


Figure 18: Design of catalysts capable of *Z*-selective cross-metathesis of terminal alkenes

Although among the alkyne metathesis catalysts published by the group of Fürstner, many are those proven to be thermally quite robust and fairly stable on exposure to Lewis acid as activator of the pre-catalysts (*e.g*. $ZnCl_2$ or $MnCl_2$), rigorously anhydrous conditions are still compulsory for productive alkyne metathesis.[113] Next to the bimolecular collision which caused the decomposition of the (pre)catalysts, the new alkylidynes supported by silanolate ligands, just like Schrock alkylidyne complexes, are still known to degrade in presence of terminal alkynes as substrates. According to Schrock and co-workers, terminal alkynes could not be metathesised by alkylidynes of type $[W(CR)(OCMe_3)_3]$ due to the ready loss of one proton from a carbon atom in a tungstenacyclobutadiene complex.[118] This critical step is believed to occur after metallacycle formation, which consists of a transannular carbon-hydrogen bond activation with formation of a deprotio-metallacyclobutadiene (**scheme 120**) and concurrent loss of one alkoxide, a drawback that also none of Fürstner's catalysts can overcome.[113]



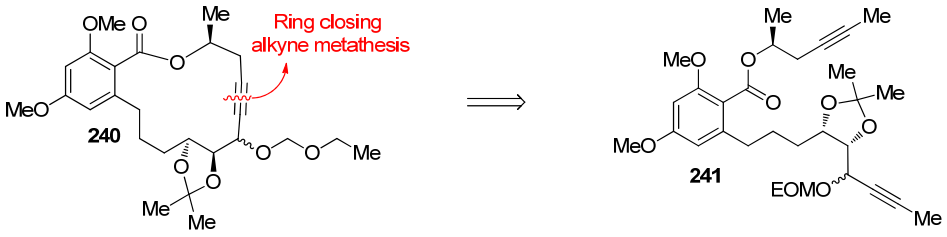
Scheme 120: Formation of deprotio-metallacyclobutadiene (DMS)

Recently, in 2012, there are a few examples of terminal alkynes metathesis recently reported in the literature by the group of Tamm, mediated by the new catalyst [MesC≡Mo{OC(CF_3)$_2$Me}$_3$], which is represented as **495** in **figure 17** above.[119] In the 1980s, the group of Schrock has already succeeded in synthesising the closely related neopentylidyne complexes [Me_3CC≡Mo{OC(CF_3)$_2$Me}$_3$(dme)] and its congener [Me_3CC≡Mo{OC(CF_3)$_2$Me}$_3$], which exhibited, according to the authors, one of the best catalytic capability, yet no terminal alkyne metathesis (TAM) was realisable in their presence. The sparkling idea of introducing the mesityl group instead of methyl by Tamm and co-workers has led to the remarkable discovery of the first class of TAM catalysts, whose rate of alkyne metathesis is appreciably faster than that of deactivation caused, for instance, by formation of deprotiometallacyclobutadiene **503** (**scheme 120**). This class of catalysts promises certainly a better atom economy, though it still remains a fairly recent domain, with the impossible metathesis of terminal aromatic alkynes as the vivid proof of its remaining obscure facet.

Prior to the disclosure of Tamm's catalysts, in 1993, terminal alkyne metathesis was first reported by the group of Mortreux on a few aliphatic alkynes, *e.g*. 1-pentyne, 1-hexyne and 1-heptyne, following their initial attempts at homogeneous metathesis catalysed by well defined ($tBuO)_3$W≡CtBu complex.[120] Nevertheless, they observed little metathesis activity in diethyl ether, while competing polymerisation tended to predominate, a rather discouraging effect that resulted in no further investigation of the neopentylidyne complex (tBuO)$_3$W≡CtBu as prominent TAM catalyst.

- **RCAM as a crucial step in our synthesis towards L-783,277 (7)**

In the course of the initial conception of the synthesis of L-783,277 (**7**), we decided to investigate the reactions catalysed by one of these Fürstner's catalysts to contrive to perform the ring-closing of the 14-membered macrocyclic section. At that time, the (*Z*)-selective alkene metathesis catalyst had not been published by Schrock and co-workers, which left Fürstner's method, a RCAM combined with partial reduction as the best alternative. Consequently, the introduction of internal alkynes (*e.g*. propynyl) at both extremities of the precursor **241** was mandatory, in order not to induce the undesired decomposition of the catalyst. Had the promising terminal alkyne metathesis catalyst system [MesC≡Mo{OC(CF_3)$_2$Me}$_3$] been readily available at the time of our strategy conception, we would still not have opted for a TAM, given that the terminal propynyl would be prone to deprotonation, especially during the benzylic alkylation key step (*cf.*section *2.2.1*). Some of Fürstner's catalysts are *a fortiori* less oxygen and moisture sensitive, compared to the widely used Schrock alkylidyne **489** and other alkyne metathesis catalysts known to date, *e.g.* the exceptionally air stable nitride complex **509**, which can be handled by conventional benchtop techniques.



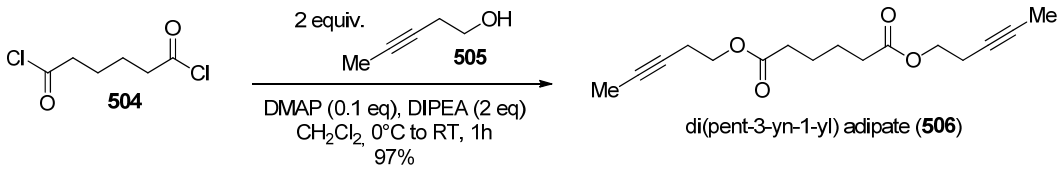
Scheme 121: Retrosynthetic macrocyclisation of dialkyne **3**

As a result of our previously described efforts, the dialkyne intermediate **241**, conceived as the testing ground for a RCAM, was finally available. This compound can be prepared on multigram scale, following a reliable synthetic route, which involves rather inexpensive and easily accessible reagents. With the precursor **3** in hands, we ventured to test the RCAM process.

For all that has been described as drawbacks of the Mortreux' catalytic system, we were yet tempted to carry out a series of trials in the presence of the "instant catalyst" (phenol+$Mo(CO)_6$), at first under the original conditions described by the authors.[108] *De facto*, since 1974, considerable improvements based on the Mo^0/ArOH *in situ* catalytic system have been made to extend its scope to more sensitive molecules.[109]

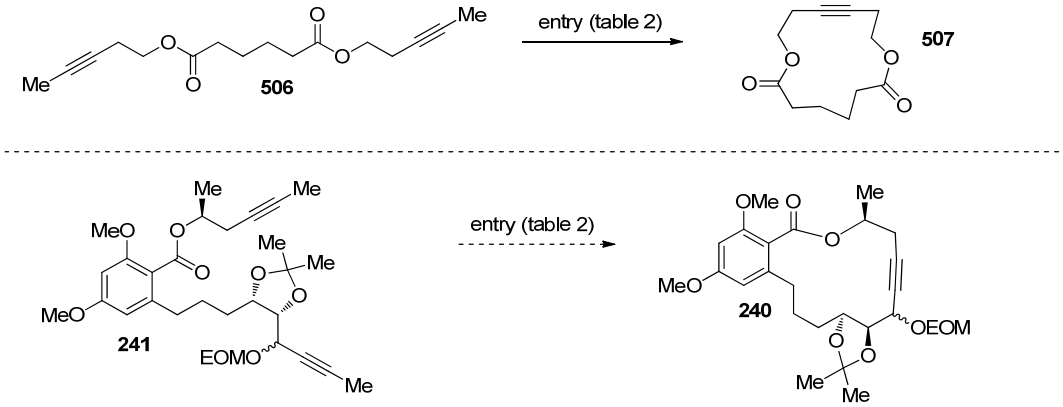
2.3.3.2 First generation strategy: "instant catalyst" of Mortreux and variations

Conceived as a model substrate, given its somewhat simpler structure, the di(pent-3-yn-1-yl) adipate **506** has also been prepared in our laboratory, involving an esterification of adipoyl chloride **504** by pent-3-yn-1-ol (**505**) in the presence of DIPEA and catalytic DMAP in CH_2Cl_2 (**scheme 122**).



Scheme 122: Pre*para*tion of di(pent-3-yn-1-yl) adipate **506**

This dialkyne has been used as a substrate, within an array of alkynes, in the previously mentioned study realised by Fürstner and Seidel in 1998, which upheld the efficiency of Schrock's alkylidyne complex $[W(\equiv CCMe_3)(OCMe_3)_3]$.[115]



Scheme 123: RCAM performed on **506** and **241**

The first attempt using "instant catalyst" by Mortreux and Blanchard[108] (10% $Mo(CO)_6$ activated by resorcinol in decaline at 160°C) has not led to the cyclisation of any of both dialkyne substrates(entry 0). As rightly anticipated, this very harsh condition only ended up in the total decomposition of precursor **241**.

While the experiments in the presence of the modified "instant system" ($Mo(CO)_6$/4-chlorophenol) by Mori *et al.* have given **507** at very low yeal (entries 1 to 4),[121] those employing the most recent fine-tune *in situ* catalyst ($Mo(CO)_6$/2-fluorophenol) by Grela *et al.* allowed higher yields, ranging from 20 to 30% after purification (entries 5 and 6).[109]

Encouraged by this outcome, we have undertaken a series of trials catalysed by 10% of $Mo(CO)_6$ and 1 equivalent of 2-fluorophenol (entries 5 to 8) with the precursor **241** as substrate. Unfortunately, these conditions have not led to the desired product. Even by decreasing the reaction temperature to around 80°C for a longer period, no trace of macrolactone **240** was observed.

Since the beginning of this century, many reactions with transition metal complexes have been reported to be accelerated by microwave irradidation. Among them is the successful alkyne metathesis catalysed by ($Mo(CO)_6$/silanol) under microwave conditions, reported by the group of Villemin.[122]

We decided to use the same procedure described by the authors: octane as solvent and silanol, *e.g.* triphenylsilanol, instead of the commonly used co-catalyst *p*-chlorobenzene. The mixture (dialkyne/ $Mo(CO)_6$/silanol : 20/1/2) was submitted to microwave irradiation during a time interval varying from 10 minutes to 1 hour (entries 9 to 11). The dark black, heterogeneous mixture did not result in the macrocyclisation of the substrates. However, in contrast with the previous results, these conditions were milder, in the sense that almost half of the initial amount of precursor **241** could be recovered, as well as the entire initial amount of the model dialkyne. Other experiments based on the same reagents used for microwave reaction were also operated at high temperature, without radiation and only ended in the total decomposition of the substrates (entries 13 and 14).

Entry	Catalyst	Co-catalyst (1 equiv.)	Reaction conditions	Yield 507	Conversion 241	Yield 240
0	$Mo(CO)_6$ (10 mol%)	resorcinol (6:1)	Decaline, 160°C, 5h	0%	100%	0%
1	$Mo(CO)_6$ (5 mol%)	4-chlorophenol	Chlorobenzene, 120-130°C, 3-7h	< 5%	100%	0%
2	$Mo(CO)_6$ (5 mol%)	4-chlorophenol	Chlorobenzene, 100°C, 12h	< 5%	>80%	0%
3	$Mo(CO)_6$ (10 mol%)	4-chlorophenol	Chlorobenzene, 120-130°C, 3-7h	< 10%	100%	0%
4	$Mo(CO)_6$ (10 mol%)	4-chlorophenol	Chlorobenzene, 100°C, 12h	< 10%	>80%	0%
5	$Mo(CO)_6$ (10 mol%)	2-fluorophenol	Chlorobenzene, 135°C, 3h	< 30%	100%	0%
6	$Mo(CO)_6$ (10 mol%)	2-fluorophenol	Chlorobenzene, 135°C, 6h	< 20%	100%	0%
7	$Mo(CO)_6$ (10mol%)	2-fluorophenol	Toluene, 110°C, 6-12h	< 15%	>70%	0%
8	$Mo(CO)_6$ (10 mol%)	2-fluorophenol	Dichloroethane, 84°C, 6-12h	< 5%	100%	0%
9	$Mo(CO)_6$ (10 mol%)	2-fluorophenol	Chlorobenzene, reflux, 8 to 16h	< 20%	>100%	0%
10	$Mo(CO)_6$ (10 mol%)	2-fluorophenol	Chlorobenzene, Microwave, 170W, 135°C, 1-2h	0%	>60%	0%
11	$Mo(CO)_6$ (5 mol%)	Silanol (10 mol%)	Octane, Microwave, 170W, 150°C, 10 to 60 min	0%	>70%	0%
12	$Mo(CO)_6$ (5 mol%)	Triphenylsilanol (10 mol%)	Octane, Microwave, 170W, 150°C, 10 to 60 min	0%	>70%	0%

13	$Mo(CO)_6$ (5 mol%)	Silanol (10 mol%)	Octane, reflux, 8 to 16h	0%	100%	0%
14	$Mo(CO)_6$ (5 mol%)	Triphenylsilanol (10 mol%)	Octane, reflux, 8 to 16h	0%	100%	0%

Table 7: Attempts of RCAM catalysed by Mortreux's "instant catalyst" and other variations

Despite the cyclisation of the model substrated **506** in the presence of the improved catalytic system ($Mo(CO)_6$/phenol), for example the fine-tune ($Mo(CO)_6$/2-fluorophenol), the same conditions applied to the more complicated dialkyne **241** did not result in any ring-closure.

The use of ($Mo(CO)_6$/phenol) systems is very attractive, as their constituents are often quite stable and off-the-shelf reagents, yet the very high temperature and long reaction time which caused the decomposition of dialkyne **241** remains the main drawback. Besides, all the systematic studies of these $Mo(CO)_6$ –based catalytic systems to extend their scope to more elaborate and fragile substrates have not yet elucidated the entire action mechanism and the active species.

From our point of view, it would not be erroneous to believe in the existence of the optimal phenolic co-catalyst for the ring-closure of our precursor **241**. This assumption implies the screening of a library of phenols, from the best ones known (*e.g*. 4-trifluoromethylphenol) to those supposed to be less activating in the literature, in sight of a tailor-made catalytic system for the substrate of our interest. Unfortunately, due to lack of time, we could not devote further efforts to this end.

Under the circumstances, we turned back to our initially conceived strategy for the pivotal RCAM step, which envisages the use of Fürstner's catalysts, the RCAM catalysts on the rise.

2.3.3.3 Second generation strategy: catalysts of Fürstner

Among all the modern RCAM catalysts, the highly active species prepared by Fürstner from $[Ar(t\text{Bu})N]_3Mo$ and methylene chloride has contributed to the accomplishment of numerous challenging total syntheses projects.[123]

Therefore, our second-generation strategy embraced the use of Fürstner's catalysts, to begin with the CH_2Cl_2-activated precursor complex **508** (**figure 19**).

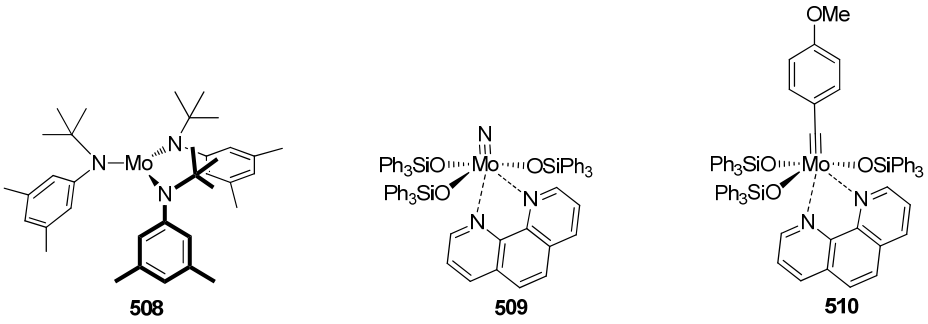
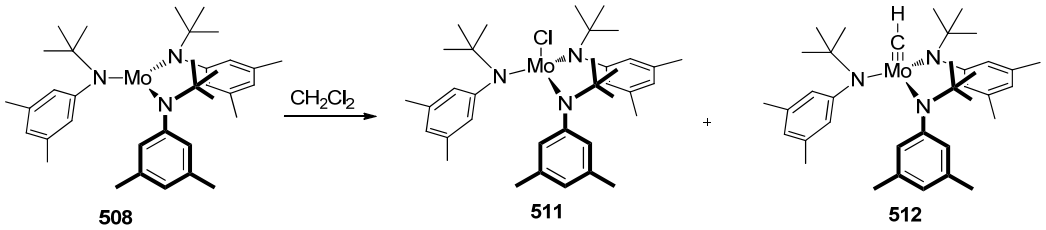


Figure 19: Commercially available Fürstner catalysts

One of the first commercially available Fürstner catalysts is the complex **508**, a sterically hindered trisamido molybdenum (II) complex which possesses remarkable application profile, a novel catalyst disclosed in 2001, which featured in the total synthesis of epothilone A and C.[124]

Originally the authors were impressed by the results published by the group of Cummins some years earlier, who found out the notable capacity of monomeric Mo (III) complexes to react with elemental sulfur, selenium, phosphorous, dinitrogen, CO, NO, etc… Quickly, Fürstner and co-workers succeeded in developing the strikingly air sensitive molybdenum complex **508** which, following its activation in the presence of CH_2Cl_2 (**scheme 124**), was reported to exhibit noteworthy competence in alkyne metathesis, especially in ring-closing alkyne metathesis applied to all ring sizes≥ 12. Being the first catalyst of the type $[Mo\{(Ot\text{Bu})(Ar)N\}_3]$ which outperformed all the existing catalysts at the time in all aspects, in particular by its extraordinary tolerance towards an impressive array of polar groups (*e.g*. unprotected aldehyde, ester, ether, ketone, sulfone, silyl ether, acetal, nitrile, sulfonamide, glycoside, alkyl chloride, and trifluoromethyl) though limits still reside in acidic protons, for instance from alcohols or acids.

The excellent profile of the combination **508**/CH_2Cl_2 has been validated, in the first decade of our century, by several accomplished total syntheses, which incorporate a decisive RCAM step applied to highly functionalised and bulky precursors.
Convinced by these results, we started a new series of experiments based on a well-described procedure by the Fürstner's group,[125] involving at first the less structurally complicated model dialkyne **506** in the presence of the precatalyst **508**.



Scheme 124: Activation of the sterically demanding trisamido molybdenum **508** to form metathesis active components

Despite its very favourable characteristics, complex **508** is strikingly sensitive and requires very careful handling. In addition to its sensitivity *vis-à-vis* oxidation and hydrolysis, this compound is active enough to cleave molecular nitrogen.[126] Accordingly, all the involved solvents were not only freshly distillated, but also submitted to freeze-pump-thaw cycles. Weighing and addition of the catalyst took place inside a glove box under argon atmosphere.

A 10^{-3} mol.L^{-1} solution of the commercial molybdenum complex **508** (10 mol%) in toluene was first activated by rigorous stirring, at room temperature, with CH_2Cl_2 (0.04 mL per mole of precatalyst). After 5 to 10 minutes, the solution of the activated catalyst was added to a $3.6x10^{-3}$ mol.L^{-1} solution of the model substrate **506** and powdered molecular sieve (MS) 5Å (1 g) in toluene. The heterogeneous mixture stirred at 80°C for 1 hour before being cooled to ambient temperature (entry 15). The solvents were totally evaporated and the crude product analysed. Unfortunately, there was no observation of the macrocycle **507**. The reaction time has also been extended in some trials (entry 16), or/and the temperature was decreased below reflux point (entry 17) in others, yet the resulting mixture remained devoid of any ring-closure product.

Additional trials have also been performed under similar conditions, continuously flushed through by an argon flow, following the addition of the CH_2Cl_2-activated catalyst (entry 16). However, the resulting mixture did not contain any trace of the expected ring-closing product. As rightly predicted, the ring-closure also did not take place in the case of the more complicated dialkyne when exposed to similar conditions (entry 15 to 20).

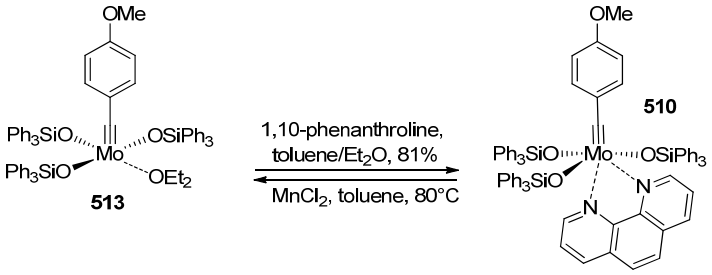
Entry	Catalyst (5 to 10 mol%)	Reaction conditions	Yield 507	Conversion 241	Yield 240
15	Fürstner pre-catalyst **508**/ CH_2Cl_2	Toluene, 5-10 min, 20°C, MS 5A, 80°C, 1h	0%	> 30%	0%
16	Fürstner catalyst **508**/ CH_2Cl_2	Toluene, 5-10min, 20°C, MS 5A, 80°C, 1h, 80 to 20°C, 12h	0%	> 60%	0%
17	Fürstner pre-catalyst **508**/ CH_2Cl_2	Toluene, 5-10 min, 20°C, MS 5A, 80°C, 20 min, 80°C to 50°C, 40min	0%	> 20%	0%
18	Fürstner pre-catalyst **508**/ CH_2Cl_2	Toluene, 5-10 min, 20°C, MS 5A, 80°C, 1h, continuous argon flow	0%	> 20%	0%
19	Fürstner pre-catalyst **508**/ CH_2Cl_2	Toluene, 5-10 min, 20°C, MS 5A, 80°C, 1h, 80 to 20°C, 12h, continuous flow	0%	> 30%	0%

20	Fürstner pre-catalyst **508**/ CH_2Cl_2	Toluene, 5-10 min, 20°C, MS 5A, 80°C, 20 min, 80°C to 50°C, 40min continuous argon flow	0%	> 30%	0%

Table 8: Attempts of RCAM catalysed by the molybdenum complex **508**

Discouraged by the outcome, we gave up on this exceedingly sensitive and unpractical pre-catalyst. Indeed, the failure of RCAM in the presence of the commercial molybdenum complex **508** could be explained by its eager decomposition, which could be caused by inappropriate storage during the transport to our laboratories. Therefore, it would be more reasonable to use this pre-catalyst as freshly prepared to verify its reactivity.

Consequently, we embarked on another series of probes usingthe molybdenum alkylidyne endowed with triarylsilanolate ligands **510** (**figure 17**) as pre-catalyst. This compound is commercially available and can be activated by $MnCl_2$ at 80°C in toluene to deliver the active species **24** (**scheme 125**), which is reported by the authors to be one of the most active metathesis catalysts known to date, but still less active in comparison to its nitrogen-sensitive congener **508**.[127] In addition, the phenanthroline adduct **510** has been reported to be surprisingly stable to the point of being handled in air without instantaneous decomposition, though still requires to be stored under argon. Practically, this precatalyst could be rapidly weighed in the air without instantaneous decomposition. Furthermore, the catalytic mixture containing the molybdenum alkylidyne **513** restored *in situ* from the pre-catalyst **510** (**scheme 125**) is so active that the metathesis can be carried out at ambient temperature.



Scheme 125: Activation of Fürstner pre-catalyst **510**

Following the procedure by Fürstner and collaborators,[127] a solution containing precatalyst **510** (5 mol%) and $MnCl_2$ (mol%) in toluene was stirred at 80°C for 30 min. After this activation phase, the mixture was allowed to reach ambient temperature before it was added to a suspension of dialkyne **506** (1.0 mmol) and powdered MS 5Å (2 mg of MS 5Å per µmol of released 2-butyne) in toluene. The resulting mixture was stirred at ambient temperature for 2 to 3h before being filtered through a short plug of silica. The residue after evaporation of the solvent was purified by flash chromatography. To our great pleasure, the macrocycle **507** was obtained in very good yield (65%).

Encouraged by this outcome, the precursor **241** was subjected to the same conditions (entry 21), which did not provide any expected ring-closing product **240**.

Entry	Catalyst	Activation conditions	Reaction conditions	Yield 507	Conversion 241	Yield 240
21	**510** (5 to 10 mol%)/$MnCl_2$ (5 to 10 mol%)	30 min, 80°C	MS 5A, 20°C, 3 to 4h	< 40%	> 30%	0%
22	**510**/$MnCl_2$ (5 mol%)	30 min, 80°C	MS 5A, 35 to 40°C, 3 to 4h	< 40%	> 30%	0%
23	**510**/$MnCl_2$ (5 to 10 mol%)	30 min, 80°C	MS 5A, 35°C to 20°C, 12h	< 50%	> 30%	0%
24	**510**/$MnCl_2$ (10 mol%)	30 to 45 min, 80°C	MS 5A, 20°C, 3 to 4h continuous argon flow	< 70%	> 30%	0%
25	**510**/$MnCl_2$ (10 mol%)	30 to 45 min, 80°C	MS 5A, 20°C, continuous argon flow, 12h	< 75%	> 30%	0%
26	**510**/$MnCl_2$ (5 to 10 mol%)	30 to 45 min, 80°C	MS 5A, 35°C, continuous argon flow, 12h	< 50%	> 30%	0%

Table 10: Attempts of RCAM catalysed by the pre-catalyst **510**

Some other experiments have been carried out with small modifications, such as longer reaction time (entries 22 and 23), or additional argon flow, following the addition of the CH_2Cl_2-activated catalyst (entries 24-26). However, tried as hard as we could, like all the previous trials, no trace of the desired intermediate **240** was detected in any case. On the other hand, analogous metathesis reactions have been simultaneously performed, involving the simple dialkyne **506** as model. In opposition to those previously described, these experiments unchangingly provided the RCAM product in acceptable yield, spanning from 50% to 60% (entry 22 to 23). Extensive studies have prevailed upon the assistance of molecular sieve, in particular the MS 5Å, in liberating the required free coordination site at molybdenum, and additionally, activated MS 5Å is capable of absorbing C4-hydrocarbons, *e.g.* the liberated 2-butyne.[127] For these reasons, despite the stated absorption of 2-butyne by MS 5Å by the authors, it is worth mentioning that continuous flushing of the reaction mixture by argon until completion resulted in somewhat better yields which lay within 65-75% (entry 24-26).

- **Conclusion**

Regardless of the cheap and easy availability of the constituents of the catalytic systems comprising $Mo(CO)_6$ and resorcinol (or other phenols), these simple and user-friendly systems have not yet reached the level of activity, nor selectivity offered by better-defined catalysts or precatalysts at this point in time. The harsh conditions, often due to the activation in high boiling solvents, render these heterogenous mixtures unsuitable for structurally complex, and thus labile targets, which includes our strategic dialkyne precursor **241**.

Nevertheless, substantial enhancement of the catalytic performance of the combination [$Mo(CO)_6$, ArOH] has been rationalized in terms of decarbonylation of $Mo(CO)_6$, as a consequence of extensive experimental studies. The phenolic activator is still to be investigated, as it would be simplistic to believe in a linear correlation between the acidity of the involved phenols and the activity of the resulting combination. Moreover, each target substrate is very like to influence the catalytic activity of the entire system, whose precise mechanism is still unknown.

The unexpected inefficiency of the crucial RCAM in the presence of Fürstner's catalysts was very likely, in the first place, linked to the excessive sensibility of the chosen pre-catalysts towards oxygen, moisture, and even molecular nitrogen in the extreme case of trisamido molybdenum **508**. There was unfortunately no warranty of the quality and intactness of the purchased pre-catalyst, supplied by the very few commercial sources. Nevertheless, the unsuccessful metathesis trials implicating the uncomplicated, and relatively robust compound **507** have discarded the presumption of conformational constrains in the cyclisation precursor as major source of failure. In all likeliness, the handle and employment of such an extremely sensitive compound requires the expert's know-how and specific techniques, a prerequisite condition which has turned into a limitation in our case.

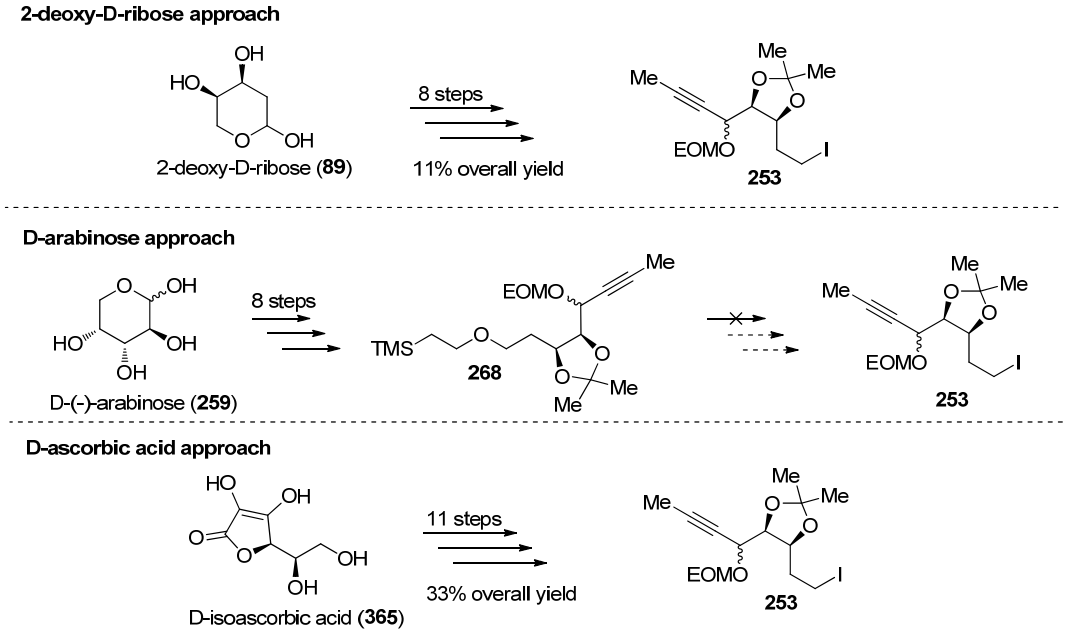
Besides, the rather high reaction temperature (80°C) mandatory for the metathesis reaction in the presence of **508**/CH_2Cl_2, which is supposed to be the best compromise found by the authors for an optimal metathesis, ironically constitutes a major cause for decomposition of the catalyst formed *in situ*. A competition between the life-time and sustainability of the active species and the rate of metathesis renders the use of the combination **508**/CH_2Cl_2 problematic.

For these reasons, to replace the unstable pre-catalyst **508**, the authors have developed other alternatives, *e.g.* the partially air-stable *p*-methoxybenzylidyne species **510**. To our great pleasure, when applied to model dialkyne **506**, this precatalyst, once activated by $MnCl_2$, delivered the ring-closure product in com*para*tively high yields (60 to 75%). And to our great dismay, the same procedure did not result in any trace of the desired compound **240**.This outcome clearly annulated the hypothesis of possible lack of expertise skills and equipment, or the decomposition of the commercially procured pre-catalyst **510** due to its inappropriate storage and handling. However, in correlation with the statement of the authors concerning the inefficiency of the active species **513** released from the activation of **510**, in cases of very bulky compounds, the conformational constrains in the target substrate **241** might be at the origin of our fruitless RCAM trials.

2.4 Conclusion

The major work of this thesis is rooted in the search for a formal synthesis targeting L-783,277 (**7**), a pathway studded with numerous stumbling blocks and detours. Our work has been based on the initial desire to realise the ring-closure by a RCAM, while securing the characteristic *cis*-enone with a Lindlar reduction to induce the *Z*-configuration.

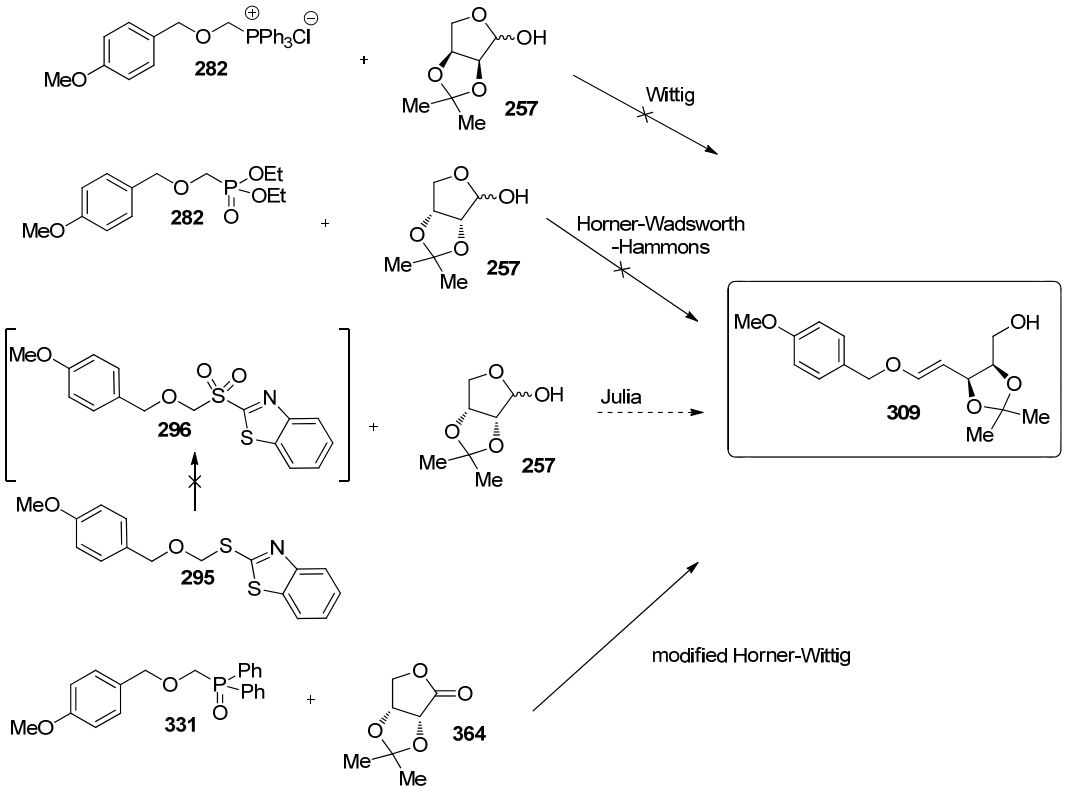
To this end, the synthesis of the dialkyne precursor **241** was of priority, which has engendered the key step employing a direct alkylation at the benzylic position. Extensive experimentation has been required to achieve operationally efficient alkylation conditions, *e.g*. the use of *sec*-butyllithium at -78°C to generate the lithium dianion derived from **401** and the appropriate choice of electrophilic function for the polyol section. Initial attempts to synthesise a series of corresponding electrophiles were mainly based on a similar synthesis in the literature (*cf*. "2-deoxy-D-ribose approach"),[8] which have resulted in the pre*para*tion of iodide segment **253** and tosylate **255**. However, the very low yields caused by unreliable procedures, together with the tricky handling and purification of the some intermediates prompted us to find another route. The second sequence, the "D-arabinose approach", ended in a fully protected polyol fragment, whose (tri-methylsilyl)ethyl ether resistant to all attempts of orthogonal deprotection to release the corresponding primary alcohol **369** as the intersecting point with the first "2-deoxy-D-ribose approach". This synthetic route sadly led to the impasse due to the highly tricky orthogonal deprotection of TMS group on the precursor **268**, as briefly illustrated in **scheme 75** below. This unexpected incident has embarked us onto a long journey to find out the most appropriate one-carbon homologation to forge the (*para*-methoxy)benzyl enol ether **309**.



Scheme 75: 2-deoxy-D-ribose approach *versus* D-isoisoascorbic acid approach

To our great relief, the use of phosphine oxide **351** to carry out a modified Horner-Wittig reaction with lactone **364** has finally led to the synthesis of intermediate **257** *via* a very short

and reliable route. Besides, phophine oxide **331** which has not been mentioned in the literature so far can be obtained in 2 steps starting from chlorodiphenylphosphine (**329**) on a multigram scale. This turning point of the pathway has bridged the "D-isoascorbic acid approach" unto the achievement of iodide segment **253** with an average yield for each synthetic step exceeding 75%. This short and efficient route has allowed us to attain a multigram amount of iodide **253** without further complication. Noteworthily, our tactical sequence of modified Horner-Wittig alternated with sodium borohydride assisted reduction and final NaH elimination to release the corresponding ether enol is interestingly promising for opening other highly functionalised lactones. Further investigations with an array of lactones have also been carried out within our group.

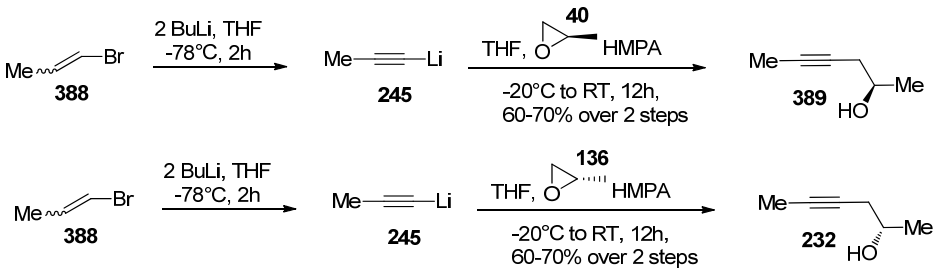


Scheme 76: Attempts to achieve PMB-enol ether **509** *via* various olefination methods

Even though the first approach towards tolsylate **255** and iodide **253** from 2-deoxy-D-ribose (**89**) has not been conclusive on a multigram scale, it has allowed us to find out iodide **6** as the best reactant for our key step: the direct benzylic alkylation. The target was to achieve the intermediate **12** without additional functionnalisation to enhance the nucleophicity of the anion derivative at the benzylic position. The original scheme of protecting the benzylic acid function before generating the lithium benzylic anion turned out to be inefficient and very lengthy. Meticulous and extensive experiments have led to the use of lithium dianion derived from orsellinic acide **401**, as well as an iodide as the best electrophile in this case. With the iodide fragment **253** in hands, we have identified the best conditions thus far for the direct attachment of **253** to **401**, affording the desired intermediate **452** in remarkable yield (up to 85%). To our great pleasure, the riskily speculated direct alkylation has been substantiated and optimised to the point of being a very reliable and efficient tool.

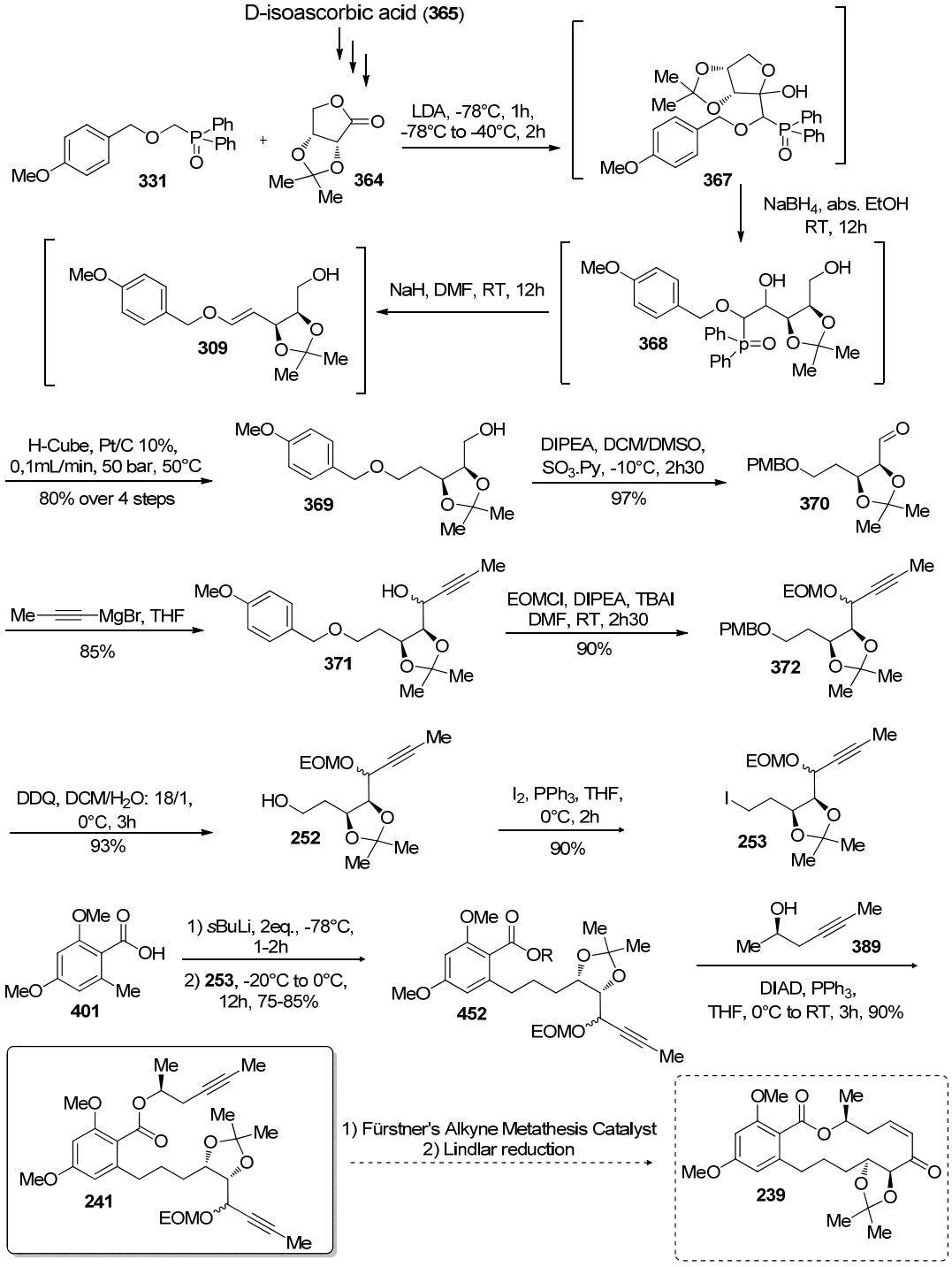
Indeed, the very same procedure can be extended to the synthesis of other RALs which also carry a single bond C1'-C2'. The most representative example is the succinct and accomplished synthesis of the naturally occurring macrolide *(R)*-(+)-lasiodiplodin (**10**), the first resorcylide, along with other natural and analogue RALs synthesised according to the designing blueprint outlined in section *3.1*.

The last fragment coupling took place between **452** and the enantiomerically pure propargylic alcohol **389** (**scheme 126**) resulting from the selective opening of the commercially available *(R)*-2-methyloxirane **41**. Starting from 1-bromopropene **388**, alcohol **389** was obtained in 2 steps with an average yield of 60 to 70%. The same procedure has been initially applied to the pre*para*tion of the other enantiomer (*S*)-2- methyloxirane **136**, which has been involved in the first trials of esterification described in section *2.2.2.2*. Due to their very low boiling point, it is advisable not to store this compound and instead to use the propargylic alcohol directly after its pre*para*tion.



Scheme 126: Synthesis of *(R)*-hex-4-yn-2-ol (**389**) and *(S)*-hex-4-yn-2-ol (**232**)

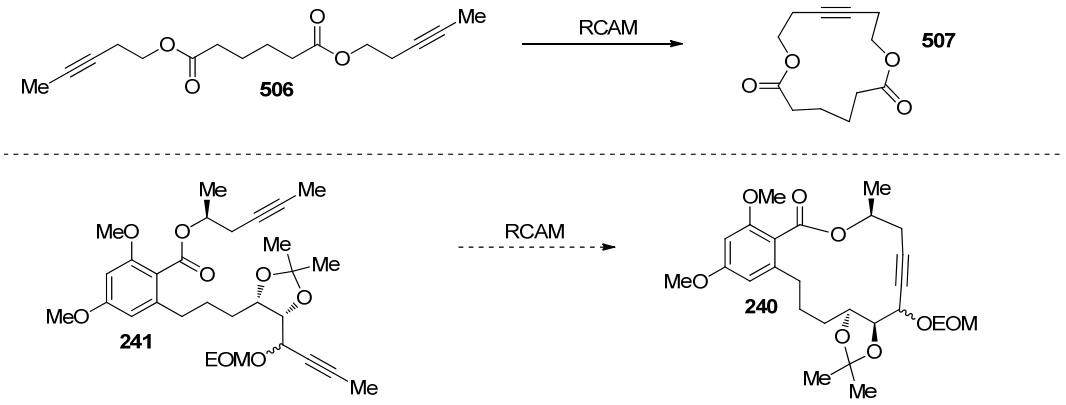
In the literature, it has been observed that the esterification involving the benzoic acid of the aromatic core of the target RAL was not as straightforward as expected, especially when the latter was implicated as electrophilic center. Nonetheless, we have, in the first place, submitted the simple orsellinic acid **401** to various esterification procedures which have been formerly used in the syntheses of RALs and are sufficiently mild for notably acid-sensitive substrates. These methods include the use of carbonyldiimidazole (CDI), cyanuric chloride **470** and Steglich conditions, all of which aim to transform the carboxylic acid into the corresponding electrophilic site. Various metal anions derived from (*S*)-hex-4-yn-2-ol (**232**) have been employed as nucleophiles. While some of these procedures worked out for the model orsellinic acid derivative **401**, they have not led to any trace of the expected precursor **241**. This outcome might be explained by the exceedingly weak electrophilicity of the carbonyl carbon due to the presence of two methoxy functions, and in particular the sterically hindered *ortho* position, which is lacking in the case of the more simple orsellinic acid **401**. Finally, the Mitsunobu reaction has allowed us to overcome this substrate barrier by transforming instead *(R)*-hex-4-yn-2-ol (**389**) into the related electrophile. This method has gratifyingly yielded the dialkyne precursor **241** in com*para*bly high yield (75 to 85%) upon flash chromatography purification. Hereafter, our most concise and efficient route towards the pivotal precursor **241** is presented in **scheme 127**.



Scheme 127: Our most concise and efficient route towards dialkyne **241**

As our granted time for this thesis work reached the end, the last intramolecular metathesis envisaged to connect both alkyne ends of precursor **241** has not been substantiated. However, a number of well-known catalysts have been tested onto the aforementioned **241**, as well as the adipoyl ester **506** as the model substrate, which represents a more simple structure and hence less conformational constrains.

The first attempts using the most-known variants of the classic "instant catalystic system" ($Mo(CO)_6$/phenol), originally disclosed by Mortreux[108] have definitely given the ring-closing product from the model substrate **506**, though at very low yields. Due to their harsh conditions (*e.g*. high boiling solvents) and ill-defined mechanism, these catalytic systems are unsuitable for more decorated, and thus labile substrates like precursor **241.** However, it seems feasible to screen for the optimal phenol, *i.d.* the fine-tune of the combination ($Mo(CO)_6$/ArOH) to attain the expected RCAM.



Scheme 123: RCAM performed on model substrate **506** and dialkyne **241**

However, the use of the combination **508**/CH_2Cl_2 (**scheme 124**), which has been developed by Fürstner's group and remains one of the most powerful metathesis catalyst known to date, did not lead to any anticipated ring-closing product for the model dialkyne **506** and the more complex substrate **241**. This outcome is very likely linked to the excessive sensitivity of **508** towards oxygen, moisture and even molecular nitrogen, which demands expert knowledge and skills, as well as specific equipment for its manipulation. Therefore, the fruitless trials catalysed by the CH_2Cl_2-activated complex **508** do not validate any assumption about the compatibility of the latter with our precursor **241**, concerning either the activity profile of the precatalyst **6**, or the structural hindrance of the substrate.

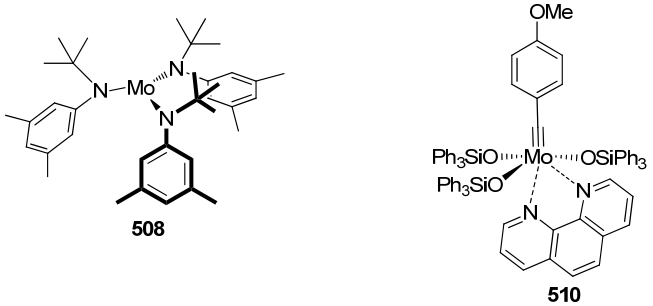


Figure 20: Commercially available Fürstner catalysts involved in our attempts of RCAM

Our last series of experiments carried out in the presence of *p*-methoxybenzylidyne **510** activated by $MnCl_2$ resulted in the achievement of the macrolactone **507** in rather high yields (50 to 75%). And against all expectations, similar conditions involving the crucial precursor **241** have not led to any ring-closure. After several attempts with some slight modifications of the original procedure by the authors, such as longer reaction time or higher reaction

temperature, even higher loading of the precatalyst **510**, we have come to the conclusion of a possible structural barrier of the highly functionalised tested substrate. Indeed, all the experiments which involved the simple adipoyl diester **506** gave the corresponding macrolactone, did not give the anticipated product when performed in the presence of the more structurally complex dialkyne **241**.

2.5 List of references

1. Hofmann, T. Resorcylic Lactone L-783277 as a New Lead Structure for kinase Inhibition-Total Synthesis and SAR Studies. Dissertation, ETH Zürich, 2009.
2. Schirmer, A.; Kennedy, J.; Murli, S.; Reid, R.; Santi, D. V., Targeted covalent inactivation of protein kinases by resorcylic acid lactone polyketides. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 4234-4239.
3. Zhao, A.; Lee, S. H.; Mojena, M.; Jenkins, R. G.; Patrick, D. R.; Huber, H. E.; Goetz, M. A.; Hensens, O. D.; Zink, D. L.; Vilella, D.; Dombrowski, A. W.; Lingham, R. B.; Huang, L., Resorcylic acid lactones: Naturally occurring potent and selective inhibitors of MEK. *Journal of Antibiotics* **1999**, *52* (12), 1086-1094.
4. Liniger, M.; Neuhaus, C.; Hofmann, T.; Fransioli-Ignazio, L.; Jordi, M.; Drueckes, P.; Trappe, J.; Fabbro, D.; Altmann, K. H., Kinase inhibition by deoxy analogues of the resorcylic lactone L-783277. *ACS Medicinal Chemistry Letters* **2011**, *2* (1), 22-27.
5. Jogireddy, R.; Dakas, P. Y.; Valot, G.; Barluenga, S.; Winssinger, N., Synthesis of a Resorcylic Acid Lactone (RAL) library using fluorous-mixture synthesis and profile of its selectivity against a panel of kinases. *Chemistry - A European Journal* **2009**, *15* (43), 11498-11506.
6. Kusuma, B. R.; Brandt, G. E. L.; Blagg, B. S. J., Synthesis of cruentaren A. *Organic Letters* **2012**, *14* (24), 6242-6245.
7. Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H., Catalytic Z-selective olefin cross-metathesis for natural product synthesis. *Nature (London, U. K.)* **2011**, *471*, 461-466.
8. Dakas, P. Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winssinger, N., Modular synthesis of radicicol A and related resorcylic acid lactones, potent kinase inhibitors. *Angewandte Chemie - International Edition* **2007**, *46* (36), 6899-6902.
9. Dakas, P. Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N., Divergent syntheses of resorcylic acid lactones: L-783277, LL-Z1640-2, and hypothemycin. *Chemistry - A European Journal* **2009**, *15* (43), 11490-11497.
10. Fürstner, A.; Bindl, M.; Jean, L., Concise total synthesis of cruentaren A. *Angewandte Chemie - International Edition* **2007**, *46* (48), 9275-9278.
11. Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R., Ring-closing alkyne metathesis. Application to the total synthesis of sophorolipid lactone. *Journal of Organic Chemistry* **2000**, *65* (25), 8758-8762.
12. Fuerstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W., Novel and Flexible Entries into Prostaglandins and Analogues Based on Ring Closing Alkyne Metathesis or Alkyne Cross Metathesis. *J. Am. Chem. Soc.* **2000**, *122*, 11799-11805.
13. Hofmann, T.; Altmann, K. H., Total synthesis of the resorcylic lactone-based kinase inhibitor L-783277. *Synlett* **2008**, (10), 1500-1504.
14. Hofmann, T.; Altmann, K. H., Resorcylic acid lactones as new lead structures for kinase inhibition. *Comptes Rendus Chimie* **2008**, *11* (11-12), 1318-1335.
15. Dakas, P. Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winddinger, N., Modular synthesis of radicicol A and related resorcylic acid lactones, potent kinase inhibitors. *Angew Chem* **2007**, *119*, 7023-6.

16. Dakas, P.-Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winssinger, N., Modular synthesis of radicicol A and related resorcylic acid lactones, potent kinase inhibitors. *Angew. Chem., Int. Ed.* **2007**, *46*, 6899-6902.

17. Parikh, J. R.; Doering, W. v. E., Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide. *Journal of the American Chemical Society* **1967**, *89* (21), 5505-5507.

18. Wang, P.; Zhang, Z.; Yu, B., Total Synthesis of CRM646-A and -B, Two Fungal Glucuronides with Potent Heparinase Inhibition Activities. *J. Org. Chem.* **2005**, *70*, 8884-8889.

19. Blum, T.; Ermert, J.; Wutz, W.; Bier, D.; Coenen, H. H., First no-carrier-added radio-selenation of an adenosine-A1 receptor ligand. *J. Labelled Compd. Radiopharm.* **2004**, *47*, 415-427.

20. Armarego, W. L. F.; Chai, C. L. L., Preface to the Sixth Edition. In *Purification of Laboratory Chemicals (Sixth Edition)*, Armarego, W. L. F.; Chai, C. L. L., Eds. Butterworth-Heinemann: Oxford, 2009; pp xii-xiii.

21. Sugimoto, O.; Mori, M.; Tanji, K.-I., A facile halogenation of some hydroxyheterocycles using triphenylphosphine and N-halosuccinimide. *Tetrahedron Lett.* **1999**, *40*, 7477-7478.

22. Johnstone, C.; Kerr, W. J.; Scott, J. S., Selective cleavage of ketals and acetals under neutral, anhydrous conditions using triphenylphosphine and carbon tetrabromide. *Chem. Commun. (Cambridge)* **1996**, 886.

23. De Luca, L.; Giacomelli, G.; Porcheddu, A., An Efficient Route to Alkyl Chlorides from Alcohols Using the Complex TCT/DMF. *Org. Lett.* **2002**, *4*, 553-555.

24. Wittig, G.; Boell, W., Phosphinealkylenes as olefination reagents. VII. The decomposition reactions of triphenylphosphoranylidene(butoxy)methylene and analogous compounds. *Chem. Ber.* **1962**, *95*, 2526-34.

25. (a) Ballou, C. E., A new synthesis of D-erythrose derivatives from D-arabinose. *J. Am. Chem. Soc.* **1957**, *79*, 165-6; (b) Kiso, M.; Hasegawa, A., The behavior of some aldoses with 2,2-dialkoxypropane-N,N-dimethylformamide-p-toluenesulfonic acid. Part V. Acetonation of some pentoses with 2,2-dimethoxypropane-N,N-dimethylformamide-p-toluenesulfonic acid. *Carbohydr. Res.* **1976**, *52*, 95-101.

26. Jones, J. K. N.; Kent, P. W.; Stacey, M., Synthesis of some derivatives of D- and L-arabinose. *J. Chem. Soc.* **1947**,, 1341-4.

27. Treu, M.; Jordis, U., 4a,5,9,10,11,12-Hexahydro-6H-benzo[a]cyclohepta[hi]benzofuran - synthesis of unnatural galanthamine analogs. *Molecules* **2002**, *7*, 374-381.

28. Schoenauer, K.; Zbiral, E., Reactions with organophosphorus compounds. 50. Trimethylsilylethoxymethylene triphenylphosphorane, a novel reagent for the homologation of carbonyl compounds. *Tetrahedron Lett.* **1983**, *24*, 573-6.

29. Schelhaas, M.; Waldmann, H., Protecting group strategies in organic synthesis. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2056-2083.

30. Paquette, L. A.; Backhaus, D.; Braun, R., Direct asymmetric entry into the cytotoxic 8,9-secokaurene diterpenoids. Total synthesis of (-)-O-methylshikoccin and (+)-O-(methylepoxy)shikoccin. *J. Am. Chem. Soc.* **1996**, *118*, 11990-11991.

31. Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D., Total synthesis of (±)-isoavenaciolide and (±)-avenaciolide. *Tetrahedron Lett.* **1986**, *27*, 3345-8.

32. Greene, T. W.; Wuts, P. G. M., *Protective Groups in Organic Synthesis. 2nd Ed*. John Wiley and Sons, Inc.: 1991; p 473 pp.

33. Gerlach, H., 2-(Trimethylsilyl)ethyl esters as a carboxyl protecting group; application in the synthesis of (-)-(S)-curvularin. *Helv. Chim. Acta* **1977**, *60*, 3039-44.

34. Clark, J. H.; Goodall, D. M.; White, M. S., Hydrogen bonding in organic synthesis: evidence for the role of hydrogen bonding in reactions of fluorene promoted by fluoride ion. *Tetrahedron Lett.* **1983**, *24*, 1097-100.

35. Ferezou, J.-P.; Julia, M.; Li, Y.; Liu, L. W.; Pancrazi, A., Total synthesis of avermectins. Part 2: Enantioselective synthesis of the C10-C25 northern fragment and final steps for the construction of the 22,23-dihydroavermectin B1b aglycon. *Bull. Soc. Chim. Fr.* **1995**, *132*, 428-52.

36. Serrano-Wu, M. H.; Regueiro-Ren, A.; St. Laurent, D. R.; Carroll, T. M.; Balasubramanian, B. N., Mild deprotection of 2-(trimethylsilyl)ethyl esters. *Tetrahedron Lett.* **2001**, *42*, 8593-8595.

37. Mori, Y.; Futamura, Y.; Horisaki, K., Regioselective aliphatic retro-[1,4]-Brook rearrangements. *Angew. Chem., Int. Ed.* **2008**, *47*, 1091-1093.

38. Paquette, L. A.; Huber, S. K.; Thompson, R. C., A means for stereocontrolled introduction of the C-2 oxygen substituent in functionalized cis-tricyclo[9.3.1.03,8]pentadecanones related to taxol. *J. Org. Chem.* **1993**, *58*, 6874-82.

39. Masaki, Y.; Iwata, I.; Mukai, I.; Oda, H.; Nagashima, H., P-Anisyloxymethyl group, a nove,l oxidatively removable acetal type hydroxy-protecting group. *Chem. Lett.* **1989**,, 659-62.

40. Loubinoux, B.; Coudert, G.; Guillaumet, G., A new method for the protection of the hydroxyl group. *Tetrahedron Lett.* **1981**, *22*, 1973-6.

41. Djerassi, C., Brominations with N-bromosuccinimide and related compounds. The Wohl-Ziegler reaction. *Chem. Rev. (Washington, DC, U. S.)* **1948**, *43*, 271-317.

42. Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J.; Thomas, A. P., The Palladium-Catalyzed Enyne Cycloisomerization Reaction in a General Approach to the Asymmetric Syntheses of the Picrotoxane Sesquiterpenes. Part I. First-Generation Total Synthesis of Corianin and Formal Syntheses of Picrotoxinin and Picrotin. *J. Am. Chem. Soc.* **1999**, *121*, 6183-6192.

43. Corey, E. J.; Bock, M. G., Protection of primary hydroxyl groups as (methylthio)methyl ethers. *Tetrahedron Lett.* **1975**,, 3269-70.

44. Medina, J. C.; Salomon, M.; Kyler, K. S., A mild method for the conversion of alcohols to methylthiomethyl ethers. *Tetrahedron Lett.* **1988**, *29*, 3773-6.

45. Feldman, K. S., Modern Pummerer-type reactions. *Tetrahedron* **2006**, *62* (21), 5003-5034.

46. Keck, G. E.; Boden, E. P.; Wiley, M. R., Total synthesis of (+)-colletodiol: new methodology for the synthesis of macrolactones. *J. Org. Chem.* **1989**, *54*, 896-906.

47. Ferwanah, A.; Pressler, W.; Reichardt, C., Synthesis with substituted malondialdehydes. 17. Synthesis and properties of cycloalkylmalondialdehydes. *Tetrahedron Lett.* **1973**,, 3979-82.

48. Blakemore, P. R., The modified Julia olefination: alkene synthesis *via* the condensation of metallated heteroarylalkylsulfones with carbonyl compounds. *J. Chem. Soc., Perkin Trans. 1* **2002**,, 2563-2585.

49. Surprenant, S.; Chan, W. Y.; Berthelette, C., Efficient Synthesis of Substituted Vinyl Ethers Using the Julia Olefination. *Org. Lett.* **2003**, *5*, 4851-4854.

50. Noyori, R.; Aoki, M.; Sato, K., Green oxidation with aqueous hydrogen peroxide. *Chem. Commun. (Cambridge, U. K.)* **2003**,, 1977-1986.

51. Kouge, K.; Koizumi, T.; Ishibashi, N.; Okai, H., New taste-blind substances. Studies on the sensory divergence of bitterness to the taste-blindness of 2-mercaptoimidazoline, 2-mercaptobenzothiazole and their derivatives, with special reference to their molecular structure. *Agric. Biol. Chem.* **1987**, *51*, 1941-5.

52. Durst, T.; Kozma, E. C.; Charlton, J. L., Stereoselectivity in the Diels-Alder reaction of phenyl- and oxy-substituted o-quinodimethanes. *J. Org. Chem.* **1985**, *50*, 4829-33.

53. Bredereck, H.; Bader, E., Polymerizations and polymerization catalysts. I. Pre*para*tion of α-hydroxy- and α-amino sulfones and of sulfinic acid salts of organic bases. *Chem. Ber.* **1954**, *87*, 129-39.

54. Kluge, A. F.; Cloudsdale, I. S., Phosphonate reagents for the synthesis of enol ethers and one-carbon homologation to aldehydes. *J. Org. Chem.* **1979**, *44*, 4847-52.

55. Clizbe, L. A.; Overman, L. E., Allylically transposed amines from allylic alcohols: 3,7-dimethyl-1,6-octadien-3-amine. *Org. Synth.* **1978**, *58*, 4-11.

56. Lavielle, G.; Reisdorf, D., Carbanions of alkoxymethylphosphonic acid esters and amides. Synthesis of enol ethers. *C. R. Acad. Sci., Ser. C* **1971**, *272*, 100-2.

57. Dayoub, W.; Doutheau, A., (E) Enol ethers from the stereoselective reduction of α-alkoxy-β-ketophosphonates and Wittig type reaction. *Sci. China: Chem.* **2010**, *53*, 1937-1945.

58. Horner, L.; Hoffman, H.; Wippel, H. G.; Klahre, G., Phosphorus organic compounds. XX. Phosphine oxides as reagents for olefin formation. *Chem. Ber.* **1959**, *92*, 2499-505.

59. Wittig, G.; Geissler, G., Course of reactions of pentaphenylphosphorus and certain derivatives. *Justus Liebigs Ann. Chem.* **1953**, *580*, 44-57.

60. Groebel, B. T.; Seebach, D., Umpolung of the reactivity of carbonyl compounds through sulfur-containing reagents. *Synthesis* **1977**,, 357-402.

61. Earnshaw, C.; Wallis, C. J.; Warren, S., Synthesis of E- and Z-vinyl ethers by the Horner-Wittig reaction. *J. Chem. Soc., Perkin Trans. 1* **1979**,, 3099-106.

62. Ireland, R. E.; Mueller, R. H.; Willard, A. K., Ester enolate Claisen rearrangement. Construction of the prostanoid skeleton. *J. Org. Chem.* **1976**, *41*, 986-96.

63. Schlosser, M.; Huynh, B. T., The Horner variant of the Wittig reaction: practical under mild conditions and endowed with stereochemical options. *Chimia* **1976**, *30*, 197-9.

64. Kiyokawa, K.; Suzuki, I.; Yasuda, M.; Baba, A., Synthesis of Cyclopropane-Containing Phosphorus Compounds by Radical Coupling of Butenylindium with Iodo Phosphorus Compounds. *Eur. J. Org. Chem.* **2011**,, 2163-2171, S2163/1-S2163/62.

65. Davidson, A. H.; Warren, S., Organic synthesis using diphenylphosphinoyl as a migrating functional group: diene synthesis. *J. Chem. Soc., Perkin Trans. 1* **1976**,, 639-44.

66. Earnshaw, C.; Grayson, J. I.; Warren, S., Migration of the diphenylphosphinoyl group in competition with the phenylthio-, methylthio-, or methoxy-groups from the same migration origin. *J. Chem. Soc., Perkin Trans. 1* **1979**,, 1506-14.

67. Ditrich, K.; Hoffmann, R. W., Simple conversion of γ- and δ-lactones into 5-(or 6)-silyloxy-3-keto phosphonates. *Tetrahedron Lett.* **1985**, *26*, 6325-8.

68. White, J. D.; Hansen, J. D., Total Synthesis of (-)-7-Epicylindrospermopsin, a Toxic Metabolite of the Freshwater Cyanobacterium Aphanizomenon ovalisporum, and Assignment of Its Absolute Configuration. *J. Org. Chem.* **2005**, *70*, 1963-1977.

69. Lanners, S.; Khiri, N.; Solladie, G.; Hanquet, G., Ring-opening of lactones with enolate nucleophiles: a simple access to functionalised β-ketoesters, β,δ-diketoesters and β-ketosulfoxides. *Tetrahedron Lett.* **2005**, *46*, 619-622.

70. Hutton, G.; Jolliff, T.; Mitchell, H.; Warren, S., The stereoselective Horner-Wittig reaction with phosphine oxides: synthesis of hindered Z alkenes *via* Luche reduction. *Tetrahedron Lett.* **1995**, *36*, 7905-8.

71. Noal Cohen, B. L. B., Anthony J. Laurenzano, Louis Carozza, 2,3-O-ISOPROPYLIDENE-D-ERYTHRONOLACTONE [Furo[3,4-d]-1,3-dioxol-4(3aH)-one, dihydro-2,2-dimethyl-(3aR-cis)-]. *Organic Syntheses* **1985**, *7*, 127.

72. Bonini, C.; Chiummiento, L.; Lopardo, M. T.; Pullez, M.; Colobert, F.; Solladie, G., A general protocol for the regio high yielding opening of different glycidol derivatives. *Tetrahedron Lett.* **2003**, *44*, 2695-2697.

73. Fukuda, K.; Miyashita, M.; Tanino, K., Practical synthesis of (E)- and (Z)-2-silyl-3-penten-1-ols with high enantiopurity. *Tetrahedron Lett.* **2010**, *51*, 4523-4525.

74. Cirakovic, J.; Driver, T. G.; Woerpel, K. A., Metal-Catalyzed Di-tert-butylsilylene Transfer: Synthesis and Reactivity of Silacyclopropanes. *J. Org. Chem.* **2004**, *69*, 4007-4012.

75. Choi, H. G.; Son, J. B.; Park, D. S.; Ham, Y. J.; Hah, J. M.; Sim, T., An efficient and enantioselective total synthesis of naturally occurring L-783277. *Tetrahedron Lett.* **2010**, *51* (38), 4942-4946.

76. Suffert, J.; Toussaint, D., An Easy and Useful Pre*para*tion of Propynyllithium from (Z/E)-1-Bromopropene. *J. Org. Chem.* **1995**, *60*, 3550-3.

77. Fuerstner, A.; Castanet, A.-S.; Radkowski, K.; Lehmann, C. W., Total synthesis of (S)-(+)-citreofuran by ring closing alkyne metathesis. *J. Org. Chem.* **2003**, *68*, 1521-1528.

78. Shin, J.-T.; Hong, S.-C.; Shin, S.; Cho, C.-G., Highly Diastereoselective Type-I IMDA Reaction Forming Medium-Sized Macrolactones. *Org. Lett.* **2006**, *8*, 3339-3341.

79. Dakas, P.-Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N., Divergent Syntheses of Resorcylic Acid Lactones: L-783277, LL-Z1640-2, and Hypothemycin. *Chem. - Eur. J.* **2009**, *15*, 11490-11497, S11490/1-S11490/44.

80. van Eijk, G. W., Isolation and identification of orsellinic acid and penicillic acid produced byPenicillium fennelliae Stolk. *Antonie van Leeuwenhoek* **1969**, *35* (1), 497-504.

81. Kato, T.; Hozumi, T., Ketene and its derivatives. XLIX. Reaction of diketene with β-ketoesters to give ethyl orsellinate, divarate, olivetol carboxylate, and sphaeropherol carboxylate. *Chem. Pharm. Bull.* **1972**, *20*, 1574-8.

82. Hubbard, J. S.; Harris, T. M., Condensations at the 6 position of the methyl ester and the dimethylamide of 3,5-dioxohexanoic acid *via* 2,4,6-trianions. *J. Org. Chem.* **1981**, *46*, 2566-70.

83. Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F., Solid-phase synthesis of macrocyclic systems by a cyclorelease strategy: application of the Stille coupling to a synthesis of (S)-zearalenone. *Angew. Chem., Int. Ed.* **1998**, *37*, 2534-2537.

84. Sieber, P., The 2-trimethylsilylethyl residue, a selectively cleavable carboxyl protecting group. *Helv. Chim. Acta* **1977**, *60*, 2711-16.

85. Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. H., ortho-Toluate carbanion chemistry: sulfenylation and selenation. *Synthesis* **1980**,, 72-4.

86. Kraus, G. A., A facile synthesis of ochratoxin A. *J. Org. Chem.* **1981**, *46*, 201-2.

87. Blanksby, S. J.; Ellison, G. B., Bond Dissociation Energies of Organic Molecules. *Accounts of Chemical Research* **2003**, *36* (4), 255-263.

88. Clark, R.; Jahangir, Synthesis of 3-substituted and 3,4-disubstituted 3,4-dihydro-1(2H)-isoquinolones by condensation of lithiated N,N-diethyl-o-toluamide with imines. *J. Org. Chem.* **1987**, *52*, 5378-82.

89. Clark, R. D.; Miller, A. B.; Berger, J.; Repke, D. B.; Weinhardt, K. K.; Kowalczyk, B. A.; Eglen, R. M.; Bonhaus, D. W.; Lee, C. H.; et, a., 2-(Quinuclidin-3-yl)pyrido[4,3-b]indol-1-ones and isoquinolin-1-ones. Potent conformationally restricted 5-HT3 receptor antagonists. *J. Med. Chem.* **1993**, *36*, 2645-57.

90. Schultz, A. G.; Green, N. J., Asymmetric syntheses of 1,6-dialkyl-1,4-cyclohexadiene derivatives. *J. Am. Chem. Soc.* **1991**, *113*, 4931-6.

91. Creger, P. L., Metalated carboxylic acids. II. Monoalkylation of metalated toluic acids and dimethylbenzoic acids. *J. Amer. Chem. Soc.* **1970**, *92*, 1396-7.

92. Clayden, J., *Organolithiums: Selectivity for Synthesis*. Elsevier Science Ltd.: 2002; p No pp. given.

93. Braun, M.; Mahler, U.; Houben, S., Synthesis of (R)-lasiodiplodin from polyhydroxybutyric acid. *Liebigs Ann. Chem.* **1990**,, 513-17.

94. Coughlin, D. J.; Salomon, R. G., New synthetic approach to 4-alkylidenecyclohexenes. Reduction-protodesilylation of benzylsilanes. *J. Org. Chem.* **1979**, *44*, 3784-90.

95. Belletire, J. L.; Spletzer, E. G., Oxidative coupling of the toluic acid dianion system. *Synth. Commun.* **1986**, *16*, 575-84.

96. Thompson, R. C.; Kallmerten, J., An annulative, carbohydrate-based approach to pancratistatin and structurally-related phenanthridone alkaloids. Synthesis of (+)-tetrabenzyllycoricidine. *J. Org. Chem.* **1990**, *55*, 6076-8.

97. Velusamy, S.; Borpuzari, S.; Punniyamurthy, T., Cobalt(II)-catalyzed direct acetylation of alcohols with acetic acid. *Tetrahedron* **2005**, *61* (8), 2011-2015.

98. Selles, P.; Lett, R., Convergent stereospecific synthesis of LL-Z1640-2 (or C292), hypothemycin and related macrolides. Part 2. *Tetrahedron Lett.* **2002**, *43*, 4627-4631.

99. Napolitano, C.; Palwai, V. R.; Eriksson, L. A.; Murphy, P. V., Synthesis, kinase activity and molecular modeling of a resorcylic acid lactone incorporating an amide and a trans-enone in the macrocycle. *Tetrahedron* **2012**, *68* (27-28), 5533-5540.

100. Tatsuta, K.; Takano, S.; Sato, T.; Nakano, S., The first total synthesis of a macrocyclic anti-protozoan, LL-Z1640-2. *Chem. Lett.* **2001**,, 172-173.

101. Vintonyak, V. V.; Maier, M. E., Total synthesis of cruentaren A. *Angewandte Chemie - International Edition* **2007**, *46* (27), 5209-5211.

102. Furstner, A.; Bindl, M.; Jean, L., Concise total synthesis of cruentaren A. *Angewandte Chemie* **2007**, *46* (48), 9275-8.

103. Yadav, J. S.; Das, S.; Satyanarayana Reddy, J.; Thrimurtulu, N.; Prasad, A. R., The first stereo-selective total synthesis of (3R),(5R)-5-hydroxy-de-O-methyllasiodiplodin and its epimer *via* an RCM protocol. *Tetrahedron Lett.* **2010**, *51*, 4050-4052.

104. Choi, H. G.; Son, J. B.; Park, D.-S.; Ham, Y. J.; Hah, J.-M.; Sim, T., An efficient and enantioselective total synthesis of naturally occurring L-783277. *Tetrahedron Lett.* **2010**, *51*, 4942-4946.

105. Venkataraman, K.; Wagle, D. R., Cyanuric chloride: a useful reagent for converting carboxylic acids into chlorides, esters, amides and peptides. *Tetrahedron Lett.* **1979**,, 3037-40.

106. Henry, N.; Robertson, M. N.; Marquez, R., Fast and efficient synthesis of the complete LL-Z1640-2 framework. *Tetrahedron Lett.* **2007**, *48*, 6088-6091.

107. Bindl, M.; Jean, L.; Herrmann, J.; Muller, R.; Furstner, A., Pre*para*tion, modification, and evaluation of cruentaren A and analogues. *Chemistry* **2009**, *15* (45), 12310-12319.

108. Mortreux, A.; Blanchard, M., Metathesis of alkynes by a molybdenum hexacarbonyl-resorcinol catalyst. *Journal of the Chemical Society, Chemical Communications* **1974**, (19), 786-787.

109. Sashuk, V.; Ignatowska, J.; Grela, K., A fine-tuned molybdenum hexacarbonyl/phenol initiator for alkyne metathesis. *Journal of Organic Chemistry* **2004**, *69* (22), 7748-7751.

110. Deraedt, C.; d'Halluin, M.; Astruc, D., Metathesis Reactions: Recent Trends and Challenges. *Eur. J. Inorg. Chem.* **2013**, *2013*, 4881-4908.

111. Fuerstner, A.; Mathes, C.; Lehmann, C. W., Alkyne metathesis: development of a novel molybdenum-based catalyst system and its application to the total synthesis of epothilone A and C. *Chem. - Eur. J.* **2001**, *7*, 5299-5317.

112. Fuerstner, A.; Guth, O.; Rumbo, A.; Seidel, G., Ring Closing Alkyne Metathesis. Com*para*tive Investigation of Two Different Catalyst Systems and Application to the Stereoselective Synthesis of Olfactory Lactones, Azamacrolides, and the Macrocyclic Perimeter of the Marine Alkaloid Nakadomarin A. *J. Am. Chem. Soc.* **1999**, *121*, 11108-11113.

113. Heppekausen, J.; Stade, R.; Kondoh, A.; Seidel, G.; Goddard, R.; Fuerstner, A., Optimized Synthesis, Structural Investigations, Ligand Tuning and Synthetic Evaluation of Silyloxy-Based Alkyne Metathesis Catalysts. *Chem. - Eur. J.* **2012**, *18*, 10281-10299, S10281/1-S10281/23.

114. Wengrovius, J. H.; Sancho, J.; Schrock, R. R., Metathesis of acetylenes by tungsten(VI)-alkylidyne complexes. *J. Am. Chem. Soc.* **1981**, *103*, 3932-4.

115. Fuerstner, A.; Seidel, G., Ring-closing metathesis of functionalized acetylene derivatives: a new entry into cycloalkynes. *Angew. Chem., Int. Ed.* **1998**, *37*, 1734-1736.

116. Nicolaou, K. C.; King, N. P.; He, Y., Ring-closing metathesis in the synthesis of epothilones and polyether natural products. *Top. Organomet. Chem.* **1998**, *1*, 73-104.

117. Lacombe, F.; Radkowski, K.; Seidel, G.; Fürstner, A., (E)-Cycloalkenes and (E,E)-cycloalkadienes by ring closing diyne- or enyne–yne metathesis/semi-reduction. *Tetrahedron* **2004**, *60* (34), 7315-7324.

118. McCullough, L. G.; Listemann, M. L.; Schrock, R. R.; Churchill, M. R.; Ziller, J. W., Multiple metal-carbon bonds. 34. Why terminal alkynes cannot be metathesized. Pre*para*tion and crystal structure of a deprotonated tungstacyclobutadiene complex, W(η5-C5H5)[C3(CMe3)2]Cl. *J. Am. Chem. Soc.* **1983**, *105*, 6729-30.

119. Haberlag, B.; Freytag, M.; Daniliuc, C. G.; Jones, P. G.; Tamm, M., Efficient Metathesis of Terminal Alkynes. *Angew. Chem., Int. Ed.* **2012**, *51*, 13019-13022.

120. Coutelier, O.; Mortreux, A., Terminal alkyne metathesis: A further step towards selectivity. *Advanced Synthesis and Catalysis* **2006**, *348* (15), 2038-2042.

121. Kaneta, N.; Hikichi, K.; Asaka, S.-i.; Uemura, M.; Mori, M., Novel synthesis of disubstituted alkyne using molybdenum catalyzed cross-alkyne metathesis. *Chem. Lett.* **1995**,, 1055-6.

122. Villemin, D.; Héroux, M.; Blot, V., Silanol-molybdenum hexacarbonyl as a new efficient catalyst for metathesis of functionalised alkynes under microwave irradiation. *Tetrahedron Lett.* **2001**, *42* (22), 3701-3703.

123. Fürstner, A.; Mathes, C.; Lehmann, C. W., Mo[N(t-Bu)(Ar)]3 complexes as catalyst precursors: In situ activation and application to metathesis reactions of alkynes and diynes [4]. *Journal of the American Chemical Society* **1999**, *121* (40), 9453-9454.

124. Fuerstner, A.; Mathes, C.; Grela, K., Concise total syntheses of epothilone A and C based on alkyne metathesis. *Chem. Commun. (Cambridge, U. K.)* **2001**,, 1057-1059.

125. Bindl, M.; Jean, L.; Herrmann, J.; Müller, R.; Fürstner, A., Pre*para*tion, modification, and evaluation of cruentaren a and analogues. *Chemistry - A European Journal* **2009**, *15* (45), 12310-12319.

126. Furstner, A., Alkyne metathesis on the rise. *Angewandte Chemie* **2013**, *52* (10), 2794-819.

127. Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner, A., Practical New Silyloxy-Based Alkyne Metathesis Catalysts with Optimized Activity and Selectivity Profiles. *Journal of the American Chemical Society* **2010**, *132* (32), 11045-11057.

Chapter 3

APPLICATION OF OUR SYNTHETIC ROUTE TO OTHER RESORCYCLIC ACID LACTONES

3 APPLICATION OF OUR SYNTHETIC ROUTE TO OTHER RALs

3.1 Conception and strategy

The second objective of this thesis targets the application of the modular synthetic strategy which was first devised for the total synthesis of the *cis*-containing L-783,277 (**7**). Initially, the strategic disconnections feature a direct alkylation at the benzylic position, followed by a Mitsunobu-based esterification and ended with a RCAM combined to a partial reduction to reveal the *cis*-enone moiety.

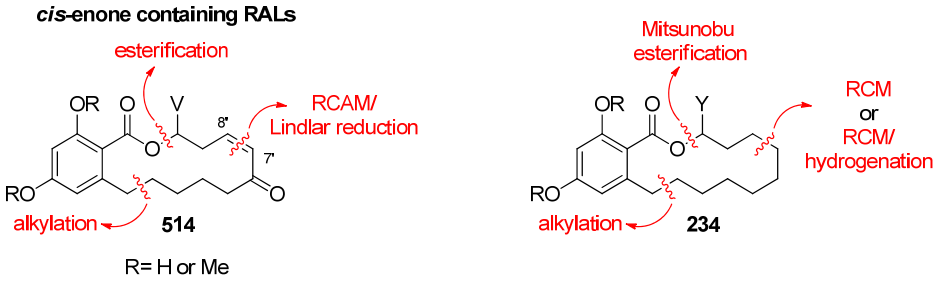
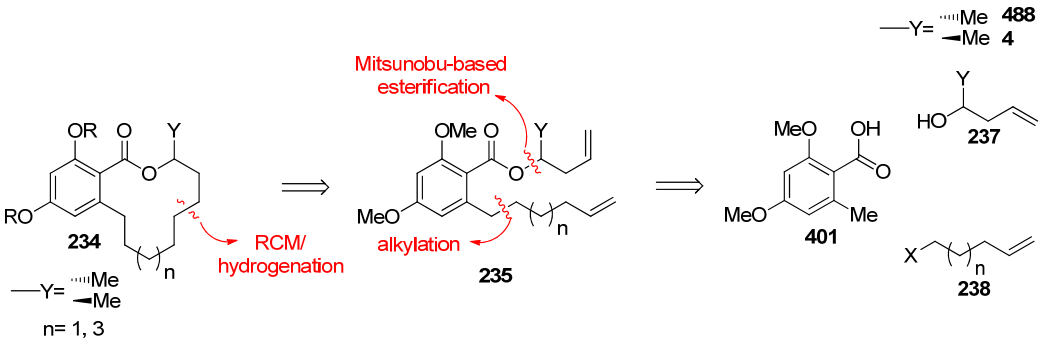


Figure 21: From the *cis*-enone containing RALs to other RALs

In spite of an on-going study of the RCAM to complete the carbon framework of L-783,277 (**7**), the concise and scalable synthesis of the dijjalkyne precursor **241** has substantiated our synthetic strategies. To a greater extent, this synthetic concept could be applied to other RALs than the restrictive subset of *cis*-enone containing RALs, in particular those bearing a single C7'-C8' bond instead.

From a synthetic point of view, the ring-closing method would be based on a RCM, followed by a hydrogenation. In terms of substrates, this transformation would imply the installation of a terminal alkene at both extremities of the ring-closure precursor. Consequently, we have dedicated the second part of the project to the syntheses of natural RALs that have been reported in the literature, as well as their rjelated unnatural compounds, on the basis of our strategies which are represented in scheme 40 beneath.



Scheme 40: General synthetic scheme for RALs without *cis*-enone

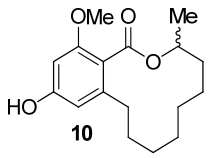
Our synthetic strategy is composed of 5 general steps: direct alkylation at the benzylic position/Mitsunobu-based esterification/ RCM/ hydrogenation/demethylation and

deconvolutes the target molecule into 3 se*para*te fragments. While the aromatic core remains the same orsellinic acid dimethyl ether **401**, the other fragments **237** and **238** would vary in function of the functional groups decorating the macrocyclic backbone. However, it was already clear to us that the allylic alcohol C could be quite convenient for the installation of the appropriate configuration of the asymmetric carbon C10'.

In the first instance, it was advisable to apply the strategy to a relatively simple target, with respect to the presence of a C7'-C8' saturated bond. And consistently, the 12-membered ring resorcylide *(R)*-(+)-lasiodiplodin (**10**) seemed to be the most relevant macrolactone as the first candidate.

3.2 Synthesis of 12-membered RALs

3.2.1 Synthesis of *(R)*-(+)-lasiodiplodin (10): naturally occurring RAL



10

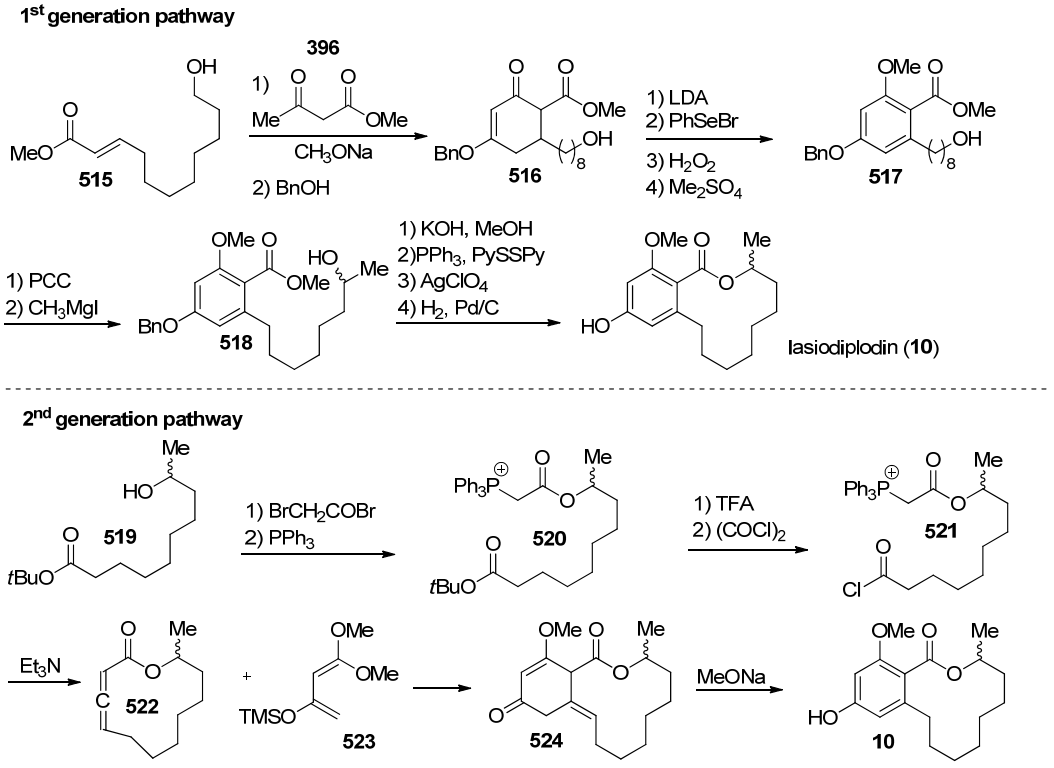
Figure 22: *(R)*-(+)-lasiodiplodin (**10**)

(R)-(+)-lasiodiplodin (**10**) was first isolated from *Lasiodiplodia theobromae*, a plant pathogen which causes rotting and dieback in most species it infects.[1] Numerous synthetic investigations of this metabolite were carried out, due to its purported ability to operate as a plant growth inhibitor,[2] an inhibitory activity which was later discovered to be linked to another metabolite from the culture filtrates of the same fungus: jasmonic acid.[3] Some years later, *in vivo* P-388 assay-directed fractionation of an active extract from *Euphorbia splendens* has also led to the isolation of lasiodiplodin (**10**).[4] Since then, lasiodiplodin (**10**) and its family were identified to be very efficient inhibitors of prostaglandin biosynthesis, exhibit anti-leukemic activities and reported to be potato micro-tuber inducing substances.[5] Lately, the Chinese group of Yang reported for the first time the antimicrobial activities of lasiodiplodin (**10**), this time isolated from the mycelium extracts of a brown alga endophytic fungus (No. ZZF36) obtained from the South China Sea.[6]

3.2.1.1 State of the art

The first racemic synthesis of lasiodiplodin was reported by Gerlach *et al.* in 1977,[2] followed at one-year interval by two other racemic syntheses from the groups of Takahashi[7] and Danishefsky.[8] In the nineties, several enantioselective routes have been reported, requiring either a chiral pool precursor,[9] or the stoichiometric use of an asymmetric controller group and subsequent purification of a diastereomeric mixture.[10] The first catalytic asymmetric synthesis was reported by Jones and Huber, [11] which outlined the enantioselective addition of Me_2Zn to an aldehyde, mediated by a tricarbonyl(η6 arene)chromium(0) catalyst. The 21st century witnessed the expansion of the catalytic toolbox for the pre*para*tion of lasiodiplodin and its congeners, featuring the first ring-closing metathesis approach by the group of Fürstner.[12] This strategy turned out to be superior in all relevant pre*para*tive aspects (in comparison to

McMurry coupling) and became one of the crucial steps in other synthetic routes, namely in the first stereo selective total synthesis of (3R),(5R)-5-hydroxy-de-*O*-methyllasiodiplodin and its epimer by Yadav *et al.,*[13]the enantioselective formal synthesis of lasiodiplodin (**10**) by the group of Feringa,[14] depicting a highly stereoselective Cu-catalysed allylic alkylation, or the chemeoenzymatic asymmetric total synthesis of *(R)*-(+)-lasiodiplodin methyl ether (**529**) by Fuchs *et al.*[15]

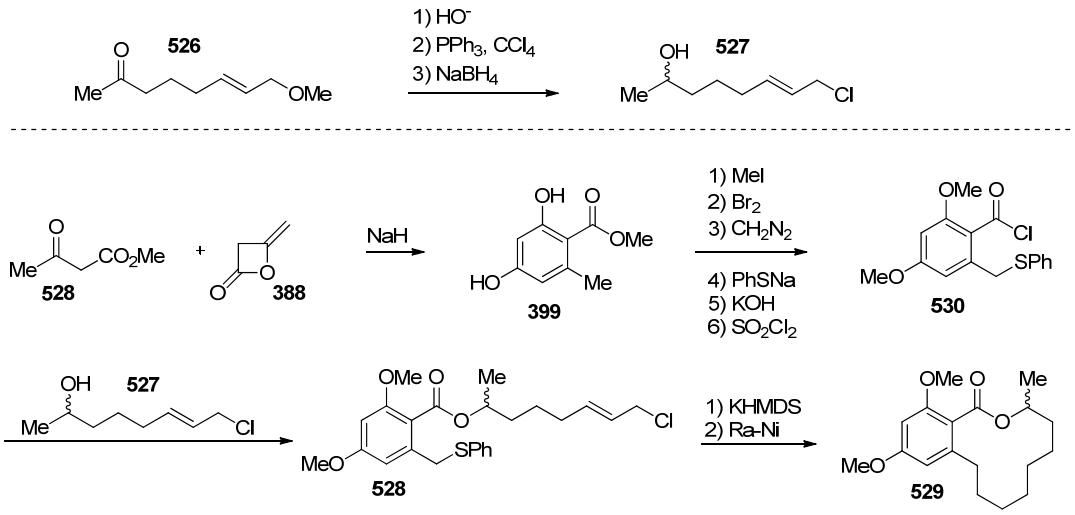


Scheme 128: Syntheses of (±)-lasiodiplodin (**10**) by Gerlach *et al*

In the first synthesis of (±)-lasiodiplodin (**10**), the group of Gerlach's strategy started with a Claisen condensation, followed by treatment with benzyl alcohol to obtain the 1,3-dioxygenated benzoic acid derivative **516** as the basic framework (**scheme 128**).[2] The aromatisation was initiated by a selenylation/oxidation/elimination sequence and subsequent protection as the methyl ether yielded the related orsellinic ester. The primary alcohol was subjected to a partial oxidation prior to the Grignard reaction with MeMgI, followed by the releasing of the benzoic acid under basic condition to provide the seco-acid **518** required for the macrocyclisation. The lactonisation was effected in the presence of 1,2-di(pyridin-2-yl)disulfane and triphenylphosphine and completed by a $AgClO_4$ assisted cyclisation, a method which was previously described by the same group. Hydrogenolysis of the *para* benzyl ether accomplished the first total synthesis of the target macrolide (**10**) as a racemic mixture in 12 steps.

The second total synthesis of *(R)*-(+)-lasiodiplodin (**10**) published by the same group implicated an interesting order alteration of the final synthetic sequence, opting for an early formation of the macrocycle and a late-staged aromatisation (**scheme 128**).[16] Their approach began with

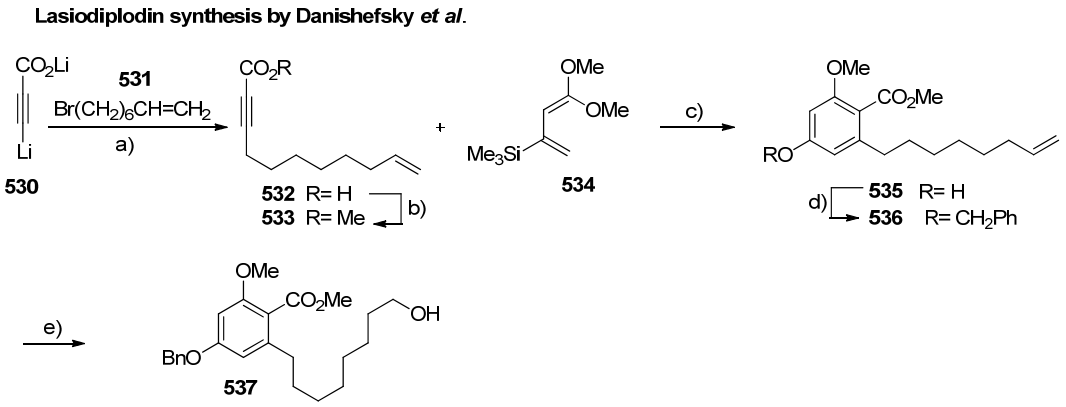
the pre*para*tion of the acyclic carbon framework **521** from *tert*-butyl 9-hydroxydecanoate. Acetylation with bromoacetyl bromide and addition of triphenylphosphine afforded the stabilised Wittig reagent **520**, followed by transformation of the *tert*-butyl ester into the related acyl chloride **521**, providing the required substrate for the novel macrocyclisation step. Upon treatment under basic condition, an intramolecular Wittig condensation took place, prior to an immediate loss of HCl to provide allenic lactone **522** in 42% of yield. The ensuing [4+2] cycloaddition of protected diene **523** with 12-membered cyclic dienophile **522** resulted in the macrolactone **524** (55% yield). The final aromatization in the presence of sodium methanolate procured 50% yield of (±)-lasiodiplodin (**10**).



Scheme 129: O-methyl lasiodiplodin by Tsuji *et al*

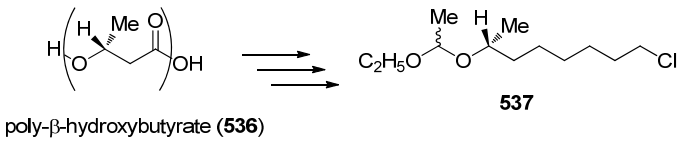
Though the natural analog O-methyl lasiodiplodin **529** has not yet been discovered in nature, its synthetic pathway towards this macrolactone is closely related to that of the natural congener **10**, which would necessitate an ultimate selective demethylation of the *para* ether.

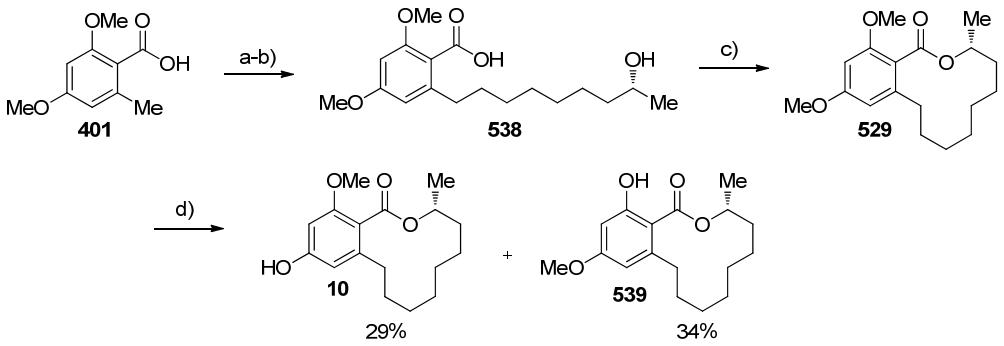
In their synthesis of O-methyl lasiodiplodin **529**, the group of Tsuji constructed the aromatic core through a condensation between the β-ketoester **528** and ketene **388**.[7] The resulting orsellinic ester **399** was then transformed into the acyl chloride **530**, bearing a phenyl sulfide at the benzylic position (**scheme 129**).The secondary alcohol **527** was linked to the acyl chloride **530** to set the stage for the intramolecular macrocyclisation, a methodology developed by the same laboratory.
The ring-closure was initiated by a KHMDS deprotonation at the benzylic position to allow the intramolecular alkylation of the ω-haloalkyl 2-phenylthiomethylbenzoate **528** in 41% of yield. The desulfurisation was effected through heating with Raney Nickel in ethanol to furnish lasiodiplodin dimethyl ether **529** in 70% of yield.



Scheme 130: Synthesis of (±)-lasiodiplodin (10) by Danishefsky *et al.* *Reagents and conditions*: a) THF/HMPA, -15 to RT, 18h; b) MeI, K_2CO_3, DMF, RT, 12h; c) xylene, 141°C, 18h; d) NaH, THF, benzyl chloride, NaI, reflux, 16h, 35% over two steps; e) i. diborane, THF, 0°C to RT, 30 min; ii. NaOH, H_2O_2, 50°C, 30 min, 80%.

One year later, Danishefsky and collaborators developed a formal synthesis of (±) lasiodiplodin (**10**),[8] targeting the tetrasubstituted aromatic system **535** which had appeared in the first synthesis of the same macrolide by Gerlach and Thalmann.[2] Their approach relied on the construction of the tetrasubstituted aromatic system using Diels-Alder cycloaddion of methyl undec-10-en-2-ynoate (**533**) with 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene (**534**). The required dienophile **(532**) was easily obtained the dianion of propiolic acid **530** by the commercial 1-bromo-7-octene (**531**),[17] employing the alkylation of, followed by methylation to give **533**. The compound **533** was heated with **534** at 140°C within 18h to provide the arene **535** which was then benzylated to merge conveniently with the Gerlach's first synthesis.[2] Despite the rapid access to the aromatic core, the overall yield of **535** over 2 steps was expectedly low, in comparison to those encountered in other models carried out between the same nucleophilic diene **533** and more electrophilic dienophiles.[18]

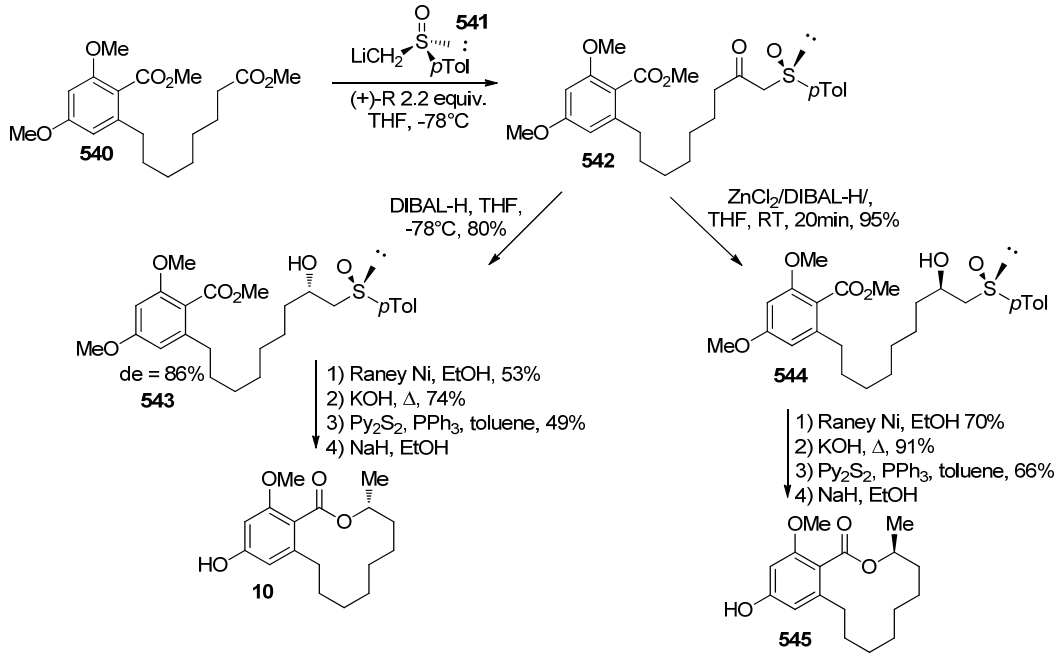




Scheme 131: Synthesis of *(R)*-(+)-lasiodiplodin by Braun *et al.* *Reagents and conditions*: a) LDA, THF, -78°C, 5min, -15°C to -10°C, 3h; b) **12**, THF, -30°C, RT, 12h, 34%; c) 1,2-di(pyridin-2-

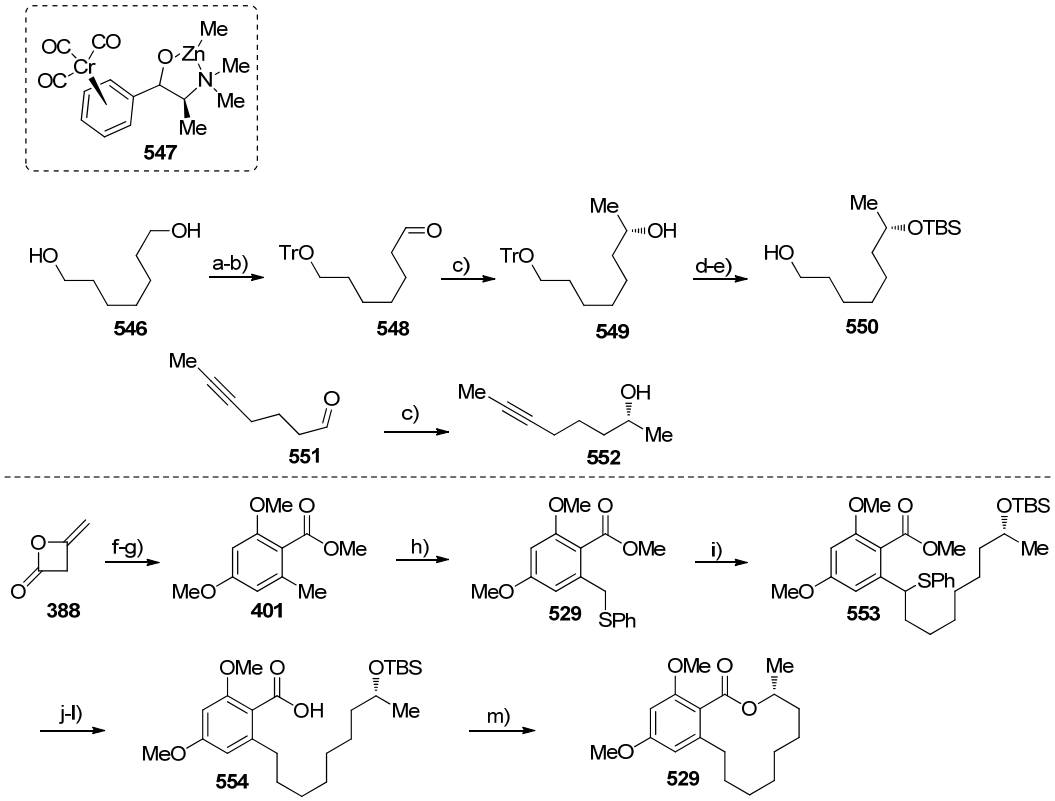
yl)disulfane, $AgClO_4$, toluene, reflux, 30 min, 49%; d) NaH, EtSH, DMF, RT, 30 min, then 130°C to 140°C, 3h, 29%.

On the other hand, conventional retrosynthesis of lasiodiplodin or its methyl ether analogs invites macrolactonisation of precursor **538**, as featured in the synthesis Braun *et al.* (**scheme 131**).[9a] The stereogenic centre was incorporated *via* the chiral pool poly-β-hydroxybutyrate (**536**), which underwent seven well-established transformations to afford the enantiomerically pure building block **537**. A direct alkylation proceeded in high yield (67%) between the lithio dianion derived from the methylated orsellinic acid **401** after deprotonation by LDA, and the chloride **537**, followed by an acidic work-up to afford the precursor **538**. This direct alkylation was earlier published by the group of Creger in 1970,[19] who opted for a wide range of bromides instead (*cf*. section *2.2.1*). The intramolecular macrolactonisation was performed according to a method previously decribed by Gerlach *et al.*,[2] involving the activation of the carboxylic acid with *(S)*-2-pyridyl thioester assisted by silver perchlorate. The synthesis was finalised by the selective demethylation at *para* position, using *in situ* sodium ethanethiolate in DMF. The somehow tricky reaction gave only 29% of isolated *(R)*-lasiodiplodin (**10**), and 34% of its isomer **539**, prompting the development of alternative syntheses with more appropriate protecting group of the aromatic starting material.



Scheme 132: Chiral sulfoxide used in the total synthesis of (±)-lasiodiplodin (10) by Solladié *et al.*

Solladié *et al.* initiated their synthesis of *(R)*-(+)-lasiodiplodin (**10**) with the pre*para*tion of the achiral diester **540** was the testing stage for the introduction of the chiral carbinol part *via* a β-ketosulfoxdide functionality (**scheme 132**), in view of obtaining both configurationq of the macrolide (**132**).[20] Reduction of the sulfoxide by two different pathways, either in the presence of DIBAL-H alone or with $ZnCl_2$ yielded (*R,R*)-β-ketosulfoxide **543** or its (*R,S*) isomer **544**. Following the Raney-Ni assisted desulfinylation, the cyclisation was carried out according to the method described by Gerlach's group for their own synthetic pathway towards (±)-lasiodiplodin (**10**) (**scheme 128**).[2]



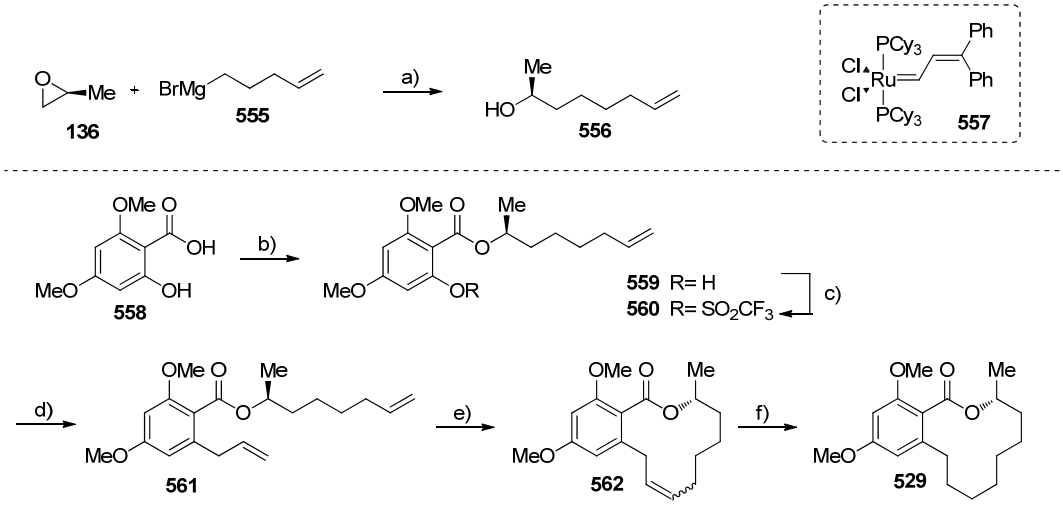
Scheme 133: Synthesis of *(R)*-(+)-lasiodiplodin dimethyl ether (**529**) by Jones *et al.*Reagents and conditions: a) TBDPSCl, imidazole, 74%; b) Dess-Martin periodinane, CH_2Cl_2, 93%; c) $(CH_3)_2Zn$, toluene, -5°C, 0.05 eq. catalyst **547**, 90% (>84% e.e.); d) TBSOTf, 2,6 lutidine (96%); e) NaH, HMPA, 60%; f) methylacetoacetate, NaH, 45%; g) CH_2CN_2, Et_2O, 89%; h) LDA, THF, Ph_2S_2, 84%; i) LDA, **552**, THF/HMPA, 74%; j) RaNi, EtOH, 100%; k) TBAF, THF, 87%; l) KOH, ethylene glycol, 165°C, 91%; m) (2-pyridyl) disulfide, PPh_3, $AgClO_4$, CH_3CN, 160°C, 70%.

As previously mentioned, the first catalytic enantioselective formal synthesis of *(R)*-(+)-lasiodiplodin (**10**) was completed by Jones and Huber.[11b] The intermediate **553** resulted from the coupling between a stabilised lithiated anion derived from **529** with C_8 chiral bromide **553**, a fragment which was prepared *via* different enantioselective routes (**scheme 133**). In both presented pre*para*tive ways, the strategic enantioselective methylation using dimethyl zinc in the presence of catalyst **547** proceeded in high yields, though the enantiomeric excess attainable for the unmasked alkynyl substrate(< 80% e.e) was far below that for substrate **548** (> 89% e.e). Hence the carbinol **529** was easily prepared on large scale in 6 steps from the diol **546**.

The arene **401** was synthetised from diketene **388** according to a well-known procedure, followed by connection of the phenylsulfide group prior to the formation of the stabilised anion essential for attachment of **552** at benzylic position. Desulfenilation and saponification released the precursor **554**, which then smoothly underwent a lactonisation under usual conditions to give *(R)*-(+)-lasiodiplodin methyl ether **529**. The *para*-demethylation successfully proceeded by use of ethylthiolate, as described in the strategy from Braun and Houben.[9a] Since the enantiomeric form of the alcohol could be easily achieve by appropriate choice of the

catalyst and the method fitting for multigram scale, this strategy proved to be favorable for related macrolides.

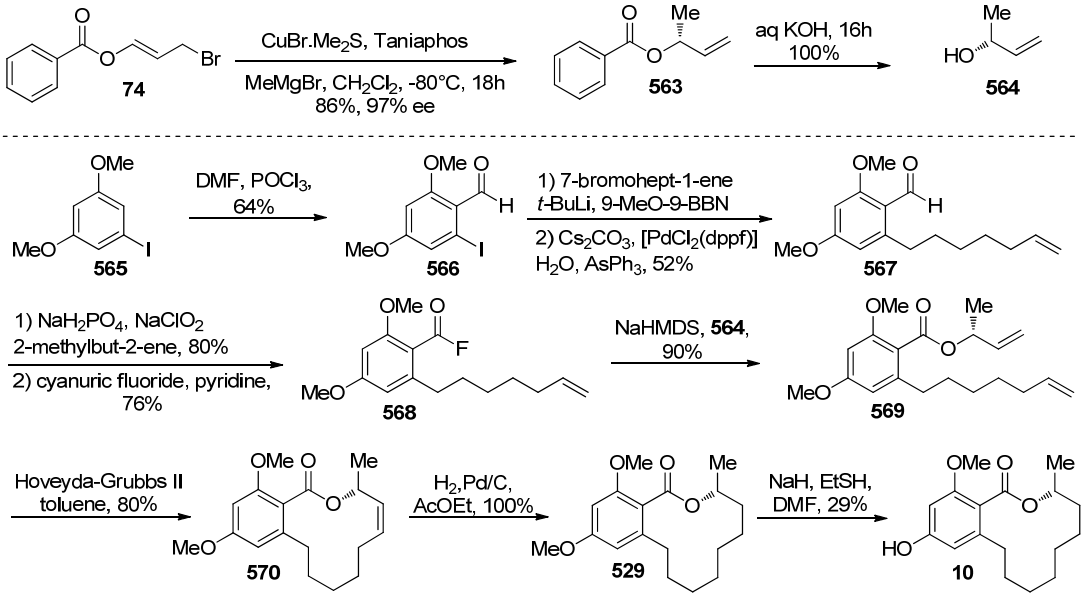
In line with the rising interest for olefin metathesis catalysts since the first defined ruthenium catalyst in 1992,[21] the group of Fürstner applied the ring closing metathesis to their synthetic scheme for lasiodiplodin (**10**) as reported in 1996.[9b] The macrocyclisation was conducted at a late stage*via* a RCM, using the ruthenium carbene **557**, introduced by Grubbs *et al.* in 1993.[22] As one of the pioneers in the field, this catalyst was noteworthily insensitive towards moisture and oxygen, while remaining highly reactive in metathetic reactions of monosubstituted olefins. At that time, macrolactonisation *via* RCM was still believed to successfully operate on conformationally restricted subtrates only, a tendency that did not convince the group of Fürstner. Therefore they reported a concise total synthesis of *(R)*-(+)-lasiodiplodin (**10**), shedding light on the efficiency of RCM to access macrocyclic systems, even if the diene precursor was devoid of conformational constraints. This metabolite's synthesis was a protruding proof for the concept, among other previously synthesised odoriferous macrolides by the same group.
In the first synthesis of lasiodiplodin (**10**) by the same group, the stereogenic center was induced by commercially available *(S)*-propylene oxide (**136**), which was subjected to a CuCl(COD)-catalysed reaction with 4-pentenylmagnesium bromide **555** to yield the building block **556**. The RCM precursor **561** was obtained by a Mitsunobu-based esterification between the methylated orsellinic acid **558** (readily prepared from cheap commercialised 3,5-dimethoxyphenol) and the enantiomerically pure alkenol **556**, followed by Stille cross coupling with allyltributylstannane using $Pd_2(dba)_3$/tris(2-furyl)phosphane as catalyst in the presence of LiCl. The RCM was performed onto **15** in the presence of the Grubbs' catalyst **557**, a process which turned out to be *via*ble and quantitative (94% yield), affording the macrolactone **562S** as a mixture of the (*E*) and (*Z*) isomers ((*E*)/(*Z*): 2.3/1). Demethylation according to the literature[9a] accomplished the total synthesis of the naturally occurring *(R)*-(+)-lasiodiplodin (**10**).



Scheme 134: Synthesis of *(R)*-(+)-lasiodiplodin dimethyl ether (**529**) by Fürstner *et al.*Reagents and conditions: a) CuCl(COD) (10 mol%), THF, -78°C to RT, 81%; b) DEAD, PPh_3, Et_20, RT, 83%; c) $(CF_3SO_2)_2$, pyridine, 0°C to RT, 91%; d) allyltributylstannane, LiCl (3 equiv.), $Pd_2(dba)_3$ (3 mol%), tris(2-furyl)phosphane (12 mol%), N-methyl-2-pyrrolidinone, 40°C, 93%; e) **557** (6 mol%), CH_2Cl_2, RT, 94%, (*E*)/(*Z*)=2.3/1 (GC); f) H_2 (1 atm), Pd/C, EtOH, RT, 94%.

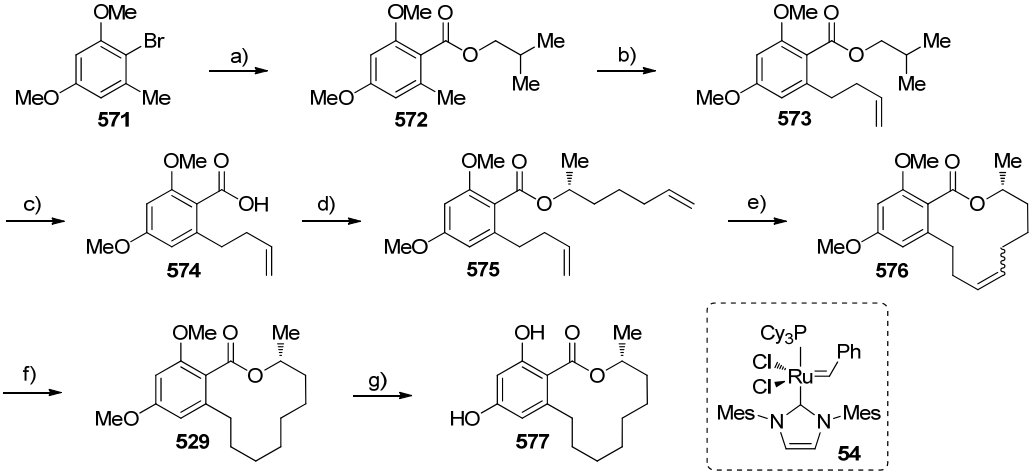
Encouraged by the outcomes, Fürstner *et al.* went on with a program on the application of RCM to the synthesis of biologically active natural products, occasionally employing the Grubbs ruthenium carbene catalyst **557** in similar total syntheses of *(S)*-zearalenone and *(R)*-(+)-lasiodiplodin (**10**) in 2000 (*cf*. section *1.1.1*).[12] In the same study, an alternative approach *via* reductive coupling of carbonyl compounds mediated by low-valent titanium [Ti] "McMurry coupling" was employed to synthesise the same natural compound. This key transformation turned out to be fairly problematic with somewhat variable yield and in contrast to RCM, the cyclised product was obtained in a mixture of both stereoisomers *E/Z*: 3.5/1. Furthermore, the McMurry coupling required dialdehyde as precursor, which led to a far less concise synthesis. The comparison ended therefore in favor of the RCM-based approach which is superior in all relevant pre*para*tive aspects, notably accessibility of substrates, total number of steps, reproducibility, stereoselectivity, and handling of the reagents.

In 2011, Minnaard *et al.* published a formal synthesis of *(R)*-(+)-lasiodiplodin methyl ether (**529**), whose enantioselective synthesis is represented in **scheme 135**. This catalytic approach employed the stereoselective Cu-catalysed allylic alkylation, a methodology developed in their laboratories in 2006,[23] as the key step to install the asymmetric centre C8' *via* optically pure alcohol **564**.[14] The synthesis started with the formylation of commercially available iodide **565** into the benzaldehyde scaffold **566**, which was subjected to an $AsPh_3$-promoted Suzuki cross-coupling with the related 7-bromohept-1-ene to afford intermediate **567**. Their attempts of esterification by Yamaguchi method or carbodiimide reagents between the corresponding acid of **567**and optically pure **564** turned out to be unsuccessful wherease the use of acyl fluoride **568**, according to the method described by Fürstner *et al.*[24] provided the ester **569** in very good yield. The obtained dialkene was submitted to a RCM using Hoveyda-Grubbs 2nd generation catalyst (**59**), furnishing an unse*para*ted *E*:*Z*/1:2 mixture of **570**. The macrolactone underwent a hydrogenation to release methylated macrolide **529** in quantitative yield and accomplished the formal synthesis of *(R)*-(+)-lasiodiplodin (**10**).



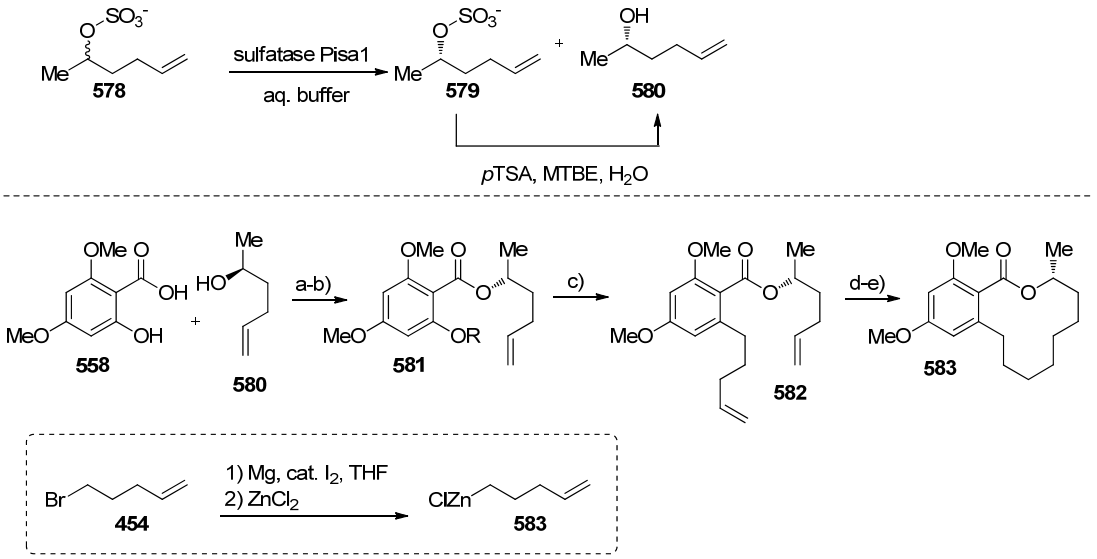
Scheme 135: Formal synthesis of *(R)*-(+)-lasiodiplodin methyl ether **529** by Minnaard *et al.*

In the same year, Jiang *et al.* achieved the synthesis of the naturally occurring *(R)*-de-O-methyllasiodiplodin (**577**),[25] which was recently reported as a potent inhibitor of pancreatic lipase (IC_{50}= 4.73 µM).[26] Their synthesis began with lithiation of the bromo derivative of orcinol **571** prior to the addition of isobutyl chloroformate to give ester **572** (**scheme 136**). Treatment of **572** with LDA followed by addition of 3-chloropropene afforded **573** which, upon saponification, released acid **574**. The readily prepared *(S)*-hept-6-en-2-ol was linked to **574** *via* a Mitsunobu esterification, setting the stage for the macrocyclisation. The RCM was effected under classical conditions in the presence of 2nd generation Grubbs catalyst **54** (3 mol%) to provide macrolactone **570** as an unse*para*ted mixture of geometrical isomers (*E*):(*Z*) = 1.5:1 in 80% yield. The hydrogenation of **570** provided O-methyllasiodiplodin **529**, an intermediate which intercepted with previously described syntheses in the literature. The final demethylation in the presence of BBr_3 accomplished the total synthesis of *(R)*-de-O-methyllasiodiplodin **577** in nine steps with 28.3% overall yield.



Scheme 136: Synthesis of *(R)*-de-O-methyllasiodiplodin (**10**) by Jiang *et al.Reagents and conditions*: a) BuLi, isobutyl chloroformate, THF, -78°C to 0°C, 3h, 89%;b) LDA, 3-chloropropene, THF, -78 to 0°C, 3 h, 90%; d) KOH, 90% EtOH, reflux, 12 h, then 10% HCl, 98%; e) DEAD, PPh_3, *(S)*-hept-6-en-2-ol, THF, RT, 1.5 h, 85%; f) **54** (3 mol %), CH_2Cl_2, reflux, 1 h, 80%; g) H_2 (1 atm), 10% Pd/C, EtOH, RT, overnight, 94%; h) BBr_3, dry CH_2Cl_2, 0°C, 15 min, 57%.

Recently, the Austrian group of Faber applied a chemoenzymatic deracemisation process based on inverting alkyl sulfatases to the formal synthesis of *(R)*-(+)-lasiodiplodin methyl ether (**529**).[15] Indeed, the recently identified sulfatase "Pisa 1" from *Pseudomonassp.* DSM 6611 was capable of inverting the *(R)*-enantiomer of **578** (> 99% ee of **579** at 50% conversion), leaving **579** untouched (**scheme 137**). The enzymatically formed **580** was subsequently obtained by extractive se*para*tion, prior to acidic hydrolysis of **579**. With the enantiomerically pure alcohol **580** in hands, a Mitsunobu-based esterification was employed followed by Negishi coupling to provide the precursor **512** aimed for Hoveyda-Grubbs II-catalysed RCM. The crude *E/Z* isomers (65:35) mixture was directly engaged into a palladium catalysed hydrogenation to afford lasiodiplodin methyl ether **529** in 93% *e.e.* in 94% isolated yield in two steps. The title compound was obtained in seven linear steps in 44% overall yield, a performance which, according to the authors, could be easily improved by one-pot fashion without intermediate product isolation.

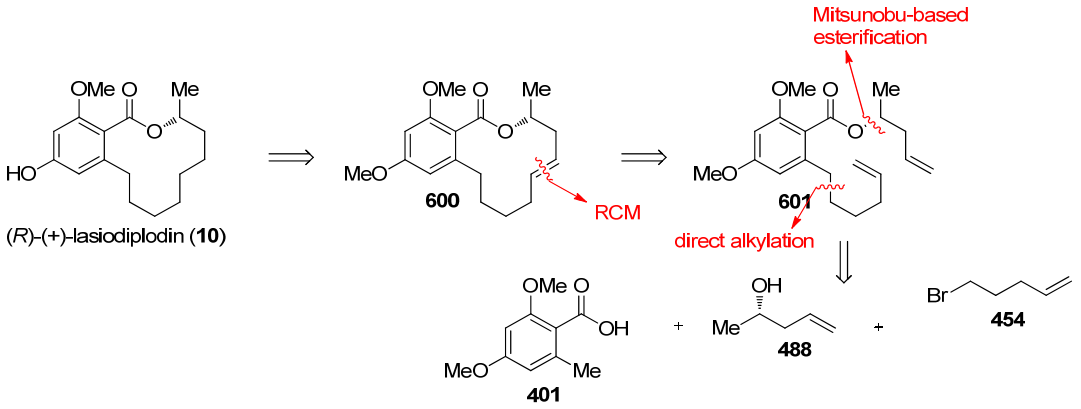


Scheme 137: Formal synthesis of *(R)*-(+)-lasiodiplodin methyl ether (**529**) by Fuchs *et al.Reagents and conditions*: a) PPh_3, DIAD, THF, RT, 16h, 64% starting from **578**; b) Tf_2O, 2,6-lutidine, CH_2Cl_2, 30 min, 95%; c) $PdCl_2$dppf, **583**, THF, 45°C, 30 min, 98%; d) Hoveyda-Grubbs II (**59**), toluene; e) Pd/C, H_2 (1 atm), 94% over 2 steps.

3.2.1.2 Our synthesis of *(R)*-(+)-lasiodiplodin (10)

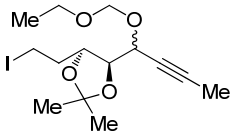
Despite the structural simplicity of *(R)*-(+)-lasiodiplodin (**10**) in comparison to other members of the same RAL family, **10** displays an interesting profile of biological activities.[3,4a,5a, 6] In order to validate our synthetic strategies mentioned in section *3.1*, this resorcylide was the first chosen candidate.

Retrosynthetically, the target molecule results from the assembling of three se*para*te fragments which would be connected *via* a Mitsunobu-based esterification, a direct benzylic alkylation and a RCM (**scheme 139**). The stereochemistry of the carbon C3' would be induced by the readily existing and commercially procurable homoallylic alcohol **488**, taking into account the inversion of configuration induced by a Mitsunobu reaction. Devoid of other functionalities, the benzylic alkylation involved simply an alkenyl halide.



Scheme 139: Retrosynthesis of *(R)*-(+)-lasiodiplodin (**10**)

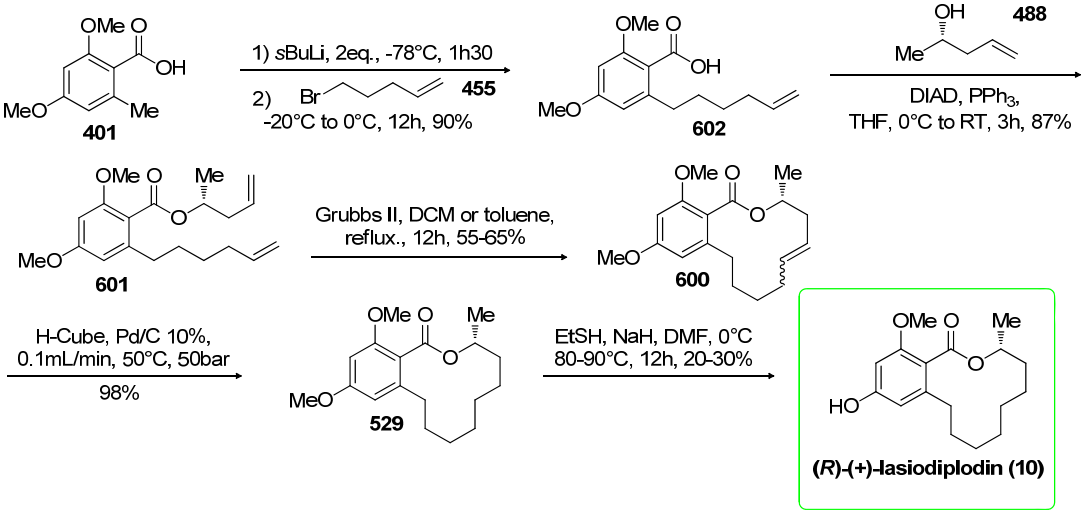
The first synthetic step involved the alkylation at the benzylic position of the readily prepared methylated orsellinic acid **401**. This key step has been successfully carried out in the presence of the alcohol fragment **253** (*cf.* section *2.2.1*). Retrosynthetically, 5-iodopent-1-ene would likely be a good alkylating reagent. However, in order to extend the scope of our benzylic alkylation to bromoalkanes, the commercially available 5-bromopent-1-ene (**454**) has been chosen as a building block for the synthesis of *(R)*-(+)-lasiodiplodin (**10**).



253

Figure 23: Iodide fragment **253** previously involved in our benzylic alkylation methodology

The synthesis of *(R)*-(+)-lasiodiplodin (**10**), as depicted in **scheme 140**, commenced with the deprotonation of orsellinic derivative **401** by a solution of *s*BuLi, followed by the addition of 5-bromopent-1-ene (**454**). Alternatively, *sec*-butyllithium could be replaced by a solution of butyllithium, with the condition that the reaction temperature should be raised from -78°C to -20°C over 2 hours. To our delight, the expected intermediate **602** was obtained in very good yield (up to 90%). In the contrary, the alkylation involving the more complex iodide fragment **253** and the dianion derived from deprotonation of **401** by butyllithium would give much lower yield (below 40%). Besides, when the crude product of **602** was engaged to the next step (Mitsunobu-based esterification), the yield over 2 steps still remained very satisfying (75 to 80%).

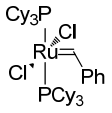


Scheme 140: Our synthesis of *(R)*-(+)-lasiodiplodin (**10**)

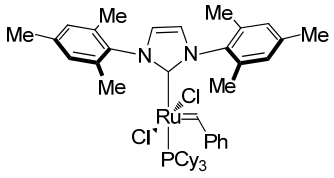
Initially, the ring closing metathesis was effected in the presence of 2nd generation Grubbs catalyst (**54**), as it has been shown that the strongly electron-donating and sterically encumbered SIMES ligand imparts stability to the active species in solution, in comparison to the PCy_3 ligand in the 1st generation Grubbs catalyst (**53**).[22] The yields span from 40% to 65%, depending on the solvent. The average yield of the first attempts, employing refluxing dichloromethane overnight, stayed below 50% with a significant amount of unconsumed diene **603**, yet higher amount of catalyst (10 mol %) tended to favor the formation of homo-coupling product. By replacing dichloromethane with toluene, the yield could be increased to 70%. But

the catalyst had to be added in several small portions to avoid its degradation at high temperature (100°C to 110°C). The macrocyclisation afforded *E* isomer of **604** as the major product, as previously denoted in the literature.[12]

Alternatively, the 1st generation Grubbs catalyst could also be used to carry out the RCM (60-70%).



1st generation Grubbs catalyst (**53**)



2nd generation Grubbs catalyst (**54**)

Figure 24: 1st generation and 2nd generation Grubbs catalysts

Hydrogenation of the macrolactone **604** was accomplished in quantitative yield *via* the H-Cube®, where the reactions took place on CatCard Pd/C 10% at a flow rate of 0.1 mL/s, under high pressure (50 bar) and high temperature (50°C). The solution of **604** in ethyl acetate was diluted at a concentration between 0.2 and 0.3 mol/L. Similar conditions were previously chosen for the hydrogenation of the crude product of **309** (*cf.* section *2.1.1.2*). Hydrogenation under more classical conditions was also accomplished in the presence of Pd/C (5 to 10%) in ethyl acetate at room temperature, leading to com*para*ble yields. Even though the resulting product could be engaged in the next step without any further purification, the catalyst had to be carefully and totally filtered off through a pad of silica gel, as its remaining traces seemed to decrease remarkably the yield of the subsequent demethylation.

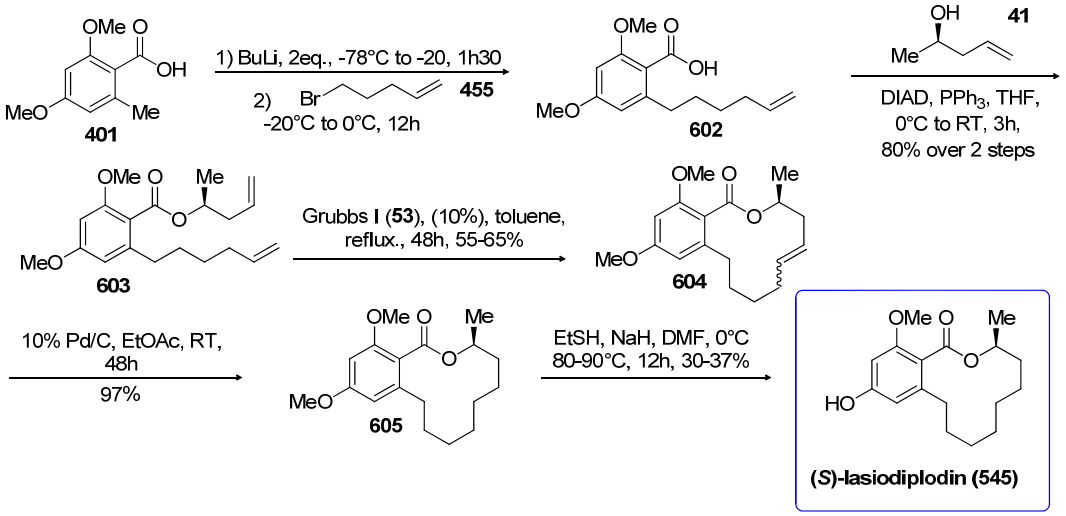
The methoxy *para* to the EWG could be selectively demethylated to deliver *(R)*-(+)-lasiodiplodin, employing *in situ* sodium ethanethiolate in DMF,[27] a relatively mild method to cleave this highly stable functionality. Nevertheless, the low yield (20 to 30%) was to be expected, as it has been observed previously by Braun *et al.* within their synthetic pathway towards the same metabolite.[9a] Indeed, when the reaction temperature was maintained between 130 and 140°C for 3h, according to the procedure by Feutrill and Mirrington,[27] the intermediate **605** was likely to decompose. Therefore, the temperature was kept below 100°C and with significantly longer reaction time (12 to 20h), which seemed to give the best result (up to 35% yield), but the resulting mixture contained the unconsumed **605** and O-de-methyllasiodiplodin **577**.

In conclusion, we have accomplished the total synthesis of the naturally occurring *(R)*-(+)-lasiodiplodin (**10**) in 5 steps as a white solid, with an overall yield of 40%. In all evidence, the direct benzylic alkylation is the pivotal procedure which has considerably shortened the synthetic route. Moreover, the ring-closure by RCM, combined with hydrogenation at C5'-C6' was highly efficient and versatile. Consequently, we have also embarked on the synthesis targeting *(S)*-(-)-lasiodiplodin (**545**), following the same synthetic path.

3.2.2 Synthesis of *(S)*-lasiodiplodin (545): synthetic 12-membered RAL

The macrocycle *(S)*-(-)-lasiodiplodin (**545**) has not been isolated or identified from any culture of fungus so far, even though from a synthetic point of view, The macrocycle *(S)*-(-)-lasiodiplodin (**545**) has not been isolated or identified from any culture of fungus so far, even though from a synthetic point of view, **545** differs from its naturally occurring enantiomer **10**

by a single carbon C8'. **Scheme 141** below depicts the synthesis of *(S)*-(-)-lasiodiplodin (**545**), which is identical to that of its natural enantiomer **10**.



Scheme 141: Our synthesis of *(S)*-lasiodiplodin (**545**)

As previously described, the pathway is composed of five steps, starting from the orsellinic derivative **401**. While the final demethylation remained identical to those for *(R)*-(+)-lasiodiplodin (**10**), some alternative synthetic conditions have been applied for the intermediate steps. The Mitsunobu-based esterification carried out between the crude product of **602** and *(R)*-pent-4-en-2-ol (**41**) provided the dialkene **603** (80% over 2 steps) required for the pivotal ring-closure step. The RCM was performed in the presence of 10% 1st generation Grubbs catalyst **53** in refluxing toluene. The yield fluctuated from 55% to 65%, depending on the addition of the catalyst. Indeed, when added in two times (5% + 5%) at 4-hour intervals, the macrocycle **605** was obtained in the best isolation yield (65%). Hydrogenation of **12** was performed under classical conditions, catalysed by 10% Pd/C in anhydrous ethyl acetate at 19°C within 2 days. The resorcylide **545** was achieved in almost quantitative yield after careful filtration over a celite/silica pad (97%). The optical activity reported in the literature by Fürstner's group for **529** was +8.7 for a concentration of 1.63 in chloroform, while the optical activity measured for its enantiomer **605** is -8.0 for a concentration of 1.7 in chloroform. The final demethylation at *para* position by *in situ* sodium ethylthiolate in DMF gave similar results as formerly described for *(R)*-(+)-lasiodiplodin (**10**) (30-37%). The straightforward achievement of the "unnatural" *(S)*-(-)-lasiodiplodin (**545**) is a further argument for the efficiency of our initial strategic pattern for C1'-C2'saturated macrocylides of the RALs family.

In spite of its "unnatural" label by several total synthesists nowadays,[9b] *(S)*-(-)-lasiodiplodin (**545**) might exist as well in the nature, as the presence of a carbon with the *S* configuration has been elucidated for other members of the same family. Prior to this discovery, all the natural compounds from the same family in the literature have been reported to bear solely *R* configuration at C8' for 12-membered ring RALs and C10' for 14-membered resorcylides.

3.2.3 Synthesis of neolasiodiplodin (606): synthetic 14-membered RAL

In order to extent the scope of our synthetic pathway to 14-membered RALs, it was appropriate to opt, in the first place, for a target which does not contain a highly decorated macrocycle, as it is the case for the two previously described RALs *(R)*-(+)-lasiodiplodin (**10**) and

(S)-(-)-lasiodiplodin (**545**). As there was no 14-membered RAL isolated so far with a com*para*bly simple structure as *(S)*-lasiodiplodin (**545**), we chose to address the issue by synthesising in the first place the simple resorcylide **606**, named "neolasiodiplodin" in respect to its unnatural 12-membered homologous *(S)*-lasiodiplodin (**545**).

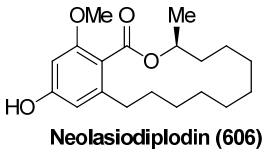
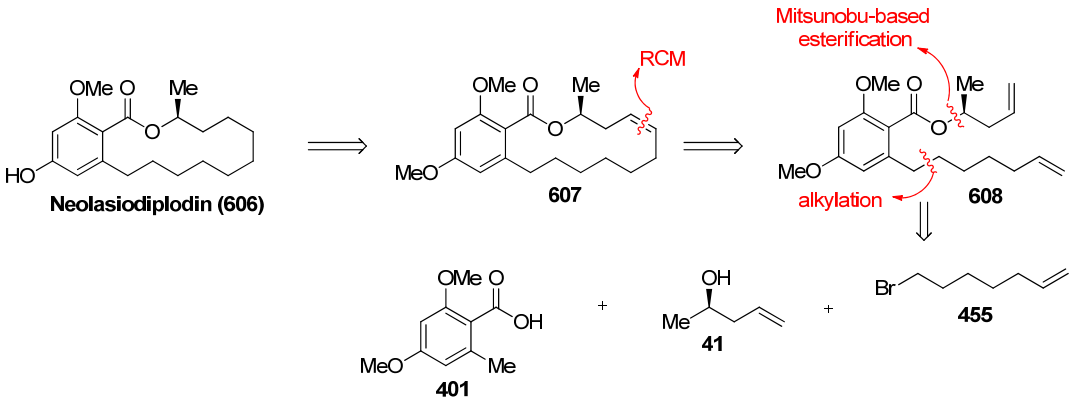


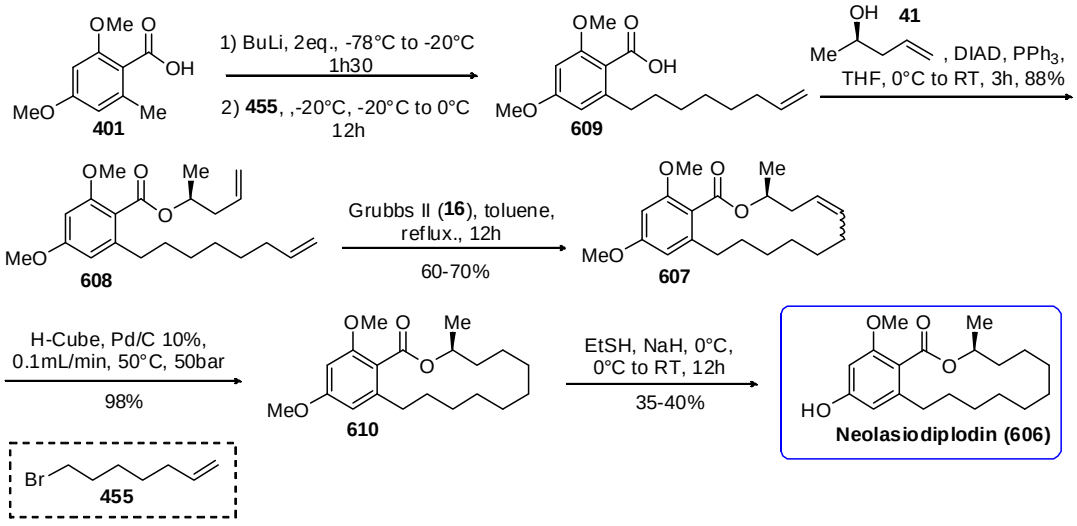
Figure 25: neolasiodiplodin (**606**)

To this end, the same modular synthesis was drawn upon, disconnecting **606** retrosynthetically into three fragments (**scheme 142**). It was convenient to realise a RCM at C7'-C8' bond, allowing to keep the same homoallylic alcohol **488** as in the synthesis of *(S)*-lasiodiplodin (**545**), as well as the aromatic core **401** readily prepared by our group. The remaining part of the macrocyclic backbone would be completed by 7-bromohept-1-ene **455**, easily accessible from commercial sources, which was required for the decisive benzylic alkylation with orsellinic acid **401**.



Scheme 142a: Retroynthesis of "neolasiodiplodin" (**606**)

Following the same strategic scheme, the reaction sequence commenced with the benzylic alkylation between the dilithiated dianion derived from **401** and 7-bromo-pent-1-ene **488** (**scheme 142a**), which resulted in a clear crude product of the expected dialkyne **608**. The crude product of **608** was directly engaged to the subsequent Mitsunobu-based esterification with the optically pure alcohol **488**, affording the precursor **608** in 88% of yield.



Scheme 142b: Synthesis of "neolasiodiplodin" (**606**)

The RCM was performed in the presence of 2nd generation Grubbs catalyst **54** in refluxing toluene over 12h to provide an unseperated *E/Z* :2/1 mixture of macrolactone **610** in acceptable yield (60-70%). Hydrogenation of **607** was carried out *via* H-Cube®, under the same conditions described for the syntheses of both enantiomers of lasiodiplodin **10** and **545**. The crude product of macrolide **610** was clear enough to be involved in the next step without further purification. Treatment of **610** with an *in situ* solution of sodium ethanethiol in DMF furnished the title compound **606** in slightly higher yield than previously observed for lasiodiplodin **10** and its unnatural enantiomer **545** (up to 40%). The demethylation completed the synthesis of the analogue "neolasiodiplodin" **606** in 5 steps with an overall yield of 25%.

The straightforward accomplishment of this novel 14-membered RAL has prompted us to extent the synthetic scope to a more structurally complex metabolite. As a consequence, the next chapter will describe the synthesis of zeranol (**611**)

3.2.4 Synthesis of zeranol (611): naturally occurring RAL

Encouraged by the successful synthesis of the macrolide "neolasiodiplodin" (**6**) as a direct application of our synthetic strategy, initially targeting L-783,277 (**7**), we ventured in the achievement of zeranol **611**, a 14-membered metabolite which is one of the most widely used chemicals in the U.S. beef industry.

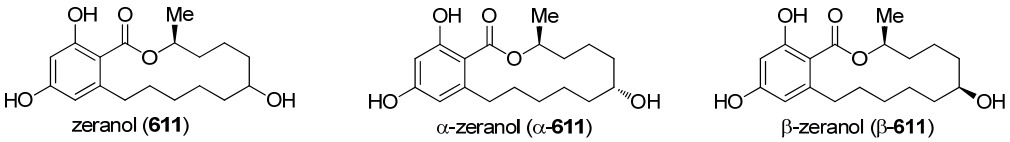


Figure 26: zeranol (**611**)

The two diastereoisomers α- and β-zeranol (α-**611** and β-**611**) were in the first place obtained as reduced products of zearalenone (**2**),[28] before the isolation from *Fusarium roseum "Gibbosum"* in rice culture in 1979,[29] closely followed by its discovery, by the same research group of Mirocha[30], in the mycelium of the fungus *Gibberella zeae* (*Fusarium graminearum*)

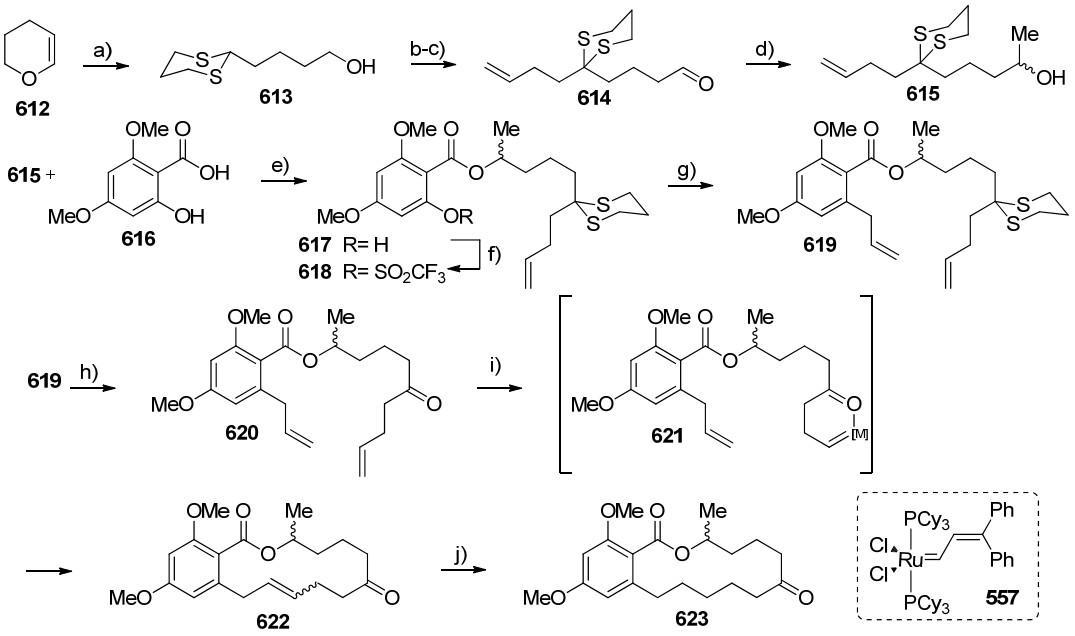
growing as a mould on corn. Researchers have proven very low residues of zeranol were present in edible tissues from animals fed with implants of this metabolite. Being approved by the FDA (based on its toxicity information) to be employed as a growth promoter, this RAL member is widely employed in the beef cattle in the United States, being one of the compounds causing the European Union to refuse the import of beef products with any growth promoter implantation from the U.S., concerned about the potentially adverse health associated with the contaminant metabolite. Given its activities as a non-steroidal estrogen agonist,beingreported to be three to four times more active than its close relativezearalenone (**2**),[31] it is also under clinical trials as a potential treatment against menopausal and post-menopausal syndrome. Yet the main use of zeranol as growth promoter still raises skepticism about its biological consequences in humans and has been subjected to controversial debates for decades. Epidemiological studies have suggested that there are many risk factors associated with breast cancer. Therefore, greater concrete evidence experimental led to results implying the potential adverse health effect of zeranol in breast cancer development, while further study is still under progress.[32]
In 2013, Hongkong researchers demonstrated that zeranol upregulated CRH mRNA expression through increased CRE binding in the JEG-3 placental cells.[33] Although the physiological significance is not yet determined, this report may help defining the exposure limit to human or the limitation of agricultural application.

More than 40 years have witnessed the rushing research in biological and chemical fields regarding this controversial, yet widely used metabolite (under various trade names: Ralgro®, Ralabol®, etc.). However, besides the achieved efforts to selectively reduce zearalenone (**2**) [34] and consequently se*para*te the diastereomeric mixture of zeranol (**611**),[35] its relatively simple structure (compared to *e.g.* more functionalised hypothemycin (**6**) or aigialomycin D (**9**)), its total synthesis has not raised considerable interest from the organic chemist community. Hereafter are two detailed total syntheses disclosed by the group of Fürstner in 1999,[36] and Yadav *et al.* in 2011.[37]

3.2.4.1 State of the art

- **Synthesis by Fürstner *et al.***

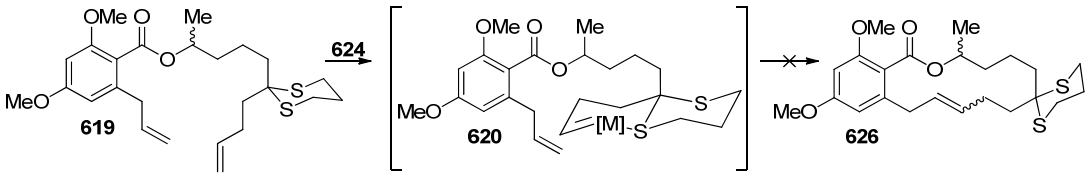
As part of the remarkable studies on RCM by the group of Fürstner since the early nineteen nineties, leading to the synthesis of naturally occurring macrolactones family,[9b] a chemical approach based on RCM as the key step was materialised in 1999, accomplishing on one hand the total synthesis of zeranol and on the other hand, a closer understanding of the essential *para*meters for successful macrocyclisation.[36]



Scheme 143: Formal synthesis of zeranol (**611**) by Fürstner *et al.Reagents and conditions:*a) $HS(CH_2)_3SH$, $BF_3.Et_2O$, MeOH, 87%; b) i. *sec*-BuLi (2 equiv.), THF,-15°C, 4h; ii. 4-bromo-1-butene, 16h, 85%; c) PCC, CH_2Cl_2, 51-62%; d) MeMgI, Et_2O, -30°C, 97%; e) DEAD,PPh_3, Et_2O, 84%; f) $(CF_3SO_2)_2O$, pyridine/CH_2Cl_2, 0°C to RT, 91%; g) 9-allyl-9-BBN, KOMe, $PdCl_2$(dppf) (3 mol%), THF, reflux, 86%; h) $(CF_3CO_2)_2IPh$, MeOH/H_2O (9/1), 84%; i) **557** (19 mol%), CH_2Cl_2, reflux, 73%; j) H_2 (1 atm), Pd/C, EtOH, quant.

In close analogy to the synthesis of lasiodiplodin (**10**) outlined in the same paper and previously described in section *3.2.1.1*, the double bond of the macrocycle was chosen as the strategic site of disconnection. The synthesis began with 3,4-dihydro-2H-pyrane (**612**) as starting material, which upon treatment with propane-1,3-dithiol in the presence of $BF_3.Et_2O$ provided the dithioacetal **613**. Deprotonation by *sec*-BuLi and quenching with 4-bromo-1-butene cleanly afforded the primary alcohol which was oxidised by PCC, the best conditions found by the authors at the time. The resulting aldehyde was then methylated, giving a racemic mixture of alcohol **615** which was submitted, together with the phloroglucinic acid derivative **616** to a Mitsunobu-based esterification to the salicy. A first coupling under Stille conditions was successfully carried out, as in the reported lasiodiplodin synthesis. Nevertheless the reaction proceeded somehow slowly in reasonable yields (40°C, 48h, 41% or 60°C, 24h, 60%), which demanded the recourse of a modified Suzuki cross coupling, resulting in the pre*para*tion of the precursor **619** on a multigram scale in 86% isolated yield after only 30 min reaction time.

To the great dismay of the authors, the cyclisation of diene **619** bearing dithioacetal moiety by Grubbs catalyst **557** failed to provide the expected **626**. The recovery of unchanged substrate was accounted by the likely chelation of emerging ruthenium carbene by the neighboring sulphur atoms, which sequesters the catalyst in an unproductive structure (**scheme 144**). Indeed, it had been reported that substrates containing sulphur (II) donor sites were generally incompatible with ruthenium based metathesis catalysts.[38]

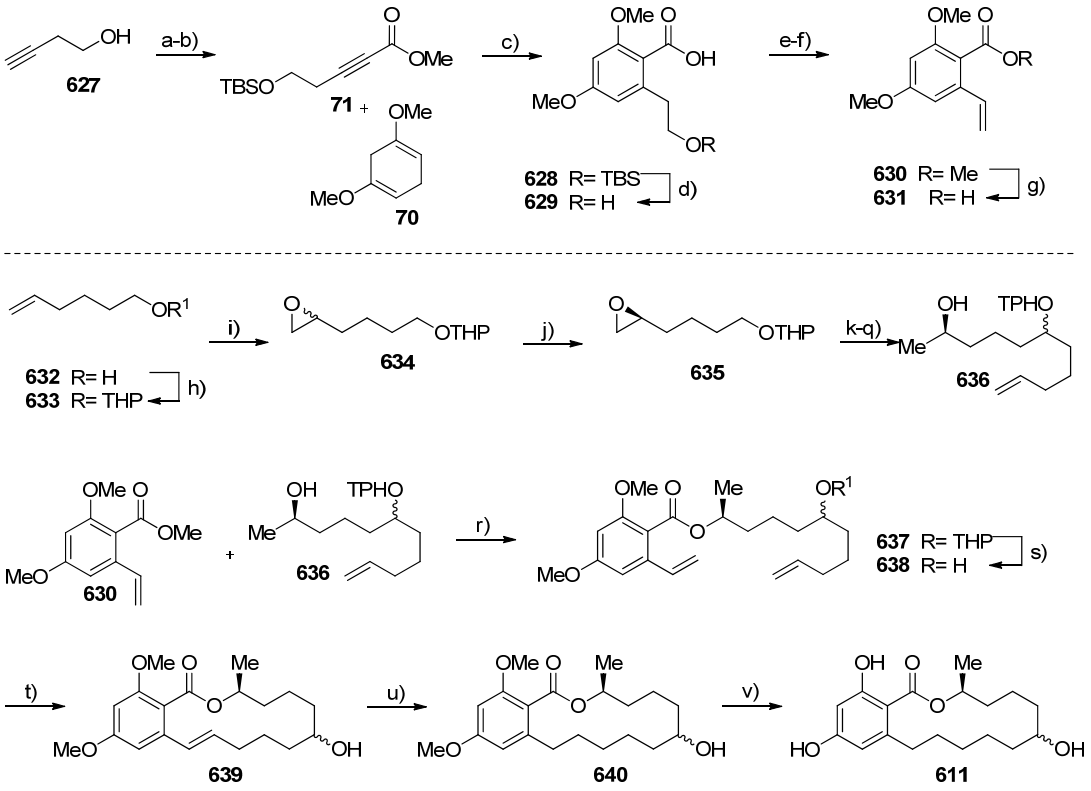


Scheme 144: Proposed chelate structure causing the uncessful RCM. [M]= Ru (II) template

To circumvent this problem, the use of (trifluoroacetoxy)iodobenzene released the corresponding ketone **620**, enabling the cyclisation of the diene in reasonable yield (73%) to provide **622**. Hydrogenation over Pd/C followed by well-described reduction in the literature completed the racemic total synthesis of zeranol (**611**). The seemingly tri*vial* isomerisation of macrolactone **622** in view of obtaining the thermodynamically more stable alkene isomer required tricky conditions which deterred the authors' efforts to perform a formal total synthesis of zearalenone (**2**) itself. The successful total synthesis of zeranol (**611**) contributed to the promising avenues to large ring systems, especially those properly adjusted.

- **Synthesis by Murthy *et al.***

Recently, Yadav and Murthy have disclosed a total synthesis of zeranol, which involved an intermolecular Diels-Alder reaction to build the resorcylic acid moiety **630**, containing a terminal alkene at the benzylic position, an esterification under Mitsunobu conditions to functionalise the acid, allowing the incorporation of both the stereogenic center bearing the methyl group and the second terminal alkene needed for the RCM-based macrolactonisation.[37]



Scheme 145: Synthesis of zeranol (**10**) by Yadav and Murthy *Reagents and conditions*: a) TBSCl, imidazole, DMAP, CH_2Cl_2, RT, 95%; b) BuLi, $ClCO_2Me$, THF, –78 °C, 80%; c) **70**, neat, *N*,*N*-dimethylaniline (cat.), 180 °C, 48 h, 40%; d) HF·Py, MeCN, RT, 90%; e) I_2, Ph_3P, MeCN–Et_2O

(1:2), RT, 95%; f) *t*-BuOK, THF, RT, 90%; g) LiOH, MeOH, reflux, 85%; h) DHP, PPTS, CH_2Cl_2, RT, 95%; (i) MCPBA, CH_2Cl_2, RT, 90%; j) (*S*,*S*)-Jacobsen catalyst, AcOH, H_2O, toluene, 40%; k) LAH, THF, 0 °C to RT, 90%; l) TBDPSCl, imidazole, CH_2Cl_2, 90%; m) PPTS, EtOH, 94%; n) IBX, DMSO, CH_2Cl_2, 89%; o) 4-pentenyl bromide, Mg, THF, 0 °C to RT, 80%; p) DHP, PPTS, CH_2Cl_2, 90%; q) TBAF, THF, 90%; r) DEAD, Ph_3P, Et_2O, RT, 90%; s) PPTS, EtOH, 85%; t) [$(PCy)_3Cl_2Ru$=CHPh] (**53**), toluene, reflux, 80%; u) Pd/C, H_2, EtOH, RT, 80%; v) AlI_3, TBAI, benzene, 70%.

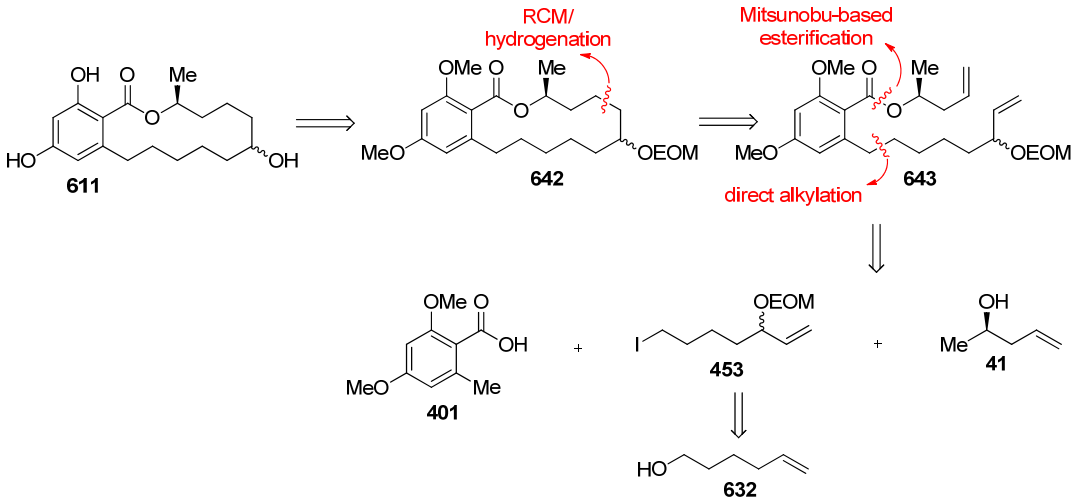
The synthesis of the aromatic core began from the commercially available homopropargylic alcohol **627**, which was first protected then treated with Buli to react with methylchloroformate to give **71**. The Diels-Alder reaction between diene **70** and acetylenic dienophile **71** at 180°C gave the aromatic product **628**. The protected primary alcohol was released, before being submitted to a clean iodination, followed by a treatment with *t*BuOK to afford **630**. Demethylation smoothly proceeded to give in high yield the expected precursor **631**.

The pre*para*tion of the chiral segment **636** started with the protection of the commercial 5-hexen-1-ol (**632**), followed by epoxidation to give a racemic mixture of **635**. A kinetic resolution with (*S,S*)-Jacobsen catalyst, followed by reductive opening in the presence of LAH and the protection of the released alcohol led to compound **635**. An orthogonal deprotection followed by IBX-based oxidation and nucleophilic addition with a Grignard reagent (previously formed by 4-pentenyl bromide and Mg) provided the diastereomeric mixture of alcohol **636**.

The two fragments **631** and **636** were successfully assembled by a Mitsunobu-based esterification. Deprotection of the alcohol preceded the RCM assisted by 1st generation Grubbs catalyst (**53**) to give the macrolactone **639**, which was submitted to a hydrogenation over Pd/C and a subsequent demethylation by AlI_3 to complete the total synthesis of zeranol (**611**). In the same paper, it was also reported that the strategy was harmoniously applicable for the synthesis of *(S)*-zeralenone (**2**), the oxidised form of zeranol (**611**). Among the methods designing resorcylic acid macrolactones, this synthetic scheme is the first method that made use of the hydrolytic kinetic resolution of Jacobsen, a fairly modern synthetic tool to acquire enantiomerically pure epoxides. Another advantage comes from the commercially available starting materials that are commonly cheap.

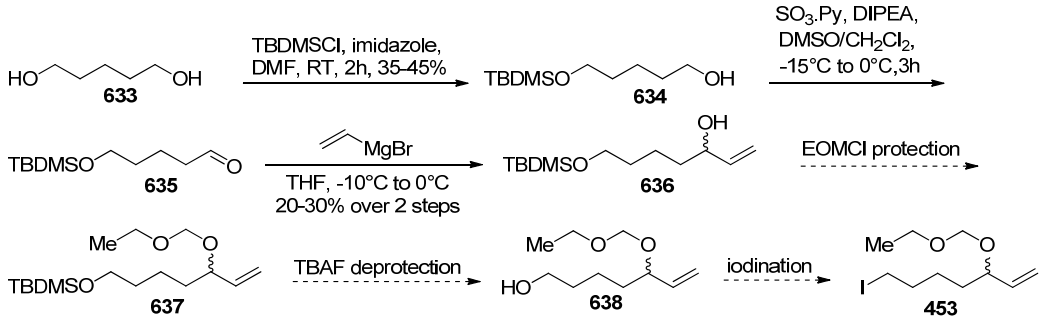
3.2.4.2 Our synthesis of zeranol (611)

Our initial synthetic target was to achieve zeranol as an unse*para*ted mixture of diastereoisomers α and β-zearalenol (**α-611** and **β-611**). Closely analogous to the synthesis of neolasiodiplodin (**606**), the retrosynthetical scheme consists in disconnecting the macrolide into 3 fragments, as depicted in **scheme 146**. One of them remained orsellinic acid derivative **401** required for the key step direct alkylation with the functionalised iodoheptene **453**. Similar to the syntheses mentioned above,[36-37] an esterification under standard Mitsunobu conditions would provide diene **643**, setting the stage for the macrocyclisation *via* a RCM, closely followed by a hydrogenation to release the fully protected macrolide.



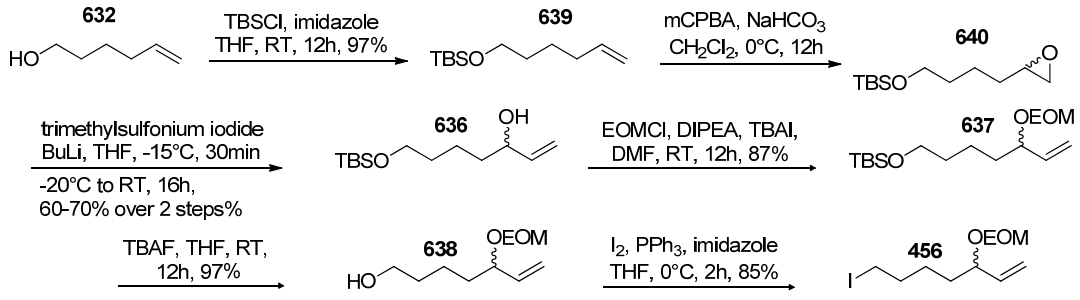
Scheme 146: Our retrosynthesis of zeranol (**611**)

Though the retrosynthesis remained analogous to that of "neolasiodiplodin" (**606**), the synthesis of zeranol **611** demanded in the first place the pre*para*tion of the iodide **453**. The first synthetic scheme opted for pentane-1,5-diol **633** as starting material, giving its easy accessibility, aiming to reach the fragment **456** in 6 steps (**scheme 147**).



Scheme 147: 1st synthesis attempt towards iodide fragment **456**

Consequently, the sequence began with a monoprotection of symmetrical diol **633** as TBDMS ether **634**, in the presence of imidazole in DMF at room temperature for 2h.[39] As expected, the resulting mixture of monoprotected/diprotected/unprotected alcohols could not provide more than 40% of **634**, after purification. However, the monoprotection could be favored by engaging 3 to 4 equivalents of the diol **633**, giving its cheap commercial availability and easy elimination through aqueous workup, providing 45% of yield. From a practical point of view, the obtained amount of ether **634** was sufficient to be engaged in the next 2 steps to construct the allylic alcohol **636**. The subsequent Parikh-Döring oxidation in the presence of SO_3·py in $DMSO/CH_2Cl_2$ smoothly afforded the aldehyde **635**. Due to the unstability of the resulting aldehyde, the crude mixture was subjected to the next addition of vinyl magnesium bromide without further purification. The Grignard reaction involving aldehyde **635** in THF gave access to allylic alcohol **636**. Unfortunately, the yield over the last two steps was very low (20-30%), prompting us to undertake the second pre*para*tive way as illustrated in **scheme 148** beneath. This alternative pathway is conceptually close to the one described by Yadav *et al.* (*cf.* section *3.3.2.1*) which starts with the protection of hex-5-en-1-ol (**632**).

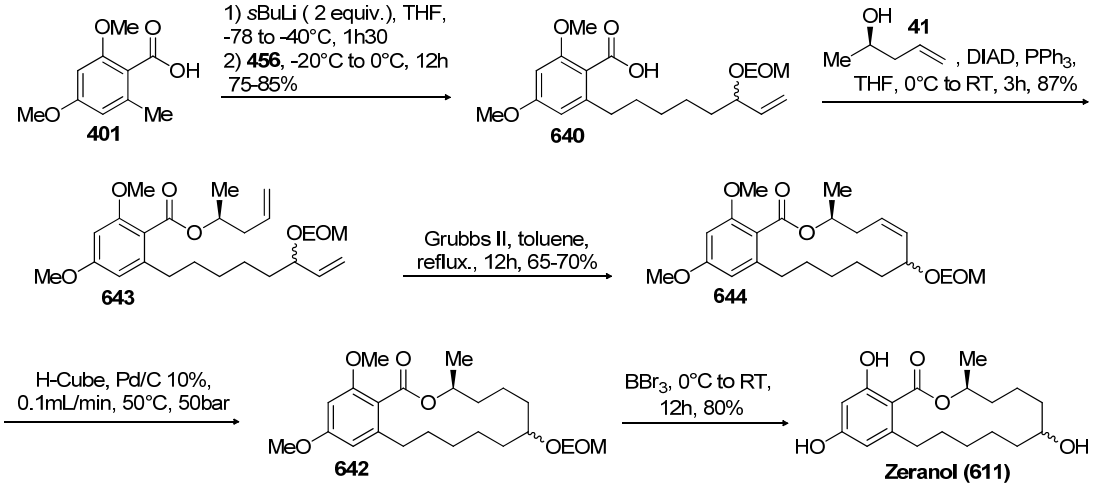


Scheme 148: Synthesis of the iodide **456**

The pre*para*tion of iodoalkane **456** began with the protection as TBS ether of hex-5-en-1-ol **632**, under standard conditions using imidazole and TBSCl, affording ether **639** in very good yield (93 to 95%) (**scheme 148**). Epoxidation of the terminal alkene in the presence of mCPBA (1.5 equiv) under buffered conditions gave a racemic mixture of **640**, which was used in the next step without further purification. The one carbon homologation to provide the allylic acohol **636** was performed by exposure of of epoxide **640** to $Me_3SI$and BuLi. The first attempts of epoxide opening closely followed the procedure described by the group of Nicolaou.[40] Accordingly, the trimethylsulfonium iodide (4 equiv.) was deprotonated by *n*BuLi (6 equiv.) at -30°C for 30 minutes before addition of the crude product of epoxide **640**. The mixture was first stirred at the same temperature for 1h before being allowed to warm up to 20°C over 3h. However the yields stayed below 50% with a conversion of less than 70%.

As a consequence, the Corey-Chaykovsky-based reaction was then carried out under the conditions described by Mioskowski *et al.*[41] Both $Me_3SI$and BuLi were engaged in lesser amount (3 equiv.) and the deprotonation temperature was maintained between -15°C and -10°C until the milky suspension became colorless, followed by addition of the solution of epoxide **640**. This procedure allowed the attainment of the desired alcohol **636** in distinctly better yields than previously described for the sequence starting with diol **633**. The secondary alcohol **636** was then uneventfully protected as EOM ether, allowing an orthogonal TBAF-promoted deprotection to release alcohol **638** (97% of yield). The iodination under Appel conditions afforded the desired iodide segment **456** in 85% of yield. This transformation completed the synthesis of iodide fragment **456** in 6 steps, with an overall yield of 49%.

Employing the same route as previously described, the iodide **456** was subjected to the direct benzylic alkylation with 2,4-dimethoxy-6-methylbenzoic acid **401** (**scheme 149**). Conformed to our expectation, this key step proceeded once again without any complication and resulted in the acquirement of the intermediate **640**, which underwent a Mitsunobu-based esterification in the presence of the optically pure allylic alcohol **488** to smoothly provide the diene **643** in 87% of yield.



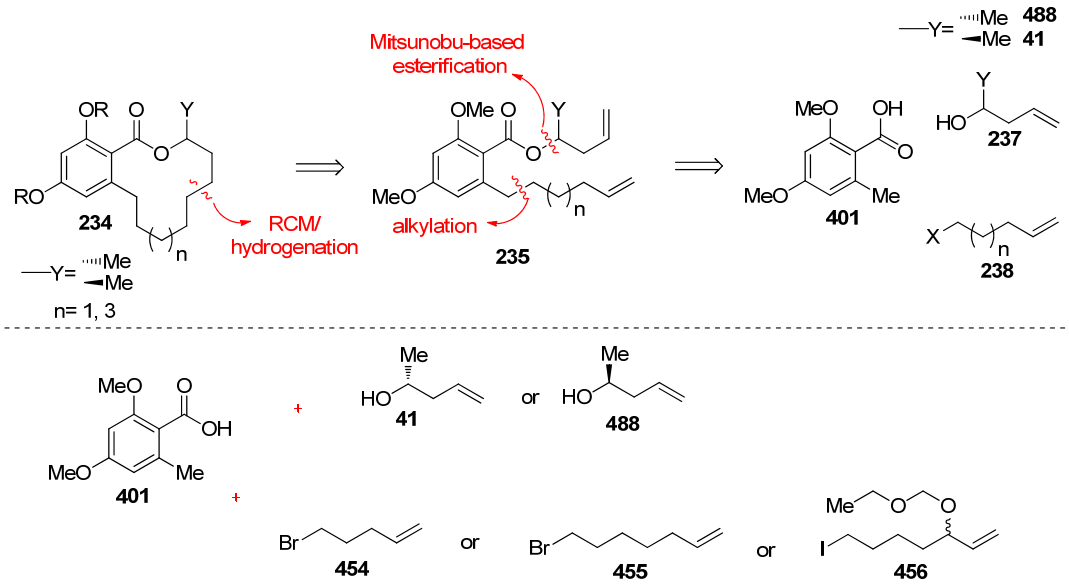
Scheme 149: Final steps of the synthesis of zeranol (**611**)

Accordingly, the sequence benzylic alkylation/esterification without intermediate purification also provided the desired compound **643** in rather high yields (75%). A highly diluted solution of diene **634** in toluene (less than 6.10^{-3} M) was then subjected to a ring-closing metathesis using the second-generation Grubbs catalyst **54** (5 mol%) to give the macrolactone **644** in 70% of yield, completing the carbon framework of zeranol (**611**). Other attempts of RCM under the same conditions, using first-generation Grubbs catalyst (**53**) instead, did not yield the same results (yield $\leq$ 50%), unless the amount of catalyst was increased to 15 mol%. The resulting macrocycle underwent a continuous-flow hydrogenation under the same conditions as previously described in section *3.3.1,* employing the H-Cube® reactor and a 10% Pd/C cartridge. Alternatively, the hydrogenation could also take place under standard conditions (10% Pd/C catalyst in AcOH at atmospheric pressure and temperature), though the reaction time was clearly longer (up to 24h). Both methods gave acceptably high yields ($\geq$ 97%). Unlike the deprotection used by the group of Yadav in their latest total synthesis of the same molecule which employed an solution of AlI_3 in benzene,[37] our demethylation was carried in the presence of boron tribromide in dichloromethane, following the procedure described by McOmie *et al.*[42] The authors observed the best results for demethylation when an extra equivalent of boron bromide was added per basic O-containing group.[42]It was therefore advisable to add at least 4 equivalents of BBr_3 to cleave both methyl ethers, together with the EOM ether of intermediate **642**. To our joy, this procedure smoothly released the fully deprotected macrolide **611** in 80% of yield, completing our synthesis of the zeralenol (**611**).

De novo, our synthetic strategy, a sequence which is composed of 5 general steps alkylation/ esterification/ RCM/ hydrogenation/ deprotection has proven its suitability for designing RALs analogues, especially those containing a saturated macrocyclic backbone. Accordingly, the applicability of the reaction sequence for natural and unnatural 12-membered RALs has been extended to 14-membered analogues.

3.3 Conclusion

As previously detailed in all the four syntheses described in this chapter, the general pattern (direct alkylation/ Mitsunobu-based esterification/ RCM/ hydrogenation) has provided a very short way to access their carbon backbones, respectively.



Scheme 150: From the conception to the molecules

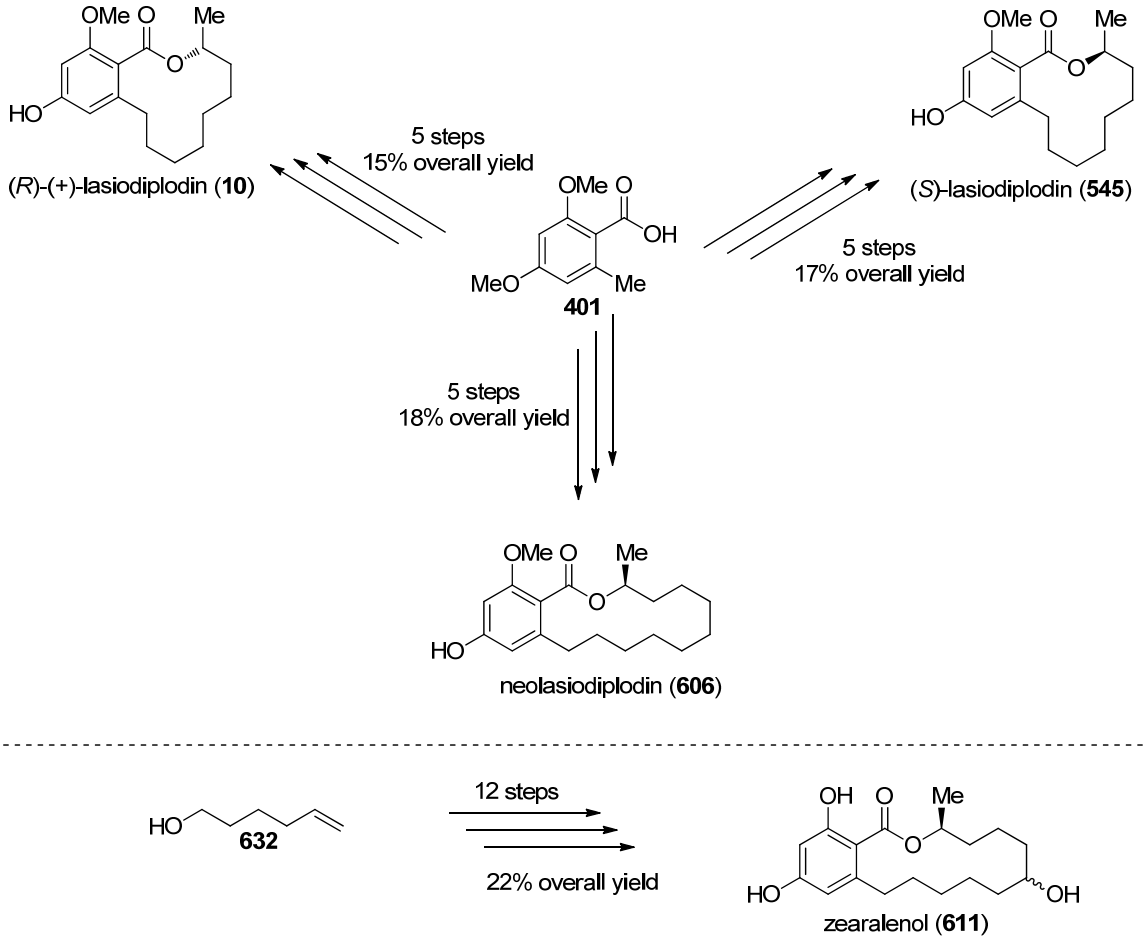
The first assembly of **401** and **237** *via* the well-studied direct benzylic alkylation has been uneventfully efficient and reproducible. The alkylation can be performed in the presence of a bromoalkanes, as well as iodoalkanes (**scheme 150**). Interestingly, the deprotonation of **401** by butyllithium did not lead to any expected product when submitted to the iodide segment **453**. While in the cases of the 4 syntheses abovementioned, the results are com*para*ble following the deprotonation of **401** by either butyllithium or *sec*-butyllithium. Despite the use of 2 equivalents of base is required to engender the lithiated dianion **401**, this key step represents a remarkable shortcut for future syntheses. Indeed, the alkylation does not require the protection of the benzylic acid, and hence an ulterior deprotection step, nor additional functionalisation at the benzylic position to stabilise the benzylic anion. The fragment **238** can be as well bromoalkanes or iodalkanes, offering a large range of operational choices. Moreover, the direct benzylic addition results in a highly clear product that it can be involved in the next step without further purification.

The Mitsunobu esterification has proven to be very mild and efficient, in comparison to the common methods mentioned in section *2.2.2.1*, especially those generating an electrophilic derivative of the corresponding benzoic acid. Indeed, this method is not hampered by the weak electrophilicity of the benzoyl carbon by transforming the alcohol fragment **237** into the corresponding electrophile instead. The configuration of C8' for 12-membered RALs and C10' for 14-membered RALs can be conveniently induced through the configuration of the homoallylic alcohol **237**. Consequently, both enantiomers of lasiodiplodin, the naturally occurring (**10**) and its unnatural enantiomer (**545**) have been achieved in 5 steps with a virtually similar overall yield which reaches *ca*. 17%.

The RCM is not only suitable for macrocycles composed of 12 to 14 members, but also reconcilable with a large spectrum of functionalities. The catalysts required for this ring-closure offer relatively easy accessibility and handling (*e.g*. Grubbs 1st generation catalyst **53**), rendering this method a convenient synthetic tool. Besides, the macrocyclic framework can be easily disconnected at different positions, offering various options for the chain size of **237** and **238**, with respect to the functional groups decorating the macrocyle.

Given that our target molecules' macrocyclic frames do not include any double bond, we have not investigated the impact of the catalysts, and other *para*meters on the ratio of *E/Z*-alkene resulted from the RCM. However, in case the RCM is applied to the synthesis of *cis*-enone containing RALs, the formation of the corresponding *trans*-isomer is inevitable.[43] In consequence, our initial synthetic approach towards L-783,277 (**7**) has recourse to the combination RCAM/ Lindlar reduction to install the *Z* configuration of the double bond.

The validation of our conception and strategy from section *3.1* is illustrated by the highly efficient and step-economic syntheses of the four RALs represented in **scheme 151**.



Scheme 151: The four syntheses based on our strategic route

Apart from zeranol (**611**) which was obtained in 11 steps with an overall yield of 22%, all the other total syntheses were completed within 5 steps with an over yield of *ca.* 15-20%. It is worth noting that the selective demethylation (30 to 40% of yield), which ends the syntheses of *(R)*-(+)-lasiodiplodin (**10**), its unnatural isomer **545** and neolasiodiplodin (**606**) have

considerably decreased the overall yield (below 30%), which would reach up to 43% without demethylation.

In order to overcome this, it is wiser to devise an aromatic core, which contains a different protecting group at *para* which is orthogonal to the *ortho* methyl ether, for example a silyl group. According to the choice of the protecting group at *para*, extensive studies concerning the electronic effects could be carried out for our key step, the direct alkylation at the benzylic position, in view of extending the scope of this reaction to macrolactones with a more decorated phenolic core.

3.4 List of references

1. Yuan, W. H.; Jiang, N.; Dong, C. H.; Wei, Z. W.; Wu, H. K.; Chen, C. F.; Zhao, Y. X.; Zhou, S. L.; Zhang, M. M.; Zheng, W. F., Lasiodiplodin analogues from the endophytic fungus Sarocladium kiliense. *Chem. Pharm. Bull.* **2013**, *61*, 363-365.
2. Gerlach, H.; Thalmann, A., Synthesis of (±)-lasiodiplodin. *Helv. Chim. Acta* **1977**, *60*, 2866-71.
3. Turner, W. B.; Aldridge, D. C.; Galt, M. S.; Giles, D., Metabolites of Lasiodiplodia theobromae. *J. Chem. Soc. C* **1971**, , 1623-7.
4. (a) Lee, K. H.; Hayashi, N.; Okano, M.; Hall, I. H.; Wu, R. Y.; McPhail, A. T., Antitumor agents. Part 51. Lasiodiplodin, a potent antileukemic macrolide from Euphorbia splendens. *Phytochemistry* **1982**, *21*, 1119-21; (b) Leet, K.-H.; Hayashi, N.; Okano, M.; Hall, I. H.; Wu, R.-Y.; McPhailti, A. T., Lasiodiplodin, a potent antileukemic macrolide from Euphorbia splendens. *Phytochemistry* **1982**, *21* (5), 1119-1121.
5. (a) Yao, X. S.; Ebizuka, Y.; Noguchi, H.; Kiuchi, F.; Shibuya, M.; Iitaka, Y.; Seto, H.; Sankawa, U., Biologically active constituents of Arnebia euchroma: structure of arnebinol, an ansa-type monoterpenylbenzenoid with inhibitory activity on prostaglandin biosynthesis. *Chem Pharm Bull (Tokyo)* **1991**, *39*, 2956-61; (b) Cambie, R. C.; Lal, A. R.; Rutledge, P. S.; Woodgate, P. D., Chemistry of Fijian plants. Part 7. ent-14[S],16β,17-Trihydroxyatisan-3-one and further constituents from Euphorbia fidjiana. *Phytochemistry* **1991**, *30*, 287-92.
6. Yang, R.-y.; Li, C.-y.; Lin, Y.-c.; Peng, G.-t.; She, Z.-g.; Zhou, S.-n., Lactones from a brown alga endophytic fungus (No. ZZF36) from the South China Sea and their antimicrobial activities. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4205-4208.
7. Takahashi, T.; Kasuga, K.; Tsuji, J., A new synthetic method for aromatic type medium and large membered lactones based on intramolecular alkylation of ω-haloalkyl 2-phenylthiomethylbenzoate, and its application to the synthesis of (±) lasiodiplodin using a butadiene telomer. *Tetrahedron Lett.* **1978**, 4917-20.
8. Danishefsky, S.; Etheredge, S. J., Simple synthetic route to lasiodiplodin. *J. Org. Chem.* **1979**, *44*, 4716-17.
9. (a) Braun, M.; Mahler, U.; Houben, S., Synthesis of (R)-lasiodiplodin from polyhydroxybutyric acid. *Liebigs Ann. Chem.* **1990**, , 513-17; (b) Fürstner, A.; Kindler, N., Macrocycle formation by ring-closing-metathesis. 2. An efficient synthesis of enantiomerically pure (R)-(+)-lasiodiplodin. *Tetrahedron Lett.* **1996**, *37* (39), 7005-7008.
10. Solladie, G.; Rubio, A.; Carreno, M. C.; Garcia Ruano, J. L., Asymmetric synthesis of orsellinic acid type macrolides: The example of lasiodiplodin. *Tetrahedron: Asymmetry* **1990**, *1*, 187-98.
11. (a) Jones, G. B.; Huber, R. S., The first catalytic enantioselective synthesis of (R)-(+)-lasiodiplodin. *Synlett* **1993**, , 367-8; (b) Jones, G. B.; Huber, R. S.; Chapman, B. J., Catalytic enantioselective synthesis of macrolides *via* asymmetric alkylation. *Tetrahedron: Asymmetry* **1997**, *8*, 1797-1809.
12. Fuerstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B., Total Syntheses of (S)-(-)-Zearalenone and Lasiodiplodin Reveal Superior Metathesis Activity of Ruthenium Carbene Complexes with Imidazol-2-ylidene Ligands. *J. Org. Chem.* **2000**, *65*, 7990-7995.

13. Yadav, J. S.; Das, S.; Satyanarayana Reddy, J.; Thrimurtulu, N.; Prasad, A. R., The first stereo-selective total synthesis of (3R),(5R)-5-hydroxy-de-O-methyllasiodiplodin and its epimer *via* an RCM protocol. *Tetrahedron Lett.* **2010**, *51*, 4050-4052.

14. Huang, Y.; Minnaard, A. J.; Feringa, B. L., Formal synthesis of (R)-(+)-lasiodiplodin. *Synthesis* **2011**, , 1055-1058.

15. Fuchs, M.; Toesch, M.; Schober, M.; Wuensch, C.; Faber, K., Chemoenzymatic asymmetric total synthesis of (R)-lasiodiplodin methyl ether through a sulfatase-based deracemization process. *Eur. J. Org. Chem.* **2013**, *2013*, 356-361.

16. Fink, M.; Gaier, H.; Gerlach, H., 2,3-Alkadienoates as dienophiles; application in the synthesis of (+)-(R)-lasiodiplodin. *Helv. Chim. Acta* **1982**, *65*, 2563-9.

17. Carlson, R. M.; Oyler, A. R.; Peterson, J. R., Synthesis of substituted 5,6-dihydro-2H-pyran-2-ones. Propiolic acid dianion as a reactive three-carbon nucleophile. *J. Org. Chem.* **1975**, *40*, 1610-16.

18. Danishefsky, S.; Singh, R. K.; Gammill, R. B., Diels-Alder reactions of 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene. *J. Org. Chem.* **1978**, *43*, 379-80.

19. Creger, P. L., Metalated carboxylic acids. II. Monoalkylation of metalated toluic acids and dimethylbenzoic acids. *J. Amer. Chem. Soc.* **1970**, *92*, 1396-7.

20. Solladie, G., Optically active sulfoxides and low-valent titanium in asymmetric synthesis of natural products. *J. Chin. Chem. Soc. (Taipei)* **1990**, *37*, 525-33.

21. Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W., Ring-opening metathesis polymerization (ROMP) of norbornene by a Group VIII carbene complex in protic media. *Journal of the American Chemical Society* **1992**, *114* (10), 3974-3975.

22. Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W., Syntheses and activities of new single-component, ruthenium-based olefin metathesis catalysts. *J. Am. Chem. Soc.* **1993**, *115*, 9858-9.

23. Geurts, K.; Fletcher, S. P.; Feringa, B. L., Copper catalyzed asymmetric synthesis of chiral allylic esters. *J. Am. Chem. Soc.* **2006**, *128*, 15572-15573.

24. Fürstner, A.; Bindl, M.; Jean, L., Concise total synthesis of cruentaren A. *Angewandte Chemie - International Edition* **2007**, *46* (48), 9275-9278.

25. Jiang, C.-S.; Zhou, R.; Gong, J.-X.; Chen, L.-L.; Kurtán, T.; Shen, X.; Guo, Y.-W., Synthesis, modification, and evaluation of (R)-de-O-methyllasiodiplodin and analogs as nonsteroidal antagonists of mineralocorticoid receptor. *Bioorganic & Medicinal Chemistry Letters* **2011**, *21* (4), 1171-1175.

26. Birari, R. B.; Bhutani, K. K., Pancreatic lipase inhibitors from natural sources: unexplored potential. *Drug Discovery Today* **2007**, *12* (19-20), 879-889.

27. Feutrill, G. I.; Mirrington, R. N., Demethylation of aryl methyl ethers with thioethoxide ion in dimethyl formamide. *Tetrahedron Lett.* **1970**, , 1327-8.

28. (a) Hodge, E. B. Mixture of diastereomeric zearalanols. DE2111618A, 1971; (b) Hodge, E. B. Reduction of zearalenone. DE2631443A1, 1977.

29. Hagler, W. M.; Mirocha, C. J.; Pathre, S. V.; Behrens, J. C., Identification of the naturally occurring isomer of zearalenol produced by Fusarium roseum 'Gibbosum' in rice culture. *Appl Environ Microbiol* **1979**, *37*, 849-53.

30. Mirocha, C. J.; Schauerhamer, B.; Christensen, C. M.; Niku-Paavola, M. L.; Nummi, M., Incidence of zearalenol (Fusarium mycotoxin) in animal feed. *Appl. Environ. Microbiol.* **1979**, *38*, 749-50.

31. Utian, W. H., *Br. Med. J.* **1973**.

32. Ye, W.; Xu, P.; Jen, R.; Feng, E.; Zhong, S.; Li, H.; Lin, S. H.; Liu, J. Y.; Lin, Y. C., Zeranol Down-Regulates p53 Expression in Primary Cultured Human Breast Cancer Epithelial Cells through Epigenetic Modification. *International journal of molecular sciences* **2011**, *12* (3), 1519-32.

33. Wang, Y.; Tan, W.; Leung, L. K., Zeranol upregulates corticotropin releasing hormone expression in the placental cell line JEG-3. *Toxicology Letters* **2013**, *219* (3), 218-222.

34. (a) Tashiro, F.; Shibata, A.; Nishimura, N.; Ueno, Y., Zearalenone reductase from rat liver. *J. Biochem.* **1983**, *93*, 1557-66; (b) Snatzke, G.; Angeli, C.; Decorte, E.; Moimas, F.; Kojic-Prodic, B.; Ruzic-Toros, Z.; Sunjic, V., Pre*para*tion *via* diastereoselective hydrogenation. Absolute conformation and configuration of exogeneous anabolic zeranol [(3S,7R)-3,4,5,6,7,8,9,10,11,12-decahydro-7,14,16-trihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1-one]. *Helv. Chim. Acta* **1986**, *69*, 734-48.

35. Sunjic, V.; Gelo, M.; Rusman, S.; DiGrazia, L.; Clauti, G., Stereoselective reduction of two zeranole precursors by bakers' yeast. *Enzyme Microb. Technol.* **1991**, *13*, 344-8.

36. Fuerstner, A.; Seidel, G.; Kindler, N., Macrocycles by ring-closing-metathesis, XI: syntheses of (R)-(+)-lasiodiplodin, zeranol and truncated salicylihalamides. *Tetrahedron* **1999**, *55*, 8215-8230.

37. Yadav, J.; Murthy, P., A Concise Total Synthesis of (S)-Zearalenone and Zeranol. *Synthesis* **2011**, *2011* (13), 2117-2124.

38. (a) Armstrong, S. K.; Christie, B. A., Synthesis of sulfur-containing heterocycles by ring closing diene metathesis. *Tetrahedron Lett.* **1996**, *37*, 9373-9376; (b) Mascarenas, J. L.; Rumbo, A.; Castedo, L., A Practical Approach to cis-2,5-Disubstituted Tetrahydrofurans and O-Bridged Medium-Sized Carbocycles from [5 + 2] Pyrone-Alkene Cycloadducts. *J. Org. Chem.* **1997**, *62*, 8620-8621; (c) Shon, Y.-S.; Lee, T. R., Catalytic ring-closing olefin metathesis of sulfur-containing species: heteroatom and other effects. *Tetrahedron Lett.* **1997**, *38*, 1283-1286.

39. Dakas, P. Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winssinger, N., Modular synthesis of radicicol A and related resorcylic acid lactones, potent kinase inhibitors. *Angewandte Chemie - International Edition* **2007**, *46* (36), 6899-6902.

40. Nicolaou, K. C.; Guduru, R.; Sun, Y. P.; Banerji, B.; Chen, D. Y., Total synthesis of the originally proposed and revised structures of palmerolide A. *Angewandte Chemie* **2007**, *46* (31), 5896-900.

41. L. Alcaraz, J. J. H., C. Mioskowski,; J.P. Martel, T. L. G., Dong-so0 Shin, J. R. Falck, Novel Conversion of Epoxides to One Carbon Homologated

Allylic Alcohols by Dimethylsulfonium Me&glide. *Tetrahedron Lett.* **1994**, *35* (30), 3.

42. McOmie, J. F. W.; Watts, M. L.; West, D. E., Demethylation of aryl methyl ethers by boron tribromide. *Tetrahedron* **1968**, *24*, 2289-92.

43. Lin, A.; Willis, A. C.; Banwell, M. G., A chemoenzymatic and enantioselective total synthesis of the resorcylic acid lactone L-783,290, the trans-isomer of L-783,277. *Tetrahedron Lett.* **2010**, *51*, 1044-1047.

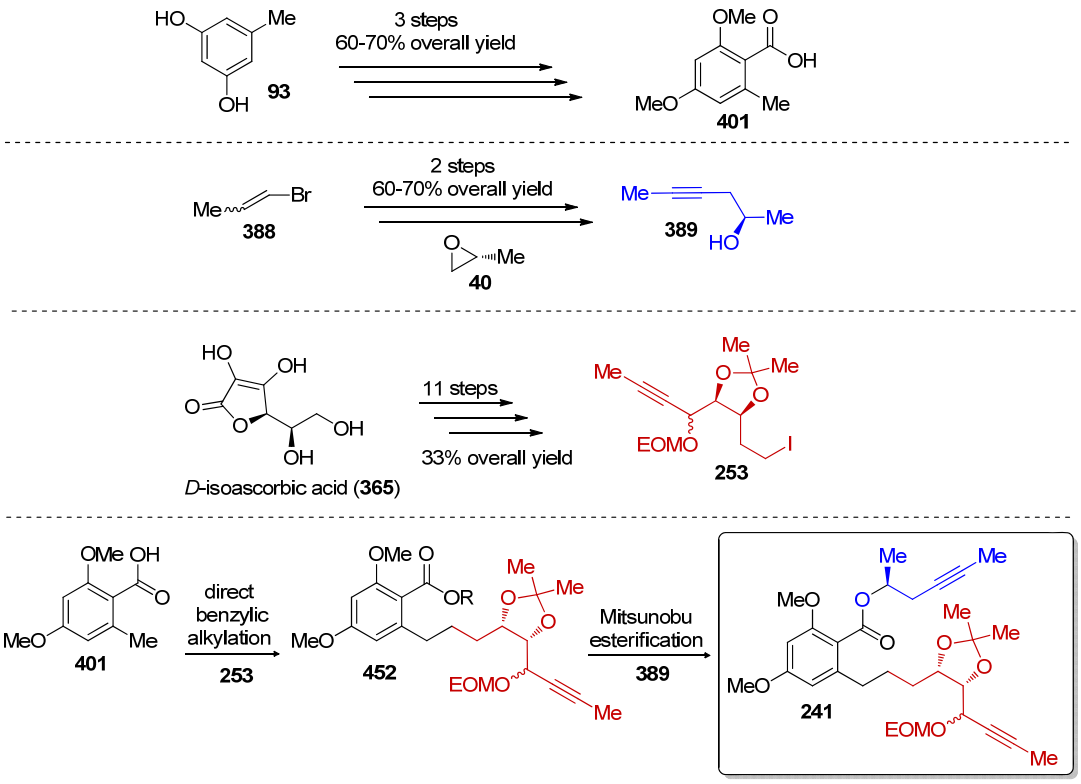
Chapter 4

CONCLUSION AND OUTLOOK

4 CONCLUSION AND OUTLOOK

4.1 Conclusion

- **Towards the synthesis of L-783,277 (7): achievement of the pivotal dialkyne precursor 3**



Scheme 152: Our most accomplished route leading to precursor **241**

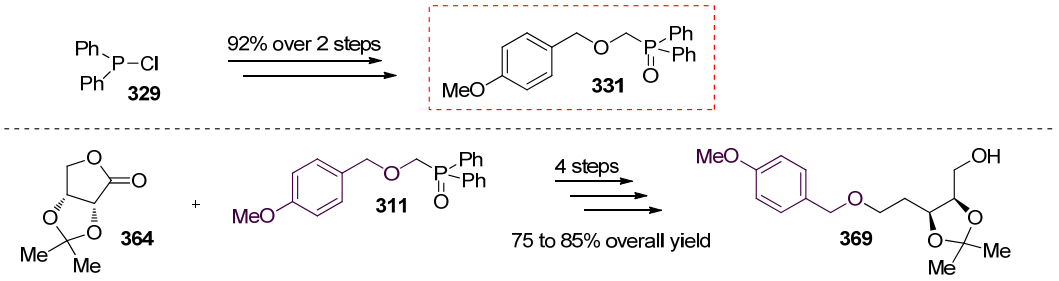
The main topic of this thesis resides in the search for a succinct and reliable route towards a formal synthesis of L-783,277 (**7**). Tenacious efforts and long-hour laboratory work have conducted to the achievement of the pivotal precursor **241**, setting the stage for further advancement on our synthetic pathway. As briefly illustrated in **scheme 152** above, the three building blocks had been first synthesised in very satisfying overall yields.

The aromatic core, though commercially available at a high price, was prepared from the classical and cheap orcinol (**93**) according to well-described procedures in the literature. The overall yield is com*para*tively high (up to 75%).

The propargylic alcohol **389** has demanded more intensive research to find out the optimal conditions for the stereoselective opening of the enantiomerically pure propylene oxide **40**. The best experimental conditions have led to the attainment of alcohol **389** in acceptable overall yield (50 to 60%).

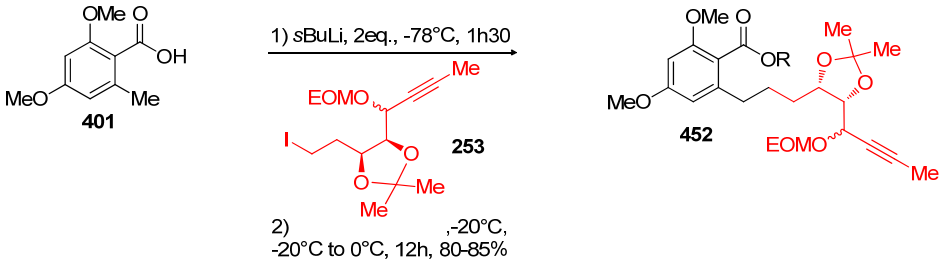
The major work has evolved around the pre*para*tion of the iodide fragment **253** in a reliable way, starting from easily and/or commercially available starting material. During the synthesis of this fragment, we have been confronted with several experimental issues (*e.g.* tricky purification of the intermediates, unreliable procedures, difficult handling of the starting materials) which led to dead-ends, and hence revision of strategies. Finally, the synthesis of this troublesome compound has been accomplished from *D*-isoascorbic acid (**365**) in 11 steps with an overall yield of 33%, following a very efficient and concise route.

As a recurrent theme from total synthesis research, the detours taken with respect to the initial synthetic itinerary often resulted in the development of innovative strategies and working tools. The best examples in our case are the use of phosphine oxide as a powerful method for the opening and homologation of lactones (*e.g*. erythronolactone **364** represented in **scheme 153**) based on a modified Horner-Wittig reaction. To date, there has been no publication disclosing the homologation of lactones to achieve the corresponding *p*-methoxybenzyl ether enols, which opens to this novel method a promising alley towards the pre*para*tion of more complex compounds.



Scheme 153: Phosphine oxide as powerful method for opening and homologation of lactones

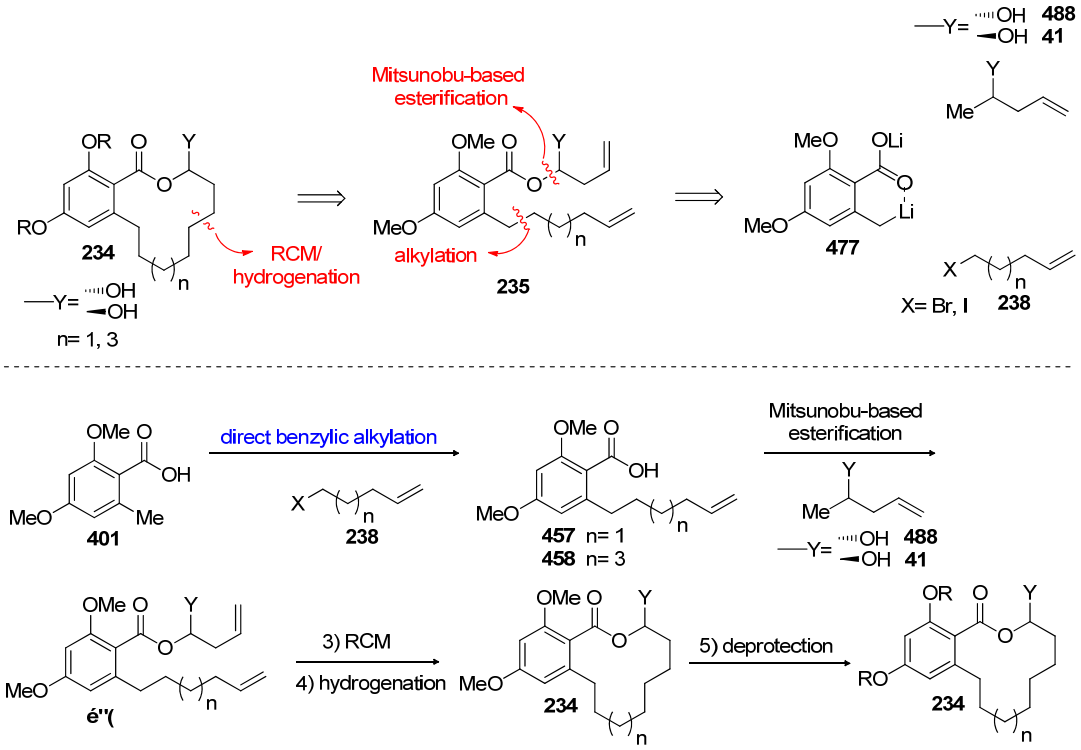
Finally, the crucial direct alkylation at the benzylic position between orsellinic acid derivative **401** and iodocalkanes has turned out to be greatly efficient, yielding the intermediate **452** in good yield, ranging from 80 to 85% (**scheme 154**).



Scheme 154: Direct alkylation at the benzylic position

The reliability of this key step has clearly been validated by its major contribution to the accomplishment of 4 other natural and synthetic RALs, following a very concise and efficient pathway.

- **From the strategic disconnection to the 4 successful syntheses of RALs**



Scheme 155: General strategic route of RALs bearing a single C1'-C2' bond

Finally, the envisaged synthetic route towards the syntheses of other RALs (**scheme 155**) has turned out to be very efficient and concise. The common building block remains the orsellinic acid derivative **401**, the main core to which were appended the remaining fragments to complete the carbon frame of the target molecules. The key step, direct alkylation at the benzylic position, has proven to be tactically powerful and versatile. This transformation is unprecedented in the field of total synthesis of RALs, making it a new and *via*ble tool among the classic synthetic toolkit.

The validation of our concepts and strategies are illustrated by the accomplishment of the 2 naturally occurring macrolides, *(R)*-(+)-lasiodiplodin (**10**) and zeranol (**611**), as well as 2 other unnatural resorcylic acid lactones, *(S)*-(-)-lasiodiplodin (**545**) and neolasiodiplodin (**606**), presented in **figure 27** below.

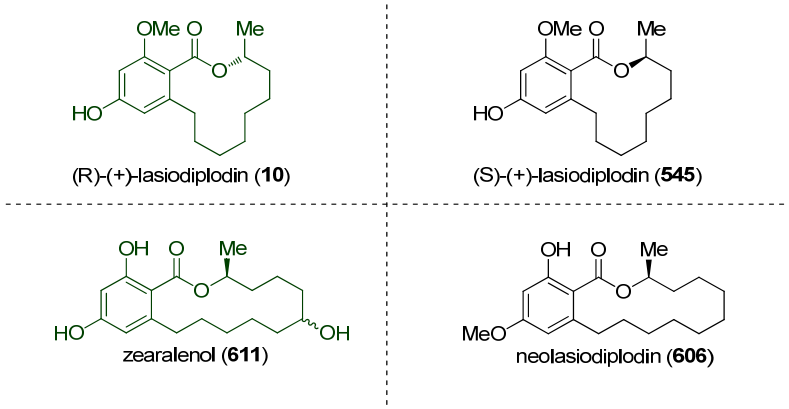
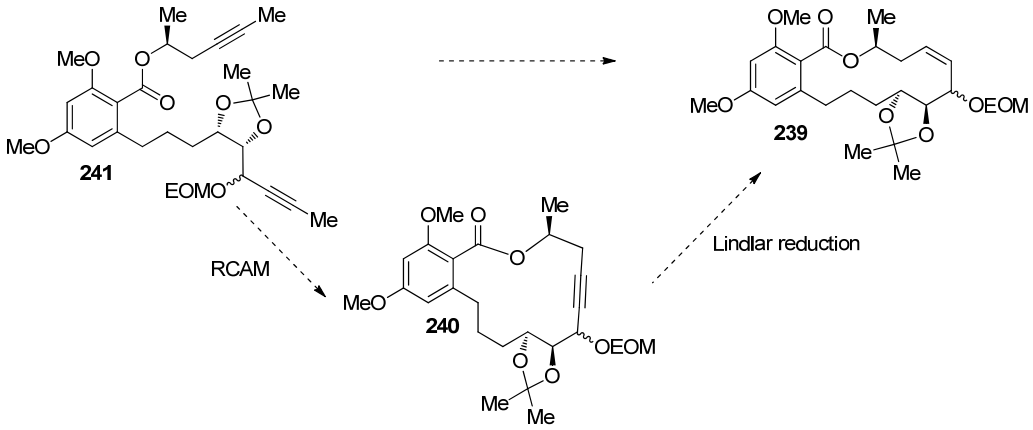


Figure 27: The natural RALs and RALs-inspired molecules achieved

4.2 Outlook

- **Construction of the cis-enone by RCAM/Lindlar reduction**

The next step towards the synthesis of L-783,277 (**7**) consists in the RCAM followed by a Lindlar reduction as featured in **scheme 156**.



Scheme 156: RCAM/Lindlar reduction step towards the formal synthesis of L-783,277 (**7**)

The ineffective RCAM trials using two of Fürstner's commercially available pre-catalysts (**figure 19**) have raised the plausible issue of structural constrictions due to the significantly decorated carbon frame of the readily prepared precursor **241**. This hypothesis can only be verified by future modifications of the structure of intermediate **241**, particularly the adjustment of the protecting groups at C4' and C5'. In all likeliness, one of the structural obstacles comes from the somewhat rigid acetonide (induced by the starting material erythronolactone **364**). In consequence, it might be expected that incorporation of less conformational constrains in the cyclisation precursor may lead to the ring-closing of dialkyne **241**. One of the potentially appropriate protecting groups is TBS (**figure 28**), which would have the advantage of being orthogonal to the coexisting EOM protecting group. This would presumably avoid the tricky selective oxidation of allylic alcohol of the triol precursor, previously mentioned by Altmann's and Winssinger's respective group.[1]

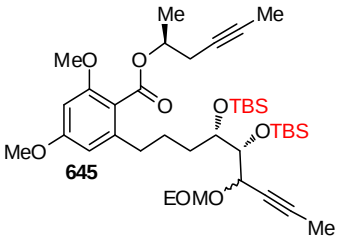
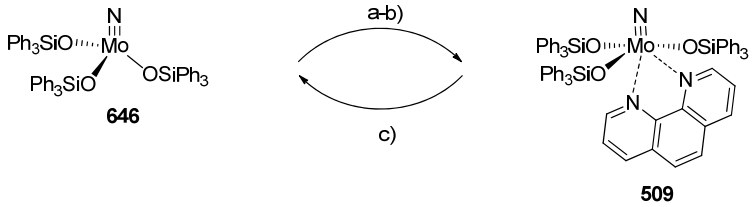


Figure 28: New dialkyne precursor for RCAM/Lindlar reduction strategy

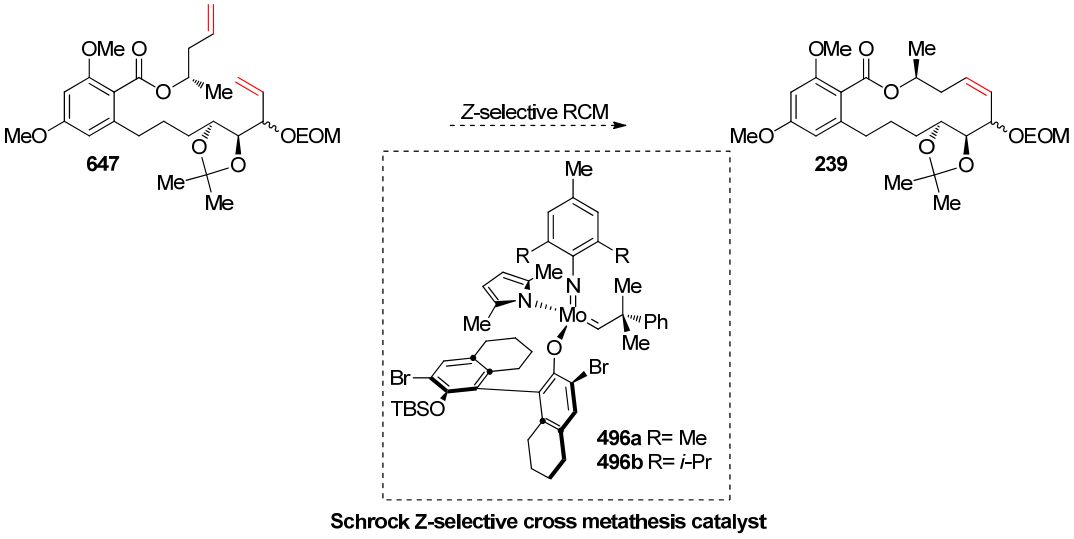
On the other hand, it would be also relevant to employ other well-known alkyne metathesis catalysts on the market to try out anew the RCAM onto the readily prepared precursor **241**.

Among all the well-defined and commercially available alkyne metathesis catalysts, the crystalline complex **509** is thought to be the next candidate, giving its reported indefinite stability on the benchtop without any precautions whatsoever (**scheme 157**).[2]



Scheme 157: *Reactions and conditions*: (a) Ph_3SiOH (3 equiv), toluene; (b) 1,10-phenanthroline, 82%; (c) $MnCl_2$, toluene, 80-100 °C.

- **Construction of the *cis*-enone by *Z*-selective RCM**



Scheme 158: RCAM/Lindlar reduction step towards the formal synthesis of L-783,277 (**7**)

As previously mentioned in section *2.1*, the assembly of the carbon framework of our target molecule **239** might be based on a *Z*-selective RCM, exploiting one of the newly disclosed catalysts by Schrock and Hoveyda (**scheme 158**).[3] To date, there has been no report yet in the literature about the use of any of the *Z*-selective olefin catalysts for ring-closing alkene metathesis for the syntheses of RALs. If successfully carried out, this would constitute an influential tool for the syntheses of naturally occurring RALs, their analogues and beyond.

- **From the "direct benzylic acylation" to the synthesis of neocosmosin A (29)**

Convinced by the usefulness of our key step, the direct alkylation at benzylic position, we have directed our attention to the extending of its reaction scope to the construction of other type of C1'-C2' bond, in particular the ketone carbonyl group at C3' in several members of the vast RALs family.

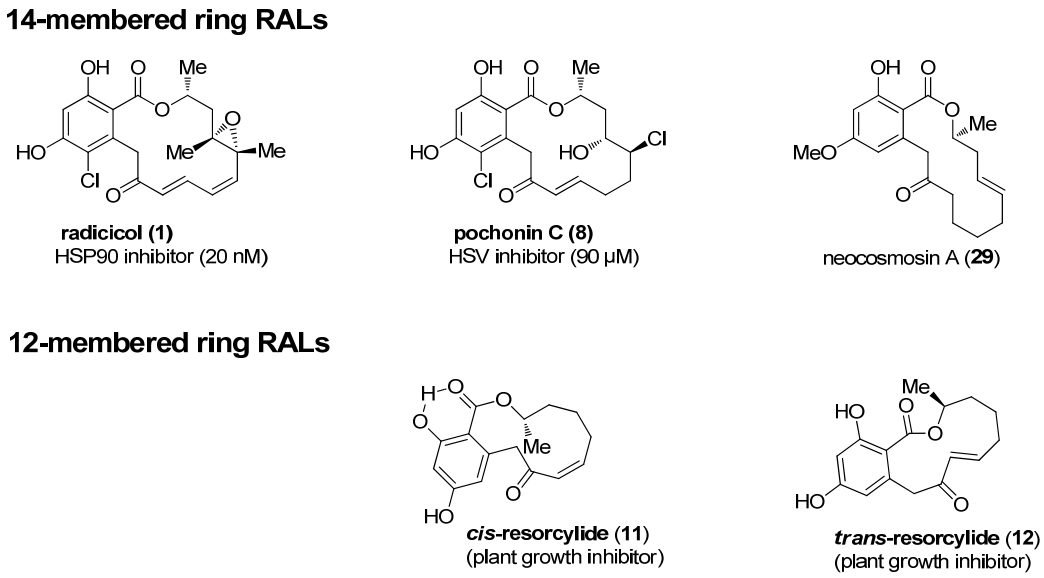
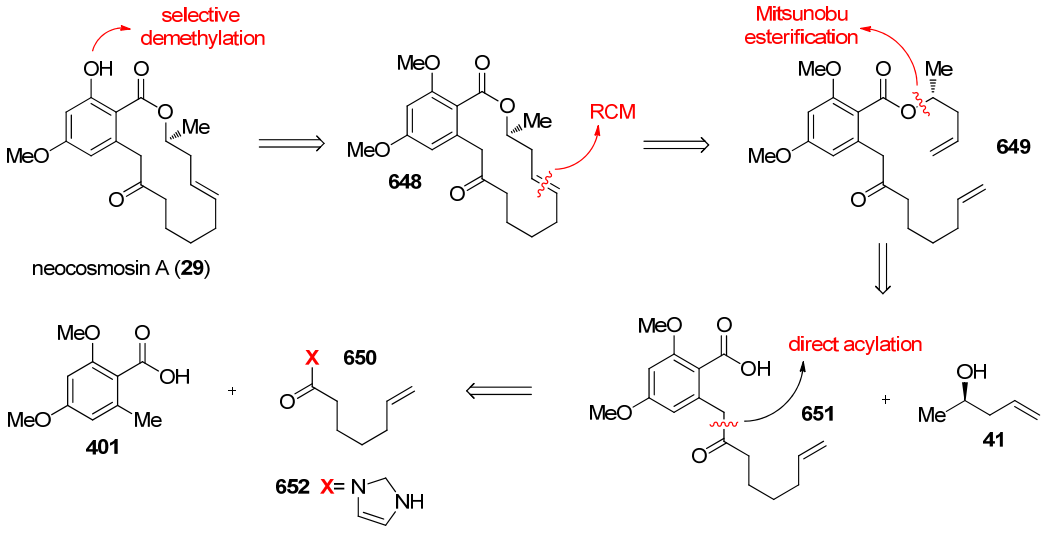


Figure 29: Some representative RALs which bear a ketone carbonyl group at C3'

The development of a reliable method for acylation at the benzylic position, based on our well established "direct alkylation at benzylic position" methodology, will enable access to the RALs illustrated in **scheme 29** above. In addition, a feasible direct benzylic acylation combined with the immediate application of our synthetic blueprint (**scheme 155**) would allow the achievement of neocosmosin A (**2**), which diplays *in vitro* binding affinity for human opioid and cannabinoid receptors.[4]

Retrosynthetically, neocosmosin A (**29**) might be disconnected, following our previously described synthetic strategy, into three se*para*te segments: the aromatic core **401**, the optically pure allylic alcohol **488** and the terminal alkene **650**. **Scheme 159** depicts the assembly of these fragments by a benzylic acylation, followed by a Mitsunobu-based esterification and a RCM to complete the carbon framework **648**. A selective demethylation would release the *ortho*-phenol, finalising the total synthesis of neocosmosin A (**29**).



Scheme 159: Proposed retrosynthetic disconnection of neocosmosin A (**29**)

Undoutedly, before embarking on the synthesis of this modestly decorated and hence structurally simple macrolide, it is mandatory to investigate the best leaving group **X** attached to the carbonyl C2' of **650**. In a broader perspective, if successfully carried out, this reaction sequence would be a short route to other analogues of neocosmosin A (**29**), the principal actors for further investigation of the biological activities of this newly discovered metabolite.

In consequence, the first attempts to find the best electrophilic candidate for the abovementioned acylation have been undertaken in our laboratories. In the first place, we have opted for an imidazoyl, *e.g*. 1-(1H-imidazol-1-yl)hept-6-en-1-one (**652**), with respect to the synthon **650** (**scheme 159**). However, extensive experimentation is required in order to find operationally useful conditions of acetylation.

Lastly, while there is no way to predict the *E:Z/ 1:1* ratio of **648** by a RCM which has been observed by the first total synthesis of neocosmosin (**29**) by Das *et al.* in 2014,[5] the group of Fürstner has lately reported a reliable method to access the *E* configuration of alkenes within macrocycles. Their paper outlined the entry to macrocyclic *E* alkenes by using a sequence of ring-closing alkyne metathesis (RCAM), trans-selective hydrosilylation of the resulting cycloalkynes catalyzed by [CppRu(MeCN)3]PF6, and a protodesilylation of the ensuing vinylsilanes with AgF in aqueous THF/MeOH.

4.3 List of references

1. (a) Hofmann, T.; Altmann, K. H., Total synthesis of the resorcylic lactone-based kinase inhibitor L-783277. *Synlett* **2008**, (10), 1500-1504; (b) Dakas, P. Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N., Divergent syntheses of resorcylic acid lactones: L-783277, LL-Z1640-2, and hypothemycin. *Chemistry - A European Journal* **2009**, *15* (43), 11490-11497.
2. Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner, A., Practical New Silyloxy-Based Alkyne Metathesis Catalysts with Optimized Activity and Selectivity Profiles. *Journal of the American Chemical Society* **2010**, *132* (32), 11045-11057.
3. Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H., Catalytic Z-selective olefin cross-metathesis for natural product synthesis. *Nature (London, U. K.)* **2011**, *471*, 461-466.
4. Gao, J.; Radwan, M. M.; Leon, F.; Dale, O. R.; Husni, A. S.; Wu, Y.; Lupien, S.; Wang, X.; Manly, S. P.; Hill, R. A.; Dugan, F. M.; Cutler, H. G.; Cutler, S. J., Neocosmospora sp.-Derived Resorcylic Acid Lactones with in Vitro Binding Affinity for Human Opioid and Cannabinoid Receptors [Erratum to document cited in CA158:692500]. *J. Nat. Prod.* **2013**, *76*, 2174.
5. Dachavaram, S. S.; Kalyankar, K. B.; Das, S., First stereoselective total synthesis of Neocosmosin A: a facile approach. *Tetrahedron Lett.* **2014**, *55*, 5629-5631.

Chapter 5

EXPERIMENTAL

5 EXPERIMENTAL

5.1 Devices and materials

5.1.1 General methods

Reagents and solvents were bought from ABCR, Acros, Aldrich, Fluka, VWR at ACS grade and used without purification, unless otherwise indicated. All absolute solvents had HPLC quality and were stored over molecular sieves.
Reactions were performed within dry solvents obtained by refluxing (dichloromethane and acetonitrile over calcium hydroxide, toluene over sodium, tetrahydrofuran and diethyl ether over sodium and benzophenone) followed by distillation.
All non-aqueous reactions were carried out using heatgun-dried glassware under a gas flow of dry argon unless otherwise indicated, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Merck Silica Gel 60 F254 plates and visualized by fluorescence quenching under UV light, then dipping inside a vanillin pre*para*tion (5 g vanillin, 100 mL ethanol, 0.4 mL H_2SO_4) followed by heatgun drying to reveal the subsequent spots. Retention factors (R_f) are indicated with the used solvent mixture in brackets.
Chromatographic purification of products (flash chromatography) was performed on Davisil® LC60A (particle size 40 - 63 µm or particle size 70-200 µm) using a forced flow of eluant at 1- 3 bar. Purifications on pre*para*tive layer chromatography were performed on silica gel coated glasses (Davisil® LC60A, 60 PF_{254}, 1.5 mm thick) which were prepared by our department.

NMR measurements

NMR spectra were recorded either on an JEOL (FNM EX-400) with a 400 MHz magnet for ^{1}H, 101 MHz for ^{13}C and 162 MHz for ^{31}P acquisitions or on a JEOL (JMN EX-270) with a 270 Hz magnet for ^{1}H acquisitions. The spectra were resolved with the Delta program. Chemical shifts (δ) are given in ppm relative to the TMS with the solvent resonance as internal standard relative to chloroform (δ 7.26), methanol (δ 3.31), dimethyl sulfoxide (δ 2.50), dichloromethane (δ 5.32), benzene (δ 7.16) and acetone (δ 2.05) for ^{1}H and chloroform (δ 77.16), methanol (δ 49.00), dimethyl sulfoxide (δ 39.52), dichloromethane (δ 53.8), benzene (δ 128.06) and acetone (δ 29.84) for ^{13}C. All ^{13}C and ^{31}P measurements were obtained with hydrogen decoupling and the coupling constants *J* with ^{31}P nucleus are given in Hertz. Data are reported as followed: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and their combinations. Assignment of protons and carbons were respectively accomplished by ^{1}H-^{1}H COSY correlation, ^{135}DEPT and ^{1}H- ^{13}C HMQC correlation experiments. The chemical shifts of ^{31}P spectra are uncorrected.
NMR data of diastereomeric mixtures are generally described for the major isomer, unless otherwise stated.

Melting Points
All the measurements were performed on a Büchi B-540 ap*para*tus, in open capillaries.

Optical Rotations

The specific rotations were measured on a Perkin-Elmer 241 polarimeter operating at the sodium D line with a 1.0 dm long cell. The specific rotations of solutions were calcd according to the Biot law:

$$[\alpha]_D^T = \frac{\alpha}{C.l}$$

α: measured value by the polarimeter
T: ambient temperature, automatically assumed at 20°C
C: concentration of the sample (g/100 ml)
l: the length of the cell (1.0 dm)

and are reported as followed:

$[\alpha]_D^{20}$ (concentration, solvent)

Mass spectrometry (MS) and High Resolution Mass Spectrometry (HRMS)

LC-MS measurements were carried out on an Agilent 6200 series TOF mass spectrometer operating in either positive or negative mode. The analyte solutions were delivered to the ESI source by an Agilent 1200 series LS system at a 0.25 mL.min $^{-1}$ flow rate. The gradient was from 10 % to 20 % eluent acetonitrile in water within 20 min.

General ESI and APCI conditions : capillary voltage (2.0 kV), cone voltage (65 kV), source temperature (250°C), desolvation temperature (350°C), drying gas (5 L.min $^{-1}$), nebulizer (60 psig).

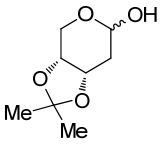
For the recording of the single-stage ESI-MS spectra, all ions are transmitted into the pusher region of the TOF analyzer where they are mass-analysed with 1 second integration time.

Dry nitrogen was used for ESI and APCI methods. All ions were transmitted into the pusher region of the TOF analyser, where they were mass-analysed with one-second integration time for the recording of the single-stage ESI-MS.

5.2 Towards the synthesis of L-783,277 (7)

5.2.1 Construction of the polyol fragment

5.2.1.1 First generation strategy: "2-deoxy-D-ribose approach"



Chemical Formula: $C_8H_{14}O_4$
Molecular Weight: 174.19 g.mol^{-1}

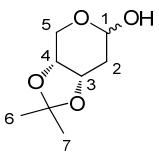
(3aR,7aS)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-ol (**246**)

To a solution of (3S,4S)-tetrahydro-2H-pyran-2,3,4-triol (**89**) (10.0 g, 74.6 mmol, 1.0 equiv.), PTSA (128 mg, 0.746 mmol, 0.01 equiv.) and previously heatgun-dried under vacuum $MgSO_4$ (2.5 g) in DMF at 0°C was added 2-methoxypropene (14.3 mL, 149.2 mmol, 2.0 equiv.). The solution was stirred at 0°C for 3h30 then allowed to warm to RT before Na_2CO_3 (*ca* 10 g) was added. The resulting mixture was filtered and the organic layer was evaporated to afford a crude product which was purified *via* silica flash chromatography (Cy/EtOAC: 9/1 → 6/1 → 4/1) to provide 73/28 anomeric mixture of **(3aR,7aS)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-ol** (**246**) as a white solid (6.1 g, 47%).

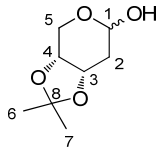
R_f= 0.38 (Cy/EtOAc: 2/3)

The analytical are identical to those from the literature.[1]

mp= 97-99°C



Numbering for the hydrogens

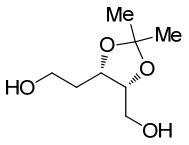


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.34 (s, 6H, H-6 or H-7), 1.49 (s, 6H, H-7 or H-6), 1.77-1.81 (m, 1H, H-2A), 2.21-2.27 (m, 1H, H-2B), 3.66-3.73 (m, 1H, H-5A), 3.92-3.98 (m, 1H, H-5B), 4.12-4.21 (m, 2H, H-3), 4.39-4.50 (m, 2H, H-4), 5.24-5.28 (m, 1H, H-1)

^{13}C NMR (100 MHz, CDCl3): δ= 25.5 (C-6 or C-7), 28.1 (C-7 or C-6), 35.5 (C-2), 63.0 (C-5), 75.5 (C-3), 77.9 (C-4), 97.7 (C-1), 107.9 (C-8)

HRMS (ESI+): calcd for $(M-H)^-$: 173.0814, found: 173.0807



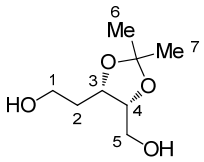
Chemical Formula: $C_8H_{16}O_4$
Molecular Weight: 176.21 $g.mol^{-1}$

2-((4R,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (247)

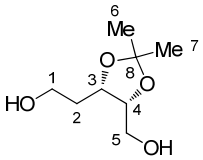
To a suspension of LAH (1.99 g, 52.5 mmol, 1.5 equiv.) in THF (70 mL) at 0°C was added dropwise a solution of **(3aR,7aS)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-ol** (**246**) (6.1 g, 35.0 mmol, 1.0 equiv.) in THF (70 mL). The mixture was stirred at RT for 5h then quenched at 0°C respectively with distillated water (1.99 mL), NaOH (15 w/v%, 1.99 mL) and distillated water (5.97 mL). The resulting mixture was then poured into Et_2O (40 mL) and stirred for 30 min before being filtrated *via* a Celite pad and the solvents were evaporated under reduced pressure. The slightly yellow crude product was purified through silica flash chromatography (Cy/EtOAC: 4/1 → 1/1 → 1/2) to afford **2-((4R,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol** (**247**) (5.6 g, 90%)as a yellow oil.

R_f= 0.50 (Cy/EtOAc: 1/3)

The analytical are identical to those from the literature.[1]



Numbering for the hydrogens

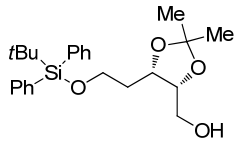


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.34 (s, 3H, H-6 or H-7), 1.49 (s, 3H, H-7 or H-6), 1.77-1.81 (m, 2H, H-2), 2.00 (bs, 1H, O*H*), 2.22 (bs, 1H, O*H*), 3.53-359 (m, 2H, H-5), 3.66-3.75 (m, 2H, H-1), 4.18-4.23 (m, 2H, H-3), 4.33-4.38 (m, 2H, H-4)

^{13}C NMR (100 MHz, CDCl3): δ= 25.5 (C-6 or C-7), 28.1 (C-7 or C-6), 32.5 (C-2), 61.0 (C-1), 63.0 (C-5), 75.5 (C-3), 77.9 (C-4), 107.9 (C-8)

HRMS (ESI+): calcd for $(M-H)^+$: 177.1126, found: 177.1120

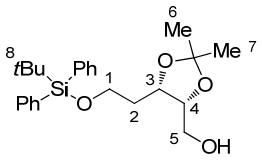


Chemical Formula: $C_{24}H_{34}O_4Si$
Molecular Weight: 414.61 g.mol^{-1}

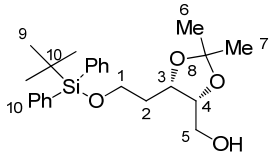
((4R,5R)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (248)

To a stirred solution of **2-((4R,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (247)** (5.5 g, 31.2 mmol, 1.0 equiv.) in DMF (25 mL) at RT was added imidazole (3.2 g, 46.8 mmol, 1.5 equiv.). The reaction was stirred at RT for 15 min before the dropwise addition of TBDPSCl (8.9 mL, 34.3 mmol, 1.1 equiv.) and the stirring was maintained at this temperature for 2h30. The mixture was diluted with EtOAc (200 mL), washed with a solution of K_2CO_3 (10 w/v%, 100 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (Cy/EtOAC: 9/1 → 5/1 → 4/1) to provide **((4R,5R)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (248)** (5.7 g, 44%) as a colorless oil.

R_f= 0.26 (Cy/EtOAc: 3/1)



Numbering for the hydrogens

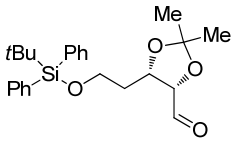


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.04 (s, 9H, H-8), 1.35 (s, 3H, H-6 or H-7), 1.44 (s, 3H, H-7 or H-6), 1.77-1.91 (m, 2H, H-2), 3.56-3.61 (m, 2H, H-1), 3.77-3.81 (m, 1H, H-5), 4.09-4.18 (m, 1H, H-3), 4.37-4.43 (m, 1H, H-4), 7.36-7.45 (m, 6H, arom), 7.65-7.69 (m, 4H, arom)

^{13}C NMR (100 MHz, CDCl3): δ= 20.2 (C-11), 25.5 (C-6 or C-7), 26.7 (C-9), 28.1 (C-7 or C-6), 32.7 (C-2), 61.0 (C-1), 63.0 (C-5), 73.5 (C-3), 77.9 (C-4), 107.9 (C-8), 127.7 (arom), 127.9 (arom), 129.7 (arom), 133.3 (arom), 133.5 (arom), 135.3 (arom), 135.9 (arom)

HRMS (ESI+): calcd for $(M-H)^+$: 415.2305, found: 415.2311

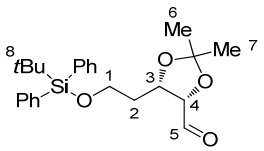


Chemical Formula: $C_{24}H_{32}O_4Si$
Molecular Weight: 412.59 g.mol^{-1}

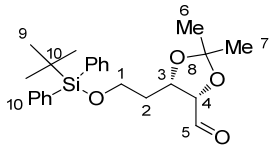
(4S,5R)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (248)

To a solution of **((4R,5R)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (247)** (5.7 g, 13.7 mmol, 1.0 equiv.) in DMSO/DCM (10 mL/20 mL) at -10°C was added DIPEA (7.1 mL, 41.2 mmol, 3.0 equiv.) and the reaction mixture was stirred at this temperature for 15 min. To the latter solution was added *via* cannula a solution of SO_3.pyr (6.6 g, 41.2 mmol, 3.0 equiv.) in DMSO (10 mL) over 15 min and the mixture was stirred between -10°C and -5°C for 4h before being diluted at 0°C with Et_2O (200 mL) and washed with distillated water (3 x 200 mL), $CuSO_4$ (10 w/v%, 2 x 100 mL) and brine (200 mL), respectively, dried over $MgSO_4$ and highly concentrated under reduced pressure. The slightly yellow crude product **248** (6.0 g) was employed in the next step without further purification.

R_f= 0.65(Cy/EtOAc: 3/1)



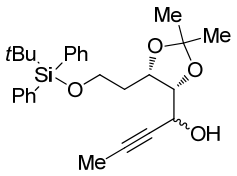
Numbering for the hydrogens



Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.04 (s, 9H, H-8), 1.35 (s, 3H, H-6 or H-7), 1.44 (s, 3H, H-7 or H-6), 1.77-1.91 (m, 2H, H-2), 3.56-3.61 (m, 2H, H-1), 4.09-4.16 (m, 1H, H-3), 4.43-4.46 (m, 1H, H-4), 7.36-7.45 (m, 6H, arom), 7.65-7.69 (m, 4H, arom), 9.79 (d, J= 2.97, 1H, H-5)

^{13}C NMR (100 MHz, CDCl3): δ= 20.2 (C-11), 25.5 (C-6 or C-7), 26.7 (C-9), 28.1 (C-7 or C-6), 32.7 (C-2), 61.0 (C-1), 73.5 (C-3), 77.9 (C-4), 107.9 (C-8), 127.7 (arom), 127.9 (arom), 129.7 (arom), 133.3 (arom), 133.5 (arom), 135.3 (arom), 135.9 (arom), 200.21 (C-5)

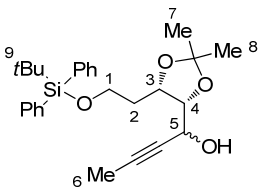


Chemical Formula: $C_{27}H_{36}O_4Si$
Molecular Weight: 452.66 g.mol^{-1}

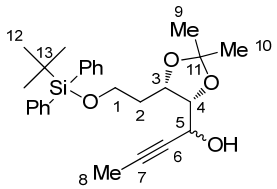
1-((4R,5R)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (250)

The crude product of **(4S,5R)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (249)** (6.0 g)was diluted in THF (50 mL) at RT then cooled down to -5°C before a 0.5 M solution of prop-1-yn-1-ylmagnesium bromide (41.4 mL, 20.7 mmol, 1.5 equiv.) was added dropwise. The mixture was vigorously stirred between -5°C and 0°C for 3h, then allowed to warm up to 0°C before getting diluted by Et_2O (70 mL) and quenched with a saturated solution of NH_4Cl (100 mL). The aqueous phase was extracted with Et_2O (2 x 30 mL). The combined organic phase was washed with a saturated solution of brine (100 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* silica flash chromatography (Cy/EtOAC: 9/1 → 6/1 → 4/1) to provide a 55/45 diastereomeric mixture of **250** (5.8 g, 93% over 2 steps) as a colorless oil.

R_f= 0.31 (Cy/EtOAc: 3/1)



Numbering for the hydrogens

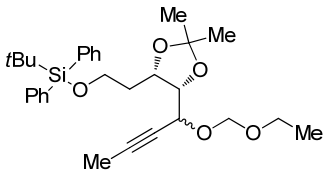


Numbering for the carbons

^{1}H NMR (400 MHz, **CDCl3):** δ= 1.04 (s, 9H, H-9), 1.37 (s, 3H, H-7 or H-8), 1.48 (s, 3H, H-8 or H-7), 1.85 (d, 3H, J= 2.1 Hz, H-6), 1.93-2.17 (m, 2H, H-2), 3.78-3.87 (m, 2H, H-1), 4.06-4.11 (m, 2H, H-3), 4.24-4.39 (m, 2H, H-4), 4.46-4.52 (m, 2H, H-5), 7.36-7.43 (m, 6H, arom), 7.65-7.69 (m, 4H, arom)

^{13}C NMR (100 MHz, **CDCl3):** δ= 3.89 (C-8), 19.30 (C-16), 25.48 (C-9 or C-10), 27.56 (C-10 or C-9), 32.25 (C-2), 61.26 (C-5), 64.64 (C-1), 71.63 (C-6 or C-7), 74.09 (C-3), 79.94 (C-4), 83.00 (C-7 or C-6), 108.55 (C-13), 127.72 (arom), 129.82 (arom), 135.67 (arom)

HRMS (ESI+): calcd for $(M-H)^+$: 453.2461, found: 453.2455



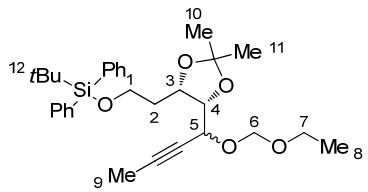
Chemical Formula: $C_{30}H_{42}O_5Si$
Molecular Weight: 510.74 g.mol^{-1}

tert-butyl(2-((4R,5S)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)diphenylsilane (251)

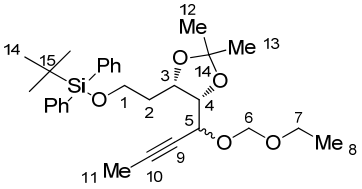
To a stirred solution of **1-((4R,5R)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (250)** (5.8 g, 12.8 mmol, 1.0 equiv.) in DMF (30 mL) at RT was added TBAI (0.13 mmol, 47.8 mg, 0.01 equiv.), DIPEA (11.0 mL, 64.0 mmol, 5.0 equiv.), respectively. The solution was stirred for 5 min at RT before the dropwise addition of EOMCl (5.7 mL, 64.0 mmol, 5.0 equiv.). The mixture was stirred at RT for 4h. The slightly orange

solution was diluted with Et_2O (150 mL) quenched at 0°C with a saturated solution of NH_4Cl (100 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phase was washed with a saturated solution of brine (150 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* silica flash chromatography (Cy/EtOAC: 95/5→ 8/1 → 6/1) to provide 55/45 diastereomeric mixture of **251** as a colorless oil (10.4 g, 97%).

R_f= 0.62 (Cy/EtOAc: 3/1)



Numbering for the hydrogens

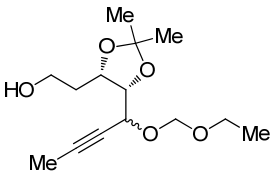


Numbering for the carbons

^{1}H NMR (400 MHz, **CDCl3):** δ= 1.04 (s, 9H, H-12), 1.19 (t, 3H, H-8), 1.36 (s, 3H, H-10 or H-11), 1.84 (d, 3H, J= 2.1Hz, H-9), 1.90-2.04 (m, 2H, H-2), 3.49-3.77 (m, 2H, H-7), 3.78-3.90 (m, 2H, H-1), 4.11-4.24 (m, 1H, H-3), 4.30-4.37 (m, H-4), 4.42-4.52 (m, 2H, H-5), 4.84 (AB, J_{AB} = 6.9 Hz, Δν= 120 Hz, 2H, H-6), 7.35-7.43 (m, 6H, arom), 7.65-7.70 (m, 4H, arom)

^{13}C NMR (100 MHz, **CDCl3):** δ= 3.93 (C-11), 15.20 (C-8), 19.32 (C-16), 25.51 (C-12 or 13), 26.93 (C-15), 27.58 (C-13 or 12), 32.20 (C-2), 60.93 (C-1), 64.24 (C-7), 66.08 (C-5), 73.68 (C-3), 74.87 (C-9 or C-10), 79.00 (C-4), 84.04 (C-10 or C-9), 92.55 (C-6), 108.46 (C-14), 127.72 (arom), 129.82 (arom), 135.68 (arom)

HRMS (ESI+): calcd for $(M-H)^+$: 511.2879, found: 511.2885

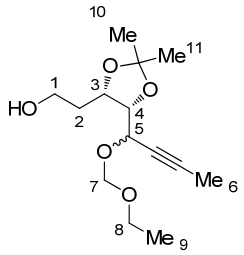


Chemical Formula: $C_{14}H_{24}O_5$
Molecular Weight: 272.34 g.mol^{-1}

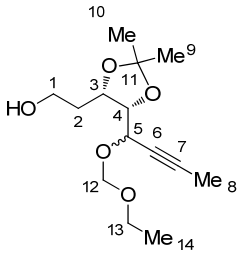
2-((4R,5S)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (252)

To a stirred solution of **tert-butyl(2-((4R,5S)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)diphenylsilane (251)** (10.2 g, 19.6 mmol, 1.0 equiv.) in THF (70 mL) at RT was added in one portion tetrabutylammonium fluoride hydrate (12.8 g, 49.0 mmol, 2.5 equiv.). The reaction mixture was stirred at RT overnight. The yellowish solution was diluted with EtOAc (100 mL), washed with a saturated solution of NH_4Cl (2 x 70 mL) then with brine (100 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* silica flash chromatography (Cy/EtOAC: 9/1→ 6/1 → 4/1) to provide 55/45 diastereomeric mixture of **252** as a colorless oil (5.2 g, 98%)

R_f= 0.30 (Cy/EtOAc: 1/1)



Numbering for the hydrogens

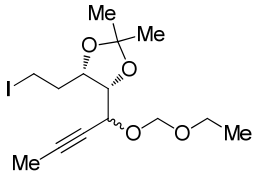


Numbering for the carbons

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 1.21 (t, J= 7.1 Hz, 3H, H-9), 1.43 (s, 3H, H-10 or H-11), 1.47 (s, 3H, H-11 or H-10), 1.86 (d, J = 2.29 Hz, 3H, H-6), 1.97-2.07 (m, 2H, H-2), 3.50-3.75 (m, 2H, H-8), 3.81-3.89 (m, 2H, H-5 and H-4), 4.18-4.22 (m, 1H, H-3), 4.45-4.85 (m, 1H H-1), 4.84 (AB, J_{AB} = 6.9 Hz, Δv= 120 Hz, 2H, H-7)

^{13}C NMR (400 MHz, $CDCl_3$) : δ = 3.86 (C-8), 15.14 (C-14), 25.52 (C-9 or C-10), 27.55 (C-10 or C-9), 31.55 (C-2), 61.33 (C-3), 64.29 (C-13), 65.87 (C-5), 75.00 (C-6 or C-7), 76.52 (C-1), 79.04 (C-4), 84.10 (C-7 or C-6), 92.47 (C-12), 108.75 (C-11)

HRMS (ESI+): calcd for $(M-H)^+$: 273.1702, found: 273.1710

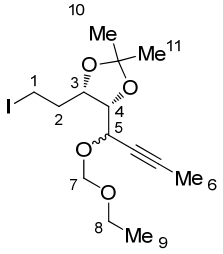


Chemical Formula: $C_{14}H_{23}IO_4$
Molecular Weight: 382.23 g.mol^{-1}

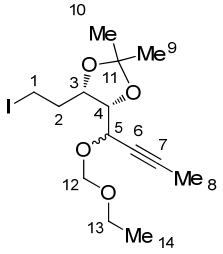
(4S,5R)-4-(1-(ethoxymethoxy)but-2-yn-1-yl)-5-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane (253)

To a solution of **2-((4R,5S)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (252)** (1.0 g, 3.7 mmol, 1.0 equiv.), PPh_3 (1.4 g, 5.5 mmol,1.5 equiv.) and imidazole (0.37 g, 5.5 mmol, 1.5 equiv.) in THF (50 mL) at 0°C was added I_2 (1.4 g, 5.5 mmol, 1.5 equiv.) in one portion. The brown-yellow reaction mixture was vigorously stirred at 0°C until until TLC indicated total consumption of starting material (2h30). The reaction mixture was warmed to room temperature then diluted with Et_2O (70mL) quenched with aqueous saturated $Na_2S_2O_5$ (100 mL). The aqueous layer was extracted with Et_2O (2 x 30mL) and the combined organic layer was washed with brine (100 mL). The crude product was subjected to previously neutralised silica gel (in cyclohexane containing 0.1% TEA over 10 min) flash chromatography (Cy/AcOEt: 97/3→95/5→90/10) to afford 55/45 diastereomeric mixture of **247**as a colorless oil (1.3 g, 91%)

R_f = 0.80 (Cy/EtOAC : 2/1)



Numbering for the hydrogens

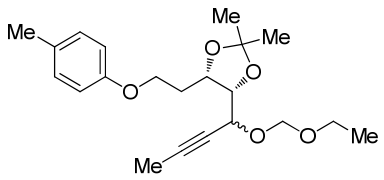


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3) : δ = 1.21 (t, J= 7.10 Hz, 3H, H-9), 1.43 (s, 3H, H-10 or H-11), 1.47 (s, 3H, H-11 or H-10), 1.87 (d, J = 2.3 Hz, 3H, H-6), 2.13-2.27 (m, 2H, H-2), 3.20-3.42 (m, 2H, H-1), 3.50-3.75 (m, 2H, H-8), 4.18-4.22 (m, 1H, H-3), 4.23-4.33 (m, 1H, H-4), 4.34-4.38 (m, 1H, H-5), 4.84 (AB, J_{AB} = 7 Hz, Δν= 120 Hz, 2H, H-6)

^{13}C NMR (100 MHz, CDCl3) : δ = 3.25 (C-1), 3.75 (C-8), 15.14 (C-14), 25.52 (C-9 or C-10), 27.55 (C-10 or C-9), 33.45 (C-2), 63.47 (C-13), 65.08 (C-5), 66.04 (C-3), 75.00 (C-6 or C-7), 79.04 (C-4), 84.11 (C-7 or C-6), 92.49 (C-12), 108.76 (C-11)

HRMS (ESI+): calcd for $(M-H)^{+}$: 383.0719, found: 383.0726

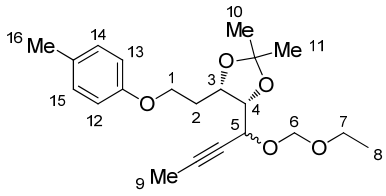


Chemical Formula: $C_{21}H_{30}O_5$
Molecular Weight: 362.46 g.mol^{-1}

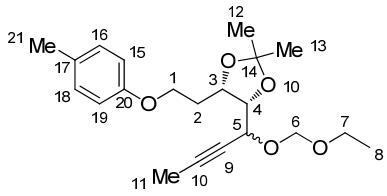
(4S,5R)-4-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-5-(2-(p-tolyloxy)ethyl)-1,3-dioxolane (255)

To a solution of **2-((4R,5S)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (252)** (1.0 g, 3.7 mmol, 1.0 equiv.) in DCM (50 mL) at 0°C was added pyridine (3.0 mL, 36.7 mmol, 10.0 equiv.) then TsCl(3.5 g, 18.4 mmol,5.0 equiv.) in DCM (50 mL). The reaction mixture was vigorously stirred at 0°C for 1h and at RT overnight before being quenched with saturated aqueous NH_4Cl (100 mL) at 0°C. The aqueous layer was extracted with DCM (2 x 30mL) and the combined organic layer was washed with brine (100 mL), dried with $MgSO_4$. The solvents were evaporate and the crude product was subjected to silica gel flash chromatography (Cy/AcOEt: 97/3→95/5→90/10) to afford **255** as a colorless oil (1.3 g, 99%).

R_f = 0.84 (Cy/EtOAC: 2/1)



Numbering for the hydrogens

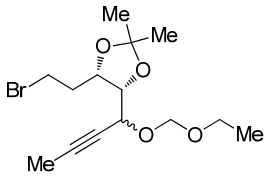


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.18 (t, 3H, J=7.1 Hz, H-8), 1.26 (s, 3H, H-10 or H-11), 1.40 (s, 3H, H-11 or H-10), 1.81 (d, 3H, J= 2.1 Hz, H-9), 1.96-2.20 (m, 2H, H-2), 2.40 (s, 3H, H-16), 3.42-3.69 (m, 2H, H-7), 4.06-4.31 (m, 5H, H-3, H-4, H-5 and H-1), 4.76 (AB, J_{AB} = 6.9 Hz, Δν= 120 Hz, 2H, H-6), 7.03 (d, 2H, J= 8.0 Hz, H-14 and H-15), 7.75 (d, 2H, J= 8.0 Hz, H-12 and H-13)

^{13}C NMR (100 MHz, CDCl3): δ= 3.81 (C-11), 15.12 (C-8), 21.66 (C-21), 25.36 (C-12 or C-13), 27.46 (C-13 or C-12), 29.22 (C-2), 64.26 (C-7), 65.70 (C-3), 68.16 (C-1), 72.86 (C-5), 78.59 (C-4), 92.47 (C-6), 108.78 (C-14), 127.98 (C-16 and C-18), 129.94 (C-15 and C-19), 133.11 (C-17), 44.79 (C-20)

HRMS (ESI+): calcd for $(M-H)^{+}$: 363.2171, found: 363.2177

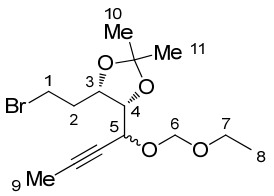


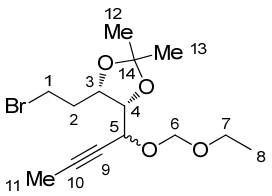
Chemical Formula: $C_{14}H_{23}BrO_4$
Molecular Weight: 335.23 g.mol^{-1}

(4R,5S)-4-(2-bromoethyl)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolane (254)

To a solution of **(4S,5R)-4-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-5-(2-(p-tolyloxy)ethyl)-1,3-dioxolane (252)** (95.5 mg, 0.22 mmol, 1.0 equiv.) in acetone (7 mL) at 25°C was added LiBr(19.44 mg, 2.24 mmol,10.0 equiv.).The brown-yellow reaction mixture was under refluxing for 16h. The reaction mixture was allowed to reach the ambient temperature over 1 hour before being filtered over a pad of Celite. The solvents totally evaporated and the crude product was subjected to previously neutralised silica gel (in cyclohexane containing 0.1% TEA over 10 min) flash chromatography (Cy/AcOEt: 97/3→90/10→80/20) to afford a 55/45 diastereomeric mixture of **254** as a colorless oil (44.3 mg, 60%)

R_f = 0.73 (Cy/EtOAC: 2/1)





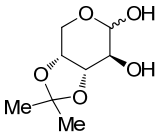
Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3) : δ = 1.21 (t, J= 7.1 Hz, 3H, H-8), 1.37 (s, 3H, H-10 or H-11), 1.47 (s, 3H, H-11 or H-10), 1.85 (d, J = 2.3 Hz, 3H, H-9), 2.05-2.32 (m, 2H, H-2),3.47-3.64 (m, 4H, H-7 and H-1), 3.66-3.73 (m, 1H, H-3), 4.29-4.40 (m, 2H, H-4 and H-5), 4.84 (AB, J_{AB} = 6.9 Hz, Δv= 120 Hz, 2H, H-6)

^{13}C NMR (100 MHz, CDCl3) : δ = 3.90 (C-11), 15.19 (C-8), 25.54 (C-12 or C-13), 27,68 (C-13 or C-12), 30.74 (C-2), 32.78 (C-1), 64.38 (C-7), 65.72 (C-5), 74.98 (C-9 or C-10), 75.20 (C-3), 78.67 (C-4), 84.15 (C-10 or C-9), 92.48 (C-6), 108.82 (C-14)

HRMS (ESI+): calcd for $(M-H)^{+}$: 335.0858, found: 335.0867

5.2.1.2 Second generation strategy: "D-arabinose approach"



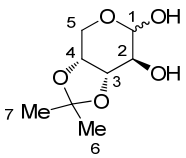
Chemical Formula: $C_8H_{14}O_5$
Molecular Weight: 190.19 g.mol^{-1}

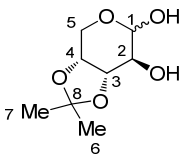
(3aR,7S,7aS)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6,7-diol (260)

To a stirred solution of D-arabinose (**259**) (8.2 g, 54.6 mmol, 1.0 equiv.) and PTSA (94.0 mg, 0.55 mmol, 0.01 equiv.) in DMF at RT was added dropwise 2,2-dimethoxypropane (20.3 mL, 164 mmol, 3.0 equiv.). The white opaque mixture was stirred at RT for 2h30 before becoming limpid and quenched by addition of Amberlite A-410 (the reaction evolution was followed by TLC and stopped before the formation of the thermodynamic product diacetonide). After 15 min of vigorous stirring, the mixture was filtered through a Celite® pad, evaporated under reduced pressure. The obtained crude product was purified *via* silica flash chromatography (Cy/EtOAC: 4/1 → 2/1→1/2) to afford **260** (9.0 g, 87%) as a white solid.

R_f= 0.41 (Cy/EtOAc: 1/3)

The analytical are identical to those from the literature.[2]



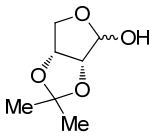


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 1.36 (s, 3H, H-6 or H-7), 1.52 (s, 3H, H-7 or H-6), 3.83-3.87 (m, 2H, H-5A), 4.14-4.30 (m, 4H, H-2, H-3, H-4 and H-5B), 5.19 (d, 1H, J= 2.9 Hz, H-1)

^{13}C NMR (100 MHz, CDCl3): δ= 24.96 (C-6 or C-7), 26.97 (C-7 or C-6), 67.70 (C-5), 72.04 (C-2), 80.02 (C-3), 85.21 (C-4), 101.93 (C-1), 112.40 (C-8)

HRMS (ESI+): calcd for $(M-H)^-$: 189.0763, found: 189.0770



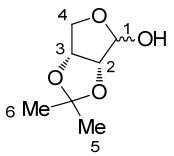
Chemical Formula: $C_7H_{12}O_4$
Molecular Weight: 160.07 g.mol^{-1}

(3aR,6aR)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (257)

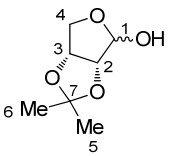
To a stirred solution of **(3aR,7S,7aS)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6,7-diol (260)** (9.0 g, 47.4 mmol, 1.0 equiv.) in Et_2O (90 mL) was added carefully a solution of $NaBH_4$ (3.6 g, 94.7 mmol, 2.0 equiv.) in absolute ethanol (70 mL). Once the gas evolution stopped, the mixture was stirred for 2h at RT then acidified with glacial acetic acid at 0°C to obtain a neutral pH. The newly formed white solid was filtered and the filtrate evaporated to eliminate Et_2O before the addition of distillated water (70 mL), followed by $NaIO_4$ (15.2 g, 71.1 mmol, 1.5 equiv.). The colorless limpid mixture was stirred at RT for 30 min before the fine white solid was filtered and the solvents evaporated under reduced pressure. The obtained white viscous product was dissolved in Et_2O (50 mL), washed with a saturated solution of $NaHCO_3$ (2 x 50 mL) then with brine (100 mL). The organic fraction was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified *via* silica flash chromatography (Cy/EtOAC: 7/1 → 5/1→4/1) to provide **257** (6.2 g, 85%)as a white solid.

R_f= 0.60 (Cy/EtOAc: 1/4)

The analytical data are identical to those from the literature.[2]



Numbering for the hydrogens

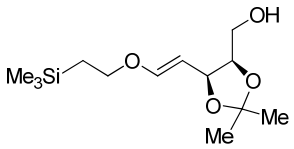


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.32 (s, 3H, H-5 or H-6), 1.47 (s, 3H, H-6 or H-5), 4.05 (*AB*X, 2H, J_{AX}= 0.7 Hz, J_{BX}= 3.7 Hz, J_{AB}= 10.3 Hz, Δν= 7 Hz), 4.82-4.85 (AB*X*, 1H, H-3), 4.58 (d, J= 5.7 Hz, H-2), 5.42 (d, J= 1.8 Hz, H-1)

^{13}C NMR (100 MHz, CDCl3): δ= 24.73 (C-5 or C-6), 26.29 (C-6 or C-5), 72.04 (C-4), 80.02 (C-3), 85.20 (C-2), 101.93 (C-1), 112.40 (C-7)

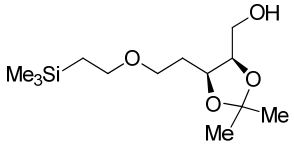
HRMS (ESI+): calcd for $(M-H)^-$: 159.0657, found: 159.0662



Chemical Formula: $C_{13}H_{26}O_4Si$
Molecular Weight: 274.43 g.mol^{-1}

((4R,5S)-2,2-dimethyl-5-((E)-2-(2-(trimethylsilyl)ethoxy)vinyl)-1,3-dioxolan-4-yl)methanol (264)

To a stirred suspension of triphenyl(((trimethylsilyl)methoxy)methyl)phosphonium chloride (**263**) (36.5 g, 85.3 mmol, 2.2 equiv.) in Et_2O (230 mL) at 0°C was added dropwise a 0.5 M solution of KHMDS in toluene (162.8 mL, 81.4 mmol, 2.1 equiv.). The solution was vigorously stirred at 0°C between 10 and 15 min while becoming gradually dark red, followed by the addition of **(3aR,6aR)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol** (**257)** (6.2 g, 38.8 mmol, 1.0 equiv.) in Et_2O (50 mL). The mixture was stirred between 0°C and 5°C for 12h, turning limpidly bright yellow, before being carefully quenched at 0°C with a saturated solution of NH_4Cl (150 mL). The aqueous phase was extracted by Et_2O (2 x 50 mL). The combined organic solution is washed with brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give a viscous yellow substance. The crude product of **264** (43 g) was involved in the next step without further purification.

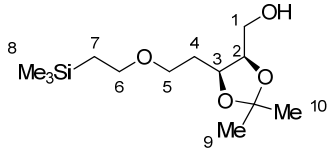


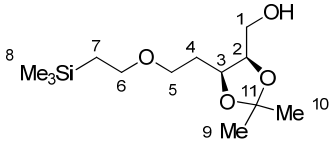
Chemical Formula: $C_{13}H_{28}O_4Si$
Molecular Weight: 276.44 g.mol^{-1}

((4R,5S)-2,2-dimethyl-5-(2-(2-(trimethylsilyl)ethoxy)ethyl)-1,3-dioxolan-4-yl)methanol (265)

The crude product of **264** (43 g) was diluted in dry EtOAc (200 mL) and run through H-cube® at a flow rate of 0.1 mL/min, the temperature was set at 50°C and 50 bar of pressure. The colorless mixture was evaporated under reduced pressure, then purified *via* silica flash chromatography (Cy/EtOAC: 9/1 → 7/1→4/1) to afford **265** (8.9 g, 83% over 2 steps) as a colorless oil.

R_f= 0.58 (Cy/EtOAc: 1/2)



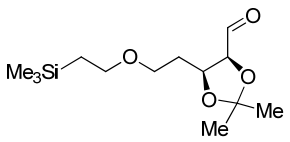


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 0 (s, 9H, H-8), 0.91-0.96 (m, 2H, H-7), 1.35 (s, 3H, H-9 or H-10), 1.43 (s, 3H, H-10 or H-9), 1.86 (dt, J_{H4-H3}= 5.9 Hz, J_{H4-H5}= 2.8 Hz, H-4), 3.44-3.68 (m, 6H, H-1, H-5 and H-6), 4.17 (dt, J_{H3-H4}= 5.9 Hz, J_{H3-H2}= 7.1 Hz, H-3), 4.28 (dt, J_{H2-H3}= J_{H2-H1}= 5.9 Hz, H-2)

^{13}C NMR (100 MHz, CDCl3): δ= -1.34 (C-8), 18.26 (C-7), 25.60 (C-9 or C-10), 28.27 (C-10 or C-9), 29.50 (C-4), 61.69 (C-1), 67.39 (C-5), 68.56 (C-6), 75.20 (C-3), 78.08 (C-2) 107.75 (C-11)

HRMS (ESI+): calcd for $(M-H)^{+}$: 277.1835, found: 277.1843

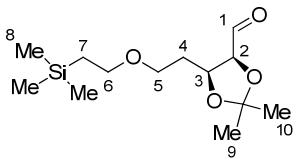


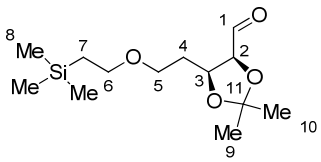
Chemical Formula: $C_{13}H_{26}O_4Si$
Molecular Weight: 274.43 g.mol^{-1}

(4S,5S)-2,2-dimethyl-5-(2-(2-(trimethylsilyl)ethoxy)ethyl)-1,3-dioxolane-4-carbaldehyde (266)

To a stirred solution of **((4R,5S)-2,2-dimethyl-5-(2-(2-(trimethylsilyl)ethoxy)ethyl)-1,3-dioxolan-4-yl)methanol** (**265)** (8.9 g, 32.2 mmol, 1.0 equiv.) in DMSO/DCM (40 mL/80 mL) at RT was added triethylamine (13.4 mL, 96.6 mmol, 3.0 equiv.). The solution was cooled down to -10°C over 15 min before a solution of SO_3.pyr (15.4 g, 96.6 mmol, 3.0 equiv.) in DMSO (40 mL) was added dropwise *via* cannula over a period of 1h. The mixture was stirred between -10°C and -5°C for 3h30 before being warmed up to 0°C and diluted with Et_2O (80 mL) then quenched with a saturated solution of brine (100 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic phase was washed with a solution of $CuSO_4$ (10% w/v, 3 x 100 mL), then with a saturated solution of brine (100 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give a bright yellow oil (9.1 g). The crude product of **266** was involved into the next reaction without further purification.

R_f = 0.61 (Cy/EtOAc: 2/1)

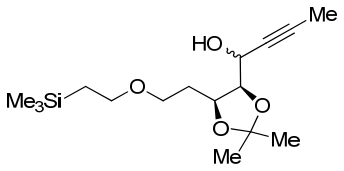




Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 0 (s, 9H, H-8), 0.91-0.96 (m, 2H, H-7), 1.35 (s, 3H, H-9 or H-10), 1.43 (s, 3H, H-10 or H-9), 1.84-1.86 (m, 1H, H-4), 3.44-3.68 (m, 6H, H-5 and H-6), 4.24-4.26 (m, 1H, H-3), 4.45-4.49 (m, 1H, H-2), 9.67 (d, 1H, J= 2.97 Hz, H-1)

^{13}C NMR (100 MHz, CDCl3): δ= -1.34 (C-8), 18.26 (C-7), 25.60 (C-9 or C-10), 28.27 (C-10 or C-9), 29.50 (C-4), 67.39 (C-5), 68.56 (C-6), 75.20 (C-3), 78.08 (C-2) 107.75 (C-11), 202.18 (C-1)

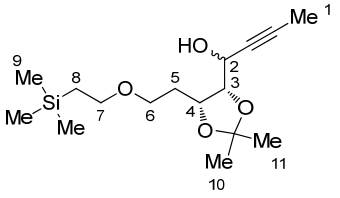


Chemical Formula: $C_{16}H_{30}O_4Si$
Molecular Weight: 314.49 g.mol^{-1}

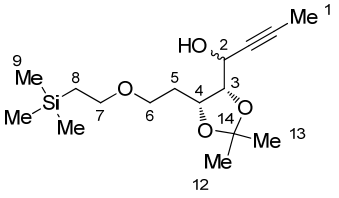
1-((4S,5R)-2,2-dimethyl-5-(2-(2-(trimethylsilyl)ethoxy)ethyl)-1,3-dioxolan-4-yl)but-2-yn-1-ol (267)

The crude product of **(4S,5S)-2,2-dimethyl-5-(2-(2-(trimethylsilyl)ethoxy)ethyl)-1,3-dioxolane-4-carbaldehyde (266)** was diluted in THF (80 mL) at RT then cooled down to -5°C before a 0.5 M solution of prop-1-yn-1-ylmagnesium bromide (96.6 mL, 48.3 mmol, 1.5 equiv.) was added dropwise. The mixture was vigorously stirred between -5°C and 0°C for 3h, then allowed to warm up to 0°C before getting diluted by Et_2O (100 mL) and quenched with a saturated solution of NH_4Cl (100 mL). The aqueous phase was extracted with Et_2O (2 x 30 mL). The combined organic phase was washed with a saturated solution of brine (150 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* silica flash chromatography (Cy/EtOAC: 90/10 → 85/15 → 80/20) to provide a 56/44 diastereomeric mixture of **267** as a colorless oil (9.1 g, 90% over 2 steps).

R_f= 0.46 (Cy/EtOAc: 3/1)



Numbering for the hydrogens

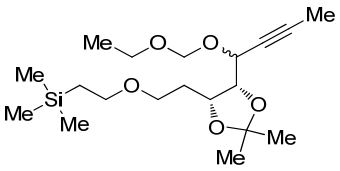


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 0 (s, 9H, H-9), 0.79-0.95 (m, 2H, H-8), 1.36 (s, 3H, H-10 or H-11), 1.47 (s, 3H, H-11 or H-10), 1.87 (d, J= 2 Hz, H-1), 1.93-2.18 (m, 2H, H-5), 3.45-3.62 (m, 5H, H-4, H-6 and H-7), 4.03-4.09 (m, 1H, H-3), 4.28-4.39 (m, 1H, H-2)

^{13}C NMR (100 MHz, CDCl3): δ= -1.29 (C-11), 3.99 (C-1), 18.24 (C10), 25.60 (C-12 or C-13), 27.77 (C-13 or C-12), 29.51 (C-7), 62.19 (C-4), 67.28 (C-8), 68.57 (C-9), 75.67 (C-6), 78.19 (C-2 or C-3), 80.06 (C-5), 82.50 (C-3 or C-2), 108.06 (C-14)

HRMS (ESI+): calcd for $(M-H)^+$: 315.1992, found: 315.1999

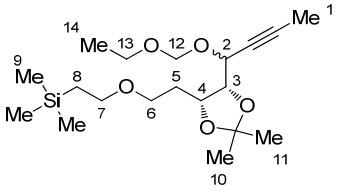


Chemical Formula: $C_{19}H_{36}O_5Si$
Molecular Weight: 372.57 g.mol^{-1}

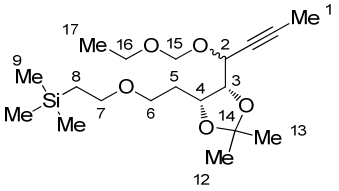
(2-(2-((4R,5R)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)ethyl)trimethylsilane (268)

To a stirred solution at RT of **1-((4S,5R)-2,2-dimethyl-5-(2-(2-(trimethylsilyl)ethoxy)ethyl)-1,3-dioxolan-4-yl)but-2-yn-1-ol (267)** (9.0 g, 28.6 mmol, 1.0 equiv.) in DMF (40 mL) was added TBAI (0.26 mmol, 95.6 mg, 0.01 equiv.), DIPEA (24.9 mL, 143.0 mmol, 5.0 equiv.), respectively. The solution was stirred for 5 min at RT before the dropwise addition of EOMCl (13.3 mL, 143.0 mmol, 5.0 equiv.). The mixture was stirred at RT for 3h and turned orange. The solution was diluted with Et_2O (200 mL) quenched at 0°C with a saturated solution of NH_4Cl (150 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phase was washed with a saturated solution of brine (200 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* silica flash chromatography (Cy/EtOAC: 95/5 → 90/10 → 85/15) to provide **268** as a colorless oil (10.4 g, 98%).

R_f= 0.62 (Cy/EtOAc: 3/1)



Numbering for the hydrogens

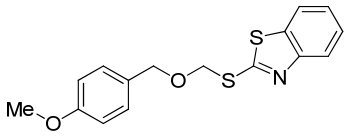


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ=0 (s, 9H, H-9), 0.79-0.95 (m, 2H, H-8), 1.20 (t, 3H, J= 7.1 Hz, H-14), 1.36 (s, 3H, H-10 or H-11), 1.47 (s, 3H, H-11 or H-10), 1.87 (d, J= 2.1 Hz, H-1), 1.93-2.08 (m, 2H, H-5), 3.45-3.76 (m, 5H, H-6, H-7 and H-13), 4.14-4.23 (m, 1H, H-3), 4.29-4.40 (m, 2H, H-2 and H-4), 4.84 (AB, 2H, J= 6.9 Hz, H-12)

^{13}C NMR (100 MHz, CDCl3): δ= -1.28 (C-11), 3.93 (C-1), 15.19 (C-17), 18.27 (C10), 25.51 (C-12 or C-13), 27.49 (C-13 or C-12), 29.79 (C-7), 64.11 (C-4), 65.17 (C-16), 67.48 (C-8), 68.24 (C-9), 74.36 (C-6), 75.19 (C-2 or C-3), 79.11 (C-5), 83.96 (C-3 or C-2), 92.47 (C-15), 108.06 (C-14)

HRMS (ESI+): calcd for $(M-H)^+$: 373.2410, found: 373.2420

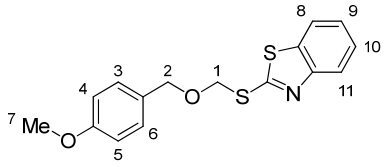


Chemical Formula: $C_{16}H_{15}NO_2S_2$
Molecular Weight: 317.43 g/mol

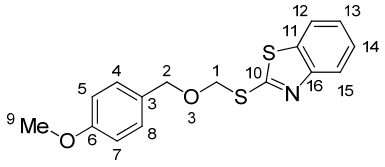
2-((((4-methoxybenzyl)oxy)methyl)thio)benzo[d]thiazole (296)

To a stirred solution of 2-mercaptobenzothiazole (**299**) (378 mg, 2.26 mmol, 1.0 equiv.) in DMF (7 mL) at 0°C was added carefully NaH (60% in mineral oil, 100 mg, 2.49 mmol, 1.1 equiv.). After 10 min stirring at 0°C was added dropwise a solution of 1-((chloromethoxy)methyl)-4-methoxybenzene (465 mg, 2.49 mmol, 1.1 equiv.) in DMF (4 mL). The yellow mixture was stirred between 0°C and RT overnight before being diluted by EtOAc (40 mL), washed by NH_4Cl (30 mL). The aqueous phase was extracted by EtOAc (2 x 20 mL). The combined organic layers were washed by brine (70 mL), dried over $MgSO_4$, filtered then concentrated under reduced pressure. The crude product was subjected to silica gel flash chromatography (Cy/AcOEt: 97/3→95/5→90/10) to afford **296** as a yellow oil (750 mg, 95%).

R_f = 0.44 (Cy/EtOAC: 4/1)



Numbering for the hydrogens

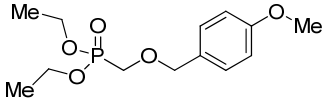


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ = 3.80 (s, 3H, H-7), 4.68 (s, 2H, H-2), 5.43 (s, 2H, H-1), 6.87 (d, 2H, J= 8.7 Hz, H-4 and H-5), 7.28 (d, 2H, J= 8.7 Hz, H-3 and H-6), 7.29-7.34 (m, 2H, H-9 or H-10), 7.41-7.45 (m, 2H, H-10 or H-9), 7.77 (d, 1H, J= 9.2 Hz, H-8), 7.91 (d, 1H, J= 12.4 Hz, H-11)

^{13}C NMR (100 MHz, CDCl3): δ = 55.38 (C-9), 70.57 (C-2), 73.58 (C-1), 114.04 (C-5 and C-7), 121.09 (C-12 and C-15), 124.64 (C-13 or C-14), 126.25 (C-14 or C-13), 130.16 (C-4 and C-8), 130.44 (C-3), 135.77 (C-11), 153.08 (C-16), 157.67 (C-6), 165.27 (C-10)

HRMS (ESI+): calcd for $(M-H)^+$: 317.0544, found 317.0555

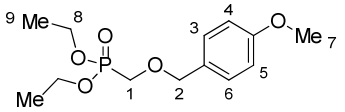


Chemical Formula: $C_{13}H_{21}O_5P$
Molecular Weight: 288.28 g/mol

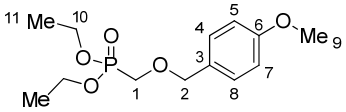
diethyl (((4-methoxybenzyl)oxy)methyl)phosphonate (308)

To a stirred solution of diethyl (hydroxymethyl)phosphonate (**356**) (177 mg, 1.05 mmol, 1.0 equiv.) in cyclohexane/DCM (4 mL/2 mL) at RT was added slowly **4-methoxybenzyl 2,2,2-trichloroacetimidate (174)** (356 mg, 1.26 mmol, 1.2 equiv.) and the mixture was vigorously stirred at RT for 16h. The reaction solution was diluted with DCM (15 mL), quenched with a saturated aqueous solution of Na_2CO_3 (20 mL). The aqueous phase was extracted with DCM (2 x 7 mL). The combined organic solution is washed with brine (20 mL), dried with anhydrous MgSO4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cy/EtOAC: 4/1 →1/4→ EtOAc) to afford **308** (257 mg, 86%) as a yellow oil.

R_f = 0.23 (EtOAc)



Numbering for the hydrogens



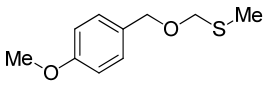
Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.32 (t, 6H, J= 7.1 Hz, H-9), 3.71 (d, 2H, J= 8.7 Hz, H-1), 3.80 (s, 3H, H-7), 4.15 (q, 4H, J= 7.1 Hz, H-8), 4.56 (s, 2H, H-1), 6.86 (d, 2H, J= 8.7 Hz, H-5 and H-6), 7.15 (d, 2H, J= 8.7 Hz, H-4 and H-7)

^{13}C NMR (100 MHz, CDCl3): δ= 16.53 (C-11), 55.38 (C-9), 62.51 (d, J= 7 Hz, C-10), 64.94 (C-10), 74.59 (C-2), 113.95 (C-5 and C-7), 129.01 (C-3), 129.89 (C-4 and C-8), 159.62 (C-6)

^{31}P NMR ($CDCl_3$): δ= 22.44

HRMS (ESI+): calcd for $(M-H)^+$: 289.1205, found: 289.1212

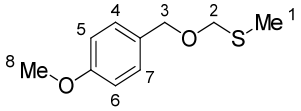


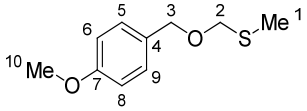
Chemical Formula: $C_{10}H_{14}O_2S$
Molecular Weight: 198.28 g/mol

(((4-methoxybenzyl)oxy)methyl)(methyl)sulfane (287)

To a solution of DMSO/Ac_2O/AcOH (15/12/3: 30 mL/24 mL/6 mL) was added (4-methoxyphenyl)methanol (**286**) (3.53 g, 25.6 mmol) at RT and the mixture was stirred for 17h. The resulting mixture was carefully quenched with $NaHCO_3$ powder until pH= 7. The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic solution is washed with brine (100 mL), dried with anhydrous MgSO4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC: 97/3 → 95/5) to afford **287** (4.4 g, 87%) as a lightly yellow oil.

R_f = 0.64 (Cy/EtOAc: 5/1)



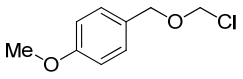


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 2.17 (s, 3H, H-1), 3.81 (s, 3H, H-8), 4.53 (s, 2H, H-2), 4.64 (s, 2H, H-3), 6.86 (d, 2H, J= 8.5 Hz, H-5 and H-6), 7.15 (d, 2H, J= 8.5 Hz, H-4 and H-7)

^{13}C NMR (100 MHz, CDCl3): δ= 13.98 (C-1), 55.38 (C-10), 69.12 (C-2), 74.13 (C-3), 113.96 (C-5 and C-9), 129.59 (C-4), 129.91 (C-6 and C-8), 159.42 (C-7)

HRMS (ESI+): calcd for $(M-H)^{+}$: 199.0793, found: 199.0789

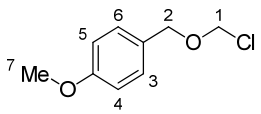


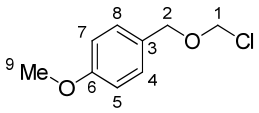
Chemical Formula: $C_9H_{11}ClO_2$
Molecular Weight: 186.63 g/mol

1-((chloromethoxy)methyl)-4-methoxybenzene (288)

To a solution of **(((4-methoxybenzyl)oxy)methyl)(methyl)sulfane (286)** (3.94 g, 17.9 mmol, 1.0 equiv.)in DCM (50 mL) at -78°C was added dropwise a solution of SO_2Cl_2 (1.45 mL, 17.9 mmol, 1.0 equiv.) in DCM (10 mL). The yellow mixture was stirred at this temperature for 1h30. The solvent was totally evaporated at RT and under reduced pressure to provide **288** (3.5 g) as a bright yellow oil which was used in the next steps without further purification.

The analytical date are identical to those from the literature.[3]

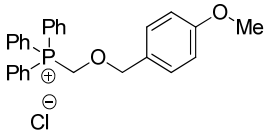




Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 3.81 (s, 3H, H-7), 4.68 (s, 2H, H-2), 5.49 (s, 2H, H-2), 6.86 (d, 2H, J= 8.5 Hz, H-5 and H-6), 7.15 (d, 2H, J= 8.5 Hz, H-4 and H-7)

^{13}C NMR (100 MHz, CDCl3): δ= 55.40 (C-9), 71.04 (C-2), 81.54 (C-1), 114.09 (C-4 and C-8), 127.57 (C-3), 130.34 (C-5 and C-7), 159.88 (C-6)



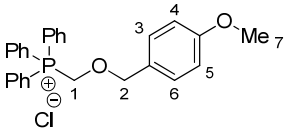
Chemical Formula: $C_{27}H_{26}ClO_2P$
Molecular Weight: 448.92 g/mol

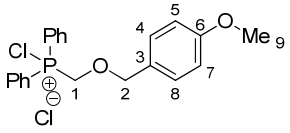
(((4-methoxybenzyl)oxy)methyl)triphenylphosphonium chloride (282)

To a solution of freshly prepared **1-((chloromethoxy)methyl)-4-methoxybenzene (288)** (1.55 g, 8.32 mmol, 1.0 equiv.) in toluene (1.8 g, 5.5 mmol at RT was added PPh_3 (2.18 g, 8.32 mmol,1.0 equiv.). The solution was vigorously stirred between 80°C and 90°C for 24h then allowed to warm up to RT over 1h. The heterogeneous mixture was filtered and the solid residue was washed by ether (3 x 25 mL) then boiling cyclohexane (3 x 20 mL) to afford **282** as a white solid (3.73 g, 80% over two steps).

The analytical data are identical to those from the literature.[4]

mp= 98-100°C





Numbering for the hydrogens *Numbering for the carbons*

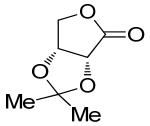
^{1}H NMR (400 MHz, CDCl3): δ= 3.76 (s, 3H, H-7), 4.88 (s, 2H, H-1), 5.86 (bs, 2H, H-2), 6.86 (d, 2H, J= 8.5 Hz, H-3 and H-6), 7.15 (d, 2H, J= 8.5 Hz, H-4 and H-5), 7.60-7.65 (m, 4H, arom), 7.72-7.77 (m, 6H, arom)

^{13}C NMR (100 MHz, CDCl3): δ= 54.51 (C-9), 62.54 (C-2), 75.85 (d, J= 12 Hz, C-1), 113.81 (C-4 and C-8), 116.41 (arom), 117.28 (arom), 127.77 (C-3), 130.16 (C-5 and C-7), 130.28 (arom), 133.88 (arom), 133.98 (arom), 135.37 (arom), 160.22 (C-6)

^{31}P NMR ($CDCl_3$): δ= 19.06

HRMS (ESI+): calcd for $(M-H)^+$: 449.1437, found: 449.1444

5.2.1.3 Third generation strategy: "D-isoascorbic acid approach"



Chemical Formula: $C_6H_{10}O$
Molecular Weight: 98.14 g/mol

(3aR,6aR)-2,2-dimethyldihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (364)

To a vigorously stirred solution of erythorbic acid (**365**) (35.2 g, 0.20 mol, 1.0 equiv.) in distillated water (500 mL) at 0°C was added in small portions anhydrous sodium carbonate (42.4 g, 0.40 mol, 2.0 equiv.). The resulting yellow solution was kept at 0°C while aqueous hydrogen peroxide (31.3 w/v%, 44 mL) was added dropwise over a 10-min period. The solution was stirred between 0°C and 27°C for 15 min then warmed up to 42°C and stirred at this temperature for further 30 min. Darco® activated charcoal (8 g) was added in portions over 10 min to decompose the excess peroxide and the mixture was heated at 100°C for 45 min before being poured through a Celite® pad. The obtained filtrate was carefully acidified by 6 M aqueous hypochloric acid until pH= 1 and concentrated under reduced pressure to give a light

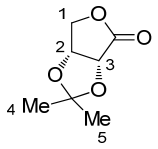
yellow solid. To this residue was added acetone (170 mL) and $MgSO_4$ (50 g) and the mixture was stirred at RT for 5 min before the addition of 2,2-dimethoxypropane (350 mL, 2.70 mol, 14.0 equiv.) and PTSA (0.40 g, 2.0 mmol, 0.01 equiv.). The mixture was stirred at RT for 20h then slowly diluted with a mixture of Et_20 (500 mL) and TEA (61.3 mL, 0.44 mol, 2.2 equiv.) at 0°C. After 15-min of stirring, the suspension was filtered and the filtrate reduced under pressure, giving a pale yellow crude product, which was purified by silica gel chromatography (Cy/EtOAc: 6/1→4/1) to afford **364** (27 g, 85%) as a white solid.

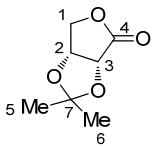
R_f = 0.43 (Cy/EtOAc: 2/1)

The analytical data are identical to the literature.[5]

$[\alpha]_D^{20}$ = -118° (c = 1.0, H_2O)

mp= 65-67 °C



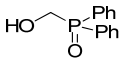


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 1.39 (s, 3H, H-4 or H-5), 1.48 (s, 3H, H-5 or H-4), 4.42 (*AB*X, 2H, J_{AX}= 3.7 Hz, J_{BX}= 11.2 Hz, J_{AB}= 4 Hz, Δν= 7 Hz), 4.74 (d, 1H, J= 5.7 Hz, H-3), 4.87 (AB*X*, 1H, H-2)

^{13}C NMR (100 MHz, CDCl3): δ= 25.73 (C-5 or C-6), 26.86 (C-6 or C-5), 70.29 (C-1), 74.71 (C-2), 75.54 (C-3), 114.15 (C-7), 174.14 (C-4)

HRMS (ESI+): calcd for $(M-H)^+$: 97.0653, found: 97.0660



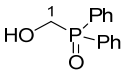
Chemical Formula: $C_{13}H_{13}O_2P$
Molecular Weight: 232.21 g/mol

(hydroxymethyl)diphenylphosphine oxide (330)

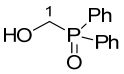
To a stirred solution of chlorodiphenylphosphine (**329**) (12.0 g, 67.0 mmol, 1.0 equiv.) in 37% aqueous HCl (120 mL) was added slowly 37% aqueous formaldehyde (120 mL). The limpid colorless mixture was stirred at 100°C for 20h then allowed to warm up to RT. The solution was carefully neutralised with a saturated solution of $NaHCO_3$ (400 mL) then with Na_2CO_3 until neutral pH. The aqueous phase was extracted with DCM (3 x 100 mL). The combined organic phases were washed with H_2O (3 x 150 mL), a saturated solution of NH_4Cl (200 mL) then with brine (300 mL), dried with anhydrous MgSO4 and concentrated under reduced pressure to give a white viscous solid. To this residue was added boiling EtOAC (100 mL) and the mixture was stirred for 20 min until the inner temperature reached 20°C, then filtered to afford **330** (13 g, 85%) as a white solid.

The analytical date are identical to those from the literature.[6]

mp = 128-130°C



Numbering for the hydrogens



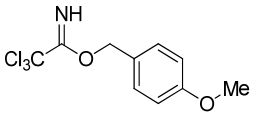
Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.85 (O*H*), 4.41 (bs, 2H, H-1), 7.44-7.56 (m, 6H, arom), 7.73-7.77 (m, 4H, arom)

^{13}C NMR (100 MHz, CDCl3): δ= 61.42 (d, J= 81 Hz, C-1), 128.81 (arom), 128.89 (arom), 130.00 (arom), 130.96 (arom), 131.40 (arom), 131.49 (arom), 132.34 (arom), 132.36 (arom)

^{31}P NMR ($CDCl_3$): δ= 31.58

HRMS (ESI+): calcd for $(M-H)^+$: 202.0993, found: 202.1007

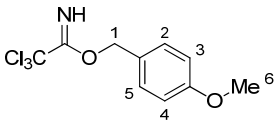


Chemical Formula: $C_{10}H_{10}Cl_3NO_2$
Molecular Weight: 282.55 g/mol

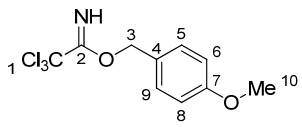
4-methoxybenzyl 2,2,2-trichloroacetimidate (174)

To as stirred solution of (4-methoxyphenyl)methanol (**286**) (8.0 g, 58.2 mmol, 1.0 equiv.) in Et_2O (50 mL) at 0°C was added in small portions NaH (60% in mineral oil, 232 mg, 5.82 mmol, 0.1 equiv.). The mixture was stirred at 0°C for 15 min then cooled down to -10°C. To the solution was added dropwise CCl_3CN (5.83 mL, 58.19 mmol, 1.0 equiv.) and the mixture turned gradually yellow-orange after stirring between -10°C and RT for 3h. The solvent was totally evaporated and to the dark orange viscous residue was added pentane (70 mL). The mixture was stirred at RT for 15 min and the dark brown gluing residue was filtered through a Celite pad, giving a bright yellow filtrate which was concentrated under reduced pressure to provide **174** (16 g, 99%) as a yellow liquid.

The analytical data are identical to the literature.[7]



Numbering for the hydrogens

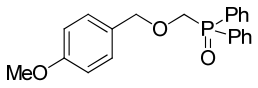


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 3.81 (s, 3H, H-6), 5.27 (s, 2H, H-1), 6.90 (d, 2H, J= 8.9 Hz, H-3 and H-4), 7.37 (d, 2H, J= 8.9 Hz, H-2 and H-5), 8.35 (bs, 1H, N*H*)

^{13}C NMR (100 MHz, CDCl3): δ= 55.37 (C-10), 70.80 (C-3), 91.58 (C-1), 114.00 (C-5 and C-7), 127.58 (C-9), 129.83 (C-4 and C-8), 159.79 (C-6), 162.69 (C-2)

HRMS (ESI+): calcd for $(M-H)^{+}$: 281.9855, found: 281.9845



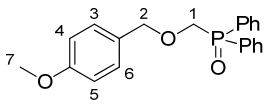
Chemical Formula: $C_{21}H_{21}O_3P$
Molecular Weight: 352.36 g/mol

(((4-methoxybenzyl)oxy)methyl)diphenylphosphine oxide (331)

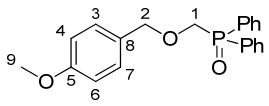
To a stirred suspension of (hydroxymethyl)diphenylphosphine oxide (**330**) (1.1 g, 4.61 mmol, 1 equiv.) in a mixture of cyclohexane/ CH_2Cl_2 (2/1 : 8 mL/4 mL) at room temperature was added in once portion 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.56 g, 5.53 mmol, 1.2 equiv.). The clear mixture was cooled down to 0°C prior to the addition of triflic acid (0.04 mL, 0.46 mmol, 0.1 equiv.). After a few minutes, a white precipitate appeared. The suspension was stirred at 0°C for 3h and warmed to room temperature. The precipitate was filtered, washed with 4mL of CH_2Cl_2 and the filtrate washed with saturated aqueous Na_2CO_3 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers was washed with brine (20 mL), dried with anhydrous MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cy/EtOAC : 4/1 → 2/1→1/4→ EtOAc) to afford **331** (1.2 g, 85% yield) as a white solid.

R_f = 0.45 (EtOAc)

mp = 87-90°C



Numbering for the hydrogens



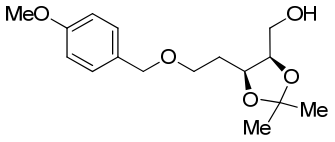
Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 3.79 (s, 3H, H-7), 4.18 (d, 2H, J_{P-H1}= 6.6 Hz, H-1), 4.53 (s, 2H, H-2), 6.82 (d, 2H, J=8.70 Hz, H-4 and H-5), 7.11 (d, 2H, J= 8.70 Hz, H-3 and H-6), 7.43-7.48 (m, 4H, Ph), 7.51-7.57 (m, 2H, Ph), 7.75-7.80 (m, 4H, Ph).

^{13}C NMR (100 MHz, CDCl3): δ= 55.07 (C9), 67.52 (d, $J_{P\text{-}C1}$= 88.2 Hz, C-1), 75.21 (C2), 113.89 (C4 and C6), 128.52 (Ph), 128.63 (Ph), 129.90 (C5 and C7), 130.83 (C8), 131.56 (Ph), 131.65 (Ph), 131.83 (Ph), 132.18 (Ph), 159.57 (C5)

^{31}P NMR ($CDCl_3$): δ=28.57

HRMS (ESI+): calcd for $(M\text{-}H)^+$: 353.1306, found: 353.1343



Chemical Formula: $C_{16}H_{24}O_5$
Molecular Weight: 296.36 g/mol

((4R,5S)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (369)

To a stirred solution of DIPA (2.85 mL, 20.19 mmol, 1.1 equiv.) in THF (5mL) at -78°C was added dropwise a 1.6 M solution of BuLi in hexanes (13.2 mL, 21.11 mmol, 1.15 equiv.). The reaction mixture was vigorously stirred at -78°C over 1h, followed by dropwise addition of **(((4-methoxybenzyl)oxy)methyl)diphenylphosphine oxide (331)** (8.41 g, 23.86 mmol, 1.3 equiv.) in THF (15 mL). The gradually dark orange reaction mixture was stirred at the same temperature for 1.5 h. A solution of **(3aR,6aR)-2,2-dimethyldihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (364)** (2.9 g, 18.35 mmol, 1 equiv.) in THF (10 mL) was added dropwise at -78°C and the mixture was stirred between -78°C and -60°C over a period of 3h, then allowed to warmed up to 0°C until TLC indicated consumption of starting material (20 min). The reaction mixture was diluted with Et_2O (70 mL) and carefully quenched with $NaHCO_3$ (50 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layer was washed with brine (150 mL), dried over $MgSO_4$, concentrated under reduced pressure to afford the crude product of **367** as a yellow gum which was first dried over night under vacuum then used directly in the next step.

To a carefully stirred solution of **367** in Et_2O (150 mL) at 0 °C was added dropwise a solution of $NaBH_4$ (1.48 g, 39.18 mmol, 2 equiv.) in EtOH (150mL) over a period of 20 minutes. The resulting mixture was vigorously stirred at room temperature over night then carefully quenched with *glacial acetic acid (6.7 mL, 3 equiv.) at 0°C, followed by a filtration upon Celite pad. Ethanol was totally evaporated under reduced pressure. The resulting viscous mixture was diluted with*Et_2O (150 mL), washed with aqueous saturated Na_2CO_3 (100 mL) and extracted with Et_2O (2 x 50 mL). The combined organic layer was washed with brine (150 mL), dried with $MgSO_4$, concentrated under reduced pressure. The resulting colorless gum was then dried under vacuum to provide **368** as a white solid which was then used in the following step without purification.

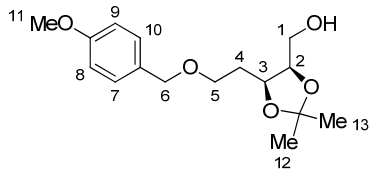
To a stirred solution of **368** in DMF (20 mL) at 0°C was added carefully in small portions NaH (60% in mineral oil, 1.03 g, 2 equiv.). When the exothermic evolution stopped, the resulting mixture was vigorously stirred from 0°C to room temperature over night. The reaction mixture was carefully quenched with $NaHCO_3$ (200 mL) at 0°C then extracted with Et_2O (3 x 100 mL).

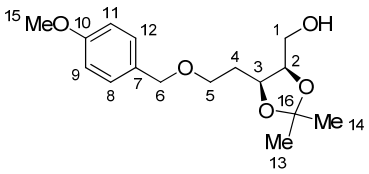
The combined organic layer was washed with brine (250 mL), dried with $MgSO_4$, concentrated under reduced pressure, providing **309** The resulting yellow gum was directly used in the next step without further purification.

A solution of **309** in ethyl acetated **(**1g/10mL) was subjected to H-Cube® through a 10% Pt/C Cartridge with a 1.5 mL/min flow rate at 50°C and 50 bar. The resulting crude product was purified by flash chromatography (Cy/EtOAC: 3/1→2/1→1/1) to afford **369** as a colorless oil (4.5g, 80%)

R_f = 0.36 (Cy/EtOAC: 2/1)

$[\alpha]_D^{20}$ = + 4.8° (c = 0.25, $CDCl_3$)



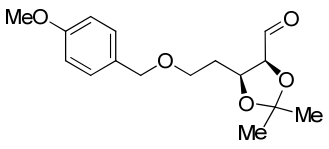


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3H, H-12 or H-13), 1.43 (s, 3H, H-13 or 12), 1.82-1.88 (m, 2H, H-4), 3.64-3.50 (m, 4H, H-1 and H-5), 3.79 (s, 3H, H-11), 4.12-4.16 (m, 1H, H-3), 4.26 to 4.31 (m, 1H, H-2), 4.43 (s, 2H, H-6), 6.74 (d, 2H, J= 8.5 Hz, H-8 and H-9), 6.89 (d, 2H, J= 8.5 Hz, H-7 and H-10)

^{13}C NMR (400 MHz, $CDCl_3$) : δ = 25.60 (C-13 or C-14), 28.91 (C-14 or C-13), 55.35 (C-15), 61.73 (C-1), 67.16 (C-5), 73.15 (C-6), 74.70 (C-2), 78.00 (C-3), 107.93 (C-16), 113.90 (C-9and C-11), 129.15 (C-8 and C-12), 130.16 (C-7), 159.32 (C-10)

HRMS (ESI+): calcd for $(M-H)^+$: 297.1702, found: 297.1723



Chemical Formula: $C_{16}H_{22}O_5$

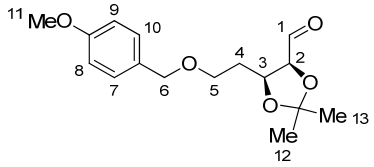
Molecular Weight: 294.34 g/mol

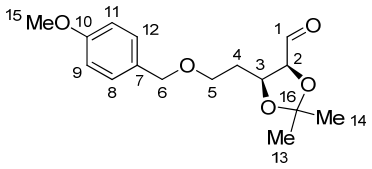
(4S,5S)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (370)

To a stirred solution of **((4R,5S)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (369)** (303 mg, 1.02 mmol, 1 equiv.) in a mixture of freshly distilled DMSO/DCM (1/2 : 3 mL/6 mL) at -10°C was added slowly $(iPr)_2NEt$ (0.53 mL, 3.07 mmol, 3 equiv.). After 10

min at -10°C, a solution of SO_3·pyr (489 mg, 3.07 mmol, 3 equiv.) in DMSO (3 mL) was added dropwise per cannula to the solution. The resulting mixture was vigorously stirred at -10°C for 2h, warmed to 0°C and stirred at this temperature until TLC indicated consumption of starting material (20 min). The reaction mixture was diluted with Et_2O (15 mL) and quenched with brine (15mL). The organic layer was washed with 10% aqueous $CuSO_4$ (3 x 20 mL) then thoroughly with distilled water (2 x 20 mL) and brine (20 mL). The solution was dried over MgSO4 and concentrated under reduced pressure. The crude product of **370** was a yellow oil which was subjected to the next step without further purification.

R_f = 0.62(Cy/EtOAC : 2/1)

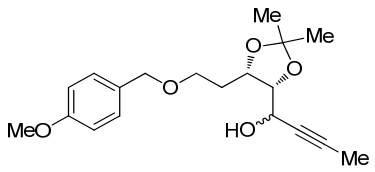




Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3H, H-12 or H-13), 1.43 (s, 3H, H-13 or 12), 1.82-1.88 (m, 2H, H-4), 3.64-3.54 (m, 4H and H-5), 3.79 (s, 3H, H-11), 4.27-4.29 (m, 1H, H-3), 4.48 to 4.52 (m, 1H, H-2), 4.43 (s, 2H, H-6), 6.74 (d, 2H, J= 8.5 Hz, H-8 and H-9), 6.89 (d, 2H, J= 8.5 Hz, H-7 and H-10), 9.67 (d, 1H, J= 2.98 Hz, H-1)

^{13}C NMR (400 MHz, $CDCl_3$): δ = 25.60 (C-13 or C-14), 28.91 (C-14 or C-13), 55.35 (C-15), 66.43 (C-5), 72.76 (C-6), 75.61 (C-3), 81.88 (C-2), 107.93 (C-16), 113.90 (C-9and C-11), 129.15 (C-8 and C-12), 130.16 (C-7), 159.32 (C-10), 202.20 (C-1)



Chemical Formula: $C_{19}H_{26}O_5$

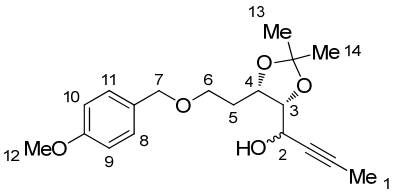
Molecular Weight: 334.41 g/mol

1-((4S,5R)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (371)

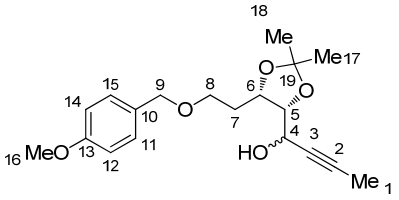
To a stirred solution of **4S,5S)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (370)** (597 mg, 2,02 mmol, 1 equiv.) in THF (4mL) at 0°C was added dropwise a 0.5 M solution of prop-1-yn-1-ylmagnesium bromide (4.0 mL, 2.02 mmol, 1 equiv.). The reaction mixture was vigorously stirred at 0°C for 2h then at room temperature until TLC indicated consumption of starting material (30 min). The reaction mixture was diluted with Et_2O (10 mL), quenched with saturated aqueous $NaHCO_3$ (10mL). The aqueous layer was extracted with Et_2O (2 x 7 mL). The combined organic solution was washed with brine (15 mL),

dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cyclohexane/EtOAc : 3/1 → 2/1) to afford **371** as a yellow oil (285 mg, 95% over 2 steps).

R_f = 0.4(Cy/EtOAC : 2/1)



Numbering for the hydrogens

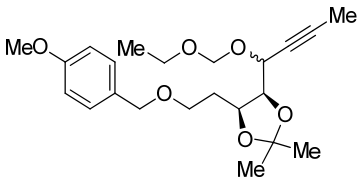


Numbering for the carbons

^{1}H NMR (400 MHz, $CDCl_3$): (*Major isomer*)δ = 1.36 (s, 3H, H-13 or H-14), 1.47 (s, 3H, H-14 or 13), 1.86 (s, J= 2.3 Hz, 3H, H-1), 1.87-2.18 (m, 2H, H-5), 3.53-3.567 (m, 3H, H-2 and H-6), 3.79 (s, 3H, H-12), 4.03-4.08 (m, 1H, H-3), 4.30 to 4.37 (m, 1H, H-4), 4.45 (s, 2H, H-7), 6.87 (d, 2H, J= 8.7 Hz, H-9 and H-10), 7.31 (d, 2H, = 8.7 Hz, H-8 and H-11)

^{13}C NMR (400 MHz, $CDCl_3$): (*Major isomer*)δ = 3.84 (C-1), 25.49 (C-17 or C-18), 27.54 (C-18 or C-17), 29.44 (C-7), 55.35 (C-16), 62.40 (C-6), 67.29 (C-8), 72.75 (C-9), 75.13 (C-3 or C-2), 78.19 (C-4), 79.97 (C-5), 82.74 (C-2 or C-3), 108.22 (C-19), 113.91 (C-12 and C-14), 129.30 (C-11 and C-15), 130.17 (C-10), 159.32 (C-13)

HRMS (ESI+): calcd for $(M-H)^+$: 335.1858, found: 335.1896



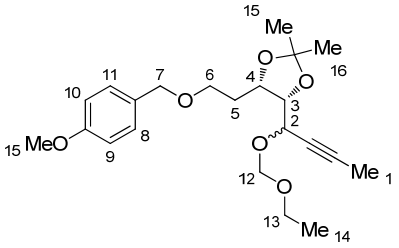
Chemical Formula: $C_{22}H_{32}O_6$

Molecular Weight: 392.49 g/mol

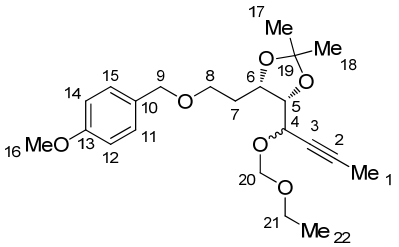
(4R,5R)-4-(1-(ethoxymethoxy)but-2-yn-1-yl)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolane (372)

To a stirred solution of **1-((4S,5R)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (371)** (574 mg, 1.72 mmol, 1 equiv.) and TBAI (63.5 mg, 0.17 mmol, 0.1 equiv.) in anhydrous DMF (4mL) at room temperature was added in one portion $(i\text{Pr})_2\text{NEt}$ (2.36 mL, 13.8 mmol, 8 equiv.) followed by dropwise addition of (chloromethoxy)ethane (1.23 mL, 13.8 mmol, 8 equiv.). The reaction mixture was vigorously stirred at room temperature over night then diluted with Et_2O (10 mL), quenched with saturated aqueous NH_4Cl(10mL). The aqueous layer was extracted with Et_2O (2 x 7 mL). The combined organic solution was washed with brine (15 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cyclohexane/EtOAc : 9/1→7/1) to afford **372** as a yellow oil (654 mg, 97%).

R_f = 0.47(Cy/EtOAC : 3/1)



Numbering for the hydrogens

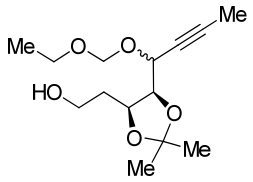


Numbering for the carbons

^{1}H NMR (400 MHz, $CDCl_3$): (*Major isomer*)δ = 1.18 (t, J= 7.1 Hz, 3H, H-14), 1.35 (s, 3H, H-16 or H-17), 1.56 (s, 3H, H-17 or H-16), 1.86 (d, J = 2.1 Hz, 3H, H-1), 1.97-2.07 (m, 2H, H-5), 3.48-3.75 (m, 5H, H-2, H-6 and H-13), 3.79 (s, 3H, H-15), 4.11-4.15 (m, 1H, H-3), 4.32-4.39 (m, 1H, H-4), 4.44 (s, 2H, H-7), 4.84 (AB, J_{AB} = 6.9 Hz, Δv= 120 Hz, 2H, H-12), 6.86 (d, J= 8.5 Hz, 2H, H-8 and H-11), 7.23 (d, J= 8.5 Hz, 2H, H-9 and H-10)

^{13}C NMR (400 MHz, $CDCl_3$) : (*Major isomer*) δ = 3.93 (C-1), 15.17 (C-22), 25.49 (C-17 or C-18), 27.47 (C-18 or C-17), 29.70 (C-7), 55.37 (C-16), 64.08 (C-21), 67.37 (C-8), 72.84 (C-9), 74.70 (C-4), 75.09 (C-3 or C-2), 79.07 (C-5), 83.96 (C-2 or C-3), 92.45 (C-20), 108.47 (C-19), 113.84 (C-12 and C-14), 129.30 (C-11 and C-15), 130.63 (C-10), 159.24 (C-13)

HRMS (ESI+): calcd for $(M-H)^+$: 393.2277, found: 393.2275



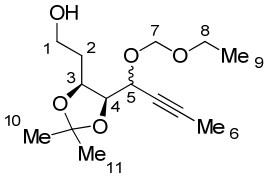
Chemical Formula: $C_{14}H_{24}O_5$

Molecular Weight: 272.16 g/mol

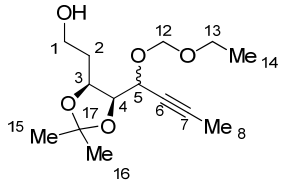
2-((4R,5R)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (252)

To a stirred solution of **(4R,5R)-4-(1-(ethoxymethoxy)but-2-yn-1-yl)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolane (372)** (335 mg, 0.883 mmol, 1 equiv.) in CH_2C_2 /H_2O (9 mL/0.5mL) at 0°C was added in one portion DDQ (240 mL, 1.058 mmol, 1.2 equiv.). The yellow- orange colour of the reaction changed into dark brown after 10 minutes. The reaction mixture was vigorously stirred at 0°C for 2h then at room temperature until TLC indicated consumption of starting material (30 min). A solution of aqueous $NaHCO_3$ (10mL) was added and the resulting mixture was stirred at room temperature for 10 minutes then extracted with DCM (2 x 7 mL). The combined organic solution was washed with brine (20 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cyclohexane/EtOAc: 3/1→1/1) to afford **252** as a colorless oil (236 mg, 98%).

R_f = 0.14 (Cy/EtOAC : 2/1)



Numbering for the hydrogens

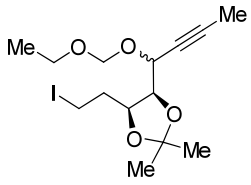


Numbering for the carbons

^{1}H NMR (400 MHz, $CDCl_3$): (*Major isomer*)δ = 1.21 (t, J= 7.1 Hz, 3H, H-9), 1.43 (s, 3H, H-10 or H-11), 1.47 (s, 3H, H-11 or H-10), 1.86 (d, J = 2.29 Hz, 3H, H-6), 1.97-2.07 (m, 2H, H-2), 3.50-3.75 (m, 2H, H-8), 3.81-3.89 (m, 2H, H-5 and H-4), 4.18-4.22 (m, 1H, H-3), 4.45-4.85 (m, 1H H-1), 4.84 (AB, J_{AB} = 6.9 Hz, Δv= 120 Hz, 2H, H-7)

^{13}C NMR (400 MHz, $CDCl_3$): (*Major isomer*)δ = 3.86 (C-8), 15.14 (C-14), 25.52 (C-9 or C-10), 27.55 (C-10 or C-9), 31.55 (C-2), 61.33 (C-3), 64.29 (C-13), 65.87 (C-5), 75.00 (C-6 or C-7), 76.52 (C-1), 79.04 (C-4), 84.10 (C-7 or C-6), 92.47 (C-12), 108.75 (C-11)

HRMS (ESI+): calcd for $(M-H)^+$: 273.1702, found: 273.1818



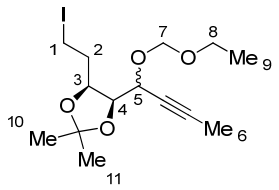
Chemical Formula: $C_{14}H_{23}IO_4$

Molecular Weight: 382.23 g/mol

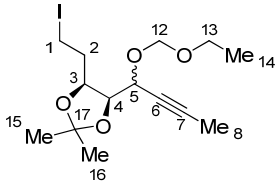
(4*R*,5*R*)-4-(1-(ethoxymethoxy)but-2-yn-1-yl)-5-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane (253)

To a stirred solution of **(4R,5R)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (252)** (77 mg, 0.29 mmol, 1 equiv.), PPh_3 (113 mg, 0.43 mmol,1.5 equiv.) and imidazole (29 mg, 0.43 mmol, 1.5 equiv.) in THF (5 mL) at 0°C was added I_2 (108 mg, 0.67 mmol, 1.5 equiv.) in one portion. The brown-yellow reaction mixture was vigorously stirred at 0°C until until TLC indicated consumption of starting material (2h). The reaction mixture was warmed to room temperature then diluted with Et_2O (10mL) quenched with aqueous saturated $Na_2S_2O_5$ (15 mL). The aqueous layer was extracted with Et_2O (2 x 10mL) and the combined organic layer was washed with brine (20 mL). The crude product was subjected to silica gel flash chromatography (Cyclohexane/AcOEt: 97/3→95/5→90/10) to afford **253** as a colorless oil (100 mg, 91%)

R_f = 0.8 (Cy/EtOAC : 2/1



Numbering for the hydrogens



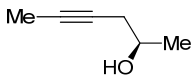
Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): (*Major isomer*)δ = 1.21 (t, J= 7.10 Hz, 3H, H-9), 1.43 (s, 3H, H-10 or H-11), 1.47 (s, 3H, H-11 or H-10), 1.87 (d, J = 2.3 Hz, 3H, H-6), 2.13-2.27 (m, 2H, H-2), 3.20-3.42 (m, 2H, H-1), 3.50-3.75 (m, 2H, H-8), 4.18-4.22 (m, 1H, H-3), 4.23-4.33 (m, 1H, H-4), 4.34-4.38 (m, 1H, H-5), 4.84 (AB, J_{AB} = 7 Hz, Δν= 120 Hz, 2H, H-6)

^{13}C NMR (100 MHz, CDCl3): (*Major isomer*) δ = 3.25 (C-1), 3.75 (C-8), 15.14 (C-14), 25.52 (C-9 or C-10), 27.55 (C-10 or C-9), 33.45 (C-2), 63.47 (C-13), 65.08 (C-5), 66.04 (C-3), 75.00 (C-6 or C-7), 79.04 (C-4), 84.11 (C-7 or C-6), 92.49 (C-12), 108.76 (C-11)

HRMS (ESI+): calcd for $(M-H)^+$: 383.0719, found 383.0733

5.2.2 Pre*para*tion of the propargylic alcohol fragment



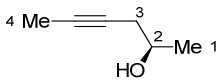
Chemical Formula: $C_6H_{10}O$
Molecular Weight: 98.14 g/mol

***(R)*-hex-4-yn-2-ol (389)**

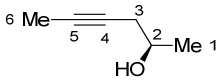
To a stirred solution of 1-bromopropene (**388**) (3.00 mL, 24.8 mmol, 1.5 equiv.) in THF (18 mL) at -78°C was added dropwise a 2.5 M solution of BuLi in hexanes (19.8 mL, 49.6 mmol, 3.0 equiv.). The colorless, limpid mixture was vigorously stirred between -78°C and -35°C for 2h before the addition of HMPA (7 mL) at -25 and the white opaque mixture was stirred for 20 min at this temperature. Afterwards, a solution of *(S)*-2-methyloxirane (1.16 mL, 16.5 mmol, 1.0 equiv.) in HMPA (7 mL) was added dropwise at -25°C and the mixture was stirred for 2h at this temperature before being allowed to warm up to 0°C overnight. The yellow opaque solution was first diluted at 0°C with Et_2O (30 mL) then quenched with a saturated solution of NH_4Cl (50 mL). The aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic solution is washed with brine (50 mL), dried with anhydrous MgSO4 and concentrated under reduced pressure (500 mbar, 0°C) as the alcohol was quite volatile. The crude product was purified by silica gel chromatography (Pentane/Et_2O: 9/1 → 6/1) to afford **389** (1.2 g, 80% yield) as a colorless oil.

R_f = 0.43 (Cy/EtOAc: 2/1)

$[\alpha]_D^{20}$ = +21.5° (c = 1.1, $CDCl_3$)



Numbering for the hydrogens

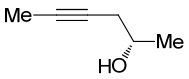


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.23 (d, 3H, J= 6.2 Hz, H-1), 1.80 (t, 3H, J= 2.5 Hz, H-4), 2.19-2.27 (m, 1H, H-3A), 2.31-2.38 (m, 1H, H-3B), 3.85-3.93 (m, 1H, H-2)

^{13}C NMR (100 MHz, CDCl3): δ= 3.56 (C-1), 22.28 (C-4), 29.73 (C-3), 66.61 (C-2), 75.44 (C-5), 78.41 (C-4)

HRMS (ESI+): calcd for $(M-H)^+$: 99.0810, found: 99.0998



Chemical Formula: $C_6H_{10}O$
Molecular Weight: 98.14 g/mol

***(S)*-hex-4-yn-2-ol (232)**

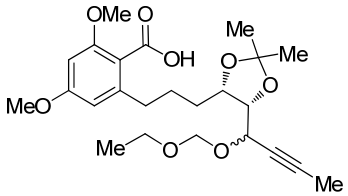
$[\alpha]_D^{20}$ = -20.7° (c = 1.0, $CDCl_3$)

^{1}H NMR (400 MHz, CDCl3): δ= 1.23 (d, 3H, J= 6.2 Hz, H-1), 1.80 (t, 3H, J= 2.5 Hz, H-4), 2.19-2.27 (m, 1H, H-3A), 2.31-2.38 (m, 1H, H-3B), 3.85-3.93 (m, 1H, H-2)

^{13}C NMR (100 MHz, CDCl3): δ= 3.56 (C-1), 22.28 (C-4), 29.73 (C-3), 66.61 (C-2), 75.44 (C-5), 78.41 (C-4)

HRMS (ESI+): calcd for $(M-H)^+$: 99.0810, found: 99.0827

5.2.3 Assembly of the three fragments



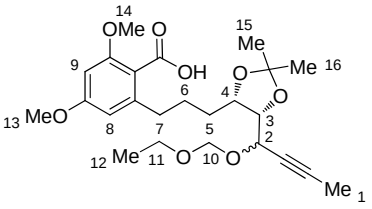
Chemical Formula: $C_{24}H_{34}O_8$
Molecular Weight: 450.52 g/mol

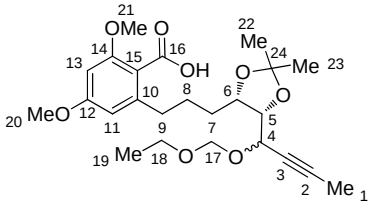
2-(3-((4S,5R)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-4,6-dimethoxybenzoic acid (452)

To a solution of 2,4-dimethoxybenzoic acid (**401**) (0.6 g, 3.40 mmol, 1.0 equiv.) in THF (50 mL) at -78°C was added dropwise a 1.4 M solution of *s*BuLi in hexanes (5.1 mL, 7.14 mmol, 2.1

equiv.). The initially colorless solution gradually turned orange then dark red after 2h between -78°C and -60°C before being warmed up to -20°C. To the clear red solution at -20°C was added dropwise a solution of **(4R,5R)-4-(1-(ethoxymethoxy)but-2-yn-1-yl)-5-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane (253)** (1.3 g, 3.40 mmol, 1.0 equiv.) in 30 mL of THF. The solution's color lightened at the end of the addition and was stirred for the next 15 min at -20°C before allowed to warm up to 0°C in 20 min and stirred for 6h at 0°C, then from 0°C to RT overnight. The bright yellow solution was quenched with a saturated solution of NH_4Cl (70 mL) at 0°C, the first organic phase was extracted with Et_2O (50 mL). The obtained aqueous phase was acidified with a solution of HCl (10% w/v) until pH = 1-2, then extracted once again with Et_2O (30 mL) and EtOAc (2 x 30 mL). The combined organic phases were washed by a saturated solution of $NaHCO_3$ (100 mL) then brine (150 mL), dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC/AcOH: 80/20/1 → 60/40/1) to afford **452** (1.3 g, 83% yield) as a colorless oil.

R_f = 0.57 (Cy/EtOAC/AcOH: 10/10/0.05)



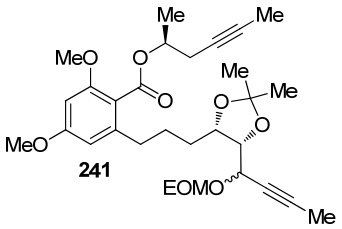


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, $CDCl_3$) : (*Major isomer*)δ = 1.20 (t, J= 7.1 Hz, 3H, H-12), 1.33 (s, 3H, H-15 or H-16), 1.49 (s, 3H, H-16 or H-15), 1.74-1.89 (m, 2H, H-6), 1.85 (d, J = 2.3 Hz, 3H, H-1), 2.79-2.95 (m, 2H, H-7), 3.52-3.78 (m, 2H, H-10), 3.82 (s, 3H, H-14), 3.89 (s, 3H, H-13), 4.12-4.27 (m, 2H, H-3 and H-4), 4.31-4.37 (m, 1H, H-2), 4.84 (AB, J_{AB} = 6.9 Hz, Δv= 120 Hz, 2H, H-11), 6.35 (s, 2H, H-8 or H-9), 6.43 (s, 2H, H-9 or H-8)

^{13}C NMR (400 MHz, $CDCl_3$): (*Major isomer*)δ = 3.93 (C-1), 15.12 (C-19), 25.46 (C-22 or C-23), 26.98 (C-23 or C-22), 28.91 (C-8), 30.23 (C-7), 34.76 (C-9), 55.51 (C-20 or C-21), 56.52 (C-21 or C-20), 64.23 (C-18), 66.13 (C-5 or C-6), 76.83 (C-2 or C-3), 79.11 (C-6 or C-5), 83.93 (C-3 or C-2), 92.38 (C-17), 96.63 (C-11 or 13), 107.65 (C-13 or 11), 108.72 (C-24), 146.35 (C-10), 159.14 (C-12), 162.17 (C-15), 169.17 (C-16)

HRMS (ESI+): calcd for $(M-H)^-$: 449.2175, found 449.2182



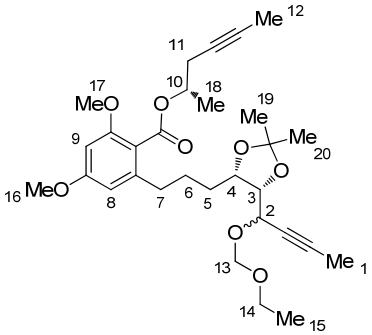
241

Chemical Formula: $C_{30}H_{42}O_8$
Molecular Weight: 530.65 g/mol

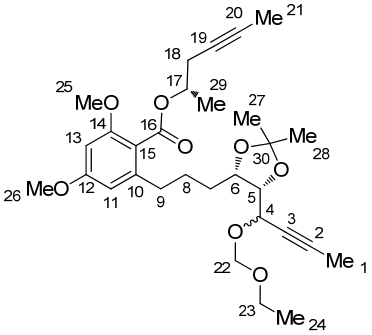
_(S)_-hex-4-yn-2-yl 2-(3-((4S,5S)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-4,6-dimethoxybenzoate (241)

To a solution of **2-(3-((4S,5R)-5-(1-(ethoxymethoxy)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-4,6-dimethoxybenzoic acid (452)** (1.70 g, 3.77 mmol, 1.0 equiv.) in THF (25 mL) were added respectively triphenylphosphine (1.97 g, 7.55 mmol, 2.0 equiv.) and **_(R)_-hex-4-yn-2-ol (488)** (0.55 g, 5.65 mmol, 1.5 equiv.) at 0°C. The solution was stirred for 5 min at 0°C before the addition of DIAD (1.67 g, 8.29 mmol, 2.2 equiv.). The colorless solution turned yellow-orange after 10 min at 0°C then stirred at RT overnight. The solvent was completely evaporated and the crude product purified by silica gel flash chromatography (Cy/EtOAC: 98/2 → 97/3→ 90/10) to afford **241** (1.74 g, 87% yield) as a light yellow oil.

R_f = 0.57 (Cy/EtOAC : 5/1)



Numbering for the hydrogens



Numbering for the carbons

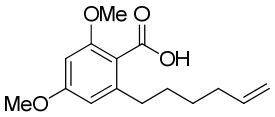
^{1}H NMR (400 MHz, $CDCl_3$): (*Major isomer*)δ = 1.20 (t, J= 7.10 Hz, 3H, H-16), 1.33 (s, 3H, H-18 or H-19), 1.41 (d, 3H, J= 6.2 Hz, H-20), 1.49 (s, 3H, H-19 or H-18), 1.51-1.75 (m, 4H, H-5 and H-6), 1.77 (s, 3H, H-12), 1.85 (d, J = 2.29 Hz, 3H, H-1), 2.53-2.67 (m, 2H, H-7 and H-11), 3.46-3.63 (m, 2H, H-14), 3.76 (s, 3H, H-18 or H-19), 3.78 (s, 3H, H-19 or H-18), 4.11-4.18 (m, 2H, H-3 and H-4), 4.28-4.32 (m, 1H, H-2), 4.67 (dd, *A*BX, J_{AB} = 6.87 Hz, J_{AX} = 1.37 Hz, 1H, H-7), 4.99 (dd, *A*BX, J_{AB} = 6.87 Hz, J_{AX} = 1.37 Hz, 1H, H-7), 5.19 (m, 1H, H-10), 6.29 (d, J= Hz, 2H, H-8 or H-9), 6.32 (d, J= Hz, 2H, H-9 or H-8)

^{13}C NMR (400 MHz, $CDCl_3$): (*Major isomer*)δ = 3.59 (C-21), 3.87 (C-1), 15.17 (C-24), 19.20 (C-29), 21.79 (C-27 or C-28), 25.45 (C-28 or C-27), 28.91 (C-8), 30.23 (C-22), 33.44 (C-9), 33.61 (C-18), 55.43 (C-25 or C-26), 55.92 (C-26 or C-25), 64.10 (C-23), 65.91 (C-4), 70.14 (C-17), 77.29 (C-5 or C-6), 77.44 (C-19 or C-20), 79.81 (C-2 or C-3), 79.81 (C-6 or C-5), 83.93 (C-3 or C-2), 84.01 (C-20 or 19), 92.41 (C-22), 96.34 (C-11 or 13), 105.83 (C-13 or 11), 108.39 (C-30), 142.16 (C-10), 158.10 (C-14), 161.74 (C-12), 167.67 (C-16)

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{30}H_{43}O_8$: 531.2957, found 531.2943

5.3 Synthesis of other RALs

5.3.1 Synthesis of *(R)*-(+)-lasiodiplodin (10)

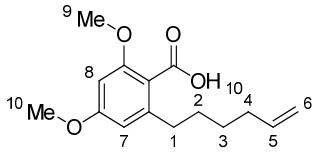


Chemical Formula: $C_{15}H_{20}O_4$
Molecular Weight: 264.32 g.mol^{-1}

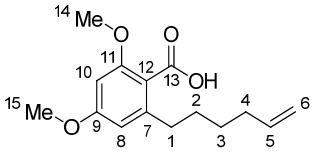
2-(hex-5-en-1-yl)-4,6-dimethoxybenzoic acid (602)

To a solution of 2,4-dimethoxybenzoic acid **401** (3.0 g, 15.30 mmol, 1.0 equiv.) in THF (70 mL) at -78°C was added dropwise a 1.4 M solution of *s*BuLi in hexanes (22.9 mL, 32.11 mmol, 2.1 equiv.). The initially colorless solution gradually turned orange then dark red after 2h between -78°C and -60°C before being warmed up to -20°C. To the clear red solution at -20°C was added dropwise a solution of **6-bromopent-1-ene (454)** (2.28 g, 15.30 mmol, 1.0 equiv.). The solution's color lightened at the end of the addition and was stirred for the next 15 min at -20°C before allowed to warm up to 0°C in 20 min and stirred for 6h at 0°C, then from 0°C to RT overnight. The bright yellow solution was quenched with a saturated solution of NH_4Cl (70 mL) at 0°C, the first organic phase was extracted with Et_2O (50 mL). The obtained aqueous phase was acidified with a solution of HCl (10% w/v) until pH = 1-2, then extracted once again with Et_2O (30 mL) and EtOAc (2 x 30 mL). The combined organic phases were washed by a saturated solution of $NaHCO_3$ (100 mL) then brine (150 mL), dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC/AcOH: 80/20/1 → 60/40/1) to afford **602** (6.3 g, 83% yield) as a colorless oil.

R_f = 0.61 (Cy/EtOAC/AcOH: 10/10/0.05)



Numbering for the hydrogens

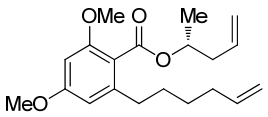


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.41-1.49 (m, 2H, H-3), 1.58-1.66 (m, 2H, H-2), 2.07 (td, 2H, J= 7.5 Hz, J= 7.1 Hz, H-4), 2.80 (t, 2H, J= 7.7 Hz, H-1), 3.82 (s, 3H, H-9), 3.88 (s, 3H, H-10), 4.95 (*AB*X, 2H, J_{AX}= 17.0 Hz, J_{BX}= 10.3 Hz, J_{AB}= 2.0 Hz, Δν= 26 Hz, H-6), 5.74-5.84 (AB*X*, 1H, H-5), 6.39 (AB, 2H, J_{AB}= 2.4 Hz, Δν= 10 Hz, H-9 and H-10)

^{13}C NMR (100 MHz, CDCl3): δ= 28.82 (C-3), 30.91 (C-2), 33.61 (C-4), 34.34 (C-1), 55.44 (C-15), 56.55 (C-14), 96.37 (C-10), 106.98 (C-8), 114.17 (C-12), 114.51 (C-6), 138.88 (C-5), 145.24 (C-7), 158.90 (C-11), 162.04 (C-9), 172.47 (C-13)

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{15}H_{21}O_4$: 265.1439; found: 265.1433.



Chemical Formula: $C_{20}H_{28}O_4$
Molecular Weight: 332.43 g.mol^{-1}

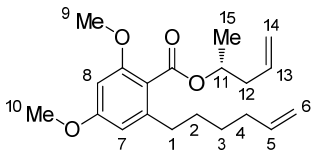
***(R)*-pent-4-en-2-yl 2-(hex-5-en-1-yl)-4,6-dimethoxybenzoate (601)**

To a solution of **2-(6-(ethoxymethoxy)oct-7-en-1-yl)-4,6-dimethoxybenzoic acid (602)** (3.3 g, 12.48 mmol, 1.0 equiv.) in THF (50 mL) were added respectively triphenylphosphine (6.55 g, 25.0 mmol, 2.0 equiv.) and *(S)*-pent-4-en-2-ol (**488**) (1.61 g, 18.73 mmol, 1.5 equiv.) at 0°C. The solution was stirred for 5 min at 0°C before the addition of DIAD (5.55 g, 27.47 mmol, 2.2 equiv.). The colorless solution turned yellow-orange after 10 min at 0°C then stirred at RT overnight. The solvent was completely evaporated and the crude product purified by silica gel flash chromatography (Cy/EtOAC: 98/2 → 97/3→ 90/10) to afford **601** (3.7 g, 90% yield) as a light yellow oil.

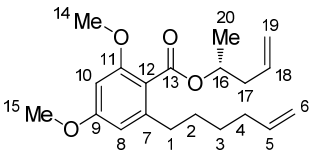
R_f = 0.52 (Cy/EtOAC: 5/1)

$[\alpha]_D^{20}$= - 0.88° (c = 1.13, $CHCl_3$)

$[\alpha]_D^{20}$= - 18.7(c= 1.0, acetone)



Numbering for the hydrogens

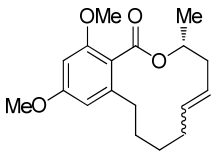


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ = 1.32 (d, 3H, J= 6.2 Hz, H-15), 1.38-1.45 (m, 2H, H-3), 1.55-1.63 (m, 2H, H-2), 2.07 (td, 2H, J= 7.5 Hz, J= 7.1 Hz, H-4), 2.31-2.38 (m, 1H, H-12A), 2.43-2.50 (m, 1H, H-12B), 2.56 (t, J= 7.3 Hz, H-1), 3.77 (s, 3H, H-9), 3.79 (s, 3H, H-10), 4.95 (*AB*X, 2H, J_{AX}= 17.0 Hz, J_{BX}= 10.3 Hz, J_{AB}= 2.0 Hz, Δν= 26 Hz, H-6), 5.21 (tq, 1H, J= 6.2 Hz, J= 6.4 Hz, H-11), 5.75-5.89 (AB*X*, 1H, H-5 and H-13), 6.30 (AB, 2H, J_{AB}= 2.2 Hz, Δν= 3.8 Hz, H-9 and H-10)

^{13}C NMR (100 MHz, CDCl3): δ= 19.58 (C-20), 28.91 (C-3), 29.05 (C-3 or C-4 or C-5), 30.87 (C-2), 33.73 (C-1 and C-4), 40.30 (C-17), 55.39 (C-15), 55.80 (C-14), 71.02 (C-16), 96.24 (C-10), 105.81 (C-8), 114.55 (C-6), 117.00 (C-12), 117.66 (C-19), 133.96 (C-18), 133.81 (C-5), 142.48 (C-7), 157.98 (C-11), 161.30 (C-9), 167.97 (C-13)

HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{20}H_{28}NaO_4$: 355.1880; found: 355.1871.

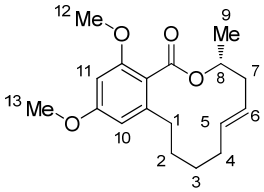


Chemical Formula: $C_{18}H_{24}O_4$
Molecular Weight: 304.38 g.mol^{-1}

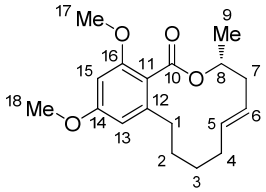
(*R*,E)-12,14-dimethoxy-3-methyl-3,4,7,8,9,10-hexahydro-1H-benzo[c][1]oxacyclododecin-1-one (600)

To a solution of ***(R)*-pent-4-en-2-yl 2-(hex-5-en-1-yl)-4,6-dimethoxybenzoate (601)** (0.92 g, 2.77 mmol, 1.0 equiv.) in degassed dry toluene (250 mL) at RT was added the 2nd Grubbs' catalyst (117.8 mg, 0.14 mmol, 0.05 equiv.). The colorless solution became orange then brown after 4h at 80°C then allowed to cool down to 40°C. Another portion of catalyst (117.8 mg, 0.14 mmol, 0.05 equiv.) was added at this temperature and the solution stirred at 80°C overnight. The reaction was cooled to RT before the filtration on a Celite® pad to se*para*te the residual solid and washed with toluene (15 mL). The solvent was completely evaporated and the crude product purified by silica gel flash chromatography (Cy/EtOAC: 97/3→ 90/10) to afford a E/Z ≈ 2/1 mixture **600** as a colorless solid in 55% yield. The E/Z mixture was not se*para*ted and the following analyses are noted for only one isomer.

R_f = 0.45 (Cy/EtOAC: 3/1)



Numbering for the hydrogens

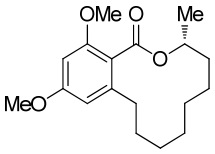


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.13-1.48 (m, 2H, H-3), 1.36 (d, 2H, J= 6.2 Hz, H-11), 1.60-1.67 (m, 2H, H-2), 1.83-1.91 (m, 2H, H-4), 2.28-2.32 (m, 2H, H-7), 2.51-2.63 (m, 2H, H-1), 3.77 (s, 3H, H-13 or H-12), 3.79 (s, 3H, H-12 or H-13), 5.39-5.43 (m, 2H, H-5 and H-6), 6.30 (d, J= 2.1 Hz, H-11 or H-10), 6.32 (d, J= 2.1 Hz, H-10 or H-11)

^{13}C NMR (100 MHz, CDCl3): δ= 20.63 (C-9), 25.61 (C-3), 30.46 (C-2), 30.62 (C-1), 31.65 (C-4), 41.05 (C-7), 55.45 (C-18), 55.90 (C-17), 70.07 (C-8), 96.17 (C-15), 105.89 (C-13), 117.26 (C-11), 127.86 (C-6), 132.38 (C-5), 142.96 (C-12), 157.48 (C-16), 161.13 (C-14), 168.45 (C-10)

MS: m/z $[M + H]^+$ calcd for $C_{18}H_{25}O_4$: 305.1752; found: 305.1671.



Chemical Formula: $C_{18}H_{26}O_4$
Molecular Weight: 306.40 g.mol^{-1}

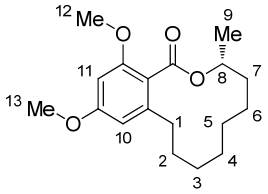
***(R)*-12,14-dimethoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclododecin-1-one (529)**

To a solution of **(R,E)-12,14-dimethoxy-3-methyl-3,4,7,8,9,10-hexahydro-1H-benzo[c][1] oxacyclododecin-1-one (600)** (0.77 g, 2.53 mmol, 1.0 equiv.) in degassed dry EtOAc (180 mL) was added $PtO_2.H_2O$ (51.2 mg, 0.25 mmol, 0.1 equiv.). The solution was continuously submitted to a bubbling source of hydrogen overnight at RT. The residual solid was filtrated through a Celite® pad and washed with EtOAc (20 mL) and the obtained filtrate evaporated under reduced pressure. The resulting mixture was purified by silica gel flash chromatography (Cy/EtOAC: 97/3→ 90/10) to afford afford **529** (0.70 g, 90%) as a colorless oil.

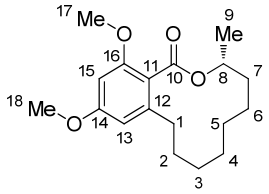
R_f = 0.71 (Cy/EtOAC: 3/1)

The analytical data are identical to those from the literature.[8]

$[\alpha]_D^{20}$+7.13° (c = 1.0, $CHCl_3$)



Numbering for the hydrogens

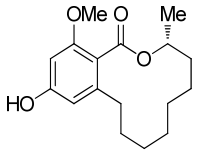


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.22-1.27 (m, 2H, H-6), 1.32 (d, 3H, J= 6.2 Hz, H-9), 1.35-1.57 (m, 6H, H-3, H-4 and H-5), 1.59-1.70 (m, 4H, H-2 and H-7), 2.56-2.42 (m, 1H, H-1A), 2.61-2.71 (m, 1H, H-1B), 3.75 (s, 3H, H-13 or H-12), 3.79 (s, 3H, H-12 or H-13), 5.21-5.31 (m, 1H, H-8), 6.30 (d, J= 2.1 Hz, H-11 or H-10), 6.32 (d, J= 2.1 Hz, H-10 or H-11)

^{13}C NMR (100 MHz, CDCl3): δ= 19.54 (C-9), 21.21 (C-6), 24.29 (C-4), 25.49 (C-3), 26.57 (C-5), 30.26 (C-2), 30.62 (C-1), 32.39 (C-7), 55.36 (C-18), 55.90 (C-17), 70.07 (C-8), 96.17 (C-15), 105.89 (C-13), 117.26 (C-11), 127.86 (C-6), 132.38 (C-5), 142.96 (C-12), 157.48 (C-16), 161.13 (C-14), 168.45 (C-10)

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{18}H_{27}O_4$: 307.1904; found: 307.1911.



Chemical Formula: $C_{17}H_{24}O_4$
Molecular Weight: 292.37 g.mol^{-1}

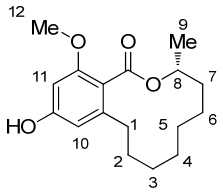
***(R)*-12-hydroxy-14-methoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclododecin-1-one (10) = (*R*)-lasiodiplodin (10)**

To a stirred suspension of NaH (60% in mineral oil, 0.63 g, 15.70 mmol, 15.0 equiv.) in THF (30 mL) at 0°C was added dropwise ethanethiol (0.98 g, 15.70 mmol, 15.0 equiv.). The biphasic mixture was warmed up to RT and stirred for 20 min until turning into a clear colorless solution. To the obtained solution was added dropwise a solution of ***(R)*-12,14-dimethoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclodode cin-1-one (529)** (0.32 g, 1.05 mmol, 1.0 equiv.) in HMPA (4 mL). The mixture was vigorously stirred at 70°C overnight. The dark red solution was carefully neutralised at 0°C with an aqueous solution of 10% w/v HCl until pH= 6-7 and became dark yellow. The aqueous layer was extracted with Et_2O (30 mL) and dichloromethane (2 x 30 mL). The combined organic layers were washed with a saturated solution of NH_4Cl (70 mL) then with brine (100 mL), dried with anhydrous MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cy/EtOAC : 9/1 → 7/1→ 4/1) to afford **10** (0.11 g, 35% yield) as a white solid.

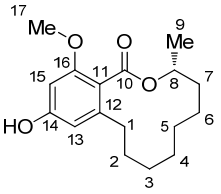
R_f = 0.27 (Cy/EtOAC: 3/1)

The analytical data are identical to those from the literature.[9]

$[\alpha]_D^{20}$ = +9.0° (c = 0.5, MeOH)



Numbering for the hydrogens



Numbering for the carbons

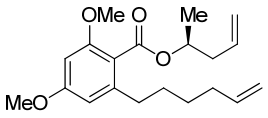
^{1}H NMR (400 MHz, CDCl3): δ= 1.22-1.27 (m, 2H, H-6), 1.32 (d, 3H, J= 6.2 Hz, H-9), 1.35-1.57 (m, 6H, H-3, H-4 and H-5), 1.59-1.70 (m, 4H, H-2 and H-7), 2.53-2.64 (m, 2H, H-1), 3.77 (s, 3H, H-13 or H-12), 3.79 (s, 3H, H-12 or H-13), 5.39-5.43 (m, 1H, H-8), 6.30 (d, J= 2.1 Hz, H-11 or H-10), 6.32 (d, J= 2.1 Hz, H-10 or H-11)

^{13}C NMR (100 MHz, CDCl3): δ= 19.54 (C-9), 21.21 (C-6), 24.29 (C-4), 25.49 (C-3), 26.57 (C-5), 30.26 (C-2), 30.62 (C-1), 32.39 (C-7), 55.90 (C-17), 70.07 (C-8), 96.17 (C-15), 105.89 (C-13), 117.26 (C-11), 127.86 (C-6), 132.38 (C-5), 142.96 (C-12), 157.48 (C-16), 161.13 (C-14), 168.45 (C-10)

MS (LC-MS): m/z $[M + H]^+$ calcd for $C_{17}H_{25}O_4$: 293.1753; found: 293.1991.

5.3.2 Synthesis of *(S)*-lasiodiplodin (545)

As the procedures for the synthesis of (*S*)-lasiodiplodin (**545**) are identical to those described in the *para*graph 5.3.1, only the experimental data of the intermediates are presented in this section.

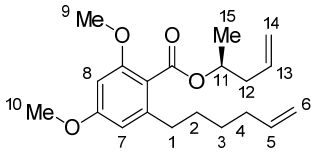


Chemical Formula: $C_{20}H_{28}O_4$
Molecular Weight: 332.43 g.mol^{-1}

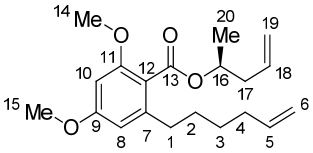
_(S)_-pent-4-en-2-yl 2-(hex-5-en-1-yl)-4,6-dimethoxybenzoate (603)

R_f = 0.52 (Cy/EtOAC: 5/1)

$[\alpha]_D^{20}$ + 0.90° (c = 1.0, $CHCl_3$)



Numbering for the hydrogens

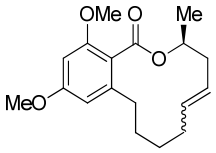


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ = 1.32 (d, 3H, J= 6.2 Hz, H-15), 1.38-1.45 (m, 2H, H-3), 1.55-1.63 (m, 2H, H-2), 2.07 (td, 2H, J= 7.5 Hz, J= 7.1 Hz, H-4), 2.31-2.38 (m, 1H, H-12A), 2.43-2.50 (m, 1H, H-12B), 2.56 (t, J= 7.3 Hz, H-1), 3.77 (s, 3H, H-9), 3.79 (s, 3H, H-10), 4.95 (*AB*X, 2H, J_{AX}= 17.0 Hz, J_{BX}= 10.3 Hz, J_{AB}= 2.0 Hz, Δν= 26 Hz, H-6), 5.21 (tq, 1H, J= 6.2 Hz, J= 6.4 Hz, H-11), 5.75-5.89 (AB*X*, 1H, H-5 and H-13), 6.30 (AB, 2H, J_{AB}= 2.2 Hz, Δν= 3.8 Hz, H-9 and H-10)

^{13}C NMR (100 MHz, CDCl3): δ= 19.58 (C-20), 28.91 (C-3), 29.05 (C-3 or C-4 or C-5), 30.87 (C-2), 33.73 (C-1 and C-4), 40.30 (C-17), 55.39 (C-15), 55.80 (C-14), 71.02 (C-16), 96.24 (C-10), 105.81 (C-8), 114.55 (C-6), 117.00 (C-12), 117.66 (C-19), 133.96 (C-18), 133.81 (C-5), 142.48 (C-7), 157.98 (C-11), 161.30 (C-9), 167.97 (C-13)

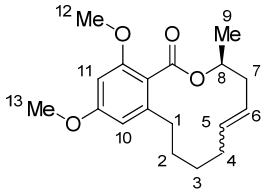
HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{20}H_{28}NaO_4$: 355.1880; found: 355.1969

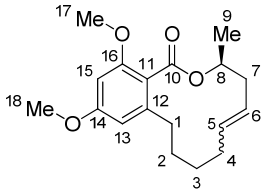


Chemical Formula: $C_{18}H_{24}O_4$
Molecular Weight: 304.38 g.mol^{-1}

(*S*,*E*)-12,14-dimethoxy-3-methyl-3,4,7,8,9,10-hexahydro-1H-benzo[c][1]oxacyclododecin-1-one (604)

R_f = 0.45 (Cy/EtOAC: 3/1)
E/Z : 2/1



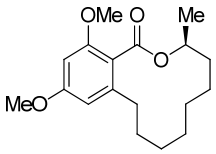


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 1.13-1.48 (m, 2H, H-3), 1.36 (d, 2H, J= 6.2 Hz, H-11), 1.60-1.67 (m, 2H, H-2), 1.83-1.91 (m, 2H, H-4), 2.28-2.32 (m, 2H, H-7), 2.51-2.63 (m, 2H, H-1), 3.77 (s, 3H, H-13 or H-12), 3.79 (s, 3H, H-12 or H-13), 5.39-5.43 (m, 2H, H-5 and H-6), 6.30 (d, J= 2.1 Hz, H-11 or H-10), 6.32 (d, J= 2.1 Hz, H-10 or H-11)

^{13}C NMR (100 MHz, CDCl3): δ= 20.63 (C-9), 25.61 (C-3), 30.46 (C-2), 30.62 (C-1), 31.65 (C-4), 41.05 (C-7), 55.45 (C-18), 55.90 (C-17), 70.07 (C-8), 96.17 (C-15), 105.89 (C-13), 117.26 (C-11), 127.86 (C-6), 132.38 (C-5), 142.96 (C-12), 157.48 (C-16), 161.13 (C-14), 168.45 (C-10)

MS (LC-MS): m/z $[M + H]^+$ calcd for $C_{18}H_{25}O_4$: 305.1752; found: 305.1713

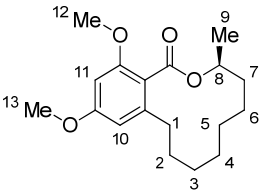


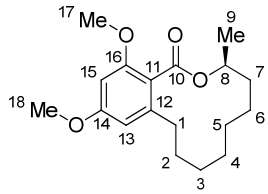
Chemical Formula: $C_{18}H_{26}O_4$
Molecular Weight: 306.40 g.mol^{-1}

***(S)*-12,14-dimethoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclododecin-1-one (605)**

R_f = 0.71 (Cy/EtOAC: 3/1)

$[\alpha]_D^{20}$= - 6.87° (c = 1.2, $CHCl_3$)





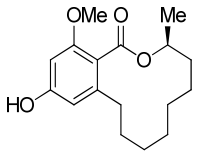
Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 1.22-1.27 (m, 2H, H-6), 1.32 (d, 3H, J= 6.2 Hz, H-9), 1.35-1.57 (m, 6H, H-3, H-4 and H-5), 1.59-1.70 (m, 4H, H-2 and H-7), 2.56-2.42 (m, 1H, H-1A), 2.61-2.71 (m,

1H, H-1B), 3.75 (s, 3H, H-13 or H-12), 3.79 (s, 3H, H-12 or H-13), 5.21-5.31 (m, 1H, H-8), 6.30 (d, J= 2.1 Hz, H-11 or H-10), 6.32 (d, J= 2.1 Hz, H-10 or H-11)

^{13}C NMR (100 MHz, CDCl3): δ= 19.54 (C-9), 21.21 (C-6), 24.29 (C-4), 25.49 (C-3), 26.57 (C-5), 30.26 (C-2), 30.62 (C-1), 32.39 (C-7), 55.36 (C-18), 55.90 (C-17), 70.07 (C-8), 96.17 (C-15), 105.89 (C-13), 117.26 (C-11), 127.86 (C-6), 132.38 (C-5), 142.96 (C-12), 157.48 (C-16), 161.13 (C-14), 168.45 (C-10)

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{18}H_{27}O_4$: 307.1904; found: 307.1979

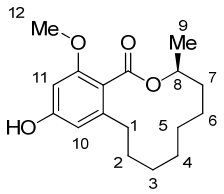


Chemical Formula: $C_{17}H_{24}O_4$
Molecular Weight: 292.37 g.mol^{-1}

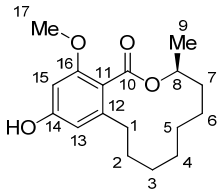
(*S*)-12-hydroxy-14-methoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclododecin-1-one (545) = (*S*)-lasiodiplodin (545)

R_f = 0.27 (Cy/EtOAC: 3/1)

$[\alpha]_D^{20}$ = - 8.6° (c = 0.7, MeOH)



Numbering for the hydrogens



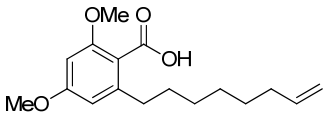
Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.22-1.27 (m, 2H, H-6), 1.32 (d, 3H, J= 6.2 Hz, H-9), 1.35-1.57 (m, 6H, H-3, H-4 and H-5), 1.59-1.70 (m, 4H, H-2 and H-7), 2.53-2.64 (m, 2H, H-1), 3.77 (s, 3H, H-13 or H-12), 3.79 (s, 3H, H-12 or H-13), 5.39-5.43 (m, 1H, H-8), 6.30 (d, J= 2.1 Hz, H-11 or H-10), 6.32 (d, J= 2.1 Hz, H-10 or H-11)

^{13}C NMR (100 MHz, CDCl3): δ= 19.54 (C-9), 21.21 (C-6), 24.29 (C-4), 25.49 (C-3), 26.57 (C-5), 30.26 (C-2), 30.62 (C-1), 32.39 (C-7), 55.90 (C-17), 70.07 (C-8), 96.17 (C-15), 105.89 (C-13), 117.26 (C-11), 127.86 (C-6), 132.38 (C-5), 142.96 (C-12), 157.48 (C-16), 161.13 (C-14), 168.45 (C-10)

MS: m/z $[M + H]^+$ calcd for $C_{17}H_{25}O_4$: 293.1753; found: 293.1762

5.3.3 Synthesis of neolasiodiplodin (606)

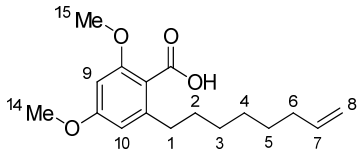


Chemical Formula: $C_{17}H_{24}O_4$
Molecular Weight: 292.37 g.mol^{-1}

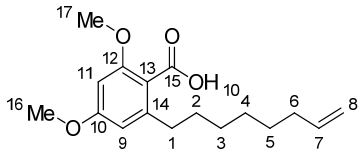
2,4-dimethoxy-6-(oct-7-en-1-yl)benzoic acid (609)

To a solution of 2,4-dimethoxybenzoic acid (**401**) (3.0 g, 15.30 mmol, 1.0 equiv.) in THF (70 mL) at -78°C was added dropwise a 1.4 M solution of *s*BuLi in hexanes (22.9 mL, 32.11 mmol, 2.1 equiv.). The initially colorless solution gradually turned orange then dark red after 2h between -78°C and -60°C before being warmed up to -20°C. To the clear red solution at -20°C was added dropwise a solution of 7-bromopent-1-ene (**603**) (2.71 g, 15.30 mmol, 1.0 equiv.). The solution's color lightened at the end of the addition and was stirred for the next 15 min at -20°C before allowed to warm up to 0°C in 20 min and stirred for 6h at 0°C, then from 0°C to RT overnight. The bright yellow solution was quenched with a saturated solution of NH_4Cl (70 mL) at 0°C, the first organic phase was extracted with Et_2O (50 mL). The obtained aqueous phase was acidified with a solution of HCl (10% w/v) until pH = 1-2, then extracted once again with Et_2O (30 mL) and EtOAc (2 x 30 mL). The combined organic phases were washed by a saturated solution of $NaHCO_3$ (100 mL) then brine (150 mL), dried over anhydrous MgSO4,filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC/AcOH: 80/20/1 → 60/40/1) to afford **609** (3.7 g, 83% yield) as a light yellow solid.

R_f = 0.27 (Cy/EtOAC/AcOH: 7/14/0.05)



Numbering for the hydrogens

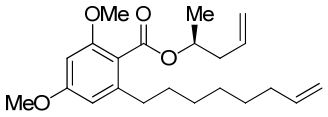


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.28-1.43 (m, 6H, H-3, H-4 and H-5), 1.55-1.64 (m, 2H, H-2), 2.00-2.50 (m, 2H, H-6), 2.88 (t, 2H, J= 7.8 Hz, H-1), 3.84 (s, 3H, H-12 or H-11), 3.93 (s, 3H, H-11 or H-12), 4.95 (*AB*X, 2H, J_{AX}= 16.9 Hz, J_{BX}= 10.1 Hz, J_{AB}= 2.0 Hz, Δν= 26 Hz, H-8), 5.74-5.85 (AB*X*, 1H, H-7), 6.39 (AB, 2H, J_{AB}= 2.3 Hz, Δν= 21 Hz, H-9 and H-10)

^{13}C NMR (100 MHz, CDCl3): δ= 28.94 (C-3 or C-4 or C-5), 29.02 (C-3 or C-4 or C-5), 29.56 (C-3 or C-4 or C-5), 31.46 (C-2), 33.86 (C-6), 34.76 (C-1), 55.49 (C-17), 56.38 (C-16), 96.43 (C-11), 107.34 (C-9), 113.58 (C-14), 114.24 (C-8), 139.26 (C-7), 146.41 (C-14), 159.02 (C-12), 162.10 (C-10), 170.90 (C-15)

MS (ESI+): m/z $[M + H]^+$ calcd for $C_{17}H_{25}O_4$: 293.175285; found: 293,1671.



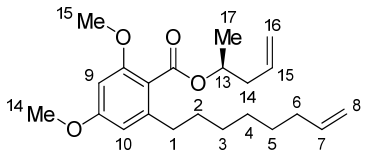
Chemical Formula: $C_{22}H_{32}O_4$
Molecular Weight: 360.49 $g.mol^{-1}$

***(S)*-pent-4-en-2-yl 2,4-dimethoxy-6-(oct-7-en-1-yl)benzoate (608)**

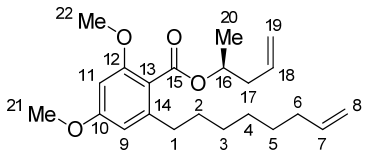
To a solution of **2,4-dimethoxy-6-(oct-7-en-1-yl)benzoic acid (609)** (3.3 g, 11.29 mmol, 1.0 equiv.) in THF (50 mL) were added respectively triphenylphosphine (5.92 g, 22.57 mmol, 2.0 equiv.) and *(R)*-pent-4-en-2-ol (**41**) (1.46 g, 16.93 mmol, 1.5 equiv.) at 0°C. The solution was stirred for 5 min at 0°C before the addition of DIAD (5.02 g, 24.84 mmol, 2.2 equiv.). The colorless solution turned yellow-orange after 10 min at 0°C then stirred at RT overnight. The solvent was completely evaporated and the crude product purified by silica gel flash chromatography (Cy/EtOAC: 98/2 → 95/5→ 90/10→ 85/15) to afford **608** (3.7 g, 90% yield) as a light yellow oil.

R_f = 0.54 (Cy/EtOAC: 3/1)

$[\alpha]_D^{20}$ = -1.3° (c = 1.0, $CHCl_3$)



Numbering for the hydrogens

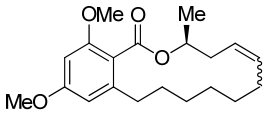


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.27-1.42 (m, 6H, H-3, H-4 and H-5), 1.32 (d, 3H, J= 6.2 Hz, H-17), 1.53-1.60 (m, 2H, H-2), 2.02 (dt, 2H, J= 6.6 Hz, J= 7.6 Hz, H-6), 2.31-2.38 (m, 1H, H-14A), 2.43-2.49 (m, 1H, H-14B), 2.55 (t, 2H, J= 7.1 Hz, H-1), 3.77 (s, 3H, H-14 or H-15), 3.79 (s, 3H, H-15 or H-14),), 4.95 (*AB*X, 2H, J_{AX}= 16.9 Hz, J_{BX}= 10.1 Hz, J_{AB}= 2.0 Hz, Δν= 26 Hz, H-8), 5.07-5.16 (m, 2H, H-16), 5.74-5.88 (m, 2H, H-15 and H-7), 6.30 (AB, J= 2.1 Hz, Δν= 5 Hz, H-9 and H-10)

^{13}C NMR (100 MHz, CDCl3): δ= 19.58 (C-20), 28.91 (C-3 or C-4 or C-5), 29.05 (C-3 or C-4 or C-5), 29.54 (C-3 or C-4 or C-5), 31.37 (C-2), 33.84 (C-6), 33.89 (C-1), 40.31 (C-17), 55.41 (C-22), 55.81 (C-21), 71.02 (C-16), 96.22 (C-11), 105.78 (C-9), 114.28 (C-8), 117.01 (C-13), 117.67 (C-19), 133.97 (C-18), 139.16 (C-7), 142.66 (C-14), 157.95 (C-12), 161.28 (C-10), 168.00 (C-15)

HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{22}H_{32}NaO_4$: 383.2198; found: 382.2190.

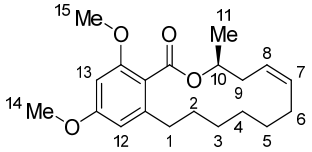


Chemical Formula: $C_{20}H_{28}O_4$
Molecular Weight: 332.43 g.mol^{-1}

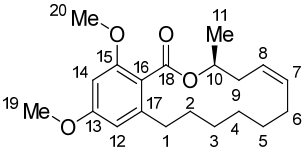
(S,Z)-14,16-dimethoxy-3-methyl-3,4,7,8,9,10,11,12-octahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (607)

To a solution of ***(S)*-pent-4-en-2-yl 2,4-dimethoxy-6-(oct-7-en-1-yl)benzoate (608)** (1.0 g, 2.77 mmol, 1.0 equiv.) in degassed dry toluene (230 mL) at RT was added the 2nd Grubbs' catalyst (117.8 mg, 0.14 mmol, 0.05 equiv.). The colorless solution became orange then brown after 4h at 80°C then allowed to cool down to 40°C. Another portion of catalyst (117.8 mg, 0.14 mmol, 0.05 equiv.) was added at this temperature and the solution stirred at 80°C overnight. The reaction was cooled to RT before the filtration on a Celite® pad to se*para*te the residual solid and washed with toluene (15 mL). The filtrate was evaporated under reduced pressure and purified by silica gel flash chromatography (Cy/EtOAC: 90/10 → 85/15) to afford a E/Z : 2.5/1 mixture of **607** (0.75 g, 81%) as a colorless oil. The following NMR spectrum analysis is described for the major isomer.

R_f = 0.76 (Cy/EtOAC: 4/1)



Numbering for the hydrogens

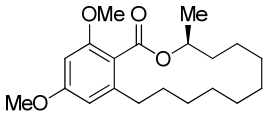


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.13-1.48 (m, 6H, H-3, H-4 and H-5), 1.36 (d, 2H, J= 6.2 Hz, H-11), 1.60-1.67 (m, 2H, H-2), 1.83-1.91 (m, 1H, H-6A), 2.06-2.13 (m, 1H, H-6B), 2.28-2.32 (m, 2H, H-9), 2.53-2.64 (m, 2H, H-1), 3.77 (s, 3H, H-14 or H-15), 3.79 (s, 3H, H-15 or H-14), 5.12-5.20 (m, 1H, H-10), 5.39-5.43 (m, 2H, H-7 and H-8), 6.32 (AB, J= 2.2 Hz, Δν= 28 Hz, H-12 and H-13)

^{13}C NMR (100 MHz, CDCl3): δ= 20.53 (C-11), 26.35 (C-3 or C-4 or C-5), 26.65 (C-3 or C-4 or C-5), 26.72 (C-3 or C-4 or C-5), 29.04 (C-2), 31.51 (C-1), 39.37 (C-9), 55.40 (C-20), 55.86 (C-19), 71.93 (C-10), 96.22 (C-14), 104.80 (C-12), 117.94 (C-16), 126.59 (C-8 or C-7), 133.72 (C-7 or C-8), 142.11 (C-17), 157.90 (C-15), 161.22 (C-13), 168.71 (C-18)

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{20}H_{28}O_4$: 332.1987; found: 332.1991.



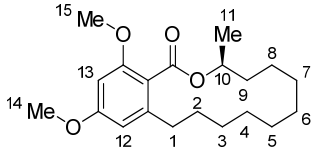
Chemical Formula: $C_{20}H_{30}O_4$
Molecular Weight: 334.45 g.mol^{-1}

***(S)*-14,16-dimethoxy-3-methyl-3,4,5,6,7,8,9,10,11,12-decahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (610)**

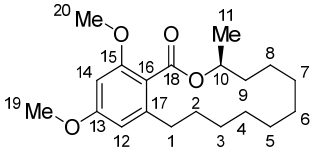
To a solution of **(S,Z)-14,16-dimethoxy-3-methyl-3,4,7,8,9,10,11,12-octahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (607)** (0.75 g, 2.26 mmol, 1.0 equiv.) in degassed dry EtOAc (180 mL) was added $PtO_2.H_2O$ (51.2 mg, 0.26 mmol, 0.1 equiv.). The solution was continuously submitted to a bubbling source of hydrogen overnight at RT. The residual solid was filtrated through a Celite® pad and washed with EtOAc (20 mL) and the obtained filtrate evaporated under reduced pressure. The resulting mixture was purified by silica gel flash chromatography (Cy/EtOAC: 90/10 → 85/15→ 80/20) to afford afford **610** (0.74 g, 99%) as a colorless oil.

R_f = 0.34 (Cy/EtOAC: 4/1)

$[\alpha]_D^{20}$ = -14,8° (c = 0.1, $CHCl_3$)



Numbering for the hydrogens

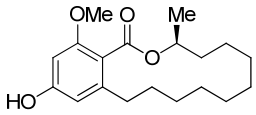


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.13-1.48 (m, 6H, H-3, H-4 and H-5), 1.33 (d, 2H, J= 6.4 Hz, H-11), 1.60-1.67 (m, 2H, H-2), 2.41-2.49 (m, 1H, H-1A), 2.65-2.74 (m, 1H, H-1B), 3.77 (s, 3H, H-14 or H-15), 3.79 (s, 3H, H-15 or H-14), 5.28 (tq, J= 6.4 Hz, J= 6.2 Hz, 1H, H-10), 6.32 (AB, J= 2.2 Hz, Δν= 28 Hz, H-9 and H-10)

^{13}C NMR (100 MHz, CDCl3): δ= 20.26 (C-11), 20.05 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 24.25 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 25.20 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 25.69 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 26.05 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 27.34 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 29.91 (C-2), 32.64 (C-1), 35.05 (C-9), 55.44 (C-20), 55.91 (C-19), 70.74 (C-10), 96.38 (C-14), 105.56 (C-12), 117.44 (C-16), 142.72 (C-17), 157.90 (C-15), 161.23 (C-13), 168.69 (C-18)

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{20}H_{30}O_4$: 334.2144; found: 334.2147.



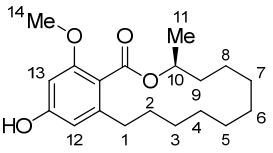
Chemical Formula: $C_{19}H_{28}O_4$
Molecular Weight: 320.42 g.mol^{-1}

***(S)*-16-hydroxy-14-methoxy-3-methyl-3,4,5,6,7,8,9,10,11,12-decahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (606)**

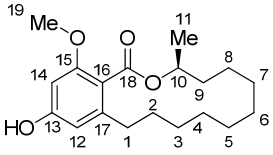
To a stirred suspension of NaH (60% in mineral oil, 0.63 g, 15.70 mmol, 15.0 equiv.) in THF (30 mL) at 0°C was added dropwise ethanethiol (0.98 g, 15.70 mmol, 15.0 equiv.). The biphasic mixture was warmed up to RT and stirred for 20 min until turning into a clear colorless solution. To the obtained solution was added dropwise a solution of ***(S)*-14,16-dimethoxy-3-methyl-3,4,5,6,7,8,9,10,11,12-decahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (610)** (0.35 g, 1.05 mmol, 1.0 equiv.) in HMPA (3 mL). The mixture was vigorously stirred at 70°C overnight. The dark red solution was carefully neutralised at 0°C with an aqueous solution of 10% w/v HCl until pH= 6-7 and became dark yellow. The aqueous layer was extracted with Et_2O (30 mL) and dichloromethane (2 x 30 mL). The combined organic layers were washed with a saturated solution of NH_4Cl (70 mL) then with brine (100 mL), dried with anhydrous MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cy/EtOAC : 9/1 → 7/1→ 4/1) to afford **606** (0.25 g, 75% yield) as a white solid.

R_f = 0.30 (Cy/EtOAC: 3/1)

$[\alpha]_D^{20}$ = -10° (c = 0.1, $CHCl_3$)



Numbering for the hydrogens



Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 1.20-1.61 (m, 14H, H-2, H-3, H-4, H-5, H-6, H-7 and H-8), 1.30 (d, 2H, J= 6.4 Hz, H-11), 1.63-1.68 (m, 2H, H-9), 2.36-2.44 (m, 1H, H-1A), 2.62-2.71 (m, 1H, H-1B), 3.75 (s, 3H, H-14 or H-15), 5.28 (tq, J= 6.0 Hz, J= 6.2 Hz, 1H, H-10), 6.26 (AB, J= 2.1 Hz, Δv= 11 Hz, H-9 and H-10)

^{13}C NMR (100 MHz, CDCl3): δ= 20.26 (C-11), 20.05 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 24.24 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 25.15 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 25.63 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 26.05 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 27.28 (C-3 or C-4 or C-5 or C-6 or C-7 or C-8), 29.73 (C-2), 32.28 (C-1), 36.03 (C-9), 55.88 (C-19), 70.93 (C-10), 96.96 (C-12), 107.89 (C-14), 117.00 (C-16), 142.95 (C-17), 157.45 (C-15), 158.14 (C-13), 168.96 (C-18)

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{20}H_{30}O_4$: 334.2144; found: 334.2147.

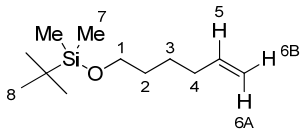
5.3.4 Synthesis of zeranol (611)

Chemical Formula: $C_{12}H_{26}OSi$
Molecular Weight: 214.42 g.mol^{-1}

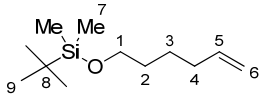
tert-butyl(hex-5-en-1-yloxy)dimethylsilane (639)

To a solution of hex-5-en-1-ol (**632**) (5.0 g, 49.9 mmol, 1.0 equiv.) in dry DMF (15 mL) at RT was added TBDMSCl (7.5 g, 49.9 mmol, 1.0 equiv.). The solution was stirred overnight at RT then quenched with a solution of saturated K_2CO_3 (30 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL) then the gathered organic phases were washed by brine (60 mL), dried with anhydrous MgSO4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC : 95/5) to afford **639** (10.6 g, 99% yield) as a colorless oil.

R_f = 0.64 (Cy/EtOAc: 5/1)



Numbering for the hydrogens

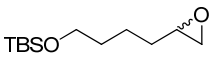


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 0.04 (s, 6H, H-7), 0.88 (s, 9H, H-8), 1.38-1.46 (m, 2H, H-3), 1.48-1.53 (m, 2H, H-2), 2.02-2.08 (m, 2H, H-4), 3.60 (t, 2H, J= 6.4 Hz, H-1), 4.96 (2H, *AB*X, J_{AB}= 1.6 Hz, J_{AX} = 15.1 Hz, J_{BX} = 10.1 Hz, Δν= 60 Hz, H-6A and H-6B), 5.80 (m, 1H, AB*X*, H-5)

^{13}C NMR (100 MHz, CDCl3): δ= -5.17 (C-7), 18.48 (C-8), 25.27 (C-3), 26.07 (C-9), 32.42 (C-2), 33.66 (C-4), 63.16 (C-1), 114.46 (C-6), 139.00 (C-5)

HRMS (ESI+): calcd for $(M-H)^+$: 215.1831, found: 215.1817



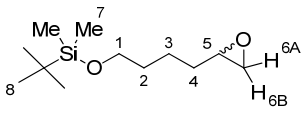
Chemical Formula: $C_{12}H_{26}O_2Si$
Molecular Weight: 230.42 g.mol^{-1}

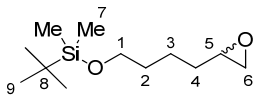
tert-butyldimethyl(4-(oxiran-2-yl)butoxy)silane (640)

To a solution of **tert-butyl(hex-5-en-1-yloxy)dimethylsilane (639)** (10.6 g, 49.4 mmol, 1.0 equiv.) in dry DCM (50 mL) at 0°C was added $NaHCO_3$ (8.3 g, 98.9 mmol, 2.0 equiv.). The solution was stirred at 0°C for 5 min then mCPBA (12.8 g, 74.2 mmol, 1.5 equiv.) was added in one portion. The biphasic solution was stirred at 0°C for 1h then allowed to warm to RT over another 2h. The resting mCPBA was neutralised by a saturated solution of $Na_2S_2O_3$ at 0°C. The aqueous phase was extracted with Et_2O (3 x 20 mL) then the gathered organic phases were washed by $NaHCO_3$ (3 x 70 mL), then by brine (100 mL), dried with anhydrous MgSO4 and

concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC: 95/5 → 8/1) to afford **640** (9.5 g, 83% yield) as a colorless oil.

R_f = 0.6 (Cy/EtOAC: 3/1)

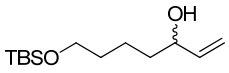




Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 0.04 (s, 6H, H-7), 0.88 (s, 9H, H-8), 1.39-1.59 (m, 6H, H-2, H-3 and H-4), 2.60 (2H, *AB*X, J_{AB}= 5.0 Hz, J_{AX} = 4.1 Hz, J_B = 2.8 Hz, Δv= 110 Hz, H-6A and H-6B), 2.91 (m, 1H, AB*X*, H-5), 3.60 (t, 2H, J= 6.2 Hz, H-1)

^{13}C NMR (100 MHz, CDCl3): δ= -5.25 (C-7), 18.39 (C-8), 22.40 (C-3), 26.01 (C-9), 32.32 (C-2), 32.61 (C-4), 47.07 (C-6), 52.32 (C-5), 62.97 (C-1)

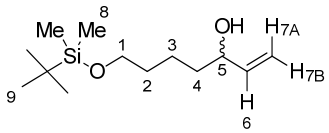


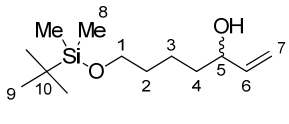
Chemical Formula: $C_{13}H_{28}O_2Si$
Molecular Weight: 244.45 g.mol^{-1}

7-((tert-butyldimethylsilyl)oxy)hept-1-en-3-ol (636)

To a solution of trimethylsulfonium iodide (25.2 g, 123.7 mmol, 3.0 equiv.) in suspension in THF (50 mL) at -15°C was added dropwise a 2.5M solution of BuLi (47.8 mL, 119.6 mmol, 2.9 equiv.). After being vigorously stirred between -15°C and -10°C for 45min, the solution turned limpid and colorless, to which was added slowly dropwise a solution of **tert-butyldimethyl(4-(oxiran-2-yl)butoxy)silane (640)** (9.5 g, 41.2 mmol, 1.0 equiv.) in dry THF (20 mL). The solution was stirred between -10°C and RT over 1h and became lightly yellow, containing a white solid. It was continuously stirred for another 2h at RT before being cooled down to 0°C, prior to the careful addition of distillated water (100 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL) then the combined organic phases were washed by brine (100 mL), dried with anhydrous MgSO4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC: 97/3 → 95/5→ 90/0) to afford **636** (9.0 g, 90% yield) as a yellow oil.

R_f = 0.65 (Cy/EtOAC: 3/1)



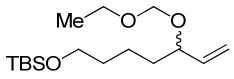


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3) : δ= 0.04 (s, 6H, H-7), 0.87 (s, 9H, H-8), 1.31-1.59 (m, 6H, H-2, H-3 and H-4), 3.60 (t, 2H, J= 6.4 Hz, H-1), 4.09 (dt, 1H, J_{H5-H4} = 6.4 Hz, J_{H5-H6} = 6.2 Hz, H-5), 5.15 (2H, *AB*X, J_{AB}= 1.2 Hz, J_{AX} = 17.2 Hz, J_B = 10.3 Hz, Δv= 50 Hz, H-7A and H-7B), 5.87 (m, 1H, AB*X*, H-6)

^{13}C NMR (100 MHz, CDCl3): δ= -5.25 (C-8), 18.45 (C-9), 21.73 (C-3), 26.06 (C-10), 32.71 (C-2), 36.81 (C-4), 63.17 (C-1), 73.29 (C-5), 114.70 (C-7), 141.29 (C-6)

HRMS (ESI+): calcd for $(M-Na)^+$: 267.1756, found: 267.1890

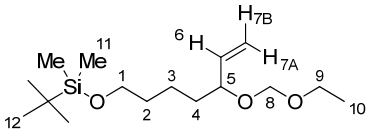


Chemical Formula: $C_{16}H_{34}O_3Si$
Molecular Weight: 302.52 g.mol^{-1}

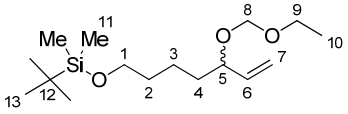
2,2,3,3-tetramethyl-9-vinyl-4,10,12-trioxa-3-silatetradecane (637)

To a solution of **7-((tert-butyldimethylsilyl)oxy)hept-1-en-3-ol (636)** (9.0 g, 36.8 mmol, 1 equiv.) in dry DMF (40 mL) at RT were added respectively TBAI (0.14 g, 0.37 mmol, 0.01 equiv.), DIPEA (42 mL, 258 mmol,7.0 equiv.) and the solution was stirred for 5 min before being cooled down to 0°C. To this yellow solution was added dropwise EOMCl (23.1 mL, 258 mmol, 7.0 equiv.) which instantly triggered a white smoke. The solution was stirred for 30 min at 0°C then 6h after reaching RT. The dark orange solution was quenched by a saturated solution of $NaHCO_3$ (30 mL) and the acqueous phase was extracted by Et_2O (3 x 70 mL). The combined organic phases were washed by a saturated solution of NH_4Cl (150 mL) then brine (150 mL), dried over anhydrous MgSO4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC: 90/10 → 85/15) to afford **637** (10.8 g, 97% yield) as a yellow oil.

R_f = 0.82 (Cy/EtOAC: 3/1)



Numbering for the hydrogens

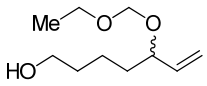


Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3): δ= 0.03 (s, 6H, H-11), 0.87 (s, 9H, H-12), 1.20 (t, AB*X*$_3$, 3H, J_{AX}= J_{BX}= 7.1 Hz), 1.31-1.65 (m, 6H, H-2, H-3 and H-4), 3.59 (t, 2H, J= 6.4 Hz, H-1), 3.59 (*AB*X$_3$, 2H, J_{AB}= 9.7 Hz, J_{AX}= J_{BX}= 7.1 Hz, Δγ= 75 Hz, H-9A and H-9B), 4.09 (m, 1H, H-5), 4.48 (AB, 2H, J_{AB}= 6.9 Hz, Δν= 40 Hz, H-8A and H-8B), 5.17 (2H, *AB*X, J_{AB}= 1.2 Hz, J_{AX} = 17.2 Hz, J_B = 10.3 Hz, Δν= 14 Hz, H-7A and H-7B), 5.64 (m, 1H, AB*X*, H-6)

^{13}C NMR (100 MHz, CDCl3): δ= -5.24 (C-11), 15.71 (C-10), 18.4 (C-12), 21.69 (C-3), 26.01 (C-13), 32.75 (C-2), 35.26 (C-4), 63.12 (C-1), 63.28 (C-9), 76.79 (C-5), 92.29 (C-8), 117.07 (C-7), 138.57 (C-6)

MS (ESI+): calcd for $(M-H)^+$: 303.2355, found: 303.2155

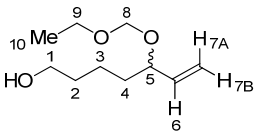


Chemical Formula: $C_{10}H_{20}O_3$
Molecular Weight: 188.26 g.mol^{-1}

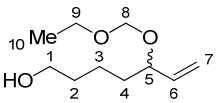
5-(ethoxymethoxy)hept-6-en-1-ol (638)

To a solution of **2**,**2**,**3**,**3-tetramethyl-9-vinyl-4**,**10**,**12-trioxa-3-silatetradecane (637)** (10.8 g, 35.7 mmol, 1 equiv.) in THF (30 mL) at RT was added at once TBAF.$3H_2O$ (28.1 g, 89.3 mmol, 2.5 equiv.). The yellow solution was stirred overnight at RT and become red-brown. The solvent was totally evaporated and the crude product purified through silica gel flash chromatography (Cy/EtOAC: 80/20 → 75/25 →60/40) to afford **638** (6.7 g, 99%) as a yellow oil.

R_f = 0.43 (Cy/EtOAC: 1/1)



Numbering for the hydrogens

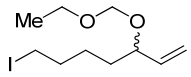


Numbering for the carbons

^{1}H NMR (400 MHz, **CDCl3):** δ= 1.20 (t, AB*X*$_3$, 3H, J_{AX}= J_{BX}= 7.1 Hz), 1.34-1.67 (m, 6H, H-2, H-3 and H-4), 3.59 (*AB*X$_3$, 2H, J_{AB}= 9.7 Hz, J_{AX}= J_{BX}= 7.1 Hz, Δγ= 75 Hz, H-9A and H-9B), 3.64 (t, 2H, J= 6 Hz, H-1), 4.01 (m, 1H, H-5), 4.48 (AB, 2H, J_{AB}= 6.9 Hz, Δν= 40 Hz, H-8A and H-8B), 5.17 (*AB*X, 2H, J_{AB}= 1.2 Hz, J_{AX} = 17.2 Hz, J_B = 10.3 Hz, Δν= 14 Hz, H-7A and H-7B), 5.66 (m, 1H, AB*X*, H-6)

^{13}C NMR (100 MHz, **CDCl3):** δ= 14.97 (C-10), 21.64 (C-3), 32.45 (C-2), 35.03 (C-4), 62.07 (C-1), 63.34 (C-9), 76.77 (C-5), 92.09 (C-8), 117.07 (C-7), 138.26 (C-6)

HRMS (ESI+): calcd for $(M-H)^+$: 189.1491, found: 189.1475



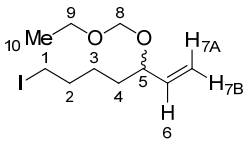
Chemical Formula: $C_{10}H_{19}IO_2$
Molecular Weight: 298.16 g.mol^{-1}

3-(ethoxymethoxy)-7-iodohept-1-ene (456)

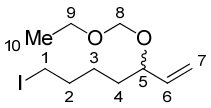
To a solution of **5-(ethoxymethoxy)hept-6-en-1-ol (638)** (6.7 g, 38.6 mmol, 1.0 equiv.) in THF (70 mL) at RT were added respectively triphenylphosphine (14.9 g, 56.9 mmol, 1.6 equiv.) and imidazole (3.6 g, 53.4 mmol, 1.5 equiv.). The solution was cooled down to 0°C before the addition of I_2 (13.5 g, 53.4 mmol, 1.5 equiv.). The solution turned progressively to a dark brown color after stirring at 0°C for 3h. The solution was quenched with a saturated solution of $Na_2S_2O_5$ (50 mL) and the acqueous phase extracted by Et_2O (3 x 50 mL). The combined organic phases were washed by a saturated solution of NH_4Cl (100 mL) then brine (150 mL), dried over anhydrous MgSO4 and concentrated under reduced pressure. The crude product was purified

by silica gel flash chromatography (Cy/EtOAC: 97/3 → 95/5) to afford **456** (6.2 g, 93% yield) as a yellow oil.

R_f = 0.75 (Cy/EtOAC: 6/1)



Numbering for the hydrogens

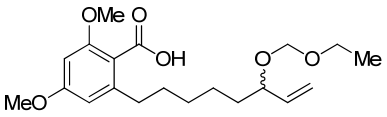


Numbering for the carbons

^{1}H NMR (C_6D_6): δ= 1.16 (t, AB*X*$_3$, 3H, J_{AX}= J_{BX}= 7.1 Hz), 1.23-1.37 (m, 3H, H-3 and H-4A), 1.40-1.55 (m, 3H, H-2 and H-4B), 2.73 (t, 2H, J= 7.1 Hz, H-1), 3.54 (*AB*X$_3$, 2H, J_{AB}= 9.4 Hz, J_{AX}= J_{BX}= 7.1 Hz, Δν= 75 Hz, H-9A and H-9B), 3.99 (m, 1H, H-5), 4.67 (AB, 2H, J_{AB}= 7 Hz, Δν= 40 Hz, H-8A and H-8B), 5.08 (*AB*X, 2H, J_{AB}= 1.8 Hz, J_{AX} = 17.2 Hz, J_B = 10.3 Hz, Δν= 28 Hz, H-7A and H-7B), 5.60 (m, 1H, AB*X*, H-6)

^{13}C NMR (C_6D_6):δ= 6.21 (C-1), 15.14 (C-10), 26.22 (C-3), 33.29 (C-2), 34.31 (C-4), 63.10 (C-9), 76.55 (C-5), 92.23 (C-8), 116.48 (C-7), 138.70 (C-6)

MS (ESI+): calcd for $(M-H)^+$: 299.0508, found: 299.1852

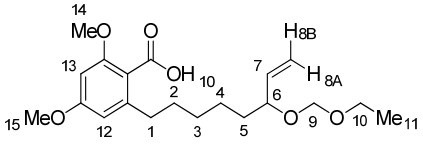


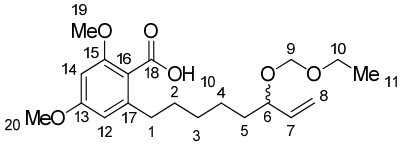
Chemical Formula: $C_{20}H_{30}O_6$
Molecular Weight: 366.45 g.mol^{-1}

2-(6-(ethoxymethoxy)oct-7-en-1-yl)-4,6-dimethoxybenzoic acid (640)

To a solution of 2,4-dimethoxybenzoic acid **(401)** (5.1 g, 26.0 mmol, 1.0 equiv.) in THF (50 mL) at -78°C was added dropwise a 1.4 M solution of *s*BuLi in hexanes (25.7 mL, 35.9 mmol, 2.1 equiv.). The initially colorless solution progressively turned orange then dark red after 2h between -78°C and -60°C. To the limpid red solution at -20°C was added dropwise a solution of **3-(ethoxymethoxy)-7-iodohept-1-ene (456)** (6.2 g, 20.8 mmol, 0.8 equiv.). The solution's color lightened at the end of the addition and was stirred for the next 15 min at -20°C before allowed to warm up to 0°C in 20 min and stirred for 6h at 0°C, then from 0°C to RT overnight. The bright yellow solution was quenched with a saturated solution of NH_4Cl (70 mL) at 0°C, the first organic phase was extracted with Et_2O (30 mL). The obtained acqueous phase was acidified with a solution of HCl (10% w/v) until pH = 1-2, then extracted once again with Et_2O (30 mL) and EtOAc (2 x 30 mL). The combined organic phases were washed by a saturated solution of $NaHCO_3$ (100 mL) then brine (150 mL), dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC/AcOH: 80/20/1 → 60/40/1) to afford **640** (6.3 g, 83% yield) as a colorless oil.

R_f = 0.47 (Cy/EtOAC/AcOH: 10/10/0.05)



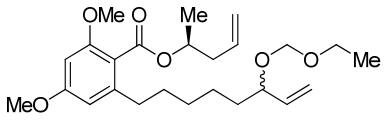


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 1.16 (t, AB*X*$_3$, 3H, J_{AX}= J_{BX}= 7.1 Hz), 1.34-1.67 (m, 8H, H-2, H-3, H-4 and H-5), 2.83-2.92 (m, 2H, H-1), 3.61 (*AB*X$_3$, 2H, J_{AB}= 10.3 Hz, J_{AX}= J_{BX}= 6.9 Hz, Δν= 70 Hz, H-9A and H-9B), 3.83 (s, 3H, H-14), 3.92 (m, 3H, H-15), 3.97-4.02 (m, 1H, H-6), 4.67 (AB, 2H, J_{AB}= 6.9 Hz, Δν= 30 Hz, H-9A and H-9B), 5.17 (*AB*X, 2H, J_{AB}= 0.9 Hz, J_{AX} = 17.4 Hz, J_{B} = 11.2 Hz, Δν= 18 Hz, H-8A and H-8B), 5.66 (m, 1H, AB*X*, H-7), 6.38 (AB, 2H, J_{AB}= 72Hz, Δν= 7 Hz, H-12 and H-13)

^{13}C NMR (100 MHz, CDCl3): δ= 15.14 (C-10), 24.96 (C-4), .29.43 (C-3), 31.28 (C-2), 34.61 (C-5), 35.19 (C-1), 55.45 (C-19), 56.29 (C-20), 63.63 (C-10), 77.46 (C-6), 92.25 (C-9), 96.41 (C-12 or C-14), 107.26 (C-14 or C-12), 113.96 (C-16), 117.12 (C-8), 138.53 (C-7), 145.97 (C-17), 158.89 (C-15), 161.95 (C-13), 170.08 (C-18)

HRMS (ESI+): calcd for $(M-H)^{+}$: 367.2121, found: 367.2116

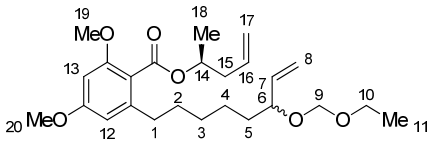


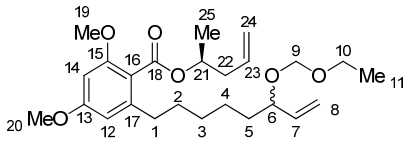
Chemical Formula: $C_{25}H_{38}O_6$
Molecular Weight: 434.57 g.mol^{-1}

***(S)*-pent-4-en-2-yl 2-(6-(ethoxymethoxy)oct-7-en-1-yl)-4,6-dimethoxybenzoate (643)**

To a solution of **2-(6-(ethoxymethoxy)oct-7-en-1-yl)-4,6-dimethoxybenzoic acid (640)** (6.3 g, 17.2 mmol, 1.0 equiv.) in THF (75 mL) were added respectively triphenylphosphine (9.0 g, 34.4 mmol, 2.0 equiv.) and *(R)*-pent-4-en-2-ol (**41**) (2.22 g, 25.8 mmol, 1.5 equiv.) at 0°C. The solution was stirred for 5 min at 0°C before the addition of DIAD (7.6 g, 37.8 mmol, 2.2 equiv.). The colorless solution turned yellow-orange after 10 min at 0°C then stirred at RT overnight. The solvent was completely evaporated and the crude product purified by silica gel flash chromatography (Cy/EtOAC: 98/2 → 95/5→ 90/10→ 85/15) to afford a 59/41 diastereomeric mixture of **643** (6.7 g, 90% yield) as a light yellow oil.

R_f = 0.48 (Cy/EtOAC: 4/1)





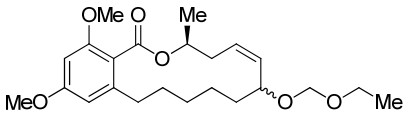
Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (400 MHz, CDCl3): δ= 1.19 (t, AB*X*$_3$, 3H, J_{AX}= J_{BX}= 7.1 Hz, H-11), 1.28 (d, J= 6.8 Hz, H-18), 1.27-1.51 (m, 6H, H-3, H-4 and H-5), 1.57-1.62 (m, 2H, H-2), 2.31-2.38 (m, 1H, H-15A), 2.43-2.95 (m, 1H, H-15B), 2.53-2.57 (m, 2H, H-1), 3.59 (*AB*X$_3$, 2H, J_{AB}= 10.3 Hz, J_{AX}= J_{BX}= 7.1 Hz, Δγ=

70 Hz, H-10A and H-10B), 3.78 (s, 3H, H-19), 3.79 (s, 3H, H-20), 3.97 (m, 1H, H-6), 4.65 (AB, 2H, J_{AB}= 6.9 Hz, Δν= 30 Hz, H-9A and H-9B), 5.07-5.17 (m, 4H, H-8 and H-17), 5.18-5.23 (m, 1H, H-14), 5.74 ($A^1B^1X^1$, 1H, J_{AX} = 17.4 Hz, J_{BX} = 9.2 Hz, J_{AB} = 10.3 Hz, H-7), 5.83 ($A^2B^2X^2$, 1H, J_{AX} = 17 Hz, J_{BX} = 10 Hz, H-16), 6.30 (s, 2H, H-12 and H-13)

^{13}C NMR (100 MHz, CDCl3): δ= 15.17 (C-11), 19.60 (C-25), 25.30 (C-4), .29.61 (C-3), 31.36 (C-2), 33.89 (C-1), 35.41 (C-5), 40.33 (C-22), 55.41 (C-19), 55.86 (C-20), 63.31 (C-10), 71.00 (C-21), 77.34 (C-6), 92.35 (C-9), 96.27 (C-12 or C-14), 105.81 (C-14 or C-12), 113.96 (C-16), 117.12 (C-8), 138.53 (C-7), 145.97 (C-17), 158.89 (C-15), 161.95 (C-13), 170.08 (C-18)

HRMS (ESI+): calcd for $(M-H)^+$: 435.2747, found: 435.2751

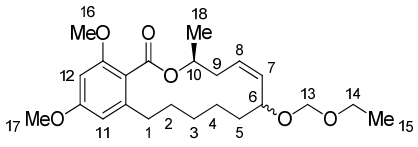


Chemical Formula: $C_{23}H_{34}O_6$
Molecular Weight: 406.51 g.mol^{-1}

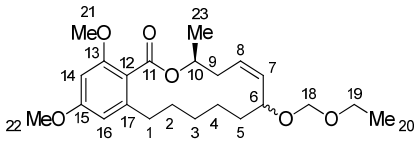
(3S,Z)-7-(ethoxymethoxy)-14,16-dimethoxy-3-methyl-3,4,7,8,9,10,11,12-octahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (644)

To a solution of ***(S)*-pent-4-en-2-yl 2-(6-(ethoxymethoxy)oct-7-en-1-yl)-4,6-dimethoxybenzoate (643)** (1.0 g, 2.3 mmol, 1.0 equiv.) in degassed dry toluene (230 mL) at RT was added the 2nd Grubbs' catalyst (97.6 mg, 0.12 mmol, 0.05 equiv.). The colorless solution became orange then brown after 4h at 80°C then allowed to cool down to 40°C. Another portion of catalyst (97.6 mg, 0.12 mmol, 0.05 equiv.) was added at this temperature and the solution stirred at 80°C overnight. The reaction was cooled to RT before the filtration on a Celite® pad to s*epara*te the residual solid and washed with toluene (15 mL). The filtrate was evaporated under reduced pressure and purified by silica gel flash chromatography (Cy/EtOAC: 90/10 → 85/15) to afford a E/Z : 2/1 mixture of **644** (0.75 g, 80%) as a colorless oil.

R_f = 0.5 (Cy/EtOAC: 4/1)



Numbering for the hydrogens



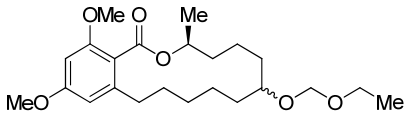
Numbering for the carbons

^{1}H NMR (C_6D_6): (major isomer) δ= 1.08 (t, ABX_3, 3H, J_{AX}= J_{BX}= 7 Hz, H-15), 1.27 (d, J= 5.9 Hz, H-18), 1.21-1.54 (m, 6H, H-3, H-4 and H-5), 1.55-1.74 (m, 2H, H-2), 2.06-2.18 (m, 2H, H-9), 2.56-2.65 (m, 1H, H-1A), 2.75-2.87 (m, 1H, H-1B), 3.24 (s, 3H, H-16), 3.25(s, 3H, H-17), 3.37-3.42 (m, 1H, H-14A), 3.52-3.62 (m, 1H, H-14B), 3.97 (dt, 1H, J_{H6-H7}= 3 Hz, J_{H6-H5}= 7 Hz, H-6), 4.61 (AB, 2H, J_{AB}= 6.6 Hz, Δν= 75 Hz, H-13A and H-13B), 5.08-5.23 (m, 1H, H-8), 5.20-5.34 (m, 1H, H-10), 5.55-5.62 (m, 1H, H-7), 6.20 (AB, 2H, J_{AB}= 2.1 Hz, Δν= 55 Hz, H-11 and H-12)

^{13}C NMR (C_6D_6): (major isomer) δ= 15.22 (C-20), 20.48 (C-23), 24.33 (C-4), 26.67 (C-3), 28.65 (C-2), 30.53 (C-1), 34.71 (C-5), 39.53 (C-22), 54.53 (C-21), 54.85 (C-22), 62.83 (C-19), 70.48 (C-10),

77.14 (C-6), 91.81 (C-18), 96.37 (C-14 or C-16), 104.36 (C-16 or C-14), 118.76 (C-12), 130.17 (C-8), 134.59 (C-7), 141.82 (C-17), 158.35 (C-13), 161.43 (C-15), 167.85 (C-11)

MS (ESI+): calcd for $(M-H)^+$: 407.2434, found: 407.2411

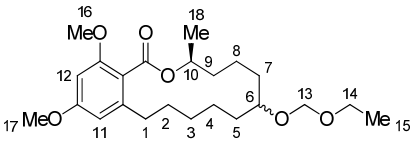


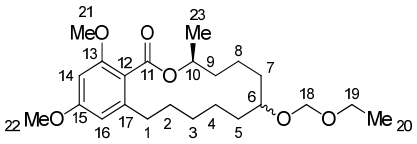
Chemical Formula: $C_{23}H_{36}O_6$
Molecular Weight: 408.53 $g.mol^{-1}$

(3S)-7-(ethoxymethoxy)-14,16-dimethoxy-3-methyl-3,4,5,6,7,8,9,10,11,12-decahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (642)

To a solution of **(3S,Z)-7-(ethoxymethoxy)-14,16-dimethoxy-3-methyl-3,4,7,8,9,10,11,12-octahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (644)** (0.75 g, 1.84 mmol, 1.0 equiv.) in degassed dry EtOAc (180 mL) was added $PtO_2.H_2O$ (44.3 mg, 0.18 mmol, 0.1 equiv.). The solution was continuously submitted to a bubbling source of hydrogen overnight at RT. The residual solid was filtrated through a Celite® pad and washed with EtOAc (20 mL) and the obtained filtrate evaporated under reduced pressure. The resulting mixture was purified by silica gel flash chromatography (Cy/EtOAC: 90/10 → 85/15→ 80/20) to afford afford a 60/40 diastereomeric mixture of **642** (0.74 g, 99%) as a colorless oil.

R_f = 0.46 (Cy/EtOAC: 3/1)



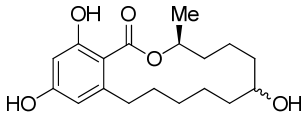


Numbering for the hydrogens *Numbering for the carbons*

^{1}H NMR (C_6D_6): δ= 1.08 (t, ABX_3, 3H, J_{AX}= J_{BX}= 7.1 Hz, H-15), 1.28 (d, J= 6.6 Hz, H-18), 1.21-1.68 (m, 10 H, H-2, H-3, H-4, H-5, H-6, H-7 and H-8), 2.38-2.48 (m, 1H, H-1A), 2.86-2.97 (m, 1H, H-1B), 3.16 (s, 3H, H-16), 3.27 (s, 3H, H-17), 3.43-3.51 (m, 2H, H-14), 3.57-3.68 (m, 1H, H-6), 4.61 (AB, 2H, J_{AB}= 6.9 Hz, Δν= 10 Hz, H-13A and H-13B), 5.27-5.34 (m, 1H, H-10), 5.20-5.34 (m, 1H, H-10), 5.55-5.62 (m, 1H, H-7), 6.20 (AB, 2H, J_{AB}= 2.1 Hz, Δν= 55 Hz,H-11 and H-12)

^{13}C NMR (C_6D_6): δ= 15.18 (C-20), 17.80 (C-8), 20.63 (C-23), 23.04 (C-4), 27.28 (C-3), 30.31 (C-2), 30.91 (C-9), 31.31 (C-5), 32.55 (C-1), 35.34 (C-7), 54.58 (C-21), 55.05 (C-22), 62.85 (C-19), 69.45 (C-10), 75.07 (C-6), 93.18 (C-18), 96.52 (C-14 or C-16), 105.32 (C-16 or C-14), 118.39 (C-12), 142.72 (C-17), 158.43 (C-13), 161.38 (C-13), 167.77 (C-11)

MS (ESI+): calcd for $(M-H)^+$: 409.2590, found: 409.2565



Chemical Formula: $C_{18}H_{26}O_5$
Molecular Weight: 322.40 g.mol^{-1}

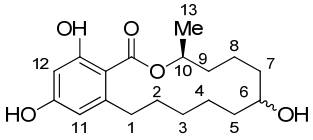
(3S)-7,14,16-trihydroxy-3-methyl-3,4,5,6,7,8,9,10,11,12-decahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (611)

To a solution of **(3S)-7-(ethoxymethoxy)-14,16-dimethoxy-3-methyl-3,4,5,6,7,8,9,10,11,12-decahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (642)** (0.74 g, 1.8 mmol, 1 equiv.) in DCM (20 mL) at 0°C was added dropwise a 1 M solution of BBr_3 (10.9 mL, 10.9 mmol, 6 equiv.). The solution turned yellow after 5 min at 0°C and was stirred for 1h at 0°C then overnight after the temperature reached RT. The reaction was quenched at 0°C with a saturated solution of $NaHCO_3$ (30 mL) then methanol (10 mL). The aqueous phase was extracted by DCM (3 x 20 mL). The combined organic phases were washed by a saturated brine (150 mL), dried over anhydrous MgSO4 and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (Cy/EtOAC: 90/10 → 60/40) to afford a 60/40 diastereomeric mixture of **611** (0.46 g, 80% yield) as a light-yellow solid.

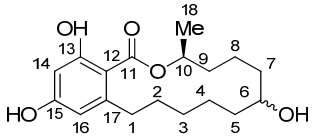
R_f = 0.6 (EtOAC)

The analytical data are identical to those from the literature.[10]

mp= 169-171°C



Numbering for the hydrogens



Numbering for the carbons

^{1}H NMR (400 MHz, CDCl3):δ= 1.36 (d, 3H, J= 2.1 Hz, H-13), 1.37-2.15 (m, 14H, H-2, H-3, H-4, H-5, H-7, H-8 and H-9), 2.25-2.64 (m, 1H, H-1), 3.22-3.30 (m, 2H, H-6), 5.13-5.20 (m, 1H, H-10), 5.32-5.53 (m, 1H, O*H*), 6.26 (AB, 2H, J_{AB}= 2.5 Hz, Δγ= 25 Hz,H-11 and H-12)

^{13}C NMR (100 MHz, CDCl3): δ= 14.2 (C-8), 20.41 (C-18), 22.98 (C-4), 24.71 (C-3), 27.90 (C-2), 29.78 (C-1), 37.20 (C-9), 37.45 (C-5), 38.08 (C-7), 73.42 (C-6), 101.60 (C-14), 110.85 (C-16), 148.86 (C-17), 164.82 (C-13), 165.95 (C-15), 171.75 (C-11)

HRMS (ESI+): calcd for $(M-Na)^+$: 345.1677, found: 345.1602

5.4 List of references

1. Dakas, P. Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winssinger, N., Modular synthesis of radicicol A and related resorcylic acid lactones, potent kinase inhibitors. *Angewandte Chemie - International Edition* **2007**, *46* (36), 6899-6902.
2. Ballou, C. E., A new synthesis of D-erythrose derivatives from D-arabinose. *J. Am. Chem. Soc.* **1957**, *79*, 165-156.
3. Kozikowski, A. P.; Wu, J. P., Protection of alcohols as their (p-methoxybenzyloxy)methyl ethers. *Tetrahedron Lett.* **1987**, *28*, 5125-8.
4. Paquette, L. A.; Huber, S. K.; Thompson, R. C., A means for stereocontrolled introduction of the C-2 oxygen substituent in functionalized cis-tricyclo[9.3.1.03,8]pentadecanones related to taxol. *J. Org. Chem.* **1993**, *58*, 6874-82.
5. Noal Cohen, B. L. B., Anthony J. Laurenzano, Louis Carozza, 2,3-O-ISOPROPYLIDENE-D-ERYTHRONOLACTONE [Furo[3,4-d]-1,3-dioxol-4(3aH)-one, dihydro-2,2-dimethyl-(3aR-cis)-]. *Organic Syntheses* **1990**, *7*, 297.
6. Schuster, E. M.; Botoshansky, M.; Gandelman, M., Pincer Click Ligands. *Angewandte Chemie International Edition* **2008**, *47* (24), 4555-4558.
7. Mana*via*zar, S.; Frigerio, M.; Bhatia, G. S.; Hummersone, M. G.; Aliev, A. E.; Hale, K. J., Enantioselective Formal Total Synthesis of the Antitumor Macrolide Bryostatin 7. *Org. Lett.* **2006**, *8*, 4477-4480.
8. Fuchs, M.; Toesch, M.; Schober, M.; Wuensch, C.; Faber, K., Chemoenzymatic asymmetric total synthesis of (R)-lasiodiplodin methyl ether through a sulfatase-based deracemization process. *Eur. J. Org. Chem.* **2013**, *2013*, 356-361.
9. Xu, Y.; Zhou, T.; Espinosa-Artiles, P.; Tang, Y.; Zhan, J.; Molnar, I., Insights into the Biosynthesis of 12-Membered Resorcylic Acid Lactones from Heterologous Production in Saccharomyces cerevisiae. *ACS Chem Biol* **2014**..
10. Fuerstner, A.; Seidel, G.; Kindler, N., Macrocycles by ring-closing-metathesis, XI: syntheses of (*R*)-(+)-lasiodiplodin, zeranol and truncated salicylihalamides. *Tetrahedron* **1999**, *55*, 8215-8230.

The true splendor of science is not so much that it names and classifies, records and predicts, but that it observes and desires to know the facts, whatever they may turn out to be. However much it may confuse facts with conventions, and reality with arbitrary divisions, in this openness and sincerity of mind it bears some resemblance to religion, understood in its other and deeper sense. The greater the scientist, the more he is impressed with his ignorance of reality, and the more he realizes that his laws and labels, descriptions and definitions, are the products of his own thought. They help him to use the world for purposes of his own devising rather than to understand and explain it.

Alan Watts (1915-1973)