TOTAL SYNTHESIS OF CRUENTAREN A

A thesis submitted by

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In partial fulfilment of the requirements for the degree of

Doctor of Philosophy

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Declaration of Originality

I, Marianne Fouché, certify that the research described in this manuscript was undertaken under the supervision of Professor Anthony G. M. Barrett, Imperial College London, and is my own unaided work unless stated otherwise.

Marianne Fouché

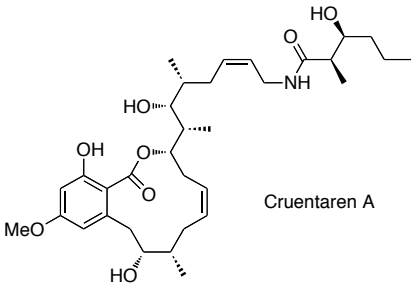
London 30th of September

Abstract

Total Synthesis *Marianne Fouché*

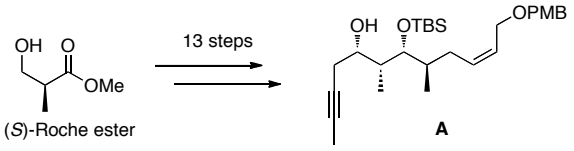
of Cruentaren A

Cruentaren A, a highly cytotoxic metabolite, which also inhibits F-ATPase, was synthesized using our recently developed methodology on resorcylic acid lactones natural products.



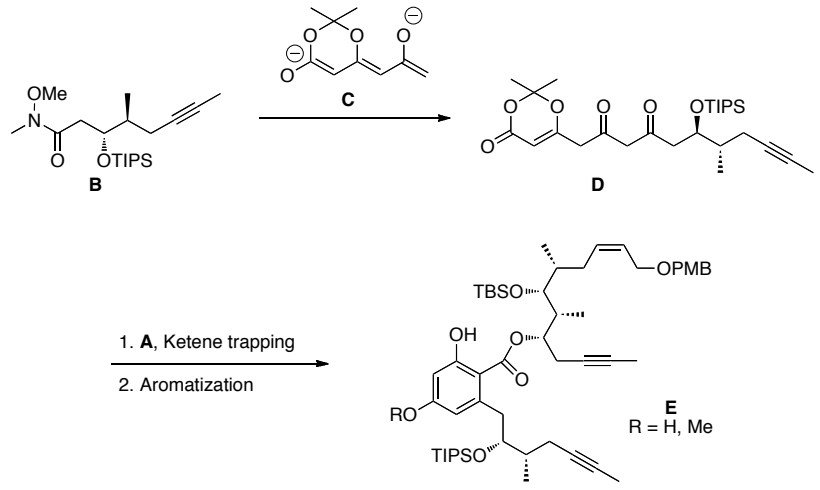
Cruentaren A

Alcohol **A** was prepared on a multigram scale in 13 steps starting from (*S*)-Roche ester and using highly stereoselective reactions such as Evans aldol reaction and asymmetric propargylation.

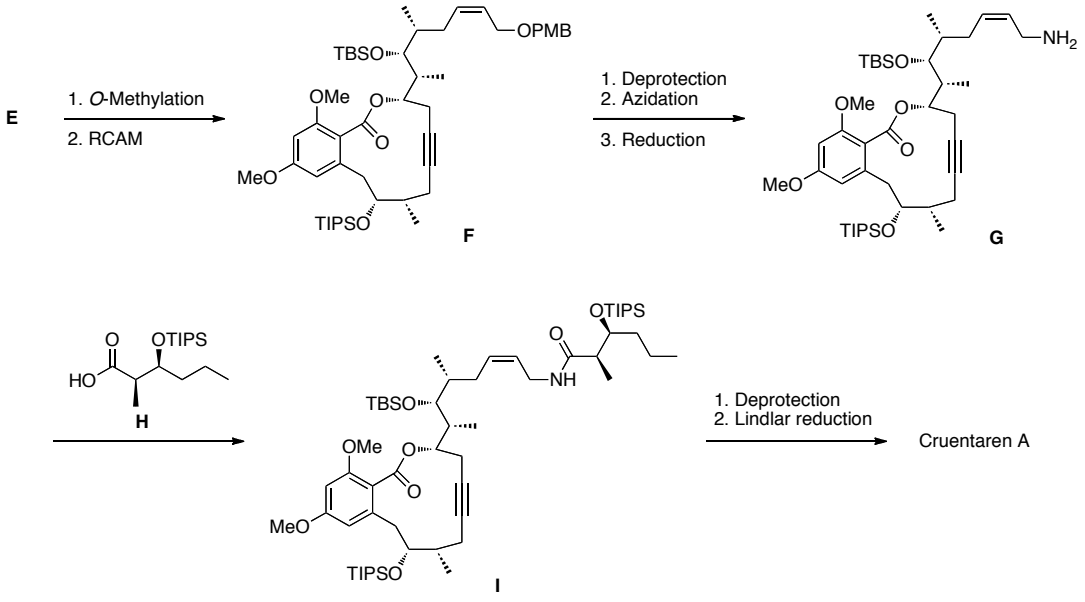


Key fragment **B** was synthesized in 11 steps from 1,3-propanediol. The *1,2-anti*-configuration was installed with a Brown crotylation. Diketo-dioxinone **D** was generated from *C*-acylation between Weinreb amide **B** and keto-dioxinone **C**.

Ketene generation by thermolysis followed by trapping with alcohol **A** and aromatization afforded resorcylate derivative **E**.



Finally after a sequence consisting of the following key steps: ring closing alkyne metathesis, coupling between amine **G** and acid **H** and Lindlar hydrogenation, cruentaren A was obtained.



Acknowledgments

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I am extremely grateful to my parents for their support and encouragement. I also wish to thanks my brothers and sisters for always being there for me.

Finally, I would like to thank my wonderful fiancé Jullien for his love, support and persistent confidence in me during those years. Words fail me to express my deepest feelings of gratitude.

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
$[\alpha]_D$	optical rotation
Å	Angstrom (10-10)
Ac	acetyl
Anal.	analysis
aq.	aqueous
Ar	aryl
ATPase	adenosine triphosphatase
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bp	boiling point
br.	broad
Bt	benzotriazole
Bu	butyl
c / conc.	concentrated
°C	degrees Celsius
ca.	*circa*
cat.	catalytic
CBS	Corey-Bakshi-Shibata
CDI	carbonyldiimidazole
CI	chemical ionization
COSY	correlation spectroscopy

CSA	camphorsulfonic acid
δ	chemical shift
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
DEAD	diethylazocarboxylate
DIAD	di*iso*propylazocarboxylate
DIBAL-H	di*iso*butyl aluminium hydride
DMAP	4-dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dq	doublet of quartets
dr	diastereomeric ratio
dt	doublet of triplets
EDA	ethylenediamine
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
ee	enantiomeric excess
EI	electron ionization
eq.	equivalent
ES	electrospray
Et	ethyl
Et_3N	triethylamine

Et_2O	diethyl ether
EtOAc	ethyl acetate
F-ATPase	F1F0-ATPase
h	hour
HBTU	*O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxy benzotriazole
HRMS	high-resolution mass spectrometry
HSP 90	90-kD eat schock protein
Hz	Hertz
i	*iso*
IBX	*o*-iodylbenzoic acid
IC_{50}	half maximal inhibitory concentration
imid.	imidazole
Ipc	*iso*pinocamphenyl
IR	infrared spectroscopy
J	coupling constant
L	litre
LDA	lithium di*iso*propylamide
LG	leaving group
µ	micro (10^{-6})
m	multiplet

M	molar
m	*meta*
MAP	mitogen activated proteins
Me	methyl
MEK	mitogen-activated protein/extracellular signal-regulated kinase
Mes	mesityl
MeOH	methanol
min	minute(s)
mL	millilitre(s)
mol	mole(s)
MOM	methoxymethyl ether
mmol	millimole(s)
mp	melting point
MPTA	methoxy(trifluoromethyl)phenylacetic acid
MS	molecular sieves
Ms	mesyl
MS	mass spectrometry
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear overhauser effect spectroscopy
Nu	nucleophile
o	*ortho*
p	*para*
PG	general protecting group

pH	potential hydrogen
Ph	phenyl
PhMe	toluene
PPh_3	triphenylphosphine
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
*p*TsOH	*para*-toluenesulfonic acid
Py.	pyridine
PyBop	(benzotriazol-1-yloxy) tripyrrolidinophosphoniumhexafluorophosphate
q	quartet
quin	quintet
R	general substituent
RALs	resorcylic acid lactones
R*f*	retention factor
RCAM	ring-closing alkyne metathesis
RCM	ring-closing metathesis
rt	room temperature
s	singlet
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
sat.	saturated
t or *tert*	tertiary
t	triplet

TASF	tris(dimethylamino)sulfonium difluorotrimethyl silicate
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
td	triplet of doublets
tt	triplet of triplets
TES	triethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	para-toluenesulfonyl (tosyl)
V-ATPase	vacuolar-H+ATPase
μL	microlitre(s)
μM	micromole(s)

Contents

1 Introduction

1.1 General introduction to resorcylic acid lactones (RALs)

1.1.1 Structure and biological properties

RALs are a large family of natural products isolated from different fungal strains. They commonly contain a 12- or 14-membered ring lactone adjoined to an aromatic unit, more precisely the 6-alkyl-2,4-dihydroxybenzoic acid unit (Figure 1, highlighted in red).[1] Despite being known for 60 years, with the isolation of radicicol (**4**) in 1953,[2] the increased interest of organic chemists in this class of natural products is very recent. In the early 1990s, the kinase inhibition properties of radicicol were first reported. Initially, Kwon *et al.* believed that radicicol was a Src kinase inhibitor,[3] however it was later proved that radicicol is in fact a potent and selective inhibitor of 90-kD heat shock protein (HSP90)[4]. Since then, many RALs have displayed promising biologically active compounds with a wide and diverse spectrum of action. Zearalenone (**1**) is a powerful estrogen agonist used as a bovine growth stimulant. Hypothemycin (**2**) has been reported to irreversibly inhibits mitogen activated proteins (MAP) kinases and structurally related LL-7783,277 (**3**) has been identified as a mitogen-activated protein/extracellular signal regulated kinase kinase (MEK) inhibitor. 15G256b (**7**) exhibits antibiotic properties and it has been discovered that aigialomycin D (**5**) has antimalarial activity.[1] Finally, recently isolated cruentaren A (**6**) proved to be highly cytotoxic (IC_{50} = 1.2 ng mL^{-1}) and inhibits mitochondrial F1F0-ATPase (F-ATPase).[5]

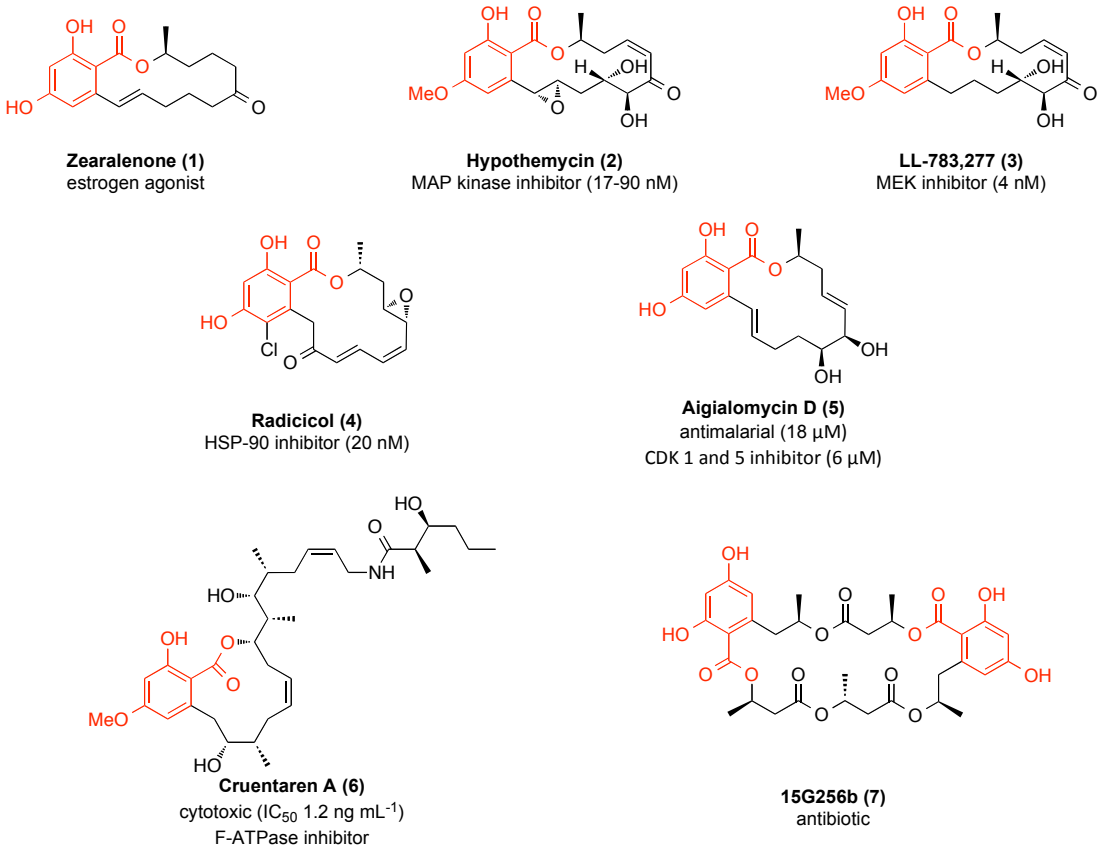
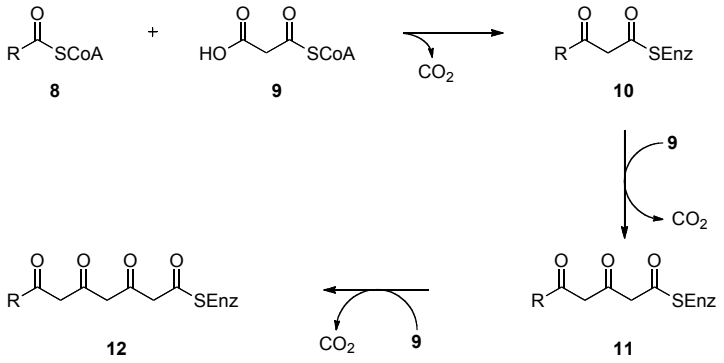


Figure 1 - Examples of RAL natural products

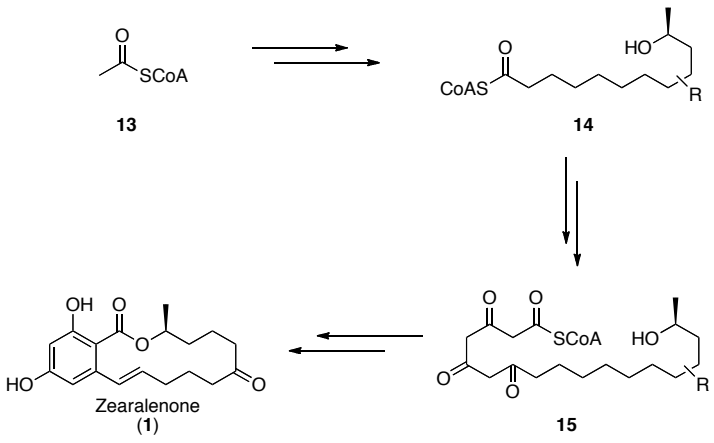
1.1.2 Biosynthesis

It is proposed and widely known that aromatic units in all RALs have a polyketide biosynthetic origin. In the 1950s, Birch developed a theory for the biosynthesis of polyketides.[6] The pathway begins with the condensation of coenzyme A esters **8**, with malonyl coenzyme A ester **9** to produce β-ketothioester **10**. These can then undergo further Claisen-type condensation with malonyl coenzyme A ester **9** to give thioesters of 3,5-diketoacids **11**. Repeating this process gives thioesters of 3,5,7-triketoacids **12** and so forth (Scheme 1).



Scheme 1 - Biosynthesis of polyketides

For the biosynthesis of zearalenone (Scheme 2), it is believed that two polyketide synthases (PKS) are involved. First, the assembly of five acetate units take place with further manipulations to obtain the right oxidation state for each carbon. The second PKS is responsible for three more condensations, which are not followed by carbonyl reduction. The product **15** obtained contains highly reactive ketones, which undergo a cyclisation/aromatization. It is worth noting that the numerous functionalities present in the RALs family are due to different combinatorial arrangements during the first five condensations.[7,1]



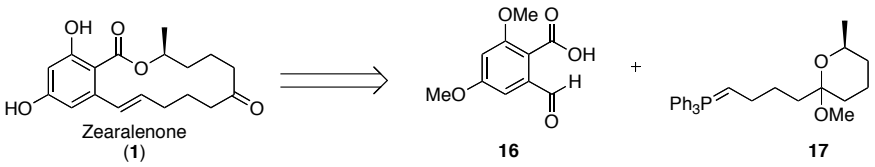
Scheme 2 - Biosynthesis of zearalenone

1.1.3 Common strategies for syntheses of RALs

Biomimetic strategies for the synthesis of resorcylate natural products have not been extensively developed until now, mainly because harsh conditions such as very basic or acidic media were necessary for the aromatization step. Therefore the use of the resorcylate unit as a starting point followed by its derivatization has been the principal method used.

Zearalenone

The first total synthesis of zearalenone (**1**) was achieved in 1968.[8] The key disconnections were a Wittig reaction between aromatic building block **16** and ylide **17**, corresponding to the aliphatic part, and a macrolactonization to close the ring. The methoxy groups were cleaved using boron tribromide (Scheme 3).

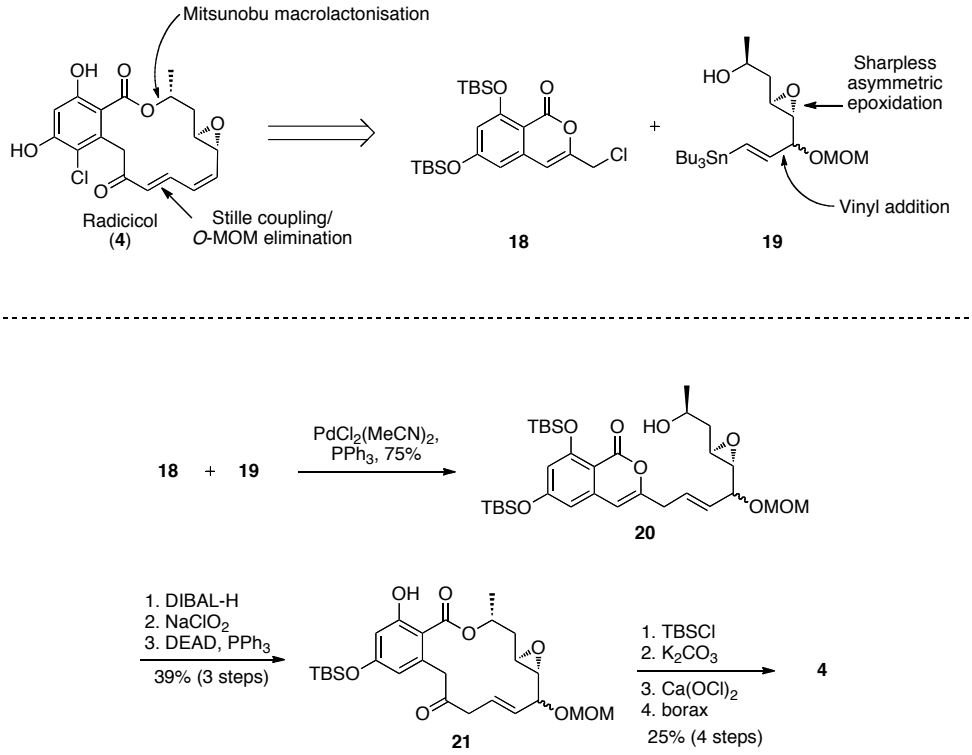


Scheme 3 - Key disconnections for zearalenone (**1**)

Radicicol

In 1992, Lett and co-workers achieved the first total synthesis of radicicol (**4**).[9] Starting from resorcylate derivative **18**, a Stille coupling was performed with tin derivative **19** and afforded **20** in good yield. The subsequent sequence, diisobutylaluminium hydride (DIBAL-H) reduction then oxidation, followed by a Mitsunobu reaction led to macrolactone **21** in 39% yield. It is worth noting that the

Mitsunobu reaction proceeded more efficiently if the *o*-phenol was unprotected. The ketone and conjugated diene were only revealed at a late stage, with the methoxymethyl ether (MOM) elimination. This strategy allowed Lett to overcome the main challenging aspect of radicicol: the allylic epoxide and the ketone functionality at the benzylic position. Finally the chlorine atom was introduced using calcium hypochlorite and subsequent deprotection afforded radicicol (**4**) (Scheme 4).

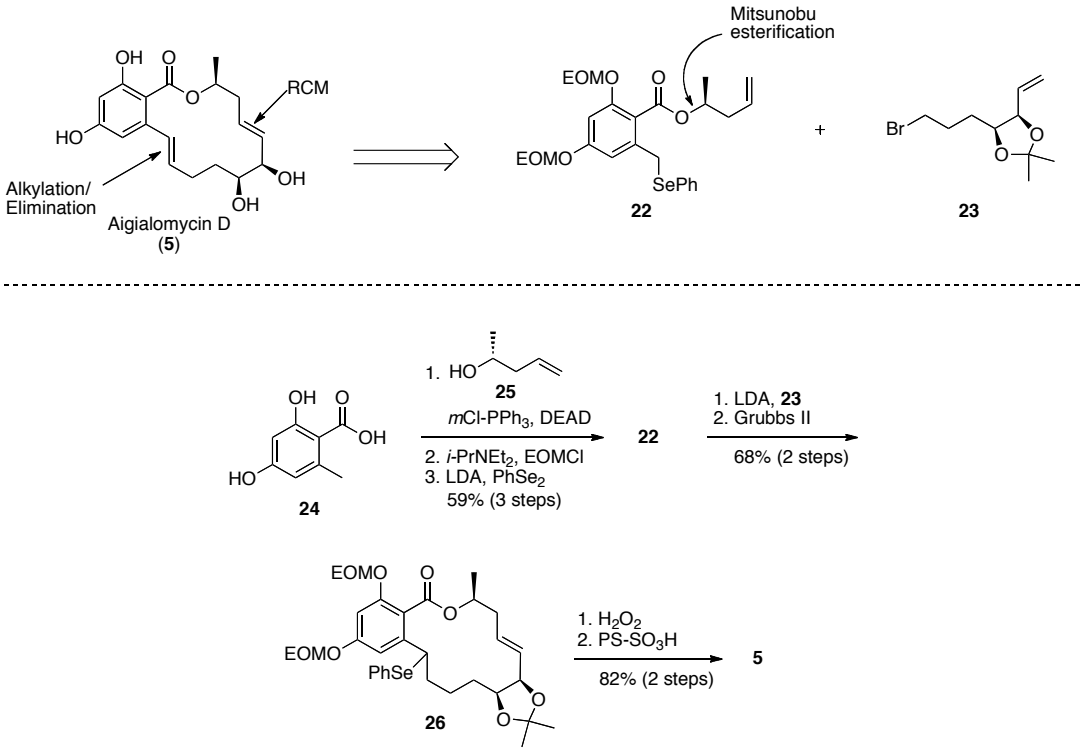


Scheme 4 - Key disconnections and synthesis of radicicol (**4**) by Lett and co-workers

Aigialomycin D

The first total synthesis of aigialomycin D was reported by Danishefsky *et al.* in 2004.[10] In 2006, Winssinger *et al.* published a new strategy, which allowed access to various analogues (Scheme 5).[11] Starting from orsellinic acid (**24)**, a Mitsunobu reaction with alcohol **24** followed by phenol protection and alkylation with diphenyl diselenide, led to **22** in good yield. Alkylation with bromide **23** and subsequent ring

closing metathesis (RCM) afforded protected resorcylate **26** in 68% yield. Finally, selenium oxidation followed by *in situ* elimination and phenol deprotection produced aigialomycin D (**5**) in 82% yield.



Scheme 5 - Key disconnections and synthesis of aigialomycin D (**5**) by Winssinger and co-workers

The previous examples show that, until recently, the strategies for the synthesis of resorcylate natural products were limited: aromatic ring as building-block followed by stepwise derivatization (palladium based coupling and stabilization of benzylic carbanion) and esterification/macrolactonization. Furthermore, the macrolactonization is generally a difficult and low yielding step because the carbonyl group involved is sterically hindered and deactivated by the phenol ring.

1.2 Cruentaren A

1.2.1 Isolation, structure and biological properties

Myxobacteria are a particulary rich source of bioactive secondary metabolites and have therefore attracted attention over the last 25 years. Cruentaren A (**6**), was isolated in 2006 by Höfle *et al.* from the myxobacterium *Byssovorax cruenta*.[5] Its structure was elucidated by detailed NMR spectroscopic analysis revealing, a 12-membered lactone with a (*Z*)-double bond and an *N*-acylallylamine side chain (Figure 2).[12] More precisely, as mentioned earlier, cruentaren A is part of the resorcylic acid lactone natural product. A minor and inactive co-metabolite, cruentaren B (**27**), was also isolated and identified as a 6-membered lactone isomer of cruentaren A.[13]

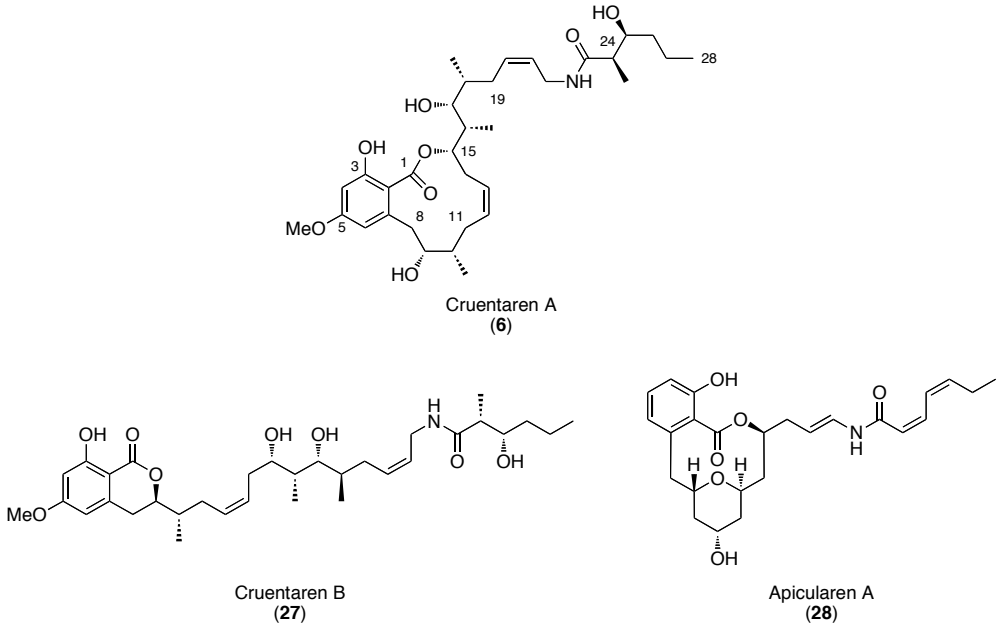


Figure 2 - Cruentaren A (**6**), B (**27**) and structurally related apicularen A (**28**)

This new compound **6** strongly inhibited the growth of yeast and filamentous fungi and showed high cytotoxicity against L929 mouse fibroblast cell with an half maximal inhibitory concentration (IC_{50}) value of 1.2 ng mL^{-1}. Despite its structural similarity with apicularen A (**28**) (Figure 2), which targets vacuolar-H+ATPase (V-ATPase), further studies revealed that cruentaren A (**6**) selectively inhibits F-ATPase.[5] In recent years, it became more evident that adenosine triphosphtatases (ATPases) play a crucial role in numerous diseases including cancer. Therefore a total synthesis would be beneficial to evaluate the full potential of cruentaren A and potentially provide access to analogues. Since the project started in late 2007, two research groups have reported the total synthesis of cruentaren A.

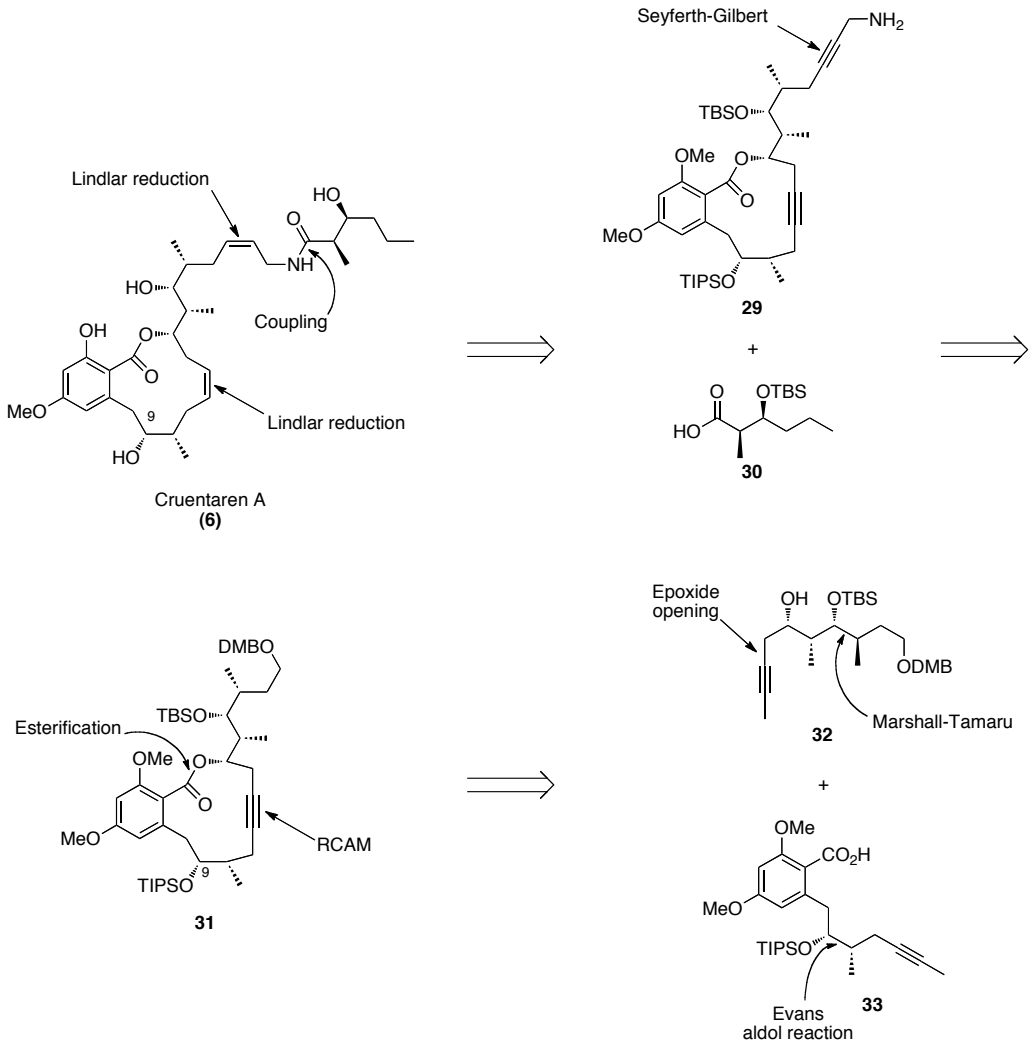
1.2.2 Published syntheses

The first total synthesis was published by Maier *et al.*[14] closely followed by Fürstner *et al.* in 2007.[15] The two syntheses beautifully showcase the use of ring-closing alkyne metathesis (RCAM) in total syntheses of natural products and present other similarities.

1.2.2.1 Maier's synthesis

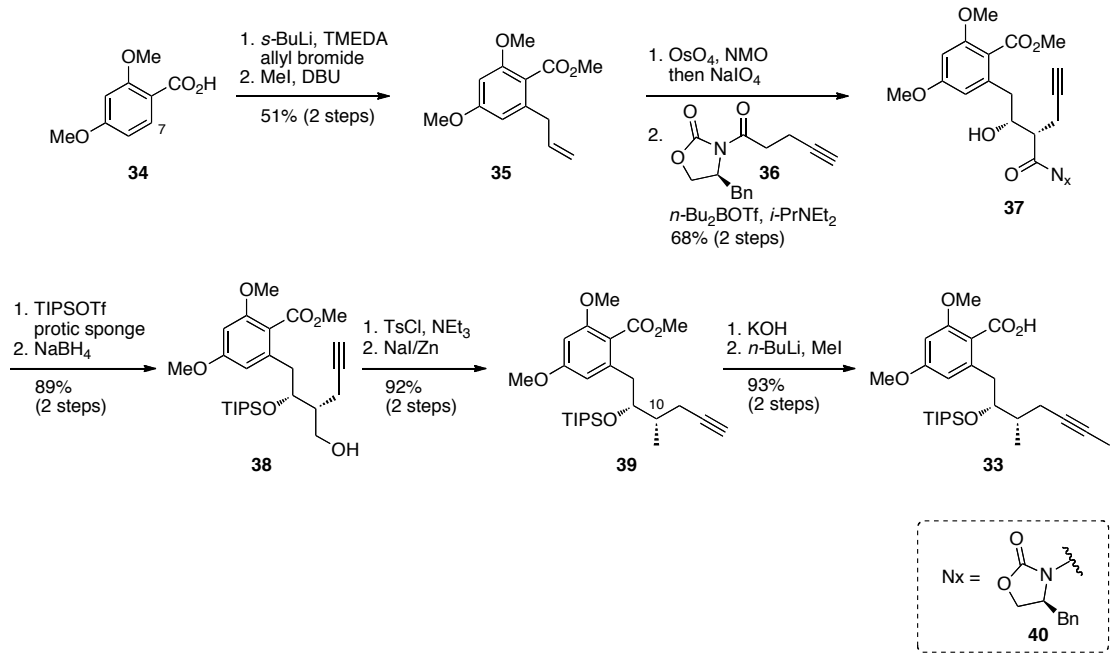
In the Maier approach, the final step was the Lindlar reduction of both triple bonds (Scheme 6). With the triple bond in place, the macrolactone is highly strained, therefore translactonisation with 9-OH bearing a tri*iso*propylsilyl (TIPS) protecting group is impossible. The construction of the side chain was based on the coupling between amine **29** and the ß-hydroxy acid **30** and on a Seyferth-Gilbert reaction in

order to introduce the alkyne moiety, which was later reduced to a (*Z*)-alkene. The macrolactone ring was formed using an esterification followed by a RCAM. Acid **33**, used for the key esterification, was derived from resorcylic acid derivative **34** and its two stereocenters were created by Evans aldol reaction. The key steps for the synthesis of alkynol **32** were a Marshall-Tamaru reaction followed by hydroboration. The homopropargylic alcohol moiety was obtained by nucleophilic attack of an epoxide, derived from the corresponding vicinal diol, with trimethylsilyl (TMS)-acetylene.[14]



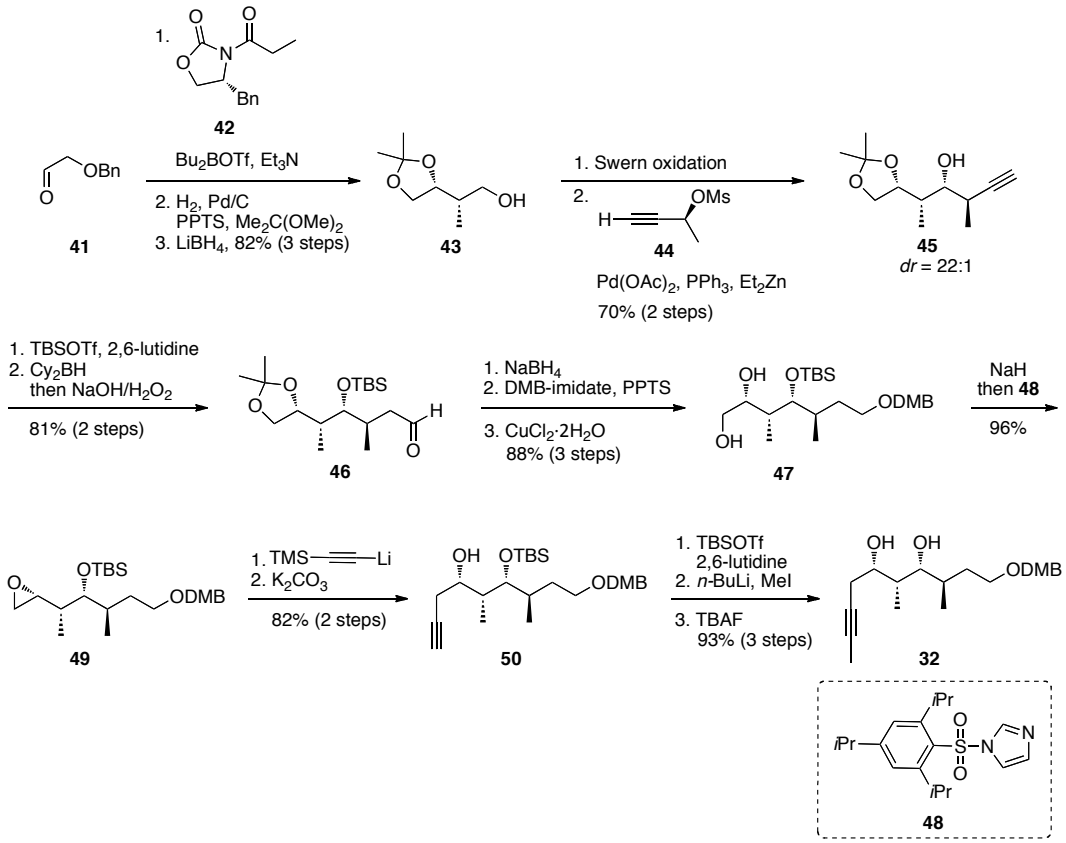
Scheme 6 - Key disconnections for Maier's synthesis of cruentaren A (**6**)

Synthesis of acid **33** started with dimethoxybenzoic acid (**34)** (Scheme 7). First **34** was allylated at C-7 after treatment with *s*-butyllithium and converted to the corresponding methyl ester in 51% yield. Oxidative cleavage of terminal alkene **35** was achieved using an osmium tetroxide-catalysed periodate oxidation and afforded the corresponding aldehyde derivative, which was engaged in an Evans aldol reaction with pentynyloxazolidinone **36** to yield the "Evans *syn*" product **37** in 68% yield over two steps. TIPS-protection and reductive cleavage of the chiral auxiliary afforded **38**. In order to obtain the desired methyl group at C-10 primary alcohol **38** was converted into its tosylate derivative and treated with sodium iodide and zinc to give intermediate **39** in 92% yield. This reductive removal of the tosylate group was first reported in 1976 by Fujimoto *et al*.[16] and takes place in two steps with first conversion of the tosylate into its iodide derivative, then reduction with zinc powder. After saponification of ester **39**, terminal alkyne was methylated and the desired key fragment **33** was obtained in 10 steps and 26% overall yield.



Scheme 7 - Synthesis of key fragment **33**

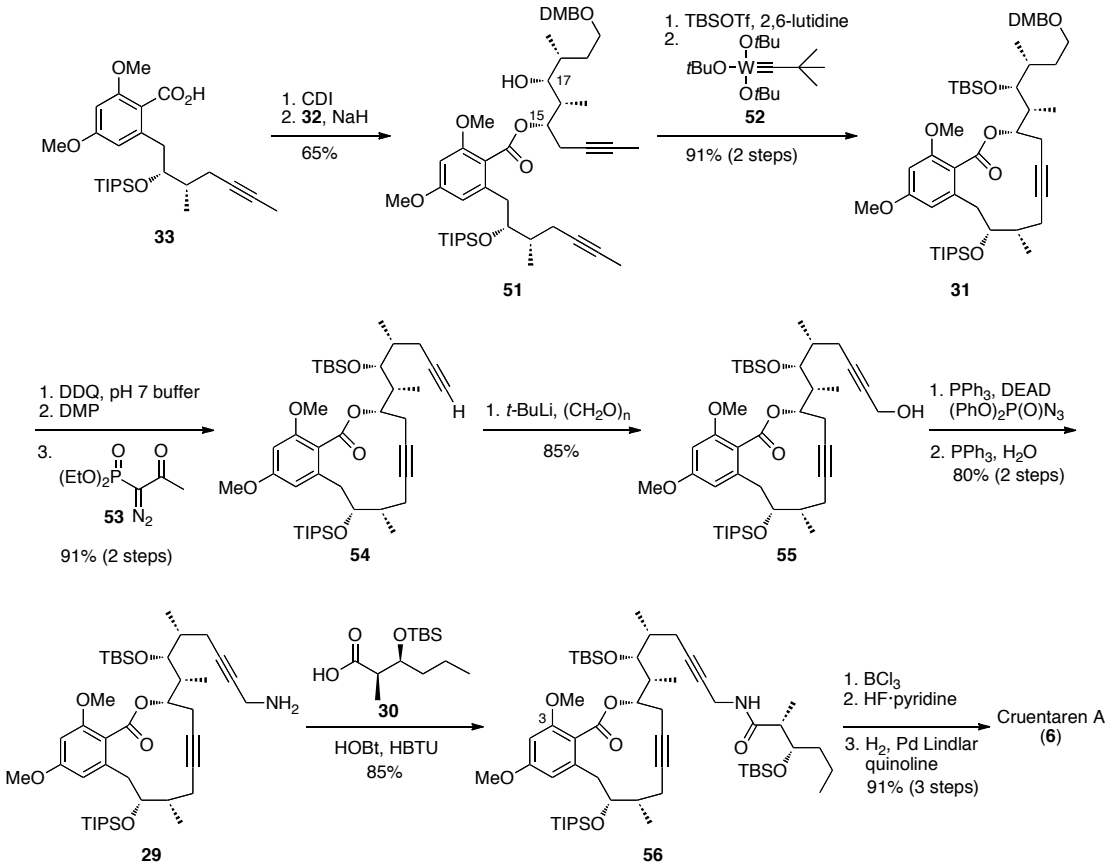
The synthesis of key alcohol **32** (Scheme 8) started from literature known triol **43** which was prepared in three steps from the procedure described by Kuwajima *et al*.[17] This procedure involved the formation of an Evans *syn* aldol aduct, acetonide protection and reductive removal of the chiral auxiliary. After oxidation of primary alcohol **43** to the corresponding aldehyde, a Marshall-Tamaru reaction,[18] featuring (*S*)-propargyl mesylate **44**, afforded compound **45** with high diastereoselectivity (*dr* = 22:1) and 70% yield over two steps. At this stage, the four stereocenters of key alcohol **32** were in place. After protection of the secondary alcohol, the terminal alkyne was hydroborated using dicyclohexyl borane to give aldehyde **46** which was then reduced to the corresponding alcohol and protected with a 3,4-dimethoxybenzyl (DMB) group. The acetonide moiety was then cleaved using a mild method to afford diol **47**.[19] In order to introduce the alkyne moiety, **47** was converted to the corresponding epoxide **49** using a one-pot procedure with sodium hydride and tosylimidazole **48**.[20] Epoxide **49** was then successfully opened with lithiated TMS-acetylene to give homopropargylic alcohol **50** in 82% yield. After temporary protection of the secondary alcohol, **50** was methylated. Finally, *tert*-butyldimethysilyl (TBS) cleavage of both secondary alcohols afforded the desired key fragment **32** (15 steps, 30% overall yield).



Scheme 8 - Synthesis of key fragment **32**

With both key fragments in hand, the esterification reaction was attempted with various standard conditions developed by Mitsunobu[21], Yamaguchi[22] and Trost[23] as well as other coupling agents but were unsuccessful. Furthermore the conversion of acid **33** to the corresponding acid chloride, the method of choice for the coupling of sterically hindered acids, only led to the 6-membered lactone despite the relatively robust TIPS-protecting group on 9-OH. The esterification was finally achieved by reacting the imidazolidine derivative of **33** with the disodium alcoholate of diol **32** (Scheme 9). Only one regioisomer was formed, confirmed with a correlation spectroscopy (COSY) experiment. The steric hindrance of 17-OH, which is in between two tertiary carbons, compared to 15-OH explains this result. After TBS-protection of the secondary alcohol, RCAM was conducted with Schrock

catalyst **52**[24] and afforded the desired macrolactone **31**. Unfortunately Lindlar reduction of the alkyne moiety, followed by the cleavage of the silyl protecting groups with hydrogen fluoride in pyridine only resulted in the formation of the δ-lactone. Therefore Maier *et al.* decided to employ the reduction as the final step in order to prevent the translactonisation. Starting from macrocyclic **31**, DMB cleavage with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) followed by oxidation of the primary alcohol to the corresponding aldehyde and subsequent Seyferth-Gilbert reaction with diazophosphonate **53** afforded terminal alkyne **54** in 91% yield over three steps. The subsequent carbon homologation was performed by treating **54** with *tert*-butyllithium and paraformaldehyde affording alcohol **55** in 85% yield. In order to convert **55** into the corresponding amine, the usual method involving azide formation with a Mitsunobu conditions followed by a Staudinger reduction was used and afforded **29** in good overall yield. The coupling with acid **30** (obtained in three steps using Evans aldol chemistry) was then carried out with 1-hydroxybenzotriazole (HOBt) and *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluroniumhexafluorophosphate (HBTU) as coupling agents and amide **56** was obtained. At this stage the full skeleton of cruentaren A was secured. The demethylation at C-3 was achieved using boron trichloride at -80 ºC. Boron trichloride selectively demethylates the methoxy group which is ortho to a carbonyl group because of the coordination of the boron atom with the two oxygen atoms.[25] Silyl group cleavage was achieved with hydrogen fluoride in pyridine and no δ-lactone was observed, indicating that the triple bond was effective in preventing translactonisation. Finally Lindlar reduction of both alkyne moieties afforded cruentaren A in 91% yield over three steps. Cruentaren A was obtained in 28 steps for the longest linear sequence and 8% overall yield.



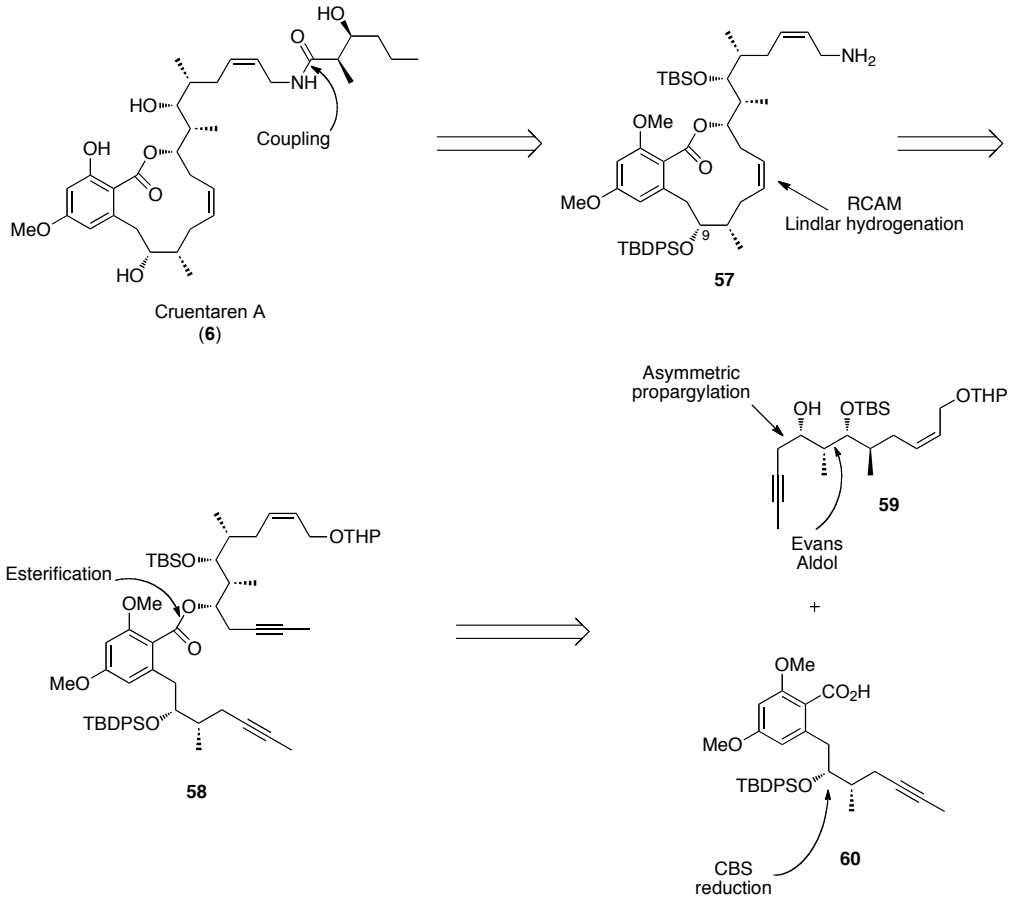
Scheme 9 - Synthesis of cruentaren A (**6**)

Following this strategy, Maier and co-workers managed to synthesize various analogues of cruentaren A.[26] Unfortunately, none of them showed any biological improvement and therefore they will not be discussed in this thesis.

1.2.3.2 Fürstner's synthesis

The global strategy proposed by Fürstner presents similarities with Maier's work (Scheme 10). The side chain was obtained by coupling amine **57** with hexanoic acid **30** and the formation of the 12-membered lactone is identical: esterification followed by RCAM/hydrogenation. It is noteworthy that in this new approach the triple bond of the macrolactone was not reduced to the (*Z*)-alkene at the end of the synthesis but

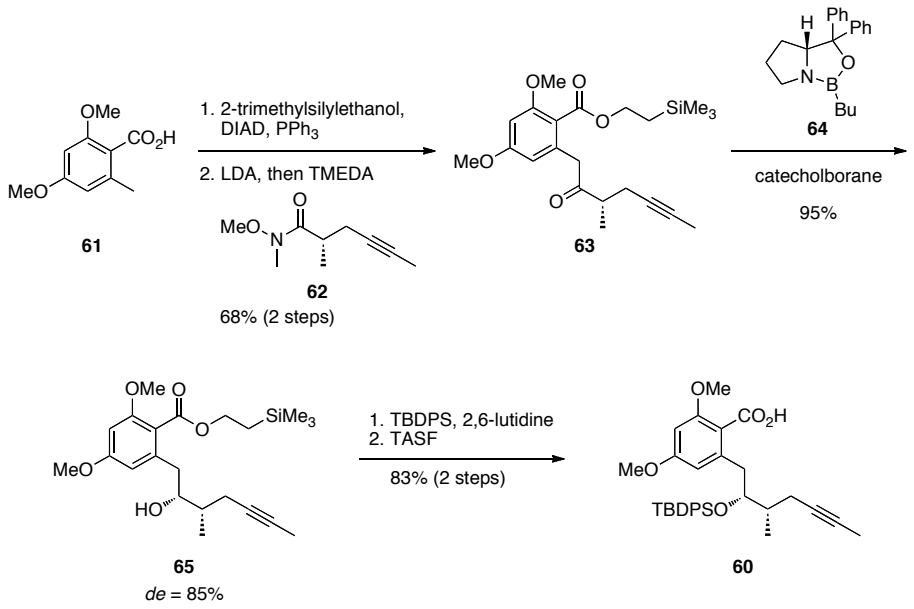
even before the deprotection steps. However, by using a stable *tert*-butyldiphenylsilyl (TBDPS) protecting group for 9-OH, no translactonisation was observed during the synthesis and the final silyl deprotection proceeded smoothly without formation of the δ-lactone. Synthesis of the key acid **60** is based as well on the derivatization of the aromatic building block and was achieved in five steps from orsellinic acid (**24)** using Evans alkylation and Corey-Bakshi-Shibata (CBS) reduction to install the two stereocenters. Key polyketide **59** was generated using highly stereoselective reactions including the Soderquist asymmetric propargylation.



Scheme 10 - Key disconnections for Fürstner's synthesis of cruentaren A (**6**)

The construction of the aromatic key fragment **60** begins with 2,4-dimethoxy-6-methylbenzoïc acid (**61**) (Scheme 11). After protection of the acid

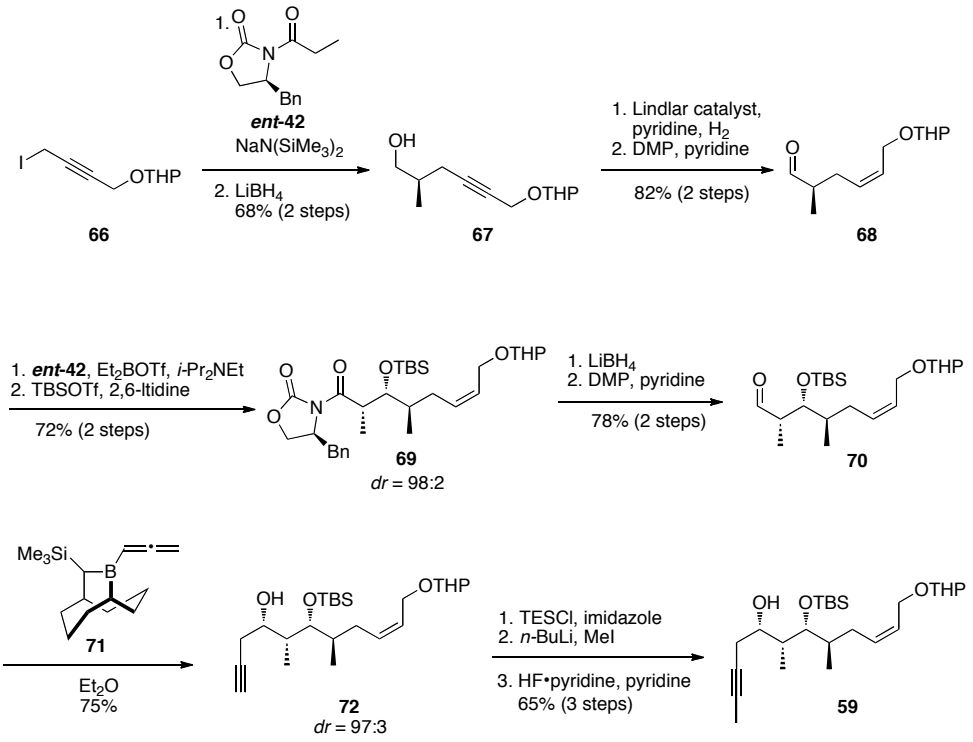
moiety, deprotonation with lithium di*iso*propylamide (LDA) followed by acylation with Weinreb amid derivative **62** (obtained *via* Evans chemistry) afforded ketone **63** in 68% yield. CBS reduction of the carbonyl group with the required (*R*)-oxazaborolidine **64** afforded **65** with good diastereoselectivity and in 95% yield.[27] Subsequent protection of the secondary alcohol with a robust TBDPS group in order to avoid possible subsequent translactonisation was followed by selective cleavage of the TMS group with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) to afford key fragment **60** in 83% yield over two steps. With six steps for the longest linear sequence (54% overall yield), Fürstner's strategy for the synthesis of **60** is much efficient and convergent than the one described by Maier.



Scheme 11 - Synthesis of key fragment **60**

The synthesis of alcohol **59** starts with an Evans alkylation[28],[29] with electrophile **66**, prepared in two steps from 1,4-butynediol, followed by reductive cleavage of the auxiliary to afford primary alcohol **67** in 68% yield (Scheme 12). Lindlar reduction followed by Dess-Martin oxidation afforded aldehyde **68** in high yield. Subsequent

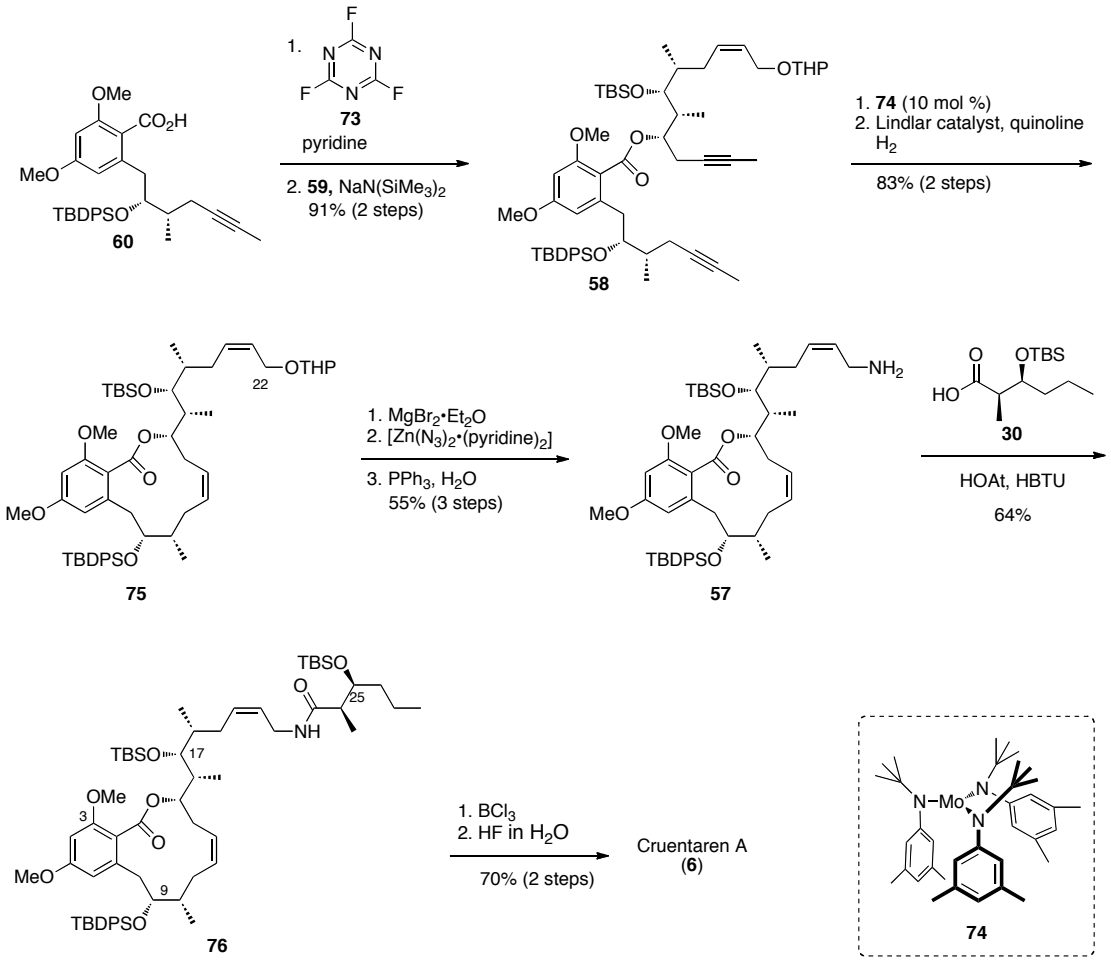
aldolisation with (*S*)-oxazolidinone ***ent*-42** led to the *syn* Evans product which was obtained with excellent diastereoselectivity. Subsequent TBS-protection of the secondary alcohol afforded **69** in 72% yield over two steps. Reductive cleavage of the auxiliary followed by Dess-Martin oxidation in pyridine in order to avoid epimerization, afforded primary alcohol **70**. In order to introduce the propargyl moiety and to set the last stereocenter, Fürstner and co-workers decided to perform an asymmetric propargylation. Asymmetric propargylation reactions have been widely studied over the past decades resulting in important progress in terms of yield and enantioselectivity. The addition reaction of propargyl or allenyl metal reagent onto a carbonyl compound is the most common type. Recently Soderquist developed a powerful asymmetric allenylboration leading to homopropargylic alcohols in good yield and high enantioselectivity.[30] It involves the treatment of chiral borabicyclodecanes with propargyl bromide through Grignard conditions to form **71** that then reacts with the aldehyde to provide the desired homopropargylic alcohol. Fürstner and co-workers applied this methodology. Aldehyde **70** was treated with **71** and underwent propargylation to afford the desired alcohol **72** in high diastereoselectivity (*dr* = 97:3) and good yield. Temporary protection of the created secondary alcohol followed by methylation of the terminal alkyne and cleavage of the TES group gave access to the **59** in 65% yield over three steps. Key alcohol **59** was obtained in 12 steps and 15% yield.



Scheme 12 - Synthesis of key fragment **59**

The esterification between acid **60** and alcohol **59** was the next key step in the synthesis of cruentaren A (Scheme 13). Fürstner and co-workers faced the same synthetic problem as Maier's as the most common esterification methods were unsuccessful. Furthermore, despite having a robust TBDPS-group on 9-OH, conversion of acid **60** into the corresponding acid chloride only led to the formation of the δ-lactone. Fürstner finally showed that the acid fluoride derived from acid **60** was a successful answer to this esterification and obtained **58** in 91% yield with no trace of the undesired lactone.[31] The acid fluoride derivative was prepared by treatment of **60** with 2,4,6-trifluoro-1,3,5-triazene (**73**) and pyridine. The next step was the RCAM, a challenging step for the Fürstner group as the alkyne metathesis is one of their predilection field of research with the discovery and development of molybdenum complex as catalyst such as **74**[32] and more recently silanolate-supported molybdenum nitrido and alkylidyne complexes.[33] Fürstner and co-workers found that

the use of the Schrock catalyst **52** for the RCAM of alkyne **58** was only responsible for the cleavage of the tetrahydropyranyl (THP) protecting group. The Schrock catalyst is indeed well known to be incompatible with numerous functional groups.[24] On the contrary, they showed that the use of their own catalyst **74** afforded the desired macrolactone. They later explored other catalytic system[33,34] for the synthesis of analogues of **6**[35] and all were successful. Despite the greater risk of translactonisation, the alkyne moiety of the macrolactone was then reduced using Lindlar catalyst to yield (*Z*)-olefin **75**. After deprotection of 22-OH, the primary alcohol was converted into the corresponding azide derivative using the Mitsunobu conditions. Subsequent Staudinger reduction afforded the corresponding amine **57** in 55% yield over three steps. **57** was then coupled with acid **30** using conventional coupling agents to afford amide **76** in 64% yield. At this stage the fully protected skeleton of cruentaren A was obtained. Demethylation at C-3 was unsurprisingly performed with boron trichloride[25] and the TBS group at C-25 was also cleaved during this step (the sterically hindered TBS group at C-17 was left untouched). Finally the conditions for the final silyl deprotection were investigated. Various fluoride sources, such as tetra-*n*-butylammonium fluoride (TBAF), TASF, hydrogen fluoride in pyridine, were unsuccessful. Only the use of aqueous hydrogen fluoride met with success and afforded cruentaren A (**6**) with no trace of cruentaren B, the product of translactonisation. Cruentaren A was obtained in 22 steps and 3% yield for the longest linear sequence.



Scheme 13 - Synthesis of cruentaren A (**6**)

Fürstner *et al.* synthesized a range of analogues. Three of them turned out to be even more active than cruentaren A itself (Figure 3).[35] The synthetic strategy to obtain those analogues was similar to the one previously described, with cycloalkene **75** as key intermediate. However, since amine **57** turned out to be rather unstable, Fürstner and co-workers developed another strategy for the azide reduction/coupling sequence: triphenylphosphine in aqueous tetrahydrofuran was replaced by tributylphosphine in dry tetrahydrofuran during the Staudinger reaction to afford an aza-ylide intermediate which could directly react with acid **30** in presence of 1-hydroxy-7-azabenzotriazole (HOAt)/HBTU to afford desired amide **76**.

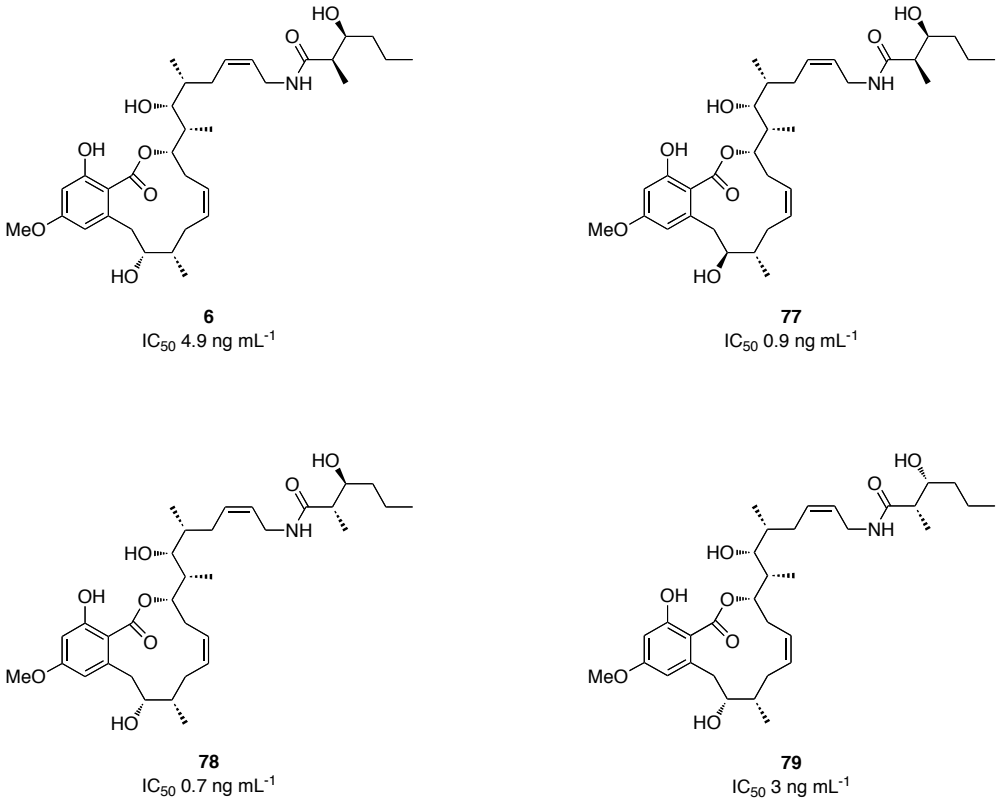


Figure 3 - Cytotoxicity of cruentaren A (**6**) and analogues synthesized by Fürstner *et al.* against L-929 mouse fibroblast cells

These two syntheses of cruentaren A are following the usual route used for the synthesis of RALs and are therefore based on three main strategies: aromatic ring as starting block followed by stepwise derivatizations and esterification/macrolactonization.[1] The main challenge in these syntheses was the esterification, which is in fact the limiting step for many resorcylate natural products synthesis. In this particular synthesis, the level of difficulty was even higher because of the steric hindrance of alcohol **59** that makes the standard method such as Mukaiyama, Mitsunobu, Yamaguchi, Trost esterification and coupling agents uneffective. The other problem was the possible formation of the six-membered lactone when trying to convert the acid into the corresponding acid chloride. Maier and co-workers eventually found that the desired ester could be obtained by

converting the acid to the imidazolidine derivative. However, Fürstner and co-workers found this approach low yielding and hardly scalable. Instead, they showed that by converting the acid to the corresponding acid fluoride, the desired esterification could be carried out in high and reproducible yield with no trace of the δ-lactone. Although the difficulties caused by the esterification could be successfully solved in this case, a general limitation of these strategies is obvious.

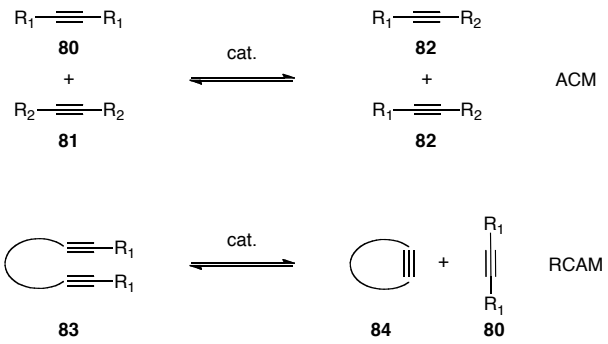
1.3 Alkyne metathesis

The RCAM/Lindlar reduction system seemed to be the obvious choice for the synthesis of cruentaren A. However, despite being known for several decades, alkyne metathesis is not yet as widely used as alkene metathesis (Scheme 14). It is only recently that its full potential is used for the synthesis of natural products, especially as a RCAM combined with Lindlar reduction to give stereoselectively access to (*Z*)-cycloalkenes. On the contrary, RCM (ring closing metathesis) do not allow to predict or to control the stereochemistry, which depends on the ring strain. Several reasons might explain why alkyne metathesis has been under used by organic chemists for a long time:

-While several catalysts for the olefin metathesis are commercially available and easy to handle, many catalysts for the alkyne metathesis are highly sensitive to air and various functional groups and require harsh reaction conditions.

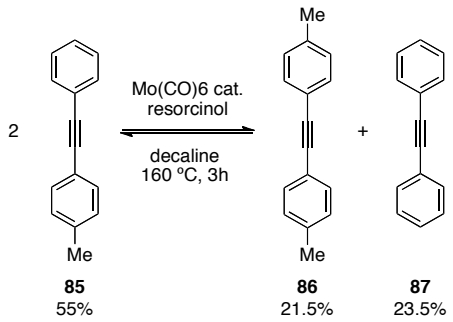
-The RCM can give access to ring size ≥ 5, whereas RCAM can only be used to synthesize ring size ≥ 12.

-Finally, terminal alkynes are not compatible with most catalytic systems.



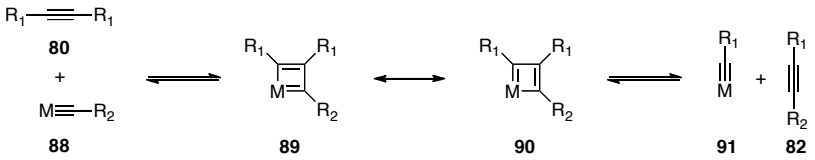
Scheme 14 - Alkyne metathesis

Until recently three main systems were available for the alkyne metathesis. The first homogeneous system was reported by Mortreux et *al.* in 1974[36] and consists of molybdenum hexacarbonyl and phenol additives (Scheme 15). Despite being user friendly (cheap and commercially available reagents), the rather harsh conditions and the low functional groups tolerability has limited its application.



Scheme 15 - Mortreux's system

The exact catalytic mechanism and the active species of alkyne metathesis still remain unknown, however Katz *et al*. proposed a mechanism in 1975 involving a metal carbene in a [2+2] cycloaddition and cycloreversion steps (Scheme 16).[37]



Scheme 16 - Katz's mechanism of alkyne metathesis

This mechanism was later investigated and proved by Schrock and co-workers when they developed a new catalytic system. The Schrock type catalysts include high oxidation state molybdenum and tungsten alkylidyne complexes, the most commonly used being the tungsten neopentylidyne complex **52**, which forms metallocyclobutadienes (refer to Katz mechanism) when treated with internal alkynes.[24,38] In 1998, Fürstner was the first to report the use of this catalyst to convert functionalized diynes into the corresponding macrocycles (Figure 4, Table 1).[39]

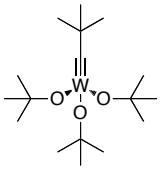


Figure 4 - Schrock catalyst **52**

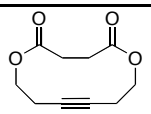
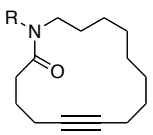
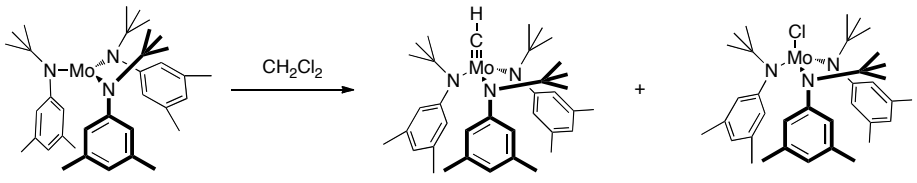
Entry	*Product*	*Yield*
a	 **92**	73%
b	 **93**	62% (R=H) 72% (R=Me)

Table 1 - Examples of RCAM using **52** (4-6 mol %) at 80 ºC in C_6H_5Cl[39]

This class of catalysts offered a broader application than the Mortreux system because of its milder reaction conditions. However its air and moisture sensitivity and appreciable Lewis acidity lowered its tolerance towards numerous functional groups and limited the development of alkyne metathesis.

Later Fürstner and co-workers developed a new catalytic system based on sterically hindered trisamido molybdenum(III) complexes of the general type [Mo{(*t*Bu)(Ar)N}$_3$] activated by dichloromethane (Scheme 17).[40] The role of dichloromethane was investigated and it was found that the active species was in fact [ClMo{(*t*Bu)(Ar)N}$_3$] **94**. During this investigation, the presence of another complex, [HCMo{(*t*Bu)(Ar)N}$_3$] (**95**), was detected. However results showed that this terminal alkylidyne complex was only active for one turn-over.



Scheme 17 - Catalyst **74** and its activation by CH_2Cl_2

This catalytic system was successfully tested for RCAM and ring sizes ≥ 12 were formed in high yields. The full potential of catalyst **74** was particularly tested towards the synthesis of challenging natural products including epothilone A and C and cruentaren A (Table 2).[40,41] Catalyst **74** exhibits a superior tolerance towards many functional groups than the Schrock catalyst **52**. However acidic protons and secondary amides are not compatible. Despite its outstanding performances this

catalyst suffers from air and moisture sensitivity and can even activates molecular nitrogen.

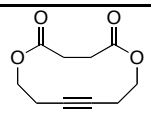
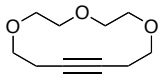
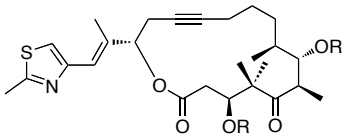
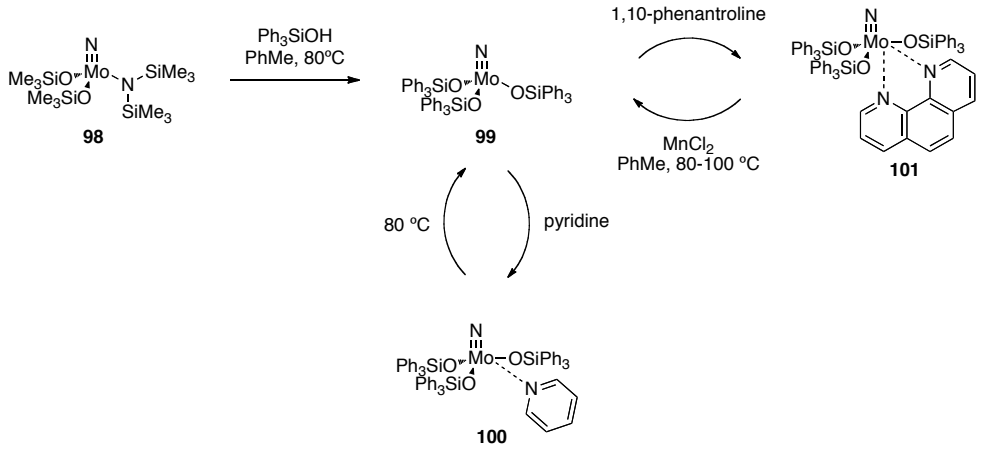
Entry	*Product*	*Yield*
a	 **92**	91%
b	 **96**	60%
c	 **97** (R = TBS) precursor of epothilone C	80%

Table 2 - Examples of RCAM using **74** (10 mol %) in PhMe/CH_2Cl_2 at 80 ºC[42]

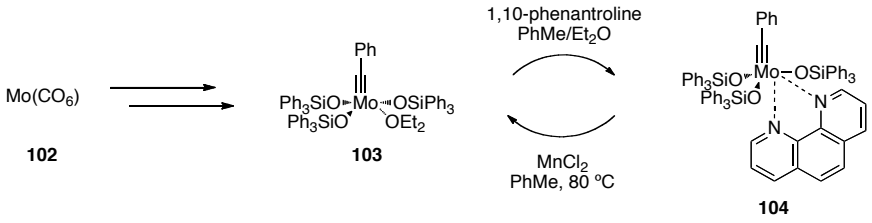
With hope to develop new user-friendly catalysts in order to expand the use of alkyne metathesis, Fürstner investigated the use of silanolates as suitable ancillary ligands. Very recently, Fürstner and co-workers reported the discovery of molybdenum nitride and alkylidyne complexes with silanolate ligands as effective alkyne metathesis (pre)catalyst (Scheme 18, Scheme 19).[33,34] In the case of nitride complexes, the active specie can be generated *in situ* from the molybdenum nitride complex **98** by addition of triphenylsilanol. Another possibility is the complexation of the active specie **99** with pyridine or phenanthroline, which affords air stable complexes, **100** and **101** respectively. The pyridine adduct is reported to be robust enough to be weighed in air whereas the phenanthroline adduct seems to be indefinitely air stable. The catalytic

activity is then restored upon heat for **100** and upon exposure to manganese dichloride for **101** (Scheme 18).



Scheme 18 - Molybdenum nitride complexes with silanolate ligands

For the alkylidyne complexes (Scheme 19), the active specie **103** can be obtained from molybdenum hexacarbonyl (**102**) following an adapted synthesis route leading to Shrock alkylidyne. Again this complex **103** can be isolated as phenanthroline adduct **104** to obtain a better stability towards air.



Scheme 19 - Molybdenum alkylidyne complexes with silanolate ligands

Since catalyst **103** is superbly active, the alkyne metathesis reaction can be performed even at room temperature.[34] While this is a great improvement for sensitive substrate, it does create a new difficulty, which involves the accumulation of but-2-yne. The

addition of 5 Å molecular sieves resolved successfully this problem. In addition to their remarkable air stability, these catalysts show an excellent functional group tolerance as well as high catalytic performance. Fürstner and co-workers have already shown their strong potential use towards the synthesis of several natural products, including cruentaren A (Table 3).

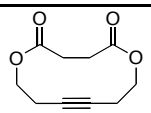
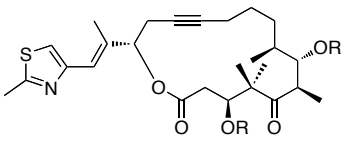
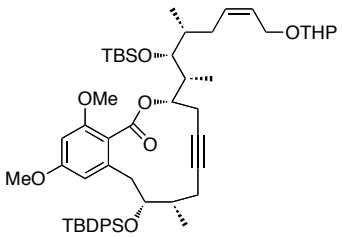
Entry	*Product*	*Yield*				
		[a]**98**	[b]**100**	[c]**101**	[d]**103**	[e]**104**
a	 **92**	83%	42%	91%	73%	78%
b	 **97** (R = TBS) precursor of epothilone C	42%	-	-	91%	-
c	 **105** precursor of cruentaren A	81%	-	-	82% (at 80 ºC)	-

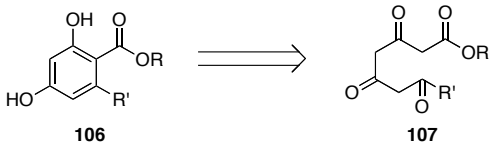
Table 3 - [a] **98** (20 mol %), Ph_3SiOH in PhMe at 80 ºC. [b] **100** (20 mol %) in PhMe at 80 ºC. [c] **101** (10 mol %), $MnCl_2$ in PhMe at 80 ºC. [d] **103** (2 mol %), MS 5 Å in PhMe at rt. [e] **105** (5 mol %), $MnCl_2$, MS 5 Å in PhMe at 80 ºC then rt.[34,35]

The new catalysts developed by Fürstner and co-workers show high catalyst properties and stability which greatly open access to the use of alkyne metathesis in organic chemistry. These user-friendly complexes should allow the development of

the RCAM combined with the Lindlar reduction. The last obstacle for the complete development of the alkyne metathesis is the fact that terminal alkyne are not compatible with most catalysts.

1.4 New biomimetic inspired strategy

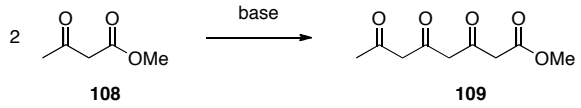
As illustrated by the previous syntheses of RALs, including cruentaren A, described earlier, the strategy for the synthesis of this class of natural product is limited. Because the resorcylate unit is a privileged pharmacophore and the RALs contain highly promising biologically active compounds there was need for the development of much more flexible strategies. The Barrett group decided therefore to develop a new biomimetic inspired strategy based on the construction of the aromatic unit from triketo-ester compounds (Scheme 20).



Scheme 20 - Construction of the resorcylate unit from polyketides

1.4.1 Aromatization of polyketides by Harris

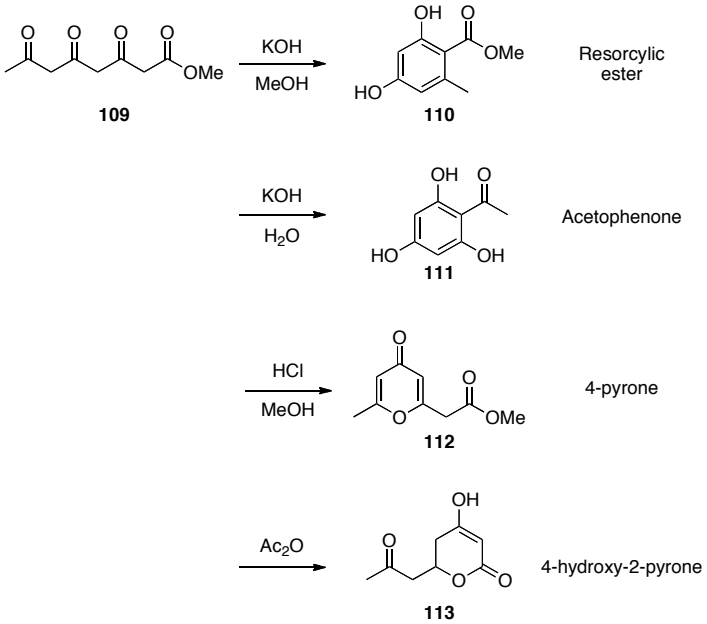
In the late 1970s, Harris reported that polyketide chains and more specifically 3,5,7-triketoester **109** could be obtained by self condensation of methyl acetoacetate units **108** under basic conditions (Scheme 21).[43]



108 109

Scheme 21 - Formation of 3,5,7-triketoester **109**

More importantly, Harris established that under specific conditions, simple polycarbonyl chains could undergo the same cyclisation reactions as in nature without enzyme catalysis. He showed that starting from 3,5,7-triketoester **109**, four different products could be obtained (Scheme 22). If treated with a strong base, **109** led to resorcylate ester **110**. Using strong basic aqueous media, acetophenone **111** was obtained through Claisen condensation. Finally under acidic conditions two different ring closures took place leading to 4-pyrone **112** and 4-hydroxy-2-pyrone **113**.



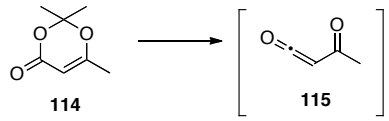
109 110 111 112 113

Scheme 22 - Synthesis of aromatic products from polyketides

Inspired by this discovery, Barrett and Barton in 1980 showed that the aromatization of simple polyketide chains could occur under mild basic conditions using pH 9.2 buffer to form resorcylate **110**.[44] This discovery paved the way to our new strategy.

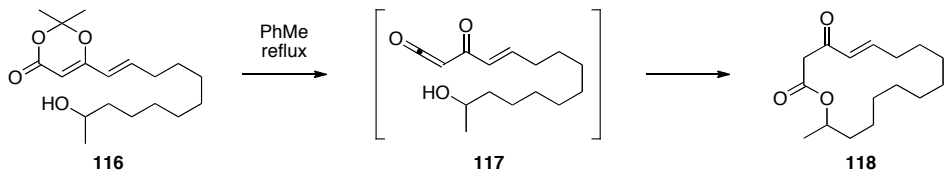
1.4.2 Dioxinone as a masked carbonyl group

A mild method, allowing various functionalities, to form 3,5,7-triketoesters was necessary to validate the new strategy. In 1984, Hyatt showed that dioxinone **114** could undergo retro Diels-Alder reaction to form the highly reactive ketene intermediate **115** which could then be trapped *in situ* with various nucleophiles (Scheme 23).[45]



Scheme 23 - Formation of ketene **115** by thermolysis

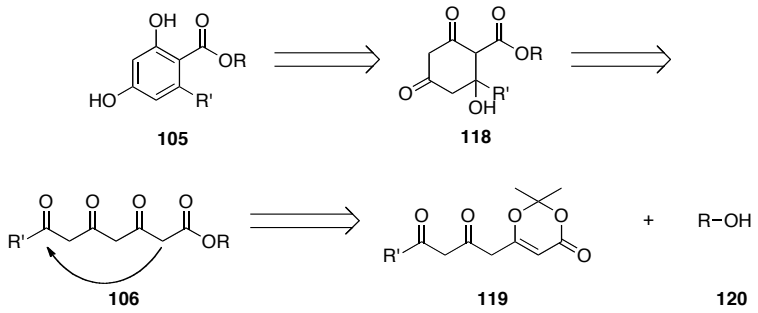
Based on this discovery, Boeckman developed a macrolactonization method in 1989 through the thermolysis of dioxinone **116** and intramolecular trapping of the corresponding ketene to form lactone **118** (Scheme 24).[46]



Scheme 24 - Macrolactonisation based of the thermolysis of dioxinone **116**

1.4.3 Barrett group strategy

The aromatization of polyketides developed by Harris and the use of a dioxinone as a masked carbonyl group for the esterification step were the grounds of our new biomimetically inspired strategy. These two discoveries led us to consider a late stage aromatization as the key step for the synthesis of RAL natural products (Scheme 25). Therefore polyketide **106** could be a precursor of resorcylate **105** *via* aldol condensation followed by dehydration. Furthermore **106** could be obtained from alcohol **120** and diketo-dioxinone **119** by thermolysis followed by ketene trapping. This last step represents a mild method for the synthesis of triketo-ester derivatives.

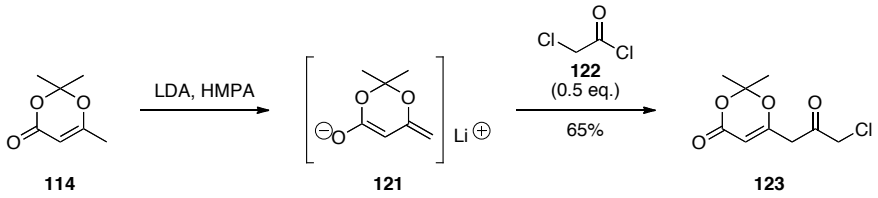


Scheme 25 - Barrett group strategy for the biomimetic synthesis of RALs

1.4.4 Synthesis of keto-dioxinone

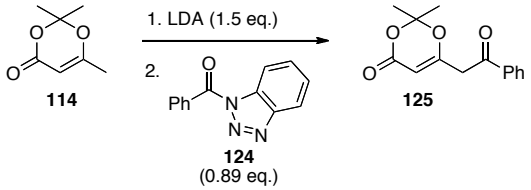
The new strategy developed by the Barrett group for the synthesis of RAL natural products would imply the synthesis of keto-dioxinone and diketo-dioxinone derivatives. Keto-dioxinone derivatives were first reported in 1991 by Kaneko and co-workers who discovered that keto-dioxinone **123** could be prepared by deprotonation of dioxinone **114** with LDA in presence of hexamethylphosphoramide

(HMPA) followed by addition of acid chloride **122**.[47] Keto-dioxinone **123** was selectively formed *via* *C*-acylation (Scheme 26). The *O*-acylation, which was a competitive reaction, could be prevented by using 0.5 equivalent of electrophile **122**.



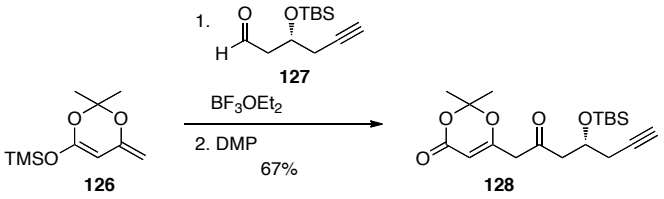
Scheme 26 - Synthesis of keto-dioxinone **123** by Kaneko and co-workers

In 2005, Katritzky *et al.* optimised and showed that *C*-acylation of lithium enolate of dioxinone could be performed by using an acylbenzotriazol derivatives, which are easier to handle and more tolerant towards several functional groups than acid chloride derivatives (Scheme 27).[48]



Scheme 27 - Synthesis of keto-dioxinone **125** by Katritzky and co-workers

In 2003, Tadano and co-workers developed a novel two-step methodology for the synthesis of keto-dioxinone through the succesful synthesis of (+)-macquarimicin A. This strategy involved a Mukaiyama type aldolisation with sililanol ether of dioxinone **126**, which reacted with aldehyde **127** to give a secondary alcohol derivative, which was then oxidised to yield keto-dioxinone **128** (Scheme 28).[49]



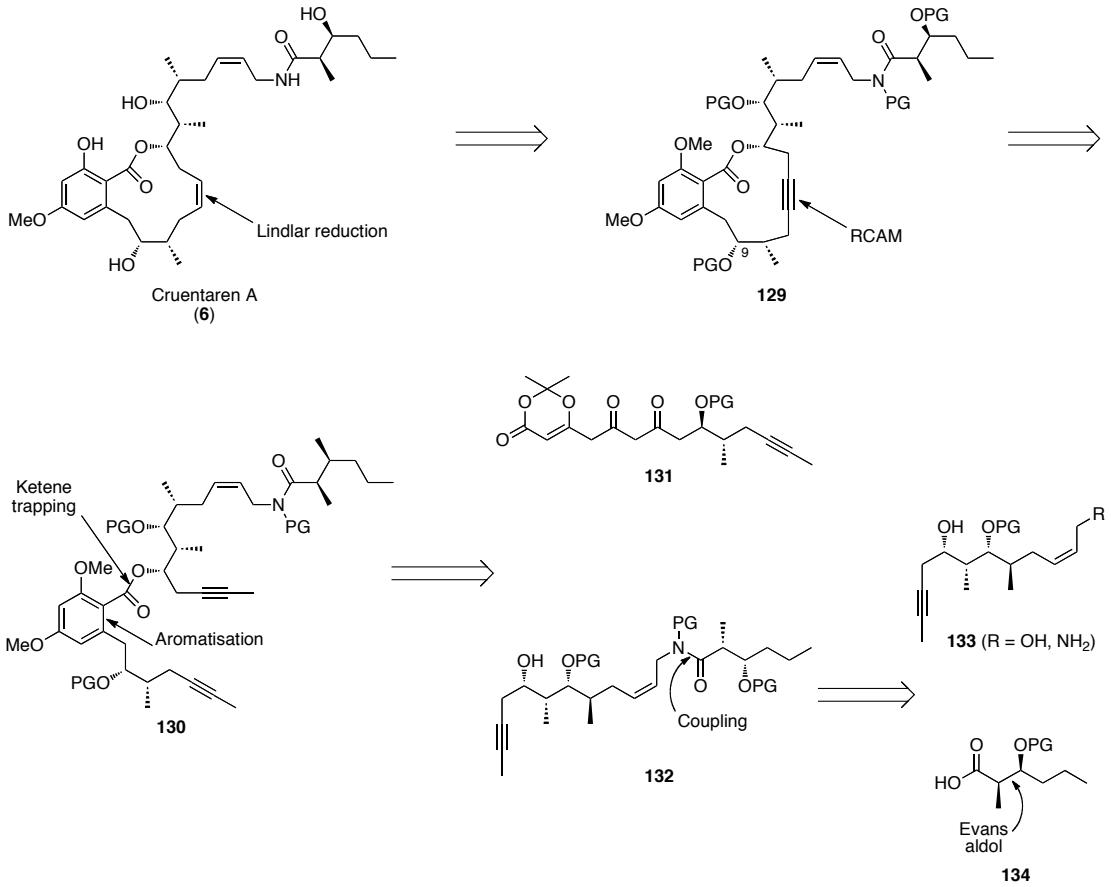
Scheme 28 - Synthesis of keto-dioxinone **128** by Tadano and co-workers

Those examples list the most common method used for the synthesis of keto-dioxinone derivatives. Keto- and diketo-dioxinone derivatives are key fragments for the synthesis of RALs in the methodology developed by the Barrett group. Therefore, extensive studies, which will be presented later, have been carried out to find efficient syntheses of keto- and diketo-dioxinone derivatives.

1.5 Objectives of this project

Cruentaren A was a perfect candidate to validate the new biomimetic inspired strategy with late stage aromatization developed in the Barrett group for the synthesis of RAL natural products. This novel methodology should allow us to circumvent the difficulties met by Maier and Fürstner during the esterification step. Our retrosynthetic plan is outlined in Scheme 29. The (*Z*)-configuration of the alkene moiety incorporated in the macrolactone ring as well as the high probability of translactonisation featuring 9-OH prove that the use of a RCAM is almost compulsory as demonstrated by Maier and Fürstner. With this in mind, it is clear that the last key step of the synthesis should be a Lindlar reduction of the alkyne functionality within the macrolactone ring, which should afford cruentaren A (**6**) with high *E:Z* selectivity. The RCAM could be envisaged as the next key step on precursor **130**, which will be required to be fully protected, as alkyne metathesis catalysts do not tolerate hydroxy- and amino-functional groups. The aromatic ring could be installed using our novel methodology. Therefore resorcylate **130** could come from the reaction between alcohol **132** and diketo-dioxinone **131** *via* ketene trapping and aromatization. Finally key fragment **132** could result from the coupling between amine **133** and acid **134**. It was unclear at the start of this project whether amide **132** would be a suitable partner for the ketene trapping/aromatization sequence or if it would be more judicious to carry out the amide formation at the end of the synthesis and work instead with the amine or the corresponding alcohol. All key fragments contain at least 2 chiral centers. We assumed that the *syn* configuration of acid **134** could be obtained *via* Evans aldol reaction, however the construction of key fragment **131** and **133** would require more investigation, which will be discussed later. To conclude, it should be

outlined that **133** was a key fragment of Fürstner's synthesis too and that the RCAM/hydrogenation strategy is similar to Maier's and Fürstner's strategies. However their syntheses were not published at the start of this project and their work unknown to us at that time.

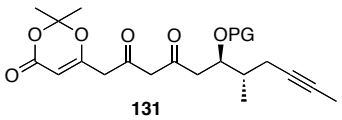


Scheme 29 - Key disconnections for the synthesis of cruentaren A (**6**) utilizing late stage aromatization

2 Results and discussion

2.1 Synthesis of diketo-dioxinone 215 (similar to key fragment 131)*

The first key fragment to prepare was diketo-dioxinone derivative **131** (Figure 5). Since this class of compound had never been described, members of the Barrett group carried out extensive researches to find general efficient methods for their synthesis.



131

Figure 5 - Key fragment diketo-dioxinone **131**

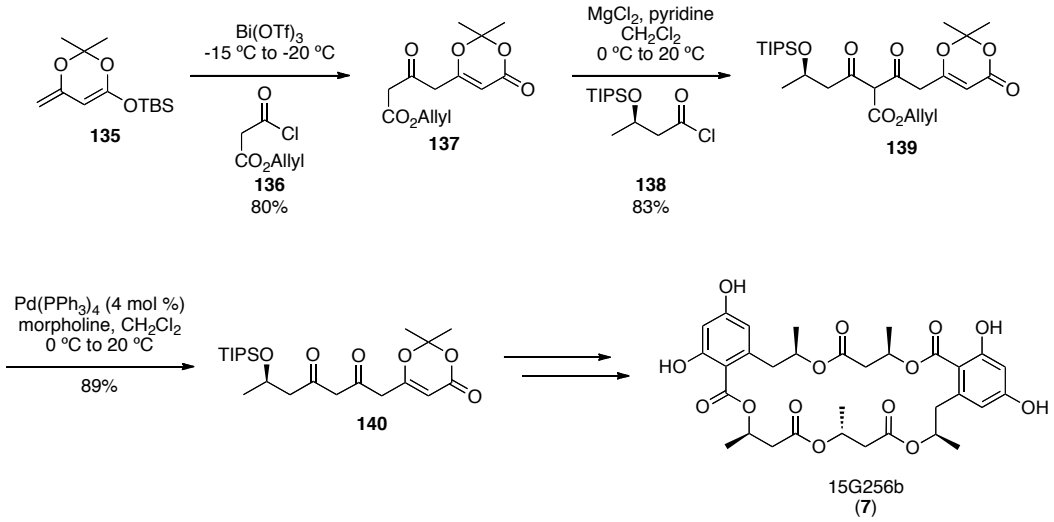
2.1.1 Studies towards the preparation of diketo-dioxinone derivatives

Based on successful syntheses of keto-dioxinone derivatives reported in the literature (Sub-section 1.4.4), it was believed that *C*-acylations and aldol reactions would be appropriate in preparing diketo-dioxinone derivatives.

* The term "similar to" refers to the fact that the compounds share the same structure but have different protecting groups (PG) or substituents (R).

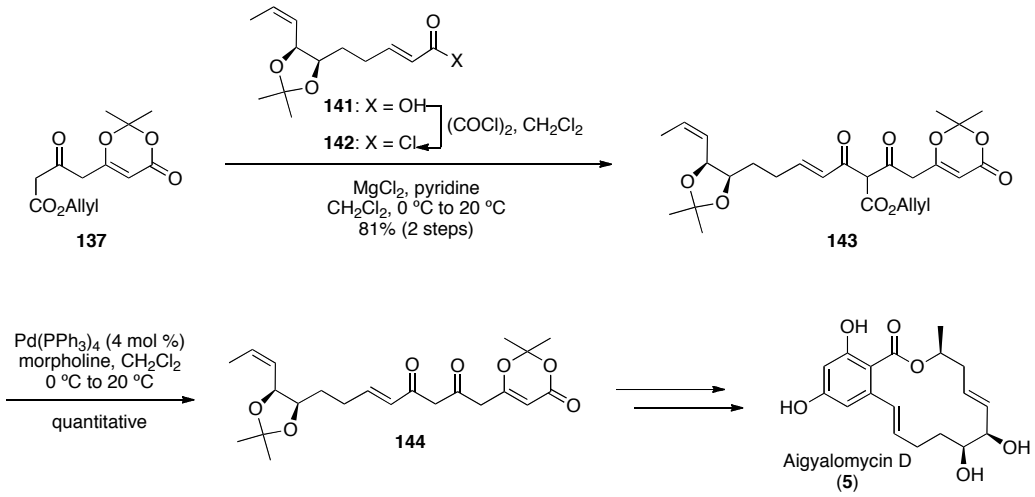
2.1.1.1 Preparation of diketo-dioxinone derivatives based on a Claisen-type condensation

The first method was developed by Navarro and Barrett in 2008 for the synthesis of 15G256.[50] Diketo-ester **139** was synthesized *via* sequential double *C*-acylation of dioxinone **135** with acid chloride **136** and **138**. Magnesium chloride was used to prevent *O*-acylation over *C*-acylation. Subsequent palladium-catalyzed deallylation-decarboxylation provided the key diketo-dioxinone **140,** which was obtained in 74% yield from key allyl ester **137** (Scheme 30).



Scheme 30 - Synthesis of diketo-dioxinone **140** by *C*-acylation

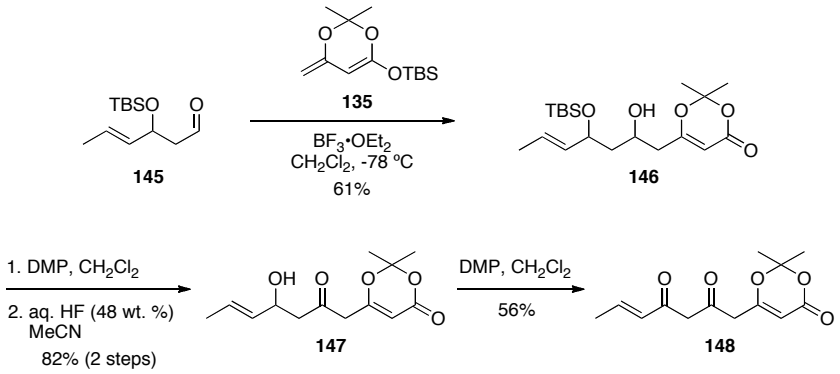
This procedure was used by Calo and Barrett towards the synthesis of aygialomycin D (**5**) and allowed the synthesis of diketo-dioxinone **144** in three steps and good yield from acid **141** (Scheme 31).[51]



Scheme 31 - Synthesis of diketo-dioxinone **144** by *C*-acylation

2.1.1.2 Preparation of diketo-dioxinone derivatives using a Mukaiyama aldol reaction

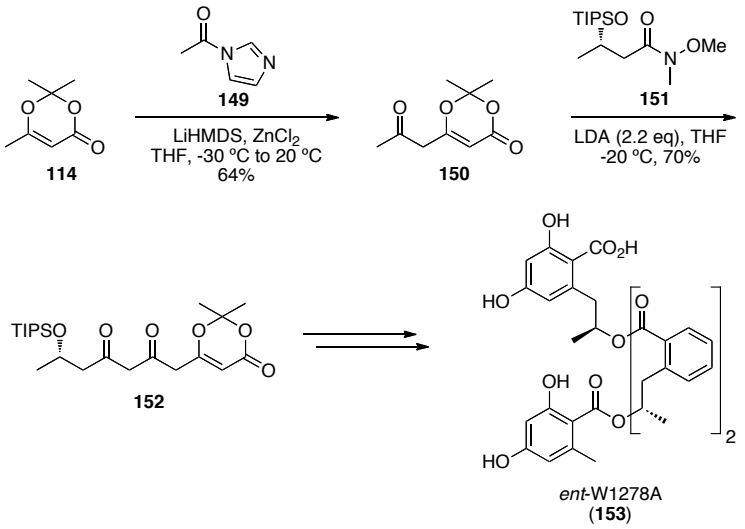
At the same time, Basset and Barrett reported a new method based on a Mukaiyama-aldol reaction towards the synthesis of (*S*)-(–)-zearalenone.[50] Addition of the silyl-enolate of dioxinone **135** to aldehyde **145**, catalyzed by trifluoroboron etherate, provided intermediate **146**. Dess-Martin oxidation followed by TBS group cleavage and Dess-Martin oxidation gave access to the desired diketo-dioxinone **148** (Scheme 32).



Scheme 32 - Synthesis of diketo-dioxinone **148** using a Mukaiyama aldol reaction

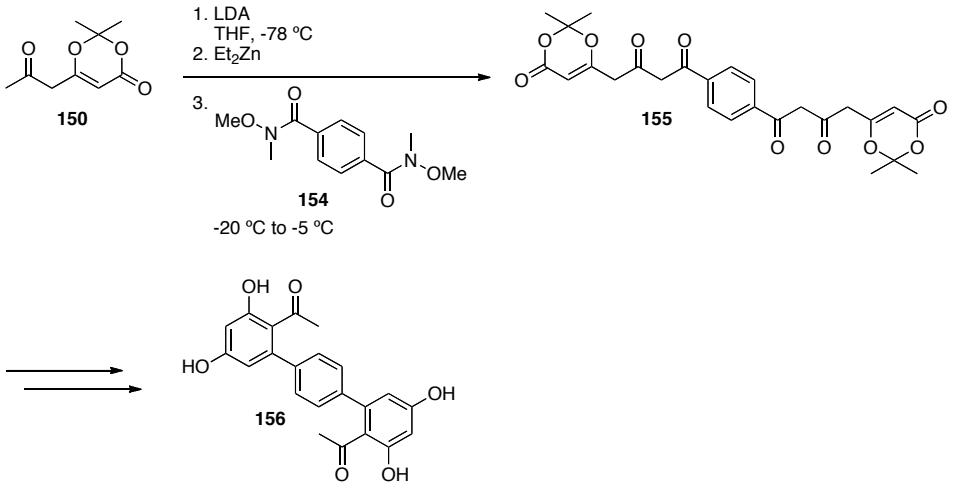
2.1.1.3 Preparation of diketo-dioxinone derivatives using Weinreb amides

In 2009, Pöverlein and Barrett developed a straightforward method for the functionalization of dioxinone **114**, which was used for the synthesis of *ent*-W1278A (**153)**.[52] Dioxinone **114**, after treatment with lithium hexamethyldisilazide (LiHMDS) followed by zinc chloride, reacted with imidazole derivative **149** to form keto-dioxinone **150**. Enolate dianion derived from **150** was formed using 2 equivalents of LDA and reacted with Weinreb amide **151** to give diketo-dioxinone derivative **152** (Scheme 33). They reported that Weinreb amide derivatives were, in this case, useful electrophiles to minimize competitive double *C*- and *O*-acylation.



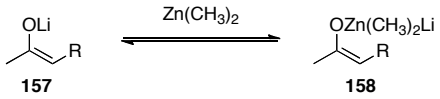
Scheme 33 - Synthesis of diketo-dioxinone **152** using Weinreb amides

Later, Patel and Barrett investigated the addition of diethylzinc during the *C*-acylation step as low yields were obtained when highly functionalized Weinreb amides were used (Scheme 34).[53] They showed that transmetalation of the lithium enolate of **150** with zinc (II) could lead to higher yield most likely by suppressing unwanted side reaction[54] (double *C*-acylation and *O*-acylation) and by inducing full consumption of the Weinreb amide derivatives.



Scheme 34 - Synthesis of diketo-dioxinone **155** using Weinreb amides

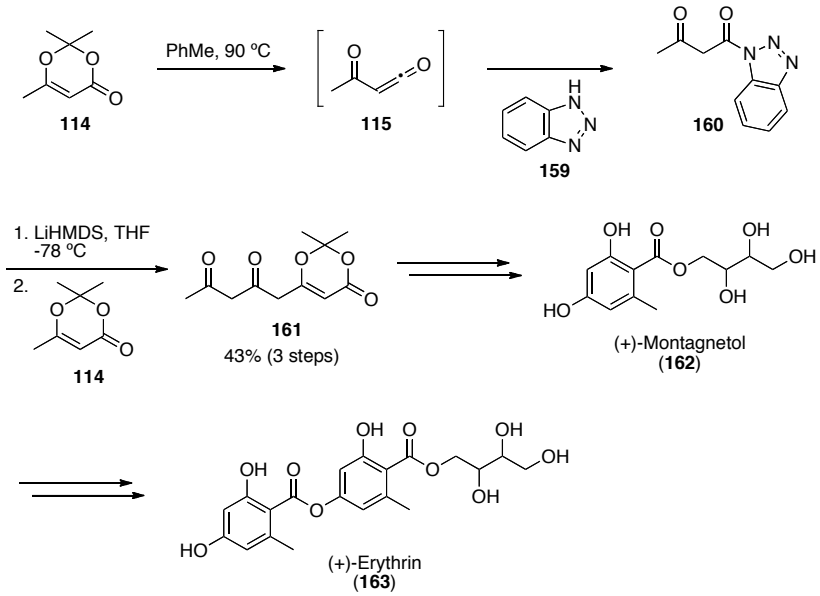
Noyori and co-workers reported in 1989 that the use of organozinc in the reaction of lithium enolates with electrophiles was effective to suppress undesired α-proton exhange and increase the yield, through the reversible formation of a lithium alkoxydialkylzincate (Scheme 35).[54]



Scheme 35 - Formation of a lithium alkoxydialkylzincate

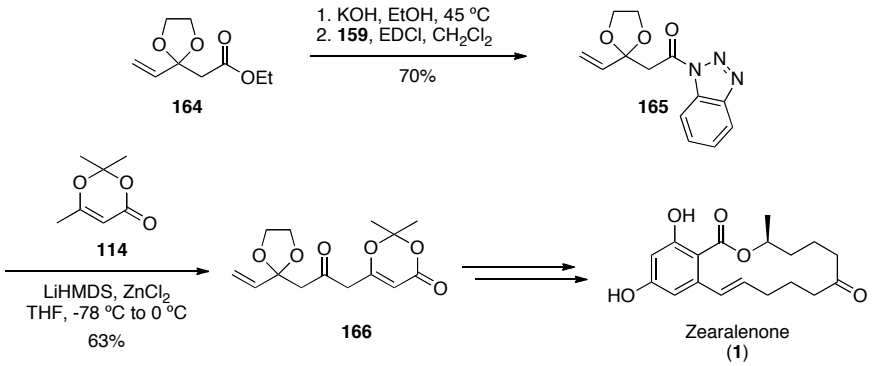
2.1.1.4 Preparation of diketo-dioxinone derivatives using benzotriazole derivatives

In 2010, Basset and Barrett reported the synthesis of (+)-montagnetol and (+)-erythrin.[55] Thermolysis of dioxinone **114** produced acyl-ketene **115** (*via* retro-Diels-Alder reaction), which was trapped with benzotriazole **159** to form amide **160**. Subsequent *C*-acylation between **160** and the lithium enolate of **114** afforded diketo-dioxinone **161** (Scheme 36).



Scheme 36 - Synthesis of diketo-dioxinone **161** using benzotriazole derivatives

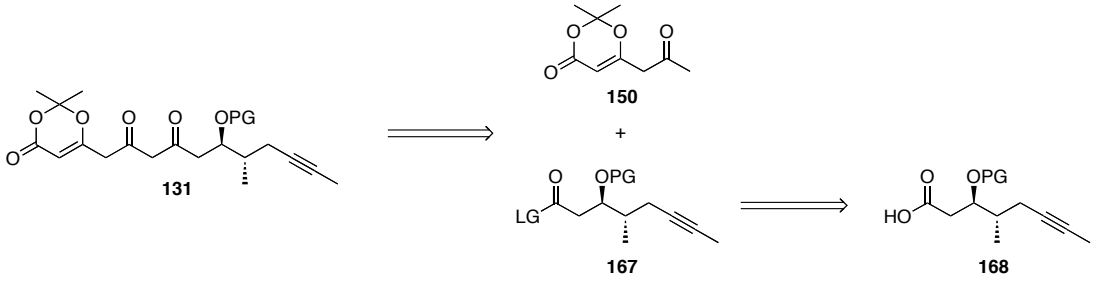
Miyatake-Ondozobal and Barrett later used a similar method to prepare compound **166** (Scheme 37), a key intermediate towards the synthesis of (*S*)-(–)-zearalenone.[56]



Scheme 37 - Synthesis of **166** using benzotriazole derivatives

2.1.2 Synthesis of acid 201 (similar to key fragment 168)

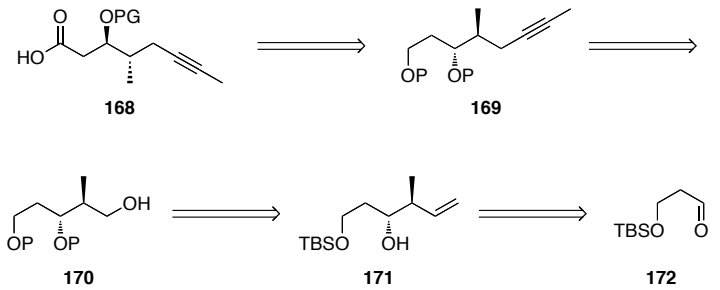
Based on these discoveries, we believed that diketo-dioxinone **131** could be obtained by *C*-acylation between keto-dioxinone **150** and a suitable electrophile derived from acid **168** (Scheme 38).



Scheme 38 - Key disconnections for diketo-dioxinone **131**

2.1.2.1 Towards the synthesis of acid 168 using an ozonolysis

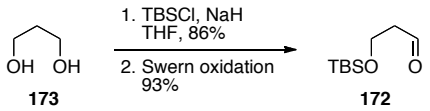
This route is mainly inspired by the synthesis of spirastrellolide A published by Fürstner *et al*.[57] Acid **168** could be obtained after selective deprotection followed by oxidation of primary alcohol **169**. The acetylene moiety could be introduced by nucleophilic substitution with propyne or its derivatives on **170** after conversion of the primary alcohol to a good leaving group. The preparation of **170** could be envisaged with the ozonolysis of the corresponding alkene **171**.[58] Finally, the *anti*-configuration of **171** could be introduced using an asymmetric crotylation on aldehyde **172** (Scheme 39).



Scheme 39 - Key disconnections for acid **168**

*2.1.2.1.1 Preparation of fragment **187** (similar to key fragment **170**)*

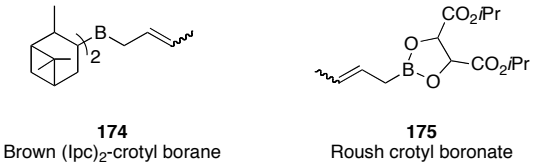
The synthesis of **170** started with preparation of aldehyde **172**. TBS-mono-protection on 1,3-propanediol (**173**) afforded the corresponding mono-protected alcohol in 86% yield. Dess-Martin oxidation was then attempted to obtain **172**. However after silica flash chromatography, the desired aldehyde was isolated in low yield. Since Swern oxidation does not require further purifications, this method was chosen and afforded **172** in good yield (Scheme 40).[59]



Scheme 40 - Synthesis of aldehyde **172**

The next step was an asymmetric crotylation reaction. Several methods have been developed for the synthesis of chiral homoallylic alcohols, crotyl boron reagents being commonly used. The Brown crotylation[60] refers to the use of chiral crotylboranes derived from terpenes (most often α–pinene), while the Roush crotylation[61] is based on chiral crotylboronates derived from tartrates. The main

difference between these two reactions is the stability of the reagents: crotylboronates are stable at room temperature and tolerant to exposure to air and moisture (Figure 6). In our case, we decided to perform a Brown crotylation to obtain **171**.

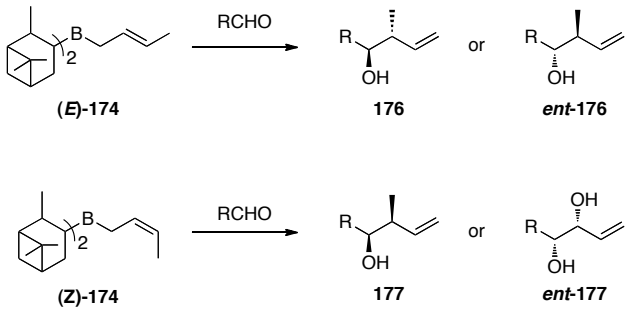


174
Brown $(Ipc)_2$-crotyl borane

175
Roush crotyl boronate

Figure 6 - Crotyl boron reagents for asymmetric crotylation

During a Brown crotylation, two stereocenters are created therefore this reaction is associated with two stereochemical aspects. The diastereoselection is controlled by the stereochemistry of the butene: *trans*-butene leads to the formation of *anti*-diastereoisomers, while *cis*-butene leads to *syn*-diastereoisomers (Scheme 41).[60]



Scheme 41 - Diastereoselection of the Brown crotylation

On the other hand, the enantioselection is controlled by the stereochemistry of the isopinocamphenylgroup. The crotylation of aldehydes proceed through a chair-like transition state and the aldehyde's facial selectivity derives from minimization of steric hindrance. The four models (Figure 7) show the preferred transition states

depending on the stereochemistry of the alkene and on the geometry of the asymmetric isopinocampheyl group.[60]

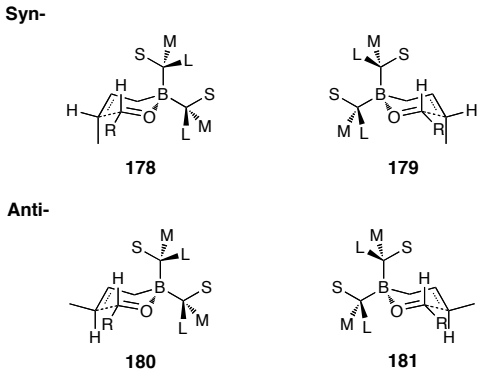
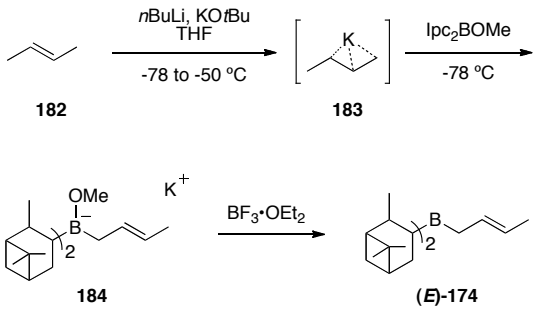


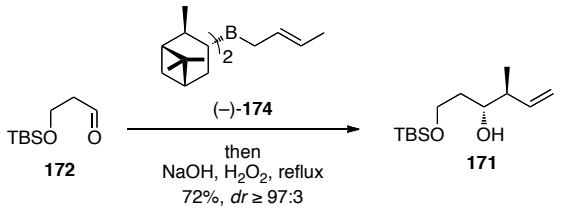
Figure 7 - Transition state of the Brown crotylation

The crotylborane is formed *in situ*: butene is metalated with a mixture of *n*-butyllithium and potassium *tert*-butoxide (Schlosser super base).[62] A particular attention should be given to this step as *trans*-butene can isomerise above -50 °C. Then the resulting crotylpotassium **183** is treated with (+/-)-methoxydi*iso*pinocampheylborane [$(Ipc)_2BOMe$] to form the "ate" complex **184**. After treatment with boron trifluoride etherate and decomplexation of methoxide, the crotylborane is treated with the desired aldehyde. Finally an oxidative work-up affords the desired product **(*E*)-174** (Scheme 42).[60]



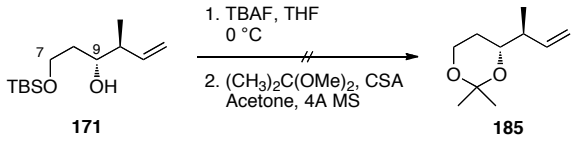
Scheme 42 - Synthesis of the crotyl boron reagent **(*E*)-174**

Since desired compound **171** exhibited an *anti*-configuration, the Brown crotylation was carried out with *trans*-butene. Furthermore, in order to obtain the desired stereochemistry, (–)-$(Ipc)_2BOMe$, derived from (+)-α-pinene, was used. Following the procedure described by Brown,[60] the first attempts led to an inseparable mixture of desired compound **171** and aldehyde **172**. In order to obtain full consumption of aldehyde **172**, crotyl borane reagent **174** was used in large excess (Scheme 43). This attempt was successful and homoallylic alcohol **171** was obtained in 72% yield. The ^1H NMR spectrum of the crude material showed that **171** was obtained as a single diastereoisomer (*dr* ≥ 97:3).



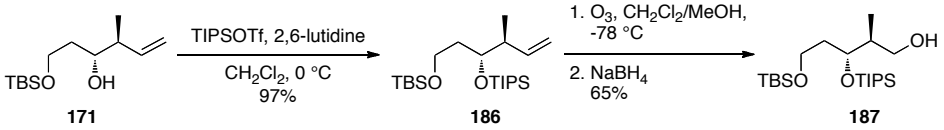
Scheme 43 - Synthesis of **171**

Before performing the ozonolysis of the terminal alkene moiety, it was necessary to protect secondary alcohol **171**. Instead of using two different protecting groups for 7-OH and 9-OH, we believed that acetonide protection of the 1,3-diol function might be suitable. After TBS-cleavage using TBAF, the resulting diol was treated with dimethoxypropane and camphor sulfonic acid (CSA) in acetone (Scheme 44).[63] However despite full conversion of the diol observed by thin layer chromatography (TLC) analysis, desired compound **185** could not be isolated. Because of its low molecular weight, we believe **185** was too volatile and therefore lost during the concentration under reduced pressure of the solvent after the work-up.



Scheme 44 - Attempted synthesis of **185**

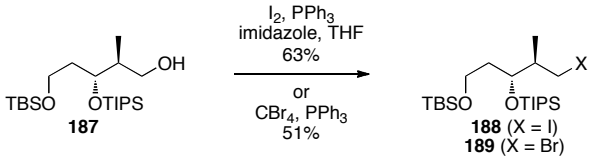
Secondary alcohol **171** was eventually protected with a TIPS group. The different reactivity of these silyl ethers (TBS (1) < TIPS (35))[64] will allow a selective deprotection of the primary alcohol over the secondary one. The ozonolysis, carried out in a mixture of dichloromethane/methanol at -78 ºC, was followed by a reductive work-up with sodium borohydride to yield alcohol **187** (Scheme 45). When isolation of the aldehyde is required, dimethylsulfide or triphenylphosphine are usually added at the end of the ozonolysis in order to quench the ozonide derivative formed during this reaction.



Scheme 45 - Synthesis of alcohol **187** *via* ozonolysis

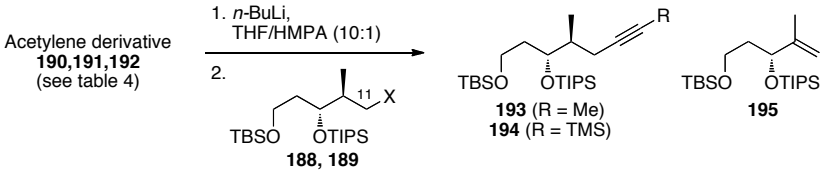
*2.1.2.1.2 Attempted synthesis of **193** (similar to key fragment 169)*

In order to introduce the propyne moiety, terminal alcohol **187** was converted into a good leaving group. Appel reaction conditions afforded iodide and bromide derivatives **188** and **189** respectively in 63% and 51% yield (Scheme 46).



Scheme 46 - Synthesis of halides **188** and **189**

The next step was the coupling of alkyl halides **188** and **189** with propyne (**190**) or its derivatives **191**, **192**. This type of reaction was generally carried out with liquid ammonia despite solubility problems.[65] However since its introduction, HMPA as a co-solvent with tetrahydrofuran is the most popular choice.[66] The reaction proceeds generally in two steps, first deprotonation of the acetylene derivative with the appropriate lithiated base in a mixture of tetrahydrofuran/HMPA at low temperature, then addition of the electrophile (Scheme 47). Following this procedure, different conditions were tried and are reported Table 4. We noticed that only elimination product **195** was isolated when the deprotonation was carried out at -78 ºC and the addition of propyne (**190**) at 0 ºC (Table 4, Entry a). When the deprotonation and addition of **190** were carried out at 0 ºC, the ^{1}H NMR spectrum of the crude mixture indicated the presence of **195** and desired product **193** in a 9:1 ratio (Table 4, Entry b). However **193** could not be isolated. It was then decided to use TMS-acetylene **191**, which is much easier to handle than propyne (boiling point = -20 ºC). Using previous conditions, no desired product was isolated (Table 4, Entry c). Furthermore, a similar attempt with bromide derivative **189** was unsuccessful (Table 4, Entry d). Finally, bromopropene (**192)** was used as a source of propyne (2 equivalents of *n*-butyllithium were necessary). However no formation of desired product **193** was observed. Instead bromide derivative **189** was isolated, indicating that a halide exchange occurred (Table 4, Entry e).



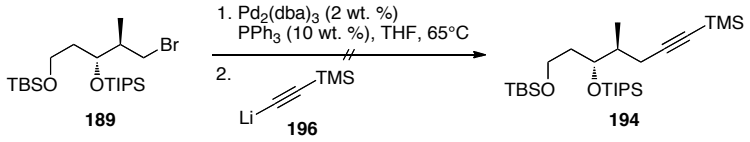
Scheme 47 - Synthesis of **193** and **194**

Entry	*Acetylene derivative*	*Halide*	*Conditions*	*Products (yield)*
a	 **190**	**188**	-Deprotonation at -78 ºC -Addition of **188** at 0 ºC	**195**
b	 **190**	**188**	-Deprotonation at 0 ºC -Addition of **188** at 0 ºC	**195/193** (9:1)
c	 **191**	**188**	-Deprotonation at 0 ºC -Addition of **188** at 0 ºC	No reaction
d	 **191**	**189**	-Deprotonation at 0 ºC -Addition of **189** at 0 ºC	No reaction
d	 **192**	**188**	-Deprotonation at -78 ºC -Addition of **188** at 0 ºC	**189**

Table 4 – Different conditions for the synthesis of **193** and **194**

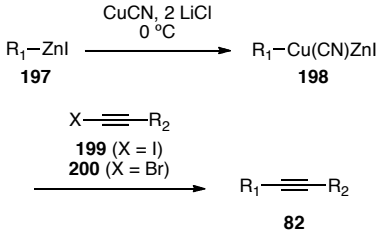
Since the use of HMPA to promote this coupling was unsuccessful, it was decided to explore other conditions. To date, there are no examples of Sonogashira couplings with non-activated alkyl halides and terminal alkynes in the presence of phosphine ligands.[67] Furthermore this reaction is known to proceed only in moderate yields in the presence of *N*-heterocyclic carbene ligands.[68] However, Luh *et al.* showed that the coupling product between primary alkyl bromide or iodide derivatives and lithiated

alkynyl compounds (or the corresponding Grignard reagents) could be obtained in good yield using tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$]/ triphenylphosphine as catalyst system.[69] This Kumada-Corriu type reaction was attempted with bromide derivative **189** and TMS-acetylene (Scheme 48). Unfortunately, no reaction occurred and only starting material was recovered.



Scheme 48 – Attempted synthesis of **194** *via* Kumada-Corriu type coupling

Finally the organozinc chemistry developed by Knochel was envisaged for this coupling. Knochel and co-workers showed that copper, zinc derivatives (RCuCNZnX) could react under mild conditions with 1-bromo- and 1-iodo-alkyne derivatives (Scheme 49).[70]

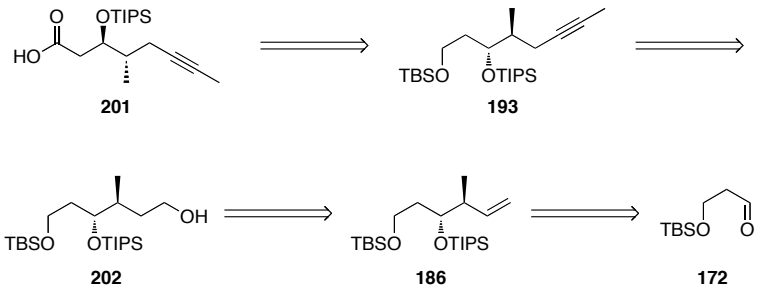


Scheme 49 - Knochel organozinc chemistry

However since the steric hindrance at C-11, caused by the adjacent methyl group and the TIPS-protecting group, was probably the reason why the coupling between halides **188** or **189** and propyne derivatives was unsuccessful, it was decided to investigate a new route.

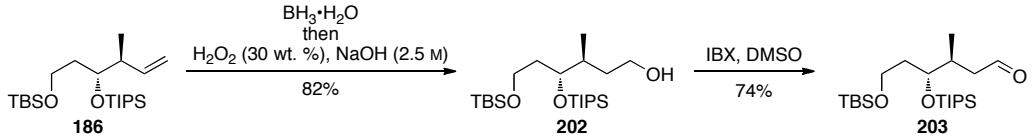
2.1.2.2 Synthesis of acid 201 (similar to key fragment 168) using a hydroboration reaction followed by carbon homologation

Similarly to the strategy developed earlier, **201** could be obtained from **193** after selective silyl cleavage and oxidation. The acetylene moiety of **193** could be installed *via* a one-carbon homologation reaction from alcohol **202**. Finally **202** could derive from the previously described alkene **186** using a hydroboration reaction (Scheme 50).



Scheme 50 - Key disconnections for acid **201**

Hydroboration[71] of alkene **186** was first attempted with 9-borabicyclo[3.3.1]nonane (9-BBN), the reagent of choice for an enhanced regioselectivity. However, TLC analysis of the crude mixture revealed a low conversion rate after 48 hours. The steric hindrance was propably the cause, therefore borane in tetrahydrofuran was used and primary alcohol **202** was obtained in 82% yield with no trace of the other regioisomer (Scheme 51). In this case the use of a dialkyl borane, such as 9-BBN, to control the regiochemistry of the reaction was unnecessary. Primary alcohol **202** was then oxidized to the corresponding aldehyde **203** using *o*-iodoxybenzoïc acid (IBX) in dimethylsulfoxide. IBX was chosen over the Dess-Martin reagent because of its simple one-step preparation (IBX being a precursor of the Dess-Martin reagent). [72]

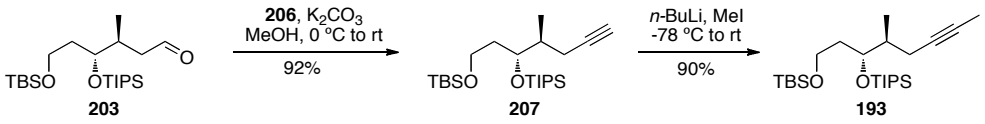


Scheme 51 - Synthesis of aldehyde **203** *via* hydroboration reaction

The next step was the homologation of **203** to the corresponding acetylenic compound **207**. The Corey-Fuchs[73] and the Seyferth-Gilbert[74] reaction are well established for the synthesis of alkynes from aldehydes. The Corey-Fuchs methodology is a two-step procedure including first, the formation of a dibromoalkene derivative, then treatment with *n*-butyllithium to obtain the desired terminal alkyne after aqueous work-up. The use of a strong base can limit its application. The Seyferth-Gilbert homologation involves the use of diazoalkylphosphonate reagents, which undergo Horner-Wadsworth-Emmons type reactions with aldehydes producing diazoalkene. After loss of nitrogen and 1,2-rearrangement of the resulting alkylidene carbene, the desired alkyne is obtained. The use of dimethyl-1-diazo-2-oxopropyl phosphonate **206** (known as Bestmann-Ohira reagent)[75] over dimethyldiazomethyl phosphonate **204** is generally preferred as it can be prepared in one step from commercially available **205** and reacts with aldehyde under very mild conditions (Scheme 52).

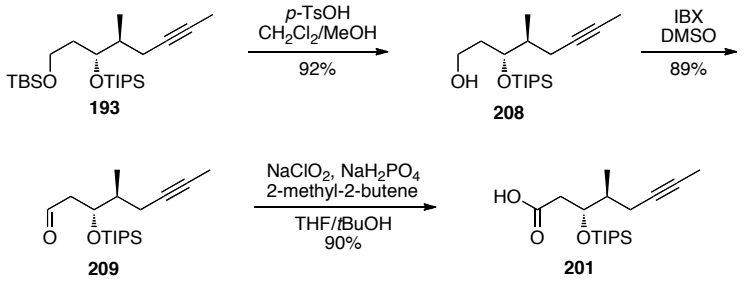
Scheme 52 - Seyferth-Gilbert (**204**) and Bestmann-Ohira (**206**) reagents

For the conversion of **203** to **207**, the Seyferth-Gilbert homologation using **206** and potassium carbonate in methanol was chosen. **207** was obtained in 92% yield.[76] Finally, methylation of terminal alkyne **207** using *n*-butyllithium and methyl iodide afforded **193** in good yield (Scheme 53).



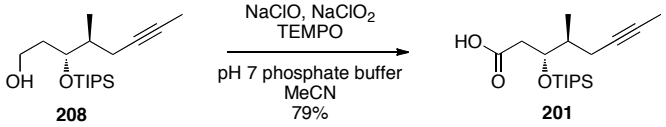
Scheme 53 - Synthesis of **193** *via* Seyferth-Gilbert reaction

Selective cleavage of the TBS-protecting group in the presence of the TIPS-protecting group was achieved following a procedure reported by Roush *et al.* for the total synthesis of angelmicin B.[77] Using 0.5 equivalent of *p*-toluenesulfonic acid, **208** was obtained in 92% yield (Scheme 54). Finally in order to obtain desired acid **201**, a two-step oxidation procedure was carried out. First primary alcohol was converted to the corresponding aldehyde **209** using IBX in dimethylsulfoxide. Then **209** was oxidised to the corresponding acid using a Pinnick reaction,[78] a mild oxidation method suitable for functionalized aldehyde and involving the use of sodium chlorite and sodium dihydrogen phosphate. Side reactions can occur during this reaction due to the formation of hypochlorite ions, however the use of a scavenger such as 2-methyl-2-butene is a simple way to circumvent this problem. Following this procedure, aldehyde **209** was oxidised to acid **201** in 90% yield.



Scheme 54 - Synthesis of acid **201**

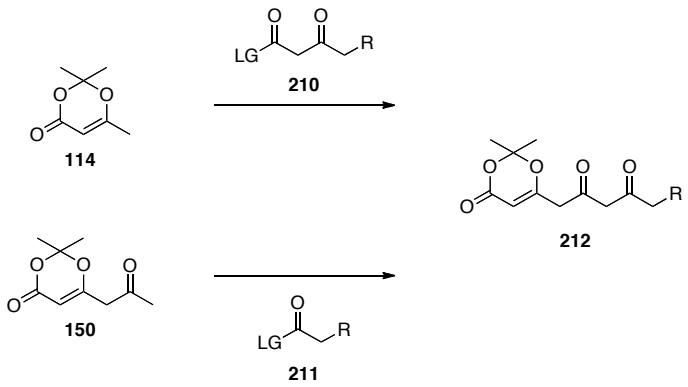
A direct oxidation of alcohol **208** to acid **201**, using stoichiometric sodium chlorite and catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and sodium hypochlorite, was attempted too (Scheme 55).[79] This one step process was preferred when a large amount of acid **201** was prepared.



Scheme 55 - TEMPO oxidation of alcohol **208** to acid **201**

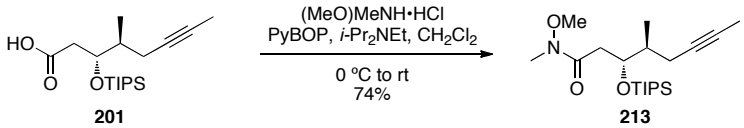
2.1.3 Synthesis of diketo-dioxinone 215 (similar to key fragment 131) from acid 201

With acid **201** in hand it was possible to envisage the synthesis of diketo-dioxinone derivative **215**. As reported in Sub-section 2.1.1, several methods for the synthesis of this class of compounds have been developed by members of the Barrett Group and can be classified in two groups: *C*-acylation with dioxinone **114** or keto-dioxinone **150** (Scheme 56).



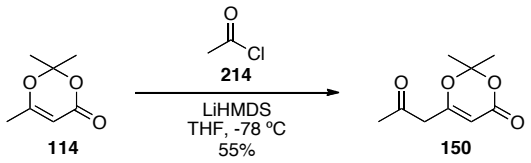
Scheme 56 - *C*-acylation with dioxinone **114** ou keto-dioxinone **150**

In our case, the procedure involving the *C*-acylation of a suitable electrophile (derived from **201**) with diketo-dioxinone **150** was chosen. The one-step procedure reported by Pöverlein and Barrett in 2008 was initially attempted.[52] This mild alternative to the strategy developed by Navarro and Barrett proved to be highly suitable for the synthesis of natural products and functionalized diketo-dioxinone[53] derivatives since it does not require prior conversion of acid derivatives to highly reactive acid chlorides. Therefore, acid **201** was transformed into the corresponding Weinreb amide **213** in good yield using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as coupling agent and *N*-methoxy-*N*-methylamine (Scheme 57).



Scheme 57 - Synthesis of Weinreb amide **213**

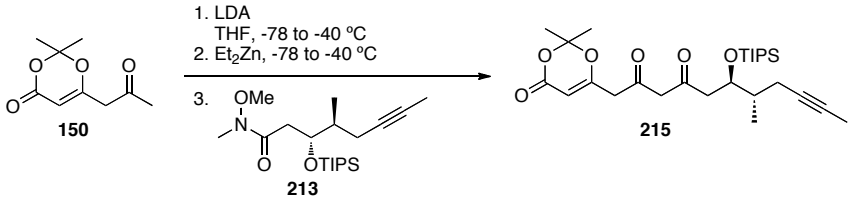
Keto-dioxinone **150** was prepared from dioxinone **114** and acyl chloride in 55% yield following the procedure described by Calo and Barrett (Scheme 58).[51]



Scheme 58 - Synthesis of keto-dioxinone **150**

As reported Table 5, different conditions to obtain diketo-dioxinone **215** were investigated. The general procedure starts with deprotonation of keto-dioxinone **150** with 2 equivalents of LDA to form the corresponding dianion. At this stage diethylzinc can be added if necessary. Finally Weinreb amide **213** is added (Scheme 59). The first attempt was carried out with 1 equivalent of keto-dioxinone **150** and no addition of diethylzinc. Desired product **215** could not be isolated and TLC analysis of the crude mixture revealed the formation of several by-products. Furthermore, 55% of the starting material was recovered (Table 5, Entry a). Addition of diethylzinc proved to be beneficial to avoid side-reactions (e.g. *O*-acylation, double *C*-acylation) as no by-products were isolated when this reagent was used (Table 5, Entry b to d). Furthermore we observed that formation of **215** occurred only at temperature above -5 ºC. However degradation of the dianion of **150** was observed above 0 ºC. Therefore carefull temperature monitoring was essential. Finally excess of keto-dioxinone **150** (3 equivalents) was necessary to obtain full conversion of Weinreb amide **213** (Table 5, Entry e). The optimized conditions for the formation of **215** are summarized entry e, and afforded diketo-dioxinone **215** in 67% yield.[†]

[†] All diketo-dioxinone derivatives exist as mixture of keto and enol tautomers but are drawn as single entities.



Scheme 59 - Synthesis of diketo-dioxinone **215**

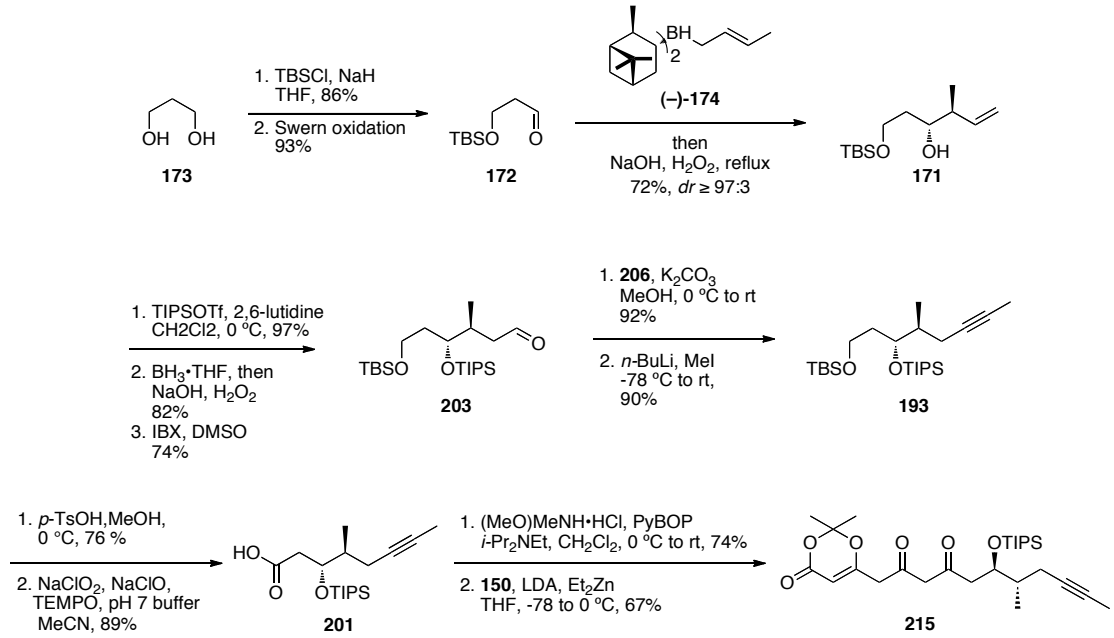
Entry	***150*** *(eq.)*	*Et_2Zn*	*Temperature after addition of **213***	*Results*
a	1	No	-40 ºC to rt (slowly)	-No **215** isolated -55% of **213** recovered
b	1	Yes	-40 to 0 ºC (slowly)	-21% of **215** isolated -40% of **213** recovered
c	1	Yes	-40 to 0 ºC (quickly) then -5 to 0 ºC	-45% of **215** isolated -27% of **213** recovered
d	2	Yes	-40 to 0 ºC (quickly) then -5 to 0 ºC	-59% of **215** isolated -9% of **213** recovered
e	3	Yes	-40 to 0 ºC (quickly) then -5 to 0 ºC	-67% of **215** isolated -No **213** recovered

Table 5 - Different conditions for the synthesis of diketo-dioxinone **215**

2.1.4 Summary

To summarize, the synthesis of diketo-dioxinone **215** has been reported following a highly straightforward route (Scheme 60). Starting from cheap and commercially available 1,3-propanediol (**173**), acid **201** was initially obtained in 10 steps and 28%

overall yield using a Brown crotylation to install the two stereocenters. Then acid **201** was successfully converted into key diketo-dioxinone **215** in two steps following one of the procedures developed in the group for the synthesis of this class of compound.

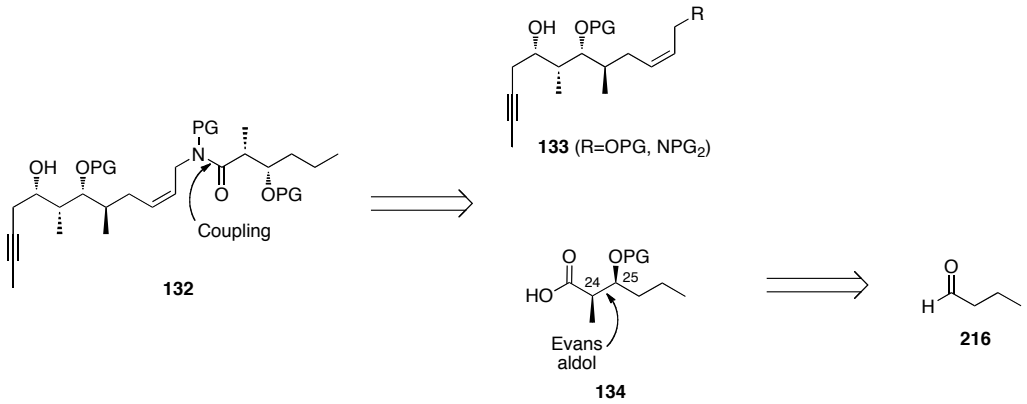


Scheme 60 - Synthesis of diketo-dioxinone **215**

Key fragment **215** was obtained in 12 steps and 13% overall yield. This straightforward strategy allowed the synthesis of 3.7 g of **215** (2 batches).

2.2 Towards the synthesis of key fragment 132

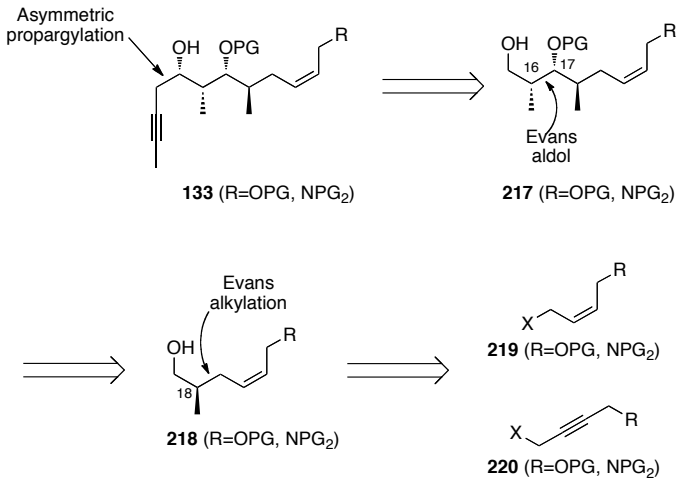
The other key fragment to prepare was **132**, which would later react with the previously described diketo-dioxinone **215**. Allyl amide **132** was a challenging fragment with 6 chiral centers. The first disconnection, which would lead to two simplified molecules, corresponds at the amide bond. Hexanoic acid **134** could clearly be constructed by asymmetric aldol reaction. The *syn*-configuration of the methyl group at C-24 and the hydroxy group at C-25 indicates that an Evans aldol reaction should be the right choice with butyraldehyde (**216**) as the electrophile. On the other hand, synthesis of **133** might not be as straightforward. Four contiguous quaternary carbons bearing hydroxy and methyl groups show that **133** could be obtained by asymmetric reaction such as alkylation, aldolisation, crotylation. Furthermore, depending on the strategy, the (*Z*)-alkene functionality could either be constructed by an olefination reaction or the reduction of a triple bond (Scheme 61).



Scheme 61 - Key disconnections for amide **132**

With these considerations in mind, a first strategy for the synthesis of **133** was established (Scheme 62). The homopropargyl moiety could be obtained *via*

asymmetric propargylation of **217**. The method chosen for this reaction will be discussed later. **217** could be synthesized *via* aldol reaction, the *syn*-configuration at C-17 and C-16 indicating that again an Evans aldol reaction should be suitable. Finally in order to obtain **218** and set the last stereocenter at C-18, an asymmetric alkylation could be used. An Evans alkylation was chosen, as this reaction is generally user-friendly and leads to the desired compound with high enantiomeric excess (*ee*). Two electrophiles **219** and **220** were suitable for this reaction. However because alkene **219** could lead to undesired S_N2' reaction, the less reactive alkyne **220** was chosen.



Scheme 62 - Key disconnections for **133**

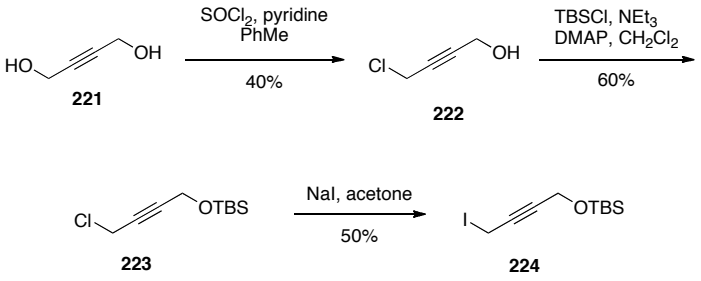
2.2.1 Towards the synthesis of key fragment 218

Our first objective was to find the right strategy to synthesize **218**. We needed a reliable method, which would allow large-scale preparation. It was decided to try the Evans alkylation because, as explained earlier, the protocol is easy and products are obtained with high enantioselectivity, even after the cleavage of the auxiliary, which

occurs in mild conditions. Furthermore compared to other asymmetric alkylation methods such as (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)/RAMP or Oppolzer's sultam, the necessary chiral auxiliary is relatively cheap.

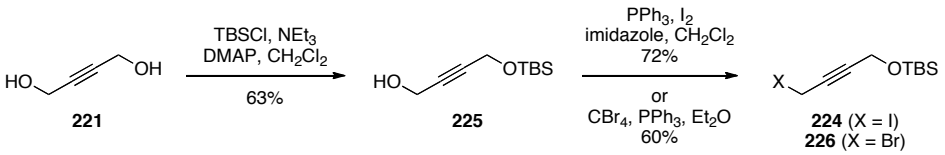
2.2.1.1 Preparation of electrophiles 224 and 226 (similar to key fragment 220)

Compound **220** could either be an amino or alcohol derivative (R = OPG or NPG_2). However since a hydroxy group was needed to introduce the halide, it was easier to start from a symmetric molecule, 1,4-butynediol (**221**), and convert the alcohol to an amine later on. The first attempt to synthesize **224** is outlined Scheme 63. The chlorination of diol **221** with thionyl chloride yielded the desired mono-chlorinated product **222** in 40%. The dichlorinated product was also observed as a side product of this reaction, which explains the moderate yield. TBS-protection of the alcohol followed by a Finkelstein reaction in order to convert the chloride atom by an iodide led to a mixture of the desired iodide **224** and starting material **223**.[80] Since it was neither possible to separate these two compounds nor to force the reaction to completion, an alternative route was desired.



Scheme 63 - Synthesis of electrophile **224**

In an alternative procedure, compound **224** could finally be obtained in two steps (Scheme 64). **221** was monoprotected using an excess of diol (5 equivalents) and directly converted to the iodide **224** using Appel reaction conditions.[81,82] This method gave the desired product in 46% yield over two steps. The bromide derivative **226** was prepared in an analogous fashion in 40% overall yield. However, attempts to prepare **224** and **226** on large scale failed.

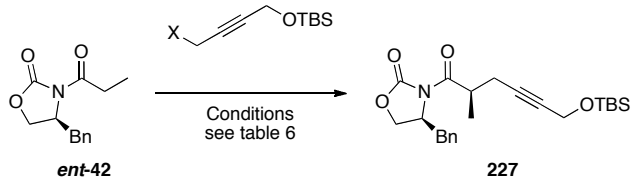


Scheme 64 - Synthesis of electrophile **224** and **226**

2.2.1.2 Synthesis of 227 *via* Evans alkylation

The next step was the alkylation between **224** or **226** and Evans auxiliary ***ent*-42** (Scheme 65).[28,29] Evans auxiliaries are successful in directing diastereoselective alkylation and, very importantly, can be cleaved easily without racemization. The chiral auxiliary **42** is deprotonated with either a lithium or sodium amide base at low temperature to give the rigidly chelated (*Z*)-enolate. Subsequent alkylation with halogenated electrophiles occurs preferentially from the less hindered face. Electrophile structure plays a role as well in stereoselectivity as small alkyl halides are less stereoselective. Different conditions were tried for the alkylation and are reported Table 6. It shows that no reaction occurred with bromide **226** (Table 6, Entry a). The different experiments show as well that it was necessary to warm the reaction temperature between -20 ºC and 0 ºC when using LiHMDS (Table 6, Entry b).

However formation of by-products was observed. The best conditions were those reported by Evans *et al.* in 1982 and combined the use of sodium bis(trimethylsilyl)amide (NaHMDS) at -78 ºC with iodide **224** as electrophile.[83] After purification of the crude by flash chromatography, ^{1}H and ^{13}C NMR analysis proved **227** to be a single diastereomer.



***ent*-42** **227**

Scheme 65 – Synthesis of **227** *via* Evans alkylation

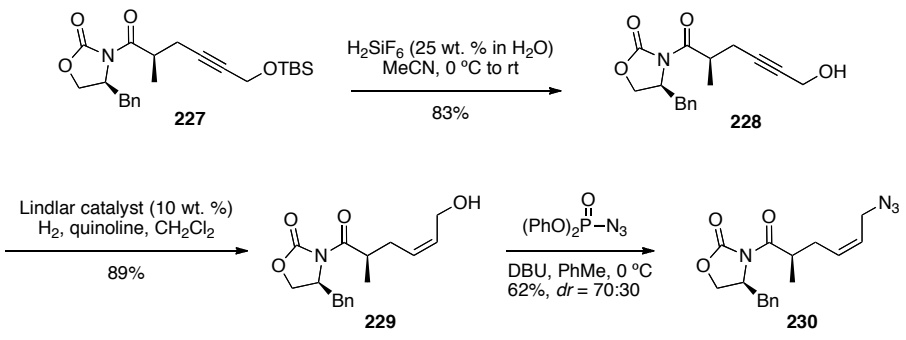
Entry	*Base*	*Electrophile*	*Temperature*	*Yield*
a	LiHMDS	**226**	-78 ºC to 0 ºC	0%
b	LiHMDS	**224**	-78 ºC to 0 ºC	33%
c	NaHMDS	**224**	-78 ºC	72% *dr* ≥ 97:3

Table 6 - Different conditions for the Evans alkylation

2.2.1.3 Attempted synthesis of 233 (similar to key fragment 218)

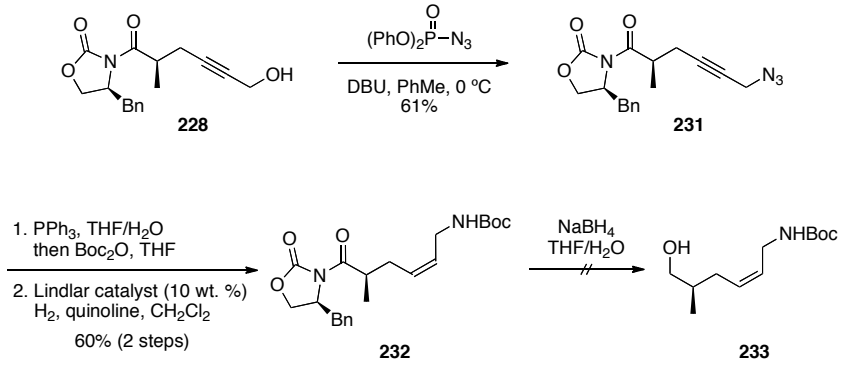
With compound **227** in hand, our next objective was to obtain amine **218** by conversion of the alcohol moiety to an amine and Lindlar reduction of the triple bond. The removal of the silyl protecting group TBS of **227** using TBAF was unsuccessful

and only led to decomposition of the starting material. The use of aqueous fluorosilicic acid as fluorinated deprotecting agent, in acetonitrile[84] gave the desired free alcohol **228** in 83% yield. Subsequent reduction using Lindlar catalyst under an H_2 atmosphere, led to (*Z*)-olefin **229**. Furthermore, quinoline was added as a poison in order to enhance the selectivity of the reduction and to also prevent over reduction.[85] The ^{1}H NMR spectrum of the crude material showed the presence of only one diastereomer with a (*Z*)-configuration confirmed by the coupling constant (J = 10.9 Hz) between the two vinylic protons (Scheme 66). A direct conversion of alcohol **229** to azide **230** using diphenyl phosphorazidate (DPPA) and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) was then attempted.[86] This reaction takes place in two steps: initial phosphate formation followed by displacement by the azide generated *in-situ*. Compared to more conventional methods, this direct azidation is advantageous because a separate tosylate formation is unnecessary and only one water-soluble by-product is formed compared to several for the Mitsunobu. In this case, the azidation was successful, however, the conditions led to epimerisation at the α-carbon. According to ^{1}H NMR spectrum, approximately 30% of product was epimerised and the two diastereomers were unable to be separated by flash chromatography (Scheme 66).



Scheme 66 - Synthesis of allyl azide **230**

We wanted to investigate the reason of this epimerisation. The azidation was tried with various bases (triethylamine, *i*-Pr_2NEt) however the same ratio of epimerisation was observed. We speculated that the cause was maybe not the base but the alkoxide formed during the reaction. Because of the (*Z*)-geometry of compound **229**, the alcoholate could easily deprotonate at the α-carbon. Therefore, the azidation was attempted with alkyne **228** (Scheme 67). In the event, the ^1H NMR spectrum only showed one diastereoisomer and the desired azide **231** was obtained in 61% yield. The next steps were the reduction of the azide to the corresponding amine and the Lindlar reduction. First, hydrogenation of the azide and the triple bond and *tert*-butyloxycarbonyl (Boc) protection were tried in one pot using Lindlar catalyst and di-*tert*-butyl dicarbonate in ethyl acetate under an H_2 atmosphere. This reaction was reported in the literature by Bohno *et al.* for the total synthesis of (+)-haemanthamine with a yield of 99%.[87] However, the desired product **232** could not be isolated. According to these results, it was decided to proceed in two steps with a Staundinger reduction of azide **231** to the corresponding amine and *in-situ* Boc-protection followed by Lindlar reduction. Following this route Boc-protected allylic amine **232** was obtained in 60% yield over two steps. The final step to obtain **233** was the reductive cleavage of the chiral auxiliary, however standard method using sodium borohydride led only to decomposition.



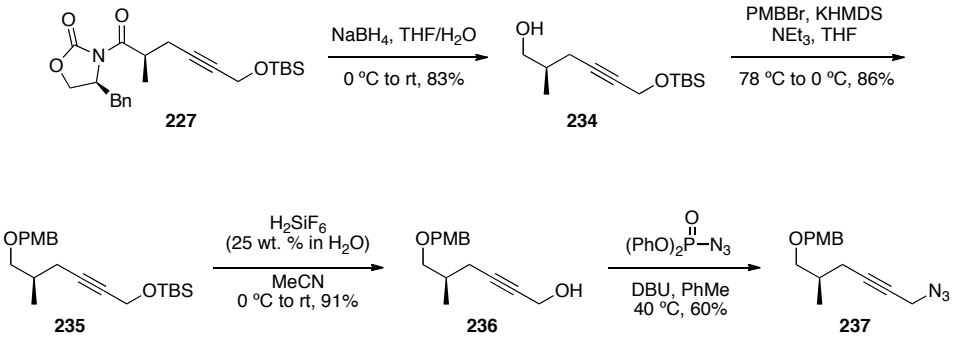
Scheme 67 - Attempted synthesis of **233**

Compound **232** was obtained in 7 steps and 8% overall yield. Unfortunately the cleavage of the auxiliary failed. However, simultaneously, a more straightforward route was investigated.

2.2.2. Synthesis of allylamine 238 (similar to key fragment 218)

In order to avoid the problems encountered with the azidation step and the cleavage of the chiral auxiliary, it was decided in this new strategy to remove the auxiliary immediately after the Evans alkylation. The cleavage of the oxazolidinone was attempted with lithium aluminium hydride at 0 °C following Evans procedure.[83] However this method led to the formation of numerous non identified by-products and the desired product was obtained with a low yield. Therefore, the cleavage was performed with sodium borohydride, a milder reducing agent, in a mixture of tetrahydrofuran/water and alcohol **234** was isolated in 83% yield (Scheme 68).[88] The protection of the free alcohol was the next step. The required protecting group had to be stable under TBS cleavage conditions, in this case aqueous hexafluorosilicic acid in acetonitrile, and its cleavage conditions had to be compatible with the molecule. Therefore, *para*-methoxybenzyl (PMB) protecting group was chosen as it could be

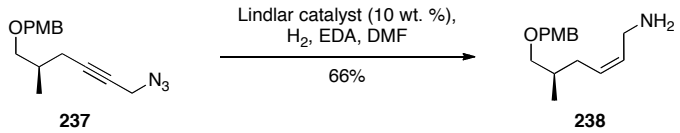
cleaved under mild conditions. Desired protected alcohol **235** was obtained using potassium bis(trimethylsilyl)amide (KHMDS) as base, *para*-methoxybenzyl bromide and triethylamine in tetrahydrofuran.[89] After TBS cleavage, alcohol **236** was converted to the corresponding azide **237** using the conditions previously described (Sub-section 2.2.1.3).[86] Since we observed the formation of a precipitate a 0 ºC, the reaction mixture was heated to 40 ºC and azide **237** was obtained in 60 % yield.



Scheme 68 - Synthesis of azide **237**

The next transformations was the reduction of the azide and the alkyne moieties as both could be achieved in one step by hydrogenation with Lindlar catalyst. The main challenge was to find the right conditions to avoid overreduction to the alkane. First, the usual conditions for Lindlar reduction, which were used to obtain **229** (Scheme 66) were tried. The reaction was monitored by TLC and stopped as soon as the starting material had disappeared. Unfortunately, the ^{1}H NMR spectrum of the crude material only indicated the presence of the aminoalkane derivative. Since the presence of an unprotected amine next to the alkyne moiety can accelerate the rate of overreduction, we believe that the reduction of the azide moiety occurred first, explaining this disappointing result. Several attempts were made with different loadings of catalyst and quinoline. Despite careful monitoring, all trials led to partial

over reduction and results were not reproducible. The use of ethylenediamine, as poison, was reported as successful to prevent overreduction of aminoalkyne derivative.[90] This observation is due to the fact that ethylenediamine, being a bidentate ligand, is more efficient than quinoline to compete for catalyst surface association. The Lindlar reduction of **237** was therefore performed with ethylenediamine and afforded **238** in 66% yield (Scheme 69).



237 **238**

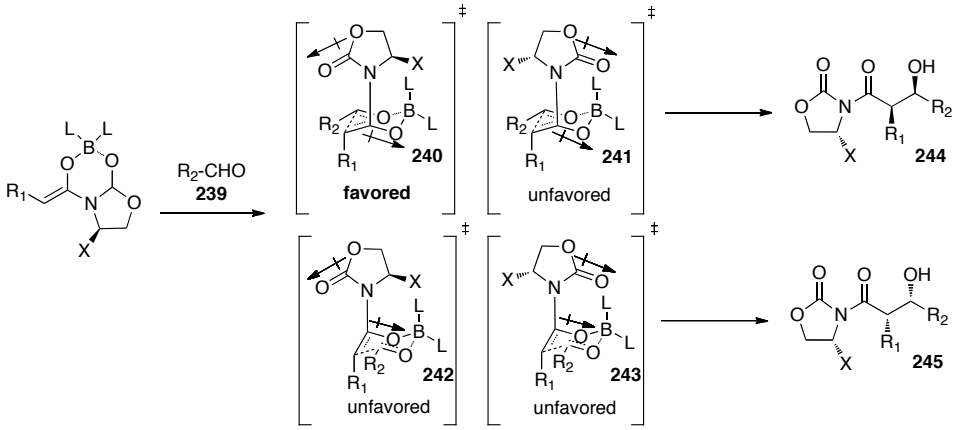
Scheme 69 - Synthesis of allylamine **238**

Allylamine **238** was obtained in 8 steps and 9% overall yield from 1,4-butynediol.

2.2.3 Synthesis of acid 247 and 248 (similar to key fragment 134) and amide 250

In order to introduce the two stereocenters of acid **134**, Evans aldol reaction was considered. This method is based on the reaction of a chiral (*Z*)-enolates, formed using boron-mediated-enolization, with an aldehyde and gives, as the major product, the Evans *syn* aldol with high diastereoselectivity. The diastereoselectivity can be explained by a Zimmerman-Traxler transition state model. The pericyclic transition state determines the *syn*/*anti* selectivity: the preferred transition state is the one which minimizes 1,3-diaxial interaction and corresponds to the one which places the aldehyde substituent in the equatorial position. This leads to the *syn* aldol products **244** and **245**. Then the chirality of the oxazolidinone differentiates the two *syn*

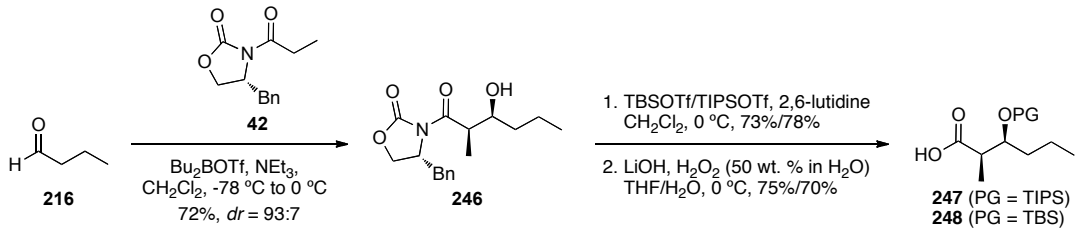
transition states. As shown in Scheme 70, the preferred transition state **240**, which gives the major product **244**, is the one where the dipoles of the enolate oxygen and carbonyl group are opposed and where there is the least number of unfavored steric interactions.[91] It is noteworthy that the *syn* aldol product will only be obtained if one equivalent the chelating agent, dibutylboron triflate is used.



Scheme 70 - Transition states for Evans aldol reaction

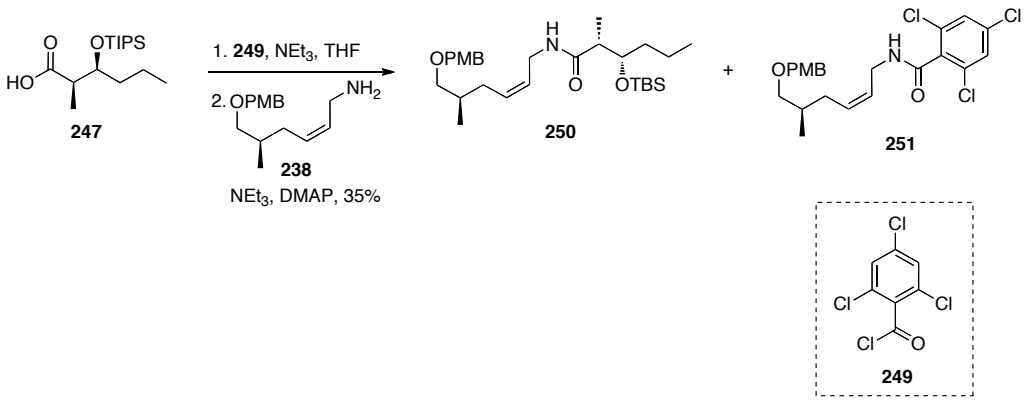
The synthesis of acids **247** and **248** started with the Evans aldol reaction with butyraldehyde **216**. ^{1}H NMR analysis of the crude material showed the presence of another diastereomer (7%). After column chromatography, NMR analysis showed the presence of a single diastereomer which was proved to have the desired configuration by comparison with literature data.[14b] For the protection of the secondary alcohol, we decided to investigate two possible silyl groups. A TIPS-protecting group would be robust enough for the rest of the synthesis but problematic to cleave, whereas a TBS would be cleaved more easily. Both protections were carried out with the corresponding triflate reagent and 2,6-lutidine as proton sponge.[92] The final step was the oxidative cleavage of the oxazolidinone following a standard protocol with lithium hydroxide and aqueous hydrogen peroxide in tetrahydrofuran at 0 °C.[93] The

desired acids **247** and **248** were obtained in a good yield and analytically pure after acidic aqueous work-up (Scheme 71).



Scheme 71 - Synthesis of acids **247** and **248**

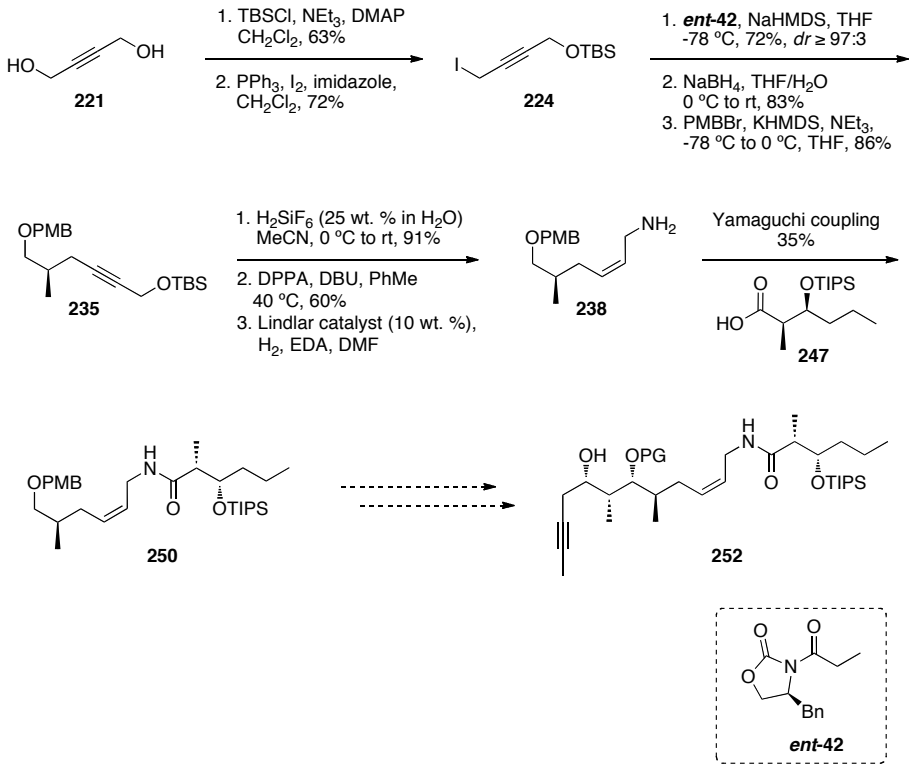
We decided to attempt the synthesis of amide **250** using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) and HOBt as coupling agents. The reaction was monitored by TLC, which showed the formation of many different products. After work-up, mass spectroscopy analysis showed the presence of the desired product **250**, but no product could be isolated after flash chromatography. The Yamaguchi coupling, known as an efficient method for translactonisation,[22] was attempted for the coupling between **250** and **238** (Scheme 72).[94] Initially acid **247** was added to the Yamaguchi reagent **249** to form the desired mixed anhydride. Without isolation of the mixte anhydride, 4-(dimethylamino)pyridine (DMAP) and amine **238** were added. Two main products were formed: the desired amide **250** in 35% yield, and amide **251** resulting from the coupling between amine **238** and the Yamaguchi reagent. At this stage it was believed that an excess of Yamaguchi reagent was responsible for the by-product formation. A better control during the addition of the Yamaguchi reagent (no excess) or simply isolation of the mixed anhydride could have overcome this problem. However, only limited amount of amine **238** was available.



Scheme 72 - Synthesis of amide **250** using Yamaguchi reagent

2.2.4 Summary

To summarize, we reported the synthesis of amide **250** from amine **238** and acid **247** in 9 steps and 3% yield for the longest linear sequence (Scheme 73). Amine **238** was obtained in 8 steps starting with 1,4-butynediol, with an Evans alkylation as a key step. Acid **247** was synthesized in 3 steps using an Evans aldol reaction to set the two stereocenters.

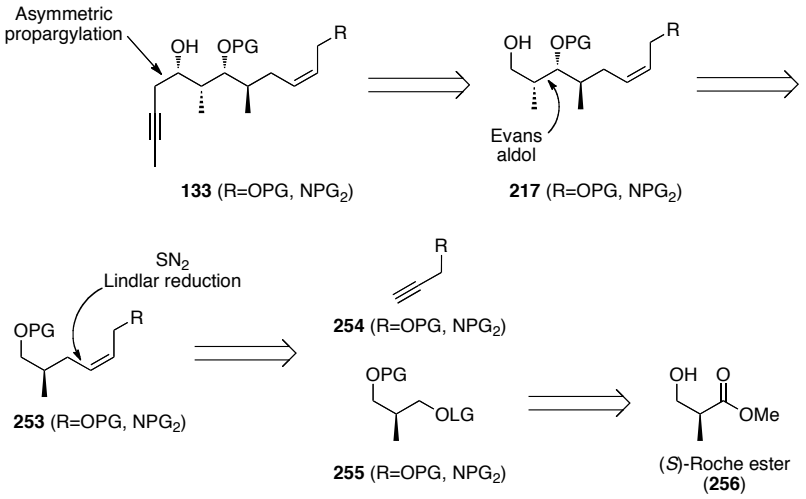


Scheme 73 - Attempted synthesis of amide **252** (similar to **132**)

The objective was to synthesize amide **252**, however this strategy allowed only obtaining small quantity of intermediate **250** especially because of the difficulties to prepare **224** on a large scale. Therefore, it was impossible to complete this synthesis and it was decided to design a more efficient strategy.

2.3 Synthesis of alcohol 312 (similar to key fragment 133)

First, regarding the sensitivity of alkyne metathesis catalysts towards free N-H, it was decided that the amide bond would be installed at a late stage of the synthesis. This would help limiting the number of protection/deprotection steps. However, it is worth noting that our first attempt of coupling resulting in the formation of amide **250** (Sub-section 2.2.3, Scheme 72) would be helpful to optimize the conditions for the late stage coupling. Furthermore, the reason why it was decided to develop a new route for the synthesis of **133** was because we needed highly efficient steps from the beginning to gain access to a large amount of **253**. Starting from chiral pool (*S*)-Roche ester would be an elegant answer, which would circumvent the problems encountered during the synthesis of electrophile **224** (Sub-section 2.2.1.1). Our new retrosynthetic plan is outlined Scheme 74, the key cuts remaining the same. The main changes are for the formation of alcohol **253**, which should be constructed by substitution reaction of nucleophile **254** on **255**, directly obtained from (*S*)-Roche ester (**256**).

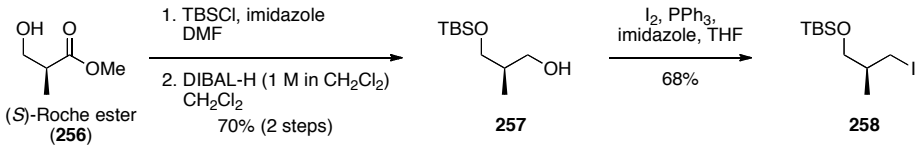


Scheme 74 - Key disconnections for key fragment **133**

2.3.1 Synthesis of 275 (similar to key fragment 253)

2.3.1.1 Synthesis of alkyne 271

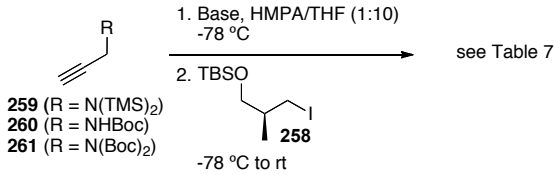
The primary objective was to obtain electrophile **255** from (*S*)-Roche ester (**256**). It was first decided to prepare the iodide derivative. Primary alcohol **256** was protected with a TBS-protecting group, then reduction of the ester was carried out with lithium aluminium hydride, as described by Koseki *et al.*,[95] but failed to give alcohol **257**. Instead, 2-methylpropane-1,3-diol was isolated. Lithium aluminiun hydride was therefore replaced by DIBAL-H, a milder reducing agent compatible with silyl-protecting groups, and **257** was obtained in 70% yield over two steps. **257** was converted into the corresponding iodide derivative **258** using Appel reaction conditions. The moderate yield for this step could be explained by the relative unstability of **258** (Scheme 75).



Scheme 75 - Synthesis of **258**

For the next step, the idea was to perform a coupling between alkyl iodide **258** and a metal acetylide derivative in order to form **253**. As reported earlier in Sub-section 2.1.2.1.2, this type of reaction generally requires the use of HMPA as a co-solvent in tetrahydrofuran. This method was unsuccessful for the synthesis of **193** (Scheme 47, Table 4), however this result was unknown to us since both couplings (for the formation of **193** and **253**) were studied at the same time. Following the usual

procedure, it was decided to first test propargylamine derivatives with various protecting groups and the appropriate base (Scheme 76, Table 7). The use of di(TMS)-protected propargylamine as a nucleophile has been extensively described by Moreau and Corriu in the late 1980s'.[96] They showed that **259** deprotonated with *n*-butyllithium could perform nucleophilic attack on various nucleophiles including alkyl halide derivatives. However, our attempts with **259** were not successful. Instead, the ^{1}H NMR spectrum of the crude reaction mixture showed that iodide **258** underwent elimination of HI and produced alkene **262**. Starting material **258** was recovered too (Table 7, Entry a). This result could be due to the rapid degradation of **258**. Boc-protected propargylamines **260**[97] and **261**[98] were then tested. In this case LDA was used. With the mono-protected amine, a mixture of two products was isolated: alkene **262** and amino derivative **263** (Table 7, Entry b). Finally alkene **262** was the only product detected by ^{1}H NMR of the crude reaction mixture from the coupling with di(Boc)-protected propargylamine **261** (Table 7, Entry c). These disappointing results led us to considerate the use of a more activated nucleophile. Since **258** was highly subject to elimination, we needed a nucleophile which would react fast enough to avoid the formation of alkene **262**.



Scheme 76 - Coupling between **258** and propargylamine derivatives

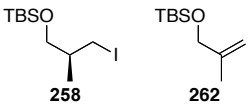
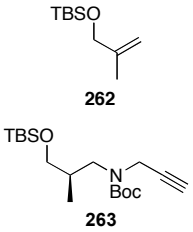
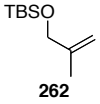
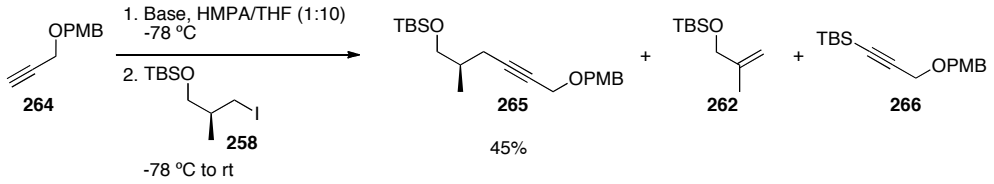
Entry	*R*	*Base*	*Product*
a	-N(TMS)$_2$ **259**	*n*-BuLi	 **258** **262**
b	-NHBoc **260**	LDA	 **262** **263**
c	-N(Boc)$_2$ **261**	LDA	 **262**

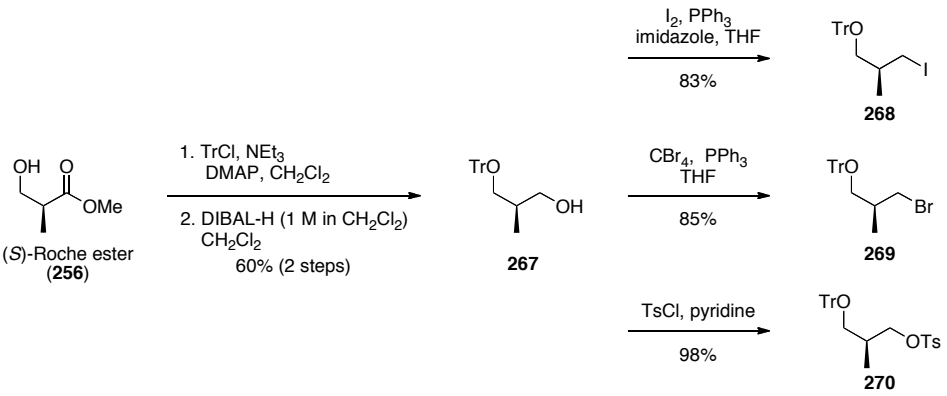
Table 7 - Different conditions for the coupling between **258** and propargyl amine derivatives

para-Methoxybenzyl (PMB)-protected propargyl alcohol **264**[99] was used to perform the coupling with **258**. With the strong donating effect of the PMB group, compared to the withdrawing groups previously used, **264** should be able to react fast enough to circumvent the elimination of HI. Following the same procedure previously used, **264** was deprotonated with *n*-butyllithium in a mixture of HMPA and tetrahydrofuran. Electrophile **258** was then added. Desired product **265** was isolated as well as a mixture of alkene **262** and **266**, product of an intermolecular silyl migration (Scheme 77). This result was encouraging, but a better yield was definitely needed.



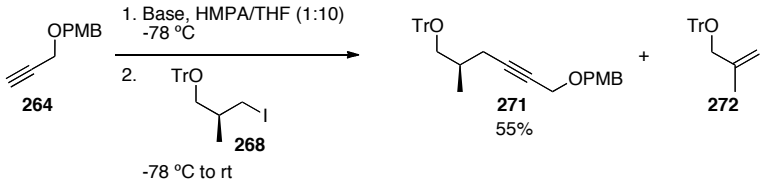
Scheme 77 - Coupling between **258** and propargyl alcohol **264**

At this stage we believed that changes should be made to electrophile **258** in order to improve the yield. The instability of **258** was most likely the cause of the formation of elimination product **262**. By replacing the iodine by less reactive leaving groups, it could have been possible to reduce or even avoid completely the elimination of HI. Furthermore, isolation of product **266** showed that a silyl migration was possible between **258** and **264**. Therefore TBS-protecting group was replaced by a trityl-protecting group. With this new plan, electrophiles **268, 269 and 270** were prepared in an analogous fashion to **258**, in three steps from (*S*)-Roche ester (Scheme 78).[100]



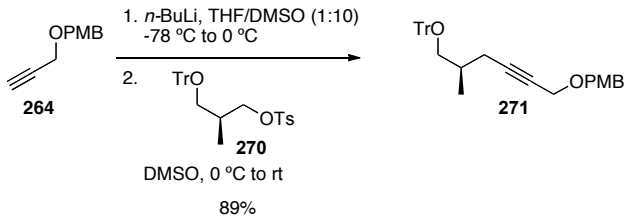
Scheme 78 - Synthesis of electrophiles **268**, **269**, **270**

The coupling was first performed with iodide **268** following the conditions previously used. Desired product **271** was obtained with 55% yield and alkene **272** was isolated too (Scheme 79).



Scheme 79 - Coupling between **268** and propargyl alcohol **264**

In 1986, Chong *et al.* reported that acetylide derivative with an inductively stabilizing group could be easily alkylated in dimethylsulfoxide as solvent despite its competing metalation.[101] This method was later used by Molander and co-workers for the alkylation of propiolaldehyde diethyl acetal with 1-chloro-3-*iso*propane.[102] This procedure was tested with the three electrophiles. Less than 20% of desired product **271** was isolated when both of the alkyl halides were employed whereas the reaction with tosylate **270** led to the exclusive formation of **271** in good yields (Scheme 80). Tosylate derivative **270** was isolated as white needles and seemed to be indefinitely stable on the bench, on the contrary to the iodide and bromide derivatives that could not be isolated pure but as a mixture with the elimination product. The stability of **270** could explain the good results obtained for the coupling and the fact that no alkene **272** was isolated.

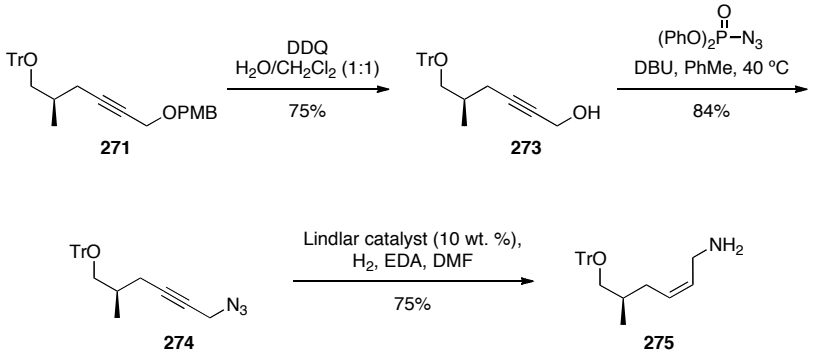


Scheme 80 - Coupling between **270** and propargyl alcohol **264**

Finally a reliable method was found for the synthesis of **271**. Compared to the first route developed for the synthesis of **238** (Sub-section 2.2.2), this new method contained only high yielding steps and had the advantage to start from chiral pool (*S*)-Roche ester. With this new method we were able to prepare 60 g of **271** in 2 batches.

2.3.1.2 Synthesis of amine 275

The synthesis of amine **275** could be achieved in three steps from **271** (Scheme 81). First PMB-cleavage was performed under standard conditions with the oxidizing agent DDQ, which afforded primary alcohol **273** in good yield. Following this, conversion to the corresponding azide was performed with the conditions used to obtain **237** (Sub-section 2.2.2) and led to desired azide **274** in 84% yield. Finally, hydrogenation of the azide group and the triple bond was carried out under H_2 atmosphere with Lindlar catalyst and ethylenediamine as poison. Amine **275** was obtained in 75% yield. However, degradation of **275** was observed, especially when dissolved in deuterated chloroform. Therefore it was decided that the amine function would be installed at a late stage of the synthesis of cruentaren A.

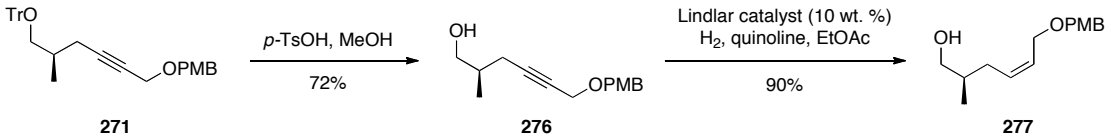


Scheme 81 - Synthesis of amine **275**

2.3.2 Synthesis of 279 (similar to key fragment 217)

2.3.2.1 Synthesis of alcohol 277 (similar to key fragment 253)

Alcohol **277** was available from **271** in two steps (Scheme 82). Trityl protecting groups are generally cleaved with protic and Lewis acid or by hydrogenolysis. In this case, *para*-toluenesulfonic acid was used in methanol. **271** had first to be dissolved in a minimum amount of dichloromethane, as it was insoluble in methanol.[103] Primary alcohol **276** was obtained in good yield. Then Lindlar reduction was performed with quinoline as poison to afford **277** in 90% yield. The ^{1}H NMR and ^{13}C NMR spectra only showed the presence of the (*Z*)-isomer.



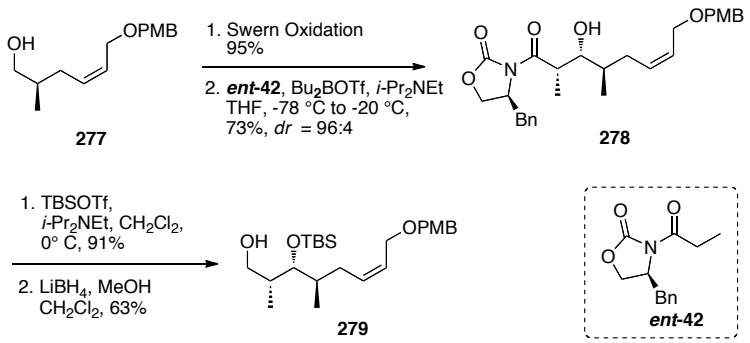
271 **276** **277**

Scheme 82 - Synthesis of alcohol **277**

2.3.2.2 Synthesis of 279 *via* Evans aldol reaction

The next key step was an Evans aldol reaction (Scheme 83). **277** was first oxidised to the corresponding aldehyde. In this case, a classic Dess-Martin oxidation was not suitable. The presence of acetic acid in this reagent could have been responsible for epimerization at the alpha-position. In this situation, pyridine or sodium bicarbonate are normally added in order to quench any acid traces.[104] Therefore oxidation of **277** was first tried with Dess-Martin reagent and pyridine in dichloromethane at 0 ºC. The corresponding aldehyde was obtained pure after flash chromatography and because no

racemization (enantiomers) could be detected by NMR spectroscopy, it was decided to carry on with the aldol reaction and check at this stage if diastereoisomers were obtained. The Evans aldol reaction was performed with dibutylboron triflate and Hünig's base and the ^{1}H NMR spectrum of the crude material showed a mixture of diastereoisomers (the ratio could not be exactly identified, *dr* ≥ 80:20). This poor result could have been the result of a mismatched reactant pair as both the enolate of **42** and the aldehyde contained pre-existing stereochemistry. However since Fürstner obtained good results with similar partners,[15] we speculated another reason for the low diastereoselectivity. After several trials leading to the same results, the oxidation method was changed for a Swern oxidation. Then, following the same procedure for the Evans aldol reaction, **278** was obtained in high yield and excellent diastereoselectivity (*dr* = 96:4). This result might be surprising, as the Dess-Martin oxidation is usually well known to circumvent the racemization problem. However, in our case, purification by flash chromatography was necessary after the Dess-Martin oxidation to remove excess of reagent and by-products. This might be the cause of the racemization since no flash chromatography was necessary after the Swern oxidation. It is worth noting that partial cleavage of the PMB group was observed when the reaction was carried out with triethylamine instead of Hünig's base. The next step was the protection of the secondary alcohol with a TBS-protecting group in 91% yield. The reductive cleavage of the Evans' auxiliary was then performed with sodium borohydride. However the reaction time (48 hours) and low yield led us to use lithium borohydride, a stronger reducing agent, which afforded **279** in 63 % yield.



Scheme 83 - Synthesis of alcohol **279**

2.3.3 Synthesis of 312 (similar to key fragment 133) *via* asymmetric propargylation

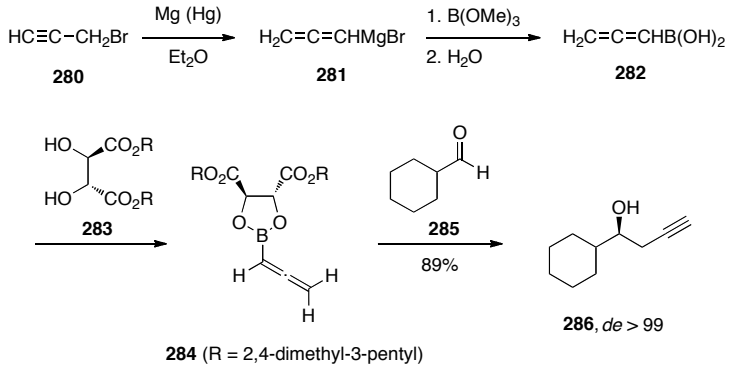
The next key step for the synthesis of key alcohol **133** was an asymmetric propargylation in order to introduce the propargyl moiety and set the last stereocenter. Asymmetric propargylation reactions have been widely studied over the past decades resulting in important progress therefore numerous methods were available to us for this step.

2.3.3.1 Asymmetric propargylation

Propargylation reactions can be classified into two types. The most common involves the formation of an organometallic reagent (allenyl or propargyl), which reacts with a carbonyl compound. The second involves the substitution of propargyl alcohols with a nucleophile. Only the first category will be discussed in this Sub-section. Numerous organometallic reagents have been successfully applied to propargylation reactions. The asymmetric version of the propargylation reaction has been essentially developed

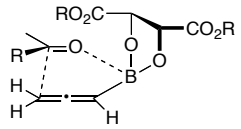
through the use of stoichiometric chiral reagents and more recently through the use of catalytic chiral Lewis acids. [105]

An early report by Yamamoto showed that the addition of chiral allenyl boronic esters (e.g. **284**) derived from tartrates onto aldehydes provided homopropargylic alcohols with excellent enantioselectivity.[106] This method has been extensively used for the synthesis of natural products despite the non-friendly preparation of the allenyl boronic esters (Scheme 84).



Scheme 84 - Yamamoto asymmetric propargylation

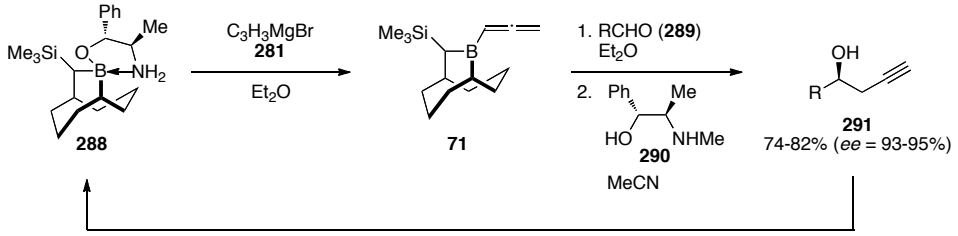
The fact that only propargylic alcohol **286** was isolated indicated that the reaction proceeds through a cyclic transition state (Figure 8), which also shows the role of the bulky chiral tartrate in controlling the enantioselectivity of the reaction. It is noteworthy that this transition state is only accepted for propargylation of an aldehyde with an allenyl organometallic reagent if no other reagents (*e.g.* Lewis acid) are added.



287

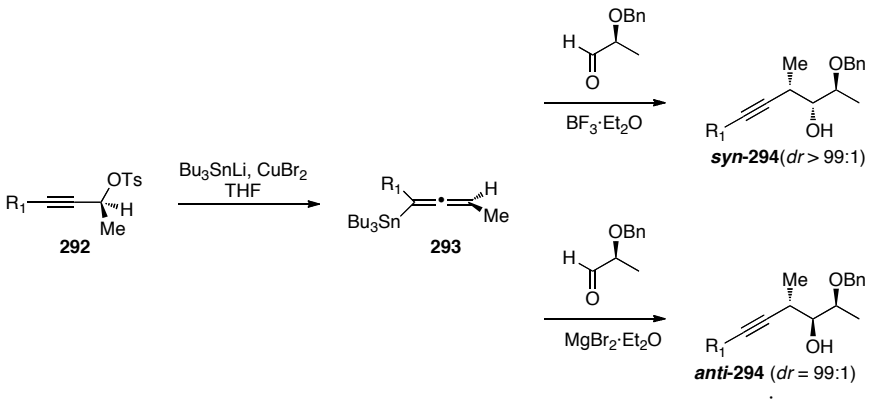
Figure 8 - Transition state for the Yamamoto asymmetric propargylation

Recently, Soderquist developed a new method for the synthesis of chiral homopropargylic alcohols *via* asymmetric allenyl boration.[30] His work represents an impressive improvement of Yamamoto and Corey's methodologies.[107] It involves the treatment of chiral borabicyclodecanes **288** with propargylmagnesium bromide, which then reacts with the aldehyde to provide the desired homopropargylic alcohol (Scheme 85). **71** is in fact a stable crystalline product, now commercially available, which makes this procedure very user-friendly.



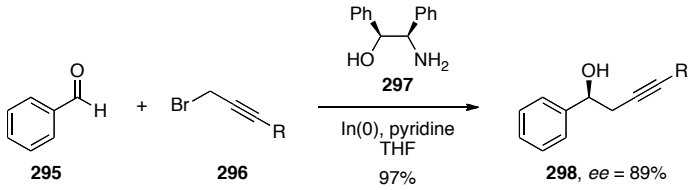
Scheme 85 - Soderquist asymmetric propargylation

The work of Marshall *et al.* on the synthesis of chiral allenic metal reagents contributed greatly to the development of enantioselective propargylation reactions. A wide range of axially chiral organometallic compounds (tin, silicon, zinc, indium) were prepared through an *anti*-S_N2' mechanism. Their addition onto aldehydes produced homopropargylic alcohols with excellent diastereoselectivity. Using different substrates or Lewis acids can modify the outcome of the reaction (Scheme 86).[108]



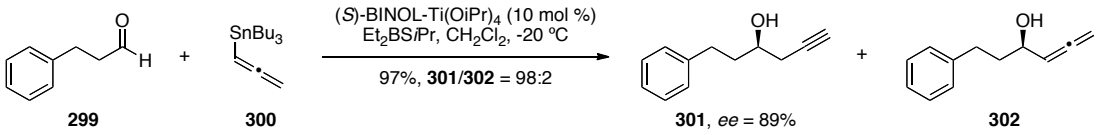
Scheme 86 - Marshall asymmetric propargylation

Barbier-type reactions with various metals have been widely used for the synthesis of homopropargylic alcohol as the addition of an external chiral reagent can make this reaction enantioselective. In particular, the use of indium has been extensively examined as it can be used in aqueous media. Furthermore, studies by Chan and co-workers showed that when indium is used with R = H, the homopropargylic alcohol is observed to be the sole product (no formation of allene derivatives observed).[109] Singaram *et al.* reported the use of stoichiometric amount of chiral (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**297**) with indium under Barbier-type reaction to produce homopropargylic alcohols in high enantiomeric excess. They showed that the use of pyridine greatly improved the enantioselectivity of the reaction during previous studies on allylation reactions (Scheme 87).[110] The great advantage of this method is that all reagents are commercially available and cheap and the protocol is very easy.



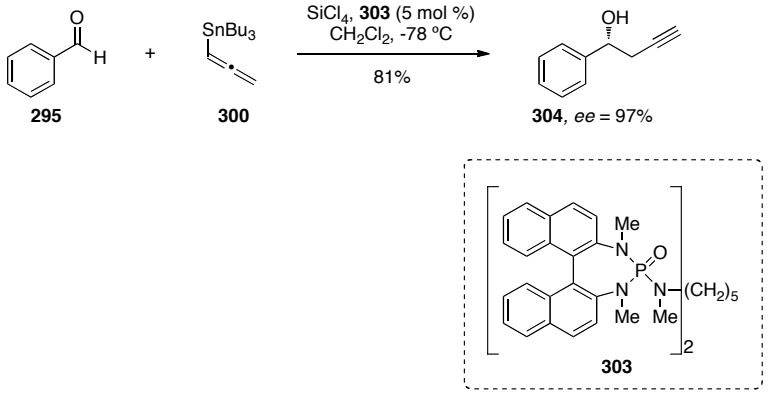
Scheme 87 - Barbier type asymmetric propargylation by Singaram *et al.*

The catalytic version of the asymmetric propargylation reaction appeared in 1994 when Keck and co-workers reported the use of a chiral Lewis acid (prepared from titanium(IV) isopropoxide and (*R*)-(+)-1,1′-bi(2-naphthol) (BINOL) to catalyse the addition of allenylstannane to aldehydes. However this reaction needed a high catalyst loading (50-100 mol%).[111] Yu *et al*. improved this method by adding *iso*-propyl diethylthioborinate (Et_2BSiPr) and extended the substrate scope to a variety of aldehydes (Scheme 88). It is believed that Et_2BSiPr is involved in the dissociation of the product from the reaction complex and in the regeneration of the catalyst, which explains the low catalyst loading needed (≤ 10 mol %) and the shorter reaction time when this reagent is added.[112]



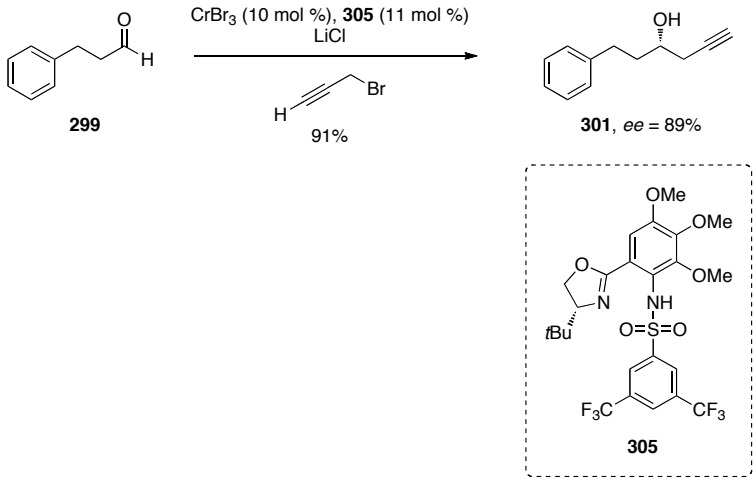
Scheme 88 - Asymmetric propargylation by Yu *et al.*

Denmark *et al.* applied the Lewis base activation of a Lewis acid strategy to the asymmetric propargylation reaction (Scheme 89). Thus, the strong chiral Lewis acid binaphthyl-based phosphoramide **303**•$SiCl_4$ was used to catalyse the addition of allenyltributylstannane (**300**) onto aldehydes. Varieties of homopropargyl alcohol were obtained in good yield and high enantiomeric excess.[113]



Scheme 89 - Asymmetric propargylation by Denmark *et al.*

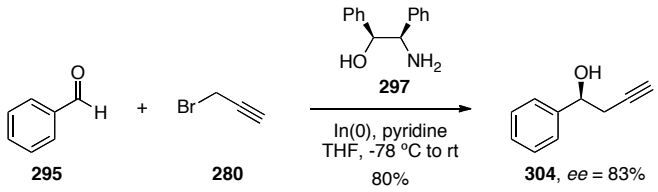
Finally, the use of chromium salts for propargylation reactions was introduced by Nozaki and Hiyama with Chromium (II) generally used in large excess to produce the organochromium reagent.[114] Cozzi and co-workers showed that, by adding the chiral complex [Cr(Salen)], asymmetric catalysis of the Nozaki-Hiyama propargylation reactions could be achieved. However results where limited by low yields and enantioselectivity.[115] Later, Kishi *et al* developed a new kind of chiral ligand derived from chromium (III) bromide and **305** that permitted to achieve highly enantioselective propargylation reactions (Scheme 90).[116]



Scheme 90 - Asymmetric propargylation by Kishi *et al.*

2.3.3.2 Application to the synthesis of 312

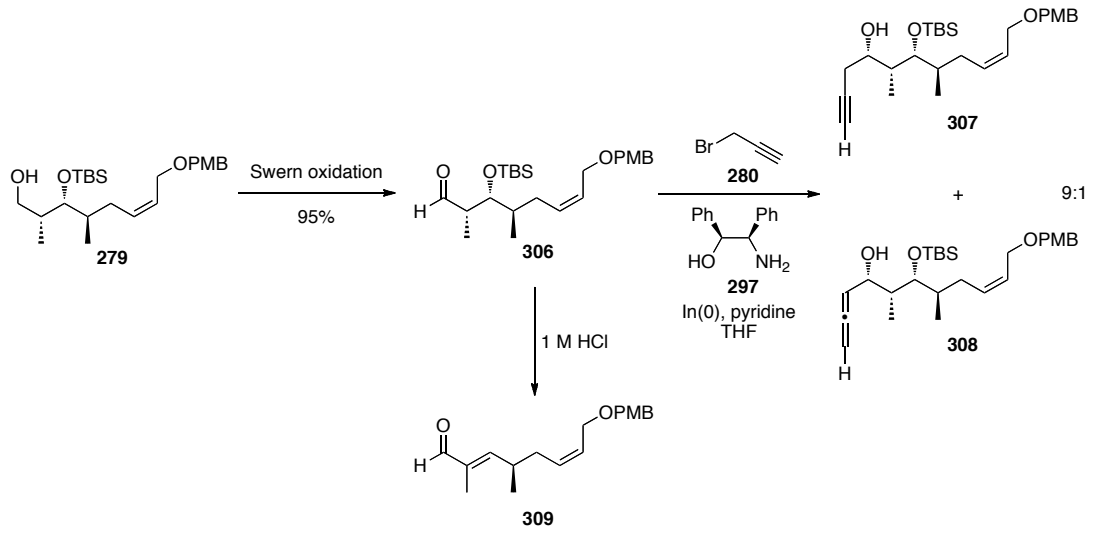
The previous Sub-section 2.3.3.1 constitutes of a non-exhaustive list of some well-known methods for asymmetric propargylation reactions that are frequently used for the synthesis of natural product. The aim was to present the different strategies that were available to us to synthesize homopropargyl alcohol **312**. As mentioned earlier, Fürstner and co-workers decided to use the Soderquist propargylation to obtain a similar fragment.[15] Their choice was indeed successful as **72** was obtained in good yield and high diastereomeric ratio (Sub-section 1.2.3.2, Scheme 12). However, despite being recognised as a user-friendly reaction, the Soderquist propargylation still involves three distinct steps from commercially available borane **71**. We believed that, if successful, a Barbier type reaction would be a much easier and quicker solution to the synthesis of **312**. Initially the protocol described by Singaram *et al.* involving the use of indium(0) with amino-alcohol **297** as a chiral ligand was tested with benzaldehyde. In the event, the desired product **304** was obtained as outlined with similar yield and *ee* (Scheme 91)[110] (checked by comparison of the optical rotation data reported in the literature[30]).



Scheme 91 - Synthesis of **304** using the Barbier type procedure described by Singaram *et al.*

With these pleasing results in hand, the same protocol was applied to aldehyde **306**, obtained as a single diastereoisomer from **279** by Swern oxidation (Scheme 92). After

2 hours at -78 ºC, TLC analysis of the reaction mixture indicated 50% conversion. The reaction was then slowly allowed to warm up over 10 h to reach room temperature. However, TLC analysis indicated the same rate of conversion. After acidic aqueous work-up, the unreacted aldehyde had been converted to the α,ß-unsaturated aldehyde **309** *via* elimination of the O-TBS group. Furthermore desired product **307** (one diastereoismer by ^{1}H NMR analysis) was obtained as a 9:1 mixture with the corresponding allene **308** (Table 8, Entry a). Since it was impossible to recover the starting material, we needed to improve the procedure to obtain a conversion rate close to 100%. Using more equivalents of reagents did not help (Table 8, Entry b). However, we were pleased to find that by stirring the reaction at -20 ºC for 18 hours, full conversion was obtained (Table 8, Entry c). Furthermore **307** was isolated as a single diastereoisomer, as confirmed by the ^{1}H NMR and ^{13}C NMR spectra, but still as a 9:1 mixture (inseparable by silica flash chromatography) with **308**, in 80% yield.



Scheme 92 - Synthesis of **307** using the Barbier type procedure described by Singaram *et al.*

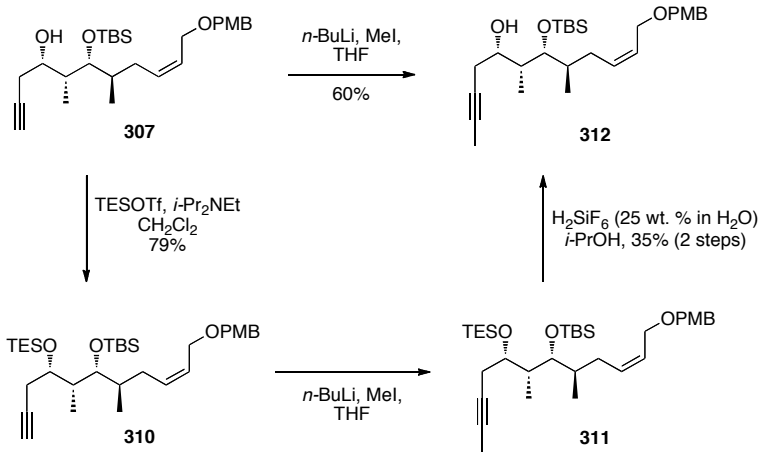
Entry	*Conditions*	*Temperature*	*Results*
a	In(0) 2 eq Pyridine 2 eq **297** 2 eq	-78 ºC to rt in 10 h	50% conversion **309** (after work-up) **307** and **308** (9:1, 37% yield, *dr* ≥ 97:3
b	In(0) 4 eq Pyridine 4 eq **297** 4 eq	-78 ºC to rt in 10 h	50% conversion **309** (after work-up) **307** and **308** (9:1, 37% yield, *dr* ≥ 97:3
c	In(0) 2 eq Pyridine 2 eq **297** 2 eq	-20 ºC for 10 h	full conversion **307** and **308** (9:1, 80% yield, *dr* ≥ 97:3

Table 8 - Different conditions for the synthesis of **307**

Since no transition state model was available for this method, it was important to ascertain the stereochemistry of **307**. To do so, **307** was converted to the corresponding (*S*)- and (*R*)-Mosher esters. By comparison of the ^{1}H-NMR spectrum, it was possible to confirm that the desired stereochemistry had been installed.

The final step of the synthesis of alcohol **312** was the methylation of the terminal alkyne (Scheme 93). First, a three-step procedure was carried out with a temporary triethylsilyl (TES)-protecting group, as described be Fürstner *et al.*[15] However, as the free alcohol of **307** was slightly hindered and that a lithium alkoxide would be less reactive than a lithium acetylide anion, we believed that direct methylation of the terminal alkyne might be possible. Using 2 equivalents of *n*-butyllithium, **307** was deprotonated at -78 ºC and stirred for 1h. After addition of methyl iodide, the reaction

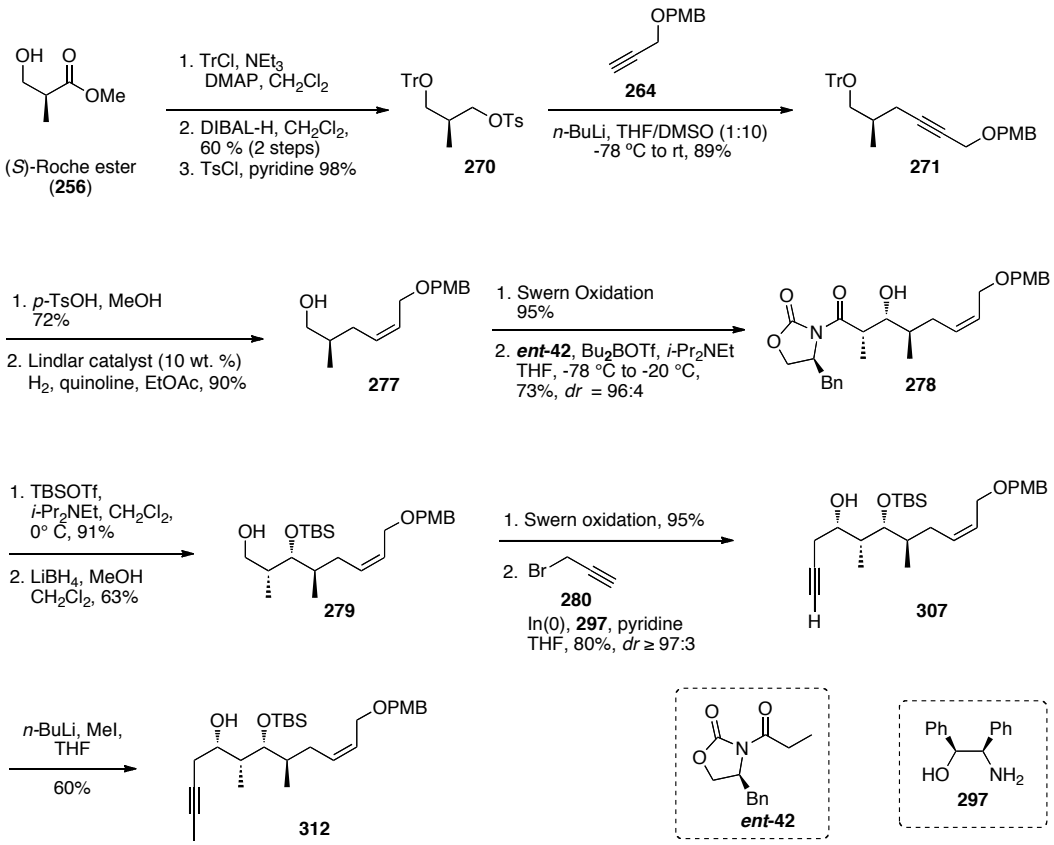
mixture was warmed up to room temperature. In 30 minutes, the methylation was completed and **312** was isolated as the sole product in 68% yield. The yield was much higher than for the three steps version (35%).



Scheme 93 – Synthesis of alcohol **312** *via* selective methylation

2.3.4 Summary

Finally, we reported the synthesis of key alcohol **312** starting from chiral pool (*S*).Roche ester (**256**) (Scheme 94). Key features included Evans aldol reaction and Barbier type asymmetric propargylation to install the 3 other stereocenters.

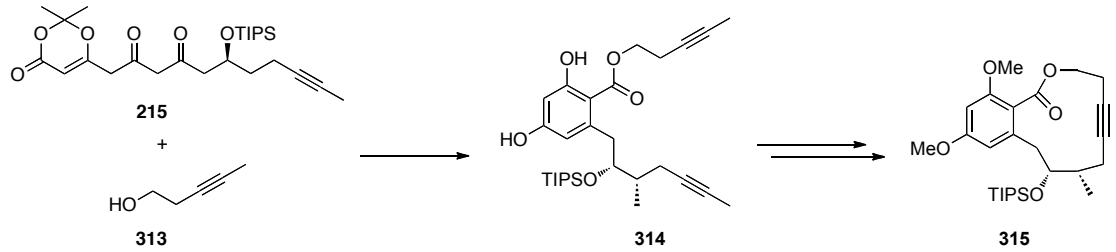


Scheme 94 - Synthesis of alcohol **312**

Finally, 2.5 g of alcohol **312** was synthesized in two batches. The overall yield is 7% for 13 steps.

2.4 Aromatization and RCAM studies on a model system

With alcohol **312** and diketo-dioxinone **215** in hand we had to find the most suitable conditions for the aromatization, the key step of our synthesis of cruentaren A. An initial set of experiments was conducted on a model system with diketo-dioxinone **215** and homopropargylic alcohol **313**. If successful, this model system should lead to the formation of resorcylate **314**, a perfect candidate to study the subsequent RCAM (Scheme 95).



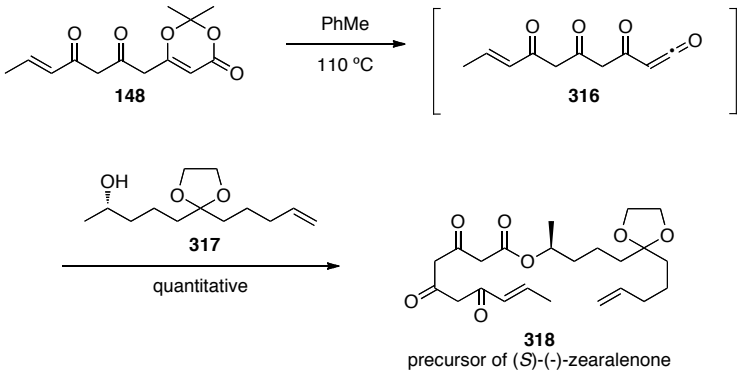
Scheme 95 – Model system

2.4.1 Aromatization studies

2.4.1.1 Total synthesis of RALs utilizing late stage aromatization

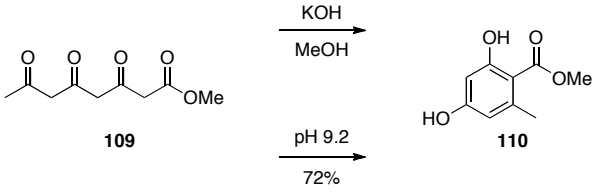
In 2008, Basset and Barrett reported the first biomimetic synthesis of *S*-(-)-zearalenone (**1**) utilizing a late stage aromatization strategy.[50] Inspired by Hyatt *et al.* (Sub-section 1.4.2, Scheme 23),[45] they reported that thermolysis of diketo-dioxinone derivative **148** led to the formation of the corresponding ketene intermediate **316**, *via* a retro-Diels-Alder reaction, which was trapped *in situ* with

alcohol **317** to give triketo-ester **318** (Scheme 96). The ^{1}H-NMR spectrum of the crude mixture showed that **318** was in fact a mixture of keto and enol tautomers.



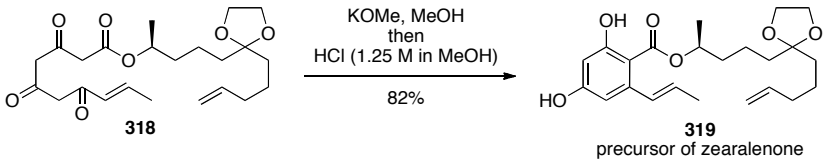
Scheme 96 - Synthesis of triketo-ester **318** *via* thermolysis and ketene trapping

Harris first showed that the resorcylic acid ring could be obtained from triketo-esters *via* aldol condensation under basic conditions (potassium hydroxide).[43] Later Barrett *et al.* reported the use of a pH 9.2 buffer solution for the same purpose (Scheme 97).[44]



Scheme 97 - Aromatization of triketo-esters

Aromatization studies for the synthesis of *S*-(–)-zearalenone (**1**) showed that **318** could undergo aldol condensation using a solution of potassium methoxide in methanol. Subsequent addition of hydrochloric acid (to pH = 1) was required to promote the dehydration and the subsequent aromatization leading to resorcylate **319** in 82% yield (Scheme 98).[50]



Scheme 98 - Synthesis of resorcylate *319 via* late stage aromatization

This biomimetic aromatization procedure was then applied to the synthesis of other RAL natural products. However, the conditions for the aromatization had to be adapted to the substrate, therefore several combinations of basic and acidic media have been used. Few examples are reported in Table 9. For the synthesis of 15G256, potassium carbonate in *iso*-propanol followed by aqueous hydrochloric acid was preferred.[50] A combination of cesium acetate in *iso*-propanol followed by trifluoroacetic acid was used towards the synthesis of *ent*-W1278.[52] Finally, the use of cesium carbonate followed by acetic acid was reported for the synthesis of LL-Z1640-2.[117]

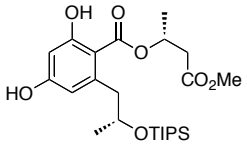
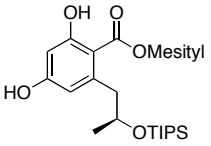
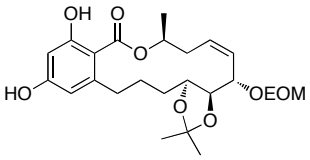
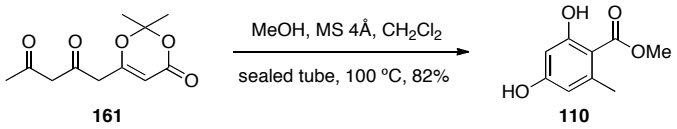
Entry	*Conditions*	*Product*
a	1. PhMe, 110 ºC 2. K_2CO_3, CH_2Cl_2/*i*-PrOH then HCl in MeOH to pH = 2	 **320** Precursor of 15G256
b	1. PhMe, 110 ºC 2. CsOAc, CH_2Cl_2/*i*-PrOH then TFA	 **321** Precursor of ent-W1278
c	1. PhMe, 110 ºC 2. Cs_2CO_3, MeOH then AcOH (glacial)	 **322** Precursor of LL-Z1640-2

Table 9 – Different conditions for the late stage aromatisation

Interestingly, Basset and Barrett also discovered that the aromatization could occur under neutral conditions (Scheme 99). When dioxinone **161** was treated with 4 Å molecular sieves in a mixture of *iso*-propanol and dichloromethane in a sealed tube at 100 ºC, orsellinate ester **110** was obtained in 82% yield.[55]

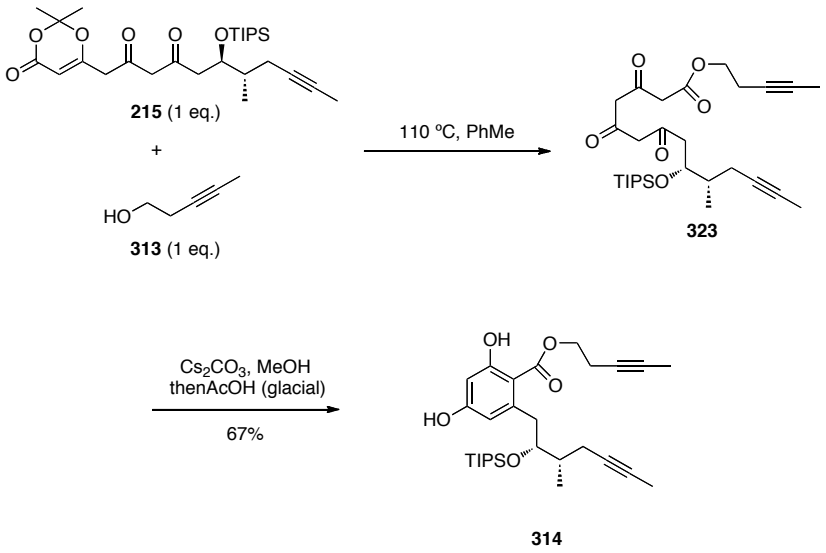


161 **110**

Scheme 99 - Aromatization under neutral conditions

2.4.1.2 Synthesis of resorcylate 314 *via* late stage aromatization

The synthesis of **314** was attempted using the two steps method previously described, which includes first trapping of the ketene derivative followed by the aromatization (Scheme 100). Diketo-dioxinone **215**, in the presence of one equivalent of alcohol **313** was heated to reflux until complete consumption of both reagents. The ^{1}H NMR spectrum of the crude material showed a mixture of keto and enol tautomeres of **323**. Without further purifications (triketo-ester derivatives are reported to be unstable), **323** in methanol was treated with cesium carbonate followed by acetic acid. **314** was isolated as the sole product in 67% yield



Scheme 100 - Aromatization studies with diketo-dioxinone **215** and alcohol **313**

2.4.2 RCAM studies

Having established the conditions for the biomimetic aromatization on our model system, we wanted to go further and optimize the conditions for the subsequent RCAM.

2.4.2.1 Synthesis of (pre)catalyst 100

The RCAM is a key step for the synthesis of cruentaren A. Maier *et al.* reported the use of the Schrock catalyst **52** while Fürstner and co-workers used one of their own catalysts, the trisamido molybdenum(III) complex **74** to complete the RCAM.[14,15] These two catalysts were successful, however, their sensitivity towards air and moisture meant they required careful handling. Therefore we decided to screen the different catalysts available to us (Sub-section 1.3). Fürstner had recently disclosed a new catalytic alkyne metathesis system offering better stability.[33] These molybdenum nitride complexes with silanolate ligands were appealing, especially the pyridine adduct **100** which was reported to be robust enough to be weighed in air (Figure 8).

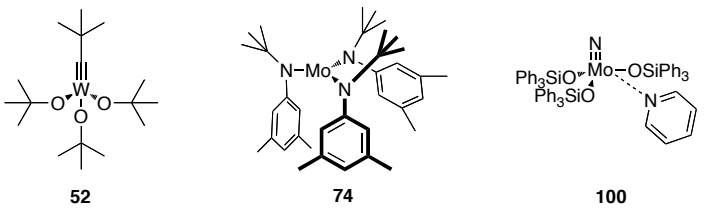
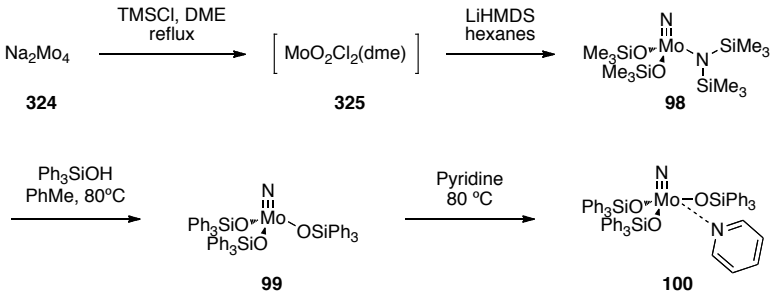


Figure 8 - Catalysts for alkyne metathesis

Since **100** was not commercially available, its synthesis was carried out following Fürstner's protocol.[33] It is worth noting that if pyridine adduct **100** can be considered

air stable, this is not the case for its intermediates. Therefore careful handling and manipulation under an inert atmosphere of argon were required throughout its synthesis. First sodium molybdate (**324**) was treated with trimethylsilyl chloride in dimethoxyethane at reflux to yield the dioxo-species **325**. LiHMDS was added to the crude mixture and complex **98** was obtained pure after filtration and distillation under high vacuum. Treatment of **98** with triphenylsilanol in hot toluene afforded active catalyst **99**. Subsequent addition of pyridine followed by recrystallisation gave access to the desired pyridine adduct **100** on gram scale (Scheme 101). It was unclear from the spectroscopic data if **100** had been successfully synthesized. However, crystallographic data showed that the desired complex had been obtained (Appendix 1).

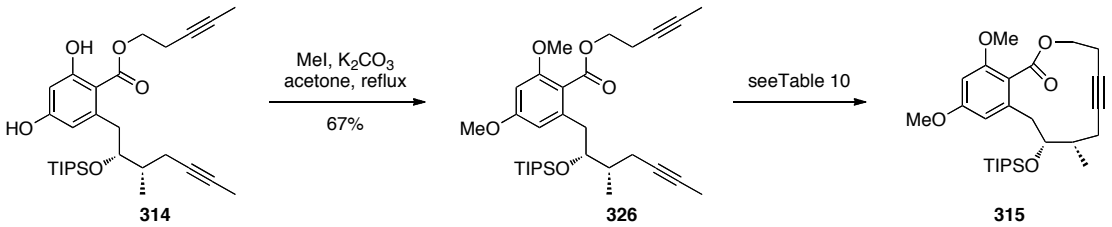


Scheme 101 - Preparation of (pre)catalyst **100**

2.4.2.2 Synthesis of macrolactone 315

Since (pre)catalyst **100** was incompatible with free hydroxy groups, resorcylate **314** was first converted to **326** using methyl iodide and potassium carbonate in refluxing acetone. The formation of macrolactone **315** by RCAM was then investigated (Scheme 102) and the different attempts are reported in Table 10. First the conditions

reported by Fürstner *et al.* were followed[33] (Table 10, Entry a), however no reaction occurred and starting material **326** was recovered. Since the catalytic activity of **100** is restored upon heat by decomplexation of pyridine, we believed that addition of **100** to a pre-heated solution of **326** in toluene at 80 ºC could be beneficial (Table 10, Entry b). The desired macrolactone **315** was identified by ^{1}H NMR spectroscopy but only with moderate conversion. Furthermore, because **315** could only be isolated as a mixture with residual triphenylsilanol, it was impossible to obtain the exact yield of the reaction. In order to obtain a higher conversion, the same procedure was repeated at 110 ºC (Table 10, Entry c). After 18 hours, the ^{1}H NMR spectrum of the crude material confirmed full conversion of **326** into **315** but once again the yield could not be determined.



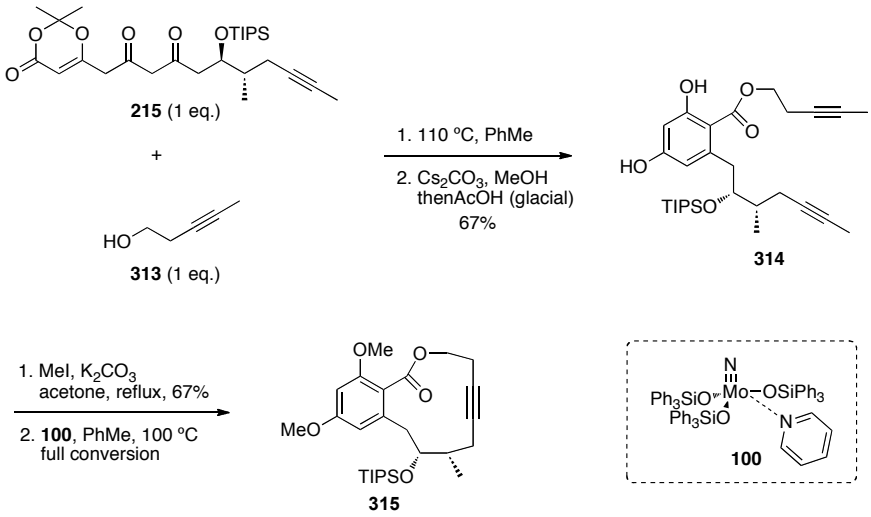
Scheme 102 - Synthesis of 315 *via* RCAM

Entry	*Reagents and Conditions*	*Results*
a	-**326** added to a suspension of **100** (20 mol %) in PhMe at rt -Mixture stirred 18 h at 80 ºC	No reaction
b	-**326** in PhMe at 80 ºC -**100** (20 mol %) added, stirred 18 h at 80 ºC	40% conversion
c	-**326** in PhMe at 110 ºC -**100** (20 mol %) added, stirred 18 h at 110 ºC	Full Conversion

Table 10 - Different conditions for the RCAM

2.4.3 Summary

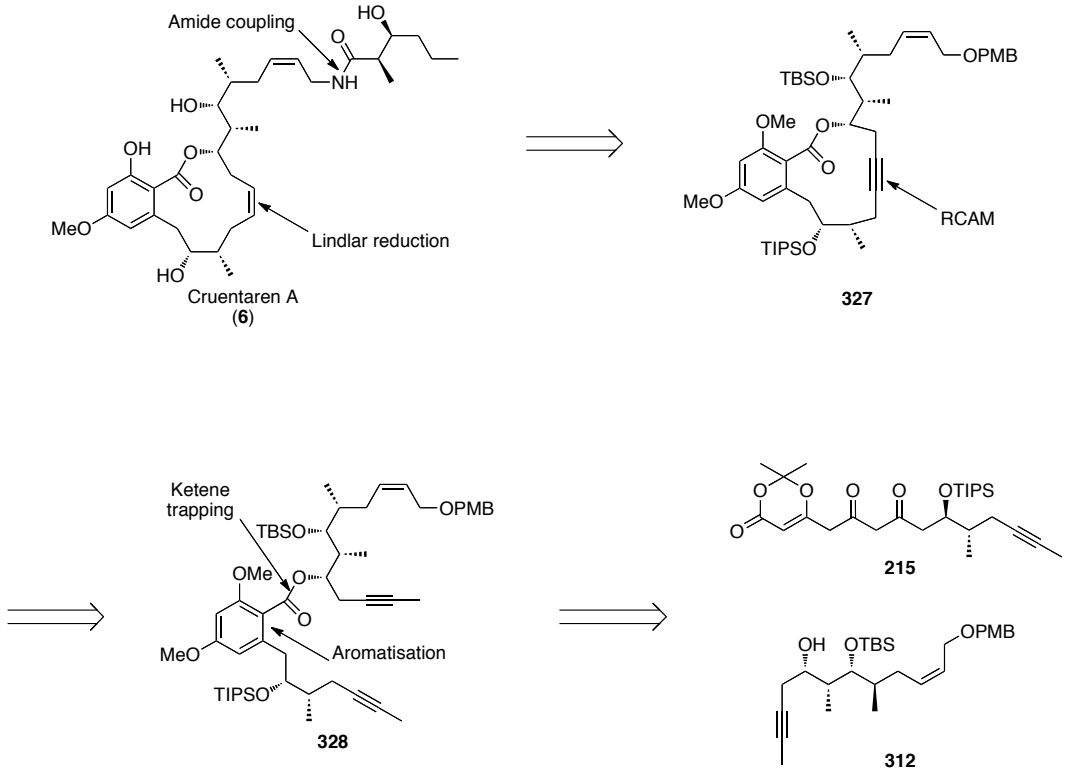
In summary, the biomimetic aromatization developed by the Barrett group proved to be successful on our model system. Furthermore, alkyne metathesis (pre)catalyst **100** was prepared and used for the construction of macrolactone **315** (Scheme 103).



Scheme 103 - Aromatization and RCAM studies towards the synthesis of **315**

2.5 Total Synthesis of cruentaren A (6)

In view of the successful results reported earlier (Sub-section 2.4) and with key building blocks **215** and **312** in hand, we could now attempt to complete the synthesis of cruentaren A. As reported in our initial retrosynthetic analysis (Sub-section 1.5, Scheme 29), we believed Lindlar reduction of the triple bound within the macrolactone should be the last step of our synthesis, thus avoiding translactonisation. The side chain could be extended at this stage too, therefore cruentaren A (**6**) could be obtained from **327**, which in turn could be synthesized *via* RCAM of precursor **328**. Finally aromatic intermediate **328** could be constructed following our biomimetic aromatization with **215** and **312** (Scheme 104).



Scheme 104 – Key cuts for the synthesis of cruentaren A (**6**)

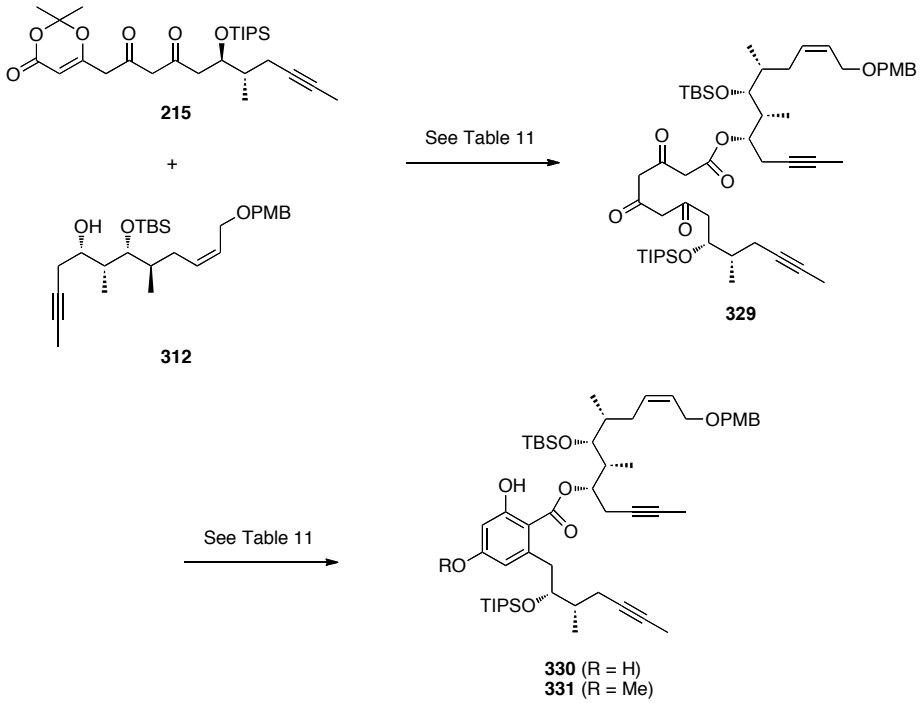
2.5.1 Synthesis of the core structure of cruentaren A

We planned to undertake the synthesis of the core structure in an analogous manner to the synthesis of the model resorcylate **315**.

2.5.1.1 Biomimetic aromatization with diketo-dioxinone 215 and alcohol 312

After the success of the biomimetic aromatization on our model system (Sub-section 2.4.1.2), we decided to follow the same protocol for the synthesis of **330** (Scheme 105, Table 11). Diketo-dioxinone **215** was subjected to thermolysis and trapping with alcohol **312** followed by aromatization using cesium carbonate and then acetic acid (Table 11, Entry a). Unfortunately, desired compound **330** was only isolated in 10% yield, which led to identifying two problems. During the trapping, degradation of diketo-dioxinone **215** occurred before alcohol **312** was fully consumed. Moreover, the dehydration step under acidic conditions, despite using a large excess of acetic acid, was very slow. Based on this first attempt it was decided to carry out the trapping with an excess of **215** and to use a stronger acid for the dehydration. First, 1.5 equivalents of diketo-dioxinone **215** reacted with alcohol **312** (Table 11, Entry b). Subsequent treatment with cesium carbonate, followed by an excess of hydrochloric acid in methanol resulted in two main products (1:1 ratio) as well as unreacted alcohol **312**. The most polar compound was identified as the expected resorcylate **330.** The other product **331** was in fact bearing a methoxy ether group instead of a hydroxy group at C-5. We believe **331** was formed during the dehydration step by acid catalysis of the ketone function. **330** and **331** were isolated in 58% yield. Finally following the same procedure, diketo-dioxinone **215** was used in 1.7 equivalents

leading to full consumption of alcohol **312** (Table 11, Entry c) and the isolation of **330** and **331** in 62% yield.



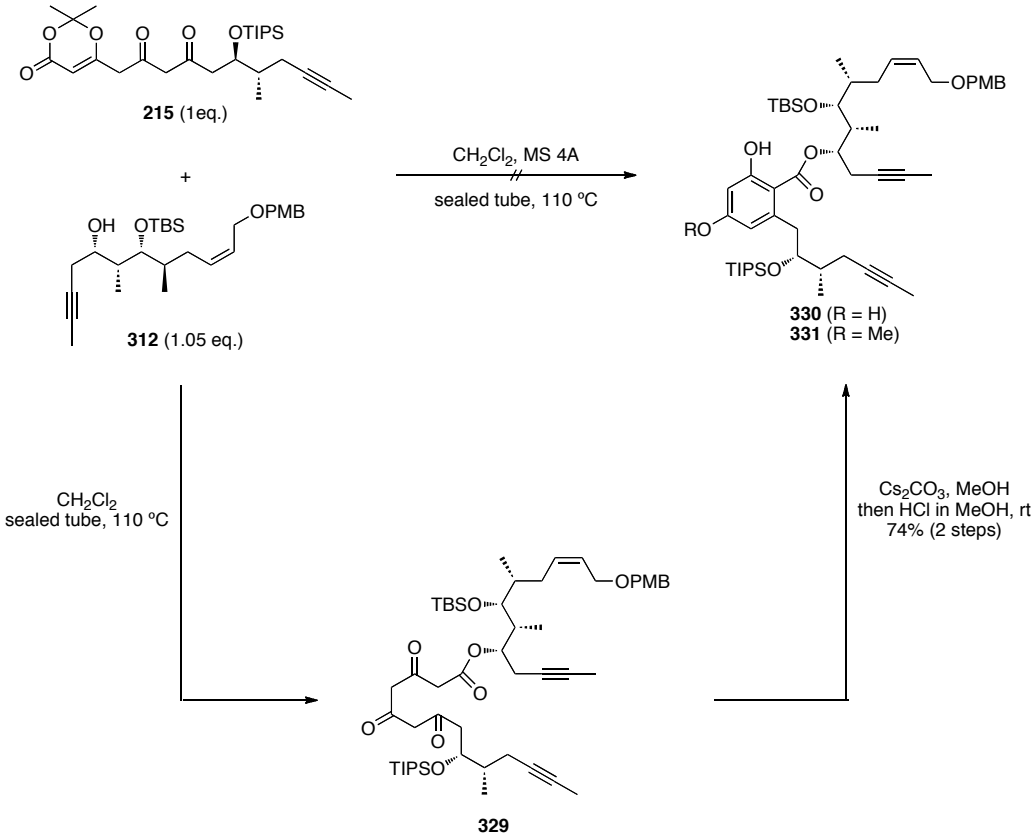
Scheme 105 - Aromatization studies with diketo-dioxinone **215** and alcohol **312**

Entry	*Reagents and Conditions (Trapping)*	*Results*	*Reagents and Conditions (Aromatization)*	*Results*
a	**215** (1 eq.) **312** (1 eq.)	- After 30 min, **215** and **312** detected - After 2 h, degradation of **215**, **312** detected	Cs_2CO_3, MeOH then AcOH	- 10 % of **330** **- 312** recovered
b	**215** (1.5 eq.) **312** (1 eq.)	- After 1 h, **215** and traces of **312** detected	Cs_2CO_3, MeOH then HCl in MeOH	**- 330** and **331** (58%) **- 312** recovered
c	**215** (1.7 eq.) **312** (1 eq.)	- Reaction completed	Cs_2CO_3, MeOH then, HCl in MeOH	**- 330** and **331** (62%)

Table 11 - Different conditions for the aromatization

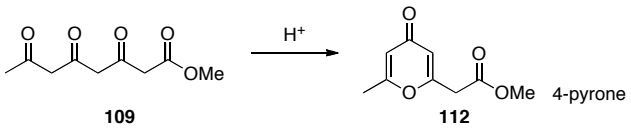
Using an excess of diketo-dioxinone **215** was problematic since its synthesis requires 12 steps and therefore an improved strategy was needed. We decided to try the one step aromatization under neutral conditions reported by Basset and Barrett (Sub-section 2.4.1.1, Scheme 99).[55] **215** and **312** were treated with 4 Å molecular sieves in dichloromethane in a sealed tube at 110 ºC. After 12 hours, no aromatic compound was isolated however full conversion of both starting material to triketo-ester **329** was obtained. With these observations in mind, a new aromatization protocol was attempted. The trapping of **215** with **312** was carried out in

dichloromethane at 110 ºC in a sealed tube for 2 hours (molecular sieves were no longer needed since they were used to promote the dehydration), followed by subsequent addition of cesium carbonate and hydrochloric acid in methanol (Scheme 106). **330** and **331** were obtained in gram scale with up to 74% yield.



Scheme 106 - Synthesis of **330** and **331** via late stage aromatization

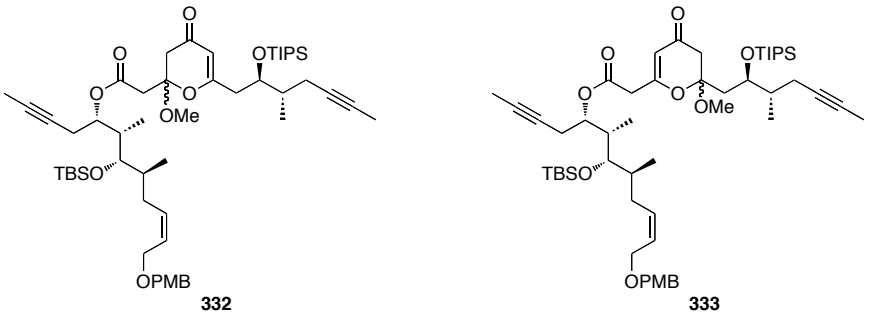
It is worth noting that when triketo-ester **329** failed to react completely under basic conditions, formation of a by-product was observed after addition of hydrochloric acid. Harris reported that triketo-ester derivatives could form pyrones derivatives under harshly acidic conditions (Scheme 107).[43]



109 112

Scheme 107 - Pyrone formation under acidic conditions

According to this observation and spectroscopic data, the by-product could be identified as compound **332** or **333** (Figure 9). Since the mechanism leading to this by-product is unclear, it is difficult to ascertain which one of these structures is the by-product. The formation of this by-product could be easily avoided by monitoring (TLC analysis) that the cyclization of **329** was complete before the acidification step.



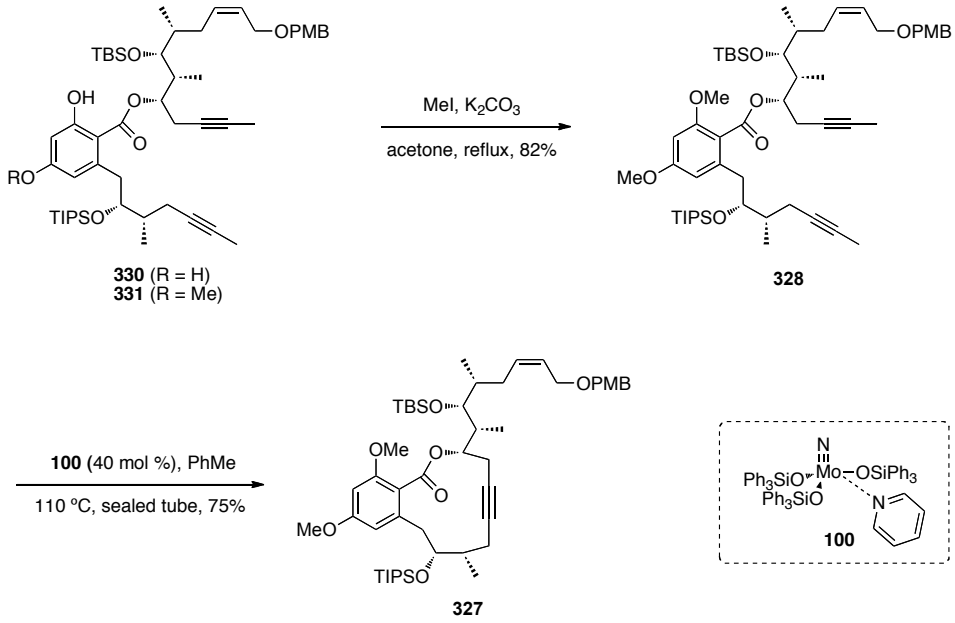
332 333

Figure 9 - By-product formed from triketo-ester **329** under acidic conditions

2.5.1.2 RCAM on precursor 328

Despite the successful use of catalyst **100** for the synthesis of model system resorcylate **315**, its application in the formation of **327** was uncertain: precursor **328** contained a dense array of functional groups that might interfere with the catalyst. First, **330** and **331** were converted to the dimethoxy-protected resorcylate **328**. With the previous results in mind (Sub-section 2.4.2.2), **100** (20 mol %) was added to a pre-heated solution of **328** in toluene at 110 ºC. We were pleased to observe full

conversion of **328** after 20 hours, however **327** was isolated in only 55% yield. We believed that the cause of this rather disappointing yield might be the long exposure of **328** and **327** to high temperature. Since heating to 110 ºC was necessary for the reaction to proceed, the only solution was to reduce the reaction time. Therefore, the catalyst loading was increased (**100**, 40 mol %) and the desired macrolactone **327** was isolated in 75% yield after 8 hours (Scheme 108). It is worth noting that any attempts carried out with commercially available (Aldrich) (pre)catalyst **100** failed.



Scheme 108 – Synthesis of macrolactone **327** *via* RCAM

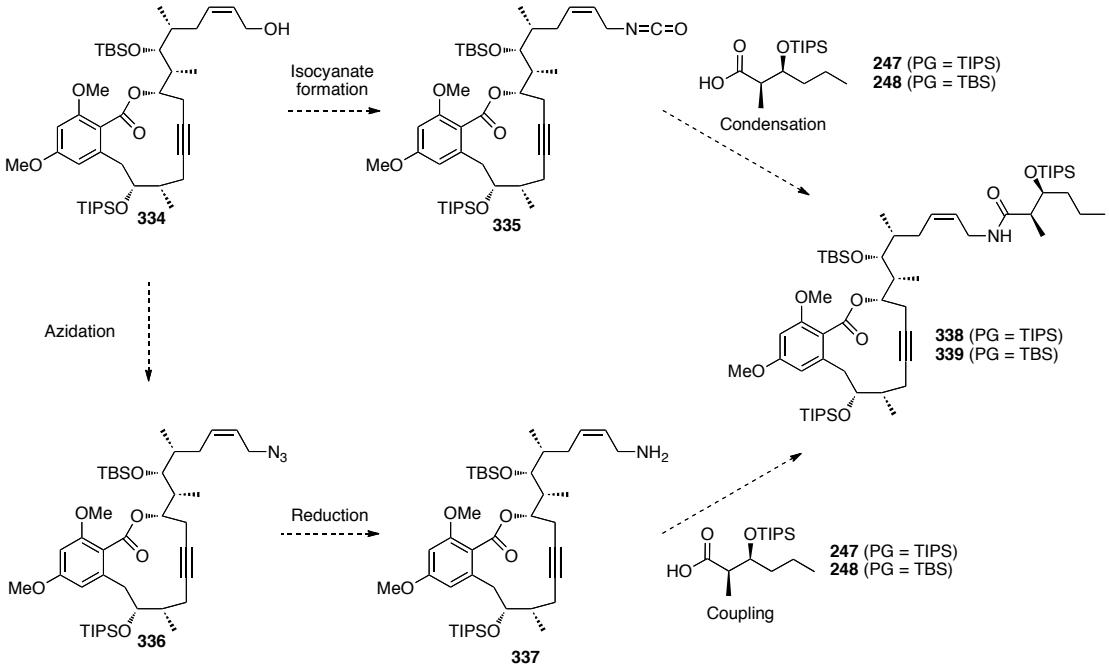
The core structure of cruentaren A **327** was synthesized over three steps in 46% yield from key fragments **215** and **312**, providing 0.85 g (three batches).

2.5.2 Introduction of the side chain and completion of the synthesis of cruentaren A

With the core structure of cruentaren A in hand, we could now envisage attaching the side chain corresponding to carboxylic acids **247** or **248** in order to obtain the allylamide derivatives **338** or **339**. Then, three more steps would be necessary to complete the synthesis of cruentaren A.

2.5.2.1 Synthesis of allylamide derivatives 33 (similar to key fragment 129)

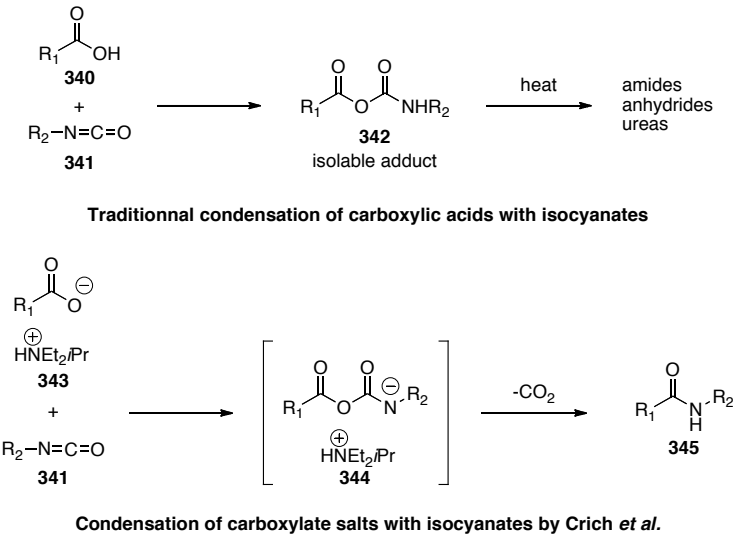
Amide bond formation is usually achieved through activation of the acid, by conversion to an acyl chloride or anhydride, or by using coupling reagents. Accordingly, amide **250** (Sub-section 2.2.3, Scheme 72) was formed using the Yamaguchi protocol.[22,94] Since this method had been successful for the synthesis of **250**, we believed similar results could be achieved to obtain **338** or **339** after deprotection of terminal alcohol **327** and conversion into the corresponding allylamine **337**. However, very recently Crich and co-workers reported the condensation of carboxylate salts with isocyanates to afford the corresponding amides in high yield.[118] Giving the fact that isocyanate derivatives can be prepared from the corresponding alcohol using a variant of the Mitsunobu reaction, this protocol could be a shorther alternative for synthesis of amides **338** or **339** and was consequently preferred (Scheme 109).



Scheme 109 - Different pathways for the formation of allylamide derivatives **338** and **339**

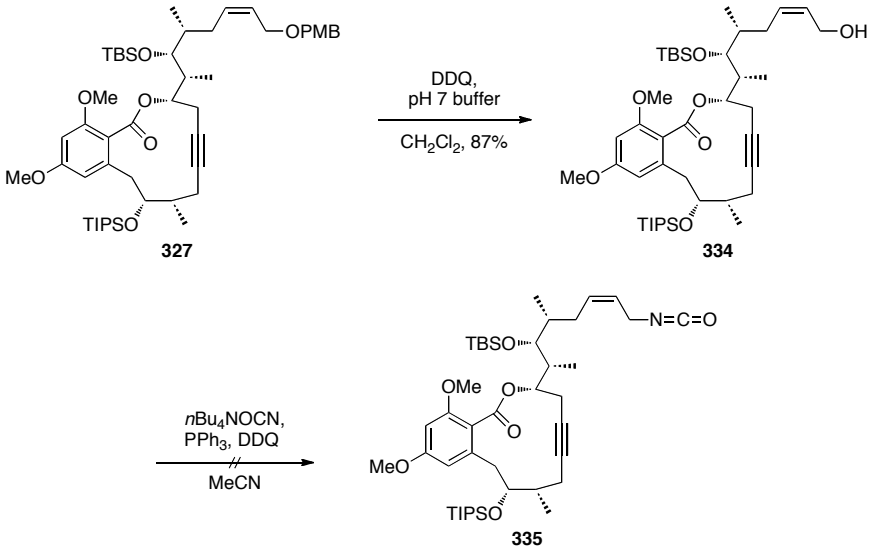
*2.5.2.1.1 Towards the synthesis of **338** via formation of isocyanate **335***

The condensation of carboxylic acids with isocyanates is a well-known reaction and the methodology developed by Crich *et al.* is appealing because it does not require thermal decomposition of the adduct (Scheme 110).[118]



Scheme 110 - Amide bond formation *via* isocyanates

First **327** was treated with DDQ in order to remove the PMB-protecting group (Scheme 111). Attempts to convert alcohol **334** into the corresponding isocyanate derivatives were carried out using a method reported by Akhlaghinia *et al.*[119] This variant of the Mitsunobu reaction involves the use of triphenylphosphine, DDQ and tetrabutylammonium cyanate (in this case DDQ proved to be a better reagent than the usual diethyl azodicarboxylate (DEAD) or di*iso*propyl azodicarboxylate (DIAD)). Following the procedure described by Akhlaghinia *et al*., and despite several trials, we were unable to isolate or even detect (NMR and mass spectrometry analysis) desired product **335**.



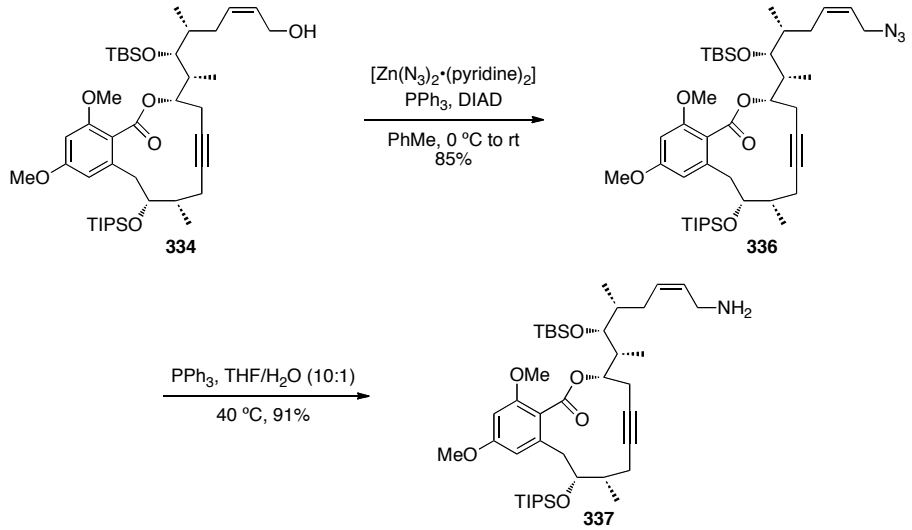
Scheme 111 - Attempted synthesis of isocyanate **335**

Isocyanates derivatives are typically produced from amines and phosgene. However, we decided not to consider this option since it was in contradiction with why we chose to investigate this route: shorter access to amide deivatives **338** or **339**.

*2.5.2.1.2 Towards the synthesis of **338** and **339** using a Yamaguchi reaction*

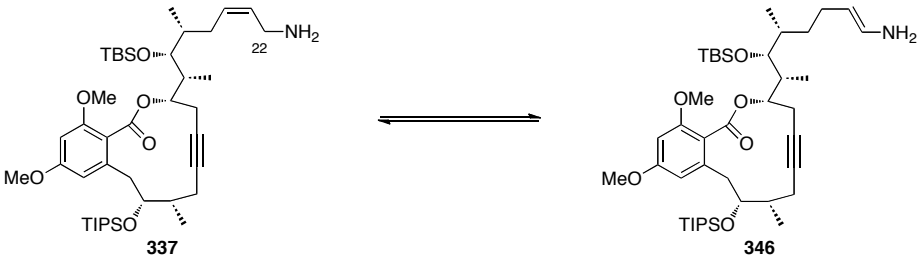
We undertook the synthesis of **338** and **339** in an analogous manner to the synthesis of amide **250**. First **334** was converted to azide **336**, by treatment with diphenylphosphorazidate and DBU in toluene at 80 ºC, in 65% yield (Scheme 112). The by-product resulting from a S_N2' was neither detected nor isolated. A possible cause for this moderate yield could be the required high temperature. In the hope to obtain a higher yield, we decided to follow the Mitsunobu procedure reported by Fürstner *et al.* for the synthesis of cruentaren A.[15] **334** was treated with triphenylphosphine, DIAD and a zinc azide/bis-pyridine complex, prepared in one step from commercially available sodium azide and zinc nitrate.[120] Desired azide **336**

was obtained in 85% yield. Finally, Staudinger reduction of azide **336** afforded amine **337** in excellent yield.



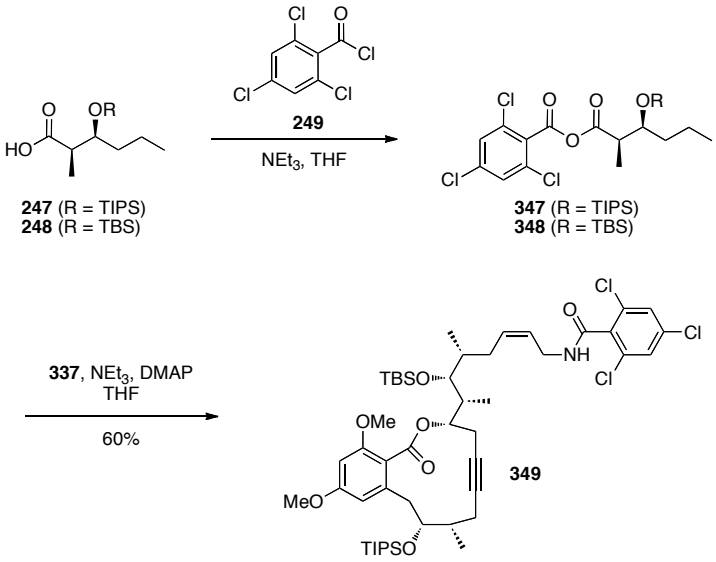
Scheme 112 - Synthesis of amine **337**

Difficulties were encountered to purify azide **336** and amine **337** because of their sensitivity towards acidic conditions. Indeed, NMR analysis showed that **336** and **337** were subject to isomerization (disappearance of 22-H on the ^{1}H NMR spectrum) (Scheme 113). Therefore, silica gel columns were flushed with a basic solution prior to purification and NMR spectra were recorded in deuterated dichloromethane instead of chloroform. Furthermore, amine **337** was found to be rather unstable (isomerisation and decomposition) and was therefore used with immediately for the subsequent amide formation.



Scheme 113 – Possible isomerisation of allylamine **337** to enamine **346**

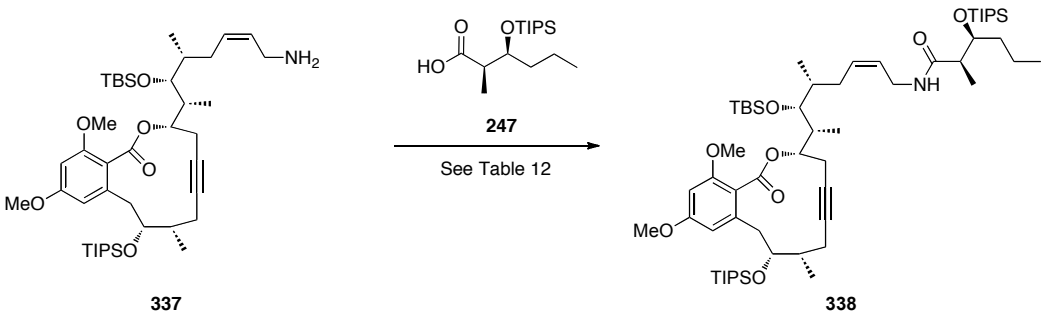
Previously reported was the synthesis of amide **250** using the Yamaguchi method. Amide **251** was isolated too as a by-product and we supposed its formation was due to an excess of Yamaguchi reagent (Sub-section 2.2.3, Scheme 72). Taking these results into account, we decided to proceed to the formation of **338** in two steps: first formation and isolation of the mixed anhydride **347**, then addition of **337**. Unfortunately this procedure led to the exclusive formation of by-product **349**. The regioselectivity of the nucleophilic attack on the Yamaguchi mixed anhydride is thought to be controlled by the steric hindrance of the aromatic part. Therefore we supposed that the steric hindrance caused by the TIPS-protecting group on **347** was responsible for this outcome. The reaction was repeated with acid **248** bearing a TBS-protecting group. Unfortunately by-product **349** was again the only product formed during this reaction (Scheme 114).



Scheme 114 - Attempted synthesis of **338** and **339** using Yamaguchi reaction

*2.5.2.1.3 Synthesis of **338** using coupling reagents*

Maier and Fürstner both reported the formation of this amide bond using coupling reagents.[14,15] We only considered this method as our last option because of the possible generation of inseparable by-products. However, studies were initiated to find the best conditions for the formation of allylamide **338** (Scheme 115, Table 12). Coupling attempts using EDC and HOBt in dichloromethane (Table 12, Entry a) and dimethylformamide (Table 12, Entry b) were unsuccessful. Then we decided to use a more reactive uronium reagent, HBTU, in combination with HOBt. No reaction occurred in dichloromethane (Table 12, Entry c), however desired amide **338** was finally isolated in 67% yield when the reaction was carried out in dimethylformamide (Table 12, Entry d), giving the full skeleton of cruentaren A.



Scheme 115 - Synthesis of **338** using coupling reagents

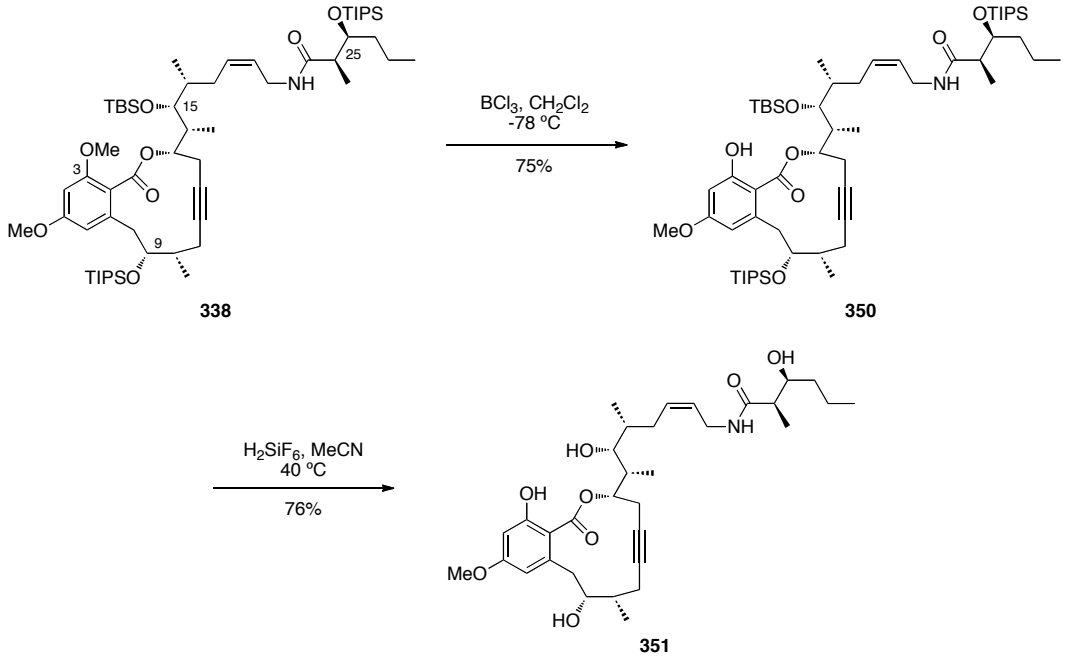
Entry	*Reagents and Conditions*	*Results*
a	EDC, HOBt, *i*-Pr_2NEt in CH_2Cl_2	No reaction
b	EDC, HOBt, *i*-Pr_2NEt in DMF	No reaction
c	HBTU, HOBt, *i*-Pr_2NEt in CH_2Cl_2	No reaction
d	HBTU, HOBt, *i*-Pr_2NEt in DMF	**338** (67%)

Table 12 - Different conditions for the synthesis of **338**

2.5.2.2 Total synthesis of cruentaren A (6)

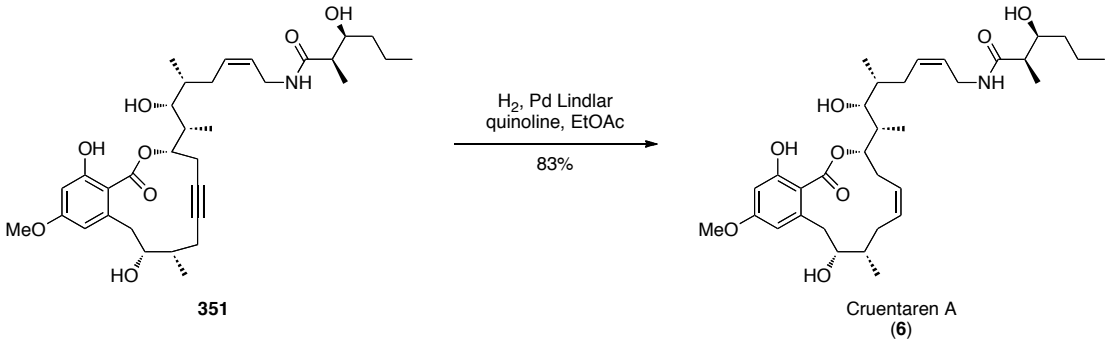
At this stage, we needed to proceed to the full deprotection of **338** followed by Lindlar reduction of the alkyne moiety within the macrolactone. As mentioned earlier, the translactonization possible with 9-OH explains this strategy. First the methyl ether adjacent to the ester was cleaved using boron trichloride, leaving the other methyl ether intact. The use of boron trichloride as selective demethylating agent was first reported in 1966 by Dean *et al*.[25] It was important to carry out this step before removal of the silyl protecting groups, as free hydroxy groups can deactivate boron

trichloride. The cleavage of the silyl groups was carried out with fluorosilicic acid in acetonitrile. The TBS- and TIPS-protecting groups, respectively at C-9 and C-25 were readily cleaved. However, the TBS-protecting group at C-15 required higher temperature (40 ºC) and longer reaction time (24 hours). This was presumably due to the steric hindrance. These conditions led to fully deprotected **351** in 76% yield (Scheme 116).



Scheme 116 - Final deprotections

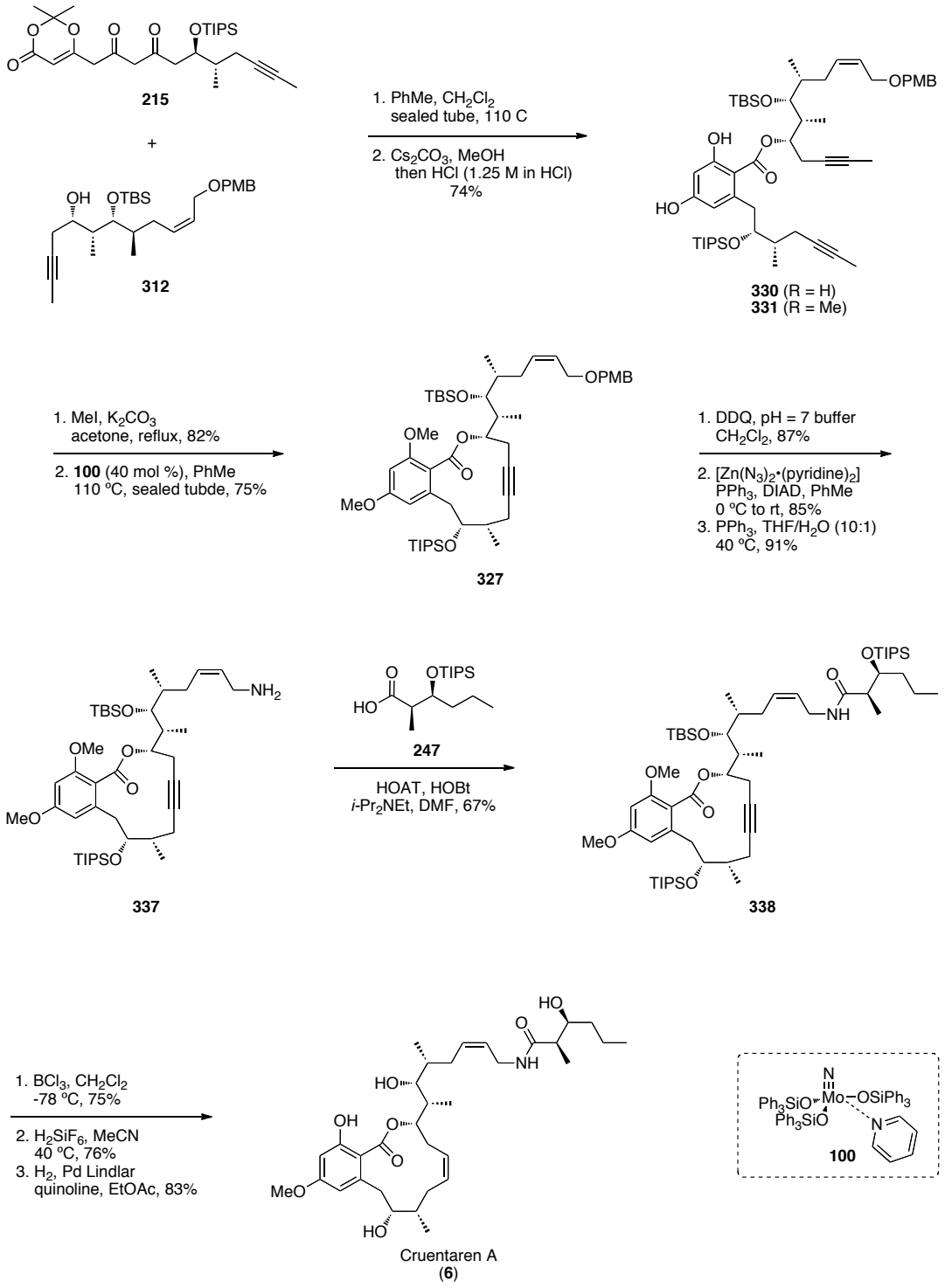
Finally, strained cycloalkyne **351** was subjected to Lindlar hydrogenation, using quinoline as a poison to give cruentaren A (**6**) in 83% yield. Two batches afforded 14 mg in total (Scheme 117). The spectroscopic and analytical data were matching with those reported for the natural product (Appendix 2, Appendix 3).[12]



Scheme 117 - Lindlar reduction and synthesis of cruentaren A (**6**)

2.5.4 Summary

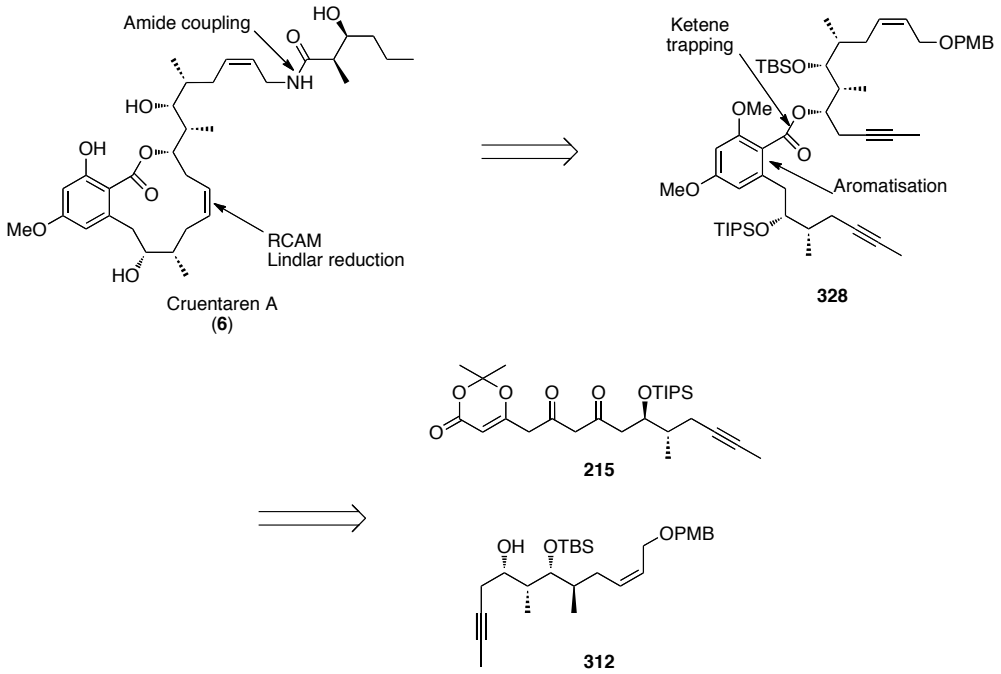
To summarize, cruentaren A was successfully obtained using our key strategy. First, the synthesis of the core of cruentaren A was achieved on gram scale in three high yielding and reproducible steps from diketo-dioxinone **215** and alcohol **312**. The successful synthesis of **330** and **331** and the stability of delicate functionalities during the generation of the resorcylate unit by aromatization proved that this biomimetic strategy developed by the Barrett group is a powerful tool towards the synthesis of RAL natural products. Equally rewarding is the fact that both Maier and Fürstner encountered major difficulties for the esterification step while only few adjustments were needed to find the right conditions for this aromatization. Furthermore, the choice of the catalyst for the RCAM was important and the use (pre)catalyst **100** gave access to macrolactone **327** showing the remarkable stability of this class of catalyst, recently introduced by Fürstner *et al*.[33] After deprotection of **327** and conversion into the corresponding amine **337,** the amide coupling was conducted using coupling agents and afforded allylamide **338**. Finally, full deprotection of **338** and Lindlar reduction afforded cruentaren A (**6**) (Scheme 118).



Scheme 118 - Synthesis of cruentaren A (**6**)

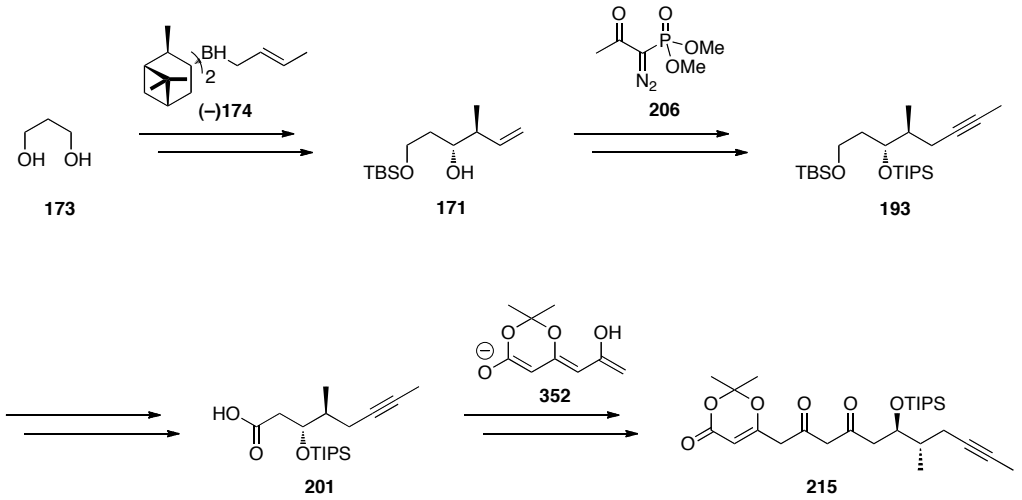
3 Conclusion

The total synthesis of cruentaren A was reported in 23 steps and 0.7% yield for the longest linear sequence. This synthesis showcases the biomimetic aromatization strategy developed within the Barrett group. Thus, the aromatic ring of cruentaren A was constructed using a ketene generation-trapping-aromatization cascade sequence featuring diketo-dioxinone **215** and alcohol **312** (Scheme 119).



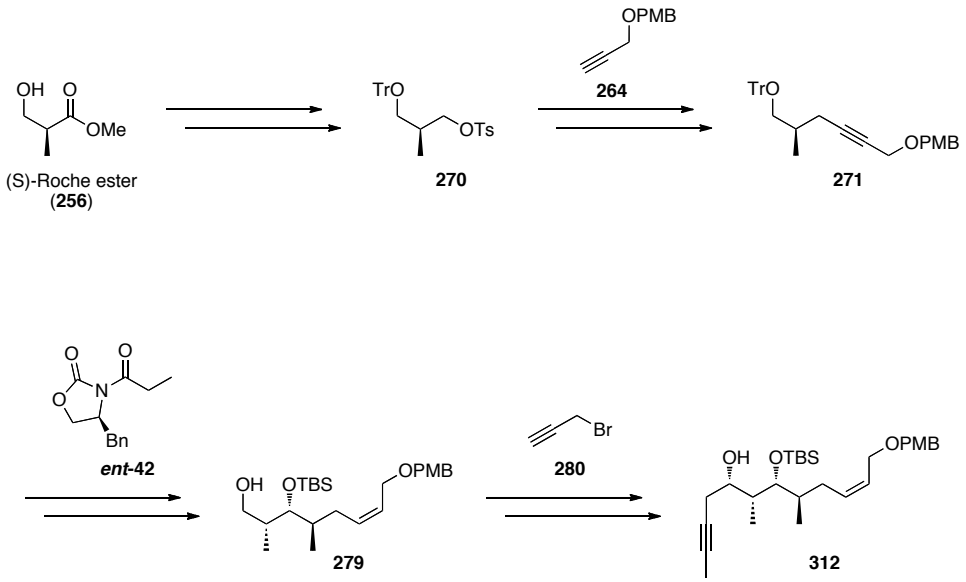
Scheme 119 - Key disconnections for cruentaren A

Diketo-dioxinone **215** was prepared in 12 steps and 13% overall yield. Key features included a Brown crotylation to install the two stereocenters and a Seyferth-Gilbert homologation. Acid **201** was converted into diketo-dioxinone **215** in two steps following a procedure developed within the group for this class of compounds (Scheme 120).



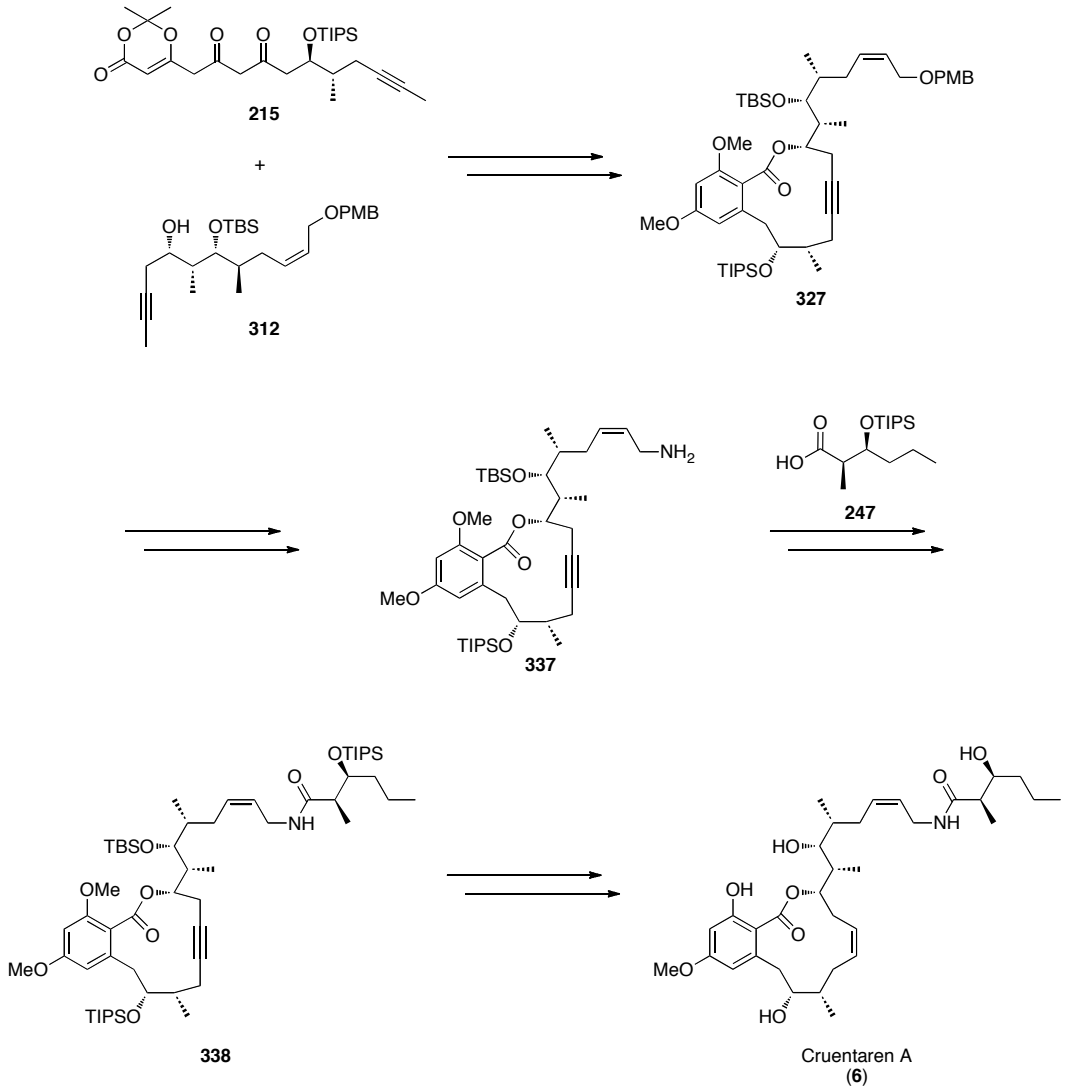
Scheme 120 - Key steps for the synthesis of diketo-dioxinone **215**

The synthesis of alcohol **312**, the most challenging fragment because of its 4 chiral centers, started with chiral pool (*S*)-Roche ester. The other stereocenters were set using an Evans aldol reaction and a Barbier type propargylation. **312** was obtained in 13 steps and 7% overall yield (Scheme 121).



Scheme 121 - Key steps for the synthesis of alcohol **312**

The core structure of cruentaren A was constructed using the biomimetic aromatization strategy followed by RCAM (Scheme 122). The amide side chain was then installed using coupling reagents to afford **338**. Final deprotection and Lindlar reduction afforded cruentaren A. In total 16 mg of cruentaren A (**6**) were obtained, which allowed full characterisation. Spectroscopic data were in full accordance with those reported for the natural product.



Scheme 122 - Key steps for the synthesis of the core structure of cruentaren A (**6**) and completion of its synthesis

To conclude, using the biomimetic aromatization strategy allowed us to circumvent the difficulties encountered by Maier and Fürstner during the esterification step. We showed how effective was this method even when sterically hindered alcohol with sensitive functional groups, such as **312**, were involved. This total synthesis of cruentaren A proves that the Barrett group has developed a highly general method for the synthesis of resorcylic acid lactones. Furthermore, since the resorcylate unit is a privileged pharmacophore, this strategy could facilitate the discovery of new medicines.

4 Experimental

All manipulations of air or moisture sensitive materials were carried out in oven-dried glassware under an inert atmosphere of nitrogen or argon unless otherwise stated. Reaction temperatures other than rt were recorded as the bath temperature unless otherwise stated. Syringes, which were used to transfer reagents and solvents, were purged with nitrogen or argon prior to use. Reaction solvents were distilled under nitrogen from CaH_2 (dichloromethane, MeOH, pyridine, triethylamine), Na/Ph_2CO (tetrahydrofuran, diethyl ether), Na (toluene) or obtained as anhydrous from Sigma-Aldrich (*N*,*N*-dimethylformamide, acetonitrile). Hexanes refers to BDH AnalaR® petroleum spirit 40-60 ºC. Water/H_2O refers to distilled H_2O. Other solvents and all reagents were obtained from commercial suppliers (Fluka, Sigma-Aldrich, Lancaster Chemicals, ABCR) and were used as obtained if purity was >98%. Flash column chromatographies were carried out on VWR silica gel 60, particle size 0.040-0.063 mm unless otherwise stated. Thin layer chromatography (TLC) was performed on pre-coated aluminium backed or glass backed plates (Merck Kieselgel 60 F_{254}), and visualised with ultraviolet light (366 nm and 254 nm) or potassium permanganate ($KMnO_4$), vanillin or ninhydrine stains as deemed appropriate.

Melting points: obtained using a Reichert-Thermovar melting point apparatus and are uncorrected.

Infrared spectra: obtained using a Mattson 5000 FTIR apparatus with automatic background subtraction. Indicative features of each spectrum are given with adsorptions reported in wavenumbers (cm^{-1})

Proton magnetic resonance spectra (^{1}H NMR)*:* recorded at 400 MHz on Bruker DRX-400 spectrometers or at 125 MHz on an AM 500 spectrometer. All spectra are referenced to the residual solvent peak. Chemical shifts (δ) are quoted in parts per million (ppm) and coupling constants (*J*) recorded in Hertz (Hz).

Carbon magnetic resonance spectra (^{13}C NMR): recorded at 100 MHz on Brüker DRX-400 spectrometers or at 125 MHz on an AM 500 spectrometer. Chemical shifts (δ) are quoted in ppm and referenced to the residual solvent peak. Spectra recorded at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR) were carried out by the Imperial College Department of Chemistry NMR service.

Mass spectrometry: Low and high resolution mass spectra were recorded by Imperial College Mass Spectrometry Service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer.

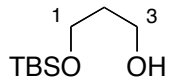
Microanalysis: determined by the University of North London Analytical Service.

Optical Rotations: recorded at 25 °C on a Perkin-Elmer 241 Polarimeter with a path length of 1 dm, using the 589.3 mn D-line of sodium. Concentrations (*c*) are quoted in g/100 mL.

X-ray Diffraction: X-ray diffraction data were recorded by the Imperial College Department of Chemistry X-ray diffraction service.

Note: carbon numbering is for NMR characterisation and does not necessarily follow the IUPAC rules.

3-(*tert*-Butyldimethylsilyl)oxy)propan-1-ol

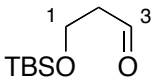


173'

To a solution of propane-1,3-diol (**173**) (20 g, 263 mmol) dissolved in THF (500 mL) was added NaH (60% in mineral oil, 10.5 g, 263 mmol). After stirring for 1 h, TBSCl (39.5 g, 263 mmol) was added portionwise and the reaction mixture was stirred for 18 h. The reaction mixture was then quenched with water and the aqueous layer was extracted with Et_2O (X 2). Combined organic layers were washed with a saturated solution of NH_4Cl, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography (20% Et_2O in hexanes) to afford mono-protected alcohol **173'** (43 g, 86%) as a colourless oil.

IR (neat): 3417, 2953, 2929, 2857, 1475, 1253, 1085, 833, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88-3.82 (m, 4H, **1**-H_2, **3**-H_2), 1.81 (tt, J = 5.6, 5.6 Hz, 2H, **2**-H_2), 0.93 (s, 9H, **TBS**-H), 0.10 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.0 (C-1), 62.5 (C-3), 34.1 (C-2), 25.8 (CTBS), 18.1 (CTBS), -5.4 (CTBS); MS (CI) *m/z* 191 $[M+H]^+$; HRMS (CI) *m/z* calculated for $C_9H_{23}O_2Si$ $[M+H]^+$ 191.1467, found 191.1466. Match the literature data.[59]

3-[(*tert*-Butyldimethylsilyl)oxy]propanal

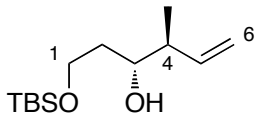


172

To a solution of oxalyl chloride (20 mL, 87 mmol) in CH_2Cl_2 (700 mL) was added DMSO (24 mL, 332 mmol) at -78 °C. The mixture was stirred for 15 min then **173'** (30 g, 158 mmol) dissolved in CH_2Cl_2 (50 mL) was added dropwise. The resulting mixture was stirred for 15 min then NEt_3 (130 mL, 790 mmol) was added. The mixture was slowly allowed to reach 0 ºC and was quenched by addition of a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layers were washed with a saturated solution of $CuSO_4$, brine and water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was dissolved in hexanes and filtered over celite to afford the crude aldehyde **172** (27.5 g, 93%), which was used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (t, *J* = 2.1, 4.0 Hz, 1H, **3**-H), 3.96 (t, *J* = 6.0 Hz, 2H, **1**-H_2), 2.61 (dt, *J* = 6.0, 2.1 Hz, 2H, **2**-H_2), 0.88 (s, 9H, **TBS**-H), 0.08 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1 (C-3), 57.4 (C-1), 46.5 (C-2), 25.8 (CTBS), 18.2 (CTBS), -5.4 (CTBS). Match the literature data.[121]

(3*R*,4*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-methylhex-5-en-3-ol



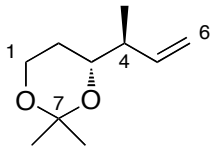
171

To a stirred mixture of potassium *tert*-butoxide (1 M in THF, 146 mL) and *trans*-2-butene (30 mL), was added *n*-BuLi (2.5 M in hexanes, 53 mL) at -78 °C. After complete addition of *n*-BuLi, the mixture was stirred at -45 °C for 10 min. The resulting solution was recooled to -78 °C, and (–)-$(Ipc)_2BOMe$ in THF (1 M, 175 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 30 min, then $BF_3•Et_2O$ (24 mL, 196 mmol) was added dropwise. The aldehyde **173** (27.5 g, 146 mmol) was then added dropwise at -78 °C. The mixture was stirred at -78 °C for 4 h and then treated with aqueous NaOH (3 M, 150 mL) H_2O_2 (50 wt. % in water, 40 mL). The resulting mixture was refluxed for 1 h. The organic layer was separated, washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography (5% Et_2O in hexanes) to afford the desired compound **171** (19.0 g, 74%) as a colourless oil. NMR of the crude material showed the presence of one diastereoisomer (*dr* ≥ 97:3).

IR (neat): 3417, 2939, 2931, 2863, 1465, 1386, 1254, 1086, 832, 775, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 17.7, 9.8, 7.8 Hz, 1H, **5**-H), 5.18-5.08 (m, 2H, **6**-H_2), 3.95-3.89 (m, 1H, **3**-H), 3.86-3.70 (m, 2H, **1**-H_2), 2.33-2.23 (m, 1H, **4**-H) 1.68-1.62 (m, 2H, **2**-H_2), 1.07 (d, *J* = 6.9 Hz, 3H, **4**-CH_3), 0.89 (s, 9H, **TBS**-H);

0.07 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8 (C-5), 115.1 (C-6), 75.1 (C-3), 62.9 (C-1), 43.9 (C-4), 35.5 (C-2), 25.9 (CTBS), 18.2 (CTBS), 15.8 (4-CH_3), -5.5 (CTBS); MS (CI) *m/z* 245 $[M+H]^+$; HRMS (CI) *m/z* calculated for $C_{13}H_{29}O_2Si$ $[M+H]^+$ 245.1937, found 245.1934; $[\alpha]_D$: -9.2 (*c* 2, $CHCl_3$). Match the literature data.[121]

(4*R*)-4-[(2*S*)-But-3-en-2-yl]-2,2-dimethyl-1,3-dioxane



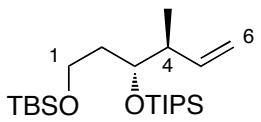
185

A-To a solution of **171** (400 mg, 1.64 mmol) in THF (10 mL) was added TBAF (1 M, 2 mL) at 0 °C and the reaction mixture was stirred for 1 h. The reaction was then quenched with a saturated solution of NH_4Cl and the aqueous layer was extracted with Et_2O (X 2). The combined organic layers were washed with brine, dried ($MgSO_4$) filtered and evaporated to afford the crude product (170 mg, 84%), which was used straight away for the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78-5.69 (m 1H, **5**-H), 5.16-5.11 (m, 2H, **6**-H_2), 3.90-3.79 (m, 2H, **1**-H_2), 3.64 (ddd, *J* = 9.4, 6.5, 2.8 Hz, 1H, **3**-H), 2.28-2.19 (m, 1H, **4**-H), 1.80-1.62 (m, 2H, **2**-H_2), 1.03 (d, *J* = 6.7 Hz, 3H, **4**-CH_3).

B-To a mixture of acetone/dimethoxypropane (2.8 mL, 2:1) with 4 Å MS were added the previous crude product (170 mg, 1.31 mmol) and camphorsulfonic acid (30 mg, 0.17 mmol. The reaction mixture was stirred for 18 h and quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with Et_2O (X 2) and combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **185** (5 mg, 2%). No NMR attempted.

(7*R*)-7-[(2*S*)-But-3-en-2-yl]-2,2,3,3,10-pentamethyl-9,9-bis(propan-2-yl)-4,8-dioxa-3,9-disilaundecane



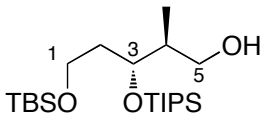
186

To a solution of **171** (19 g, 78 mmol) dissolved in CH_2Cl_2 (500 mL) was added 2,6-lutidine (19 mL, 195 mmol) followed by TIPSOTf (31 mL, 94 mmol) at 0 °C. The reaction mixture was stirred for 4 h then quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% Et_2O in hexanes) to afford **186** (30 g, 97%) as a colourless oil.

IR (neat): 2937, 2865, 1464, 1391, 1253, 1097, 883, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84-5.76 (m, 1H, **5**-H), 5.03-4.96 (m, 2H, **6**-H_2), 3.98 (td, J = 6.1, 3.1 Hz,

1H, **3**-H), 3.66 (m, 2H, **1**-H_2), 2.41-2.37 (m, 1H, **4**-H) 1.65-1.60 (m, 2H, **2**-H_2), 1.07 (s, 21H, **TIPS**-H), 1.05 (d, J = 6.9 Hz, 3H, **4**-CH_3), 0.88 (s, 9H, **TBS**-H); 0.03 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8 (C-5), 114.4 (C-6), 72.7 (C-3), 60.3 (C-1), 43.2 (C-4), 36.5 (C-2), 25.9 (CTBS), 18.2 (CTBS, CTIPS), 14.5 (4-CH_3), 12.9 (CTIPS) -5.5 (CTBS). MS (ESI) *m/z* 401 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{22}H_{49}O_2Si_2$ $[M+H]^+$ 401.3271, found 401.3260; $[\alpha]_D$: +4.9 (*c* 2.1, CH_2Cl_2); Elem. Anal. Calculated for $C_{22}H_{48}O_2Si_2$ C 65.93, H 7.98, found C 66.00, H 8.05.

(2*S*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy)-2-methyl-3-{[tris(propan-2-yl)silyl]oxy}pentan-1-ol

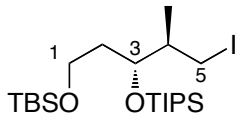


187

186 (2.9 g, 6.74mmol) was dissolved in CH_2Cl_2/MeOH (100 mL, 1:1) and O_3 was bubbled through this solution at -78 °C until a characteristic blue colour appeared (15 min). The mixture was flushed with N_2, then $NaBH_4$ (2.0 g, 20.2 mmol) was added at -78 °C and the reaction mixture was slowly allowed to reach rt and stirred for 1 h. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% EtOAc in hexanes) to afford **187** (1.9 g, 65%) as a colourless oil.

IR (neat): 3390, 2937, 2864, 1465, 1253, 1091, 832, 774, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15-4.11 (m, 1H), 3.80 (dd, *J* = 11.1, 4.1, Hz, 1H, **5**-Ha), 3.70-3.67 (m, 2H, **1**-H_2), 3.55 (dd, *J* = 11.1, 5.5 Hz, 1H, **5**-Hb), 2.66 (*br* s, 1H, **O**-H), 1.87-1.83 (m, 3H, **2**-H_2, **4**-H), 1.1 (*br* s, 24H, **TIPS**-H, **4**-CH_3), 0.88 (s, 9H, **TBS**-H), 0.04 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.3 (C-3), 65.0 (C-5), 60.0 (C-1), 38.4 (C-4), 37.4 (C-2), 25.9 (CTBS), 18.2 (CTBS, CTIPS), 14.5 (4-CH_3), 12.9 (CTIPS) -5.5 (CTBS); MS (ES) *m/z* 405 $[M+H]^+$; HRMS (ES) *m/z* calculated for $C_{21}H_{48}O_{23}Si_2$ $[M+H]^+$ 405. 3220, found 405.3231; $[\alpha]_D$: +3.5 (*c* 2.3, CH_2Cl_2).

(7*R*)-7-[(2*R*)-1-Iodopropan-2-yl]-2,2,3,3,10-pentamethyl-9,9-bis(propan-2-yl)-4,8-dioxa-3,9-disilaundecane



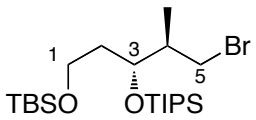
188

To a solution of I_2 (355 mg, 1.4 mmol), imidazole (140 mg, 2.0 mmol) and PPh_3 (370 mg, 1.4 mmol) in CH_2Cl_2 (5 mL) was added **187** (400 mg, 1.0 mmol). The reaction mixture was stirred at rt for 24 h and was then concentrated under reduced pressure. The crude material was dissolved in a minimum amount of CH_2Cl_2 then pentane was added and this solution was filtered through celite. The filtrate was concentrated under reduced pressure and the resulting crude material was dissolved in Et_2O, washed with a saturated solution of $NaHCO_3$, a saturated solution of $Na_2S_2O_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated under

reduced pressure. The crude material was purified by silica flash chromatography to afford **188** (280 mg, 63%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09-4.05 (m, 1H, **3**-H), 3.75-3.24 (m, 2H, **1**-H_2), 3.24 (dd, *J* = 9.8, 5.8, Hz, 1H, **5**-Ha), 3.07 (dd, *J* = 9.8, 8.3 Hz, 1H, **5**-Hb), 2.05-1.96 (m, 1H, **4**-H), 1.71-1.62 (m, 2H, **2**-H_2), 1.1 (*br* s, 24H, **TIPS**-H, **4**-CH_3), 0.88 (s, 9H, **TBS**-H); 0.04 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.5 (C-3), 59.8 (C-1), 41.6, 30.9, 25.9 (CTBS), 18.3 (CTBS, CTIPS), 16.1 (4-CH_3), 12.9 (CTBS), 10.9 (C-5), -5.4 (CTBS); MS (ES) *m/z* 515 $[M+H]^+$; HRMS (ES) *m/z* calculated for $C_{21}H_{48}O_2Si_2I$ $[M+H]^+$ 515.2238, found 515.2258.

(7*R*)-7-[(2*R*)-1-Bromopropan-2-yl]-2,2,3,3,10-pentamethyl-9,9-bis(propan-2-yl)-4,8-dioxa-3,9-disilaundecane

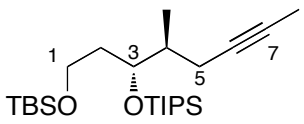


189

To a solution of **187** (0.8 g, 1.9 mmol) and CBr_4 (0.8 g, 2.4 mmol) in CH_2Cl_2 (10 mL) was added PPh_3 (1.0 g, 3.8 mmol). The reaction mixture was stirred for 18 h then Et_2O was added. The mixture was filtered over celite and the resulting filtrate was concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography (5% Et_2O in hexanes) to afford **189** (0.45 mg, 51%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20-4.12 (m, 1H, **3**-H), 3.75-3.72 (m, 2H, **1**-H_2), 3.47 (dd, *J* = 9.8, 5.8 Hz, 1H, **5**-Ha), 3.30 (dd, *J* = 9.8, 8.3 Hz, 1H, **5**-Hb), 2.15-2.03 (m, 1H, **4**-H), 1.70-1.62 (m, 2H, **2**-H_2), 1.04 (*br* s, 24H, **TIPS**-H, **4**-CH_3), 0.90 (s, 9H, **TBS**-H); 0.05 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 71.7 (C-3), 59.8 (C-5), 41.3, 36.9, 36.0, 25.9 (CTBS), 18.3 (CTBS, CTIPS), 14.8 (4-CH_3), 12.9 (CTBS), -5.4 (CTBS); MS (ES) *m/z* 267 and 269 $[M+H]^+$.

(7*R*)-7-[(2*S*)-Hex-4-yn-2-yl]-2,2,3,3,10-pentamethyl-9,9-bis(propan-2-yl)-4,8-dioxa-3,9-disilaundecane



193

Procedure A

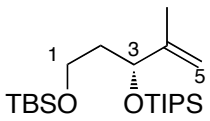
To a solution of propyne (**190**) (36 µL, 0.63 mmol) dissolved in THF (3 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 0.5 mL) at 0 °C. The reaction mixture was stirred for 30 min, then HMPA (0.3 mL) was added, followed by **188** (65 mg, 0.15 mmol). The reaction mixture was slowly allowed to reach rt, was stirred for another hour and quenched by addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were washed with a saturated solution of LiCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash

chromatography (10% Et_2O in hexanes) to afford by-product **195** (no reproducible yield) as a light yellow oil. The desired product **193** was not isolated.

Procedure B

To a solution of bromopropene (**192**) (36 μL, 0.63 mmol) dissolved in THF (3 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 0.5 mL) at 0 °C. The reaction mixture was stirred for 30 min, then **188** (65 mg, 0.15 mmol) was added. The reaction mixture was slowly allowed to reach rt, was stirred for another hour and then quenched by addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% Et_2O in hexanes) to afford by-product **189** as a light yellow oil. Desired product **188** was not isolated.

(7*R*)-2,2,3,3,10-pentamethyl-7-(prop-1-en-2-yl)-9,9-bis(propan-2-yl)-4,8-dioxa-3,9-disilaundecane

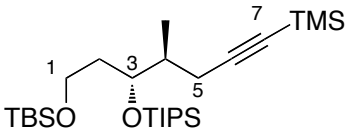


195

^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (s, 1H, **5**-Ha), 4.72 (s, 1H, **5**-Hb), 4.29 (dd, *J* = 7.5, 5.4 Hz, 1H, **3**-H), 3.59-3.42 (m, 2H, **1**-H_2), 1.80-1.57 (m, 2H, **2**-H_2), 1.63 (s, 3H, **4**-CH_3), 1.05-1.03 (m, 21H, **4**-CH_3), 0.90 (s, 9H, **TBS**-H), -0.03 (s, 3H, **TBS**-H),

-0.04 (s, 3H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0 (C-4), 111.1 (C-5), 74.0 (C-3), 59.6 (C-5), 39.0 (C-2), 25.9 (CTBS), 18.2 (CTBS, CTIPS), 16.7 (4-CH_3), 12.4 (CTBS), -5.4 (CTBS).

(7*R*)-2,2,3,3,10-Pentamethyl-9,9-bis(propan-2-yl)-7-[(2*S*)-5-(trimethylsilyl)pent-4-yn-2-yl]-4,8-dioxa-3,9-disilaundecane



194

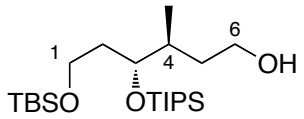
Procedure A

To a solution of TMS-acetylene (**191**) (0.1 mL, 0.8 mmol) dissolved in THF (1 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 0.33 mL) at 0 °C. The reaction mixture was stirred for 30 min, then HMPA (0.4 mL) was added, followed by **188** (120 mg, 0.38 mmol). The reaction mixture was slowly allowed to reach rt, however TLC analysis showed no conversion and starting material **188** was recovered.

Procedure B

To a mixture of **189** (150 mg, 0.3 mmol), $Pd_2(dba)_3$ (10 mg, 15 mol %) and PPh_3 (50 mg, 60 mol %) in THF (1 mL) was added at 60 ºC a solution of TMS-acetylene (**191**) (32 μL, 0.32 mmol) and *n*-BuLi (1.6 M in hexanes, 128 μL) in THF (1 mL). The resulting mixture was stirred at 60 ºC for 24 h. After this time TLC analysis showed no conversion and starting material **189** was recovered.

(3*S*,4*R*)-6-[*tert*-Butyldimethylsilyl)oxy]-3-methyl-4-{[tris(propan-2-yl)silyl]oxy}hexan-1-ol



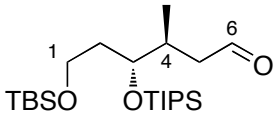
202

To a solution of **186** (18.0 g, 45 mmol) in THF (150 mL) was slowly added BH_3•THF (1 M, 135 mL) at 0 °C. The reaction mixture was allowed to reach rt and stirred for 18 h. After cooling to 0 ºC, the reaction mixture was slowly cannulated to aqueous NaOH (2.5 M, 300 mL) at 0 °C, then aqueous H_2O_2 (30 wt. %, 150 mL) was added and the reaction mixture was stirred for another hour at rt. The mixture was diluted with Et_2O, and the organic layer was washed with a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (20% Et_2O in hexanes) to afford **202** as a colourless oil (15.4 g, 82%).

IR (neat): 3330, 2934, 2864, 1464, 1384, 1253, 1092, 1052, 1005, 940, 832, 774, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.97 (*br* s, 1H, **3**-H), 3.75-3.58 (m, 4H, **1**-H_2**,** **6**-H_2), 1.86-1.50 (m, 5H, **2**-H_2, **4**-H, **5**-H_2), 1.08 (s, 21H, **TIPS**-H), 1.01 (d, J = 6.9 Hz, 3H, **4**-CH_3), 0.88 (s, 9H, **TBS**-H), 0.04 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.2 (C-3), 60.6 (CH_2), 60.2 (CH_2), 36.1 (C-2), 35.0 (C-4, C-5), 25.8 (CTBS), 18.3 (CTIPS, CTBS), 15.0 (4-CH_3), 12.9 (CTIPS), -5.4 (CTBS); MS (ESI) *m/z* 419 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{22}H_{51}O3Si_2$ $[M+H]^+$ 419.3377,

found 419.3366; $[\alpha]_D$: +9.1 (*c* 2.2, CH_2Cl_2); Elem. Anal. Calculated for $C_{22}H_{50}O_3Si_2$ C 63.09, H 12.03, found C 63.15, H 12.05

(3*S*,4*R*)-6-[*tert*-Butyldimethylsilyl)oxy]-3-methyl-4-{[tris(propan-2-yl)silyl]oxy}hexanal



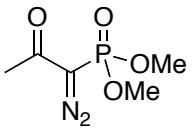
203

To a solution of IBX (9.0 g, 30 mmol) dissolved in DMSO (50 mL) and stirred for approximately 10 min, was added **202** (6.5 g, 15.5 mmol) dissolved in DMSO (10 mL). The reaction mixture was stirred for 4 h and was then filtered. The filtrate was diluted with Et_2O and washed with water. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude material was filtered on a short pad of silica (5% Et_2O in hexanes) to afford **203** (4.8 g, 74%) as a colourless oil.

IR (neat): 2940, 2864, 2712, 1727, 1464, 1252, 1093, 1049, 832, 774, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H, **6**-H), 3.94 (dt, *J* = 6.1, 2.8 Hz, 1H, **3**-H), 3.67 (d, *J* = 6.1 Hz, 2H, **1**-H_2), 2.32-2.23 (m, 2H, **5**-H_2), 1.77-1.48 (m, 3H, **2**-H_2, **4**-H), 1.07 (s, 21H, **TIPS**-H), 1.02 (d, *J* = 6.9 Hz, 3H, **4**-CH_3), 0.88 (s, 9H, **TBS**-H); 0.03 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0 (C-6), 73.2 (C-3), 59.8 (C-1), 46.3 (C-5), 36.8 (C-2), 32.9 (C-4), 25.9 (CTBS), 18.3 (CTBS, CTIPS), 16.3 (4-CH_3), 12.9

(CTIPS), -5.4 (CTBS); MS (ESI) *m/z* 417 $[M-H]^+$; HRMS (ESI) *m/z* calculated for $C_{22}H_{49}O_3Si_2$ $[M+H]^+$ 417.3220, found 417.3213.

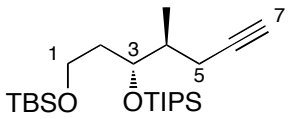
Dimethyl-1-diazi-2-oxopropylphosphonate



206

To a solution of dimethyl (2-oxopropyl)phosphonate (**205**) (25.0 g, 150 mmol) in a mixture of PhMe/THF (750 mL, 8:2) was slowly added NaH (60% in mineral oil) (6.6 g, 165 mmol) at 0 ºC. After 1 h, 4-acetamido-benzenesulfonyl azide (40.0 g, 165 mmol) was added and the resulting mixture was stirred for 12 h. After filtration over celite, the filtrate was concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography (50% EtOAc in hexanes) to afford **206** (15 g, 51%) as a light yellow oil. Match the literature data.[122]

(7*R*)-2,2,3,3,10-Pentamethyl-7-[(2*S*)-pent-4-yn-2-yl]-9,9-bis(propan-2-yl)-4,8-dioxa-3,9-disilaundecane



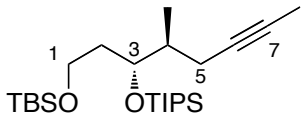
207

To a solution of **203** (4.7 g, 11.3 mmol) and anhydrous K_2CO_3 (5.7 g, 33.9 mmol) in MeOH (200 mL) was added freshly prepared Bestmann-Ohira diazophosphonate **206** (5.7 g, 22.6 mmol). The solution was stirred at rt and rapidly turned milky green. After 3 h, the solution was diluted with Et_2O. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (5% Et_2O in hexanes) to afford **207** (4.3 g, 92%) as a colourless oil.

IR (neat): 3318, 2950, 2930, 2898, 2869, 1467, 1390, 1256, 1092, 1011, 939, 882, 834, 777, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (dt, *J* = 6.2, 3.8 Hz, 1H, **3**-H), 3.70-3.64 (m, 2H, **1**-H_2), 2.18 (ddd, *J* = 16.8, 6.3, 2.6 Hz, 1H, **5**-Ha), 2.05 (ddd, *J* = 16.8, 8.2, 2.6 Hz, 1H, **5**-Hb), 1.91 (t, *J* = 2.6 Hz, 1H, **7**-H), 1.90-1.85 (m, 1H, **4**-H), 1.64-1.54 (m, 2H, **2**-H_2), 1.04 (s, 21H, **TIPS**-H), 1.00 (d, *J* = 6.8 Hz, 3H, **4**-CH_3), 0.86 (s, 9H, **TBS**-H); 0.01 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.8 (C-6), 72.2 (C-3), 69.0 (C-7), 60.0 (C-1), 38.0 (C-4), 36.0 (C-2), 25.9 (CTBS), 21.4 (C-5), 18.3 (CTIPS, CTBS), 15.1 (4-CH_3), 12.9 (CTIPS), -5.4 (CTBS); MS (ESI) *m/z* 413 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{23}H_{49}O_2Si_2$ $[M+H]^+$ 413.3271,

found 413.3271; $[\alpha]_D$: +5.4 (*c* 2.6, CH_2Cl_2); Elem. Anal. Calculated for $C_{23}H_{48}O_2Si_2$ C 66.92, H 11.72, found C 66.94, H 12.00.

(7*R*)-7-[(2*S*)-Hex-4-yn-2-yl]-2,2,3,3,10-pentamethyl-9,9-bis(propan-2-yl)-4,8-dioxa-3,9-disilaundecane



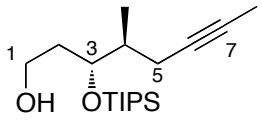
193

To a solution of **207** (4.3 g, 10.4 mmol) in THF (60 mL) cooled to -78 °C was slowly added *n*-BuLi (2.5 M in hexanes, 6.2 mL). After 45 min, MeI (1.3 mL, 20.8 mmol) was added and the reaction mixture was stirred at rt for 3 h. The reaction was then quenched by addition of a saturated solution of NH_4Cl and the aqueous layer was extracted with Et_2O (X 2). Combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (5% Et_2O in hexanes) to afford **193** (4.0 g, 90%) as a colourless oil.

IR (neat): 3317, 2937, 2865, 1465, 1391, 1363, 1253, 1097, 834, 376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09-4.05 (m, 1H, **1**-H), 3.75-3.66 (m, 2H, 3-**H_2**), 2.12-1.98 (m, 2H, **5**-H_2), 1.91-1.81 (m, 1H, **4**-H), 1.76 (t, *J* = 2.4 Hz, 3H, **7**-CH_3), 1.63-1.58 (m, 2H, **2**-H_2), 1.07 (s, 21H, **TIPS**-H), 0.97 (d, *J* = 6.8 Hz, 3H, **4**-CH_3), 0.86 (s, 9H, **TBS**-H), 0.01 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.2 (C-6), 76.2 (C-7), 71.9

(C-3), 60.2 (C-1), 38.7 (C-4), 35.6 (C-2), 25.9 (CTBS), 22.0 (C-5), 18.2 (CTBS, CTIPS), 14.8 (4-CH_3), 12.9 (CTIPS), 3.5 (7-CH_3), -5.4 (CTBS); MS (ESI) *m/z* 427 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{24}H_{51}O_2Si_2$ $[M+H]^+$ 427.3428, found 427.3415; $[\alpha]_D$: +8.1 (*c* 1.8, CH_2Cl_2).

(3*R*,4*S*)-4-methyl-3-{[tris(propan-2-yl)silyl]oxy}oct-6-yn-1-ol



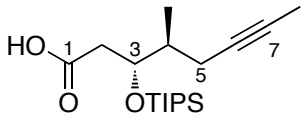
208

To a solution of **193** (4.0 g, 9.4 mmol) in MeOH (100 mL) was added *p*-TsOH (0.9 g, 4.7 mmol) at 0 °C. The mixture was stirred for 2 h at rt and was then quenched by addition of $NaHCO_3$ (1.5 g). The mixture was stirred for 10 min then filtered and the resulting filtrate was concentrated under reduced pressure. The crude material was diluted with Et_2O and washed with brine. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% Et_2O in hexanes) to afford **208** (2.7 g, 92%) as a colourless oil.

IR (neat): 3347, 2942, 2866, 1463, 1384, 1092, 1060, 1034, 882, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17-4.13 (m, 1H, **3**-H), 3.80 (t, *J* = 6.3 Hz, 2H, **1**-H_2), 2.08-2.05 (m, 2H, **5**-H_2), 1.95-1.89 (m, 1H, **4**-H), 1.76 (t, *J* = 2.5 Hz, 3H, **7**-CH_3), 1.71-1.67 (m, 2H, **2**-H_2), 1.09 (s, 21H, **TIPS**-H), 0.97 (d, *J* = 6.8 Hz, 3H, **4**-CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ 77.7 (C-6), 77.2 (C-7), 73.5 (C-3), 60.7 (C-1), 38.6 (C-4), 34.0 (C-2), 22.6 (C-5), 18.2 (CTIPS), 14.4 (4-CH_3), 13.0 (CTIPS), 3.4 (7-CH_3), -5.4 (CTBS); MS (ESI) *m/z* 313 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{37}O_2Si$ $[M+H]^+$ 313.2563, found 313.2547; $[\alpha]_D$: +8.1 (*c* 1.8, CH_2Cl_2).

(3*R*,4*S*)-4-Methyl-3-{[tris(propan-2-yl)silyl]oxy}oct-6-ynoïc acid



201

Procedure A

A-To a solution of IBX (800 mg, 1.46 mmol) dissolved in DMSO (2.5 mL) and stirred for approximately 10 min, was added **208** (227 mg, 0.73 mmol) dissolved in DMSO (0.5 mL). The reaction mixture was stirred for 4 h and was then filtrated. The filtrate was diluted with Et_2O and washed with water. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude material was filtered on a short pad of silica (5% Et_2O in hexanes) to afford **209** (201 mg, 89%) as a colourless oil.

B-To a solution of **209** (201 mg, 0.65 mmol) dissolved in THF/*tert*-butanol (9 mL, 2:1) was added 2-methyl-2-butene (616 µL, 5.8 mmol), followed by a mixture of $NaClO_2$ (145 mg, 1.6 mmol) and NaH_2PO_4•H_2O (193 mg, 1.4 mmol) dissolved in water (3 mL). The yellow reaction mixture was then stirred for 1 hour, carefully quenched by addition of aqueous HCl (1 M) and diluted with Et_2O. The aqueous layer

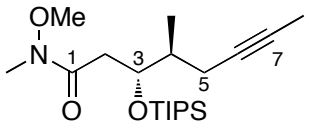
was extracted with Et_2O (X 2) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (20% EtOAc in hexanes) to afford **201** (180 mg, 90%) as a yellow oil.

Procedure B

To a solution of **208** (2.5 g, 8 mmol) dissolved in MeCN (60 mL) and cooled to 0 ºC were added phosphate buffer (pH = 7, 60 mL), $NaClO_2$ (1.8 g, 20.0 mmol), TEMPO (0.1 g, 0.64 mmol), and aqueous NaClO (few drops) at 0 ºC. After 20 min, the reaction was quenched by addition of a saturated solution of $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc (X 2) and the combined organic layers were washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (20% in EtOAc) to afford **201** (2.0 g, 79%) as a colourless oil.

IR (thin layer): 2948, 2926, 2869, 1712, 1467, 1300, 1090, 1068, 1002, 948, 882, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.46-4.42 (m, 1H, **3**-H), 2.54 (ddq, *J* = 15.6, 5.2, 2.4 Hz 1H, **5**-Ha), 2.47 (ddq, *J* = 15.6, 6.4, 2.4 Hz, 1H, **5**-Hb), 2.10-2.08 (m, 2H, **2**-H_2), 2.00-1.94 (m, 1H, **4**-H), 1.50 (t, *J* = 2.4 Hz, 3H, **7**-CH_3), 1.08 (s, 21H, **TIPS**-H), 1.00 (d, *J* = 6.8 Hz, 3H, **4**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (C-1), 77.2 (C-6), 77.1 (C-7), 71.8 (C-3), 39.0 (C-4), 37.6 (C-2), 22.4 (C-5), 18.1 (CTIPS), 14.4 (4-CH_3), 12.7 (CTIPS), 3.4 (7-CH_3); MS (ESI) *m/z* 325 $[M-H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{33}O_3Si$ $[M-H]^+$ 325.2199, found 325.2200; $[\alpha]_D$: +3.5 (*c* 0.8, $CHCl_3$); Elem. Anal. Calculated for $C_{18}H_{34}O_3Si$ C 66.21, H 10.49, found C 66.26, H 10.39.

(3*R*,4*S*)-*N*-methoxy-*N*,4-dimethyl-3-{[tris(propan-2-yl)silyl]oxy}oct-6-ynamide



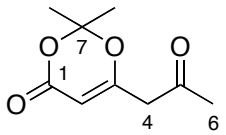
213

To a solution of **201** (2.5 g, 7.7 mmol), *N*-methoxy-*N*-methylamine (1.0 g, 10 mmol) and PyBOP (4.0 g, 8 mmol) in CH_2Cl_2 (20 mL) was added *i*-Pr_2NEt (4.0 mL, 23 mmol) at 0 °C. The reaction was allowed to warm to rt and stirred for 30 min. The reaction mixture was poured into Et_2O, and the organic layer was washed with aqueous HCl (1 M), a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude oil was purified by silica flash chromatography (20% EtOAc in hexanes) to afford **213** as a colourless oil (2.1 g, 74%).

IR (neat): 2935, 2926, 2866, 1664, 1383, 1181, 1093, 1064, 1013, 940, 882, 741, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.53 (ddd, *J* = 7.5, 4.8, 3.3 Hz, 1H, **3**-H), 3.69 (s, 3H, **N**-CH_3), 3.16 (s, 3H, **O**-CH_3), 2.63 (dd, *J* = 15.2, 7.5 Hz, 1H, **2**-Ha), 2.42 (dd, *J* = 15.2, 4.8 Hz, 1H, **2**-Hb), 2.17-1.96 (m, 2H, **5**-H_2), 1.95-1.90 (m, 1H, **4**-H), 1.77 (t, *J* = 2.44 Hz, 3H, **7**-CH_3), 1.09 (s, 21H, **TIPS**-H), 1.02 (d, *J* = 6.70 Hz, 3H, **4**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.8 (C-6), 73.5 (C-7), 71.5 (C-3), 61.2 (O-CH_3), 39.3 (C-4), 35.1 (C-2), 32.1 (N-CH_3), 22.0 (C-5), 18.1 (CTIPS), 14.6 (4-CH_3), 12.7 (CTIPS), 3.5 (7-CH_3), (C-1 missing); MS (ESI) *m/z* 370 $[M-H]^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{40}NO_3Si$ $[M+H]^+$ 370.2777, found 370.2771 ; $[\alpha]_D$: +16.3 (*c* 0.3,

$CHCl_3$); Elem. Anal. Calculated for $C_{20}H_{39}O_3Si$ C 64.99, H 10.64, N 3.79, found C 65.12, H 10.71, N 3.82.

2,2-Dimethyl-6-(2-oxopropyl)-2,4-dihydro-1,3-dioxin-4-one

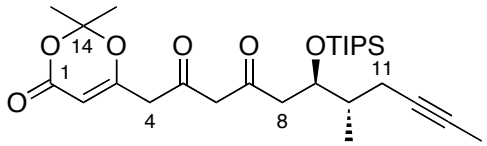


150

To a solution of dioxinone **114** (3.0 g, 21 mmol) in THF (60 mL) was added LiHMDS (1 M in THF, 21 mL) at -78 ºC. The reaction mixture was stirred for 1 h, then AcCl (0.9 mL, 12,6 mmol) was added. The reaction mixture was stirred for another 30 min at -78 ºC and then poured into aqueous HCl (1 M). The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (50% Et_2O in hexanes to give **150** (2.1 g, 55%) as a pale yellow solid.

mp: 46-50 ºC (hexanes/CH_2Cl_2); IR (neat): 1733, 1714, 1639, 1379, 1317, 1270, 1253, 1197, 1160, 904, 862, 821, 794 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H, **2**-H), 3.31 (s, 2H, **4**-H), 2.21 (s, 3H, **6**-H), 1.68 (s, 6H, **7**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 164.5, 160.8, 107.4, 96.9, 48.2, 30.3, 25.2; HRMS (CI) *m/z* calculated for $C_9H_{13}O_4$ $[M+H]^+$ 185.0814, found 185.0812.

(6*R*,7*S*)-1-(2,2-Dimethyl-6-oxo-2,6-dihydro-1,3-dioxin-4-yl)-7-methyl-6-{[tris(propan-2-yl)silyl]oxy}undec-9-yne-2,4-dione



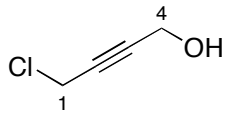
215

To a freshly prepared solution of LDA (27.8 mmol) in THF (25 mL) was added keto-dioxinone **150** (2.4 g, 12.8 mmol) at -78 °C. After 30 min at -40 °C the reaction mixture was cooled to -78 °C and Et_2Zn (1 M in THF, 25.7 mL) was added. After another 30 min at -40 °C, **213** (1.6 g, 4.28 mmol) was added. The mixture was stirred for 4 h at a temperature comprises between -5 °C. After this time the mixture was quenched with aqueous HCl (1 M) and diluted with EtOAc (X 2). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10 to 20% Et_2O in hexanes) to afford **215** (1.4 g, 67%) as a light yellow oil.

IR (neat): 2938, 2920, 2866, 1731, 1604, 1378, 1271, 1014, 882 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 15.1 (*br* s, 1H, **O**-H), 5.63 (s, 1H), 5.40 (s, 1H), 4.47-4.43 (m, 1H, **9**-H), 3.19 (s, 2H), 2.42 (dd, *J* = 14.2, 4.7 Hz, 1H, **8**-Ha), 2.34 (dd, *J* = 14.2, 7.8 Hz, 1H, **8**-Hb), 2.07-2.05 (m, 2H, **11**-H_2), 1.96-1.89 (m, 1H, **10**-H), 1.77 (t, *J* = 2.46 Hz, 3H, **13**-CH_3), 1.7 (s, 6H, **14**-$(CH_3)_2$), 1.04 (s, 21H, **TIPS**-H), 0.97 (d, *J* = 6.83 Hz, 3H, **10**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 188.3, 165.0, 160.7, 107.1, 101.5, 96.4, 77.2 (C-12), 76.8 (C-13), 72.1 (C-9), 43.5, 41.2, 39.1, 25.0

(14-(CH_3)$_2$), 22.2, 18.1 (CTIPS), 14.4 (CH_3), 12.7 (CTIPS), 3.5 (CH_3); MS (ESI) *m/z* 493 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{27}H_{45}O_6Si$ $[M+H]^+$ 493.2985, found 493.3003; Elem. Anal. Calculated for $C_{27}H_{44}O_6Si$ C 65.82, H 9.00, found C 65.75, H 8.99; $[\alpha]_D$: +9.5 (*c* 0.6, $CHCl_3$).

4-Chloro-2-yn-1-ol



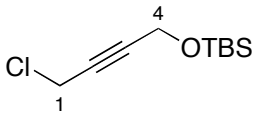
222

To a solution of 2-butyne-1,4-diol (**221**) (10 g, 116.2 mmol) dissolved in pyridine (10 mL, 127.8 mmol) and PhMe (20 mL) was added dropwise thionyl chloride (9 mL, 127.8 mmol) at 10 °C. The reaction mixture was then slowly allowed to reach rt and was stirred for 18 h. The reaction was quenched with iced-water and the aqueous layer was extracted with Et_2O (X 3). The combined organic layers were washed with a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by distillation (0.5 mmHg, 84 °C oil bath) to afford **222** (2.2 g, 40%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (t, J = 2.0 Hz, 2H, **4**-H_2), 4.16 (t, J = 2.0 Hz, 2H, **1**-H_2), 1.75 (*br* s, 1H, **O**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.7 (C), 80.4 (C), 50.9(C-4), 30.0 (C-1).

Match the literature data.[80]

***tert*-Butyl[(4-chlorobut-2-yn-1-yl)oxy]dimethylsilane**

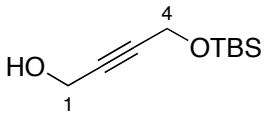


223

To a solution of **222** (1.5 g, 14.3 mmol) dissolved in CH_2Cl_2 (20 mL) were added NEt_3 (4 mL, 28.6 mmol) and DMAP (0.2 g, 1.4 mmol). The solution was cooled to 0 °C and TBSCl (3.0 g, 20 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was slowly allowed to reach rt and stirred for 5 h. The reaction was quenched by addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% EtOAc in hexanes) to afford **223** (1.9 g, 60%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (t, J = 2.0 Hz, 2H, **4**-H_2), 4.19 (t, J = 2.0 Hz, 2H, **1**-H_2), 0.93 (s, 9H, **TBS**-H), 0.14 (s, 6H, **TBS**-H**)**; ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.7 (C), 80.4 (C), 51.4 (C-4), 30.4 (C-1), 25.8 (CTBS), 18.4 (CTBS), -5.4 (CTBS). Match the literature data.[123]

4-[(*tert*-Butyldimethylsilyl)oxy]but-2-yn-1-ol

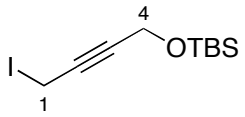


225

To a solution of 2-butyne-1,4 diol (**221**) (80 g, 930 mmol) dissolved in CH_2Cl_2 (700 mL) was added imidazole (32 g, 465 mmol). The solution was cooled to 0 °C and TBSCl (35 g, 233 mmol) dissolved in CH_2Cl_2 (300 mL) was added dropwise. The reaction mixture was slowly allowed to reach rt and stirred for 18 h. The reaction mixture was filtered and half of the filtrate was concentrated under reduced pressure. The resulting solution was washed with water. The aqueous layer was extracted with CH_2Cl_2 (X 2) and the combined organic layers were washed with a saturated solution of NH_4Cl, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a mixture of the desired mono-protected alcohol and of the di-protected alcohol. The crude material was purified by silica flash chromatography (5% Et_2O in hexanes) to afford mono-protected alcohol **225** (28 g, 63%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (t, *J* = 2.0 Hz, 2H), 4.33 (t, *J* = 2.0 Hz, 2H), 0.94 (s, 9H, **TBS**-H); 0.15 (s, 6H, **TBS**-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 84.2 (C), 82.8 (C), 51.6 (CH_2), 51.0 (CH_2), 25.6 (CTBS), 18.1 (CTBS), -5.3 (CTBS). Match the literature data.[124]

tert-Butyl[(4-iodobut-2-yn-1-yl)oxy]dimethylsilane



224

Procedure A

To a solution of NaI (2.4 g, 15.8 mmol) dissolved in acetone was added **223** (2.3 g, 10.5 mmol) and the reaction mixture was stirred for 12 h. The mixture was then filtered and concentrated under reduced pressure. The resulting crude oil was dissolved in a minimum amount of $CHCl_3$ and hexanes was added. The precipitate was filtered and the resulting solution was concentrated under reduced pressure to afford **224** (1.2 g, 50%) as a mixture with starting material **223** (7:3).

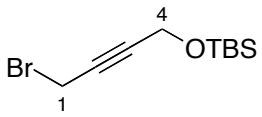
Procedure B

To a solution of **225** (33 g, 147 mmol) dissolved in THF (300 mL) were added imidazole (25 g, 3.7 mmol), PPh_3 (46 g, 176.4 mmol) and iodine (48.5 g, 191.1 mmol). The reaction mixture was stirred for 30 min then concentrated under reduced pressure. The resulting crude product was purified by silica flash chromatography (5% EtOAc in hexanes) to afford **224** (28 g, 72%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (t, J = 2.0 Hz, 2H, **4**-H_2), 3.74 (t, J = 2.0 Hz, 2H, **1**-H_2), 0.93 (s, 9H, **TBS**-H); 0.14 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 83.9 (C), 81.5 (C), 51.9 (C-4), 25.8 (CTBS), 18.3 (CTBS), -5.4 (CTBS), -18.6 (C-1). Match the literature data.[125]

[(4-Bromobut-2-yn-1-yl)oxy](*tert*-butyl)dimethylsilane

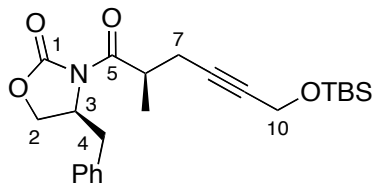


226

To a solution of **225** (5.0 g, 25 mmol) in Et_2O (95 mL) were added PPh_3 (13.1 g, 50 mmol) and CBr_4 (16.6 g, 50 mmol). The reaction mixture was stirred for 4 h then filtered through celite and concentrated under reduced pressure. The resulting crude product was purified by silica flash chromatography (5% EtOAc in hexanes) to afford **226** as a light brown oil (3.9 g, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.34 (t, J = 2.0 Hz, 2H, **4**-H_2), 3.91 (t, J = 2.0 Hz, 2H, **1**-H_2), 0.88 (s, 9H, **TBS**-H), 0.10 (s, 6H, **TBS**-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 83.3 (C), 79.8 (C), 51.7 (C-4), 25.8 (CTBS), 18.2 (CTBS), 14.4 (C-1), -5.2 (CTBS). Match the literature data.[125]

(4*S*)-4-Benzyl-3-[(2*R*)-6-[(*tert*-butyldimethylsilyl)oxy]-2-methylhex-4-ynoyl]-1,3-oxazolidin-2-one



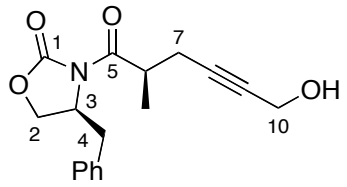
227

To a solution of propionyloxazolidinone ***ent*-42** (7.5 g, 32.3 mmol) was added dropwise a solution of NaHMDS (1 M in THF, 35.5 mL) at -78 °C. After the mixture was stirred for 1 h at -78 °C, iodide **224** (30.0 g, 96.7 mmol) was added and the reaction was stirred for 3 h at -78 °C. The reaction was quenched with brine and the aqueous layer was extracted with Et_2O (X 2). The combined organic layers were washed with a saturated solution of $NaHCO_3$ and a saturated solution of NH_4Cl, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% Et_2O in hexanes) to afford **227** (7.5 g, 72%, dr ≥ 97:3) as a colourless oil.

IR (thin layer): 3420, 2900, 1800, 1720, 1400, 1320, 1050, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H, **Ar**-H), 4.74-4.68, (m, 1H, **3**-H), 4.31 (t, *J* = 2.0 Hz, 2H, **10**-H_2), 4.25-4.18 (m, 2H, **2**-H_2), 3.98-3.91 (dt, *J* = 6.8, 6.8 Hz, 1H, **6**-H), 3.32 (dd, *J* = 13.4, 3.2 Hz, 1H, **4**-Ha), 2.79 (dd, *J* = 13.4, 9.6 Hz, 1H, **4**-Hb), 2.66 (ddt, *J* = 16.7, 6.8, 2.1 Hz, 1H, **7**-Ha), 2.52 (ddt, *J* = 16.7, 6.8, 2.1 Hz, 1H, **7**-Hb), 1.29 (d, *J* = 6.8 Hz, 3H, **6**-CH_3), 0.91 (s, 9H, **TBS**-H), 0.12 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4 (C-5), 153.0 (C-1), 135.3 (CAr), 129.4 (2 X CAr), 129.0

(2 X CAr), 127.4 (CAr), 82.0 (C), 80.5 (C), 66.1 (C-2), 55.3 (C-10), 51.9 (C-3), 37.9 (C-4), 37.4 (C-6), 25.8 (CTBS), 22.9 (C-7), 17.8 (CTBS), 16.7 (6-CH_3), -5.1 (CTBS); MS (ESI) *m/z* 416 $[M+H]^+$; HRMS (ESI) calculated for $C_{23}H_{34}NO_4Si$ $[M+H]^+$ 416.2279, found 416.2276; $[\alpha]_D$: + 22.2 (*c* 1.2, $CHCl_3$); Elem. Anal. calculated for $C_{23}H_{33}NO_4Si$ C 66.47 H 8.00 N 3.37, found C 66.57, H 7.93, N 3.32.

(4*S*)-4-Benzyl-3-[(2*R*)-6-hydroxy-2-methylhex-4-ynoyl]-1,3-oxazolidin-2-one



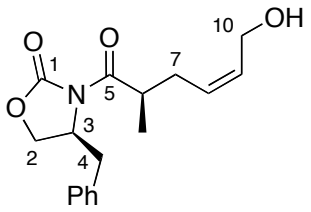
227

To a solution of **227** (627 mg, 2.08 mmol) dissolved in MeCN (30 mL) was added a solution of H_2SiF_6 (25 wt. % in water, 1.25 mL). The reaction mixture was stirred for 2 h and was then poured into water. The aqueous layer was extracted with CH_2Cl_2 (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude material was purified by silica flash chromatography (30% EtOAc in hexanes) to afford **228** (563 mg, 83%) as a colourless oil.

IR (thin layer): 3470, 2930, 1780, 1700, 1390, 1300, 1050, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H, **Ar**-H), 4.76-4.70, (m, 1H, **3**-H), 4.24 (t, *J* = 2.0 Hz, 2H, **10**-H_2), 4.22-4.17 (m, 2H, **2**-H_2), 3.95 (dt, *J* = 6.8, 6.8 Hz, 1H, **6**-H),

3.32 (dd, J = 13.4, 3.2 Hz, 1H, **4**-Ha), 2.80 (dd, J = 13.4, 9.5 Hz, 1H, **4**-Hb), 2.64 (ddt, J = 16.7, 6.8, 2.1 Hz, 1H, **7**-Ha), 2.58 (ddt, J = 16.7, 6.8, 2.1 Hz, 1H, **7**-Hb), 1.30 (d, J = 6.8 Hz, 3H, **6**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4 (C-5), 153.0 (C-1), 135.0 (CAr), 129.3 (2 X CAr), 128.2 (2 X CAr), 127.2 (CAr), 83.1 (C), 80.5 (C), 66.0 (C-2), 55.2 (C-10), 51.1 (C-3), 37.7 (C-4), 37.2 (C-6), 22.8 (C-7), 16.5 (6-CH_3); $[\alpha]_D$: + 55.5 (*c* 0.9, $CHCl_3$); MS (ESI) *m/z* 302 $[M+H]^+$; HRMS (ESI) calculated for $C_{17}H_{19}NO_4$ $[M+H]^+$ 302.1392, found 302.1393.

(4*S*)-Benzyl-3-[(2*R*,4*Z*)-6-hydroxy-2-methylhex-4-enoyl]-1,3-oxazolidin-2-one



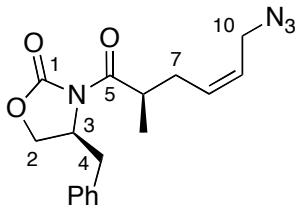
229

To a solution of **228** (345 mg, 1.1 mmol) in CH_2Cl_2 (75 mL) was added quinoline (70 μL, mmol) followed by Lindlar catalyst (5 wt. % Pd on $CaCO_3$, poisoned with lead, 350 mg, 100 wt. %). The reaction was placed under H_2 atmosphere and stirred for 1 h. The reaction mixture was filtered through celite, washed with aqueous HCl (0.5 M) and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **229** (310 mg, 89%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.23 (m, 5H, **Ar**-H), 5.78 (dt, J = 10.9, 7.0 Hz, 1H), 5.60 (dt, J = 10.9, 7.0 Hz, 1H), 4.73-4.68, (m, 1H, **3**-H), 4.35-4.14 (m, 4H,

10-H_2, **2**-H_2), 3.95 (dt, *J* = 7.0, 7.0 Hz, 1H, **6**-H), 3.32 (dd, *J* = 13.4, 3.2 Hz, 1H, **4**-Ha), 2.77 (dd, *J* = 13.4, 9.6 Hz, 1H, **4**-Hb), 2.73-2.65 (m, 1H, **7**-Ha), 2.24-2.18 (m, 1H, **7**-Hb), 1.23 (d, *J* = 7.0 Hz, 3H, **6**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (C-5), 153.1 (C-1), 135.2 (CAr), 130.8 (CH), 129.5 (2 X CAr), 129.4 (CH), 129.0 (2 X CAr), 127.4 (CAr), 66.1 (C-2), 58.3 (C-10), 55.4 (C-3), 38.1 (C-4), 37.8 (C-6), 31.5 (C-7), 17.0 (6-CH_3); MS (CI) m/z 304 $[M+H]^+$.

(4*S*)-3-[(2*R*,4*Z*)-6-Azido-2-methylhex-4-enoyl]-4-benzyl-1,3-oxazolidin-2-one

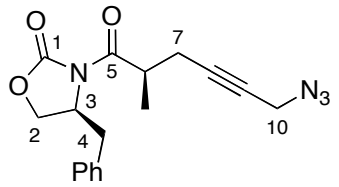


230

To a solution of **229** (50 mg, 0.15 mmol) dissolved in PhMe (500 μL) and cooled to 0 °C was added dropwise DBU (25 μL) followed by DPPA (53 μL). The reaction mixture was slowly allowed to reach rt and stirred for 3 h. The reaction was quenched with water and the aqueous layer was extracted with EtOAc (X 2). The combined organic layers were washed with aqueous HCl (0.5 M), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (30% Et_2O in hexanes) to afford **230** (34 mg, 62%, *dr* = 70:30) as a colourless oil.

IR (thin layer): 2975, 2933, 2360, 2341, 2100, 1778, 1697, 1386, 1240, 1212, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (Epimer 70%) δ 7.40-7.23 (m, 5H, **Ar**-H), 5.84-5.63 (m, 2H), 4.74-4.68 (m, 1H, **3**-H), 4.26-4.19 (m, 2H, **2**-H_2), 3.93-3.75 (m, 3H, **10**-H_2, **6**-H), 3.29 (dd, *J* = 13.3, 3.2 Hz, 1H, **4**-Ha), 2.77 (dd, *J* = 13.3, 10.0 Hz, 1H, **4**-Hb), 2.66-2.24 (m, 2H, **7**-H_2), 1.25 (d, *J* = 7.4 Hz, 3H, **6**-CH_3); ^1H NMR (400 MHz, $CDCl_3$) (Epimer 30%) δ 7.40-7.23 (m, 5H, **Ar**-H), 5.38-5.30 (m, 2H), 4.74-4.68 (m, 1H, **3**-H), 4.26-4.19 (m, 2H, **2**-H_2), 3.93-3.75 (m, 3H, **10**-H_2, **6**-H), 3.32 (dd, *J* = 13.3, 3.2 Hz, 1H, **4**-Ha), 2.74 (dd, *J* = 13.3, 10.0 Hz, 1H, **4**-Hb), 2.66-2.24 (m, 2H, **7**-H_2), 1.23 (d, *J* = 7.4 Hz, 3 H, **6**-CH_3); MS (ESI) m/z 327 $[M-H]^-$.

(4*S*)-3-[(2*R*)-6-Azido-2-methylhex-4-ynoyl]-4-benzyl-1,3-oxazolidin-2-one



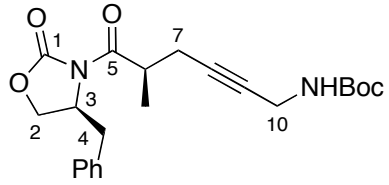
231

To a solution of **228** (310 mg) dissolved in CH_2Cl_2 (2.5 mL) and cooled to 0 °C was added dropwise DBU (154 μL, 1.03 mmol) followed by DPPA (333 μL, 1.55 mmol). The reaction mixture was slowly allowed to reach rt and stirred for 3 h. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layers were washed with aqueous HCl (0.5 M), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by

silica flash chromatography (2% MeOH in CH_2Cl_2) to afford **231** as a colourless oil. (200 mg, 61%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H, **Ar**-H), 4.73-4.67, (m, 1H, **3**-H), 4.24-4.17 (m, 2H, **2**-H_2), 3.97 (dt, *J* = 6.8, 6.8 Hz, 1H, **6**-H), 3.90 (t, *J* = 1.9 Hz, 2H, **10**-H_2), 3.31 (dd, *J* = 13.4, 3.2 Hz, 1H, **4**-Ha), 2.78 (dd, *J* = 13.4, 9.6 Hz, 1H, **4**-Hb), 2.64 (ddt, *J* = 16.8, 6.8, 2.2 Hz, 1H, **7**-Ha), 2.58 (ddt, *J* = 16.8, 6.8, 2.2 Hz, 1H, **7**-Hb), 1.30 (d, *J* = 6.8 Hz, 3H, **6**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C-5), 153.0 (C-1), 135.2 (CAr), 129.4 (2 X CAr), 128.9 (2 X CAr), 127.4 (CAr), 85.0 (C), 73.9 (C), 66.2 (C-2), 55.4 (C-3), 40.2 (C-10), 37.9 (C-4), 37.4 (C-6), 22.8 (C-7), 16.6 (6-CH_3); MS (ES) *m/z* 327 $[M+H]^+$; HRMS (ES) *m/z* calculated for $C_{17}H_{18}N_4O_3$ $[M+H]^+$ 327.1379, found 327.0779.

tert-Butyl _N_-[(5_R_)-6-[(4_S_)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-5-methyl-6-oxohex-2-ynyl]carbamate



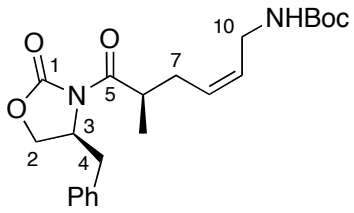
231'

To a solution of **231** (361 mg, 1.11 mmol) in THF/water (13 mL, 8:2) was added PPh_3 (320 mg, 1.22 mmol). The mixture was stirred for 18 h at rt. The solvents were removed by co-evaporation with PhMe. Di-*tert*-butyldicarbonate (315 mg,

1.44 mmol) dissolved in THF (11 mL) was added. The resulting mixture was stirred at rt for 3 h and was then concentrated under reduced pressure. The crude material was purified by silica flash chromatography (20% EtOAc in hexanes) to afford **231'** (400 mg, 92%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H, **Ar**-H), 4.75-4.69, (m, 1H, **3**-H), 4.26-4.19 (m, 2H, **2**-H_2), 3.99-3.85 (m, 3H, **6**-H, **10**-H_2), 3.31 (dd, *J* = 13.5, 3.2 Hz, 1H, **4**-Ha), 2.81 (dd, *J* = 13.5, 9.6 Hz, 1H, **4**-Hb), 2.61 (ddt, *J* = 16.9, 6.8, 2.2 Hz, 1H, **7**-Ha), 2.49 (ddt, *J* = 16.9, 6.8, 2.2 Hz, 1H, **7**-Hb), 1.43 (s, 9 H, **Boc**-H), 1.29 (d, *J* = 7.0 Hz, 3H, **6**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3 (C-5), 153.0 (C-1), 135.2 (CAr), 129.4 (2 X CAr), 128.9 (2 X CAr), 127.4 (CAr), 80.4 (C), 78.3 (C), 66.1 (C-2), 55.3 (C-3), 37.9 (C-4), 37.4(C-6), 30.8 (C-10), 28.3 (CBoc), 22.9 (C-7), 16.6 (6-CH_3); MS (CI) *m/z* 423 $[M+Na]^+$, 301 $[M+H\text{-}Boc]^+$; HRMS (ESI) *m/z* calculated for $C_{22}H_{29}N_2O_5$ $[M+H]^+$ 401.2076, found 401.2081.

***tert*-Butyl *N*-[(2*Z*,5*R*)-6-[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-5-methyl-6-oxohex-2-1-yl]carbamate**

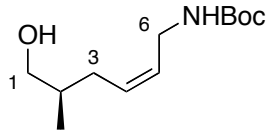


232

To a solution of **231'** (400 mg, mmol) in CH_2Cl_2 (90 mL) was added quinoline (80-µL, mmol) followed by Lindlar catalyst (5 wt. % Pd on $CaCO_3$, poisoned with lead, 400 mg, 100 wt. %). The reaction was placed under H_2 atmosphere and stirred for 4 h. The reaction mixture was filtered through celite and concentrated under reduced pressure. The crude oil was purified by silica flash chromatography (50% EtOAc in hexanes) to afford **232** (260 mg, 65%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H, **Ar**-H), 5.61-5.53 (m, 2H, **8**-H, **9**-H), 4.73-4.68 (m, 1H, **3**-H), 4.25-4.18 (m, 2H, **2**-H_2), 3.88-3.74 (m, 3H, **6**-H, **10**-H_2), 3.28 (dd, J = 13.4, 3.2 Hz, 1H, **4**-Ha), 2.76 (dd, J = 13.4, 9.6 Hz, 1H, **4**-Hb), 2.65-2.58 (m, 1H, **7**-Ha), 2.27-2.20 (m, 1H, **7**-Hb), 1.44 (s, 9H, **Boc**-H), 1.28 (d, J = 7.4 Hz, 3H, **6**-CH_3); MS (CI) *m/z* 403 $[M+H]^+$; HRMS (EI) *m/z* calculated for $C_{22}H_{31}N_2O_5$ $[M+H]^+$ 403.2233, found 403.2237.

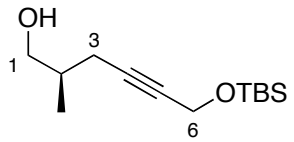
***tert*-Butyl *N*-[(2*Z*,5*R*)-6-hydroxy-5-methylhex-2-en-1-yl]carbamate**



233

To a solution of **232** (75 mg, 19 mmol) in THF (2 mL) was added a solution of $NaBH_4$ (40 mg, 0.93 mmol) in water (0.6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, allowed to warm to rt and stirred for 4 h. The reaction was quenched by addition of a saturated solution of NH_4Cl and then stirred for 1 h. The aqueous layer was extracted with EtOAc (X 2) and the combined organic layers were washed with a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Alcohol **233** could no be isolated after silica flash chromatography.

(2*R*)-6-[(*tert*-Butyldimethylsilyl)oxy)-2-methylhex-4-yn-1-ol



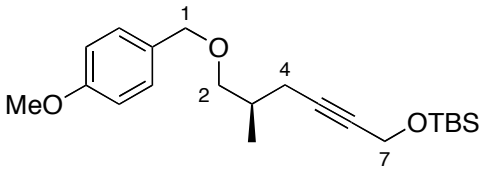
234

To a solution of **227** (9.8 g, 23 mmol) in THF (230 mL) was added a solution of $NaBH_4$ (4.4 g, 117 mmol) in water (80 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, allowed to warm to rt and stirred for 4 h. The reaction was

quenched by addition of a saturated solution of NH_4Cl and then stirred for 1 h. The aqueous layer was extracted with EtOAc (X 2) and the combined organic layers were washed with a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude oil was purified by silica flash chromatography to afford **234** (4.6 g, 83%) as a colourless oil.

IR (thin layer): 3372, 2956, 2929, 2858, 1463, 1371, 1255, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (t, *J* =2.2 Hz, 2H, **6**-H_2), 3.58 (d, *J* = 6.3 Hz, 2H, **1**-H_2), 2.31 (ddt, *J* = 16.9, 6.3, 2.2 Hz, 1H, **3**-Ha), 2.24 (ddt, *J* = 16.9, 6.3, 2.2 Hz, 1H, **3**-Hb), 1.93-1.85 (m, 1H, **2**-H), 1.01 (d, *J* = 6.8 Hz, 3H, **2**-CH_3), 0.93 (s, 9H, **TBS**-H), 0.13 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.2 (C), 80.1 (C), 67.1 (CH_2), 51.9 (CH_2), 35.1 (C-2), 25.8 (CTBS), 22.7 (C-3), 18.3 (CTBS), 16.2 (2-CH_3), -5.1 (CTBS); MS (CI) *m/z* 243 $[M+H]^+$, 260 $[M+NH_3]^+$; HRMS (EI) *m/z* calculated for $C_{13}H_{27}O_2Si$ $[M+H]^+$ 243.1780, found 243.1787; $[\alpha]_D$: + 10.61 (*c* 1.4, $CHCl_3$); Elem. Anal. calculated for $C_{13}H_{26}O_2Si$ C 64.41 H 10.81, found C 64.50, H 10.75.

(*tert*-Butyl)({[(5*R*)-(6-[(4-methoxyphenyl)methoxy]-5-methylhex-2-yn-1-yl]oxy})dimethylsilane



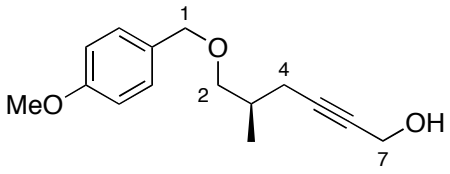
235

To a solution of **234** (2.0 g, 8.3 mmol) in THF (80 mL) was added NEt_3 (3.5 ml, 24.9 mmol) followed by PMBBr (2.2 ml, 14.9 mmol). The mixture was cooled to -78 °C and a freshly prepared solution of KHMDS (0.5 M in THF, 20 mL) was added dropwise. This mixture was stirred for 15 min at -78 ºC then was warmed to 0 °C and stirred for an additional 30 min before a saturated solution of $NaHCO_3$ was added. This mixture was stirred for 1 h at rt. The mixture was diluted with Et_2O and the organic layer was washed with a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% Et_2O in hexanes) to afford **235** (2.5 g, 86%) as a colourless oil.

IR (thin layer): 3350 (*br*), 2955, 2930, 2857, 2234, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.24 (m, 2H, **Ar**-H), 6.89-6.86 (m, 2H, **Ar**-H), 4.43 (s, 2H, **1**-H_2), 4.29 (t, J =2.2 Hz, 2H, **7**-H_2), 3.81 (s, 3H, **O**-CH_3), 3.37-3.30 (m, 2H, **2**-H_2), 2.33 (ddt, J = 16.6, 5.5, 2.2 Hz, 1H, **4**-Ha), 2.18 (ddt, J = 16.6, 6.9, 2.2 Hz, 1H, **4**-Hb), 2.01-1.93 (m, 1H, **3**-H), 0.99 (d, J = 6.8 Hz, 3H, **3**-CH_3), 0.91 (s, 9H**, TBS**-H), 0.11 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (CAr), 130.7 (CAr), 129.1 (2 X CAr), 113.7 (2 X CAr), 83.5 (C), 79.8 (C), 74.0 (CH_2), 72.7 (CH_2), 55.3 (O-CH_3), 52.0

(CH_2), 33.0 (C-3), 25.9 (CTBS), 23.0 (C-4), 18.34 (CTBS), 16.6 (3-CH_3), -5.08 (CTBS); MS (CI) *m/z* 380 $[M+NH_4]^+$; HRMS (EI) *m/z* calculated for $C_{21}H_{38}NO_3Si$ $[M+NH_4]^+$ 380.2621, found 380.2620; $[\alpha]_D$: + 12.8 (*c* 1, $CHCl_3$); Elem. Anal. calculated for $C_{21}H_{34}O_3Si$ C 69.56 H 9.45, found C 69.64, H 9.35.

(5*R*)-6-[(4-Methoxyphenyl)methoxy]-5-methylhex-2-yn-1-ol



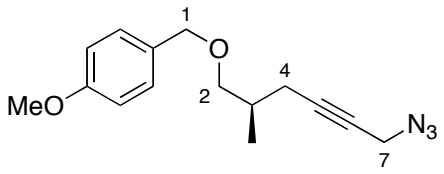
236

To a solution of **235** (2.3 g, 6.35 mmol) dissolved in MeCN (100 mL) was added a solution of H_2SiF_6 (25 wt. % in water, 4.6 mL). The reaction mixture was stirred for 2 h and was then poured into water. The aqueous layer was extracted with CH_2Cl_2 (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude material was purified by silica flash chromatography (30% EtOAc in hexanes) to afford **236** (1.4 g, 91%) as a colourless oil.

IR (thin layer): 3410, 2958, 2930, 2910, 2866, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.28 (m, 2H, **Ar**-H), 6.92-6.90 (m, 2H, **Ar**-H), 4.47 (s, 2H, **1**-H), 4.26 (t, *J* =2.2 Hz, 2H, **7**-H_2), 3.83 (s, 3H, O-CH_3), 3.37-3.30 (m, 2H, **2**-H_2), 2.37 (ddt, *J* = 16.6, 5.7, 2.2 Hz, 1H, **4**-Ha), 2.23 (ddt, *J* = 16.6, 6.9, 2.2 Hz, 1H, **4**-Hb), 2.06-1.94

(m, 1H, **3**-H), 1.02 (d, J = 6.8 Hz, 3H, **3**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (CAr), 130.7 (CAr), 129.1 (2 X CAr), 113.7 (2 X CAr), 83.5 (C), 79.8 (C), 74.0 (CH_2), 72.7 (CH_2), 55.3 (O-CH_3), 52.0 (CH_2), 33.0 (C-3), 22.9 (C-4), 16.5 (3-CH_3); MS (CI) *m/z* 266 $[M+NH_4]^+$; HRMS (EI) *m/z* calculated for $C_{15}H_{24}NO_3$ $[M+NH_4]^+$ 256.1756, found 256.1764; $[\alpha]_D$: + 11.6 (*c* 1.5, $CHCl_3$); Elem. Anal. calculated for $C_{15}H_{20}O_3$ C 72.55 H 8.12, found C 72.43, H 8.01.

1-({[(2*R*)-6-Azido-2-methylhex-4-yn-1-yl]oxy}methyl)-4-methoxybenzene



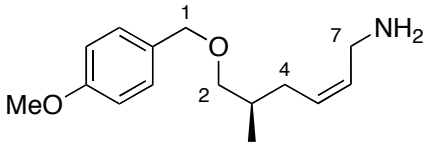
237

To a solution of **236** (100 mg, 0.36 mmol) dissolved in PhMe (800 μL) and cooled to 0 °C was added dropwise DBU (80 μL) followed by DPPA (112 μL). The reaction mixture was slowly allowed to reach rt and was then stirred for 4 h at 50 ºC. The reaction was then quenched with water. Organic layer was washed with 0.5 M HCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% EtOAc in hexanes) to afford **237** (59 mg, 60%) as a colourless oil.

IR (thin layer): 2957, 2931, 2857, 2838, 2125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H, **Ar**-H), 6.89-6.87 (m, 2H, **Ar**-H), 4.44 (s, 2H, **1**-H_2), 3.88 (t,

J = 2.2 Hz, 2H, **7**-H_2), 3.81 (s, 3H, O-CH_3), 3.37-3.34 (m, 2H, **2**-H_2), 2.38 (ddt, J = 16.6, 5.4, 2.2 Hz, 1H, **4**-Ha), 2.23 (ddt, J = 16.6, 6.8, 2.2 Hz, 1H, **4**-Hb), 2.04-1.95 (m, 1H, **3**-H), 1.01 (d, J = 6.8 Hz, 3H, **3**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (CAr), 130.7 (CAr), 129.2 (2 X CAr), 113.7 (2 X CAr), 84.6 (C), 79.4 (C), 73.8 (CH_2), 73.0 (CH_2), 72.7 (CH_2), 55.3 (CH_3), 32.9 (C-3), 22.9 (C-4), 16.5 (3-CH_3); MS (CI) *m/z* 291 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{15}H_{23}N_4O_2$ $[M+NH_4]^+$ 291.1821, found 291.1823; $[\alpha]_D$: + 10.21 (*c* 1, $CHCl_3$); Elem. Anal. calculated for $C_{12}H_{28}O_3Si$ C 65.91 H 7.01 N 15.37, found C 65.86, H 6.93 N 15.43.

(2*Z*,5*R*)-6-[(4-Methoxyphenyl)methoxy]-5-methylhex-2-en-1-amine

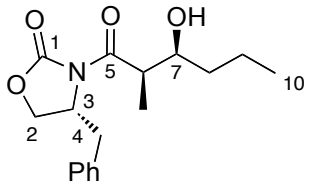


238

To a solution of **237** (50 mg, 0.18 mmol) dissolved in DMF (400 μL), was added ethylenediamine (30 μL, 0.45 mmol) followed by Lindlar catalyst (5 wt. % Pd on $CaCO_3$, poisoned with lead, 10 mg, 10 wt. %). The reaction was placed under a H_2 atmosphere and stirred for 1 h. The reaction mixture was filtered through Celite and washed with MeOH. The resulting solution was concentrated under reduced pressure, dissolved in EtOAc and washed with water and aqueous NH_4Cl (2 wt. %). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **238** (30 mg, 66%) as a yellow oil with good purity without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H, **Ar**-H), 6.90 (d, *J* = 8.5 Hz, 2H, **Ar**-H), 5.60-5.44 (m, 2H, **5**-H, **6**-H), 4.45 (s, 2H, **1**-H_2), 3.83 (s, 3H, **O**-CH_3), 3.37 (d, *J* = 6.6 Hz, 2H, **2**-H_2), 3.32-3.27 (m, 2H, **7**-H_2), 2.27-2.17 (m, 1H, **4**-Ha), 2.00-1.93 (m, 1H, **4**-Hb), 1.87-1.82 (m, 1H, **3**-H), 0.93 (d, *J* = 6.8 Hz, 3H, **3**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (CAr), 130.7 (CAr), 130.1 (CH), 130.0 (CH), 129.2 (2 X CAr), 113.8 (2 X CAr), 74.8 (CH_2), 72.7 (CH_2), 55.3 (CH_3), 38.4 (C-7), 33.8 (C-3), 31.2 (C-4), 16.9 (3-CH_3); MS (ES) *m/z* 250 $[M+H]^+$; HRMS (ES) *m/z* calculated for $C_{15}H_{24}NO_2$ $[M+H]^+$ 250.1807, found 250.1812; $[\alpha]_D$: +12.6 (*c* 0.7, $CHCl_3$).

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-3-hydroxy-2-methylhexanoyl]-1,3-oxazolidin-2-one



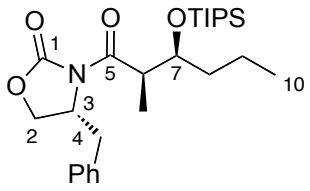
246

To a solution of **42** (3.0 g, 12.9 mmol) dissolved in CH_2Cl_2 and cooled to -78 °C was added dropwise Bu_2BOTf (1 M in CH_2Cl_2, 12.9 mL) followed by NEt_3 (2.3 mL, 16.7 mmol). The reaction mixture was stirred for 1 h at -78 °C and 15 min at 0 °C. The solution was then cooled to -78 °C and butyraldehyde (**216**) (1.5 mL, 16.7 mmol) was added dropwise. The resulting mixture was stirred for 30 min at -78 °C, then 30 min at 0 °C. The reaction was poured into aqueous HCl (1 M, 60 mL) and the aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layers were dried

($MgSO_4$), filtered and concentrated under reduced pressure. The crude material (*dr* = 93:7) was purified by silica flash chromatography (0 to 5% Et_2O in CH_2Cl_2) to afford **246** as a colourless oil and single diastereomer (2.9 g, 72%).

IR (neat): 3526, 2958, 2933, 2871, 2360, 1719, 1693, 1385, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.03 (m, 5H, **Ar**-H), 4.71-4.67, (m, 1H, **3**-H), 4.28-4.18 (m, 2H, **2**-H_2), 4.01-3.98 (m, 1H, **7**-H), 3.79 (dq, *J* = 7.1, 2.6 Hz, 1H, **6**-H), 3.29 (dd, *J* = 13.3, 3.2 Hz, 1H, **4**-Ha), 2.81 (dd, *J* = 13.3, 9.6 Hz, 1H, **4**-Hb), 1.60-1.35 (m, 4H, **8**-H_2, **9**-H_2), 1.29 (d, *J* = 7.1 Hz, 3H, **6**-CH_3), 0.97 (t, *J* = 7.1 Hz, 3H, **10**-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (C-5), 153.0 (C-1), 135.0 (CAr), 129.4 (2 X CAr), 129.0 (2 X CAr), 127.4 (CAr), 71.2 (C-7), 66.1 (C-2), 55.1 (C-3), 42.0 (C-6), 37.8 (C-4), 35.5 (C-8), 19.2 (C-9), 14.0 (CH_3), 10.3 (CH_3); MS (ES) *m/z* 306 $[M+H]^+$; HRMS (ES) *m/z* calculated for $C_{17}H_{24}NO_4$ $[M+H]^+$ 306.1704, found 306.1712; Elem. Anal. calculated for $C_{17}H_{23}NO_4$ C 66.86 H 7.59 N 4.59, found C 66.95, H 7.49 N 4.68; $[\alpha]_D$: -53.8 (*c* 2.6, $CHCl_3$). Match the literature data.[14]

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-2-methyl-3-{[tris(propan-2-yl)silyl]oxy}hexanoyl]-1,3-oxazolidin-2-one



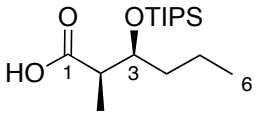
246'

To a solution of **246** (1.1 g, 3.6 mmol) and 2,6-lutidine (1 mL, 9 mmol) in CH_2Cl_2 (75 mL) at 0 °C was added TIPSOTf (1.2 mL, 4.7 mmol). The mixture was stirred for 4 h at 0 °C and quenched with water. The aqueous layer was extracted with CH_2Cl_2 (X 2) and the combined organic layer were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (10% EtOAc in hexanes) to afford **246'** (1.3 g, 78%) as a white solid.

mp = 115 ºC; IR (thin layer): 3526, 2958, 2933, 2871, 2360, 2341, 1719, 1693, 1385, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H, **Ar**-H), 4.62-4.55, (tdd, *J* = 9.8, 7.3, 2.6 Hz, 1H, **3**-H), 4.28-4.24 (m, 1H, **7**-H), 4.20-4.11 (m, 2H, **2**-H_2), 3.85 (dq, *J* = 6.9, 4.0 Hz, 1H, **6**-H), 3.33 (dd, *J* = 13.5, 2.6 Hz, 1H, **4**-Ha), 2.79 (dd, *J* = 13.5, 9.8 Hz, 1H, **4**-Hb), 1.69-1.55 (m, 2 H), 1.42-1.32 (m, 2 H), 1.24 (d, *J* = 6.9 Hz, 3H, **6**-CH_3), 1.07 (*br* s, 21 H, H-**TIPS**), 0.97 (t, *J* = 7.3 Hz, 3H, **10**-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (C-5), 153.1 (C-1), 135.4 (CAr), 129.4 (2 X CAr), 128.9 (2 X CAr), 127.3 (CAr), 73.0 (C-7), 66.0 (C-2), 55.9 (C-3), 42.5 (C-6), 38.0 (C-4), 37.0 (C-8), 18.2 (C-9), 17.7 (CTIPS), 14.4 (CH_3), 13.1(CTIPS),

10.3 (CH_3); MS (ESI) *m/z* 462 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{26}H_{44}NO_4Si$ $[M+H]^+$ 462.3040, found 462.3035; $[\alpha]_D$: -60.1 (*c* 1.5, $CHCl_3$).

(2*R*,3*S*)-2-Methyl-3-{[tris(propan-2-yl)silyl]oxy}hexanoïc acid



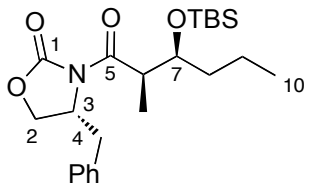
247

To a solution of LiOH (0.4 g, 10 mmol) dissolved in water (10 mL) was added H_2O_2 (2 mL, 30 wt. % in water). This mixture was added to a solution of **246'** (1.9 g, 4.1 mmol) dissolved in THF (40 mL) and the resulting mixture was stirred for 4 h at rt. The reaction was quenched by addition of aqueous Na_2SO_3 (1.3 M) and stirred for 30 min. The aqueous layer was first extracted with CH_2Cl_2 then acidified to pH = 3 with aqueous HCl (1 M) and finally (re)extracted with CH_2Cl_2 (X 3). The combined organic layers (of the 2nd extraction) were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **247** as a colourless oil (0.9 g, 70%).

IR (neat): 2942, 2867, 1706, 1462, 1385, 1234, 1137, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (dt, *J* = 10.0, 5.5 Hz, 1H, **3**-H), 2.72-2.66 (dq, *J* = 7.1, 5.5 Hz, 1H, **2**-H), 1.65-1.51 (m, 2H), 1.47-1.31 (m, 2H), 1.60 (d, *J* = 7.1 Hz, 3H, **2**-CH_3), 1.10 (s, 21H, **TIPS**-H), 0.94 (t, *J* = 7.2 Hz, 3H, **6**-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C-1), 74.1 (C-3), 43.9 (C-2), 36.0 (C-4), 18.5 (C-5), 18.1 (CTIPS), 14.2 (CH_3), 12.3

(CTIPS), 10.9 (CH_3); MS (ESI) *m/z* 301 $[M-H]^-$; HRMS (ESI) *m/z* calculated for $C_{16}H_{33}O_3Si$ $[M-H]^-$ 301.2199, found 301.2192; $[\alpha]_D$: -9.8 (*c* 2.1, $CHCl_3$).

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-3-[(*tert*-(butyldimethylsilyl)oxy]-2-methylhexanoyl]-1,3-oxazolidin-2-one



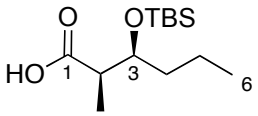
246''

To a solution of **246** (800 mg, 2.6 mmol) and 2,6-lutidine (0.8 mL, 6.5 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added TBSOTf (0.8 mL, 3.4 mmol). The mixture was stirred for 4 h at 0 °C and quenched with water. The aqueous layer was extracted with CH_2Cl_2 (X 2) and the combined organic layer were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (10% EtOAc in hexanes) to afford **246''** (850 mg, 73%) as a white solid.

mp = 110 ºC; ^{1}H NMR (400 MHz, CDCl3) δ 7.37-7.15 (m, 5H, **Ar**-H), 4.64-4.54 (m, 1H, **3**-H), 4.19-4.12 (m, 2H, **2**-H_2), 4.05-3.99 (m, 1H, **7**-H), 3.90-3.80 (m, 1H, **6**-H), 3.30 (dd, *J* = 13.4, 2.8 Hz, 1H, **4**-Ha), 2.77 (dd, *J* = 13.4, 9.5 Hz, 1H, **4**-Hb), 1.55-1.45 (m, 2H), 1.42-1.27 (m, 2H), 1.19 (d, *J* = 6.8 Hz, 3H, **6**-CH_3) 0.84-0.94 (m, 12H, **10**-H_3, **TBS**-H), 0.02 (s, 3H, **TBS**-H), 0.00 (s, 3H, **TBS**-H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 175.3 (C-5) 153.1 (C-1), 135.4 (CAr), 129.5 (2 X CAr*)*), 128.9 (2 X CAr), 127.3 (CAr), 72.7 (C-7), 66.0 (C-2), 55.8 (C-3), 42.8 (C-6), 37.8 (C-4), 37.6 (C-8), 25.8 (CTBS), 18.4 (C-9), 18.0 (CTBS), 14.4 (C-10), 11.4 (6-CH_3), -4.1 (CTBS), -4.8 (CTBS); MS (ESI) *m/z* 420 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{26}H_{44}NO_4$ $[M+H]^+$ 420.2570, found 420.2560; $[\alpha]_D$ = -58.0 (*c* 2, CH_2Cl_2). Match the literature data.[14]

(2*R*,3*S*)-3-[(*tert*-(butyldimethylsilyl)oxy]-2-methylhexanoïc acid



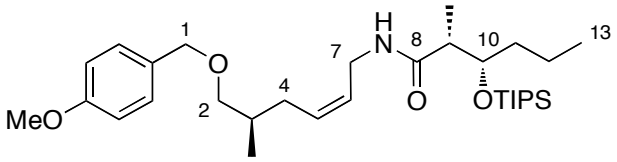
248

To a solution of LiOH (200 mg, 4.8 mmol) dissolved in water (5 mL) was added H_2O_2 (1 mL, 30 wt. % in water). This mixture was added to a solution of **246''** (800 mg, 1.9 mmol) dissolved in THF (20 mL) and the resulting mixture was stirred for 4 h at rt. The reaction was quenched by addition of aqueous Na_2SO_3 (1.3 M) and stirred for 30 min. The aqueous layer was first extracted with CH_2Cl_2, then acidified to pH = 3 with aqueous HCl (1 M) and finally extracted with CH_2Cl_2 (X 3). The combined organic layers (of the 2nd extraction) were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **248** as a colourless oil (370 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05-3.95 (dt, *J* = 10.0, 6.4 Hz, 1H, **3**-H), 2.65-2.55 (dq, *J* = 7.1, 4.3 Hz, 1H, **2**-H), 1.58-1.40 (m, 3H), 1.32-1.22 (m, 1H), 1.14 (d, *J* = 7.1

Hz, 3H, **2**-CH3), 0.98-0.88 (m, 12H, **6**-H_3, **TBS**-H), 0.08 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.8 (C-3), 44.4 (C-2), 35.8 (C-4), 25.7 (CTBS), 18.8 (C-5), 18.0 (CTBS), 14.2 (CH_3), 11.4 (CH_3), -4.4 (CTBS), -4.8 (CTBS); $[\alpha]_D$ = -19.7 (*c* 2, CH_2Cl_2). Match the literature data.[14]

(2*R*,3*S*)-*N*-[(2*Z*,5*R*)-6-[(4-Methoxyphenyl)methoxy]-5-methylhex-2-en-1-yl]-2-methyl-3-{(tris(propan-2-yl)silyloxy)hexanamide



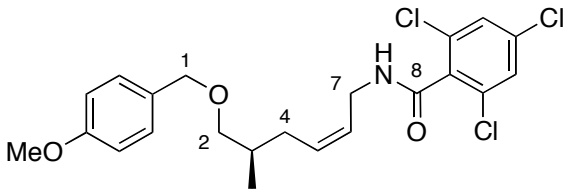
250

To a solution of **247** (80 mg, 0.26 mmol) dissolved in THF (520 μL) were added NEt_3 (36 μL, 0.26 mmol) and 2,4,6-trichlorobenzoyl chloride (**249**) (39 μL, 0.26 mmol) at 0 ºC. The mixture was allowed to reach rt and stirred for 2 h. When the starting material was consumed, amine **238** (70 mg, 0.20 mmol), NEt_3 (40 μL, 0.28 mmol) and DMAP (31 mg, 0.26 mmol) were added. After 3 h the reaction mixture was diluted with Et_2O, washed with aqueous HCl (1 M), a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography (10% EtOAc in hexanes) to afford by product **251** (46 mg) and **250** (52 mg, 35%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.1 Hz, 2H, **Ar**-H), 6.90 (d, *J* = 9.1 Hz, 2H, **Ar**-H), 5.58-5.44 (m, 2H, **5**-H, **6**-H), 4.44 (s, 2H, **1**-H_2), 3.99-3.84 (m, 3H, **2**-H_2,

10-H), 3.82 (s, 3H, O-CH_3), 3.32-3.24 (m, 2H, **7**-H_2), 2.56 (dq, *J* = 7.2, 3.5 Hz, 1H, **9**-H), 2.25-2.19 (m, 1H, **4**-Ha), 2.03-1.95 (m, 1H, **4**-Hb), 1.88-1.80 (m, 1H, **3**-H), 1.60-1.14 (m, 7H, **11**-H_2, **12**-H_2, 9-CH_3), 1.12-1.09 (m, 24H, **3**-CH_3, **TIPS**-H), 0.91 (t, *J* = 7.2 Hz, 3H, **13**-H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9 (C-8), 159.1 (CAr), 131.2 (CH), 130.7 (CAr), 129.1 (2 X CAr), 126.5 (CH), 113.5 (2 X CAr), 75.2 (CH_2), 74.9 (CH_2), 72.6 (CH), 55.2 (O-CH_3), 45.5 (C-9), 36.4 (CH_2), 35.8 (CH_2), 33.7 (CH), 31.2 (CH_2), 19.3 (CH_3), 18.2 (CTIPS), 16.8 (CH_2), 14.4 (CH_3), 12.7 (CTIPS), 12.6 (CH_3); MS (ESI) *m/z* 534 $[M+H]^+$, 556 $[M+Na]^+$; HRMS (CI) *m/z* calculated for $C_{31}H_{56}NO_4Si$ $[M+H]^+$ 534.3979, found 534.3972; $[\alpha]_D$: +4.7 (*c* 3, $CHCl_3$).

2,4,6-Trichloro-*N*-[(2*Z*, 5*R*)-6-[4-methoxyphenyl)methoxy]-5-methylhex-2-en-1-yl)benzamide

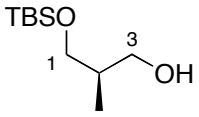


251

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 2H, **Ar**-H), 7.16 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.83 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.08 (*br* s, 1H, **N**-H), 5.66-5.57 (m, 2H, **5**-H, **6**-H), 4.35 (d, *J* = 1.6 Hz, 2H), 4.07 (t, *J* = 4.6 Hz, 2H), 3.80 (s, 3H, O-CH_3), 3.32-3.24 (m, 2H), 2.28-2.21 (m, 1H), 2.11-2.04 (m, 1H), 1.92-1.84 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 3H, **3**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (C-8), 159.1, 135.6, 134.6 (2 X CAr), 132.9, 132.4 (CH), 130.4, 129.2 (2 X CAr), 128.0 (2 X CAr), 125.3 (CH), 113.7 (2 X

CAr), 74.4, 72.6, 55.3 (O-CH_3), 36.8, 33.4, 31.1, 16.8; MS (ESI) *m/z* 456 $[M+H]^+$, 478 $[M+Na]^+$.

(2*R*)-3-[(*tert*-Butyldimethylsilyl)oxy)-2-methylpropan-1-ol



257

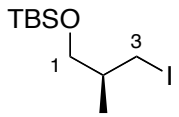
A-To a solution of imidazole (1.7 g, 25.5 mmol) and TBSCl (3.8 g, 25.5 mmol) dissolved in DMF (15 mL) was added dropwise (2*S*)-3-hydroxy-2-methyl-propionic acid methyl ester (**256**) (2.0 g, 17 mmol). The reaction mixture was stirred for 16 h at rt and then quenched by addition of water. The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was used without further purification.

B-To a solution of the previous crude product (1.3 g, 5.6 mmol) dissolved in CH_2Cl_2 (16 mL) was added dropwise DIBAL-H (1.0 M in CH_2Cl_2, 15 mL) at -40 ºC. The reaction mixture was stirred for 3 h at this temperature and was then allowed to reach rt. The reaction was quenched by addition of water followed by aqueous NaOH (10 wt. %, 50 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by silica flash chromatography

(30% Et_2O in hexanes) to give alcohol **257** as a colourless oil (0.8 mg, 70% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76-3.52 (m, 4H, **1**-H_2, **3**-H_2), 2.9 (*br* s, 1H, **O**-H), 1.96-1.90 (m, 1H, **2**-H), 0.90 (s, 9H, **TBS**-H), 0.83 (d, J = 7.0 Hz, 3H, **2**-CH_3), 0.07 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.9 (CH_2), 68.5 (CH_2), 37.0 (C-2), 25.8 (CTBS), 18.1 (CTBS), 13.1 (2-CH_3), -5.4 (CTBS). Match the literature data.[126]

tert-Butyl[(2*S*)-3-iodo-2-methylpropoxy)dimethylsilane



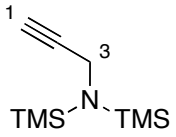
258

To a solution of I_2 (535 mg, 12.1 mmol), imidazole (204 mg, 3 mmol) and PPh_3 (533 mg, 1.4 mmol) dissolved in THF (5 mL) was added **257** (300 mg, 1.5 mmol) dissolved in THF (5 mL). The reaction mixture was stirred for 24 h at rt. The reaction mixture was concentrated under reduced pressure and the crude material was dissolved in a minimum amount of CH_2Cl_2. Pentane was added and the resulting solution was filtered off. The filtrate was concentrated under reduced pressure. The resulting mixture was dissolved in Et_2O, washed with a saturated solution of $NaHCO_3$, a saturated solution of $Na_2S_2O_3$ and brine. The organic layer were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was

purified by silica flash chromatography to afford **258** (322 mg, 68%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (dd, *J* = 9.9, 5.0 Hz, 1H, **1**-Ha), 3.39 (dd, *J* = 9.9, 6.9 Hz, 1H, **1**-Hb), 3.32 (dd, *J* = 9.5, 5.1 Hz, 1H, **3**-Ha), 3.25 (dd, *J* = 9.5, 5.6 Hz, 1H, **3**-Hb), 1.68-1.60 (m, 1H, **2**-H), 0.95 (d, *J* = 6.8 Hz, 3H, **2**-CH_3), 0.90 (s, 9H, **TBS**-H), 0.07 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.7 (C-1), 37.4 (C-2), 25.8 (CTBS), 18.3 (CTBS), 17.2 (C-3), 13.8 (2-CH_3), -5.4 (CTBS).

(Prop-2-yn-1-yl)bis(trimethylsilyl)amine

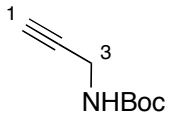


259

To a solution of propargyl amine (1.0 g, 18 mmol) dissolved in CH_2Cl_2 (30 mL) were added TMSCl (4.8 mL, 37.8 mmol) and NEt_3 (7.7 mL, 55.2 mmol). The reaction mixture was stirred at rt for 12 h and quenched by addition of brine. The aqueous layer was extracted with $CHCl_3$ (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **259** as a pale yellow oil (1.5 g, 42%). The compound was highly unstable and was used straight away.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (m, J = 2.4 Hz, 2H), 2.13 (t, J = 2.4 Hz, 1H), 0.15 (s, 18H). Match the literature data.[96]

tert-Butyl *N*-(prop-2-yn-1-yl)carbamate

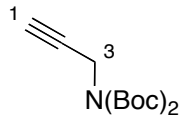


260

To a solution of propargyl amine (1.0 g, 18.2 mmol) dissolved in water (25 mL) was added $NaHCO_3$ (1.5 g, 18.2 mmol) followed by Boc_2O (4 g, 18.2 mmol) dissolved in $CHCl_3$ (35 mL). The reaction mixture was stirred for 3 h at rt and the organic layer was subsequently separated. The aqueous layer was extracted with $CHCl_3$ (X 2) and the combined organic layers were washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude solid was purified by silica flash chromatography to afford **260** as a colourless oil (2.2 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.8 (s, 2H, **3**-H_2), 2.15 (m, 1H, **1**-H), 1.45-1.35 (3s, 9H, **Boc**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 80.1, 79.9, 71.1, 28.2. Match the literature data.[97]

***tert*-Butyl *N*-[(tert-butoxy)carbonyl]-*N*-(prop-2-yn-1-yl)carbamate**

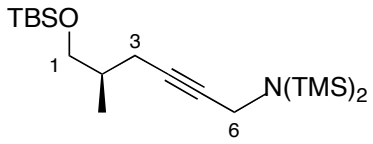


261

To a solution of **260** (250 mg, 1.6 mmol) dissolved in MeCN (5 mL) were added DMAP (195 mg, 1.6 mmol) and Boc_2O (1.05 g, 4.8 mmol). The reaction mixture was stirred for 1 h at rt and was then concentrated under reduced pressure. The crude solid was purified by silica flash chromatography (5% Et_2O in hexanes) to afford **261** (359 mg, 88%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (d, J = 2.5 Hz, 2H, **3**-H_2), 2.18 (t, J = 2.5 Hz, 1H, **1**-H), 1.53 (s, 18H, **Boc**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 82.2, 79.1, 70.2, 35.2, 27.4. Match the literature data.[98]

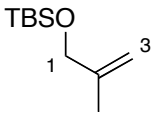
(8*R*)-2,2,8,11,11,12,12-Heptamethyl-3-(trimethylsilyl)-10-oxa-3-aza-2,11-disilatridec-5-yne



259'

To a solution of **259** (110 mg, 0.55 mmol) dissolved in THF (1 mL) was added freshly prepared LDA (1 M in THF, 0.55 mL) at -78 ºC. After 2 h, HMPA (0.1 mL) was added followed by **258** (160 mg, 0.5 mmol). The reaction mixture was slowly allowed to reach rt and was stirred for 1 h. The reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc (X 2). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material indicated no trace of desired product **259'** but the presence of by-product **262** and starting material **258**.

***tert*-Butyldimethyl[(2-methylprop-2-en-1-yl)oxy]silane**

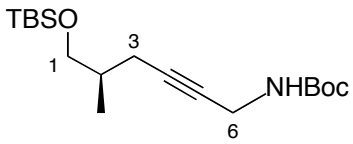


262

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (s, 1H, **3**-Ha), 4.82 (s, 1H, **3**-Hb), 4.05 (s, 2H, **1**-H), 1.72 (s, 3H, **2**-CH_3) 0.93 (s, 9H, **TBS**-H), 0.06 (s, 6H, **TBS**-H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 144.6 (C-2), 109.1 (C-3), 66.8 (C-1), 25.7 (CTBS), 18.9 (2-CH_3), 18.4 (CTBS), -5.6 (CTBS).

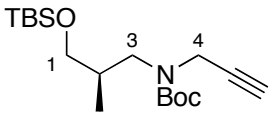
tert-Butyl _N_-[(5_R_)-6-[(_tert_-butyldimethylsilyl)oxy]-5-methylhex-2-yn-1-yl]carbamate



260'

To a solution of **260** (85 mg, 0.55 mmol) dissolved in THF (1 mL) was added freshly prepared LDA (1 M in THF, 1.1 mL) at -78 ºC. After 2 h, HMPA (0.1 mL) was added followed by **258** (160 mg, 0.5 mmol). The reaction mixture was slowly allowed to reach rt and was stirred for 1 h. The reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc (X 2). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% EtOAC in hexanes) but no desired product was isolated. Instead **263** was isolated as a mixture with by-product **262**.

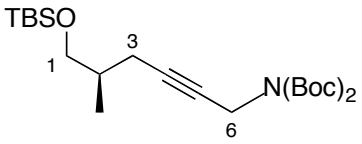
***tert*-Butyl *N*-[(2*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl]-*N*-(prop-2-yn-1-yl)carbamate**



263

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18-3.90 (m, 2H), 3.47 (d, *J* = 5.5 Hz, 2H), 3.27-3.24 (m, 2H), 2.17 (s, 1H), 2.01-1.93 (m, 1H), 1.46 (s, 9H, **Boc**-H), 0.89-0.86 (s, 9H, **TBS**-H, **2**-CH_3), 0.04 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.1, 76.8 (CBoc), 65.9, 49.5, 37.2, 28.4 (CBoc), 25.9 (CTBS), 18.3 (CTBS), 14.8 (CH_3), 5.6 (CTBS), (two missing quaternary C).

***tert*-Butyl *N*-[(*tert*-butoxy)carbonyl]-*N*-[(5*R*)-6-[(*tert*-butyldimethoxysilyl)oxy]-5-methylhex-2-yn-1-yl]carbamate**

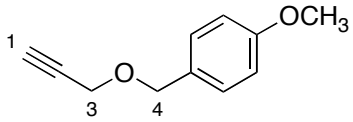


261'

To a solution of **261** (140 mg, 0.55 mmol) dissolved in THF (1 mL) was added freshly prepared LDA (1 M in THF, 0.55 mL) at -78 ºC. After 2 h, HMPA (0.1 mL) was added followed by **258** (160 mg, 0.5 mmol). The reaction mixture was slowly allowed to reach rt and was stirred for 1 h. The reaction was quenched by addition of

water. The aqueous layer was extracted with EtOAc (X 2). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material indicated the presence of by-product **262** and no trace of starting material.

1-Methoxy-4-[(prop-2-yn-1-yloxy)methyl)benzene



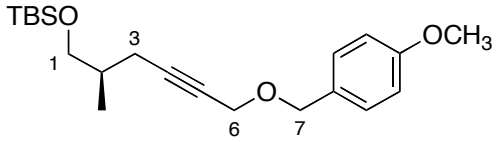
264

To a solution of propargyl alcohol (15 g, 267 mmol) dissolved in THF/DMF (400 mL, 8:2) was added NaH (60% in mineral oil, 21.5 mg, 534 mmol) at 0 °C. The reaction mixture was stirred for 1 h, then PMBCl (36.2 mL, 267 mmol) was added and the reaction mixture was stirred for 48 h. The reaction was then quenched with water. The aqueous layer was extracted with CH_2Cl_2 (X 3) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% EtOAc in hexanes) to **264** (55%, 13 g) as a colourless oil.

IR (neat): 3286, 2941, 2840, 1612, 1512, 1301, 1245, 1175, 1074, 1031, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H, **Ar**-H), 6.88 (d, *J* = 8.7 Hz, 2H, **Ar**-H), 4.55 (s, 2H, **4**-H_2), 4.14 (d, *J* = 2.4 Hz, 2H, **3**-H_2), 3.81 (s, 3H, **O**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (CAr), 129.8 (CAr), 129.3 (CAr), 113.8 (CAr),

79.8 (C), 74.5 (C), 71.1 (C-4), 56.7 (C-3), 53.4 (O-CH_3); MS (ESI) *m/z* 176 $[M-H]^-$; HRMS (ESI) *m/z* calculated for $C_{11}H_{12}O_2$ $[M+H]^+$ 176.0837, found 176.0839. Match the literature data.[127]

tert-Butyl({[(2*R*)-6-[(4-methoxyphenyl)methoxy]-2-methylhex-4-yn-1-yl]oxy})dimethylsilane



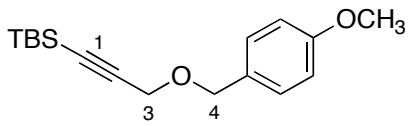
265

To a solution of **264** (205 mg, 1.15 mmol) dissolved in THF (2.5 mL) was added dropwise *n*-BuLi (2.5 M in hexanes, 0.46 mL) at 0 °C. The reaction mixture was stirred for 30 min, then HMPA (0.4 mL) was added, followed by **258** (120 mg, 0.38 mmol). The reaction mixture was slowly allowed to reach rt, was stirred for another hour and quenched by a saturated solution of NH_4Cl. The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were washed with a saturated solution of LiCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% Et_2O in hexanes) to afford a mixture of **265** and by-products **262** and **266** as a pale yellow oil (65 mg, 45%) (mass and yield calculated for **265**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.88 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 4.52 (s, 2H, **7**-H), 4.14-4.13 (m, 2H), 3.81 (s, 3H, **O**-CH_3), 3.53-3.46 (m,

2H), 2.35 (ddt, *J* = 16.4, 5.4, 3.0 Hz, 1H, **3**-Ha), 2.17 (ddt, *J* = 16.4, 7.0, 2.0 Hz, 1H, **3**-Hb), 1.90-1.79 (m, 1H, **2**-H), 0.98 (d, *J* = 6.8 Hz, 3H, **2**-CH_3), 0.93 (s, 9H, **TBS**-H), 0.06 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (CAr), 129.8 (CAr), 129.7 (2 X CAr), 113.8 (2 X CAr), 85.6 (C), 70.8, 66.8, 57.2, 55.1, 35.2, 25.7 (CTBS), 22.3, 16.8 15.9 (CTBS), -5.6 (CTBS), (one quaternary C missing); MS (CI) *m/z* 363 $[M+H]^+$, 380 $[M+NH_4]^+$.

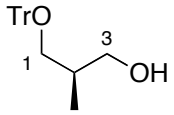
tert-Butyl({3-[(4-methoxyphenyl)methoxy)prop-1-yn-1-yl})dimethylsilane



266

^{1}H NMR δ 7.29 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.88 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 4.55 (s, 2H), 4.15 (s, 2H), 3.81 (s, 3H, **O**-CH_3), 0.96 (s, 9H, **TBS**-H), 0.13 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (CAr), 129.7 (2 X CAr), 129.3 (CAr), 113.6 (2 X CAr), 77.0 (2C), 70.9, 57.2, 55.1, 25.7 (CTBS), 16.2 (CTBS), -5.6 (CTBS).

(2*R*)-2-Methyl-3-(triphenylmethoxy)propan-1-ol



267

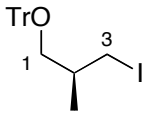
A-To a solution of trityl chloride (95 g, 339 mmol) dissolved in CH_2Cl_2 (600 mL) were added NEt_3 (52 mL, 372 mmol), DMAP (4.1 g, 33.9 mmol) and (2*S*)-3-hydroxy-2-methyl-propionic acid methyl ester (**256**) (20 g, 169 mmol). The reaction mixture was stirred for 12 h at rt and then quenched by addition of water. The aqueous layer was extracted with CH_2Cl_2 (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude ester was used without further purification.

B-To a solution of the crude ester dissolved in CH_2Cl_2 (500 mL) was added dropwise DIBAL-H (1.0 M in CH_2Cl_2, 400 mL) at -40 ºC. The reaction mixture was stirred for 3 h at this temperature and was then allowed to reach rt. The reaction was quenched by addition of water followed by aqueous NaOH (10 wt. %) and stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2 (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (30% Et_2O in hexanes) to give alcohol **267** (34 g, 60%) as white needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.40 (m, 6H, **Ar**-H), 7.37-7.18 (m, 9H, **Ar**-H), 3.70-3.51 (m, 2H), 3.24 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.03 (dd, *J* = 9.1, 5.1 Hz, 1H), 2.35-2.31 (m, **2**-H), 0.87 (d, *J* = 7.0 Hz, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 143.8 (CAr), 128.5 (CAr), 127.8 (2Ar), 127.0 (2 X CAr), 87.0, 67.8, 67.5, 35.9, 13.7; $[\alpha]_D$: +25 (*c* 2.7, CH_2Cl_2). Match the literature data.[128]

{[(2*S*)-3-Iodo-2-methylpropoxy]diphenylmethyl}benzene



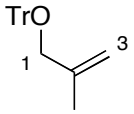
268

To a solution of I_2 (1.3 g, 5 mmol), imidazole (350 mg, 5 mmol) and PPh_3 (1.3 mg, 5 mmol) dissolved in CH_2Cl_2 (5 mL) was added **267** (300 mg, 1.5 mmol) dissolved in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 24 h at rt. The reaction mixture was concentrated under reduced pressure and the crude material was dissolved in a minimum amount of CH_2Cl_2. Pentane was added and the resulting solution was filtered and concentrated under reduced pressure. The resulting mixture was dissolved in Et_2O, washed with a saturated solution of $NaHCO_3$, a saturated solution of $Na_2S_2O_3$ and brine. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography to afford **268** (550 mg, 83%) as a yellow oil. **268** was isolated pure (TLC analysis) however due to its instability ^1H and ^{13}C show a mixture of **268** and elimination product **272**.

^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.40 (m, 6H, **Ar**-H), 7.37-7.18 (m, 9H, **Ar**-H), 3.44 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.34 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.11 (dd, *J* = 9.2,

5.1 Hz, 1H), 2.98 (dd, J = 9.2, 7.2 Hz, 1H), 1.90-1.78 (m, 1H, **2**-H), 1.00 (d, J = 6.7 Hz, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6 (CAr), 128.6 (CAr), 127.8 (2 X CAr), 127.0 (2 X CAr), 66.9, 36.0, 18.0, 13.2, (one quaternary C missing). Match the literature data.[129]

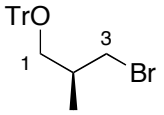
{[(2-Methylprop-2-en-1-yl)oxy]diphenylmethyl}benzene



272

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.40 (m, 6H, **Ar**-H), 7.37-7.18 (m, 9H, **Ar**-H), 5.28 (s, 1H, **3**-Ha), 4.96 (s, 1H, **3**-Hb), 3.54 (s, 2H, **1**-H), 1.74 (s, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (C-2), 142.6 (CAr), 128.7 (CAr), 127.8 (2 X CAr), 126.9 (2 X CAr), 110.2 (C-3), 67.4 (C-1), 19.9 (2-CH_3), (one quaternary C missing).

{[(2*S*)-3-Bromo-2-methylpropoxy]diphenylmethyl}benzene

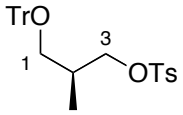


269

To a solution of NBS (0.8 mg, 4.5 mmol), and PPh_3 (1.20 g, 4.5 mmol) dissolved in CH_2Cl_2 (50 mL) was added **267** (0.5 mg, 1.5 mmol) dissolved in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 24 h at rt. The reaction mixture was concentrated under reduced pressure and the crude material was dissolved in a minimum amount of CH_2Cl_2. Pentane was added and the resulting solution was filtered and concentrated under reduced pressure. The resulting mixture was dissolved in Et_2O, washed with a saturated solution of $NaHCO_3$, a saturated solution of $Na_2S_2O_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography to afford **269** as a yellow oil (0.5 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.40 (m, 6H, **Ar**-H), 7.37-7.18 (m, 9H, **Ar**-H), 3.62 (dd, *J* = 9.8, 5.0 Hz, 2H), 3.52 (dd, *J* = 9.8, 6.2 Hz, 1H), 3.13 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.05 (dd, *J* = 9.2, 7.0 Hz, 1H), 1.37-1.29 (m, 1H, **2**-H), 1.00 (d, *J* = 6.7 Hz, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1 (CAr), 128.7 (CAr), 127.8 (2 X CAr), 127.0 (2 X CAr), 65.7, 38.4, 18.0, 16.0, (**C**(Ph_3) missing).

(2*S*)-2-Methyl-3-(triphenylmethoxy)propyl 4-methylbenzene-1-sulfonate

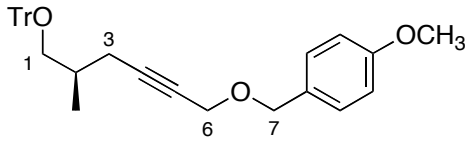


270

To a solution of TsCl (17 g, 90 mmol) dissolved in pyridine (50 mL) was added **267** (20 g, 60 mmol) in pyridine (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h. The reaction was quenched with water and stirred for 10 min in order to hydrolyse the excess of TsCl. The aqueous layer was then extracted with CH_2Cl_2 (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude solid was purified by trituration in hexanes to afford **270** as a white solid (28 g, 98%).

mp: 90-92 ºC (CH_2Cl_2/hexane); IR (neat): 2967, 2880, 1492, 1448, 1360, 1174, 976, 809, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.79 (m, 2H, **Ar**-H), 7.36-7.26 (m, 17H, **Ar**-H), 4.04 (dd, *J* = 9.0, 4.6 Hz, 1H, **3**-Ha), 4.00 (dd, *J* = 9.0, 5.2 Hz, 1H, **3**-Hb), 3.60 (dd, *J* = 10.9, 5.0 Hz, 1H, **1**-Ha), 3.03 (dd, *J* = 10.9, 6.5 Hz, 1H, **1**-Hb), 2.45 (s, 3H, CH_3), 2.04-1.970 (m, 1H, **2**-H), 0.86 (d, *J* = 7.06 Hz, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144 6 (CAr), 143.9 (CAr), 133.0 (CAr), 129.8 (CAr), 128.6 (CAr), 127.9 (CAr), 127.7 (CAr), 127.0 (CAr), 113.8 (CAr), 86.4 (C), 72.5 (CH), 64.2 (CH), 34.0 (CH), 21.7 (CH_3), 13.9 (CH_3); MS (ESI) *m/z* 509 $[M+Na]^+$, 525 $[M+K]^+$, 243 $[CPh_3]^+$; HRMS (ESI) *m/z* calculated for $C_{30}H_{30}O_4SNa$ $[M+Na]^+$ 509.1763, found 509.1743; $[\alpha]_D$: +10.0 (*c* 1.8, CH_2Cl_2).

1-Methoxy-4-({[(5*R*)-5-methyl-6-(triphenylmethoxy)hexyl]oxy}methyl)benzene



271

Procedure A

To a solution of proparylic alcohol **264** (120 mg , 0.7 mmol) dissolved in THF (1 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 0.44 mL) at -78 °C. The reaction mixture was stirred for 30 min at 0 °C, then **268** (350 mg, 7.2 mmol) dissolved in DMSO (2 mL) was added. The reaction mixture was stirred for 2 h and quenched by addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (5% Et_2O in hexanes) to afford **271** (60 mg, 20%) as a colourless oil and as the minor product. A mixture of starting material **268** and elimination product **272** was isolated too.

Procedure B

To a solution of proparylic alcohol **264** (120 mg, 0.7 mmol) dissolved in THF (1 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 0.44 mL,) at -78 °C. The reaction mixture was stirred for 30 min at 0 °C, then **269** (250 mg, 0.63 mmol) dissolved in DMSO (2 mL) was added. The reaction mixture was stirred for 2 h and quenched by addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$),

filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (5% Et_2O in hexanes) to afford **271** (35 mg, 12%) as a colourless oil and the minor product. A mixture of starting material **269** and elimination product **272** was isolated too.

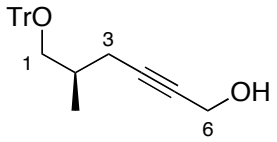
Procedure C

To a solution of proparylic alcohol **264** (17.9 g, 101 mmol) dissolved in THF (20 mL) was added dropwise *n*-BuLi (2.5 M in hexanes, 40.6 mL,) at -78 °C. The reaction mixture was stirred for 30 min at 0 °C, then **270** (26.0 g, 53 mmol) dissolved in DMSO (180 mL) was added. The reaction mixture was stirred for 2 h and quenched by addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (5% Et_2O in hexanes) to afford **271** (22.0 g, 89%) as a colourless oil.

IR (neat): 3059, 2959, 2913, 2865, 1611, 1586, 1512, 1490, 1461, 1356, 1247, 1173, 1067, 1033, 986, 819, 763, 697 cm^{-1}; ^1H NMR δ 7.44-7.42 (m, 6H, **Ar**-H), 7.30-7.21 (m, 11H, **Ar**-H), 6.91-6.82 (m, 2H, **Ar**-H), 4.50 (s, 2H, **7**-H_2), 4.14 (t, J = 2.1 Hz, 2H, **6**-H_2), 3.80 (s, 3H, **O**-CH_3), 3.03 (dd, J = 8.9, 5.5 Hz, 1H, **1**-Ha), 3.03 (dd, J = 8.9, 6.9 Hz, 1H, **1**-Hb), 2.50-2.42 (m, 1H, **3**-Ha), 2.30-2.23 (m, 1H, **3**-Hb), 2.03-1.94 (m, 1H, **2**-H), 1.01 (d, J = 6.8 Hz, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (CAr), 144.3 (CAr), 129.8 (2 X CAr), 128.8(2 X CAr), 127.7 (2 X CAr), 126.9 (2 X CAr), 113.8 (2 X CAr), 86.2 (C), 85.5 (C), 70.9 (C-7), 67.0 (C-1), 57.3 (C-6), 55.3 (O-CH_3), 33.6, 23.3, 16.8, (**C**(Ph_3) missing); MS (ESI) *m/z* 513 $[M+Na]^+$, 529

$[M+K]^+$, 243 $[CPh_3]^+$; HRMS (ESI) *m/z* calculated for $C_{34}H_{34}O_3Na$ $[M+Na]^+$ 513.2406, found 513.2414; $[\alpha]_D$: +4.3 (*c* 1, $CHCl_3$); Elem. Anal. Calculated for $C_{34}H_{34}O_3$ C 83.23, H 6.98, found C 83.17, H 6.86.

(5*R*)-5-Methyl-6-(triphenylmethoxy)hex-2-yn-1-ol

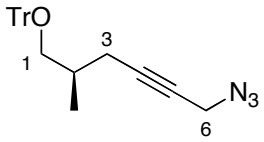


273

To a solution of **271** (400 mg, 0.82 mmol) dissolved in CH_2Cl_2/water (30 mL, 2:1) was added DDQ (374 mg, 1.63 mmol). The mixture was vigorously stirred for 3 h. Then the reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography to afford **273** (225 mg, 75%) as a white gum.

^{1}H NMR δ 7.48-7.44 (m, 6H, **Ar**-H), 7.35-7.24 (m, 9H, **Ar**-H), 4.20 (t, *J* = 2.1 Hz, 1H, **6**-Ha), 4.19 (t, *J* = 2.1 Hz, 1H, **6**-Hb), 3.09-3.00 (m, 2H, **1**-H_2), 2.44 (ddt, *J* = 16.6, 5.8, 2.1 Hz, 1H, **3**-Ha), 2.30-2.23 (ddt, *J* = 16.6, 6.9, 2.1 Hz, 1H, **3**-Hb), 2.05-2.00 (m, 1H, **2**-H), 1.02 (d, *J* = 6.8 Hz, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (CAr), 128.8 (CAr), 127.9 (CAr), 127.7 (CAr), 126.9 (2 X CAr), 86.0 (C), 79.8 (C), 66.7, 51.4, 33.5, 23.1, 16.8, (**C**(Ph_3) missing); $[\alpha]_D$: +4.3 (*c* 1, $CHCl_3$).

({[(2*R*)-6-Azido-2-methylhex-4-yn-1-yl]oxy}diphenylmethyl)benzene

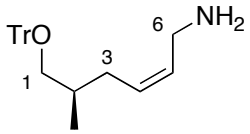


274

To a solution of **273** (400 mg, 1.08 mmol) dissolved in PhMe (4 mL) and cooled to 0 °C was added dropwise DBU (210 μL) followed by DPPA (303 μL). The reaction mixture was slowly allowed to reach rt then heated to 50 °C and stirred for 4 h. The reaction was quenched with water and the aqueous layer was extracted with EtOAC (X 2). The combined organic layers were washed with aqueous HCl (0.5 M), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% EtOAc in hexanes) to afford **274** (360 mg, 84%) as a colourless oil. This intermediate was unstable.

IR (thin layer): 3058, 2962, 2931, 2865, 2131, 1491, 1448, 1069, 901, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.44 (m, 6H, **Ar**-H), 7.35-7.24 (m, 9H, **Ar**-H), 3.86 (t, J = 2.2 Hz, 2H, **6**-H_2), 3.08 (dd, J = 8.9, 5.3 Hz, 1H, **1**-Ha), 3.02 (dd, J = 8.9, 7.0 Hz, 1H, **1**-Hb), 2.52-2.47 (m, 1H, **3**-Ha), 2.35-2.28 (m, 1H, **3**-Hb), 2.08-1.98 (m, 1H, **2**-H), 1.04 (d, J = 6.8 Hz, 3H, 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (CAr), 128.7 (CAr), 127.7 (2 X CAr), 126.9 (2 X CAr), 86.7 (C), 86.2 (C), 66.7, 40.3, 33.5, 23.0, 16.7, (**C**(Ph_3) missing).

(2*Z*,5*R*)-5-Methyl-6-(triphenylmethoxy)hex-2-en-1-amine

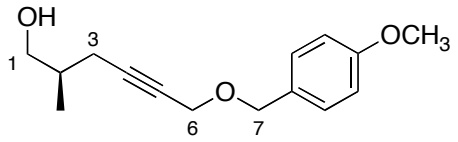


275

To a solution of **274** (80 mg, 0.2 mmol) dissolved in DMF (1 mL) were added EDA (35 μL, 0.53 mmol) and Lindlar catalyst (5 wt. % Pd on $CaCO_3$, poisoned with lead, 8 mg, 10 wt. %). The reaction was placed under H_2 atmosphere and stirred for 1 h. The reaction mixture was filtered through celite, washed with MeOH and concentrated under reduced pressure. The resulting mixture was dissolved in EtOAc and washed with water and aqueous NH_4Cl (2 wt. %). The organic layer was concentrated under reduced pressure and the crude material was purified by silica flash chromatography (10% MeOH in $CHCl_3$) to afford amine **275** (56 mg, 75%) as a colourless oil with good purity without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.44 (m, 6H, **Ar**-H), 7.35-7.24 (m, 9H, **Ar**-H), 5.50 (dt, *J* = 10.8, 6.8 Hz, 1H), 5.39 (dt, *J* = 10.8, 7.4 Hz, 1H), 3.29 (d, *J* = 6.7 Hz, 2H, **6**-H_2), 3.02 (d, *J* = 6.0 Hz, 1H, **1**-Ha), 2.97 (d, *J* = 6.0 Hz, 1H, **1**-Hb), 2.27-2.21 (m, 1H, **3**-Ha), 2.00-1.93 (m, 1H, **3**-Hb), 1.88-1.82 (m, 3H, **2**-H, **N**-H_2), 0.96 (d, *J* = 6.8 Hz, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (CAr), 131.3 (CH), 129.0 (CH), 128.8 (CAr), 127.7 (2 X .CAr), 126.8 (2 X CAr), 86.2 (C), 67.9 (C-1), 38.7 (C-6), 34.3 (C-3), 31.3 (C-2) 17.1 (2-CH_3).

(2*R*)-6-[(4-Methoxyphenyl)methoxy]-2-methylhex-4-yn-1-ol



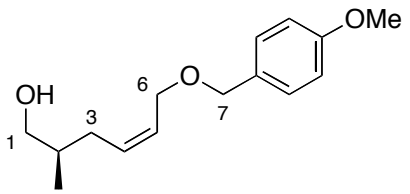
276

To a solution of **271** (23.5 g, 480 mmol) in MeOH (250 mL) was added *p*-TsOH (13.7 g, 720 mmol) at 0 °C. The mixture was allowed to reach rt and stirred for 2 h. The reaction was quenched by addition of $NaHCO_3$, stirred for 15 min, then filtered and concentrated under reduced pressure. The resulting oil was dissolved in Et_2O and the solution was washed with brine. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (15 to 20% Et_2O in hexanes) to afford **276** (8.5 g, 72%) as a colourless oil.

IR (neat): 3423, 2960, 2919, 2871, 1614, 1588, 1516, 1461, 1356, 1356, 1246, 1175, 1034, 989, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H, **Ar**-H), 6.90 (d, *J* 8.7 Hz, 2H, **Ar**-H), 4.54 (s, 2H, **7**-H_2), 4.15 (t, *J* = 2.2 Hz, 2H, **6**-H_2), 3.83 (s, 3H, **O**-CH_3), 3.60 (d, *J* = 6.1 Hz, 2H, **1**-H_2), 2.36 (ddt, *J* = 16.8, 6.2, 2.2 Hz, 1H, **3**-Ha), 2.29 (ddt, *J* = 16.8, 6.4, 2.2 Hz, 1H, **3**-Hb), 1.98-1.86 (m, 1H, **2**-H), 1.04 (d, *J* = 6.8 Hz, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (CAr), 129.7 (CAr), 128.6 (2 X CAr), 113.8 (2 X CAr), 85.0 (C), 71.0 (C-7), 67.0 (C-1), 57.3 (C-6), 55.3 (O-CH_3), 33.1 (C-2), 22.7 (C-3), 16.3 (2-CH_3); MS (CI) *m/z* 266 $[M+NH_4]^+$, HRMS (ESI) *m/z* calculated for $C_{15}H_{24}NO_3$ $[M+NH_4]^+$ 266.1756, found 266.1686; $[\alpha]_D$: +6.0

(c 1, CH_2Cl_2); Elem. Anal. Calculated for $C_{15}H_{20}O_3$ C 72.55, H 8.12, found C 72.61, H 7.96.

(2*R*,4*Z*)-6-[(4-Methoxyphenyl)methoxy]-2-methylhex-4-en-1-ol



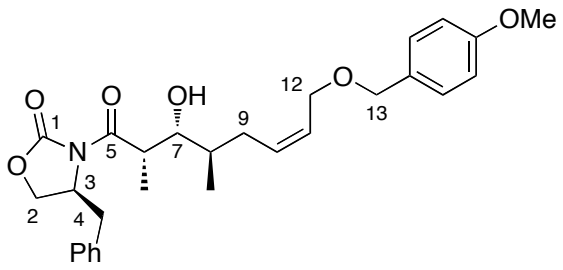
277

To a solution of **276** (13.5 g, 54 mmol) dissolved in EtOAc (150 mL) were added quinoline (11 mL, 6.6 mmol) and Lindlar catalyst (5 wt. % Pd on $CaCO_3$, poisoned with lead, 130 mg, 10 wt. %). The reaction was placed under a H_2 atmosphere and stirred for 2 h. The reaction mixture was filtered through celite and the resulting solution was washed with aqueous HCl (1 M). The organic layer was concentrated under reduced pressure and the crude material was purified by silica flash chromatography (short pad, 20% EtOAc in hexanes) to afford **277** (12.2 g, 90%, less than 5% of *E* isomere by ^{1}H NMR) as a colourless oil.

IR (neat): 3423, 3019, 2960, 2959, 2933, 2913, 2875, 2833, 1614, 1590, 1515, 1464, 1356, 1303, 1248, 1178, 1080, 1034, 986, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.9 Hz, 2H, **Ar**-H), 6.88 (d, J = 8.9 Hz, 2H, **Ar**-H), 5.73-5.61 (m, 2H), 4.45 (s, 2H, **7**-H_2), 4.07-3.97 (m, 2H, **6**-H_2), 3.80 (s, 3H, **O**-CH_3), 3.51-3.41 (m, 2H, **1**-H_2), 2.21-2.14 (m, 1H, **3**-Ha), 2.04-1.97 (m, 1H, **3**-Hb), 1.77-1.69 (m, 1H, **2**-H),

0.93 (d, J = 6.8 Hz, 3H, **2**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (CAr), 132.5 (CH), 129.5 (CAr), 126.96 (CH), 113.8 (CAr), 72.1 (C-7), 67.0 (C-1), 65.1 (C-6), 55.3 (O-CH_3), 35.8 (C-2), 31.0 (C-3), 16.5 (2-CH_3); MS (ESI) *m/z* 251 $[M+H]^+$, HRMS (ESI) *m/z* calculated for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1643; $[\alpha]_D$: -2.0 (*c* 1.1, CH_2Cl_2); Elem. Anal. Calculated for $C_{15}H_{22}O_3$ C 71.97, H 8.86, found C 72.89 H 8.73.

(*4*S)-4-Benzyl-3-[(2*S*,3*R*,4*R*,6*Z*)-3-hydroxy-8-[(4-methoxyphenyl)methoxy]-2,4-dimethyloct-6-enoyl]-1,3-oxazolidin-2-one



278

A-To a solution of oxalyl chloride (7.6 mL, 89.6 mmol) in CH_2Cl_2 (200 mL) was added DMSO (11.2 mL, 157 mmol) at -78 °C. The mixture was stirred 20 min, then **277** (11.2 g, 44.8 mmol) dissolved in CH_2Cl_2 (40 mL) was slowly added. The mixture was stirred 45 min then NEt_3 (30.0 mL, 179 mmol) was added. The mixture was slowly allowed to reach 0 °C and quenched by addition of a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (X 3) and the combined organic layers were washed with a saturated solution of $CuSO_4$, brine and water, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude

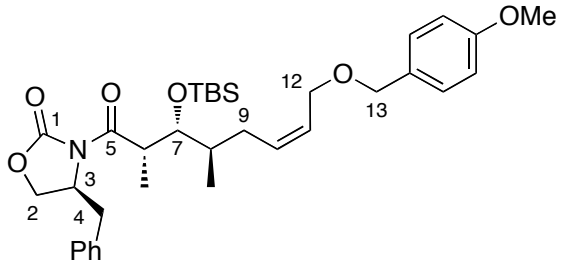
aldehyde (11.0 g, 100%) which was used immediately without any further purification.

B-To a solution of ***ent*-42** (11.5 g, 49.2 mmol) in CH_2Cl_2 (100 mL) was added Bu_2BOTf (40 mL, 1 M) followed by *i*-Pr_2NEt (7 mL, 40.3 mmol) at -78 °C. The mixture was stirred at rt for 1 h. At -78 °C was slowly added previous aldehyde (11.0 g, 44.8 mmol) dissolved in CH_2Cl_2 (10 mL). The mixture was stirred for 3 h at -78 °C then slowly warmed up to -20 °C. The mixture was poured into a saturated solution of $NaHCO_3$. Aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (20 to 40% EtOAc in hexane) to afford **279** (15.7 g, 73% yield over two steps, *dr* = 96:4 by ^{1}H NMR of the crude material) as a colourless oil.

IR (neat): 3529, 2969, 2935, 2865, 1776, 1693, 1612, 1585, 1512, 1454, 1384, 1351, 1241, 1208, 1075, 1032, 983, 819, 750, 701 cm^{-1}; ^{1}H NMR δ 7.39-7.22 (m, 7H, **Ar**-H), 6.90 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 5.75-5.64 (m, 2H), 4.72-4.66 (m, 1H, **3**-H), 4.47 (s, 2H, **13**-H_2), 4.22-4.20 (m, 2H, **2**-H_2), 4.15-4.05 (m, 2H, **12**-H_2), 4.00-3.93 (m, 1H, **6**-H), 3.82 (s, 3H, **O**-CH_3), 3.68-3.65 (m, 1H,**7**-H), 3.28 (dd, *J* = 13.4, 3.3 Hz, 1H, **4**-Ha), 2.82 (dd, *J* = 13.4, 9.5 Hz, 1H, **4**-Hb), 2.45-2.39 (m, 1H, **9**-Ha), 2.20-2.13 (m, 1H, **9**-Hb), 1.78-1.69 (m, 1H, **8**-H), 1.26 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C-5), 159.1 (CAr), 152.8 (C-1), 135.0 (CAr), 131.5 (CH), 130.4 (CAr), 129.4 (3CAr), 128.9 (2 X CAr), 127.7 (CH), 127.4 (2 X CAr), 113.7 (2 X CAr), 74.3 (C-7), 71.9 (C-13), 66.1 (C-2), 65.5 (C-12), 55.2 (C-3), 55.1 (O-CH_3), 39.4 (C-6), 37.7 (C-4), 35.8 (C-8), 30.7 (C-9), 15.3 (CH_3), 9.5 (CH_3); MS (ESI) *m/z* 482 $[M+H]^+$, 504 $[M+Na]^+$, 520 $[M+K]^+$; HRMS (ESI) *m/z*

calculated for $C_{28}H_{36}NO_6$ $[M+H]^+$ 482.2543, found 482.2535; $[\alpha]_D$: +27.5 (*c* 2.3, CH_2Cl_2); Elem. Anal. Calculated for $C_{28}H_{35}NO_6$ C 69.83, H 7.33, found C 69.98, H 7.50.

(*4*S)-4-Benzyl-3-[(2*S*,3*R*,4*R*,6*Z*)-3-[(*tert*-butyldimethylsilyl)oxy]-8-[(4-methoxyphenyl)methoxy]-2,4-dimethyloct-6-enoyl]-1,3-oxazolidin-2-one



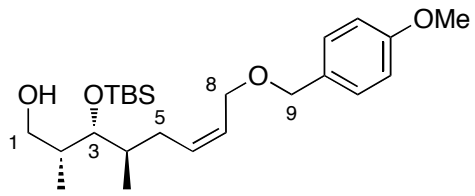
278'

To a solution of **278** (11.3 g, 23.5 mmol) in CH_2Cl_2 (150 mL) at 0 °C was slowly added *i*-Pr_2NEt (16.4 mL, 94 mmol) followed by TBSOTf (11 mL, 47 mmol). The reaction mixture was stirred for 3 h at 0 °C and poured into a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layer were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% EtOAC in hexanes) to afford the **278'** (12.7 g, 91%) as a colourless oil.

IR (neat): 2961, 2927, 2855, 1781, 1696, 1612, 1513, 1463, 1381, 1351, 1249, 1210, 1085, 1036, 971, 836, 774, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 7H, **Ar**-H), 6.87 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 5.66-5.53 (m, 2H), 4.62-4.56 (m, 1H,

3-H), 4.42 (s, 2H, **13**-H_2), 4.16-3.97 (m, 6H, **2**-H_2, **6**-H, **7**-H, **12**-H_2,), 3.82 (s, 3H, **O**-CH_3), 3.25 (dd, *J* = 13.3, 3.2 Hz, 1H, **4**-Ha), 2.75 (dd, *J* = 13.3, 9.6 Hz, 1H, **4**-Hb), 2.24-2.18 (m, 1H, **9**-Ha), 1.85-1.77 (m, 1H, **9**-Hb), 1.67-1.59 (m, 1H, **8**-H), 1.24 (d, *J* = 6.5 Hz, 3H), 0.95-0.93 (m, 12H), 0.07 (s, 3H, **TBS**-H), 0.05 (s, 3H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (C-5), 159.1 (CAr), 152.9 (C-1), 135.2 (CAr), 132.3 (CH), 130.4 (CAr), 129.4 (CAr), 129.3 (CAr), 128.9 (CH), 127.3 (CAr), 113.7 (CAr), 76.3 (C-7), 71.8 (C-13), 66.0 (C-2), 65.6 (C-12), 55.6 (C-3), 55.2 (O-CH_3), 41.3 (C-6), 39.2 (C-8), 37.6 (C-4), 30.0 (C-9), 26.1 (CTBS), 18.3 (CTBS), 16.3 (CH_3), 13.9 (CH_3), -3.6 (CTBS), -4.0 (CTBS); MS (ESI) *m/z* 596 $[M+H]^+$, 618 $[M+Na]^+$, 634 $[M+K]^+$; HRMS (ESI) *m/z* calculated for $C_{34}H_{50}NO_6Si$ $[M+H]^+$ 596.3407, found 596.3417; $[\alpha]_D$: +52.1 (0.6, CH_2Cl_2); Elem. Anal. Calculated for $C_{34}H_{49}NO_6Si$ C 68.54, H 8.29, N 2.35, found C 68.58, H 8.18, N 2.29.

(2*R*,3*R*,4*R*,6*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-8-[(4-methoxyphenyl)methoxy]-2,4-dimethyloct-6-en-1-ol



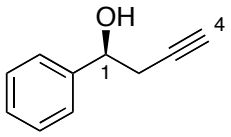
279

To a solution of **278'** (9.0 g, 15.1 mmol) in CH_2Cl_2/MeOH (100mL, 10:1) was added $LiBH_4$ (0.7 g, 30 mmol) at 0 °C. The reaction was stirred 15 min at 0 °C and 2 h at rt. The mixture was quenched by addition of a saturated solution of NH_4Cl and the

aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (20% EtOAc in hexanes) to afford the alcohol **279** (3.8 g, 63%) as a colourless oil.

IR (neat): 3939, 2955, 2927, 2855, 1613, 1513, 1463, 1381, 1302, 1249, 1172, 1092, 1037, 836, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.9 Hz, 2H, **Ar**-H), 6.87 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 5.69-5.55 (m, 2H), 4.44 (s, 2H, **9**-H_2), 4.09-3.94 (m, 2H, **8**-H_2), 3.80 (s, 3H, **O**-CH_3), 3.68 (dd, *J* = 5.2, 2.2 Hz, 1H, **3**-H), 3.51-3.36 (m, 2H, **1**-H_2), 2.28-2.21 (m, 1H, **5**-Ha), 1.91-1.69 (m, 3H, **5**-Hb, **1**-H_2), 0.90-0.83 (m, 15H, **2**-CH_3, **4**-CH_3, **TBS**-H), 0.07 (s, 3H, **TBS**-H), 0.05 (s, 3H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (CAr), 132.3 (CH), 130.4 (CAr), 129.4 (2 X CAr), 126.7 (CH), 113.7 (2 X CAr), 75.4 (C-3), 72.1 (C-9), 66.3 (C-1), 65.5 (C-8), 55.3 (O-CH_3), 38.2 (C-4), 38.1 (C-2), 31.3 (C-5), 26.1 (CTBS), 18.3 (CTBS), 16.5 (CH_3), 11.8 (CH_3), -4.0 (CTBS), -4.3 (CTBS); MS (ESI) *m/z* 423 $[M+H]^+$, 445 $[M+Na]^+$, 461 $[M+K]^+$; HRMS (ESI) *m/z* calculated for $C_{24}H_{43}O_6Si$ $[M+H]^+$ 423.2931, found 423.2936; $[\alpha]_D$: -5.2 (*c* 0.6, CH_2Cl_2); Elem. Anal. Calculated for $C_{24}H_{42}O_4Si$ C 68.20, H 10.02, found C 68.20, H 9.88.

(1*S*)-1-phenylbut-3-yn-1-ol

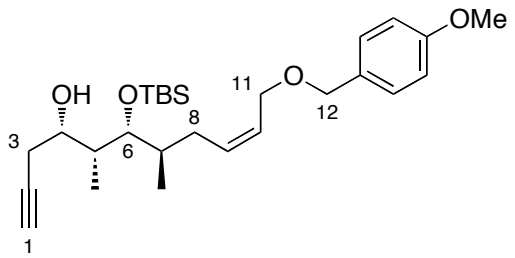


286

To a suspension of In(0) (0.58 g, 5 mmol), chiral auxiliary **297** (1.08 mg, 5 mmol) and pyridine (400 μL, 5 mmol) in THF (30 mL) under argon at rt was slowly added propargyl bromide (600 μL, 5 mmol). The cloudy suspension was stirred for 30 min. Benzaldehyde (**295**) (250 μL, 2.5 mmol) was added dropwise at -78 °C and the reaction was stirred for 24 h, then 5 h during a slow warming to rt. The reaction mixture was then quenched with aqueous HCl (1 M). The aqueous layer was extracted with EtOAc/hexanes (1:1) (X 3) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. ^{1}H NMR of the crude material revealed 80% of conversion. The crude oil was purified by silica flash chromatography (10% EtOAc in hexanes) to afford **286** as a colourless oil. (Optical rotation comparison indicated *ee* = 83%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H, **Ar**-H), 4.84 (t, *J* = 6.5 Hz, 1H, **1**-H), 2.62 (dd, *J* = 6.5, 2.5 Hz, 2H, **2**-H), 2.49 (*br* s, 1H, **O**-H), 2.05 (t, *J* = 2.7 Hz, 1H, **4**-H); ^{13}C NMR (100 MHz, C_6D_6) δ 141.8 128.1, 127.5, 125.6, 80.5, 72.2, 69.8, 29.0; $[\alpha]_D$: -9.9 (*c* 1.5, MeOH) [lit[30] (*R*)-enantiomer, $[\alpha]_D$: +11.18 (*c* 1.7, MeOH, 93% *ee*)]. Match the literature data[30]

(4*S*,5*R*,6*R*,7*R*,9*Z*)-6-[(*tert*-Butyldimethylsilyl)oxy]-11-[(4-methoxyphenyl)methoxy]-5,7-dimethylundec-9-en-1-yn-4-ol



307

A-To a solution of oxalyl chloride (1.5 mL, 18 mmol) in CH_2Cl_2 (60 mL) was added DMSO (2.2 mL, 32 mmol) at -78 °C. The mixture was stirred 20 min, then **279** (3.8 g, 9 mmol) dissolved in CH_2Cl_2 (5 mL) was slowly added. The mixture was stirred 45 min then NEt_3 (750 µL, 4.4 mmol) was added. The mixture was slowly allowed to reach 0 °C then quenched by addition of a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (X 3) and the combined organic layers were washed with a saturated solution of $CuSO_4$, brine, water, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude aldehyde (3.6 g, 95%), which was used without any further purification (the crude material was divided into 2 batches for the next step)

B-To a suspension of In(0) (1.5 g, 3.07 mmol) in THF (25 mL), were added chiral auxiliary **297** (2.8 mg, 13 mmol), pyridine (1.0 mL, 13 mmol) and propargyl bromide (80 wt. % in PhMe, 1.4 mL, 13 mmol) at -20 °C. The mixture was stirred for 45 min then the crude aldehyde (1.8 g, 4.3 mmol) was added. The reaction mixture was stirred for 16 h. The mixture was then slowly allowed to reach rt and quenched with an aqueous HCl (1 M). The aqueous layer was extracted with 1:1 EtOAc/hexanes

(X 2) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% EtOAc in hexanes) to afford a mixture of **307** and **308** (1:10, 1.5 g, 75%) as a colourless oil. ^{1}H NMR and mosher ester analysis showed the presence of one diastereoisomer (*dr* ≥ 97:3). Two batches = 3g.

IR (neat): 3450, 3304, 2955, 2930, 2856, 1686, 1613, 1513, 1463, 1302, 1249, 1173, 1086, 1034, 836, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.88 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 5.68-5.54 (m, 2H), 4.44 (s, 2H, **12**-H_2), 4.04 (d, *J* = 6.0 Hz, 2H, **11**-H_2), 3.81-3.76 (s, 4H, **4**-H, **O**-CH_3), 3.66 (dd, *J* = 4.6, 2.6 Hz, 1H, **6**-H), 2.38 (dd, *J* = 6.5, 2.6 Hz, 2H, **3**-H_2), 2.19 2.12 (m, 1H, **8**-Ha), 2.01 (t, *J* = 2.62 Hz, 1H, **1**-H), 1.89 1.87 (m, 2H, **8**-Hb, **5**-H**)**, 1.78 1.71 (m, 1H, **7**-H), 0.94-0.89 (m, 15H, **5**-CH_3, **7**-CH_3, **TBS**-H), 0.08 (s, 3H, **TBS**-H), 0.06 (s, 3H, **TBS**-H), (Allene 10%, characteristic peaks δ 5.20-5.18 (m, 2H), 4.86 (dt, *J* = 6.5, 2.2 Hz, 1H)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (CAr), 132.3 (CH), 130.4 (CAr), 129.4 (2 X CAr), 127.2 (CH), 113.8 (2 X CAr), 81.2 (C-2), 77.9 (C-6), 72.9 (C-4), 71.9 (C-12), 70.5 (C-1), 65.6 (C-11), 55.3 (O-CH_3), 38.2 (C-7), 38.1 (C-5), 31.0 (C-8), 26.0 (CTBS), 25.0 (C-3), 18.3 (CTBS), 16.0 (CH_3), 8.81 (CH_3), -3.5 (CTBS), -4.2 (CTBS); MS (ESI) *m/z* 461 $[M+H]^+$, 483 $[M+Na]^+$, 499 $[M+K]^+$; HRMS (ESI) *m/z* calculated for $C_{27}H_{45}O_4S_i$ $[M+H]^+$ 461.3087, found 461.3085; $[\alpha]_D$: -8.5 (*c* 0.8, CH_2Cl_2); Elem. Anal. Calculated for $C_{27}H_{44}O_4Si$ C 70.39, H 9.63, found C 72.46, H 9.57.

*Preparation of the (S)- and (R)-MTPA-esters of **307***[130]

To a solution of **307** (50 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) were added EDC (65 mg, 0.34 mmol), (*S*)-MTPA-OH (80 mg, 0.34 mmol) and DMAP (42 mg, 0.34 mmol). The reaction was stirred for 48 h and quenched by addition of water. The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography (5% Et_2O in hexanes) to give the (*S*)-MPTA-ester of **307** (30 mg, 40%) as a white solid.

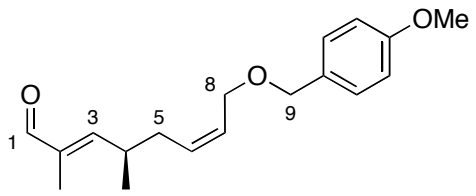
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.53 (m, 2H), 7.42-7.40 (m, 3H), 7.26 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 5.68-5.61 (m, 1H), 5.59-5.53 (m, 1H), 5.16 (dd, *J* = 5.8 Hz, 1H), 4.43 (s, 2H), 4.04 (d, *J* = 6.2 Hz, 1H), 3.80 (s, 3H), 3.50 (s, 3H), 3.40 (t, *J* = 4.7 Hz, 1H), 2.65-2.54 (m, 2H), 2.23-2.14 (m, 2H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.88-1.82 (m, 1H), 1.74-1.67 (m, 1H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H).

In an entirely analogous fashion, the (*R*)-MPTA-ester of **307** was prepared using (*R*)-MPTA-OH.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.58 (m, 2H), 7.42-7.40 (m, 3H), 7.28 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 5.69-5.63 (m, 1H), 5.59-5.52 (m, 1H), 5.19-5.15 (m, 1H), 4.45 (s, 2H), 4.05 (d, *J* = 6.2 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 3.35 (t, *J* = 4.7 Hz, 1H), 2.70 (ddd, *J* = 7.5, 2.5, 2.5 Hz, 1H), 2.62 (ddd, *J* = 7.5, 2.7, 2.7 Hz, 1H), 2.20-2.13 (m, 2H), 2.02 (t, *J* = 2.4 Hz, 1H), 1.84-1.78 (m, 1H), 1.68-1.65

(m, 1H), 0.90 (s, 9H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

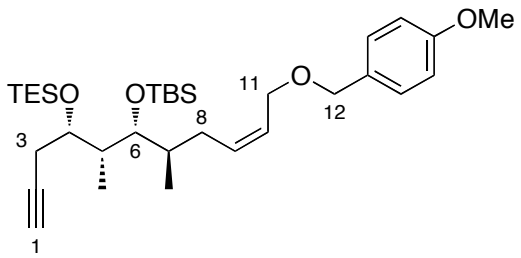
(4*R*,6*Z*)-8-[(4-Methoxyphenyl)methoxy]-2,4-dimethylocta-2,6-dienal



309

IR (neat): 3466, 2952, 2929, 2866, 1727, 1659, 1616, 1512, 1464, 1381, 1252, 1039, 885, 834, 773, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H **1**-H), 7.26 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.88 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.24 (dd, *J* = 9.9, 1.3 Hz, 1H, **3**-H), 5.70-5.54 (m, 1H), 5.55-5.48 (m, 1H), 4.44 (s, 2H, **9**-H_2), 4.02 (d, *J* = 6.4 Hz, 2H, **8**-H_2), 3.81 (s, 4H, **O**-CH_3), 2.81-2.71 (m, 1H, **4**-H), 2.24-2.09 (m, 2H, **5**-H), 1.74 (d, *J* = 1.3 Hz, 3H, **2**-CH_3), 1.08 (d, *J* = 6.6 Hz, **4**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4 (C-1), 159.2 (CAr), 158.9 (C-2), 138.3 (CH), 130.3 (CH), 130.1 (CAr), 129.4 (2 X CAr), 128.2 (CAr), 113.8 (2 X CAr), 71.9 (C-8), 65.3 (C-9), 55.3 (O-CH_3), 34.2 (C-4), 33.7 (C-5), 19.3 (2-CH_3), 9.4 (4-CH_3).

(5*R*,6*R*,7*S*)-9,9-Diethyl-5-[(2*R*,4*Z*)-6-[(4-methoxyphenyl)methoxy]hex-4-en-2-yl]-2,2,3,3,6-pentamethyl-7-(prop-2-yn-1-yl)-4,8-dioxa-3,9-disilaundecane



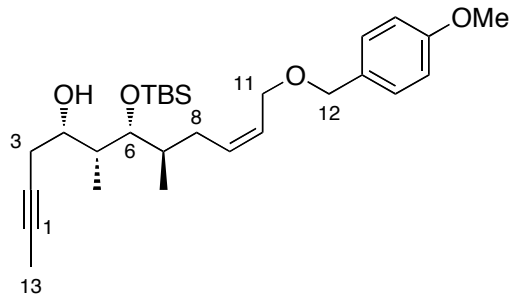
310

To a solution of **307** (110 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) was added *i*-Pr_2NEt (170 µL, 0.96 mmol) followed by TESOTf (75 µL, 0.5 mmol) at 0 °C. The reaction was stirred for 2 h then was quenched by addition of a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (X 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% Et_2O in hexanes) to afford **310** (108 mg, 79%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.88 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 5.67-5.55 (m, 2H), 4.44 (s, 2H, **12**-H_2), 4.06 (d, *J* = 5.8 Hz, 2H, **11**-H_2), 3.81-3.76 (m, 4H, **4**-H, **O**-CH_3), 3.54 (dd, *J* = 5.3, 4.0 Hz, 1H, **6**-H), 2.40 (ddd, *J* = 17.0, 6.5, 2.7 Hz, 2H, **3**-Ha), 2.37 (ddd, *J* = 17.0, 5.0, 2.7 Hz, 2H, **3b**-H), 2.23-2.18 (m, 1H, **8**-Ha), 2.00-1.85 (m, 3H, **8**-Hb, **5**-H, **1**-H**)**, 1.73-1.65 (m, 1H, **7**-H), 0.99-0.89 (m, 25H, **5**-CH_3, **7**-CH_3, **TES**-H, **TBS**-H), 0.65-0.59 (m, 6H, **TES**-H), 0.05 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (CAr), 132.6 (CH), 130.5(CAr), 129.3 (2 X CAr), 127.1 (CH), 113.8 (2 X CAr), 81.4 (C-2), 76.5 (C-6),

72.0 (C-4), 71.9 (C-12), 70.4 (C-1), 65.6 (C-11), 55.2 (O-CH_3), 40.4 (C-7), 38.0 (C-5), 29.7 (C-8), 26.2 (CTBS), 25.5 (C-3), 18.5 (CTBS), 16.9 (7-CH_3), 10.3 (5-CH_3), 6.9 (CTES), 5.1 (CTES), -3.5 (CTBS); MS (ESI) *m/z* 575 $[M+H]^+$, 592 $[M+H_2O]^+$, 597 $[M+Na]^+$, 613 $[M+K]^+$; HRMS (ESI) *m/z* calculated for $C_{33}H_{59}O_4Si_2$ $[M+H]^+$ 575.3952, found 575.3962; $[\alpha]_D$: -8.5 (*c* 0.5, $CHCl_3$).

(5*S*,6*R*,7*R*,8*R*,10*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-12-[(4-methoxyphenyl)methoxy]-6,8-dimethyldodec-10-en-2-yn-5-ol



312

Procedure A

To a solution of **310** (100 mg, 0.17 mmol) dissolved in THF (2 mL) was added *n*-BuLi (2.5 M in hexanes, 83 µL,) followed by MeI (32 µL, 0.5 mmol) at -78 °C. The solution was stirred at rt for 2 h, then poured into a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was then redissolved in *i*-PrOH (2 mL) and H_2SiF_6 (25 wt. % in water, 32 µL) was added at 0 °C. The reaction was slowly allowed to reach rt and stirred for 30 min. Then the reaction was poured into water. The organic layer was

dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% EtOAc in hexane) to afford **312** (35 mg, 42%) as a colourless oil.

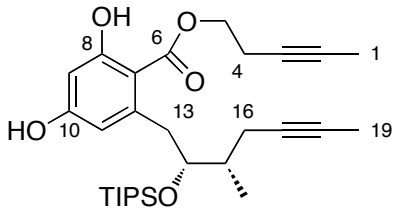
Procedure B

To a solution of **307** (1.7 g, 3.7 mmol) dissolved in THF (3 mL) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 3.0 mL) followed by MeI (1.2 mL, 18.5 mmol). The solution was stirred at rt for 2 h, then poured into a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (X 2). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% Et_2O in hexanes) to afford **312** (1.0 g, 60%) as a colourless oil.

IR (neat): 3450, 2956, 2928, 2855, 1613, 1513, 1463, 1302, 1249, 1173, 1086, 1034, 836, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H, **Ar**-H), 6.88 (d, J = 8.6 Hz, 2H, **Ar**-H), 5.68 5.55 (m, 2H), 4.44 (s, 2H, **12**-H_2), 4.04 (d, J = 5.8 Hz, 2H, **11**-H_2), 3.81 (s, 3H, **O**-CH_3), 3.70 (m, 1H, **4**-H), 3.63 (dd, J = 4.6, 3.4 Hz, 1H, **6**-H), 2.34-2.31 (m, 2H, **3**-H_2), 2.20-2.14 (m, 1H, **8**-Ha), 1.91-1.81 (m, 2H, **8**-Hb, **5**-H**)**, 1.75-1.70 (m, 4H, **7**-H, **1**-CH_3), 0.94-0.88 (m, 15H, **5**-CH_3, **7**-CH_3, **TBS**-H), 0.07 (s, 3H, **TBS**-H), 0.06 (s, 3H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (CAr), 132.4 (CH), 130.4 (CAr), 129.4 (2 X CAr), 127.2 (CH), 113.8 (2 X CAr), 78.1 (C-2), 77.8 (C-6), 75.6 (C-1), 72.9 (C-4), 71.9 (C-12), 65.6 (C-11), 55.3 (O-CH_3), 39.3 (C-7), 38.7 (C-5), 30.8 (C-8), 26.1 (CTBS), 25.5 (C-3), 18.4 (CTBS), 16.2 (CH_3), 9.1 (CH_3), 3.5 (1-CH_3), -3.5 (CTBS), -4.1 (CTBS); MS (ESI) *m/z* 475 $[M+H]^+$, 497 $[M+Na]^+$, 513 $[M+K]^+$; HRMS (ESI) *m/z* calculated for $C_{28}H_{47}O_4S_i$ $[M+H]^+$

475.3244, found 475.3245; $[\alpha]_D$: -9.5 (0.4, $CHCl_3$); Elem. Anal. Calculated for $C_{27}H_{44}O_4Si$ C 70.84, H 9.77, found C 70.96, H 9.69.

Pent-3-yn-1-yl 2,4-dihydroxy-6-[(2*R*,3*S*)-3-methyl-2-{[tris(propan-2-yl)silyl]oxy}hept-5-yn-1-yl]benzoate



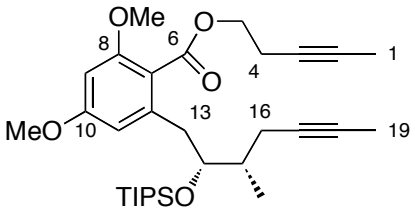
314

To a solution of **215** (180 mg, 0.3 mmol) in PhMe (3.5 mL) was added 3-pentyn-1-ol (**313**) (55 μL, 0.3 mmol). The mixture was stirred at reflux for 30 min and was then concentrated under reduced pressure. The resulting yellow oil was dissolved in MeOH (3.5 mL) and treated with Cs_2CO_3 (200 mg, 0.6 mmol). The resulting mixture was stirred for 1 h then AcOH (63 μL, 1.1 mmol) was added and was stirred for further 10 min. Water and EtOAc were added and the aqueous layer was extracted with EtOAc (X 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified by silica flash chromatography to afford **314** (105 mg, 67%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H, **8**-OH), 6.32-6.30 (m, 2H, Ar-H), 5.20 (s, 1H, **10**-OH), 4.54 (dt, *J* = 10.6, 6.7 Hz, 1H, **5**-Ha), 4.38 (dt, *J* = 10.6, 7.1 Hz, 1H, **5**-Hb) 4.20 (dt, *J* = 9.5, 2.8, 1H, **14**-H), 3.27 (dd, *J* = 13.2, 2.8 Hz, 1H, **13**-Ha), 2.73

(dd, *J* = 13.2, 9.5 Hz, 1H, **13**-Hb), 2.62-2.47 (m, 2H, 4-H_2), 2.22-2.08 (m, 2H, **16**-H_2), 2.00-1.94 (m, 1H, **15**-H), 1.78-1.76 (m, 6H, **1**-H_3, **19**-H_3), 1.04 (d, *J* = 6.8 Hz, 3H, **15**-CH_3), 0.96-0.88 (s, 21H, **TIPS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (C-6), 164.9, 159.8, 145.5, 113.4, 106.1, 101.6, 78.2, 77.9, 75.5, 74.8 (2 X C) 63.5, 39.9, 37.6, 22.6, 19.4, 18.1 (CTIPS), 14.4, 13.1 (CTIPS), 3.4 (2 X C); MS (ESI) *m/z* 501 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{29}H_{45}O_5Si$ $[M+H]^+$ 501.3036, found 501.3029; $[\alpha]_D$: +4.5 (*c* 0.5, $CHCl_3$).

Pent-3-yn-1-yl 2,4-dimethoxy-6-[(2*R*,3*S*)-3-methyl-2-{[tris(propan-2-yl)silyl]oxy}hept-5-yn-1-yl]benzoate

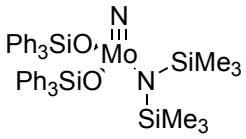


326

To a solution of **314** (100 mg, 0.2 mmol) in acetone (15 mL) was added K_2CO_3 (672 mg, 4.8 mmol) followed by MeI (500 μL, 8 mmol). The resulting mixture was stirred for 6 h. The reaction was quenched by addition of water and the aqueous layer was extracted with EtOAc (X 2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (10% Et_2O in hexanes) to afford **326** (70 mg, 67%) as a colourless oil.

IR (neat): 2940, 2922, 2865, 1724, 1599, 1459, 1422, 1327, 1267, 1203, 1157, 1091, 1047, 883, 830, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (d, *J* = 2.1 Hz, 1H, Ar-H), 6.34 (d, *J* = 2.1 Hz, 1H, Ar-H), 4.44-4.31 (m, 2H, **5**-H_2), 4.19 (ddd, *J* = 7.5, 4.6, 3.2 Hz, 1H, **14**-H), 3.82 (s, 3H, **O**-CH_3), 3.80 (s, 3H, **O**-CH_3), 2.84 (dd, *J* = 13.8, 4.6 Hz, 1H, **13**-Ha), 2.64-2.54 (m, 3H, **13**-Hb, **4**-H_2), 2.21-2.03 (m, 2H, **16**-H_2), 1.94-1.84 (m, 1H, **15**-H), 1.82-1.80 (m, 6H, **1**-H_3, **19**-H_3), 1.03-0.99 (m, 24H, **TIPS**-H, **14**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 160.9, 158.2, 139.7, 117.0, 107.5, 96.9, 78.2, 77.3, 76.4, 75.6, 74.8, 63.4, 56.0, 55.3, 38.7, 36.6, 21.8, 19.2, 18.1 (CTIPS), 14.7, 12.9 (CTIPS), 3.4 (2 X C); MS (ESI) *m/z* 529 $[M+H]^+$ 551 $[M+Na]^+$ 567 $[M+K]^+$; HRMS (ESI) *m/z* calculated for $C_{31}H_{49}O_5Si$ $[M+H]^+$ 529.3349, found 529.3343; $[\alpha]_D$: +3.7 (*c* 0.8, $CHCl_3$).

5,5-Dimethyl-1,1,1-triphenyl-4-(trimethylsilyl)-3-[(triphenylsilyl)oxy]-2-oxa-4-aza-1,5-disila-3-molybdaoctan-4-amine

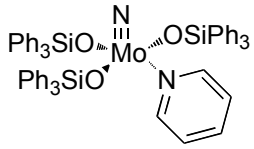


98

To a suspension of Na_2MoO_4 (3.3 g, 16 mmol) in DME (100 mL) under Ar was added Me_3SiCl (8 mL, 64 mmol). The reaction mixture was vigorously stirred under reflux for 16 h and was then concentrated under reduced pressure. The light blue residue was suspended in hexanes (70 mL). A solution of freshly prepared LiHMDS (31.7 mmol) in hexanes (27 mL) was added to a suspension of the resulting fine powder and the

mixture was stirred at rt for 2 h. Then the suspension was filtered through a canula under Ar, the filtrate was evaporated and the residue purified by high vacuum distillation to give **98** (4.0 g, 57%) as a pale yellow oil. This air-sensitive product was not characterized.

1,1,1,5,5,5-Hexaphenyl-3-[(triphenylsilyl)oxy]-2,4-dioxa-1,5-disila-3-molbdapenta-3-amine, pyridine adduct

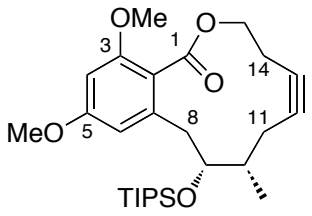


100

To a solution of complex **98** (2.6 g, 5.7 mmol) in PhMe (80 mL) was added Ph_3SiOH (4.7 g, 17.1 mmol) and the resulting mixture was stirred at 80 °C for 30 min. After reaching rt, pyridine (2.3 mL, 28.5 mmol) was introduced and the resulting solution was stirred for 18 h. The solvent was evaporated and the resulting foam was recrystallized twice from PhMe to give complex **100** (yield not recorded) as a yellow powder. Single crystals could be obtained and X-Ray proved the structure (Appendix 1).

IR (neat): 3065, 3049, 3025, 3010, 2999, 1609, 1588, 1484, 1449, 1427, 1113, 989, 890, 738, 708, 697 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.04 (*br* s, 2H), 7.60-7.36 (m, 17H), 7.34-6.98 (m, 29H), 6.60 (b*r* s, 2H). Match the literature data.[33]

(8*S*,9*R*)-12,14-Dimethoxy-8-methyl-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1H-2-benzocyclodecan-1-one



315

To a solution of **326**(15 mg, 0.03 mmol), dissolved in PhMe (1.5 mL) and heated at 110 °C under a closed Ar atmosphere, was added catalyst **10** (7 mg, 20 mol %). After 4 h, the reaction mixture was cooled to rt, filtered on a short pad of silica and the resulting filtrate was concentrated under reduced pressure. The crude material was purified by silica flash chromatography (10% Et_2O in hexanes) to afford **315** as colourless oil (11 mg). The product could not be obtained pure but contaminated with Ph_3SiOH therefore no yield was recorded.

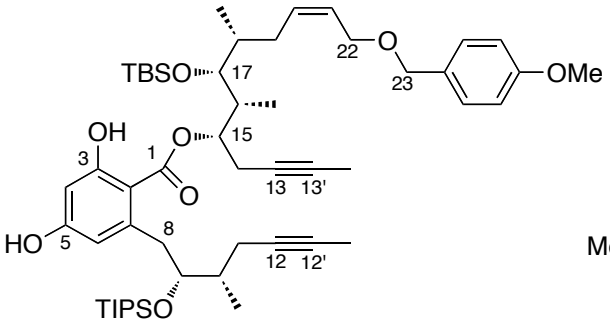
IR (neat): 2965, 2947, 2943, 2921, 2865, 1728, 1608; 1465, 1376, 1160, 1100, 1047, 884, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, *J* = 2.3 Hz, 1H, **Ar**-H), 6.34 (d, *J* = 2.3 Hz, 1H, **Ar**-H), 5.25-5.19 (m, 1H, **15**-Ha), 4.50-4.47 (m, 1H, **9**-H), 4.01-3.97 (m, 1H, **15**-Hb), 3.81 (s, 3H, **O**-CH_3), 3.79 (s, 3H, OC**H**$_3$), 3.05 (dd, *J* = 13.1, 1.5 Hz, 1H, **8**-Ha), 2.65-2.56 (m, 1H, **14**-Ha), 2.43-2.22 (m, 3H, **8**-Hb, **10**-H, **14**-Hb), 2.09-2.00 (m, 2H, **11**-H_2), 1.00-0.89 (m, 24H, TIPS-H, **10**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 160.5, 158.8, 140.3, 115.3, 109.4, 96.9, 80.1, 79.5, 74.8, 61.4, 56.2, 55.1, 37.8, 34.1, 23.5, 20.3, 18.1 (CTIPS), 13.8, 12.9 (CTIPS); MS (ESI) *m/z* 475

$[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{27}H_{43}O_5Si$ $[M+H]^+$ 475.2880, found 475.2878; $[\alpha]_D$: not relevant.

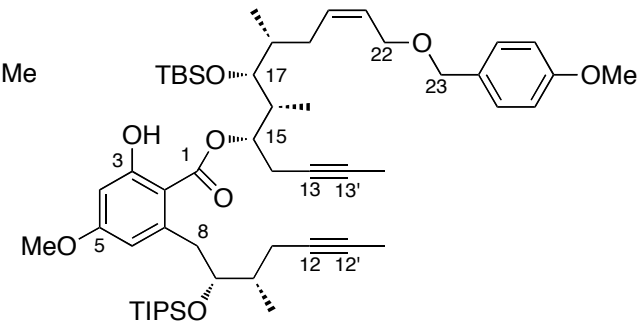
(5*S*,6*R*,7*R*,8*R*,10*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-12-[4-methoxyphenyl)methoxy]6,8-dimethyldodec-10-en-2-yn-5-yl 2,4-dihydroxy-6-[(2R,3S)-3-methyl-2-{[tris(propan-2-yl)silyl]oxy}hept-5-yn-1-yl]benzoate

and

(5*S*,6*R*,7*R*,8*R*,10*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-12-[4-methoxyphenyl)methoxy]6,8-dimethyldodec-10-en-2-yn-5-yl 2-dihydroxy-4-methoxy-6-[(2*R*,3*S*)-3-methyl-2-{[tris(propan-2-yl)silyl]oxy}hept-5-yn-1-yl]-4-methoxybenzoate



330



331

A solution of diketo-dioxinone **215** (1.26 g, 2.55 mmol) and alcohol **312** (1.15 g, 2.42 mmol) in CH_2Cl_2 (20 mL) were heated to 110 ºC in a sealed tube. After 2 h, the solvent was concentrated under reduced pressure. The resulting mixture was dissolved in MeOH (20 mL) and Cs_2CO_3 (2.4 g, 7.0 mmol) was added. After 20 min, HCl (1.25 M in MeOH, 30 mL) was added and the reaction was stirred for 30 min. The

mixture was dissolved with EtOAc (X 3) and the combined organic layers were washed with aqueous HCl (1 M) followed by brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (5% Et_2O in hexanes) to afford **330** (0.68 g) and **331** (0.52 mg) with a combined yield of 55%. Furthermore by-product **332** or **333** (0.13 mg, 6%) was isolated.

330

IR (neat): 3372, 2929, 2867, 1614, 1515, 1466, 1248, 1086, 1035, 834, 772, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H, **3**-OH), 7.27 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.87 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.34 (d, *J* = 2.6 Hz, 1H, **Ar**-H), 6.28 (d, *J* = 2.6 Hz, 1H, **Ar**-H), 5.68-5.52 (m, 2H, **20**-H, **21**-H), 5.33-5.26 (m, 1H, **15**-H), 5.10 (s, 1H, **5**-OH), 4.44 (s, 2H, **23**-H_2), 4.22 (dt, *J* = 8.2, 4.0 Hz, 1H, **9**-H), 4.06-4.03 (m, 2H, **22**-H_2), 3.80 (s, 3H, **O**-CH_3), 3.50 (dd, *J* = 5.7, 2.8 Hz, 1H, **17**-H), 3.30 (dd, *J* = 14.1, 4.0 Hz, 1H, **8**-Ha), 2.90 (dd, *J* = 14.1, 8.2 Hz, 1H, **8**-Hb), 2.65-2.60 (m, 2H, **14**-H_2), 2.39-1.97 (m, 7H, **10**-H, **11**-H_2, **18**-H, **16**-H, **19**-H_2), 1.79-1.76 (m, 6H, **12'**-CH_3, **13'**-CH_3), 1.06-0.86 (m, 39H, **TBS**-H, **TIPS**-H, **10**-CH_3, **16**-CH_3, **18**-CH_3), 0.08-0.04 (m, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (C-1), 164.6 (CAr), 160.0 (CAr), 159.6 (CAr), 145.5 (CAr), 132.1 (CH), 130.5 (CAr), 129.4 (2 X CAr), 127.5 (CH), 113.8 (2 X CAr), 112.2 (CAr), 106.5 (CAr), 101.7 (CAr), 78.3 (C), 77.7 (C), 75.9 (C-17), 75.7 (C-15, C-9), 74.2 (2C), 71.9 (C-23), 65.7 (C-22), 55.3 (O-CH_3), 39.4 (CH), 38.5 (CH), 38.2 (CH), 37.6 (C-8), 30.1 (CH_2), 26.1 (CTBS), 22.7 (CH_2), 22.0 (CH_2), 18.2 + 18.1 (CTBS, CTIPS), 16.1 (CH_3), 14.7 (CH_3), 13.0 (CTIPS), 10.8 (CH_3), 3.5 (12'-CH_3, 13'-CH_3), -3.7 (CTBS); MS (ESI) *m/z* 891 $[M+H]^+$, 913

$[M+Na]^+$; HRMS (ESI) *m/z* calculated for $C_{52}H_{83}O_8Si_2$ $[M+H]^+$ 891.5681, found 891.5654; $[\alpha]_D$: +12.0 (0.4, $CHCl_3$).

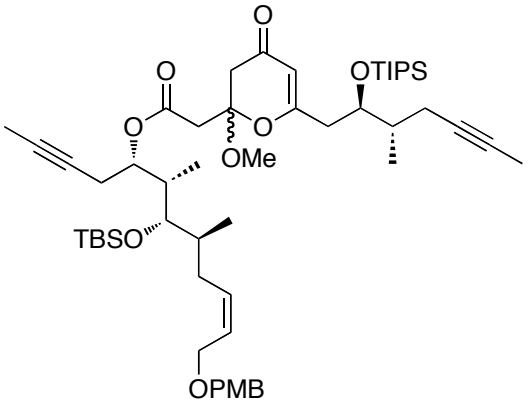
331

IR (neat): 3475, 2944, 2869, 1618, 1462, 1248, 1086, 1039, 834, 773, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H, **3**-OH), 7.27 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.88 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.41 (d, *J* = 2.5 Hz, 1H, **Ar**-H), 6.31 (d, *J* = 2.5 Hz, 1H, **Ar**-H), 5.68-5.51 (m, 2H, **20**-H, **21**-H), 5.31-5.27 (m, 1H, **15**-H), 4.44 (s, 2H, **23**-H_2), 4.26-4.22 (m, 1H, **9**-H), 4.05 (d, *J* = 6.1 Hz, 2H, **22**-H_2), 3.80 (s, 3H, **O**-CH_3), 3.79 (s, 3H, **O**-CH_3), 3.50 (dd, *J* = 5.7, 2.8 Hz, 1H, **17**-H), 3.30 (dd, *J* = 14.1, 4.3 Hz, 1H, **8**-Ha), 2.90 (dd, *J* = 14.1, 8.6 Hz, 1H, **8**-Hb), 2.69-2.66 (m, 2H, **14**-H_2), 2.32-1.81 (m, 7H, **10**-H, **11**-H_2, **18**-H, **16**-H, **19**-H_2), 1.76 (s, 6H, **12'**-CH_3, **13'**-CH_3), 1.07-0.86 (m, 39H, **TBS**-H, **TIPS**-H, **10**-CH_3, **16**-CH_3, **18**-CH_3), 0.08-0.03 (m, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C-1), 164.7 (CAr), 163.5 (CAr), 159.2 (CAr), 144.6 (CAr), 132.1 (CH), 130.5 (CAr), 129.4 (2 X CAr), 127.5 (CH), 113.8 (2 X CAr), 111.9 (CAr), 106.1 (CAr), 99.3 (CAr), 78.8 (C), 78.3 (C), 75.9 (CH), 75.8 (CH), 75.5 (CH), 74.2 (2C), 71.9 (C-23), 65.7 (C-22), 55.3 (2 O-CH_3), 39.4 (CH), 38.5 (CH), 38.4 (CH), 37.7 (C-8), 30.9 (CH_2), 26.1 (CTBS), 22.7 (CH_2), 22.0 (CH_2), 18.2 + 18.1 (CTBS, CTIPS), 16.1 (CH_3), 14.8 (CH_3), 13.0 (CTIPS), 10.8 (CH_3), 3.5 (12'-CH_3, 13'-CH_3), -3.7 (CTBS). MS (ESI) *m/z* 905 $[M+H]^+$, 927 $[M+Na]^+$; HRMS (ESI) *m/z* calculated for $C_{53}H_{85}O_8Si_2$ $[M+H]^+$ 905.5783, found 905.5786; $[\alpha]_D$: +14.0 (*c* 0.4, $CHCl_3$).

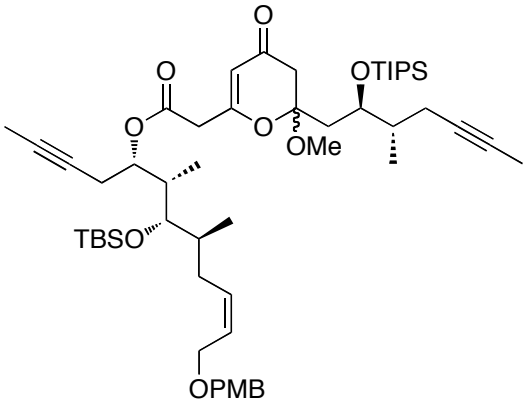
(6*S*,7*S*,8*S*,10*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-12-[(4-methoxyphenyl)methoxy]-6,8-dimethyldodec-10-en-2-yn-5-yl 2-{2-methoxy-6-[(2*R*,3*S*)-3-methyl-2-{[tris(propan-2-yl)silyl]oxy}hept-5-yn-1-yl]-4-oxo-3,4-dihydro-2H-pyran-2-yl)acetate

or

(6*S*,7*S*,8*S*,10*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-12-[(4-methoxyphenyl)methoxy]-6,8-dimethyldodec-10-en-2-yn-5-yl 2-{2-methoxy-2-[(2*R*,3*S*)-3-methyl-2-{[tris(propan-2-yl)silyl]oxy}hept-5-yn-1-yl]-4-oxo-3,4-dihydro-2H-pyran-6-yl)acetate



332

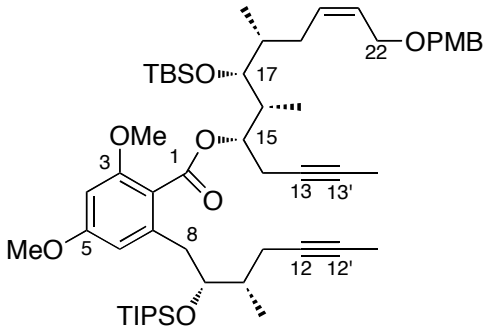


333

IR (neat): 3466, 2952, 2929, 2866, 1727, 1659, 1616, 1512, 1464, 1381, 1252, 1229, 1161, 1039, 885, 834, 773, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26, (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.66-5.56 (m, 2H), 5.39 (s, 1H), 5.05 (td, *J* = 5.5, 5.5 Hz, 1H), 4.48 (dt, *J* = 8.3, 2.8 Hz, 1H), 4.43 (s, 2H), 4.29 (s, 1H), 4.07 (d, *J* = 5.3 Hz, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.60 (s, 1H), 3.54 (dd, J = 5.5, 4.2 Hz, 1H), 3.04 (d, *J* = 17.8 Hz, 1H), 2.53 (m, 3H), 2.24 (m, 2H), 2.08-2.05 (m, 4H), 1.78-1.71 (m, 9H), 1.14 (s, 21H, **TIPS**-H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H),

0.91 (s, 9H, **TBS**-H), 0.89 (d, J = 6.9 Hz, 3H), 0.08 (s, 3H, **TBS**-H), 0.07 (s, 3H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) 191.8, 176.5, 169.7, 159.1, 132.7, 130.5, 129.3 (2 X C), 127.1, 113.7 (2 X C), 100.2, 78.2, 77.5, 76.9, 76.3, 74.7, 74.0, 73.0, 71.8, 71.6, 65.8, 62.4, 56.0, 55.2, 40.3, 40.2, 38.7, 38.1, 37.4, 29.6, 26.2 (CTBS), 22.5, 22.4, 18.5 + 18.3 (CTBS, CTIPS), 17.0, 14.2, 13.3 (CTISP), 10.4, 3.5, 3.4, -3.6 (CTBS), -3.7 (CTBS); MS (ESI) *m/z* 923 $[M+H]^+$, 945 $[M+Na]^+$; HRMS (ESI) *m/z* calculated for $C_{53}H_{87}O_9Si_2$ $[M+H]^+$ 923.5889, found 923.5873.

(5*S*,6*R*,7*R*,8*R*,10*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-12-[4-methoxyphenyl)methoxy]6,8-dimethyldodec-10-en-2-yn-5-yl 2,4-dimethoxy-6-[(2R,3S)-3-methyl-2-{[tris(propan-2-yl)silyl]oxy}hept-5-yn-1-yl]benzoate



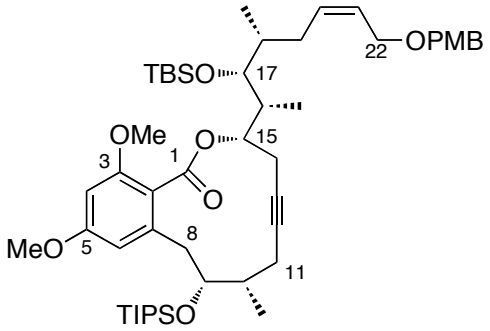
328

To a solution of **330** and **331** (0.9 g, 1.06 mmol) in acetone (40 mL) was added K_2CO_3 (1.5 mg, 21.1 mmol) followed by MeI (1.3 mL, 21.1 mmol). The reaction was heated at 60 ºC. After 2 h, the reaction was quenched by addition of a saturated solution of NH_4Cl and the aqueous layer was extracted with EtOAc (X 2). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under

reduced pressure. The crude material was purified by silica flash chromatography (5% Et_2O in hexanes) to afford **328** (0.80 mg, 82%) as a colourless oil.

IR (neat): 2932, 2864, 1721, 1605, 1513, 1463, 1249, 1159, 1087, 1044, 835, 773 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.88 (d, *J* = 8.6 Hz, 2H, **Ar**-H), 6.50 (d, *J* = 2.6 Hz, 1H, **Ar**-H), 6.31 (d, *J* = 2.6 Hz, 1H, **Ar**-H), 5.68-5.56 (m, 2H, **20**-H, **21**-H), 5.09-5.03 (m, 1H, **15**-H), 4.44 (s, 2H, **23**-H_2), 4.31-4.27 (m, 1H, **9**-H), 4.05 (d, *J* = 6.1 Hz, 2H, **22**-H_2), 3.80 (s, 6H, 2 **O**-CH_3), 3.79 (s, 3H, **O**-CH_3), 3.57-3.55 (m, 1H, **17**-H), 2.75-2.58 (m, 4H, **8**-H_2, **14**-H_2), 2.32-1.74 (m, 7H, **10**-H, **11**-H_2, **18**-H, **16**-H, **19**-H_2), 1.77 (s, 3H), 1.76 (s, 3H), 1.07-0.86 (m, 39H, **TBS**-H, **TIPS**-H, **10**-CH_3, **16**-CH_3, **18**-CH_3), 0.08-0.03 (m, 6H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7 (C-1), 160.7 (CAr), 159.1 (CAr), 157.8 (CAr), 139.1 (CAr), 132.6 (CH), 130.5 (CAr), 129.3 (2 X CAr), 127.2 (CH), 117.8 (CAr), 113.8 (2 X CAr), 107.0 (CAr), 96.7 (CAr), 78.1 (2 X C), 78.0 (2 X C), 76.2 (C-17), 75.2 (C-9), 74.6 (C-15), 71.8 (C-23), 65.7 (C-22), 55.6 (O-CH3), 55.2 (2 O-CH_3), 38.8 (CH), 37.9 (CH), 37.8 (CH), 36.1 (C-8), 30.1 (CH_2), 26.1 (CTBS), 22.7 (CH_2), 22.0 (CH_2), 18.2 + 18.1 (CTBS, CTIPS), 16.7 (CH_3), 14.6 (CH_3), 13.0 (CTIPS), 10.4 (CH_3), 3.6 + 3.5 (12'-CH_3, 13'-CH_3), -3.7 (CTBS); MS (ESI) *m/z* 919 $[M+H]^+$, 941 $[M+Na]^+$; HRMS (ESI) *m/z* calculated for $C_{54}H_{87}O_8Si_2$ $[M+H]^+$ 919.5940, found 919.5960; $[\alpha]_D$: +14.0 (*c* 0.6, $CHCl_3$).

(3*S*,8*S*,9*R*)-3-[(2*R*,3*R*,4*R*,6Z)-3-[(*tert*-Butyldimethylsilyl)oxy]-8-[4-methoxyphenyl)methoxy]-4-methyloct-6-en-2-yl]-12,14-dimethoxy-8-methyl-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododecan-1-one



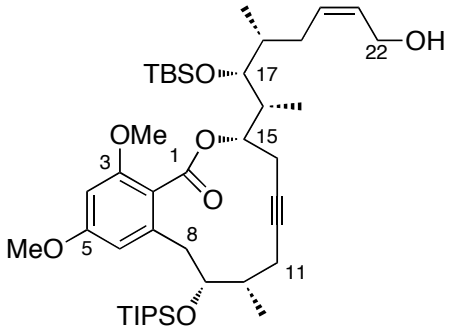
327

To a solution of **328** (300 mg, 0.33 mmol) dissolved in PhMe (20 mL) and heated at 110 °C under a closed Ar atmosphere was added catalyst **100** (130 mg, 40 mol %). After 8 h, the reaction mixture was filtered on a short pad of silica and the resulting filtrate was concentrated under reduced pressure. The crude oil was purified by silica flash chromatography (10% Et_2O in hexanes) to afford **327** (215 mg 75%) as a colourless oil.

IR (neat): 2940, 2865, 1739, 1604, 1514, 1466, 1258, 1157, 1087, 1055, 837, 772, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.87 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.42 (d, *J* = 2.5 Hz, 1H, **4**-H), 6.32 (d, *J* = 2.5 Hz, 1H, **6**-H), 5.66-5.53 (m, 2H, **20**-H, **21**-H), 5.47 (*br* s, 1H, **15**-H), 4.43 (s, 2H, **23**-H_2), 4.06-4.01 (m, 3H, **9**-H, **22**-H_2), 3.80-3.72 (m, 10H, **8**-Ha, 3 OCH_3), 3.49 (dd, *J* = 4.2, 4.2 Hz, 1H, **17**-H), 2.51-2.39 (m, 4H, **8**-Hb, **11**-Hb, **14**-H_2), 2.18-2.14 (m, 2H, **11**-H, **19**-Ha),

1.99-1.92 (m, 1H, **18**-H) 1.88-1.78 (m, 3H, **10**-H, **16**-H, **19**-Hb), 1.05 (d, J = 6.9 Hz, 3H, **16**-CH_3), 0.97-0.91 (m, 33H, **TIPS**-H, **TBS**-H, **18**-CH_3), 0.88 (d, J = 6,3 Hz, 3H, **10**-CH_3), 0.72 (s, 3H, **TBS**-H), 0.48 (s, 3H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4 (C-1), 160.3 (CAr) 159.2 (CAr), 157.3 (CAr), 139.5 (CAr), 132.4 (C-20), 130.5 (CAr), 129.3 (2 X CAr), 127.2 (C-21), 118.2 (CAr), 113.8 (2 X CAr), 108.3 (C-6), 96.7 (C-4), 81.3 (C) 79.6 (C), 77.2 (C-9), 76.4 (C-17), 74.8 (C-15), 71.9 (C-23), 65.7 (C-22), 55.8 (O-CH_3), 55.2 (O-CH_3 X 2), 40.8 (C-10), 38.6 (C-8), 37.7 (C-16), 37.6 (C-18), 30.1 (C-19), 26.1 (CTBS), 23.8 + 23.3 (C-14, C-11), 18.4 (10-CH_3), 18.1 + 17.9 (CTBS, CTIPS) 17.0 (16-CH_3), 13.0 (CTIPS), 11.4 (18- CH_3), -3.6 (CTBS), -3.5 (CTBS); MS (ESI) *m/z* 865 $[M+H]^+$, 882 $[M+H_2O]^+$, 887 $[M+Na]^+$, 903 $[M+K]^+$; HRMS (ESI) *m/z* calculated for $C_{50}H_{80}O_8Si_2$ $[M+H]^+$ 865.5470, found 865.5468; $[\alpha]_D$: -14,4 (*c* 0.6, $CHCl_3$).

(3*S*,8*S*,9*R*)-3-[(2*R*,3*R*,4*R*,6*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-8-hydroxy-4-methyloct-6-en-2-yl]-12,14-dimethoxy-8-methyl-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1*H*-2-benzoxacyclododecan-1-one



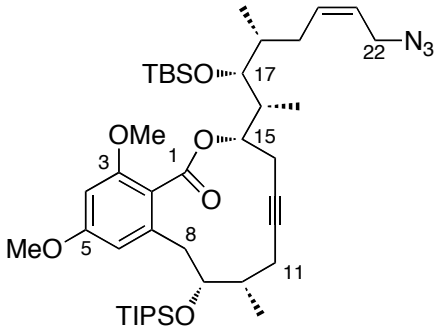
334

To a solution of **327** (200 mg, 0.23 mmol) dissolved in CH_2Cl_2/water (2 mL, 1:1) was added DDQ (100 mg, 0.3 mmol). The resulting mixture was vigorously stirred at rt for 20 min. The solution was then poured into a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the organic layers was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (5 to 20% Et_2O in hexanes) to afford **334** (150 mg, 87%) as a colourless oil.

IR (neat): 3427, 2941, 2860, 1732, 1603, 1461, 1265, 1158, 1083, 1051, 832, 769, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, *J* = 2.5 Hz, 1H, **4**-H), 6.31 (d, *J* = 2.5 Hz, 1H, **6**-H), 5.65 (dtt, *J* = 12.1, 6.6, 1.2 Hz, 1H, **21**-H), 5.65 (dtt, *J* = 12.1, 5.7, 1.3 Hz, 1H, **20**-H), 5.48 (s, 1H, **15-H**), 4.22 (dd, *J* = 12.6, 6.6 Hz, 1H, **22**-Ha), 4.14 (dd, *J* = 12.6, 6.6 Hz, 1H, **22**-Hb), 4.0 (dt, *J* = 8.8, 2.1 Hz, 1H, **9-H**), 3.80-3.74 (m, 7H, **8**-Ha, **3**-OCH_3, **5**-OCH_3), 3.50 (dd, *J* = 4.4, 4.4 Hz, 1H, **17-H**), 2.56-2.40 (m,

4H, **8**-Hb, **11**-Ha, **14**-H_2), 2.28-2.15 (m, 2H, **11**-Hb, **19**-Ha), 1.99-1.91 (m, 1H, **18**-H), 1.89-1.77 (m, 3H, **10**-H, **16**-H, **19**-Hb), 1.05 (d, *J* = 6.9 Hz, 3H, **17**-CH_3), 0.91-0.98 (m, 36H, T**IPS**-H, **TBS**-H, **10**-CH_3, **19**-CH_3), 0.65 (s, 3H, **TBS**-H), 0.59 (s, 3H, **TBS**-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C-1), 160.3 (CAr), 157.3 (CAr), 139.5 (CAr), 131.8 (C-20), 129.5 (C-21), 118.1 (CAr), 108.4 (C-6), 96.7 (C-4), 81.3 (C), 79.6 (C), 77.2 (C-9), 76.7(C-17), 74.8 (C-15), 58.7 (C-22), 55.8 + 55.2 (2 X O-CH_3), 41.0 (C-10), 38.6 (C-8), 37.6 (C-18), 37.5 (C-16), 29.9 (C-19), 26.2 (CTBS), 23.9 (C-14), 23.3 (C-11), 18.4 (10-CH_3), 18.1 + 17.9 (CTBS, CTIPS), 17.3 (16-CH_3), 13.0 (CTIPS), 11.6 (18-CH_3), -3.6 (CTBS); MS (ESI) *m/z* 745 $[M+H]^+$, 767 $[M+Na]^+$, 783 $[M+K]^+$; HRMS (ESI) *m/z* calculated for $C_{42}H_{73}O_7Si_2$ $[M+H]^+$ 745.4895, found 745.4921; $[\alpha]_D$: -16.0 (*c* 0.9, $CHCl_3$).

(3*S*,8*S*,9*R*)-3-[(2*R*,3*R*,4*R*,6*Z*)-8-Azido-3-[(*tert*-butyldimethylsilyl)oxy]- 4-methyloct-6-en-2-yl]-12,14-dimethoxy-8-methyl-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1*H*-2-benzoxacyclododecan-1-one



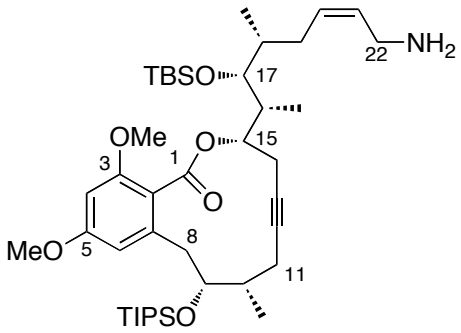
336

To a solution of **334** (130 mg, mmol) in PhMe (20 mL) was added $Zn(N_3)_2$•(pyridine)$_2$ (213 mg, 0.7 mmol) and PPh_3 (190 mg, 0.7 mmol). The mixture was cooled to 0 ºC and DIAD (140 μL, 0.7 mmol) was added. The reaction mixture was stirred for 4 h at rt and then filtered. The resulting filtrate was concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography (10% Et_2O in hexanes) to afford the desired product **336** (115 mg, 85%) as an amorphous solid.

IR (neat): 2960, 2944, 2867, 2099, 1739, 1608, 1461, 1263, 1161, 1091, 1057, 833, 774 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.43 (d, J = 2.2 Hz, 1H, **4**-H), 6.34 (d, J = 2.2 Hz, 1H, **6**-H), 5.74 (m, 1H, **20**-H), 5.57 (m, 1H, **21**-H), 5.47-5.40 (m, 1H, **15**-H), 4.00 (d, J = 8.9 Hz, 1H, **9**-H), 3.81-3.69 (m, 9H, 2 X **O**-CH_3, **8**-Ha, **22**-H_2), 3.52 (dd, J = 4.6, 4.6 Hz, 1H, **17**-H), 2.48-2.38 (m, 4H, **8**-Hb, **11**-Ha, **14**-H_2), 2.26-2.14 (m, 2H, **11**-Hb, **19**-Ha), 1.98-1.79 (m, 4H, **10**-H, **16**-H, **18**-H, **19**-Hb), 1.05

(d, J = 7.1 Hz, 3H), 0.98-0.91 (m, 36 H), 0.09 (s, 6H, **TBS**-H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 167.8 (C-1), 161.0 (CAr), 157.8 (CAr), 140.0 (CAr), 135.6 (C-20), 123.7 (C-21), 118.7 (CAr), 109.1 (CAr), 97.1 (CAr), 81.7 (C-13), 80.2 (C-12), 77.9 (C-9), 77.0 (C-17), 75.1 (C-15), 56.3 + 55.8 (2 X O-CH_3), 44.9 (C-22), 41.5 (C-10), 39.1 (C-8), 38.2 (C-18), 38.1 (C-16), 30.4 (C-19), 26.5 (CTIPS), 23.6 (C-14), 23.6 (C-11), 18.9 (10-CH_3), 18.5 + 18.2 (CTBS, CTIPS), 17.5 (16-CH_3), 13.6 (CTIPS), 11.7 (18-CH_3), -3.3 + -3.4 (CTBS); MS (ESI) *m/z* 770 $[M+H]^+$, 792 $[M+Na]^+$, 808 $[M+K]^+$; HRMS (ESI) *m/z* calculated for $C_{42}H_{73}O_7Si_2$ $[M+H]^+$ 770.4960, found 770.4966; $[\alpha]_D$: -24.1 (*c* 0.8, CH_2Cl_2).

(3*S*,8*S*,9*R*)-3-[(2*R*,3*R*,4*R*,6*Z*)-8-Amino-3-[(*tert*-butyldimethylsilyl)oxy]-4-methyloct-6-en-2-yl]-12,14-dimethoxy-8-methyl-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododecan-1-one

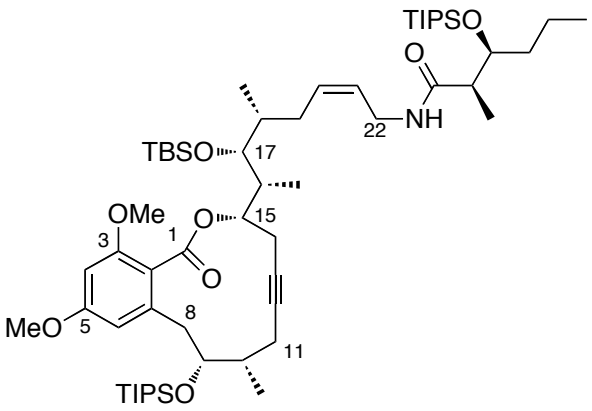


337

To a solution of **336** (105 mg, 0.14 mmol) in THF/water (1.5mL, 10:1) was added PPh_3 (360 mg, 13.7 mmol). The reaction mixture was stirred at 50 ºC for 4 h and was then concentrated under reduced pressure. The crude material was purified by silica

flash chromatography CH_2Cl_2/MeOH/NH_4OH. (9:1:0.1) to afford **337** (90 mg, 91%) as an amorphous solid. Due to its unstability, amine **337** was not characterised.

(2*R*,3*S*)-*N*-[(2*Z*,5*R*,6*R*,7*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-7-[(3*S*,8*S*,9*R*)-12-14-dimethoxy-8-methyl-1-oxo-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1*H*-2-benzoxacyclododeca-3-yl]-5-methyloct-2-en-1-yl]-2-methyl-3-{[tris(propan-2-yl)silyl]oxy}hexanamide



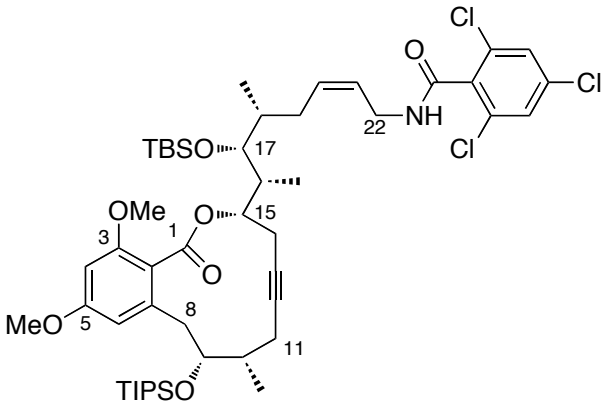
338

Procedure A

To a solution of **247** (40 mg, 0.13 mmol) in THF were added NEt_3 (20 μL, 0.13 mmol) and Yamaguchi reagent **249** (20 μL, 0.13 mmol). The mixture was stirred for 2 h and was then diluted with Et_2O and filtered over celite. The resulting filtrate was concentrated under reduced pressure and purified by silica flash chromatography (10% Et_2O in hexanes) to afford the desired mixed anhydride **347** (20 mg). To a solution of **337** (10 mg, 0.014 mmol) and the previous mixed anhydride **347** (20 mg, 0.042) in THF (1 mL) were added NEt_3 (6 μL, 0.042 mmol) and DMAP (5 mg,

0.042 mmol). The reaction mixture was stirred for 1 h then dissolved in EtOAc and quenched by addition of water. The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography (20% of EtOAc in hexanes) but no desired product was isolated. Instead, amide **349** (8 mg, 60%) was isolated.

_N_-[(2_Z_,5_R_,6_R_,7_R_)-6-[(_tert_-Butyldimethylsilyl)oxy]-7-[(3_S_,8_S_,9_R_)-12,14-Dimethoxy-8-methyl-1-oxo-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1_H_-2-benzoxacyclododecan-3-yl]-5-methyloct-2-en-1-yl]-2,4,6-trichlorobenzamide



349

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.42 (s, 2H, **Ar**-H), 6.50 (d, *J* = 2.5 Hz, 1H, **Ar**-H), 6.31 (d, *J* = 2.5 Hz, 1H, **Ar**-H), 5.65-5.50 (m, 3H, **21**-H**, 22**-H**, 15**-H), 4.24-4.13 (m, 2H), 4.03-4.01 (m, 1H), 3.80 (s, 3H, O-CH_3), 3.76-3.74 (s, 4H), 3.52 (m, 1H), 2.56-2.40 (m, 4H), 2.28-2.15 (m, 2H), 1.99-1.89 (m, 4H), 1.07-0.86 (m, 39H), 0.08-0.03 (m, 6H, **TBS**-H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 167.5, 162.3, 160.8,

157.9, 139.7, 135.7 (2 X CAr), 135.2, 133.2, 132.4, 129.5 (2 X CAr), 119.4, 109.0, 97.3, 81.5 (C), 80.5 (C), 77.6, 77.2, 74.5, 55.8 + 55.2 (2 X O-CH3), 41.1, 39.2, 38.2, 38.1, 37.1, 30.1, 26.2 (CTBS), 24.2, 23.8, 18.4, 18.1 + 17.9 (CTBS, CTIPS), 17.3, 13.0 (CTIPS), 11.6, -3.6 (CTBS), C-23 missing; MS (ESI) *m/z* 950 $[M+H]^+$, 972 $[M+Na]^+$; HRMS (ESI) *m/z* calculated for $C_{49}H_{75}NO_7Si_2Cl_3$ $[M+H]^+$ 950.4170, found 950.4148.

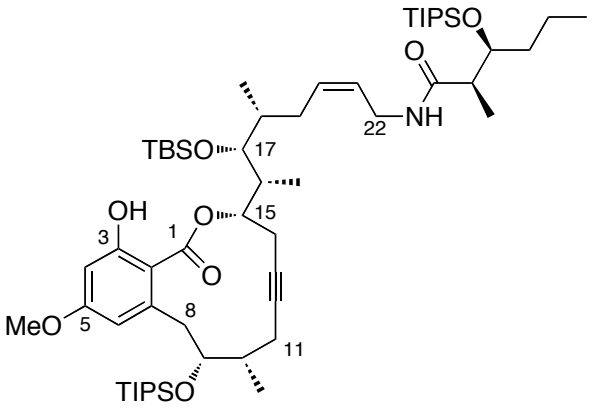
Procedure B

To a solution of **247** (100 mg, 0.33 mmol) dissolved in DMF (5 mL) were added HBTU (80 mg, 0.33 mmol), HOBt (30 mg, 0.33 mmol) and *i*-Pr_2NEt (0.1 mL, 0.62 mmol). The mixture was stirred for 30 min before **337** (75 mg, 0.1 mmol) was added. The resulting mixture was stirred for an additional 30 min. The reaction was then quenched by addition of water. The aqueous layer was extracted with Et_2O (X 2) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (20% of EtOAc in hexanes) to afford **338** (85 mg, 67%) as a white gum.

IR (neat): 3347, 2960, 2944, 2865, 1735, 1660, 1611, 1464, 1260, 1224, 1163, 1091, 1062, 883, 838, 779 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 6.44 (t, *J* = 5.3 Hz, 1H, **N**-H), 6.42 (d, *J* = 2.2 Hz, 1H, **4**-H), 6.34 (d, *J* = 2.2 Hz, 1H, **6**-H), 5.54-5.49 (m, 1H, **20**-H), 5.46-5.41 (m, 2H, **15**-H, **21**-H), 4.00-3.96 (m, 2H, **9**-H, **25**-H), 3.90-3.78 (m, **22**-H_2), 3.79 (s, 3H, **O**-CH_3), 3.76 (s, 3H, **O**-CH_3), 3.72 (d, *J* = 13.0 Hz, 1H, **8**-Ha), 3.51 (dd, *J* = 4.6, 4.6 Hz, 1H, **17**-H), 2.53-2.549 (m, 5H, **8**-Hb, **11**-Ha, **14**-H_2, **24**-H), 2.23-2.14 (m, 2H, **11**-Hb, **19**-Ha), 1.97-1.76 (m, 4H, **10**-H, **16**-H, **18**-H, **19**-Hb), 1.53-1.27 (m, 4H, **26**-Ha, **26**-Hb, **27**-H_2), 1.10-0.88 (m, 66H, **28**-H_3, **10**-CH_3, **16**-CH_3,

18-CH_3, **24**-CH_3, **TIPS**-H, **TBS**-H), 0.04 (s, 6H, **TBS**-H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 173.7 (C-23), 165.5 (C-1), 160.6 (C-3), 157.4 (C-5), 139.6 (C-7), 132.0 (C-20), 126.7 (C-21), 118.4 (C-2), 108.7 (C-6), 96.7 (C-4), 81.3 (C-13), 79.9 (C-12), 77.5 (C-17), 76.7 (C-9), 75.4 (C-25), 74.9 (C-15), 56.0 (O-CH_3), C55.4 (O-CH_3), 46.0 (C-24), 41.4 (C-16), 39.1 (C-8), 38.2 (C-18), 38.1 (C-10), 36.9 (C-22), 35.8 (C-26), 30.3 (C-19), 26.5 (CTIPS), 24.3 (C-14), 23.8 (C-11), 19.8 (C-27), 18.9 (18-CH_3), 18.6 + 18.4 + 18.2 (2 X CTIPS, CTBS), 17.4 (10-CH_3), 14.7 (C-28), 13.6 + 13.3 (2 X CTIPS), 12.9 (24-CH_3), 11.6 (16-CH_3), -3.3 (CTBS), -3.4 (CTBS); MS (ESI) *m/z* 1028 $[M+H]^+$, 1050 $[M+Na]^+$; HRMS (ESI) *m/z* calculated for $C_{58}H_{106}NO_8Si_3$ $[M+H]^+$ 1028.7226, found 1028.7209; $[\alpha]_D$: -17.5 (*c* 0.4, CH_2Cl_2).

(2*R*,3*S*)-*N*-[(2*Z*,5*R*,6*R*,7*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-7-[(3*S*,8*S*,9*R*)-14-hydroxy-12-methoxy-8-methyl-1-oxo-9-{[tris(propan-2-yl)silyl]oxy}-3,4,7,8,9,10-hexahydro-1*H*-2-benzoxacyclododeca-3-yl]-5-methyloct-2-en-1-yl]-2-methyl-3-{[tris(propan-2-yl)silyl]oxy}hexanamide



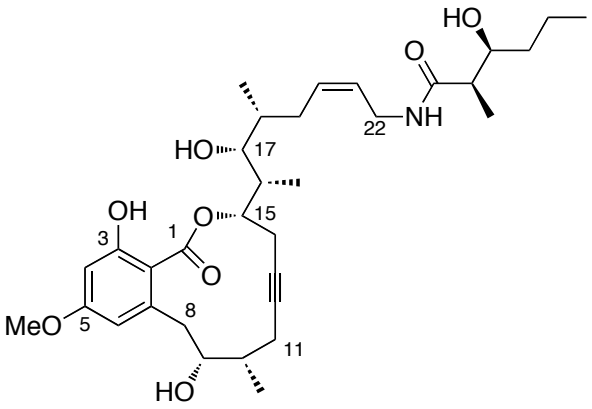
350

To a solution of **338** (35 mg, 0.034 mmol) in CH_2Cl_2 at -78 ºC was added BCl_3 (1 M in CH_2Cl_2, 75 µL). The reaction mixture was stirred for 1 h at -78 ºC and quenched by addition of MeOH. The resulting solution was concentrated under reduced pressure. The residue was dissolved again in MeOH and the solution concentrated under reduced pressure. The crude oil was purified by silica flash chromatography (5% MeOH in CH_2Cl_2) to afford **350** (26 mg, 75%) as an amorphous solid.

IR (neat): 3347, 2946, 2869, 1649, 1620, 1469, 1276, 1260, 1163, 1100, 1041, 765, 750 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 11.48 (s, 1H **3**-OH), 6.43 (t, *J* = 5.4 Hz, 1H, **N**-H), 6.37 (d, *J* = 2.2 Hz, 1H, **4**-H), 6.34 (d, *J* = 2.2 Hz, 1H, **6**-H), 5.50-5.41 (m, 2H, **20**-H, **21**-H), 5.22 (*br* s, 1H, **15**-H,), 4.23 (m, 2H, **9**-H, **25**-H), 3.98 (ddd, *J* = 5.7, 5.6, 3.6 Hz, 1H, **8**-Ha), 3.87 (ddd, *J* = 14.6, 5.9, 5.5 Hz, 1H, **22**-Ha), 3.81 (ddd, *J* = 14.6,

5.9, 5.5 Hz, 1H, **22**-Hb), 3.79 (s, 3H, **5**-OCH_3), 3.53 (dd, *J* = 5.8, 2.1 Hz, 1H, **17**-H), 2.9 (m, 1H, **14**-Ha), 2.64-2.58 (m, 1H, **8**-Hb), 2.50 (dq, *J* = 7.3, 3.6 Hz, 1H, **24**-H), 2.47 (d, *J* = 7.0 Hz, 1H, **14**-Hb), 2.36-2.26 (m, 1H, **18**-H), 2.23-2.18 (m, 2H, **16**-H, **19**-Ha), 2.08-2.05 (m, 1H, **11**-Ha), 1.92-1.85 (m, 2H, **10**-H, **19**-Hb), 1.72-1.67 (m, 1H, **11**-Hb), 1.54-1.27 (m, 4H, **26**-H_2, **27**-H_2), 1.10-0.86 (m, 66H, **28**-H_3, **10**-CH_3, **16**-CH_3, **18**-CH_3, **24**-CH_3, **TIPS**-H, **TBS**-H), 0.08 (s, 3H, **TBS**-H), 0.07 (s, 3H, **TBS**); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 174.1 (C-23), 171.6 (C-1), 164.9 (C-3), 164.0 (C-5), 144.2 (C-7), 132.0 (C-20), 127.6 (C-21), 107.4 (C-6, C-2), 99.4 (C-4), 76.6 (C-15, C-9), 76.2 (C-17), 75.8 (C-25), 55.8 (O-CH_3), 46.1 (C-24), 39.5 (C-16), 39.4 (C-18, C-10), 38.2 (C-8), 37.0 (C-22), 36.5 (C-26), 31.3 (C-19), 26.4 (CTIPS), 22.4 (C-14, C-11), 19.8 (C-27), 18.9 (18-CH_3), 18.6 + 18.3 (CTIPS, CTBS), 16.2 (10-CH_3), 14.7 (C-28), 13.7 + 13.4 (2 X CTIPS), 12.9 (24-CH_3), 11.6 (16-CH_3), -3.3 (CTBS), -3.4 (CTBS), C-12 and C-13 missing; MS (ESI) *m/z* 1014 $[M+H]^+$, 1036 $[M+Na]^+$; HRMS (ESI) *m/z* calculated for $C_{57}H_{104}NO_8Si_3$ $[M+H]^+$ 1014.7070, found 1014.7049; $[\alpha]_D$: -17.5 (*c* 0.4, CH_2Cl_2).

(2*R*,3*S*)-*N*-[(2*Z*,5*R*,6*R*,7*S*)-7-[(3*S*,8*S*,9*R*)-9,14-Dihydroxy-12-methoxy-8-methyl-1-oxo-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododecan-3-yl]-6-hydroxy-5-methyloct-2-en-1-yl]-3-hydroxy-2-methylhexanamide



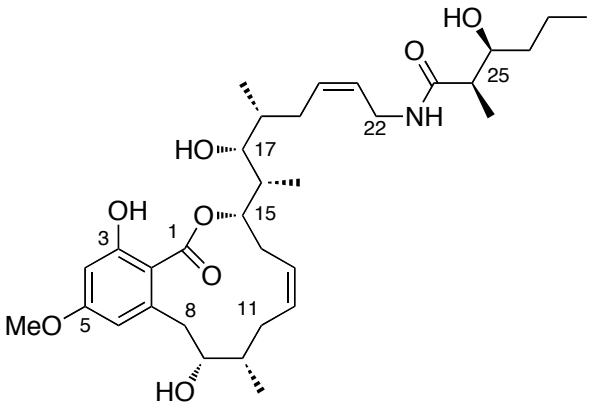
351

To a solution of **350** (20 mg, 0.02 mmol), in MeCN (0.5 mL), was added H_2SiF_6 (25 wt. % in water, 0.5 mL) at rt. The resulting mixture was stirred at 40 ºC for 8 h. The reaction mixture was then cooled to 0 ºC before the reaction was diluted with CH_2Cl_2 and poured into a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (X 3) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by silica flash chromatography (5% MeOH in CH_2Cl_2) to afford **351** (9 mg, 76%) as an amorphous solid.

IR (neat): 3355, 2958, 2924, 2855, 1712, 1616, 1460, 1260, 1162, 1097, 1019, 803 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.93 (s, 1H, **3**-OH), 6.40 (d, *J* = 2.5 Hz, 1H, **4**-H), 6.37 (d, *J* = 2.5 Hz, 1H, **6**-H), 6.25 (s, 1H, **N**-H), 5.65-5.59 (m, 1H, **20**-H), 5.445.39 (m, 1H, **21**-H), 5.36 (ddd, *J* = 8.2, 4.1, 4.1 Hz, 1H, **15**-H), 4.00 (dddd,

J = 14.9, 7.6, 6.5, 1.2 Hz, 1H, **22**-Ha), 3.94 (ddd, *J* = 10.3, 3.0, 3.0 Hz, 1H, **9**-H), 3.81 (s, 3H, O-CH_3), 3.80-3.70 (m, 3H, **8**-Ha, **22**-Hb, **25**-H), 3.46-3.40 (m, 2H, **17**-H, O-H), 3.05 (*br* s, 1H, O-H), 2.80-2.76 (m, 2H, **8**-Hb, **14**-Ha), 2.63-2.58 (m, 1H, **14**-Hb), 2.42-2.36 (m, 1H, **19**-Ha), 2.31-2.22 (m, 3H, **11**-Ha, **19**-Hb, **24**-H), 2.18-2.12 (m, 2H, **11**-Hb, **16**-H), 2.05-2.00 (m, 1H, **18**-H), 1.75-1.67 (m, 2H, **10**-H, **O**-H), 1.471.38 (m, 2H, **26**-Ha, **27**-Ha), 1.34-1.26 (m, 2H, **26**-Hb, **27**-Hb), 1.11 (d, *J* = 7.1 Hz, 3H, **24**-CH_3), 1.01 (d, *J* = 7.0 Hz, 3H, **18**-CH_3), 0.93-0.87 (m, 9H, **28**-H_3, **10**-CH_3, **16**-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5 (C-23), 170.7 (C-1), 164.0 (C-3), 163.4 (C-5), 143.4 (C-7), 130.0 (C-20), 127.0 (C-21), 111.3 (C-6), 107.0 (C-2), 99.3 (C-4), 82.7 (C), 79.4 (C), 77.6 (C-17), 74.9 (C-9), 73.6 (C-25), 71.8 (C-15), 55.4 (O-CH_3), 44.9 (C-24), 38.1 (C-16), 37.3 (C-10), 36.8 (C-18), 36.6 (C-8), 36.5 (C-22), 35.8 (C-26), 30.6 (C-19), 22.6 (C-14), 21.3 (C-11), 19.2 (C-27), 15.8 (18-CH_3), 15.1 (C-10), 13.9 (C-28), 11.0 (24-CH_3), 8.2 (16-CH_3); MS (ESI) *m/z* 588 $[M+H]^+$, 610 $[M+Na]^+$; HRMS (ESI) *m/z* calculated for $C_{33}H_{50}NO_8$ $[M+H]^+$ 588.3536, found 588.3522; $[\alpha]_D$: +1.5 (*c* 0.2, CH_2Cl_2).

(2*R*,3*S*)-*N*-[(2*Z*,5*R*,6*R*,7*S*)-7-[(3*S*,8*S*,9*R*)-9,14-Dihydroxy-12-methoxy-8-methyl-1-oxo-3,4,7,8,9,10-hexahydro-1H-2-benzoxacyclododecin-3-yl]-6-hydroxy-5-methyloct-2-en-1-yl]-3-hydroxy-2-methylhexanamide



Cruentaren A

(6)

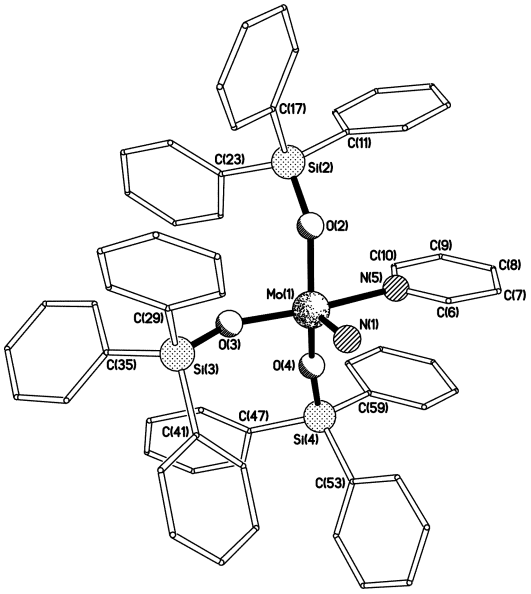
To a solution of **351** (6 mg, 0.015 mmol) in EtOAc (2 mL) was added quinoline (2.5 µL, mmol) followed by Lindlar's catalyst (5 wt. % Pd on $CaCO_3$, poisoned with lead, 6 mg, 100 wt. %). The reaction was placed under a H_2 atmosphere and stirred for 20 min. The reaction mixture was filtered through celite and concentrated under reduced pressure. The crude oil was purified by silica flash chromatography (5% MeOH in CH_2Cl_2) to afford cruentaren A (**6**) (5 mg, 83%) as a colourless oil. (15 mg in two batches).

IR (neat): 3345, 2962, 2934, 2878, 1643, 1616, 1580, 1542, 1460, 1444, 1380, 1317, 1253, 1224, 1204, 1141, 1104, 1055, 1041, 1017, 990, 955 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.48 (*br* s, 1H, **3**-OH), 6.37 (d, *J* = 2.7 Hz, 1H, **4**-H), 6.31 (d, *J* = 2.7 Hz, 1H, **6**-H), 6.14 (t, *J* = 5.7 Hz, 1H, **N**-H), 5.56 (m, 1H, **20**-H), 5.48 (ddd, *J* = 11.0, 2.9,

1.0 Hz, 1H, **12**-H), 5.44 (ddd, *J* = 11.0, 4.5, 1.9 Hz, 1H, **13**-H), 5.42-5.39 (m, 1H, **21**-H), 5.30 (ddd, *J* = 11.6, 5.6, 1.8 Hz, 1H, **15**-H), 3.92 (dddd, *J* = 14.9, 7.5, 5.7, 1.2 Hz, 1H, **22**-Ha), 3.86-3.82 (m, 2H, **22**-Hb, **25**-H), 3.81 (s, 3H, **5**-OCH_3), 3.76 (dd, *J* = 12.8, 1.4 Hz, 1H, **8**-Ha), 3.65 (ddd, *J* = 10.8, 2.3, 1.4 Hz, 1H, **9**-H), 3.46 (d, *J* = 8.9 Hz, 1H, **17**-H), 3.15 (*br* s, 1H, **9**-OH), 2.83 (dt, *J* = 14.3, 11.6 Hz, 1H, **14**-Ha), 2.76 (b*r* s, 1H, **17**-OH), 2.33 (dt, *J* = 14.2, 11.8 Hz, 1H, **11**-Ha), 2.29 (qd, *J* = 7.2, 2.8 Hz, 1H, **24**-H), 2.30-2.20 (m, 4H, **8**-Hb, **14**-Hb, **19**-H_2), 2.05-1.95 (m, 3H, **10**-H, **11**-Hb, **16**-H), 1.70 (qddd, *J* = 6.8, 6.8, 2.3, 2.0 Hz, 1H, **18**-H), 1.52-1.42 (m, 2H, **26**-Ha, **27**-Ha), 1.38 (*br* s, 1H, **9**-OH), 1.28-1.36 (m, 2H, **26**-Hb, **27**-Hb), 1.15 (d, *J* = 7.2 Hz, 3H, **24**-CH_3), 1.02 (d, *J* = 6.8 Hz, 3H, **10**-CH_3), 0.93 (t, *J* = 7.1 Hz, 3H, **28**-H_3), 0.90 (d, *J* = 7.0 Hz, 3H, **16**-CH_3), 0.80 (d, *J* = 6.8 Hz, 3H, **18**-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (C-23), 171.5 (C-1), 165.7 (C-3), 163.5 (C-5), 143.7 (C-7), 132.1 (C-12), 130.9 (C-20), 126.7 (C-21), 125.8 (C-13), 112.3 (C-6), 104.9 (C-2), 99.7 (C-4), 78.0 (C-15), 74.7 (C-17), 73.1 (C-9), 71.8 (C-25), 55.4 (O-CH_3), 44.8 (C-24), 39.2 (C-16), 38.2 (C-10), 36.8 (C-18), 36.6 (C-8), 36.5 (C-22), 35.8 (C-26), 31.6 (C-11), 30.7 (C-19), 29.8 (C-14), 19.2 (C-27), 16.1 (18-CH_3), 14.2 (10-CH_3), 14.0 (C-28), 11.2 (24-CH_3), 8.6 (16-CH_3); MS (ESI) *m/z* 590 $[M+H]^+$, 497 $[M+Na]^+$; HRMS (ESI) *m/z* calculated for $C_{33}H_{52}NO_8$ $[M+H]^+$ 590,3693, found 590.3701; $[\alpha]_D$: -3,0 (*c* 0.4, CH_2Cl_2). Match the literature data (Appendix 2, Appendix 3).[12]

5 Appendices

Appendix 1 - Crystal structure for compound 100



Empirical formula	C_{59} H_{50} Mo N_2 O_3 Si_3. C7 H8
Formula weight	1107.35
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 13.1793(2) Å, a = 87.0373(14)° b = 13.6503(2) Å, b = 77.3013(14)° c = 18.2684(3) Å, g = 64.0513(16)°
Volume, Z	2879.19(9) $Å^3$, 2
Density (calculated)	1.277 Mg/m^3
Absorption coefficient	0.338 mm^{-1}
F(000)	1152
Crystal colour / morphology	Yellow blocks
Crystal size	0.56 x 0.33 x 0.20 mm^3
q range for data collection	3.13 to 32.73°
Index ranges	-18<=h<=19, -19<=k<=16, -27<=l<=26
Reflns collected / unique	36984 / 18846 [R(int) = 0.0182]
Reflns observed [F>4s(F)]	14630
Absorption correction	Analytical
Max. and min. transmission	0.951 and 0.908

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	18846 / 123 / 712
Goodness-of-fit on F^2	1.054
Final R indices [F>4s(F)]	R1 = 0.0394, wR2 = 0.1189
R indices (all data)	R1 = 0.0551, wR2 = 0.1230
Largest diff. peak, hole	0.926, -0.718 eÅ^{-3}
Mean and maximum shift/error	0.000 and 0.002

Table 1 - Bond lengths [Å]

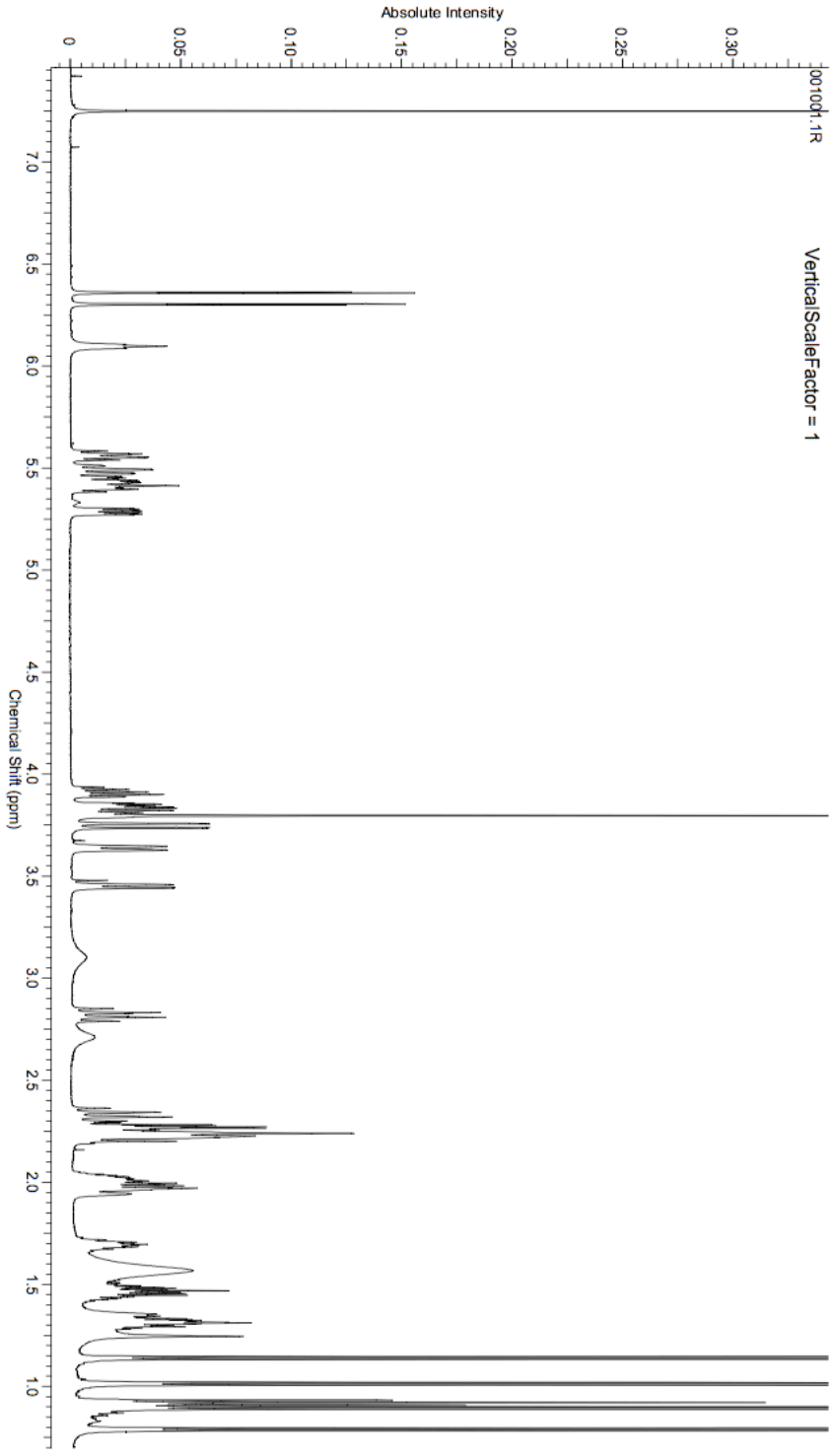
Bond	*Lenghts [Å]*	*Bond*	*Lenghts [Å]*
Mo(1)-N(1)	1.6532(16)	C(29)-C(34)	1.388(3)
Mo(1)-O(4)	1.9017(12)	C(29)-C(30)	1.403(3)
Mo(1)-O(3)	1.9026(13)	C(30)-C(31)	1.403(3)
Mo(1)-O(2)	1.9074(13)	C(31)-C(32)	1.368(4)
Mo(1)-N(5)	2.2743(15)	C(32)-C(33)	1.384(4)
O(2)-Si(2)	1.6315(14)	C(33)-C(34)	1.390(3)
Si(2)-C(17)	1.865(2)	C(35)-C(36)	1.395(3)
Si(2)-C(23)	1.868(2)	C(35)-C(40)	1.401(3)
Si(2)-C(11)	1.880(2)	C(36)-C(37)	1.392(3)
O(3)-Si(3)	1.6273(13)	C(37)-C(38)	1.360(4)
Si(3)-C(41)	1.8654(19)	C(38)-C(39)	1.364(4)
Si(3)-C(35)	1.8679(18)	C(39)-C(40)	1.390(3)
Si(3)-C(29)	1.8740(18)	C(41)-C(46)	1.395(3)
O(4)-Si(4)	1.6270(12)	C(41)-C(42)	1.408(3)
Si(4)-C(47)	1.8677(18)	C(42)-C(43)	1.395(3)
Si(4)-C(53)	1.8731(19)	C(43)-C(44)	1.367(4)
Si(4)-C(59)	1.8898(13)	C(44)-C(45)	1.370(3)
Si(4)-C(59')	1.926(6)	C(45)-C(46)	1.404(3)
N(5)-C(6)	1.327(2)	C(47)-C(48)	1.389(3)
N(5)-C(10)	1.339(2)	C(47)-C(52)	1.408(2)
C(6)-C(7)	1.381(3)	C(48)-C(49)	1.386(3)
C(7)-C(8)	1.368(3)	C(49)-C(50)	1.400(3)
C(8)-C(9)	1.376(3)	C(50)-C(51)	1.372(3)
C(9)-C(10)	1.372(3)	C(51)-C(52)	1.380(3)
C(11)-C(12)	1.391(3)	C(53)-C(58)	1.393(3)
C(11)-C(16)	1.402(3)	C(53)-C(54)	1.395(2)
C(12)-C(13)	1.390(4)	C(54)-C(55)	1.389(3)
C(13)-C(14)	1.396(4)	C(55)-C(56)	1.386(3)
C(14)-C(15)	1.413(5)	C(56)-C(57)	1.388(4)
C(15)-C(16)	1.384(4)	C(57)-C(58)	1.383(3)
C(17)-C(18)	1.397(3)	C(59)-C(60)	1.3900
C(17)-C(22)	1.397(3)	C(59)-C(64)	1.3900
C(18)-C(19)	1.395(3)	C(60)-C(61)	1.3900
C(19)-C(20)	1.371(4)	C(61)-C(62)	1.3900
C(20)-C(21)	1.375(4)	C(62)-C(63)	1.3900
C(21)-C(22)	1.377(3)	C(63)-C(64)	1.3900
C(23)-C(24)	1.392(3)	C(59')-C(60')	1.3900
C(23)-C(28)	1.405(3)	C(59')-C(64')	1.3900
C(24)-C(25)	1.388(4)	C(60')-C(61')	1.3900
C(25)-C(26)	1.392(5)	C(61')-C(62')	1.3900
C(26)-C(27)	1.371(5)	C(62')-C(63')	1.3900
C(27)-C(28)	1.381(4)	C(63')-C(64')	1.3900

Table 2- Bond Angles [°]

Bond	*Angles [°]*	*Bond*	*Angles [°]*
N(1)-Mo(1)-O(4)	107.78(8)	C(25)-C(24)-C(23)	121.9(3)
N(1)-Mo(1)-O(3)	102.78(7)	C(24)-C(25)-C(26)	119.5(3)
O(4)-Mo(1)-O(3)	93.43(5)	C(27)-C(26)-C(25)	120.1(3)
N(1)-Mo(1)-O(2)	105.40(8)	C(26)-C(27)-C(28)	119.8(3)
O(4)-Mo(1)-O(2)	141.98(6)	C(27)-C(28)-C(23)	122.1(3)
O(3)-Mo(1)-O(2)	96.89(6)	C(34)-C(29)-C(30)	117.99(17)
N(1)-Mo(1)-N(5)	92.00(7)	C(34)-C(29)-Si(3)	122.69(14)
O(4)-Mo(1)-N(5)	78.86(5)	C(30)-C(29)-Si(3)	119.32(14)
O(3)-Mo(1)-N(5)	164.89(6)	C(29)-C(30)-C(31)	120.0(2)
O(2)-Mo(1)-N(5)	81.97(6)	C(32)-C(31)-C(30)	120.6(2)
Si(2)-O(2)-Mo(1)	147.70(9)	C(31)-C(32)-C(33)	120.2(2)
O(2)-Si(2)-C(17)	108.56(8)	C(32)-C(33)-C(34)	119.4(2)
O(2)-Si(2)-C(23)	109.07(9)	C(29)-C(34)-C(33)	121.8(2)
C(17)-Si(2)-C(23)	110.07(10)	C(36)-C(35)-C(40)	117.34(19)
O(2)-Si(2)-C(11)	108.47(9)	C(36)-C(35)-Si(3)	120.16(16)
C(17)-Si(2)-C(11)	110.13(9)	C(40)-C(35)-Si(3)	122.48(15)
C(23)-Si(2)-C(11)	110.50(11)	C(37)-C(36)-C(35)	120.3(2)
Si(3)-O(3)-Mo(1)	148.62(9)	C(38)-C(37)-C(36)	121.4(3)
O(3)-Si(3)-C(41)	111.19(8)	C(37)-C(38)-C(39)	119.6(2)
O(3)-Si(3)-C(35)	107.34(8)	C(38)-C(39)-C(40)	120.5(2)
C(41)-Si(3)-C(35)	108.98(8)	C(39)-C(40)-C(35)	120.9(2)
O(3)-Si(3)-C(29)	109.86(8)	C(46)-C(41)-C(42)	116.95(17)
C(41)-Si(3)-C(29)	108.53(8)	C(46)-C(41)-Si(3)	122.80(14)
C(35)-Si(3)-C(29)	110.94(8)	C(42)-C(41)-Si(3)	120.22(14)
Si(4)-O(4)-Mo(1)	170.81(10)	C(43)-C(42)-C(41)	121.02(19)
O(4)-Si(4)-C(47)	106.38(7)	C(44)-C(43)-C(42)	120.3(2)
O(4)-Si(4)-C(53)	110.41(8)	C(43)-C(44)-C(45)	120.6(2)
C(47)-Si(4)-C(53)	111.90(8)	C(44)-C(45)-C(46)	119.6(2)
O(4)-Si(4)-C(59)	109.57(8)	C(41)-C(46)-C(45)	121.51(19)
C(47)-Si(4)-C(59)	111.95(9)	C(48)-C(47)-C(52)	117.58(17)
C(53)-Si(4)-C(59)	106.65(9)	C(48)-C(47)-Si(4)	120.21(13)
O(4)-Si(4)-C(59')	108.0(2)	C(52)-C(47)-Si(4)	122.21(14)
C(47)-Si(4)-C(59')	99.6(3)	C(49)-C(48)-C(47)	121.49(18)
C(53)-Si(4)-C(59')	119.4(2)	C(48)-C(49)-C(50)	119.4(2)
C(6)-N(5)-C(10)	117.92(17)	C(51)-C(50)-C(49)	120.1(2)
C(6)-N(5)-Mo(1)	121.35(13)	C(50)-C(51)-C(52)	120.04(19)
C(10)-N(5)-Mo(1)	120.60(13)	C(51)-C(52)-C(47)	121.33(18)
N(5)-C(6)-C(7)	122.03(19)	C(58)-C(53)-C(54)	117.79(18)
C(8)-C(7)-C(6)	119.8(2)	C(58)-C(53)-Si(4)	120.61(15)
C(7)-C(8)-C(9)	118.5(2)	C(54)-C(53)-Si(4)	121.56(14)
C(10)-C(9)-C(8)	118.67(19)	C(55)-C(54)-C(53)	120.89(18)
N(5)-C(10)-C(9)	123.08(18)	C(56)-C(55)-C(54)	120.3(2)
C(12)-C(11)-C(16)	117.3(2)	C(55)-C(56)-C(57)	119.5(2)
C(12)-C(11)-Si(2)	121.06(18)	C(58)-C(57)-C(56)	119.9(2)
C(16)-C(11)-Si(2)	121.7(2)	C(57)-C(58)-C(53)	121.6(2)
C(13)-C(12)-C(11)	123.1(3)	C(60)-C(59)-C(64)	120.0
C(12)-C(13)-C(14)	118.9(3)	C(60)-C(59)-Si(4)	121.48(11)
C(13)-C(14)-C(15)	119.1(3)	C(64)-C(59)-Si(4)	118.49(11)
C(16)-C(15)-C(14)	120.5(3)	C(59)-C(60)-C(61)	120.0
C(15)-C(16)-C(11)	121.1(3)	C(62)-C(61)-C(60)	120.0
C(18)-C(17)-C(22)	117.08(19)	C(61)-C(62)-C(63)	120.0
C(18)-C(17)-Si(2)	122.95(17)	C(62)-C(63)-C(64)	120.0
C(22)-C(17)-Si(2)	119.97(16)	C(63)-C(64)-C(59)	120.0
C(19)-C(18)-C(17)	121.2(2)	C(60')-C(59')-C(64')	120.0
C(20)-C(19)-C(18)	120.1(2)	C(60')-C(59')-Si(4)	118.6(4)
C(19)-C(20)-C(21)	119.7(2)	C(64')-C(59')-Si(4)	121.4(4)
C(20)-C(21)-C(22)	120.6(3)	C(59')-C(60')-C(61')	120.0
C(21)-C(22)-C(17)	121.4(2)	C(62')-C(61')-C(60')	120.0
C(24)-C(23)-C(28)	116.6(2)	C(61')-C(62')-C(63')	120.0
C(24)-C(23)-Si(2)	122.47(18)	C(64')-C(63')-C(62')	120.0
C(28)-C(23)-Si(2)	120.9(2)	C(63')-C(64')-C(59')	120.0

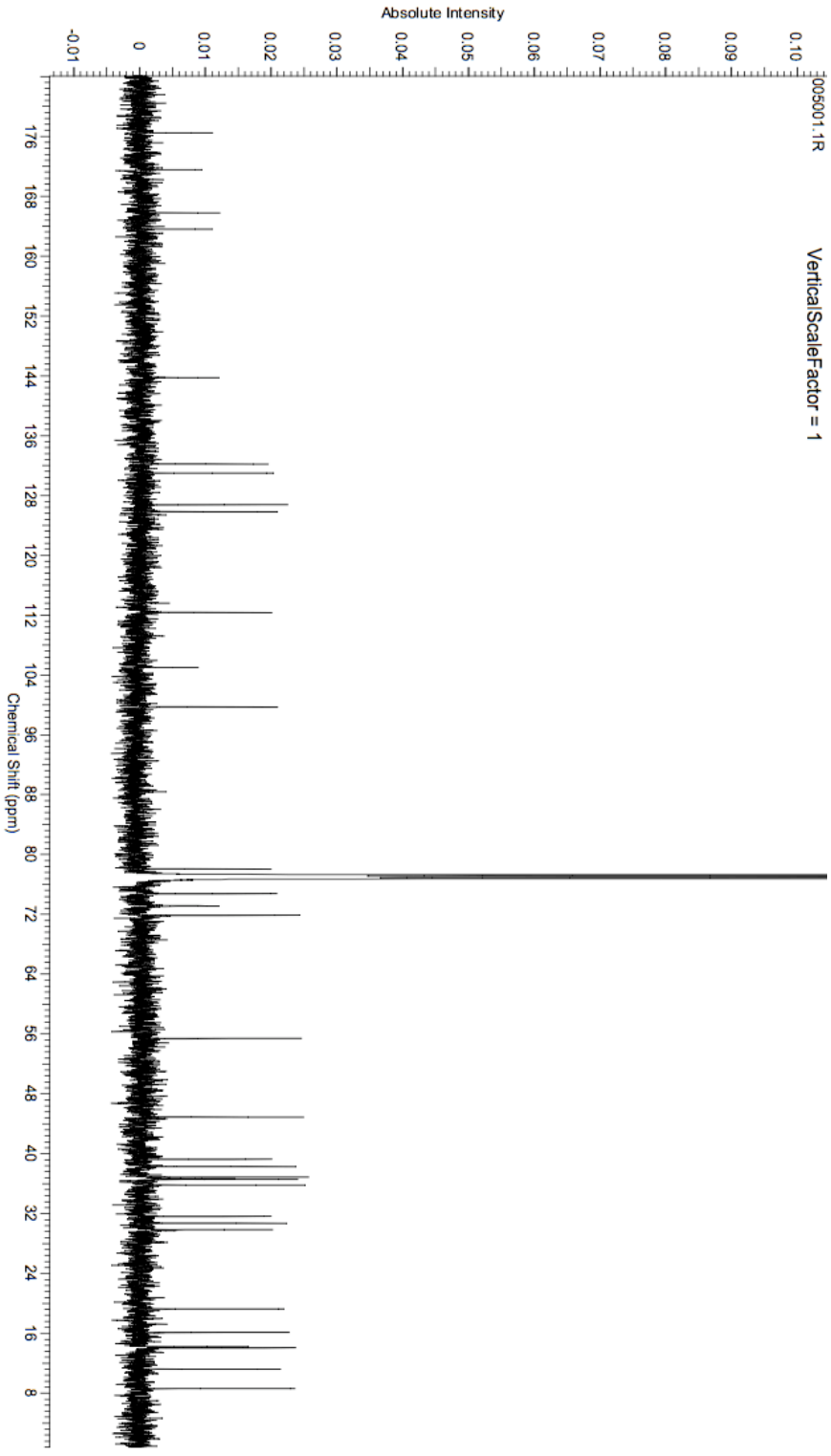
Appendix 2 – NMR spectra of isolated cruentaren A (Höfle *et al.*)[‡]

^{1}H NMR (600 MHz, $CDCl_3$)



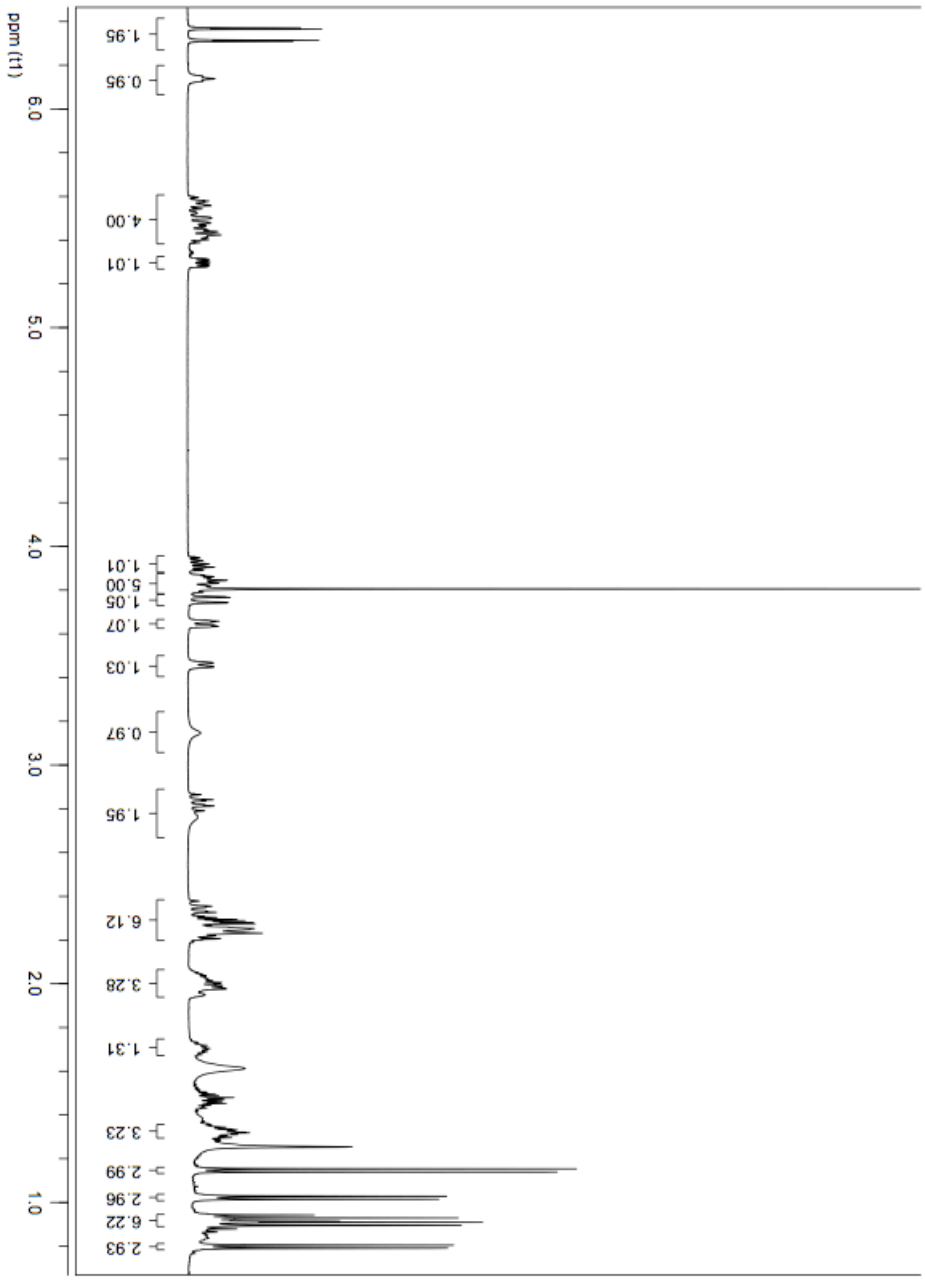
[‡] NMR spectra of isolated cruentaren A were obtained from Professor Gerhard Höfle.

^{13}C NMR (150 MHz, $CDCl_3$)

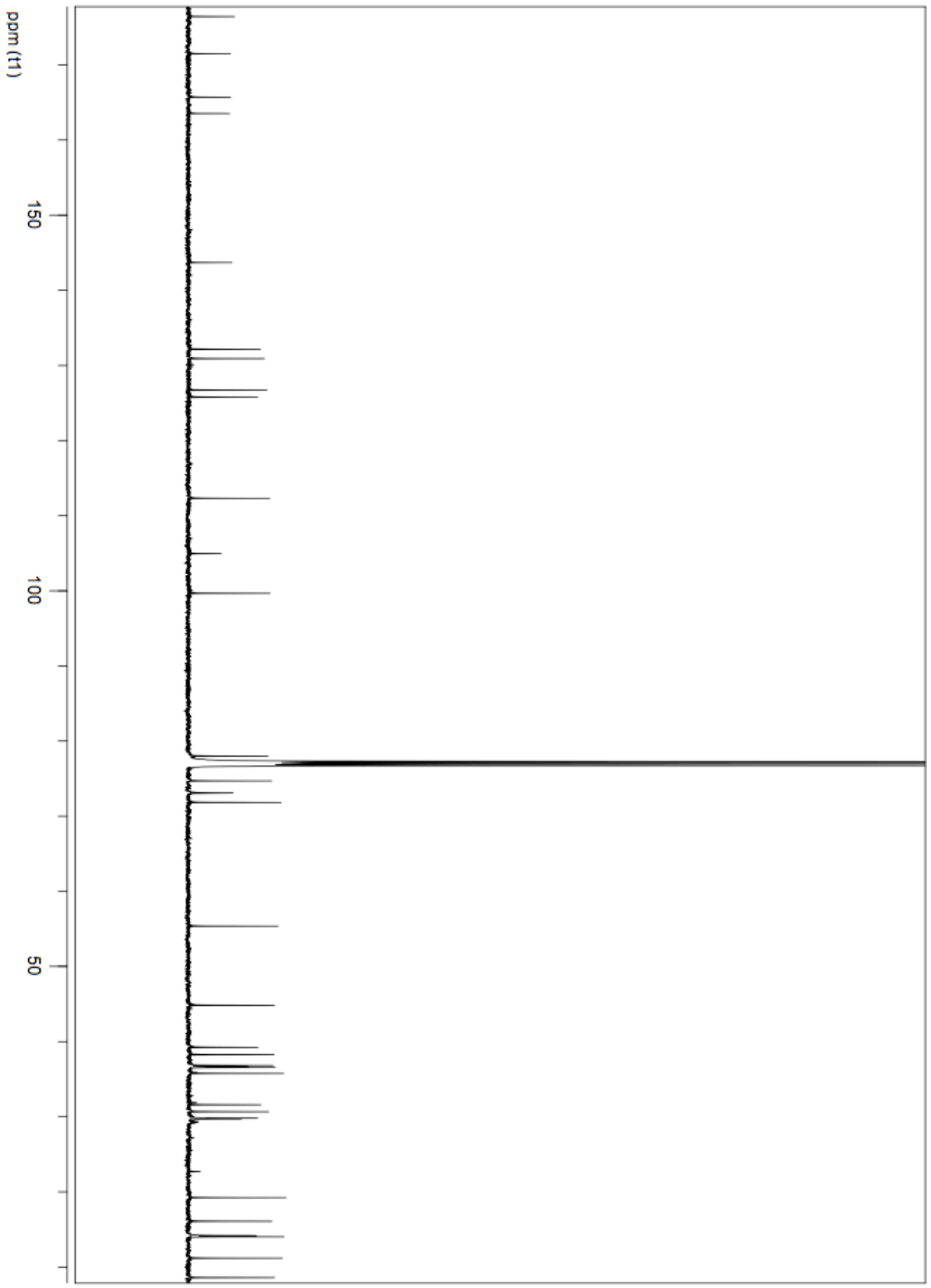


Appendix 3 – NMR spectra of synthesized cruentaren A (MF822)

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)



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