Towards the Total Synthesis of Amphidinolide T

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Declaration

I declare that, except where explicit reference is made to the contribution of others, the substance of this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

A portion of the work described herein has been published elsewhere as listed below.

Concise Synthesis of the C-1–C-12 Fragment of Amphidinolides T1–T5; J. Stephen Clark, Flavien Labre and Lynne H. Thomas *Org. Biomol. Chem.* **2011**, *9*, 4823–4830.

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Flavien Labre

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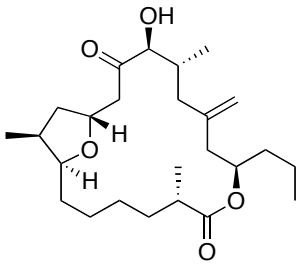
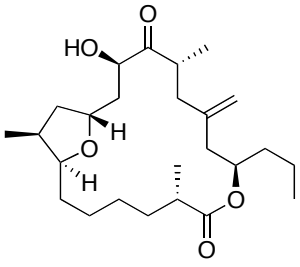
Prof. J. Stephen Clark

Abstract

Natural products from marine dinoflagellates of the genus *Amphidinium* were isolated by Kobayashi and co-workers. Among them, amphidinolides T are challenging targets for the total synthesis community because of their unique structural architecture. This thesis describes the investigations of the establishment of a novel and convenient route to synthesise four members of the natural product family, amphidinolides T1 and T3-5, from a common late-stage intermediate.



T1



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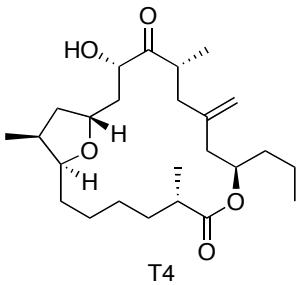
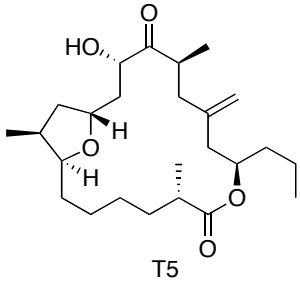


T4



T5

The key transformations towards the synthetic pathway are ring formation reactions. The *trans*-tetrahydrofuran ring is forged efficiently *via* diastereoselective [2,3]-sigmatropic rearrangement of an oxonium ylide from diazo-generated metal carbenoids. Coupling of a side chain is achieved using a sequence of esterification and RCM reactions. Alternatively, a one-pot RCM followed by hydrogenation is described to shorten the synthetic route.

The final stages of the project are focused on the closure of the 19-membered lactone. Various strategies are reported, starting from enyne RCM, siloxane-assisted macrocyclic alkene RCM and relay dienyne RCM. Finally, a formal synthesis is achieved by intercepting a late stage intermediate of a previous total synthesis of amphidinolide T3.

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I am very grateful to the people who proofread this thesis: Tony, Paloma, Andy, Alistair, Laura, Dave, Agnès and Flo. Your time and suggestions were very appreciated.

Special though to the Glasgow Drum Circle for the great drumming sessions. “One-bana-na” will always remind you, guys.

I would like to thank my family and friends, which have been a great support by listening to me and showing interest to what I have done. Thanks a lot for always believing that I was able to complete this work.

Special thanks to Flo for her constant support, even if you do not recognise how much you helped.

Last but not least, I would like to finish by thanking you, the reader, who, if not interested by profession, will be a close friend and surely should have deserved a special mention.

Abbreviations

ºC	degree Celsius
$(DHQD)_2AQN$	dihydroquinidine (anthraquinone-1,4-diyl) diether
Å	ångström
acac	acetylacetonate
Ac	acetate
ADMET	acyclic diene metathesis
AIBN	azo-*bis*-isobutyronitrile
aq	aqueous
atm	1 atmosphere
BAIB	[*bis*(acetoxy)iodo]benzene
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOM	benzyloxymethyl
bp	boiling point
brsm	based on recovered starting material
Bu	butyl
CI	chemical ionization
CM	cross metathesis
cod	1,5-cyclooctadiene
COSY	Correlation Spectroscopy
Cp	cyclopentadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CSA	camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
decomp.	decomposition
Dibal-H	di-*iso*-butylaluminium hydride

DIPEA	di-*iso*propylethylamine
DIPT	di-idopropyltartrate
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppb	1,3-*bis*(diphenylphosphino)butane
dr	diastereomeric ratio
dTMP	thymidine 5′-monophosphate
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
ee	enantiomeric excess
EI	electron ionization
eq	equivalent
ES	electrospray ionization
Et	ethyl
et al.	*et alii*
FAB	fast atom bombardment
GI	Grubbs first generation catalyst
GII	Grubbs second generation catalyst
h	hour
hfacac	hexafluoro acetylacetonate
HGII	Hoveyda-Grubbs second generation catalyst
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation experiment
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry
i	*iso*
IC_{50}	half maximal inhibitory concentration
Ipc	*iso*-pinocampheyl
IR	infrared spectroscopy
LDA	lithium diisopropylamide
liq.	liquid
LRMS	low resolution mass spectrometry

M	mol per litre
mCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	2,4,6-trimethylphenyl or mesityl
MLn	transition metal with ligands
MHz	mega hertz
min	minute
mod.	modified
MOM	methyloxymethyl
mp	melting point
Ms	methanesulfonyl or mesyl
MS	mass spectrometry
MTPA	2-methoxy-2-trifluoromethyl-2-phenylacetic acid
NBS	*N*-bromosuccinimide
NOESY	nuclear Overhauser effect spectroscopy
NMR	nuclear magnetic resonance
MW	microwave
NMO	4-methylmorpholine N-oxide
NHC	*N*-heterocyclic carbene
o	*ortho*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	protective group
Ph	phenyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Py	pyridine
RCM	ring closing metathesis
Rf	retention factor
ROM	ring opening metathesis
ROMP	ring opening metathesis polymerisation
RRM	ring rearrangement metathesis
rt	room temperature
S_N2	bimolecular nucleophilic substitution

sp	species
t	*tert*
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
temp.	temperature
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
TFA	trifluoroacetic acid
tfacac	trifluoroacetylacetonate
TfOH	trifluoromethanesulfonic acid or triflic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
tol	tolyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Ts	tosyl

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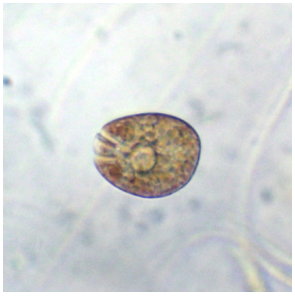
Chapter 1 Introduction

1. Amphidinolide T Family

1.1 Overview of Amphidinolide Family

Figure 1: Okinawa Islands

Marine microorganisms such as bacteria, cyanobacteria and dinoflagellates have attracted considerable attention as potential sources of marine natural products. Marine vertebrates and fish provide a large library of bioactive natural products that are constantly being evaluated and diversified by synthetic chemists, isolation chemists and biologists. Among marine organisms, dinoflagellates have turned out to be an important source of marine toxins and have been investigated worldwide by chemists engaged in natural product isolation. The Kobayashi group has extracted a number of natural products from microorganisms found in Okinawan coral reefs (Figure 1). More specifically, the amphidinolides have been isolated from marine dinoflagellates of the genus *Amphidinium* sp. (Figure 2).[1] They are symbionts found in the inner wall cells of the acoel flatworms of the harmless *Amphiscolops* sp. (Figure 3).



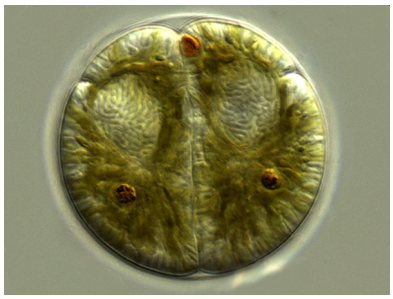


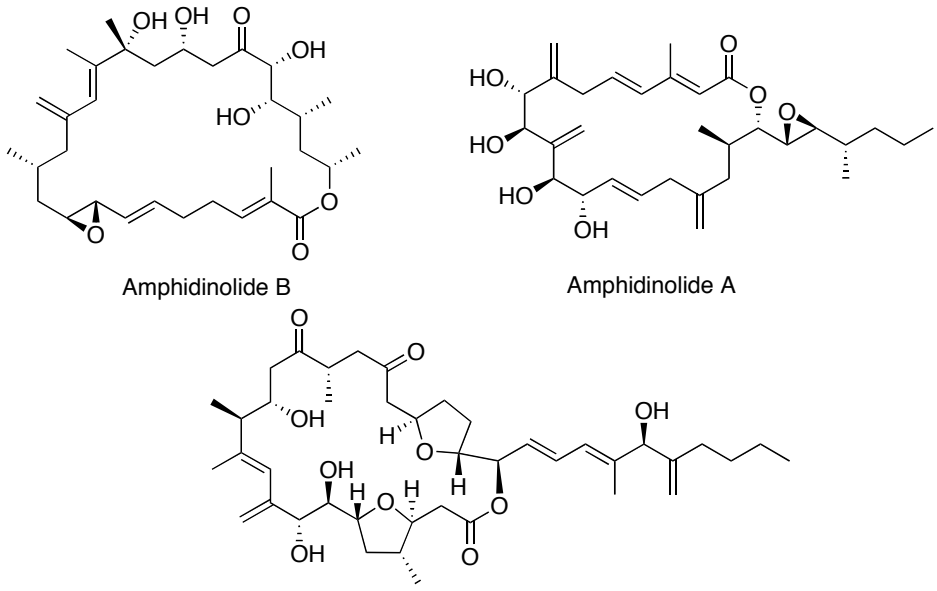
Figure 2: Amphidinium sp.

Figure 3: Amphiscolops sp.

[1]Kobayashi, J.; Ishibashi, M.; Walchli, M. R.; Nakamura, H.; Hirata, Y.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490–494.

To date, the structures of 35 structurally diverse members of the amphidinolide family have been elucidated. Some of these natural products show potent cytotoxicities down to 5 pg/mL concentration against murine leukaemia cells and KB human epidermoid carcinoma cells.[2,3] Therefore, they have IC_{50} values comparable to the most potent anti-cancer agents that are known.

In addition to their biological activities, amphidinolides possess interesting structural features. This family of macrolides shows diversity in ring size and includes lactones of odd-numbered ring size (Scheme 1). These macrolactones contain a large number of stereogenic centres, *exo*- and *endo*cyclic alkenes and oxygen-containing functionalities such as epoxides, tetrahydrofuran and tetrahydropyran rings, hydroxyl and ketone groups.

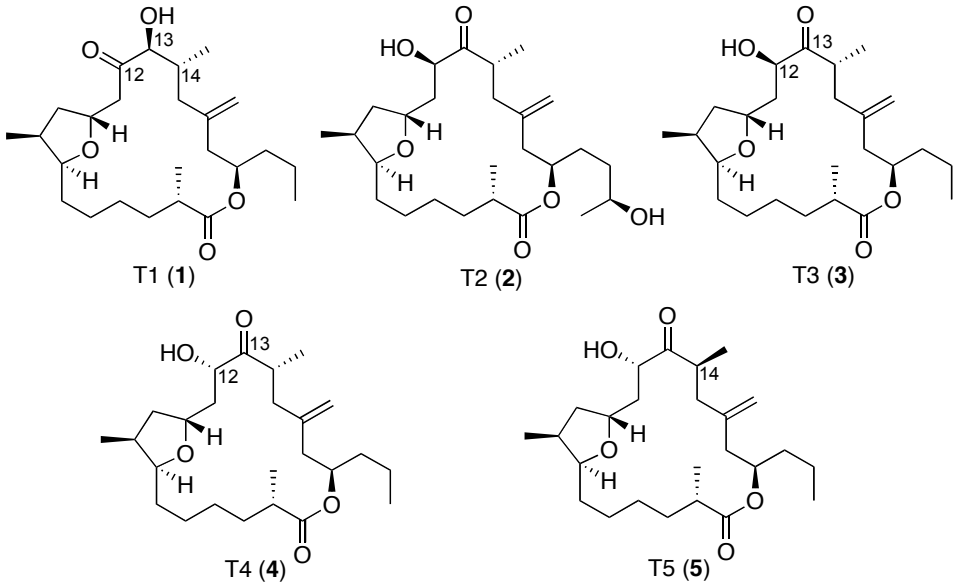


Scheme 1: Structures of amphidinolides A, B and C

Amphidinolides T1–T5 (**1**–**5**) are attractive targets for total synthesis because of their formidable structural architectures. In 2000, the Kobayashi

[2] Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70,* 451–460.
[3] Ishibashi, M.; Yamaguchi, N.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc. Chem. Commun.* **1994**, 1455–1456.

group identified amphidinolide T1, which was followed by the isolation and structural elucidation of amphidinolides T2–T5 (Scheme 2).[4,5,6]



Scheme 2: Amphidinolides T1-5

1.2 Amphidinolide T Family

Members of the amphidinolide T series are compact 19-membered macrolactones, possessing seven or eight stereogenic centres, an exocyclic double bond and a substituted tetrahydrofuran ring (Scheme 2). It is noteworthy that members of the family are isomers, with the exception of amphidinolide T2 (**2**), which has a different side chain. Amphidinolides T3 to T5 have diastereoisomeric relationships at C12 and C14; **1** and **3** are regioisomers due to a reversal of the α-hydroxy ketone group on C12 and C13.

Amphidinolides T1–T5 are somewhat less cytotoxic than some of the other amphidinolides but **1** to **5** still possess activities with IC_{50} values from 7–18 μg/mL against murine leukaemia cells and from 10–35 μg/mL against KB human epidermoid carcinoma cells.[5] To the best of our knowledge, their biological activities with respect to other diseases have not been studied.

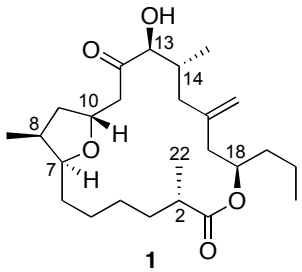
[4] Kobayashi, J.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2000**, *65*, 1349–1352.
[5] Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2001**, *66*, 134–142.
[6] Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M.; Shiro, M. *Tetrahedron* **2001**, *57*, 6175–6179.

1.2.1 Isolation of Natural Amphidinolides T

The dinoflagellate *Amphidinium* sp. was isolated from *Amphiscolops* sp. collected off from Sunabe, Okinawa. Large-scale cultures of the *Amphidinium* sp. were prepared using 1300 L of seawater medium enriched with Provasoli Erdschreiber supplement.[4,5] Static incubation with illumination cycles of 16 h of light and 8 h of darkness was carried out for 2 weeks at 25 °C. The cultures were harvested and centrifugation then delivered the algal cells (1200 g, wet weight), which were extracted with methanol and toluene. The toluene extracts were purified by repeated silica gel chromatography then successive preparative C_{18} column chromatography followed by C_{18} HPLC to afford amphidinolide T1 (**1**, 0.005%), T2 (**2**, 0.0001%), T3 (**3**, 0.0006%), T4 (**4**, 0.0004%) and T5 (**5**, 0.0004%). Scarcity of material made the structural elucidation of these natural products even more challenging.

1.2.2 Structural Elucidation

Amphidinolide T1 (**1**) was the first macrolide of the series to be fully characterised and the same methods were applied by the Kobayashi group to establish the architecture and the stereochemistry of the other members of the family subsequently (Figure 4).[3]



1

Figure 4: Amphidinolide T1 structure

Firstly, HRMS FAB revealed a molecular formula of $C_{25}H_{42}O_5$ for amphidinolide T1 and IR absorptions indicated the presence of hydroxyl and carbonyl group(s). Extensive ^{1}H and ^{13}C NMR spectroscopy analyses were performed and various techniques such as COSY, TOCSY and HMBC were used to determine the overall structure. The relative stereochemistry of the three

protons (H7, H8, and H10) in the tetrahydrofuran ring was suggested to be 7,8-*syn* and 7,10-*anti*, since NOESY correlations were observed (Figure 5).

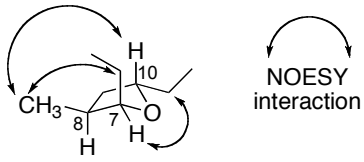
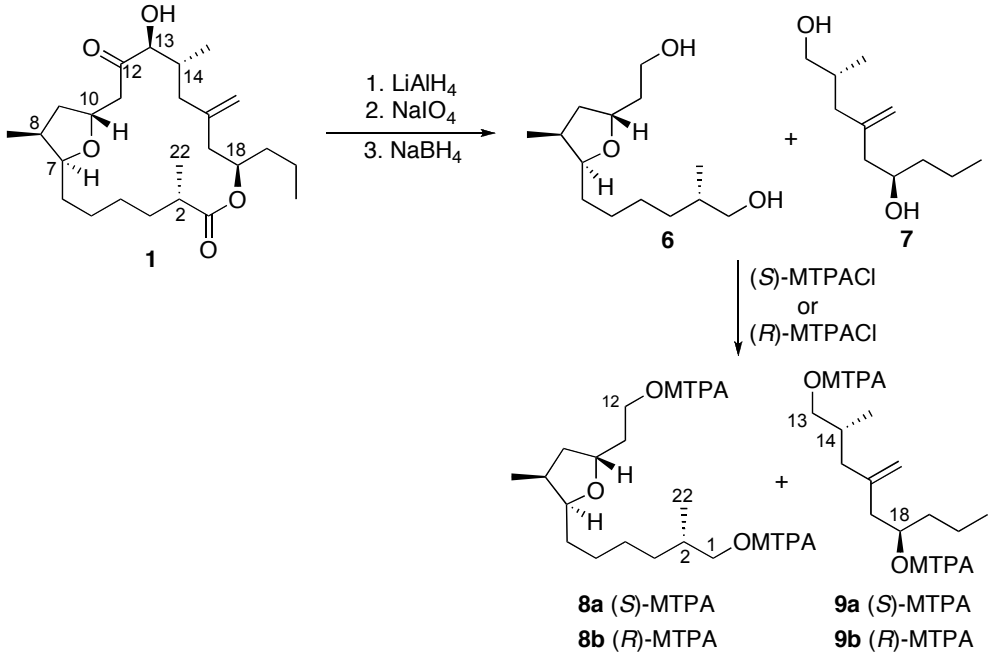


Figure 5: NOESY correlations

The absolute configuration at C13 was assigned using modified Mosher's method following preparation of (*S*)- and (*R*)-MTPA (2-methoxy-2-trifluoromethyl-2-phenylacetic acid) esters.[7]

The configurations of the remaining stereocentres were determined following NMR investigations on the degradation product of **1**. Amphidinolide T1 was subjected to $LiAlH_4$ reduction, followed by $NaIO_4$ oxidation to split the molecule in two fragments **6** and **7** (Scheme 3). Reduction of both carbonyl groups with $NaBH_4$ and subsequent esterification with (*S*)-MTPACl delivered the esters **8a** and **9a**. Alternatively, esterification with (*R*)-MTPACl gave the esters **8b** and **9b**.



Scheme 3: Chemical decomposition for stereochemistry elucidation

[7] Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4095.

In addition to the above analyses, the structure was confirmed by single crystal X-ray diffraction spectroscopy.[5] This analysis indicated tight transannular contacts between the C3-C5 and the C14-C25 regions of the molecule and showed that the C24 methyl is pointing inside the ring (Figure 4). Consequently, the macrocycle is much more congested and compact than two-dimensional representations of architecture might suggest.

1.2.3 Biosynthesis

Attempts to elucidate the biosynthetic pathway by which members of the amphidinolide T family are constructed, were made by way of various feeding experiments on *Amphidinium* sp. with ^{13}C-labelled nutrients.[5] Three separate batches of the dinoflagellate were supplemented respectively with [1-^{13}C]-sodium acetate, [2-^{13}C]-sodium acetate and [1,2-^{13}C]-sodium acetate. After cell extractions and purifications, ^{13}C-labelled amphidinolide T1 was analysed by NMR spectroscopy and all 25 carbon atoms contained in **10** were shown to be labelled with ^{13}C (Figure 6). Seven positions showed significant ^{13}C enrichment with [1-^{13}C]-sodium acetate and eighteen carbons with [2-^{13}C]-sodium acetate.

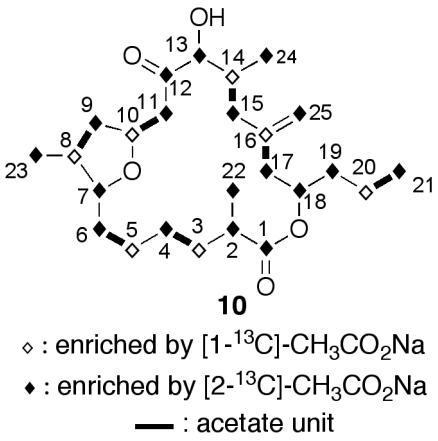


Figure 6: ^{13}C labelling pattern of amphidinolide T1

These results suggested that four segments – C3 to C6, C8 to C11, C14 to C17 and C20 to C21 – were likely to be classical polyketide chains derived from two, two, two and one acetate units respectively. Three irregular labelling patterns (♦-♦) derived only from [2-^{13}C]-sodium acetate were observed for C1/C2, C12/C13, and C18/C19 and an isolated unit on C7. These unusual incorporation patterns, which might be generated from non-successive mixed

polyketide biosynthesis, can be found in most dinoflagellate polyketides.[8] The one-carbon branches corresponding to C22, C23, C24, C25 were all derived from [2-^{13}C]-sodium acetate, in which the carboxyl carbons have been lost. Furthermore, the five oxygenated carbons – C1, C7, C12, C13 and C18 – were not derived from carboxyl groups but from carbons on the C2 position of acetate.

Another feeding experiment was conducted using ^{13}C-labelled sodium bicarbonate to give a relatively high incorporation ratio in the carbon scaffold of amphidinolide T1 compared to ^{13}C-labelled acetates. This result indicated that the main carbon source of **10** was derived from carbon dioxide and acetates were minor carbon sources. It is envisaged that sodium bicarbonate is converted into carbon dioxide, which is subsequently used for the biosynthesis of amphidinolide T1 *via* photosynthesis in chloroplasts.

The complex structures and potential bioactivities of the amphidinolides T1 and T3-5 make them very attractive targets for total synthesis. As part of our interest in the total synthesis of natural products, our goal was to establish a convenient route for the synthesis of amphidinolides T1 and T3-5 from a common intermediate.

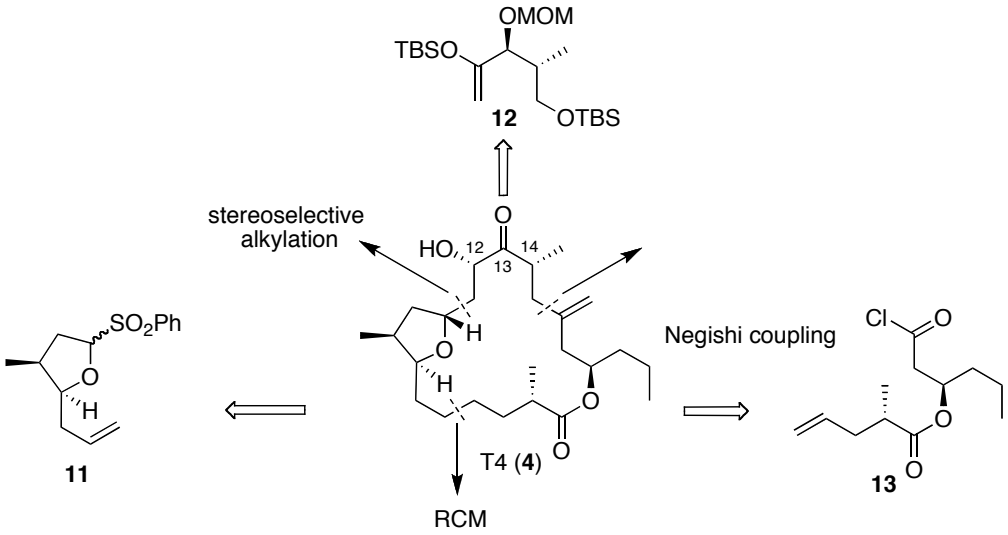
2. Previous Syntheses

In the literature to date, there has been significant focus on developing synthetic pathways to produce macrolides of the amphidinolide T family.[9] Total syntheses have been reported concerning the amphidinolides T1-T5, including studies from the research groups of Fürstner (**4**[10] then **1**, **3** and **5**[11]), Ghosh (**1**[12]), Jamison (**1**[13] and **4**[14]), Zhao (**3**[15]), Yadav (**1**[16]) and Dai (**2**[17] and **3**[18]).

[8] Moore, B. S. *Nat. Prod. Rep.* **2004**, *22*, 580–593.
[9] See literature cited herein: Fürstner, A. *Isr. J. Chem.* **2011**, *51*, 329–345.
[10] Fürstner, A.; Aïssa, C.; Riveiros, R.; Ragot, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4763–4766.
[11] Fürstner, A.; Aïssa, C.; Riveiros, R.; Ragot, J. *J. Am. Chem. Soc.* **2003**, *25*, 15512–15520.
[12] Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374–2375.
[13] Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998–999.
[14] Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297–4307.
[15] Deng, L.; Huang, X.; Zhao, G. *J. Org. Chem.* **2006**, *71*, 4625–4635.
[16] Yadav, J. S.; Suresh Reddy, Ch. *Org. Lett.* **2009**, *11*, 1705–1708.
[17] Li, H.; Wu, J.; Luo, J.; Dai, W.-M. *Chem. Eur. J.* **2010**, *16*, 11530–11534.
[18] Wu, D.; Li, H.; Jin, J.; Wu, J.; Dai, W.-M. *Synlett* **2011**, *7*, 895–898.

2.1 Fürstner Strategy

Just one year after publication of the structural elucidation of the amphidinolide T family, Fürstner *et al*. reported the first total synthesis of amphidinolide T4.[10] Additionally, amphidinolides T1, T3 and T5 were synthesised in 2003 using the same approach.[11] Fürstner's strategy for the synthesis of the macrolactone system involved the coupling of three building blocks (**11**, **12** and **13**) by stereoselective Lewis acid-mediated alkylation of a sulfone and by Negishi acyl chloride coupling (Scheme 4). The use of a ring-closing metathesis (RCM) reaction to close the macrocycle was envisaged.

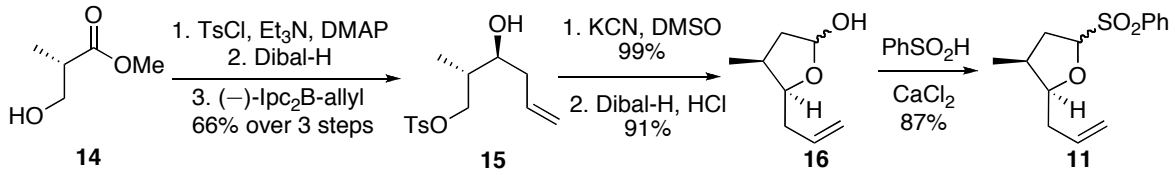


Scheme 4: *Fürstner's retrosynthetic analysis*

This approach would allow amphidinolides T1 and T3-5 to be synthesised following a common synthetic route with alternative oxidations, deprotections and epimerisations on the C12, C13 and C14 (*vide supra*).

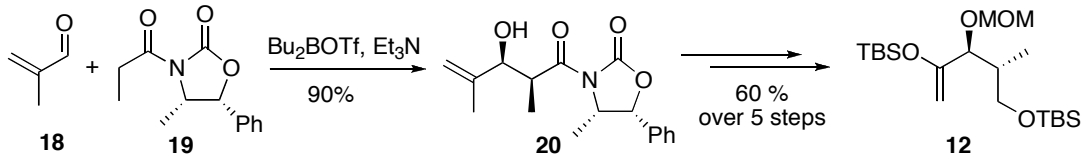
The synthesis of amphidinolide T4 commenced with the key fragment **11** derived from the commercially available hydroxy ester **14** (Scheme 5). Tosylation of the primary hydroxyl group followed by selective reduction of the methyl ester delivered the corresponding aldehyde, which was subjected to an asymmetric allyl addition reaction using (−)-Ipc_2B-allyl to afford alcohol **15** in diastereomerically pure form. The tosylate was displaced by cyanide anion to afford a nitrile and successive reduction and hydrolysis closed the tetrahydrofuran ring. The hemiacetal **16** was converted into a sulfone providing the fragment **11**. Thus, the tetrahydrofuran was prepared by reductive

cyclisation of a nitrile group and the stereogenic centres came from the chiral pool and Brown allylation.



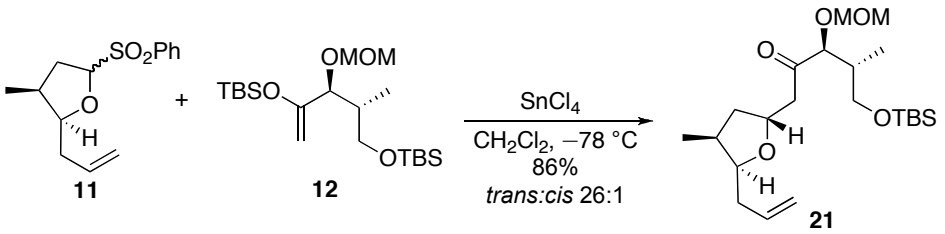
*Scheme 5: Synthesis of the tetrahydrofuran **11***

The coupling partner of **11** was prepared using the aldol reaction with Evans auxiliary starting from the methacrolein **18** and commercially available oxazolidinone **19**. A high-yielding five-step sequence completed the synthesis of silyl enol ether **12** (Scheme 6).



*Scheme 6: Synthesis of **12***

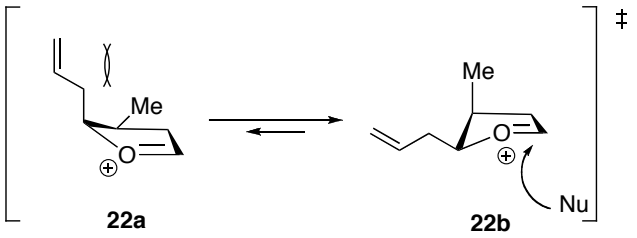
Union of the fragments **11** and **12** was performed under Lewis acid mediated alkylation conditions *via* an oxonium intermediate **22** generated in the tetrahydrofuran ring (Scheme 7 and 8). This method was optimised to afford good yield of the coupled product **21** with an excellent diastereoisomeric ratio of 26:1 (*trans*/*cis*).



Scheme 7: Lewis acid-mediated coupling

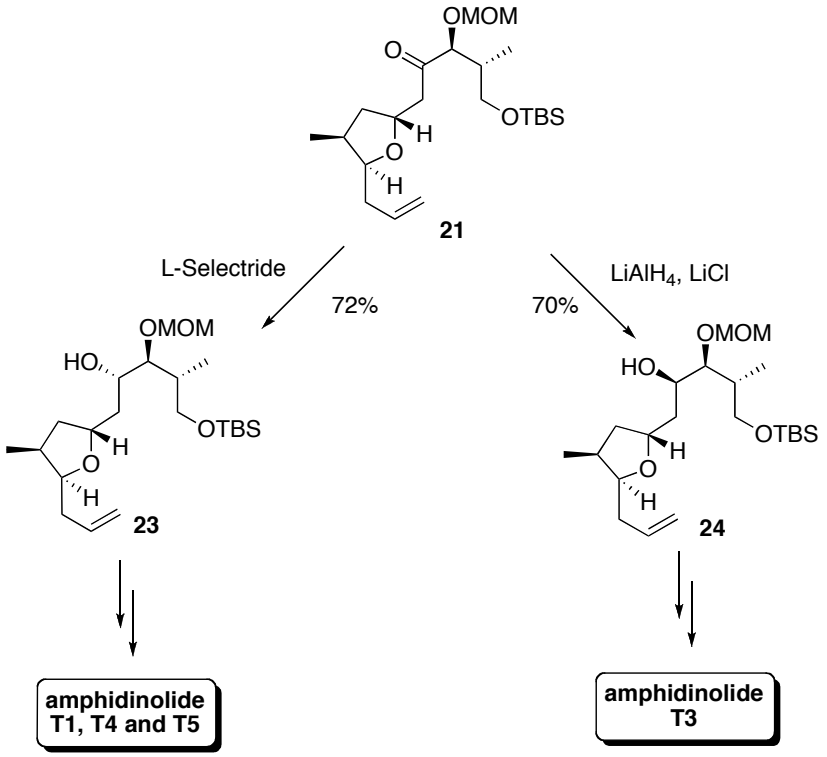
The diastereoselectivity was explained by reaction through a favoured conformation of the oxonium ion **22b** in which the methyl group is positioned in an axial position (Scheme 8). The lowest energy transition state then results

from nucleophilic addition of the side chain to the face that lies opposite to the methyl group.[19]



Scheme 8: Oxonium intermediate

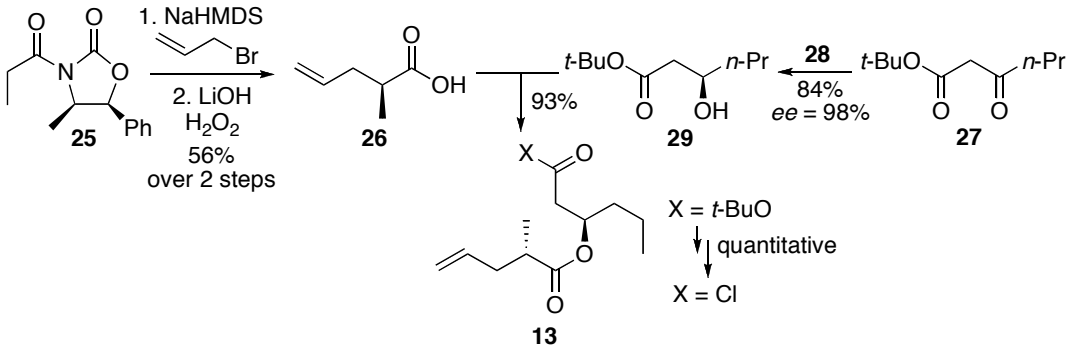
This highly efficient coupling procedure provided the key intermediate **21**, which was to serve as a common fragment for all targets. By performing stereoselective reduction reactions and making appropriate protecting group choices, the Fürstner group was able to synthesise the amphidinolides T1 and T3-5 (Scheme 9).



Scheme 9: One intermediate to four natural products

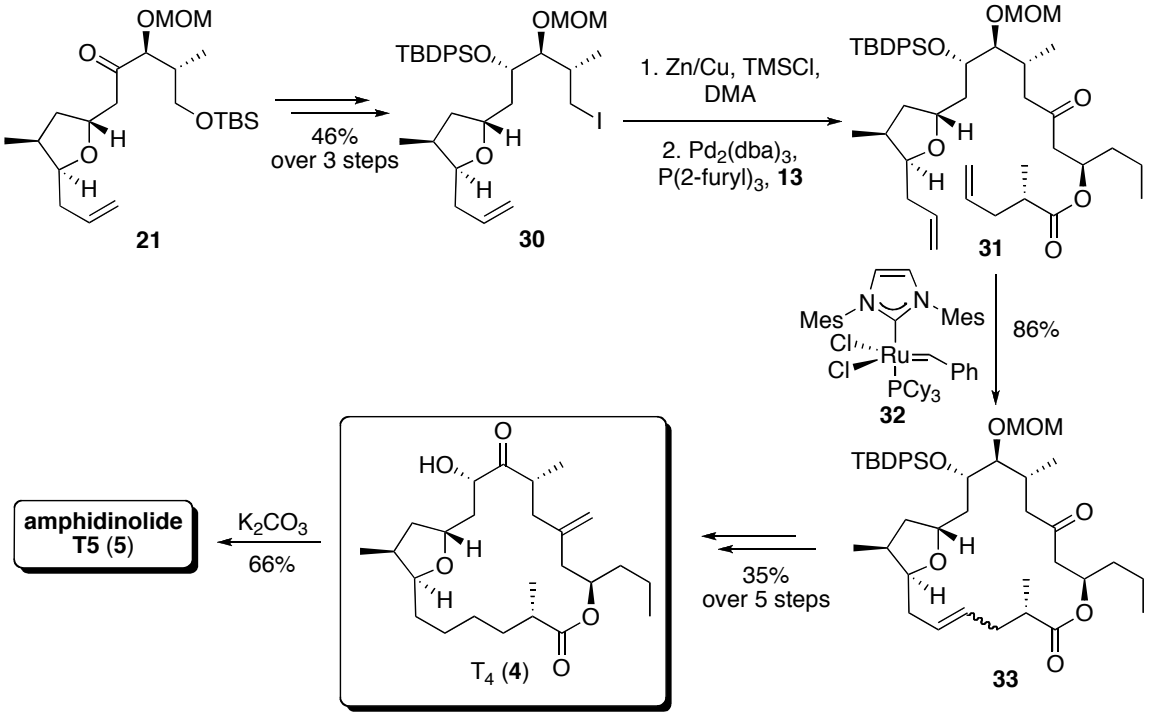
[19] Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121,* 51, 12208−12209.

In order to complete the synthesis of the targets, the final building block **13** was prepared by esterification between the acid **26** and the hydroxy ester **29** (Scheme 10). The carboxylic acid **26** was fashioned from oxazolidinone **25** using a two-step sequence of asymmetric allylation and oxidation, in moderate overall yield. The hydroxy ester **29** was prepared successfully by reduction of the corresponding ketone **27** using $\{[(R)\text{-BINAP})RuCl_2]_2\}$-($Et_3N$) **28** as an asymmetric catalyst.



*Scheme 10: To the last building block **13***

Fragment **21** was halogenated to deliver **30** in three steps and union of the fragments was performed by acyl chloride Negishi coupling using zinc-copper couple to afford the coupled product **31** in moderate yield (Scheme 11). **31** was subjected to a highly efficient RCM using the modified second generation Grubbs catalyst **32** to give the macrolactone **33** in 86% yield. Many efforts had been carried out for the olefination of the ketone functionality present in **33** but without success. Because the amphidinolide T macrocycle is very compact, the approach of a bulky reagent is difficult. The methylenation issue was overcame by changing the protecting groups and performing the reaction with the Nysted reagent. The total syntheses were finally completed by an efficient sequence of deprotection/oxidation/deprotection. Basic epimerisation then delivered amphidinolide T5 (**5**) from amphidinolide T4 (**4**).



Scheme 11: Completion of the total synthese of the amphidinolide T4 and T5

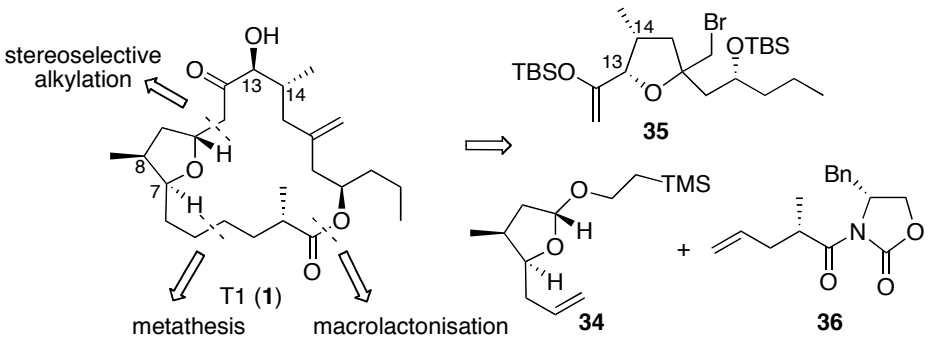
The total synthesis of amphidinolide T1 was completed with a longest linear sequence of 18 steps in 1.5% yield, amphidinolide T3 was prepared in 17 steps and a yield of 1.7%, amphidinolide T4 was synthesised in 18 steps in 2.1% yield and amphidinolide T5 was completed in 19 steps in 1.2% yield.[11]

This straightforward synthesis is remarkable for several reasons. Firstly, a common route leads to four structurally complex natural products in a highly diastereocontrolled manner. It is particularly interesting that the syntheses of the amphidinolides T1, T3, T4 and T5 are convergent, which means that the two longest sequences have the same number of steps.

Secondly, it is noteworthy that the synthesis of amphidinolide T4 was published only two years after the original structural elucidation of amphidinolide T family and one year after the characterisation of amphidinolide T4. This success has inspired other groups working on the syntheses of the amphidinolide T macrolides.

2.2 Ghosh's Total Synthesis of Amphidinolide T1

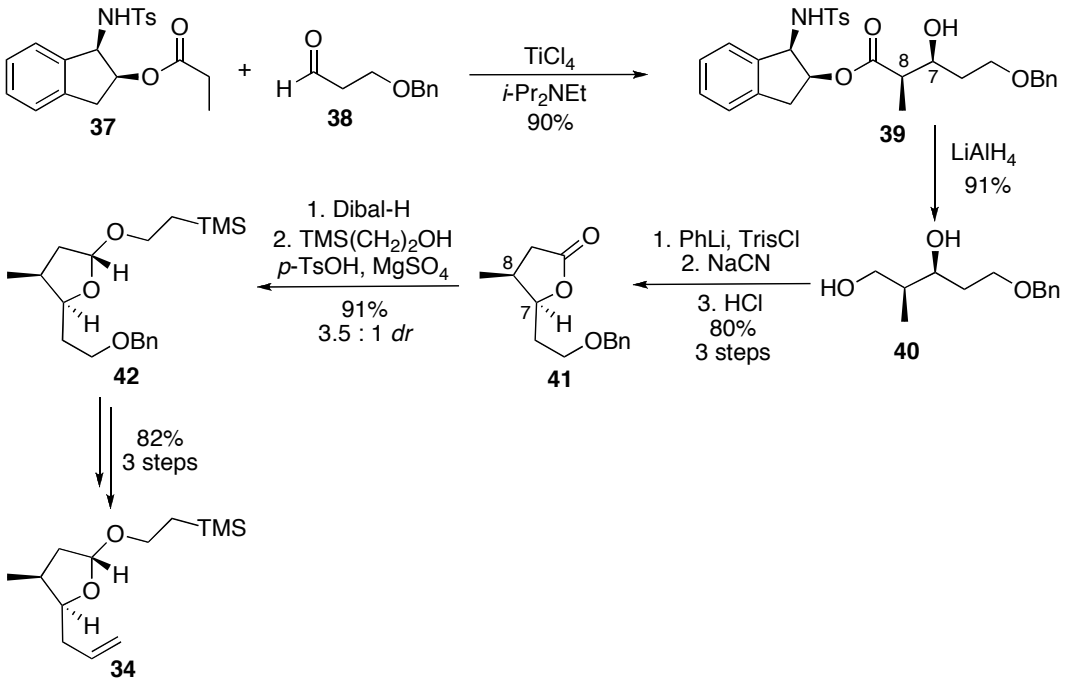
A few months following Fürstner and co-workers article, the Ghosh group published the first total synthesis of amphidinolide T1.[12] With regard to construction of the tetrahydrofuran **34**, a similar strategy was employed to that used by the Fürstner group (Scheme 12). Fragment coupling of **34**, **35** and **36** was performed using cross metathesis and stereoselective Lewis acid–mediated alkylation reactions. Finally, the macrocycle was formed using a macrolactonisation procedure.



Scheme 12: Ghosh's retrosynthesic analysis of amphidinolide T1

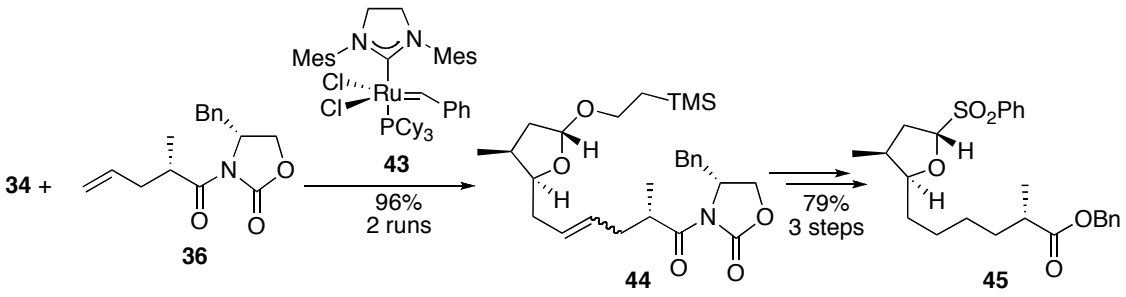
The desired stereochemistry at C7 and C8 was achieved by aldol condensation with an indanyl-derived chiral auxiliary **37** to deliver the hydroxy ester **39** in high yield and with total diastereocontrol (Scheme 13).[20] Removal of the chiral auxiliary, followed by selective sulfonylation of the primary alcohol, displacement of the resulting sulfonate with cyanide anion and acid-promoted lactonisation afforded **41**. Subsequent reduction and protection delivered the tetrahydrofuran **42** with a moderate level of diastereocontrol. A three-step sequence converted the protected alcohol group into terminal alkene **34**, which was the coupling partner of oxazolidinone **36** (Scheme 12).

[20] Ghosh, A. K.; Fidanze, S.; Onishi, M.; Hussain, K. A. *Tetrahedron Lett*. **1997**, *38,* 7171–7174.



Scheme 13: Ghosh methodology and tetrahydrofuran ring formation

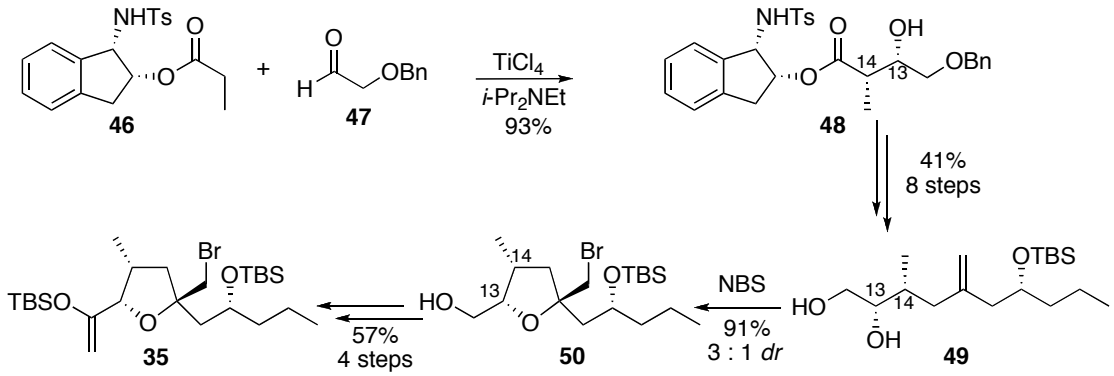
Oxazolidinone **36** was prepared in a few steps using the Evans auxiliary. Exposure of the two fragments to the Grubbs second generation catalyst **43** afforded the cross metathesis product **44** in 36% yield (Scheme 14). Second treatment by Grubbs II catalyst was necessary to recycle dimers and by products affording 96% yield of the desired product **44**. Further functionalisation of **44** delivered the sulfone **45**, the coupling partner for the Lewis acid-mediated addition.



Scheme 14: Cross metathesis coupling

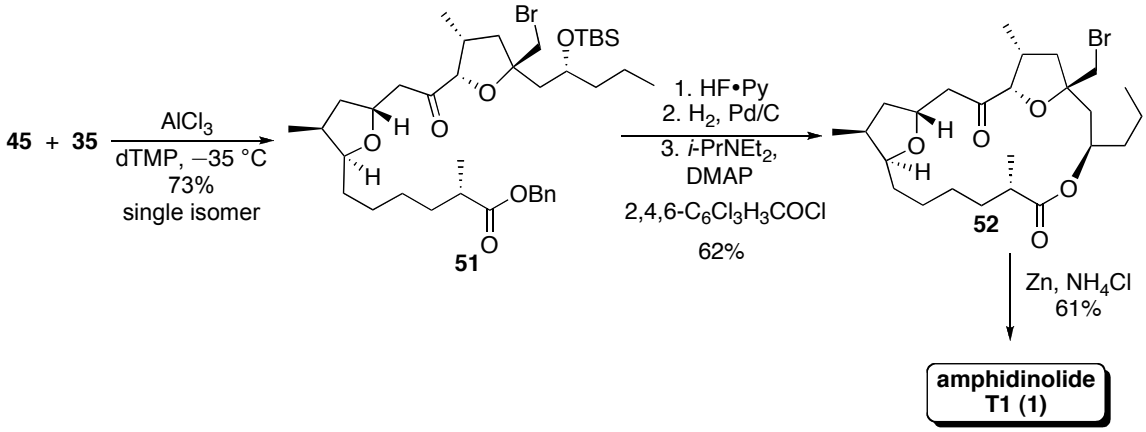
Ghosh and co-workers used the same methodology to introduce the chiral centres on C13 and C14 in excellent yield and with total diasterocontrol, while delivering hydroxyester **48** (Scheme 15).[20] Diol **49** was generated in eight steps from **48** and NBS-mediated protection of the alcohol functionality on C13 and the *exo*-methylene group afforded bromo-tetrahydrofuran **50** with a moderate

level of diastereocontrol (3 : 1 ratio of diastereoisomers). The protection overcame the difficulty with the methylenation of the ketone group to the exocyclic double bond (see Fürstner's strategy). A four-step sequence completed the synthesis of the fragment **35** in good yield.



*Scheme 15: Fragment **35** synthesis*

An oxonium-mediated alkylation was optimised for the coupling of the fragments **45** and **35**, which delivered compound **51** in good yield (Scheme 16). Further deprotection delivered the precursor required for Yamaguchi macrolactonisation, which appeared to be a very efficient way to close the 19-membered ring.[21] Reductive bromo-tetrahydrofuran opening completed the first synthesis of amphidinolide T1 (**1**).



Scheme 16: Final steps to amphidinolide T1

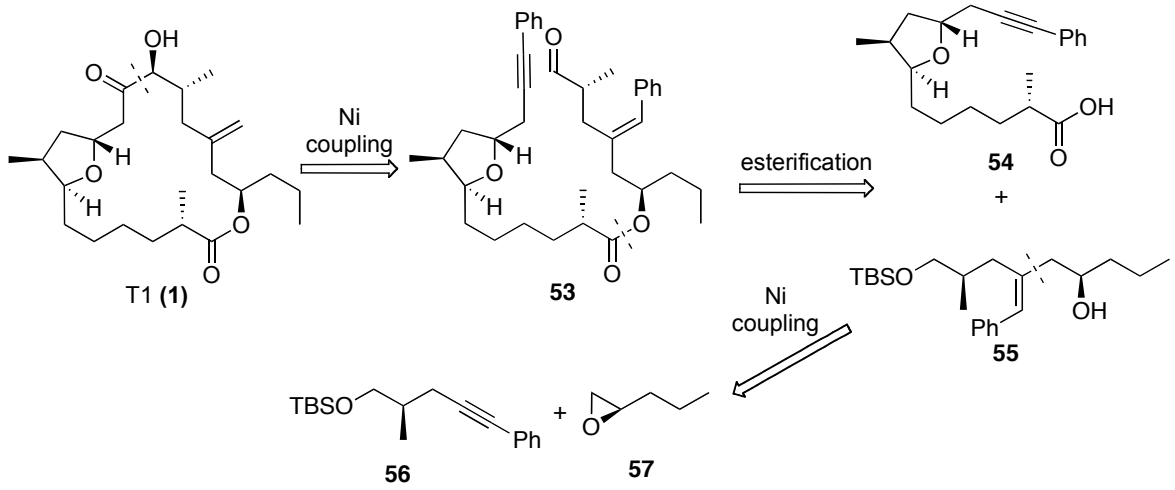
The longest linear sequence in Ghosh's synthesis was 19 steps and the strategy was to functionalise each fragment to avoid the lower-yielding steps after fragment coupling. The overall yield was 5.8%, which is the highest yield

[21] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

achieved so far. The Ghosh group has not reported the synthesis of any other members of the amphidinolide T series.

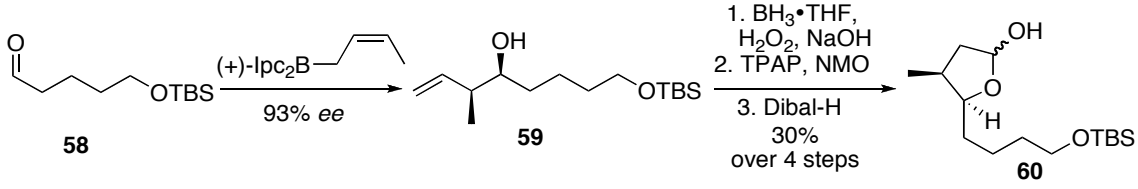
2.3 The Jamison Approach Towards Amphidinolides T1 and T4

The retrosynthetic strategy from Jamison group involved closure of the macrocycle by nickel-catalysed reductive coupling of an alkyne and an aldehyde of the precursor **53**.[13,22] The main fragments **54** and **55** were first coupled by esterification and creation of stereogenic centres was envisioned *via* stereoselective nickel-catalysed coupling of the alkyne **56** and epoxide **57** (Scheme 17).[23]



Scheme 17: Jamison's strategy for amphidinolide T1 synthesis

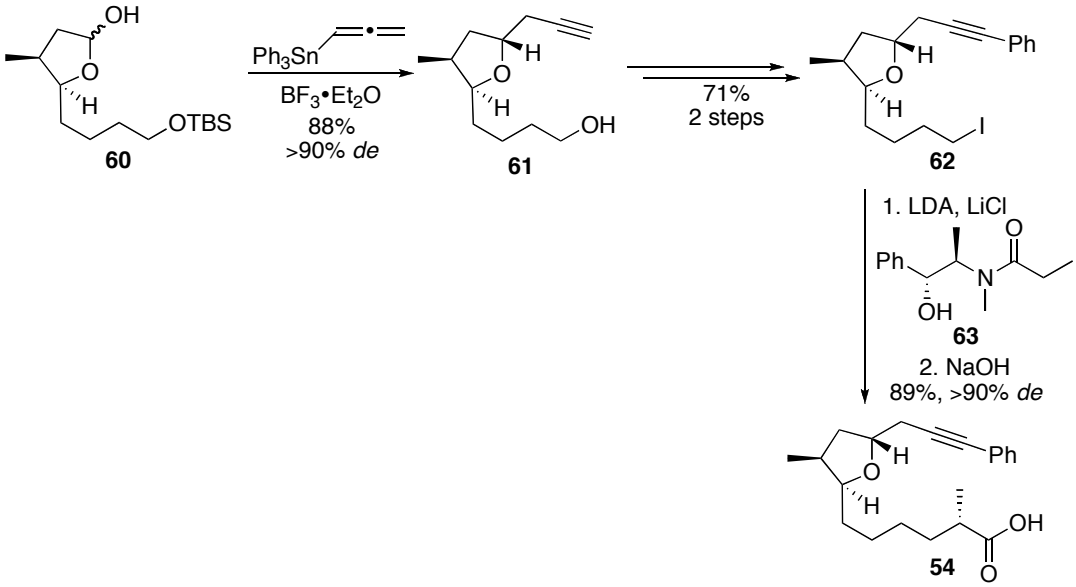
The tetrahydrofuran ring was forged in a straightforward manner, starting with the enantioselective crotylation of aldehyde **58** developed by Brown (Scheme 18).[24] The resulting homoallylic alcohol **59** was treated under hydroboration conditions, subsequent oxidative cyclisation and partial reduction afforded the lactol **60** (93% ee) in 30% yield over 4 steps.



Scheme 18: Tetrahydrofuran formation on Jamison's strategy

[22] Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076–8077.
[23] Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000,** *2*, 4221–4223.
[24] Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923.

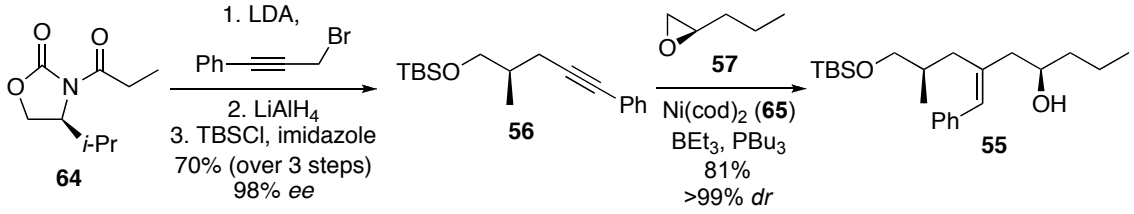
Subsequent allenylstannane addition to introduce the alkyne moiety and concomitant removal of the TBS protective group was achieved by Lewis acid-mediated alkylation which delivered **61** in the highest yield and diastereoselectivity as compared to other propargylic addition reactions that were tested (Scheme 19).[13] Alcohol **61** was then converted into the iodide **62**, which was an effective electrophile for the pseudoephedrine-based alkylation procedure developed by Myers.[25] Subsequent auxiliary removal by hydrolysis delivered the carboxylic acid **54**.



Scheme 19: Tetrahydrofuran moiety functionalisations

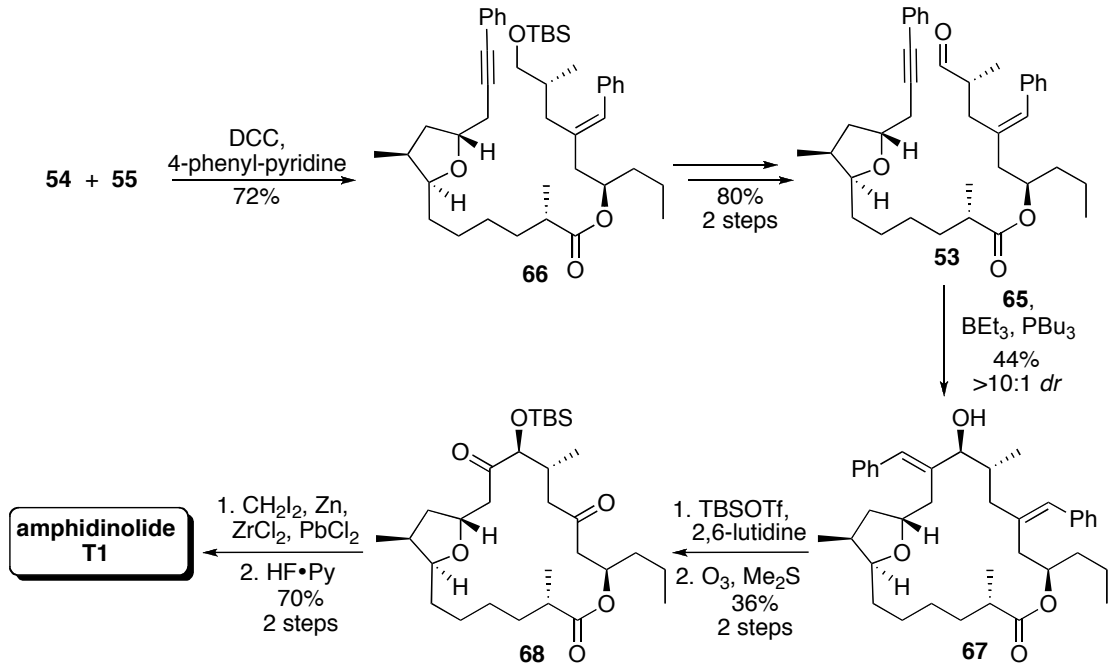
Next, Jamison *et al.* synthesised the fragment **55** in just four steps. Aryl alkyne **56** was prepared efficiently by alkylation of the Evans *N*-acyloxazolidinone system **64** (Scheme 20). The enantiomerically enriched epoxide **57** was obtained by Jacobsen hydrolytic kinetic resolution.[26] Nickel-catalysed opening of the epoxide **57** with the alkyne **56** delivered the homoallylic alcohol **55** in good yield and with excellent regioselectivity (>98:2) and total diastereocontrol.[23] This extremely efficient sequence provided the alcohol **55** in four steps, with excellent stereocontrol of both stereocentres.

[25] Myers, A. G.; Yang, B. Y.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.
[26] Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938.



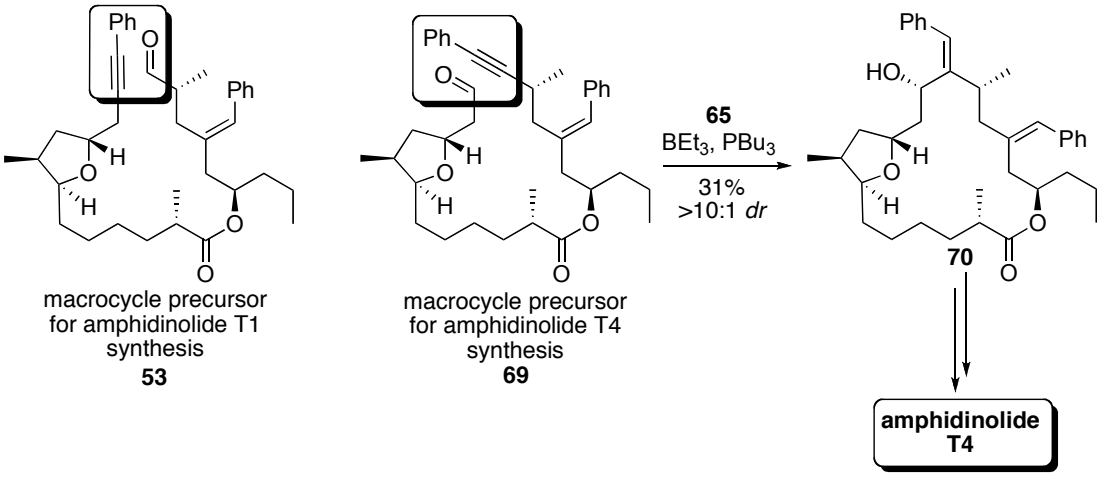
Scheme 20: Jamison methodology applied to amphidinolide T1 synthesis

Coupling of the main fragments **54** and **55** was performed by DCC-assisted esterification (Scheme 21). Deprotection and oxidation delivered the precursor **53** for nickel-catalysed macrocyclisation in 80% overall yield. Optimised conditions furnished the 19-membered lactone **67** in 44% yield with a good ratio of diastereoisomers (>10:1). Alcohol protection and ozonolysis afforded the diketone **68** in low yield over two steps. Differences in steric hindrance around the carbonyl groups allowed selective methylenation and subsequent deprotection delivered the target in 17 steps with an overall yield of 1.1%.



Scheme 21: Jamison's end game to amphidinolide T1.

Jamison and co-workers adopted a slightly different strategy in order to complete the synthesis of amphidinolide T4.[14] Reversal of the positions of the aldehyde and alkyne groups prior to cyclisation on **53** resulted in an exchange of positions of the alcohol and the trisubstituted alkene in the macrocycle **70** (Scheme 22). The sequence employed in the amphidinolide T1 route was then used to complete the synthesis of amphidinolide T4 in a total of 15 steps with an overall yield of 1.7%.

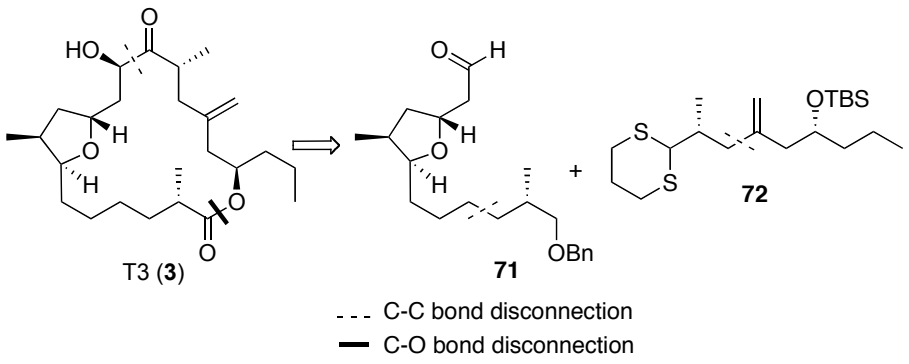


Scheme 22: Strategy applied to amphidinolide T4 synthesis

The synthetic strategy described above was applied to the synthesis of the entire amphidinolide T family of natural products. However, to date Jamison and co-workers have only published syntheses of amphidinolides T1 and T4;[13,14] the approach proved unsuccessful for the synthesis of amphidinolide T2.[27] Despite this, they reported the shortest route to amphidinolide T4, which was accomplished in 15 steps and with an overall yield of 1.7%.

2.4 Zhao's Strategy Towards Amphidinolide T3

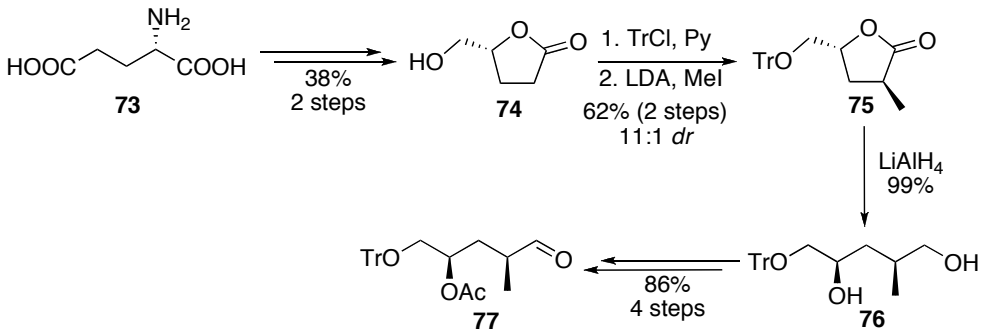
The Zhao group implemented a different strategy to prepare amphidinolide T3 (Scheme 23).[15] They envisaged Yamaguchi macrolactonisation to accomplish macrocycle formation and subsequent carbon-carbon bond disconnection revealed the aldehyde **71** and the dithiane **72**. Extensive use of Umpolung chemistry makes this strategy very distinctive.



Scheme 23: The Zhao retrosynthesis for amphidinolide T3

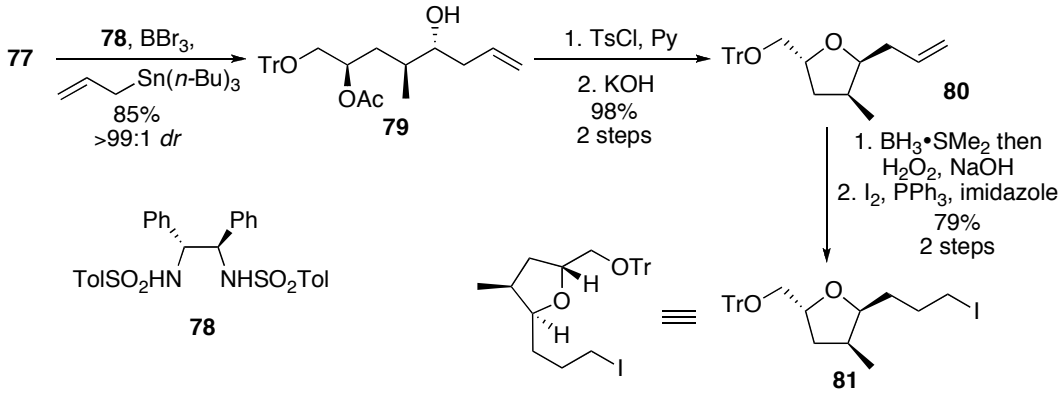
[27] Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *Tetrahedron* **2005**, *61*, 6243–6348.

The hydroxy lactone **74** was prepared from D-glutamic acid **73** in moderate yield and was subsequently protected and methylated to afford **75** in a highly diastereoselective manner (Scheme 24).[28] Reductive ring opening delivered the diol **76** in quantitative yield, which was converted to the aldehyde **77** in excellent yield over four steps.



*Scheme 24: Preparation of aldehyde **77***

After much experimentation, diastereoselective allylation of the aldehyde **77** was accomplished using reagent control provided by the diamine **78** (Scheme 25).[29] The resulting alcohol **79** was tosylated and treatment with potassium hydroxide delivered the tetrahydrofuran ring **80**. Hydroboration followed by iodination furnished iodide **81**, installing an electrophilic site ready for further manipulation.

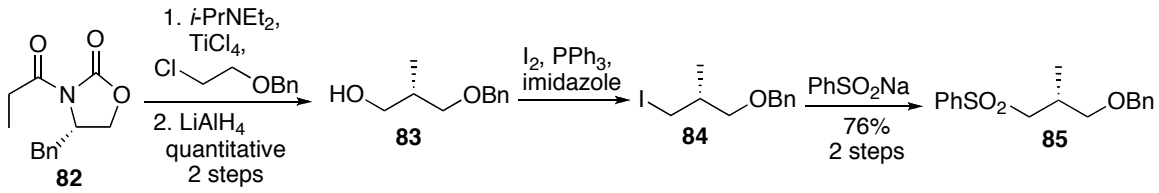


Scheme 25: Tetrahydrofuran ring formation

Evans' methodology was used to prepare the alcohol **83** in a very concise manner (Scheme 26). The alcohol **83** was subjected to iodination and the first

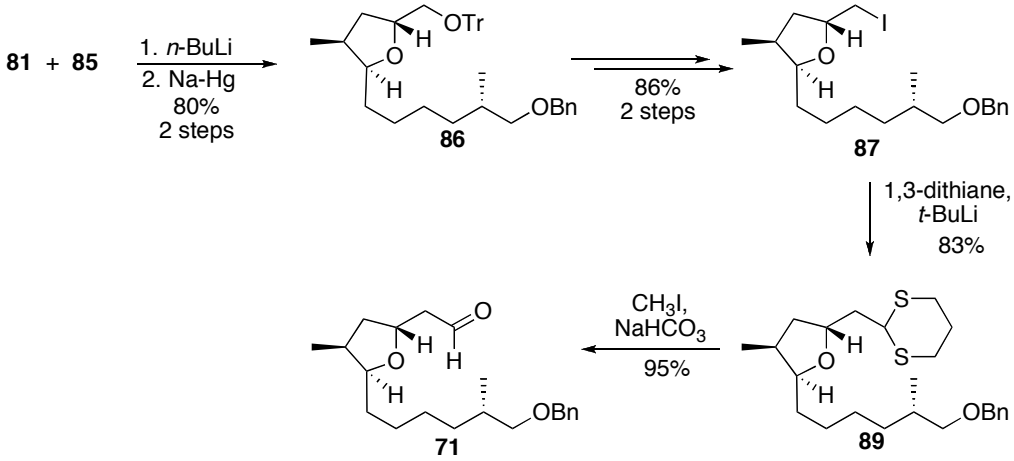
[28] Tomioka, K.; Cho, Y. S.; Sato, F.; Koga K. *J. Org. Chem.* **1988**, *53,* 17, 4094–4098.
[29] Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111,* 5495–5496.

inversion of polarity was performed by displacement of the iodide **84** with a sulfone to generate the side chain **85** in good yield.



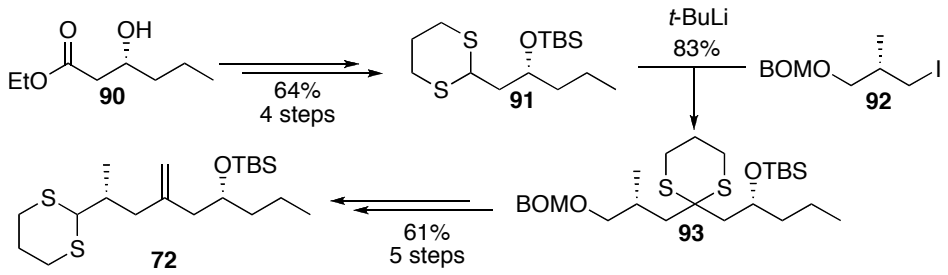
Scheme 26: Side chain preparation

Deprotonation of sulfone **85** generated the required nucleophile to react with the iodide **81** (Scheme 27). Subsequent removal of the sulfonyl group delivered the coupled product **86** in good yield over two steps. Side chain homologation was performed by dithiane displacement of the iodide on **87** and subsequent hydrolytic dithiane cleavage using iodomethane generated the aldehyde **71** in good yield.



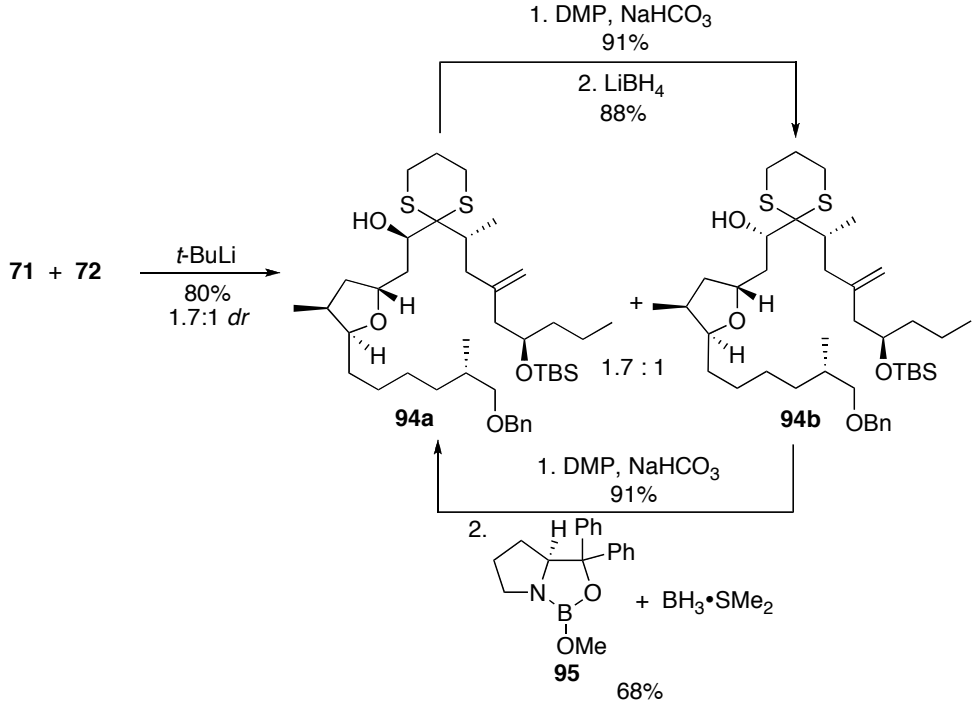
*Scheme 27: Fragment **71** construction*

Synthesis of the eastern fragment **72** commenced from β-hydroxy ester **90**, which was prepared by enantioselective hydrogenation using the Noyori protocol. The β-hydroxyester **90** was converted into the corresponding dithiane **91** (Scheme 28). The coupling partner **92** was synthesised the same way as **84** albeit with opposite stereochemistry. Subsequent dithiane coupling was carried out in good yield to deliver couple product **93** and further manipulations completed the synthesis of the fragment **72**.



*Scheme 28: Fragment **72** synthesis*

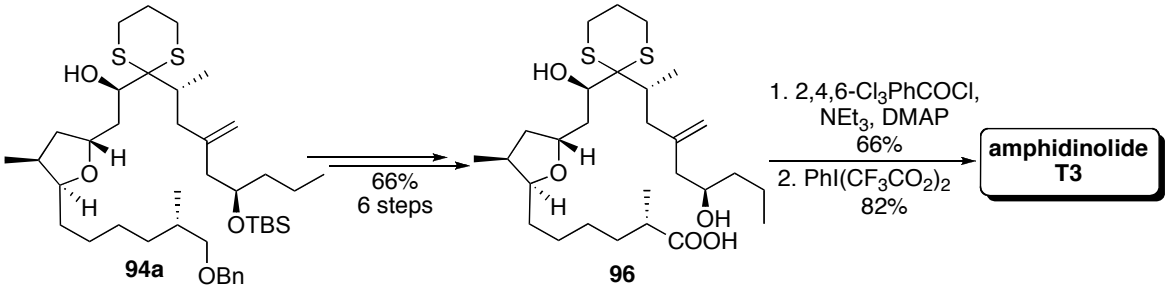
The susbequent addition of the anion generated from dithiane **72** with aldehyde **71** was high yielding, but the diastereomeric ratio was rather poor (1.7:1) (Scheme 29). Further oxidation of **94b** followed by stereoselective Corey-Bakshi-Shibata reduction of the resulting ketone allowed the desired diastereoisomer to be recycled as **94a** in 68% yield.[30] The diastereomeric compound **94a** could be also converted to **94b** in order to complete a synthesis of amphidinolide T4.



*Scheme 29: Coupling and recycling of the undesired diastereomer **94b***

Six steps were necessary to oxidise, protect and then deprotect the groups required for the Yamaguchi's macrolactonisation reaction (Scheme 30).[21] Finally, dithiane deprotection to reveal the C13 ketone concluded the total synthesis of amphidinolide T3.

[30] Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.

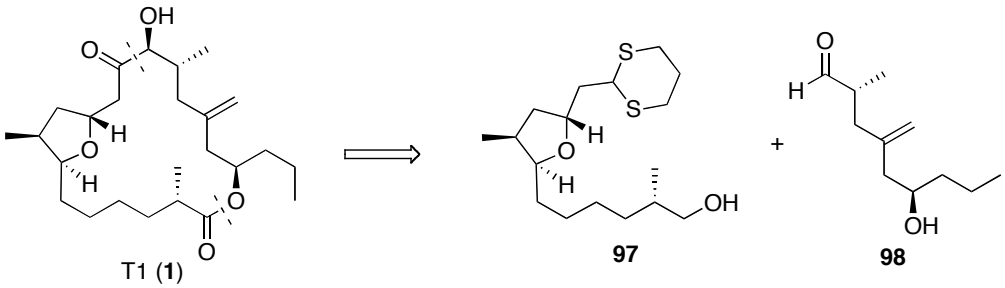


Scheme 30: End game to amphidinolide T3

Amphidinolide T3 was prepared in 29 steps and in an overall yield of 1.8%. The strategy could also be applied to the synthesis of amphidinolide T4.

2.5 Yadav's Synthesis of Amphidinolide T1

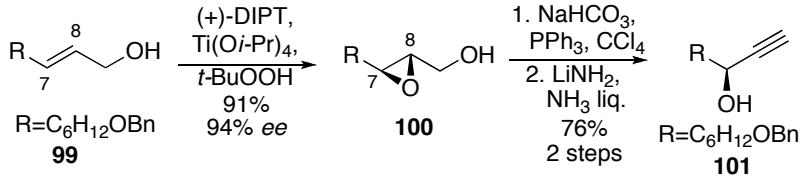
Yadav and co-workers published the synthesis of amphidinolide T1 (Scheme 31), showcasing a radical cyclisation reaction developed by their research group.[16,31] The primary disconnections were similar to that employed by Zhao, as some of the key bond-forming reactions including dithiane coupling and macrolactonisation, revealing the dithiane **97** and the aldehyde **98**.



Scheme 31: Yadav's retrosynthetic plan

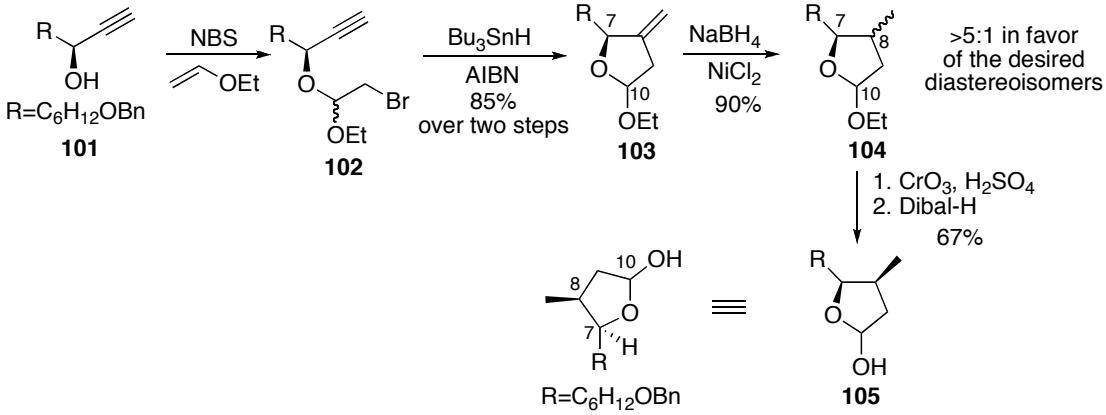
The desired stereochemistry of the tetrahydrofuran ring at C7 was obtained by Sharpless asymmetric epoxidation on the homoallylic alcohol **99** affording the epoxyde **100** in excellent yield and with good enantioselectivity (Scheme 32). A two-step sequence furnished the cyclisation precursor **101** in good yield.

[31] Yadav, J. S.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1824–1825.



Scheme 32: Sharpless epoxidation towards the cyclisation precursor

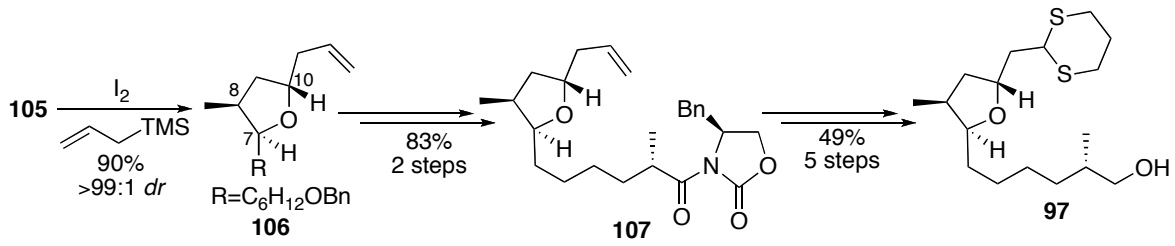
Closure of the tetrahydrofuran ring was performed *via* radical cyclisation of the bromoacetal and alkyne moieties within **102**, which was derived from **101** (Scheme 33). Hydride reduction of the alkene **103** afforded the desired product **104** with greater than 5:1 distereoselectivity. However, a further oxidation/reduction sequence was required to separate the diastereoisomers, adding two extra steps to obtain the lactol **105**.



Scheme 33: Yadav's radical cyclisation methodology

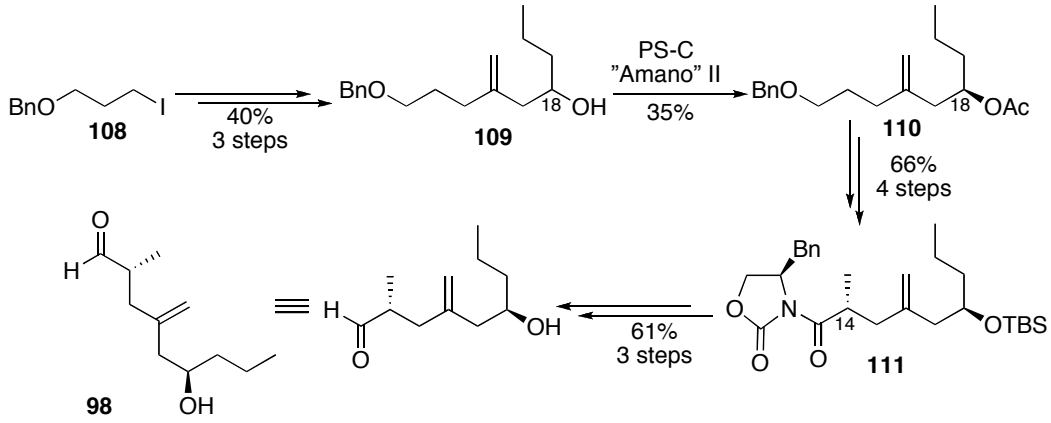
Concomitant debenzylation and diastereocontrolled allylation was performed by simple treatment of **105** with iodine and allyltrimethylsilane to yield the thermodynamically favoured *trans* tetrahydrofuran product **106** (Scheme 34).[32] The Evans oxazolidinone auxiliary was efficiently introduced and methylation at C2 was then performed to deliver **107**. Five further steps were required to prepare the precursor **97** to be used in the dithiane coupling reaction.

[32] Yadav, J.S.; Subba Reddy, B.V.; Thrimurtulu, N.; Mallikarjuna Reddy, N.; Prasad A.R. *Tetrahedron Lett.* **2008**, *49*, 12, 2031–2033.



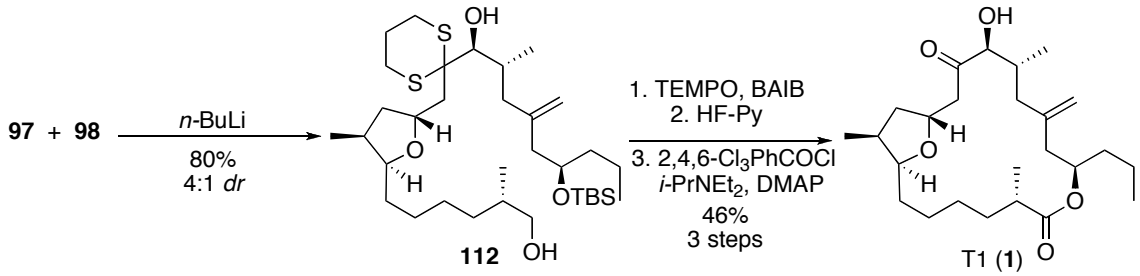
*Scheme 34: Synthesis of segment **97***

The synthesis of the last fragment started from the iodide **108**, which was converted into the racemic alcohol **109** in three steps (Scheme 35). Enzymatic resolution of the racemic alcohol **109** by the lipase "Amano" II (35% yield, 98% *ee*) provided the acetate **110** of the required enantiomer. The final chiral centre at C14 was introduced by an Evans methylation reaction delivering **111** and the synthesis of the fragment **98** was completed in three additional steps.



*Scheme 35: Fragment **98** synthesis*

Dithiane coupling of **97** and **98** delivered the required Cram product **112** as the major product along with the diastereomeric alcohol in a 4:1 ratio (Scheme 36). Selective oxidation of the primary alcohol with concomitant removal of the dithiane group was performed by treatment with TEMPO and BAIB. Removal of the TBS group followed by macrolactonisation under Yamaguchi conditions afforded amphidinolide T1.[21]

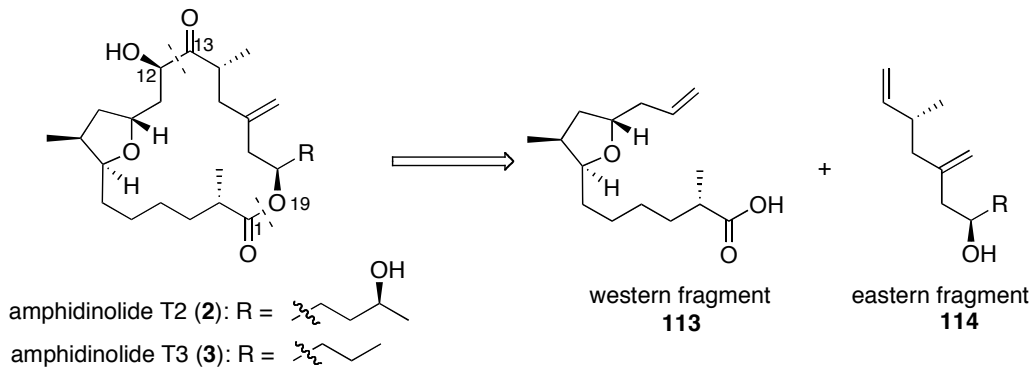


Scheme 36: End game to the amphidinolide T1 synthesis

The synthesis of amphidinolide T1 was performed in 23 steps and with an overall yield of 3.4%. Only this member of the amphidinolide T family was prepared using the route.

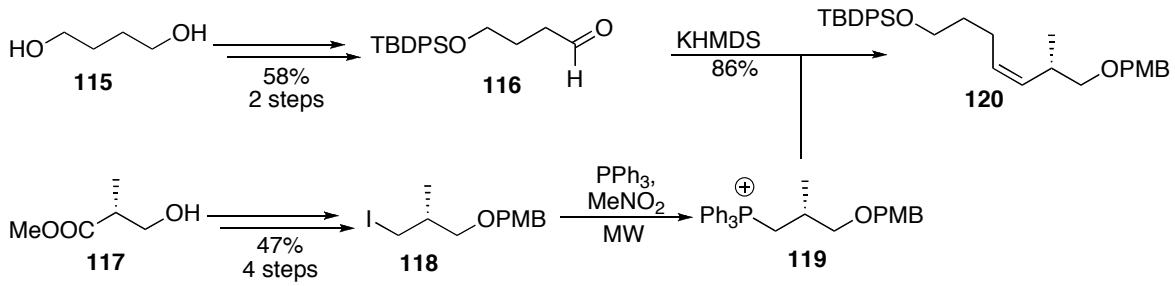
2.6 Dai's Approach to Amphidinolide T2 and T3

Dai and co-workers published the most recent total syntheses of two members of the amphidinolide T family in 2010.[17,18] Retrosynthetic analysis started with C-C bond disconnection (C12 to C13) at the α-hydroxy ketone (Scheme 37). The structure was split further into two fragments **113** and **114** by cleavage of the ester C–O bond.



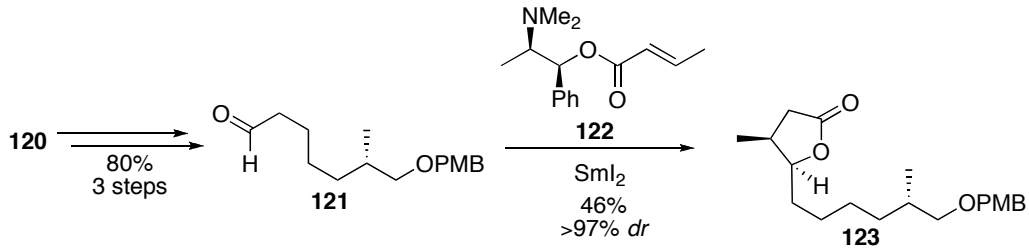
Scheme 37: Dai's strategy

Synthesis of acid **113** commenced from 1,4-butanediol **115**, which was converted to aldehyde **116** in two steps (Scheme 38). The iodide **118** was prepared from the (*R*)-(−)-Roche ester **117**. Microwave-assisted iodide displacement generated the phosphonium salt **119** and a Wittig reaction between the aldehyde **116** and the ylide generated from the salt **119** produced the *Z*-alkene **120** in good yield.



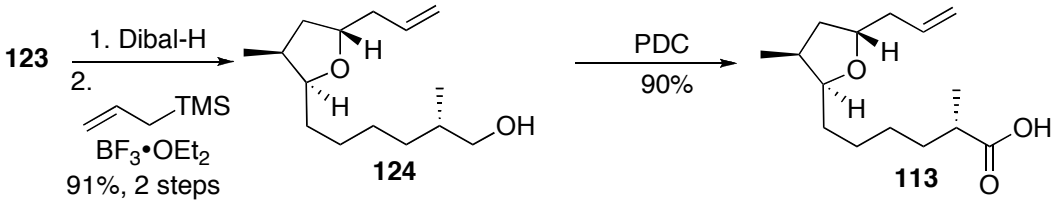
Scheme 38: Wittig coupling

Dai and co-workers prepared the lactone **123** by employing a samarium iodide mediated cyclisation reaction (Scheme 39). The aldehyde precursor **121** was derived from the alkene **120** using a three-step sequence in good yield. After optimisation, the reductive coupling delivered the lactone **123** in moderate yield but with excellent diasteroselectivity due to the ephedrine-induced stereocontrol.



Scheme 39: Samarium iodide-mediated cyclisation

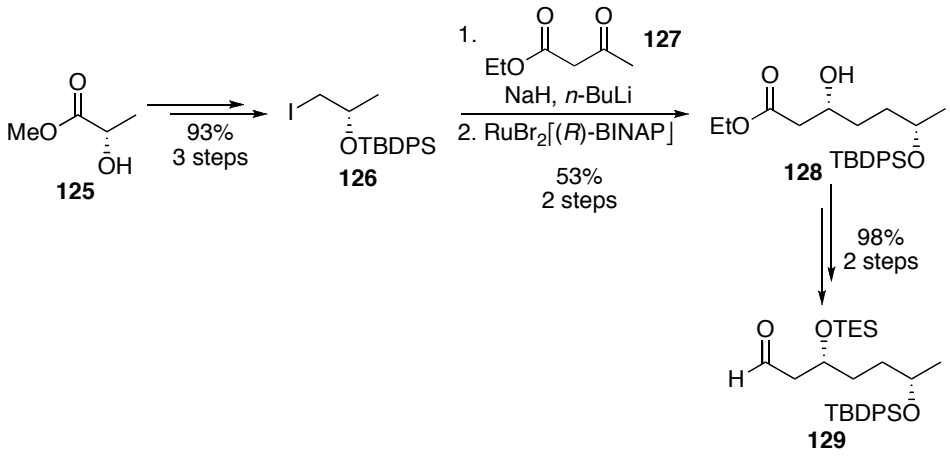
Dibal-H reduction of **123**, followed by simultaneous Lewis acid-induced allylation and deprotection delivered the alcohol **124** in good yield (Scheme 40). Oxidation completed construction of the requisite western fragment **113**.



*Scheme 40: Preparation of the western fragment **113***

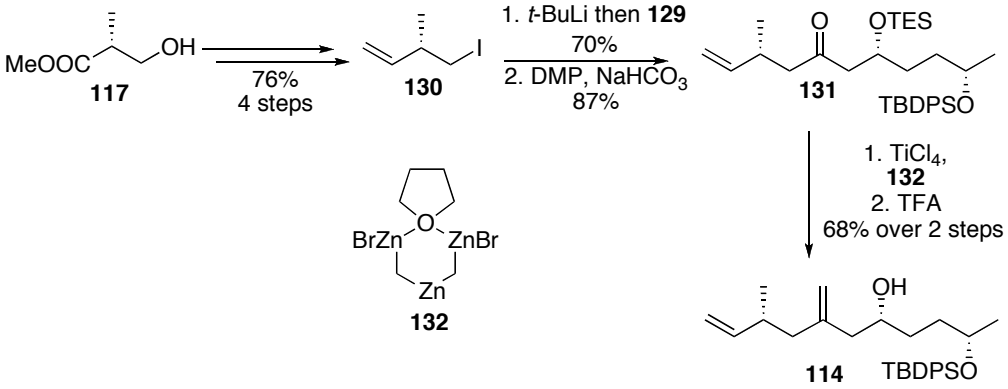
Following synthesis of the western fragment **113**, the synthesis of the eastern segment **114** was performed starting from methyl (*S*)-lactate **125** (Scheme 41). A sequence of protection, reduction and iodination delivered the iodide **126** in excellent yield. **126** was coupled to acetoacetate **127** and

stereoselectively reduced by employing Noyori's ruthenium-catalysed hydrogenation conditions affording **128**. Protection, followed by reduction furnished the aldehyde **129**.



*Scheme 41: Preparation of the aldehyde **129***

The coupling partner was the iodide **130**, which was synthesised from the (*R*)-(−)-Roche ester **117** and coupled to the aldehyde **129** by treatment with *tert*-butyllithium (Scheme 42). Oxidation to the ketone, olefination using Nysted reagent **132** and selective silyl deprotection delivered the alcohol **114**, the coupling partner required for coupling with fragment **113**.

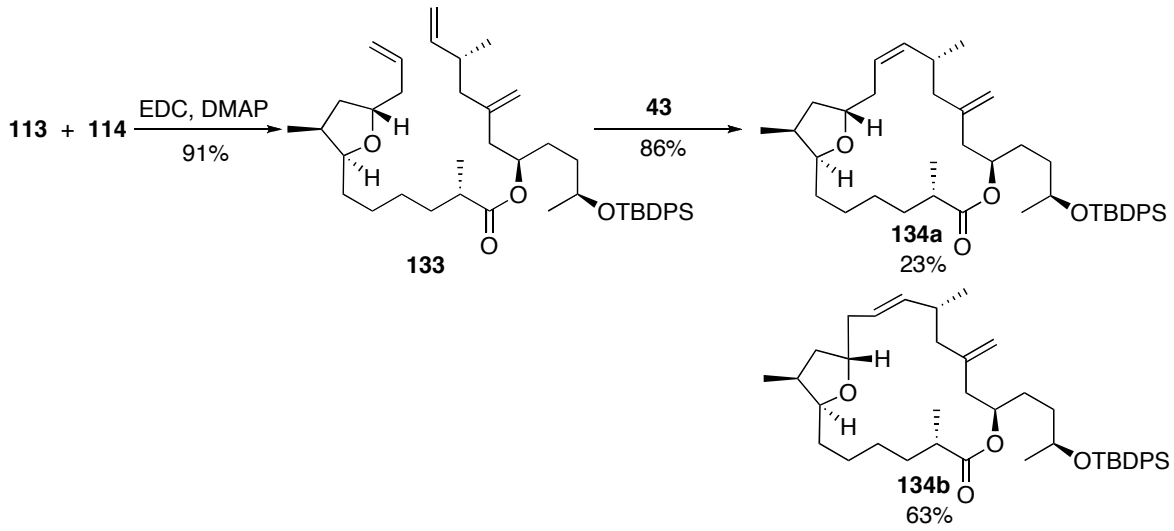


*Scheme 42: Synthesis of the last fragment **114***

Coupling of the fragments **113** and **114** was performed by Steglich esterification delivering the triene **133** and the macrocycle was closed by RCM (Scheme 43).[33] Various conditions and catalysts were screened and the best result was obtained using Grubbs second generation catalyst **43**, which delivered

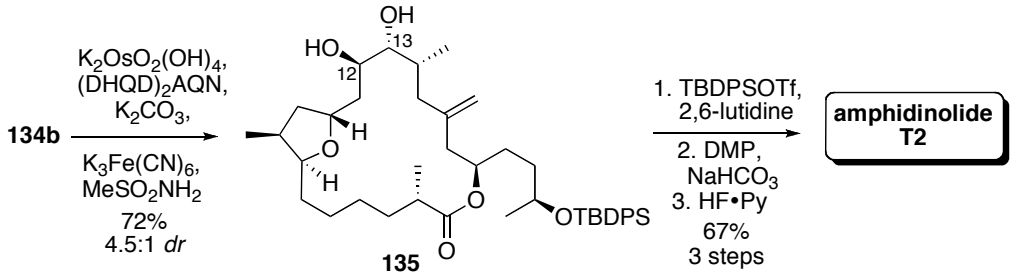
[33] Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17* , 522–524.

a 2.7:1 ratio of alkenes favouring the *E* alkene **134b**. The exocyclic double bond remained unaffected in all the metathesis experiments.



Scheme 43: Coupling and RCM

The next step involved the regioselective and diastereofacial dihydroxylation of **134b** (Scheme 44). Again, much attention was given to the optimisation of reaction conditions, but complex mixtures were obtained. Optimum reaction conditions led to a 10:1 ratio of regioisomers and a 4.5:1 ratio of diastereoisomers of diol **135**. The hydroxyl group on C12 was selectively protected and the alcohol functionality on C13 was oxidised. The total synthesis of amphidinolide T2 was completed by global desilylation.



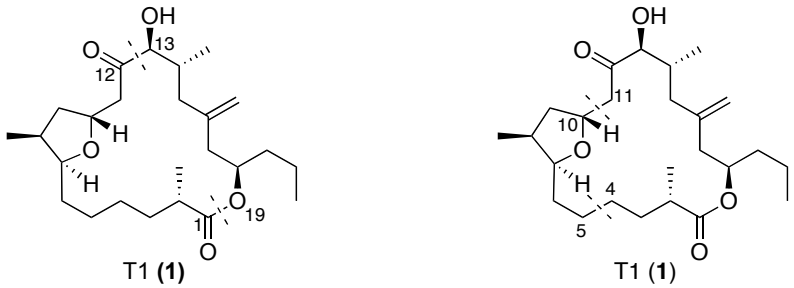
Scheme 44: End game to amphidinolide T2

The first total synthesis of amphidinolide T2 was completed in 19 steps in an overall yield of 4.2%. The same approach was applied to the total synthesis of amphidinolide T3 total synthesis which was accomplished in 19 steps in an overall yield of 1.9%.

2.7 Summary of the Total Syntheses of Amphidinolide T members

The above total syntheses of members of amphidinolide T family present an array of interesting chemistry and diverse approaches have been employed. The shortest route to a member of the family consisted of 15 steps and the best overall yield was 5.8%.[12,13]

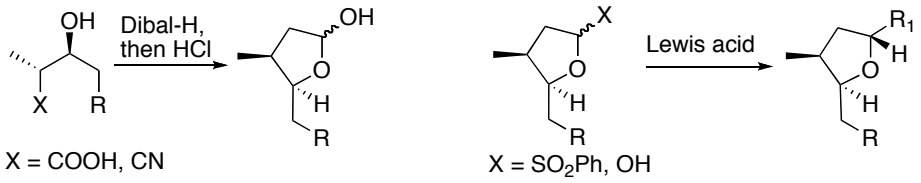
Among the diverse disconnections described in the retrosynthetic studies, two main general approaches can be discerned: the scission at the C12-C13 bond with ester hydrolysis (Jamieson, Zhao, Yadav and Dai) and the disconnections around the tetrahydrofuran ring (Fürstner and Ghosh) (Scheme 45).



Scheme 45: Two strategies to the total syntheses of amphidinolides T

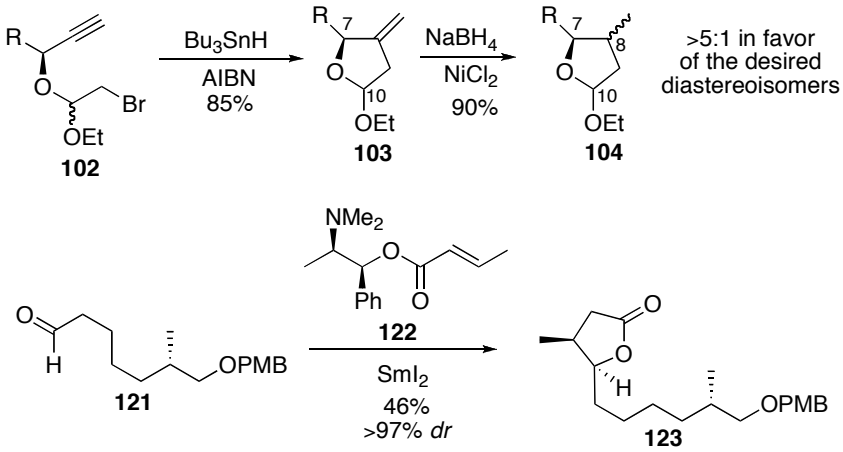
Both approaches proved to be successful and the "perfect" synthesis would, most likely, involve aspects of many of the described pathways. Macrolactonisation and esterification appear to be very efficient ring closing/coupling steps. Additionally, creation of the C4-C5 bond using metathesis was a good strategy to join the fragments and induce ring closure. Concerning functionalisation at the C12-C13 bond, issues arose about reactivity or lack of stereoselectivity (*vide infra*) allowing scope for further improvement.

Among the other synthetic issues to be addressed, the most popular method for the formation of the tetrahydrofuran ring involved intramolecular acid-mediated alcohol addition to an aldehyde or an imine functionality (Fürstner, Ghosh and Jamison). This ring closure was high yielding but extra steps were required to introduce the *trans* side chain by Lewis acid-induced alkylation (Scheme 46).



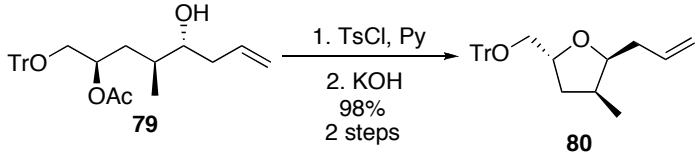
Scheme 46: Tetrahydrofuran formation by acid-mediated addition

Various radical cyclisation reactions were also employed to produce the tetrahydrofuran ring: radical ring-closing reaction by Yadav's group and samarium-mediated reductive condensation by Dai and co-workers (Scheme 47). Once again, extra steps were necessary to install the side chain by Lewis acid-mediated alkylation.



Scheme 47: Radical-mediated cyclisations

Zhao's strategy was based on intramolecular displacement of a tosylate generated from a secondary hydroxyl group (Scheme 48). This approach permitted synthesis of the trisubstituted tetrahydrofuran in good yield and with total diastereocontrol, but the route used to prepare the precursor was rather lengthy (12 steps).



Scheme 48: Tetrahydrofuran ring formation by tosyl displacement

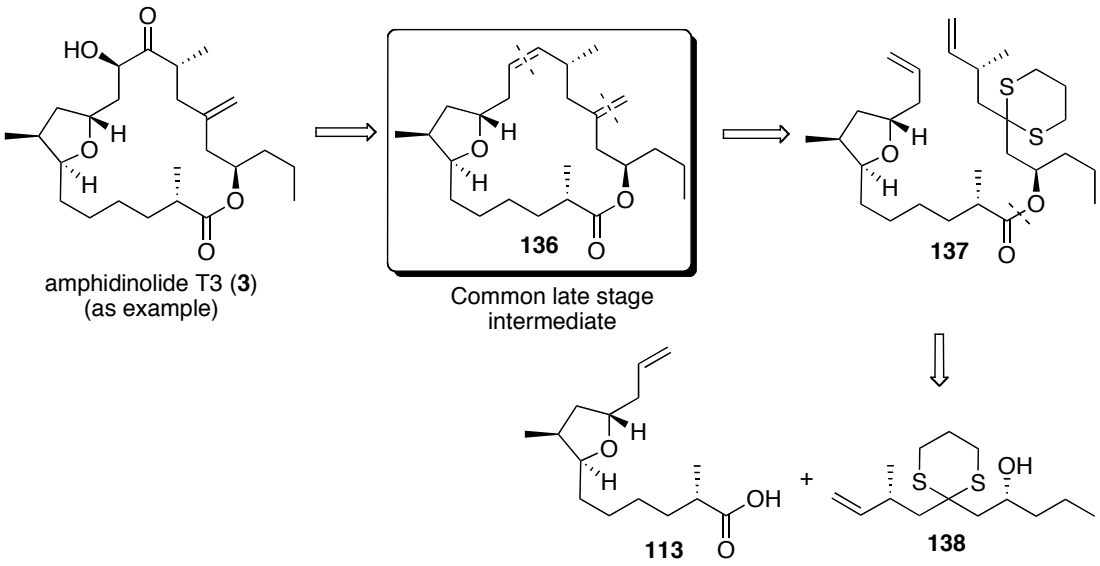
Despite the synthetic studies of various research groups culminating in the total syntheses of members of the amphidinolide T family, there remains an

opportunity to develop a truly robust and efficient pathways towards these natural targets. The complexity of their compact structures, the stereocontrol in key steps, the coupling of fragments, the concise formation of a functionalised tetrahydrofuran building block and overall convergency of the synthesis are some of the issues that need to be addressed.

3. Clark Retrosynthetic Analysis

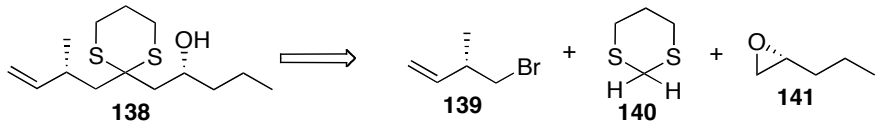
The aim of this project is to establish a concise, straightforward and high-yielding route towards the amphidinolide T1 and T3-5 from a common intermediate.

Our proposed pathway for gaining access to the amphidinolides T1 and T3-5 centred on the formation of a late stage intermediate **136** common to all natural targets. Consequently, conversion of the α-hydroxy ketone moiety present in the amphidinolide family to the (*E*)- or (*Z*)-alkene **136**, was our initial retrosynthetic step leading to the precursor for all four targets (Scheme 49). Scission of both the endocyclic and the exocyclic double bonds revealed the dithiane intermediate **137**. Subsequently, ester hydrolysis would afford the alcohol **138** (eastern fragment) and the carboxylic acid **113** (western fragment).



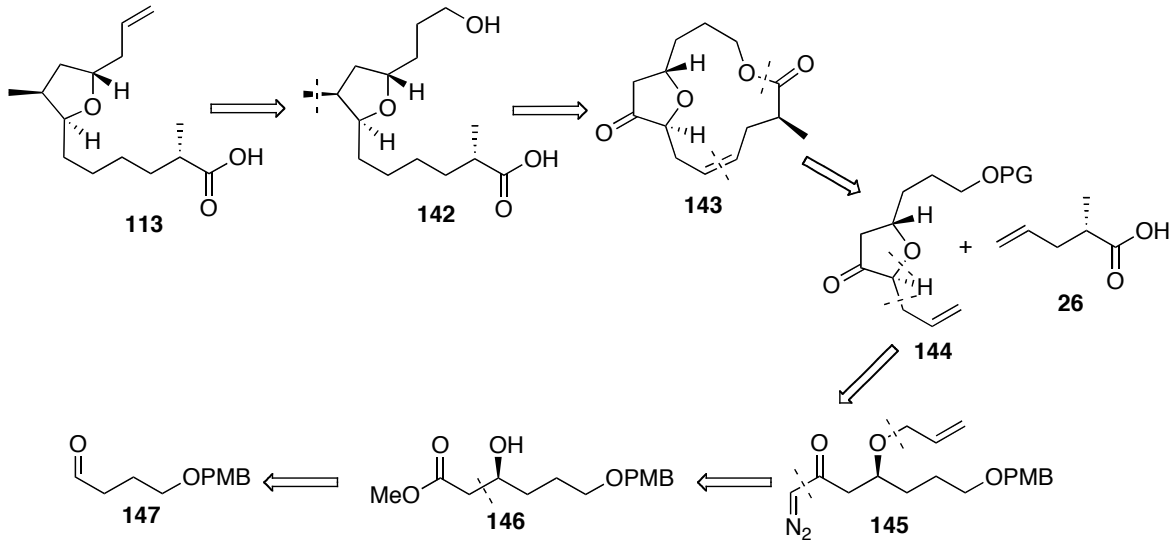
Scheme 49: Retrosynthetic analysis

The eastern fragment **138** was easily disconnected to provide the bromide **139**, dithiane **140** and the epoxide **141**, which are simple to prepare following the established procedures within the literature (Scheme 50).[34,35]



*Scheme 50: Disconnection of fragment **138***

With regard to the western fragment **113**, we envisaged that the terminal alkene present in **113** could be prepared from the primary alcohol group on **142** (Scheme 51). The methyl group present on the tetrahydrofuran ring was dehydrogenated to give an alkene and retrosynthetic Wittig olefination delivered the ketone **143**. Additionally, intermediate **142** is produced by removal of the double bond and saponification of macrocyclic ester present in **143**. Alkene scission *via* retro-RCM and ester cleavage would provide the fragments **26** and **144**. The preparation of the requisite allylic acid **26** has been described in literature.[36] The tetrahydrofuranone **144** can be prepared by rearrangement of the oxonium ylide generated from the diazoketone **145**, which, in turn, could be prepared from the β-hydroxy ester **146**. Finally, compound **146** can be prepared *via* an aldol condensation with the simple aldehyde **147**.



*Scheme 51: Disconnection of fragment **113***

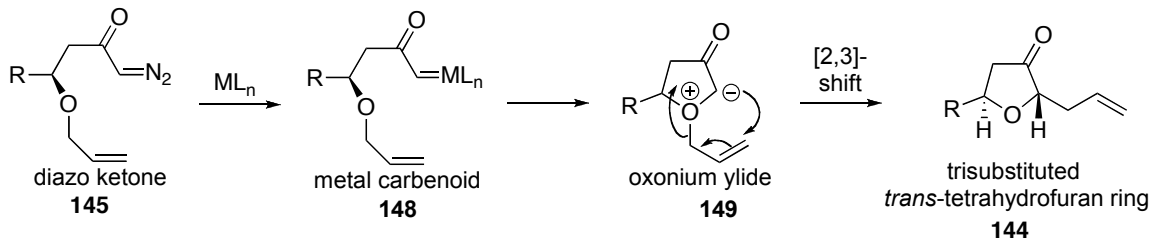
[34] Holub, N.; Neidhöfer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227–1229.
[35] Batchelor, M. J.; Gillespie, R. J.; Hedgecock, C.; Murdoch, R. *Tetrahedron* **1994**, *3*, 809–826.
[36] Hansen, D. B. *Tetrahedron : Asymmetry* **2005**, *16*, 3623–3627.

The novelty of this proposed route would be to access amphidinolides T1 and T3-5 through the single common late-stage intermediate **136**. The tetrahydrofuran ring is formed *via* a well-established methodology developed by the Clark group.[37] This key step involves a tandem oxonium ylide formation and rearrangement reaction *via* a metal carbenoid generated by decomposition of a diazoketone using a transition metal complex.

[37] Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193-6196.

Chapter 2: Synthesis of the Tetrahydrofuran Core

The main structural feature present in all five members of the amphidinolide T family consists of a trisubstituted *trans*-tetrahydrofuran ring. Ready access to the five-membered cyclic ether is the key to the completion of efficient total syntheses of these natural targets. This crucial fragment could be prepared efficiently using synthetic methodology developed in the Clark group (Scheme 52). Thus, [2,3]-sigmatropic rearrangement of an allylic oxonium ylide **149**, formed from intramolecular reaction of an allylic ether with a diazo-generated transition metal carbenoid **148**, would be expected to give the tetrahydrofuranone **144**.



Scheme 52: Clark approach to the formation of the tetrahydrofuran ring

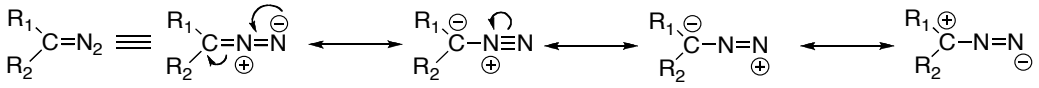
2.1. From Diazoketone to Oxonium Ylide Rearrangement

Over the last 20 years, the Clark group has explored reactions of diazo carbonyl compounds under various reaction conditions in order to access many useful structural motifs *via* rearrangement reactions.[37] Our research group is focusing on the application of these reactions to natural products synthesis.

2.1.1 Diazo Carbonyl Chemistry

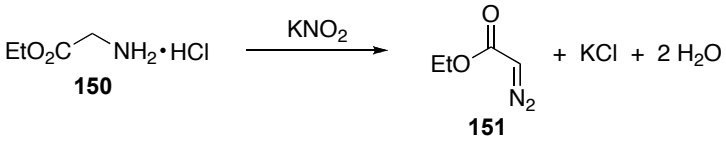
Their ease of preparation, their properties of decomposition into carbenoids and facile rearrangement to give interesting structural features, make diazo carbonyl compounds important intermediates in organic synthesis.

The diazo functionality is a neutral dipole consisting of terminal nitrogen atoms. The electronic distribution is illustrated in Scheme 53.



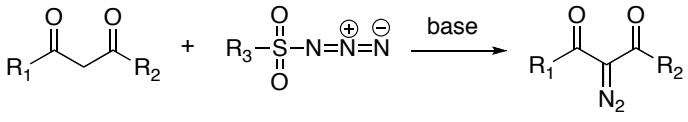
Scheme 53: Diazo compound resonance forms

In 1883, Curtius reported the generation of diazo esters by treating amino acid derivates with potassium nitrite (Scheme 54).[38] The diazotisation of glycine ethyl ester hydrochloride **150** was the first synthesis of diazo carbonyl compound **151**.



Scheme 54: Curtius first diazo ester synthesis

Diazo transfer to activated carbonyl compounds was discovered by Dimroth in 1910 and was studied extensively by Regitz in 1967.[39,40] This method of diazo carbonyl generation, using sulfonylazides, worked best for cyclic systems and also for some acyclic carbonyl systems that are difficult to access using other methods (Scheme 55). The reaction requires basic media and the common substrates are malonic esters, β-ketoesters, β-ketoamides and β-diketones. In addition, this method is applicable to ketones and base-sensitive substrates with some preparative steps.[41]



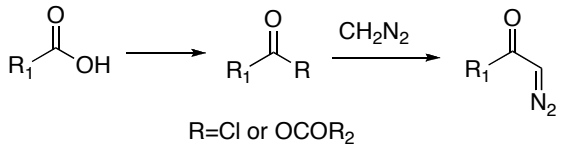
R_1, R_2=aryl, alkyl, NH_2, NR_2, ; R_3=Me, *p*-tolyl, *p*-CO_2H-phenyl

Scheme 55: Diazo carbonyl formation on activated carbonyl compounds

Another general procedure used to prepare the diazo compounds is by acylation of diazomethane (Scheme 56). The method was developed by Arndt

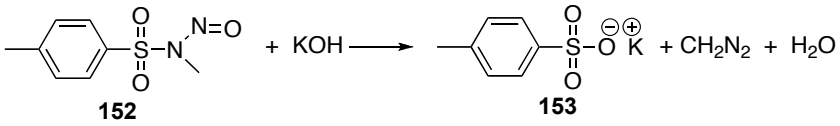
[38] Curtius, T. *Chem. Ber.* **1883**, *16*, 2230–2231.
[39] Dimroth, O. *Liebigs Ann. Chem.* **1910**, *373*, 336–370.
[40] Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 733–749.
[41] Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964.

and Eistert in 1927 and remains the most commonly used process to prepare terminal acyclic diazoketones.[42] The diazoketone precursors can be acid chlorides or mixed anhydrides, which are prepared from the corresponding carboxylic acid and then added to an ethereal diazomethane solution.



Scheme 56: Diazoketone formation by acylation of diazomethane

A practical way to prepare an ethereal solution of diazomethane is by basic treatment of *N*-methyl-*N*-nitrosotoluensulfonamide **152** (or Diazald®) followed by co-distillation of the resulting diazomethane with diethyl ether (Scheme 57).[43]



Scheme 57: Generation of diazomethane by Diazald®

Dehydrogenation of a hydrazone or fragmentation of a triazene offers an alternative for the generation of a diazo compound.[44] However, these procedures are employed less commonly due to issues of low chemoselectivity.

Diazoketones are stable for weeks at low temperature due to the stabilising electron-withdrawing effect of the ketone functionality. In addition to the relative stability and the ease of preparation of diazo ketones, their main property is their reactivity with transition metal complexes to generate metal carbenoids, which allows access to a broad range of reactions such as C-H insertion, cyclisation and rearrangement. Metals carbenoids are related closely to carbenes with a metal bonded to stabilise and allow different properties.

[42] Arndt, F.; Eistert, B.; Partale, W. *Chem. Ber.* **1927**, *60*, 1364–1370.
[43] For preparations and reactions, see: *Aldrichimica Acta*, **1983**, *16* (1), 3–10.
[44] For recent review of preparations: Maas, G. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 8186–8195.

2.1.2 Carbenes

Carbene is a neutral species with six valence electrons; four bonding and two non-bonding.[45,46] Depending on the arrangement of the two non-bonding electrons in the two non-bonding orbitals, two distinct types of carbene can be formed: singlet **154** and triplet **155**. Singlet carbenes **154** possess a pair of electrons with opposite spin in a sp^2 orbital; triplet carbenes **155** have one non-bonding electron in an sp^2 orbital and one in a p orbital with parallel spins (Figure 7).

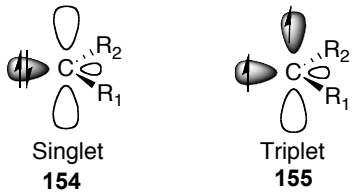
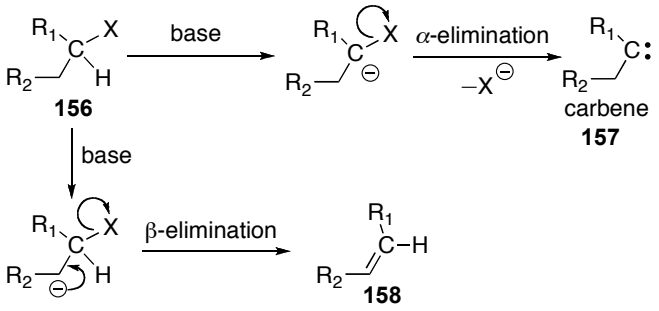


Figure 7: Singlet and triplet carbenes

The electronic organisation depends on the method of preparation, as well as the electronic nature of the substituents (R_1 and R_2). Generally, carbenes are short-lived reactive species, although persistent carbenes are known. Triplet carbenes **155** are more stable than the singlet types **154** and display a different reactivity profile. Singlet carbenes **154** generally react either as electrophiles or nucleophiles, whilst triplet carbenes **155** can be considered as diradicals and participate in stepwise radical reactions.

Carbenes are usually formed by loss of a stable molecule or by an α-elimination reaction. The latter occurs when a haloalkane **156** is deprotonated using a strong base and subsequent loss of a halide anion generates the carbene **157** (Scheme 58). The requirement for a strong base in this procedure, such as an organolithium reagent, can cause an undesired β-elimination reaction generating an undesired alkene **158**. The preparation of the desired carbene is more efficient using a trihalomethane to generate the corresponding dihalocarbene in the presence of a base such as hydroxide.

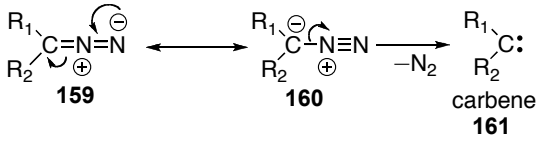
[45] Grasse, P. B.; Brauer, B. E.; Zupancic, J. J.; Kaufmann, K. J.; Schuster, G. B. *J. Am. Chem. Soc.* **1983**, *105*, 6833–6845 and references cited herein.
[46] Herndon, J.W. *Coord. Chem. Rev.* **2000**, *206*, 237–262.



156 157 158

Scheme 58: Carbene formation by α-elimination

As mentioned above, an alternative method for the generation of a carbene **161** involves loss of a stable molecule, for example nitrogen gas (Scheme 59). Diazo compound **159** decomposition results in cleavage of nitrogen-carbon bond. Such a reaction can occur under thermal, photochemical or acidic conditions, or by treatment with a suitable transition metal complex. Our interest is the generation of metal carbenoids from diazo ketones *via* decomposition with a metal complex.



159 160 161

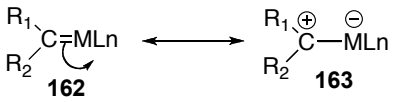
Scheme 59: From diazo compound to carbene

2.1.3 Metal Carbenoids

As previously mentioned, the treatment of a diazo compound with a transition metal complex affords a metal carbenoid, also called a metallocarbene.[47] In fact, metal carbenoids display many of the reactivity features of free carbenes. The synthetic utility of free carbenes is limited because of their high reactivity and consequent low selectivity. In contrast, metal carbenoid-mediated transformations usually proceed with higher chemoselectivity due to the influence of the metal and its ligands. The reactivity and stability of a metallocarbene is directly linked to the degree of π-back donation from the metal to the carbene. The electrophilicity of the complex is

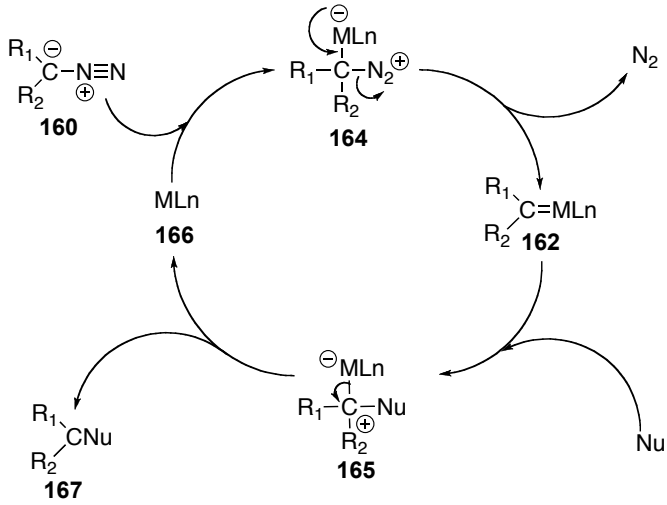
[47] Doyle, M. P. in: *Comprehensive Organometallic Chemistry II*, Hegedus, L. S. E.: Pergamon Press: New York, **1995**, Chap. 5.2.

evident when one considers the major resonance forms: the metal carbene **162** and the metal stabilised carbocation **163** (Scheme 60).



Scheme 60: Resonance forms of metal carbenoid

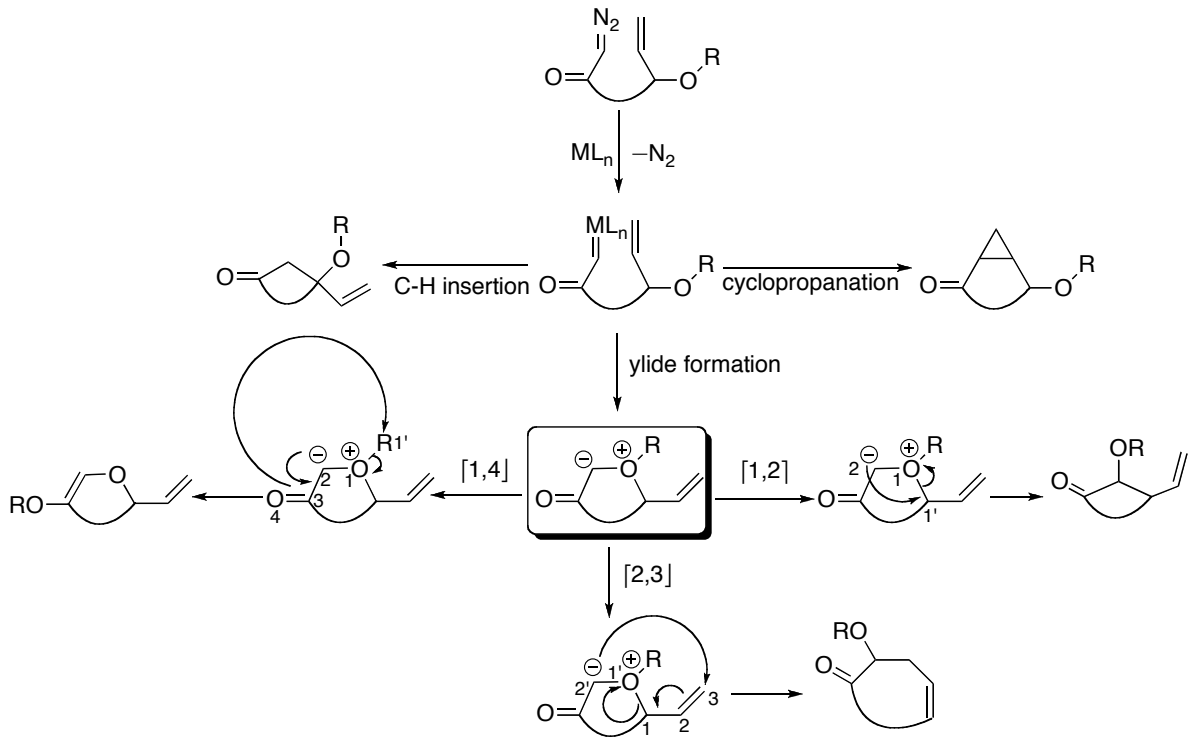
A common process employed to generate a metallocarbene **162** involves nucleophilic attack of a diazo compound **160** on sub-stoichiometric amount of a Lewis acidic transition metal complex **166** (Scheme 61).[48] The metal back-donates an electron pair from one of its filled d-orbitals to displace a molecule of nitrogen generating the metal carbenoid **162**. The resulting complex is very reactive and is not isolable. Consequently, the metallocarbene **162** usually reacts *in situ* with an electron-rich substrate (Nu) to form a new bond and regenerate the transition metal catalyst **166**; a sub-stoichiometric amount of transition metal complex **166** is sufficient for the catalytic cycle.



Scheme 61: Catalytic cycle of diazo compound decomposition

The choice of metal and appropriate ligands is crucial for the desired reaction of Nu with the metal carbenoid. In fact, metallocarbenes can undergo a variety of reactions, such as cyclopropanation, X-H insertion (X = C, O, S, N, Si) and ylide generation followed by rearrangement (Scheme 62).

[48] Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 7686–7693.



Scheme 62: Summary of metal carbenoid reactions

Many research groups have studied the reactivity of metallocarbenes extensively.[49] Amongst the reactions described above, oxonium ylide generation and subsequent rearrangement is the key step in our synthetic route to members of the amphidinolides T family and it will be discussed in further detail (*vide infra*).[50] With regard to the transition-metal catalyst employed, rhodium carbenoids generally participate in X-H insertion reactions and copper carbenoids favour ylide formation and cyclopropanation, but both copper and rhodium carbenoids can undergo all three reactions.

2.1.4 Metal Catalysts for Diazo Carbonyl Chemistry

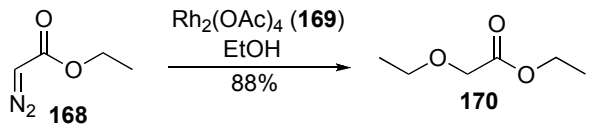
Although the first example of a metal catalyst being involved in diazo chemistry was published more than hundred years ago, recent advances in the design of transition metal catalysts have raised significantly the interest in the field.[51] From various studies over the years, copper and rhodium complexes have been the most widely employed catalysts. There have also been a few examples

[49] Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; Wiley-Interscience: New Jersey, **2009**, 5th edition.
[50] Doyle, M. P.; McKervey, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, **1998**.
[51] Silberrad, O.; Roy, C. S. *J. Chem. Soc.* **1906**, *89*, 179–182.

where a cobalt, palladium, ruthenium, osmium, iron, platinum or nickel complex has been used for the catalytic decomposition of diazo compounds to give metallocarbenes.[49,50]

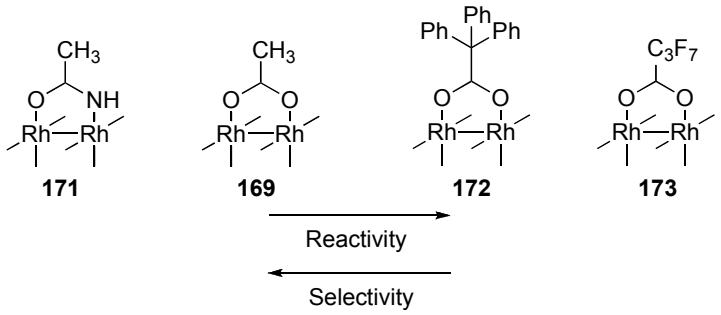
2.1.4.1 Rhodium Complexes

Dirhodium(II) catalysts incorporating bridging bidentate ligands provide a broad range of selectivity and reactivity. The first treatment of a diazo ester **168** with dirhodium(II) acetate dimer **169** was performed in 1973 and resulted in efficient O-H insertion reaction (Scheme 63).[52]



Scheme 63: Rhodium-catalysed O-H insertion

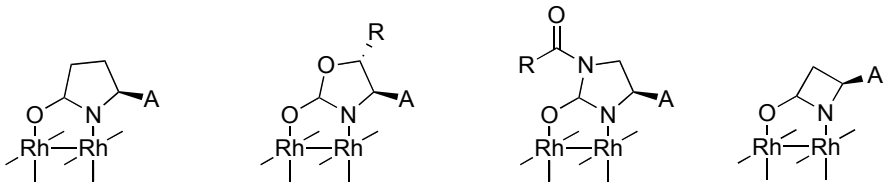
From this explorative work, research groups moved on to investigate the replacement of the acetate ligands with alternative bidentate carboxylate groups. It was found that electron-withdrawing ligands increased the activity of the metal and C-H insertion was performed efficiently using dirhodium(II) triphenylacetate dimer **172** to generate the carbenoid (Scheme 64).[53] Higher reactivity was obtained by even more electron-withdrawing groups such as dirhodium(II) perfluorobutyrate dimer **173**.[54] In contrast, dirhodium(II) acetamide dimer **171** exhibited lower reactivity albeit better chemoselectivity.



Scheme 64: Dirhodium(II) complexes

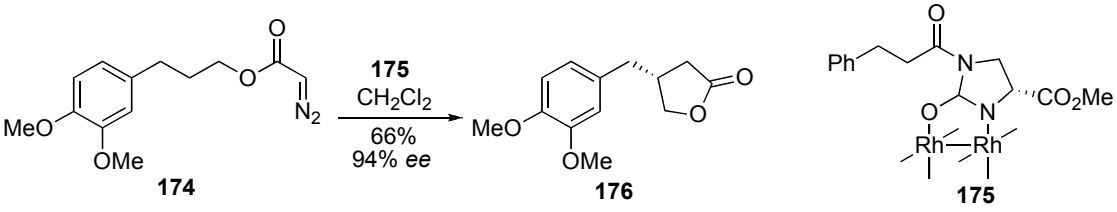
[52] Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A.J.; Teyssié, Ph. *Tetrahedron Lett.* **1973**, *24*, 2233–2236.
[53] Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709–2712.
[54] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958–964.

Doyle and co-workers explored asymmetric induction and studied a large array of chiral ligands.[54] The choice of chiral catalyst was found to have a remarkable influence on diastereo- and regiocontrol when C-H insertion reactions were employed for the syntheses of lactams and lactones (Scheme 65 and 66).[55,56]



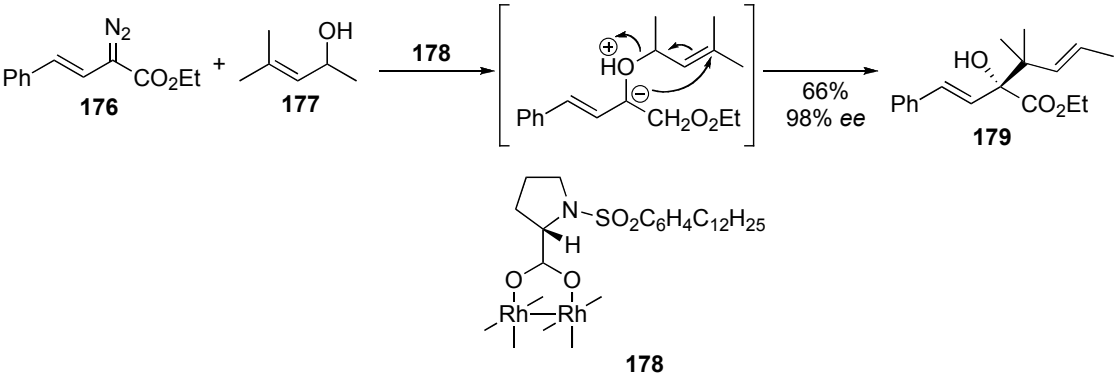
A = COOMe, $COOCH_2$*t*-Bu, $COOCH_2$*i*-Pr, $COOCH_2Ph$, $COO(CH_2)_{17}CH_3$, Bn, Ph, *i*-Pr
R = H, CH_3, Ph, Bn, CH_2CH_2Ph

Scheme 65: Asymmetric dirhodium catalysts



Scheme 66: Example of enantioselective rhodium-catalysed C-H insertion

Davies *et al.* demonstrated recently that chiral dirhodium complexes are efficient catalysts for enantioselective intermolecular coupling followed by [2,3] sigmatropic rearrangement (Scheme 67).[57] Decomposition of diazo acetate **176** by chiral dirhodium complex **178** in the presence of allyl alcohol **177** led to chemoselective oxonium ylide generation and stereoselective [2,3]-shift in moderate yield.



Scheme 67: Enantioselective rhodium-mediated coupling

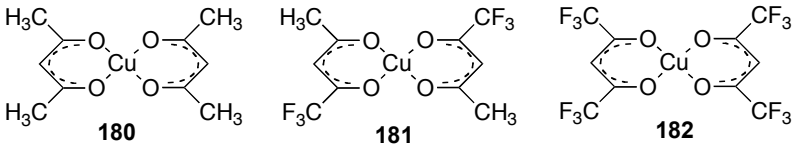
[55] Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–926.
[56] Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L.; Bode, J. W.; Simonsen, S. H.; Lynch, V. *J. Org. Chem.* **1995**, *60*, 6654–6655.
[57] Li, Z.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 396–401.

Unfortunately, this methodology is of limited scope and is restricted to specific substrates. Consequently, it is not general enough to be part of the synthetic toolbox used for total synthesis. Dirhodium catalysts have proven their efficiency in C-H insertion reactions, but copper catalysts display different properties.

2.1.4.2 Copper catalysts

Insoluble copper(0) and copper(II) salts were the first copper catalysts used for diazo decomposition. In 1966, Nozaki introduced soluble copper complexes bearing bidentate ligands such as bis(acetylacetonato)copper (II) **180** and Moser reported the use of soluble trialkyl- and (triarylphosphite)copper(I) species.[58,59] In 1973, Kochi and co-workers discovered that copper triflate is an efficient catalyst for the cyclopropanation of diazo compounds and that the cyclisation involves reduction of copper(II) to copper(I) *in situ*.[60] It is now generally accepted that the active form of copper is oxidation state +I. Two bidendate ligands are bonded to the copper(II) and when the copper centre is reduced, one of the ligands is presumed to dissociate from the metal.

The most popular complexes for diazo compound decomposition are copper acetylacetonate [$Cu(acac)_2$] **180**, copper trifluoroacetylacetonate [$Cu(tfacac)_2$] **181** and copper hexafluoroacetylacetonate [$Cu(hfacac)_2$] **182** (Scheme 68).

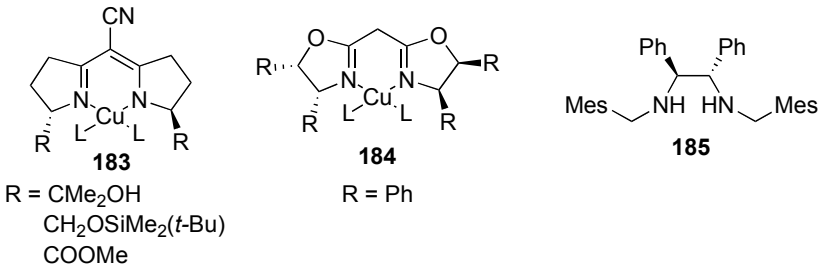


Scheme 68: Common copper complexes for diazo decomposition

Copper catalysts with chiral ligands were developed to provide asymmetric induction during metal carbenoid cyclopropanation reactions (Scheme 69). Chiral copper complexes that function as highly effective catalysts

[58] Nozaki, H.; Moriuti, S.; Yamabe, M.; Noyori, R. *Tetrahedron Lett*. **1966**, *1*, 59–63.
[59] Moser, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 1135–1141.
[60] Salomon, R. G .; Kochi, J. K. *J. Am. Chem. Soc*. **1973**, *95*, 3300–3310.

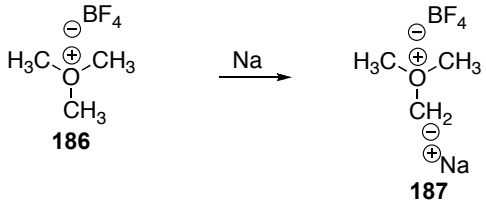
for enantioselective carbene transformations include Pfaltz's chiral semicorrins **183**, bis-oxazolines such as **184** and the diamine **185**.[61,62,63,64]



Scheme 69: Chiral copper complexes

2.1.5 Oxonium Ylide Formation and Subsequent Rearrangements

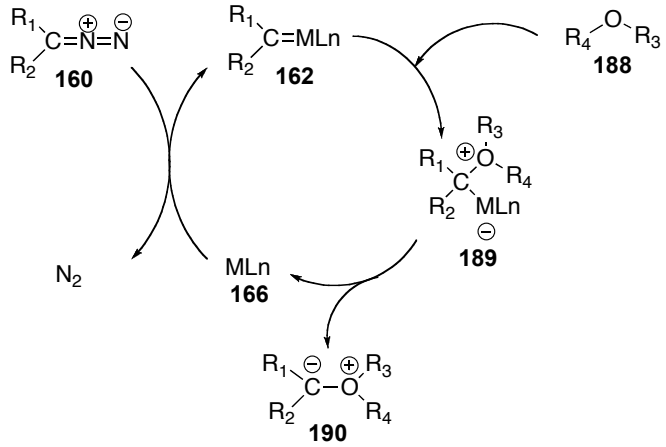
Ylides are species that contain a positively charged heteroatom (oxygen, nitrogen, sulfur, phosphorus or a halogen) bonded directly to a negatively charged carbon atom.[65] Even though ylides are highly reactive dipolar compounds, phosphonium, ammonium and sulfonium equivalents have been isolated.[66,67,68] The oxonium ylides are commonly generated by the reaction of ethers with an electrophilic transition metal carbenoid or by deprotonation of an oxonium ion **186**. The latter method was developed by Olah and co-workers (Scheme 70).[69]



Scheme 70: Olah's oxonium ylide generation

[61] Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta.* **1988**, *71*, 1553–1565.
[62] Evans, D. A.; Woerpel, K. A.; Hinman, M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726–728.
[63] Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373–7376.
[64] Kanemasa, S.; Hamura, S.; Harada, E.; Yamamoto, H. *Tetrahedron Lett.* **1994**, *35*, 7985–7988.
[65] Clark, J. S. *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Oxford University Press: New York, **2002**.
[66] Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G.; *J. Am. Chem. Soc.* **1988**, *110*, 6463–6466.
[67] Mageswaran, S.; Ollis, W.D.; Sutherland, I.O. *J. Chem. Soc. Perkin. Trans. I*, **1981**, 1953–1962.
[68] Chow, T. J.; Tan, U.-K.; Peng., S. M. *Synth. Commun.* **1988**, *18,* 519–523.
[69] Olah, G. A.; Doggweiler, H.; Felberg, J. D. *J. Org. Chem.* **1984**, *49*, 2112–2120.

A practical way to generate an oxonium ylide **190** is by treatment of a diazo compound **160** with a suitable transition-metal catalyst **166** in the presence of an ether **188** (Scheme 71). The reaction leads to the formation of metal-bonded oxonium ylide **189**, which can then react further to give the free ylide **190**.



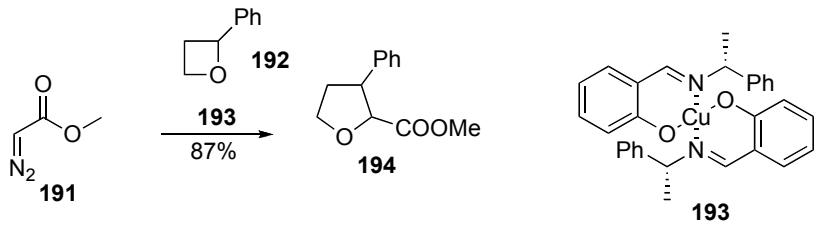
Scheme 71: Catalytic degradation of diazo compounds in the presence of ethers

Oxonium ylides are extremely reactive species and function as intermediates in a wide variety of reactions and rearrangement processes such as β-hydride elimination, Stevens [1,2] rearrangement, [2,3] sigmatropic rearrangement or a [1,4]-shift rearrangement. In fact, competition between these reactions is one of the major drawbacks of oxonium ylide chemistry.[65] The key step in our synthesis will involve the [2,3] sigmatropic rearrangement of an oxonium ylide diazo-generated.

2.1.5.1 Stevens Rearrangement and [1,4]-Shift

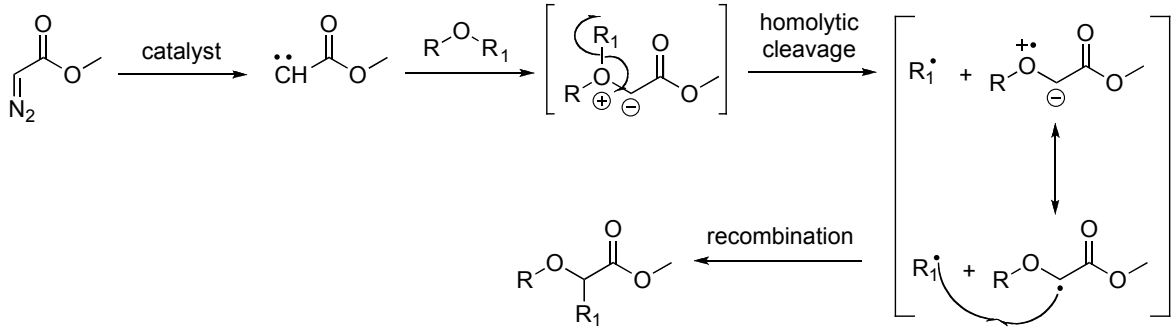
Nozaki and co-workers highlighted that nucleophilic addition of an etheral oxygen to a diazo-generated metallocarbene could be followed by migration of an alkyl group.[70] In any early example of this phenomenon, treatment of the diazo ester **191** with the copper catalyst **193** in presence of oxetane **192** resulted in ring expansion by a [1,2]-shift (Scheme 72).

[70] Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655–3669.



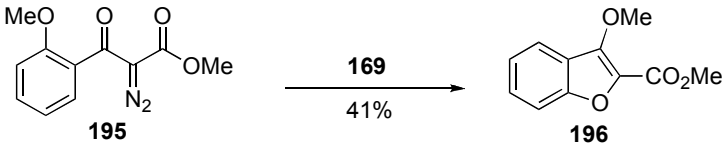
Scheme 72: Stevens rearrangement from diazo compound

With regard to the proposed mechanism of this transformation, a concerted [1,2]-shift rearrangement is not allowed by the Woodward Hoffman rules.[71] To explain the outcome of the reaction, it is suggested that the reaction proceeds by homolytic cleavage followed by radical recombination within a solvent cage (Scheme 73).[72]



Scheme 73: [1,2]-Shift rearrangement radical mechanism

During their total synthesis of (+)-griseofulvin, Pirrung and co-workers isolated the first [1,4]-shift product **196** from the decomposition of diazo ester **195** by **169** followed by an oxonium ylide rearrangement reaction (Scheme 74).[73]

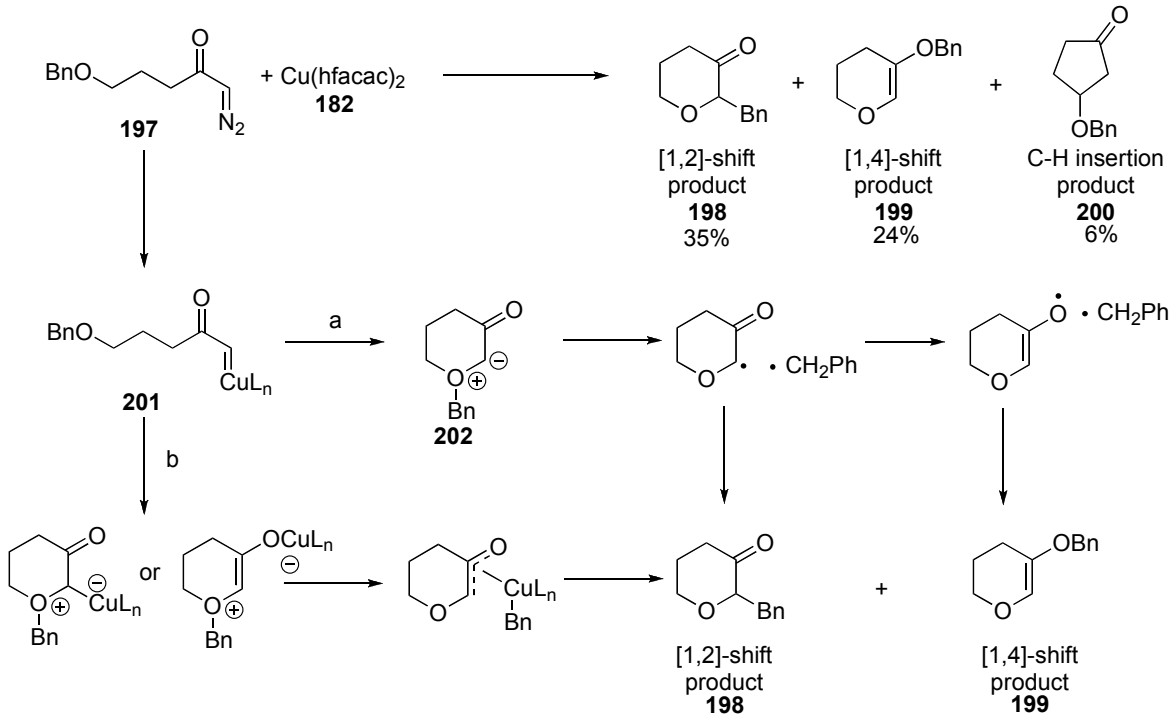


Scheme 74: Rhodium-catalysed [1,4]-shift rearrangement

When generating copper carbenoids from the diazo ester **197**, the West group isolated both the [1,2]- and [1,4]-shift products (respectively **198** and

[71] Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395-397.
[72] Iwamura, H.; Imahashi, Y.; Kushida, K. *Tetrahedron Lett.* **1975**, *16*, 1401–1404.
[73] Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561–8562.

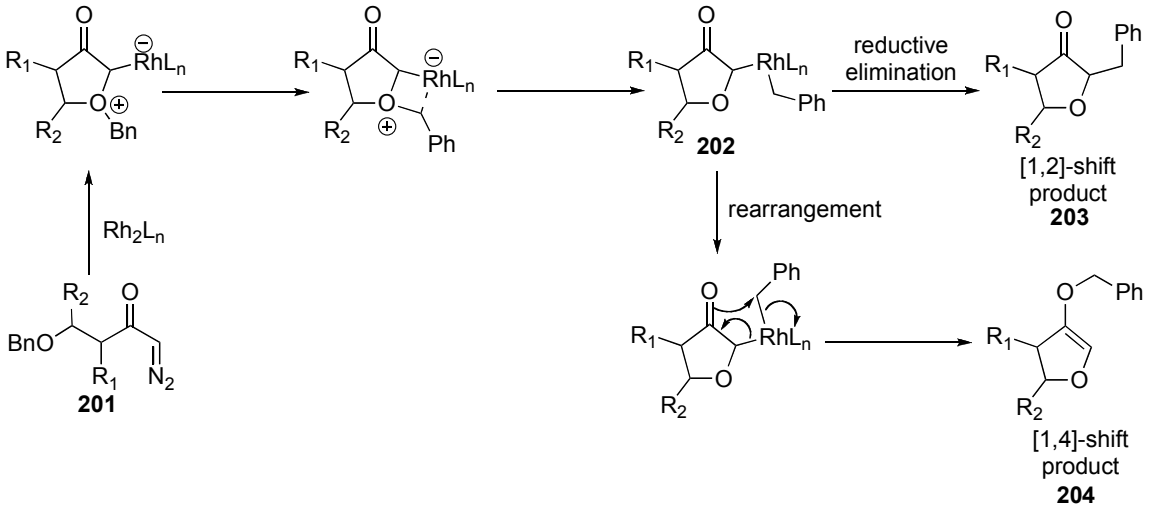
199), as well as small amounts of the C-H insertion product **200** (Scheme 75).[74] Clark and West suggested two mechanistic pathways. Homolytic cleavage generated radicals and subsequent recombination at carbon position resulted in [1,2]-shift product **198** (pathway a). Radical delocalisation to oxygen could undergo recombination on oxygen site instead of carbon site consequently affording the enol ether **199**, *via* a [1,4]-shift. However, none of the transitional homodimerisation products was isolated, therefore alternative pathway b was assumed to involve coordination of the metal to oxonium ylide and benzyl group migration delivered either [1,2]- and [1,4]-shift products.



Scheme 75: West and Clark proposed mechanisms

Dhavale suggested a different mechanism based on his observations concerning rhodium-catalysed oxonium ylide rearrangement reaction (Scheme 76).[75] In this model, rather than coordination of the metal to the oxygen, the rhodium complex would remain attached to carbon and subsequent reductive elimination would provide the [1,2]-shift product **203**. Alternatively, the [1,4]-shift product **204** could be formed *via* the rearrangement of intermediate **202**.

[74] West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892–6894.
[75] Karche, N. P.; Jachak, S. M.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 6323–6332.



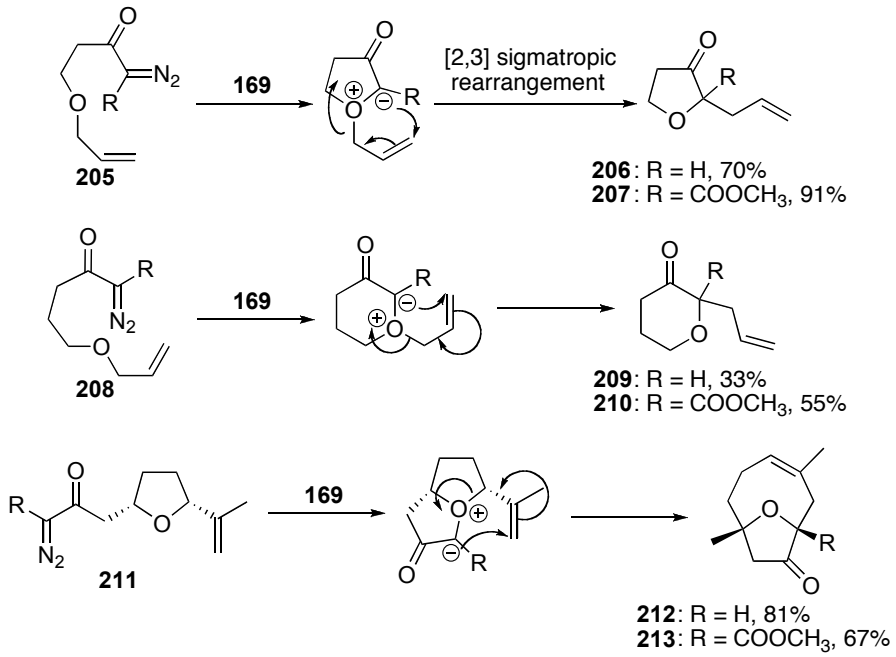
Scheme 76: Dhavale mechanism

The oxonium ylide Stevens rearrangement and [1,4]-shift reactions have been studied by several research groups, but competition with other rearrangement reactions means that the transformation is difficult to apply in the context of a total synthesis. On the other hand, C-H insertion reactions and [2,3] sigmatropic rearrangements are more favoured reactions.

2.1.5.2 [2,3] Sigmatropic Rearrangement

When oxonium ylides are generated by the reaction of a metallocarbene with an allylic or propargylic ether, [2,3] sigmatropic rearrangement occurs spontaneously. Kirmse and Kapps were the first to report an apparent [2,3] rearrangement product as a by-product while they were attempting to perform a cyclopropanation reaction.[76] In 1986, methods for tandem oxonium ylide formation and [2,3] sigmatropic rearrangement were established by Pirrung and Johnson.[77,78] Allyloxy diazoketones (**205**, **208** and **211**), decomposed by dirhodium acetate **169**, afforded cyclic ethers in moderate to excellent yield (Scheme 77). This method was applied to the synthesis of simple five-membered (**206** and **207**), six-membered (**209** and **210**) and eight-membered cyclic ethers (**212** and **213**).

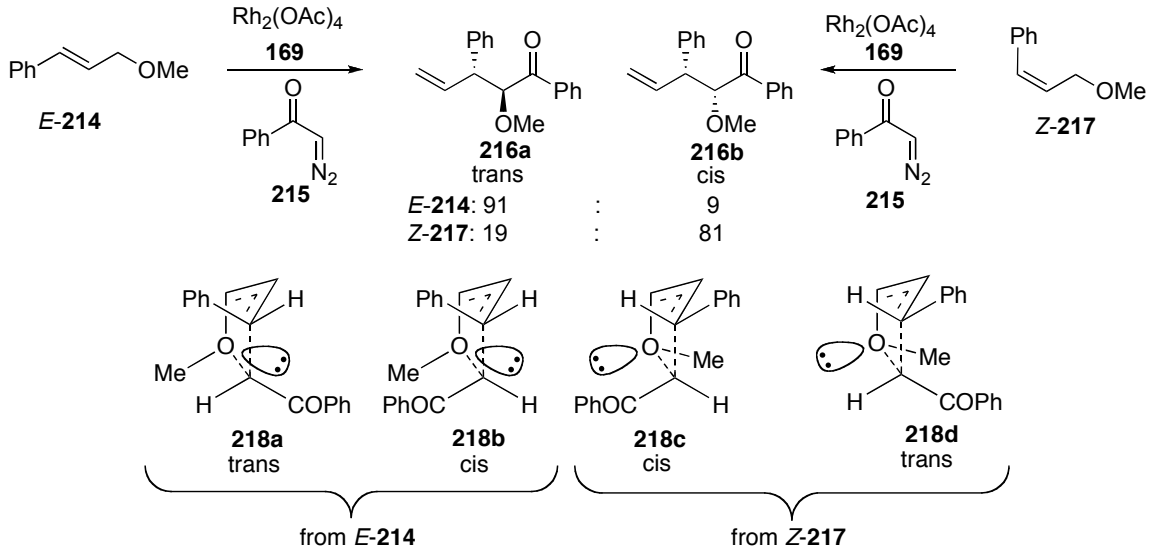
[76] Kirmse, W.; Kapps, M. *Chem. Ber.* **1968**, *101*, 994–1003.
[77] Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *101*, 6060–6062.
[78] Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *101*, 6062–6063.



Scheme 77: Pirrung and Johnson methodology

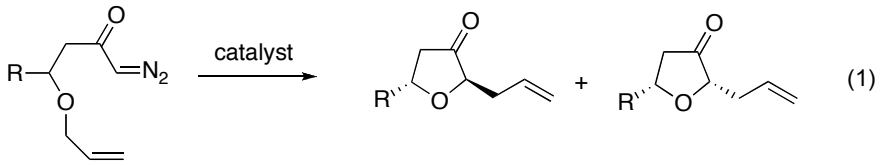
Doyle's group studied the stereochemical outcome of the intermolecular reaction (Scheme 78).[79] Intermolecular oxonium ylide formation is often challenged by competing cyclopropanation. The steric environments of the reactive sites in the substrate and the choice of catalyst are usually crucial factors in dictating whether chemoselective ylide formation occurs. Treatment of *E*-cinnamyl methyl ether *E*-**214** with **169** in the presence of **215** produced both diastereoisomers, with the *trans* product **216a** predominating. Under similar conditions, exposing *Z*-cinnamyl ether *Z*-**217** to **169** and **215** afforded a mixture of both diastereoisomers, but with the *cis* product **216b** predominating. The reaction selectivities were explained by the proposal that the reaction proceeds *via* the envelope transition states **218a** to **218d**. The transition states **218b** and **218d** were assumed to be disfavoured due to eclipsing interactions of the methyl and the carbonyl groups. Consequently, the geometry of the starting alkene dictates the stereochemical outcome of the reaction with the *trans* product being obtained through the transition state **218a** when *E*-**214** is employed as the starting material and the *cis*-isomer being formed through the transition state **218c** when the *Z*-isomer **217** is used.

[79] Doyle, M. P.; Bagheri, V.; Harn, N. K. *Tetrahedron Lett.* **1988**, *29*, 5119–5122.



Scheme 78: Doyle's proposed transition states

Clark developed the tandem copper catalyst-induced chemoselective ylide formation followed by diastereoselective [2,3] sigmatropic rearrangement process.[37] The copper-mediated transformation proceeded with improved yields and with excellent *trans*/*cis* ratios compared to rhodium-catalysed transformation (Equation 1 and Table 1). It was assumed that the greater electrophilicity of the metal carbenoid intermediate favours the oxonium ylide generation.



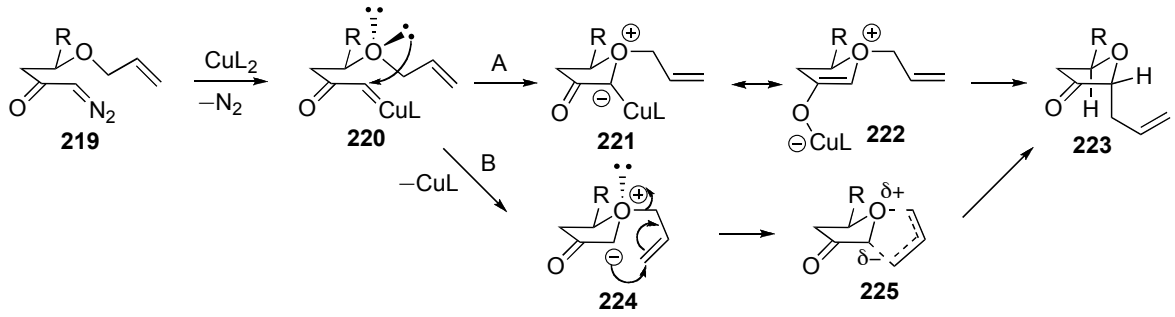
Entry	Catalyst	R	Yield[a]	*trans* : *cis*[b]
1	$Rh_2(OAc)_4$ (**169**)	*n*-Pr	68%	81:19
2	$Rh_2(OAc)_4$ (**169**)	*i*-Pr	51%	65:35
3	$Cu(acac)_2$ (**180**)	*n*-Pr	85%	>97:3
4	$Cu(acac)_2$ (**180**)	*i*-Pr	83%	>97:3

a) Isolated yield; b) Ratio were determined by NMR.

Table 1: Catalysts and side chain screening

Further studies by the Clark group revealed that alkyl group adjacent to the oxonium ylide and the electrophilicity of the catalyst have an influence on the diastereoselectivity of the reaction.[80]

In spite of the fact that the exact reaction mechanism has not been fully elucidated, the data suggest that two different pathways are possible. Improvement by altering the catalyst suggests that the metal complex directs ylide rearrangement while remaining bonded to the substrate *via* path A (Scheme 79). If this is the case, the metal complex would influence the stereochemical outcome through intermediates **221** and **222**. Alternatively, in pathway B one of the diastereotopic lone pairs of the oxygen selectively displaces the metal and efficient transfer of stereochemical information from the transient stereocentre on oxygen occurs during the rearrangement step. Transformation through path B seems possible because the rate of inversion of the oxonium centre present on **224** was considered to be slow compared to the oxonium ylide rearrangement process.[81]

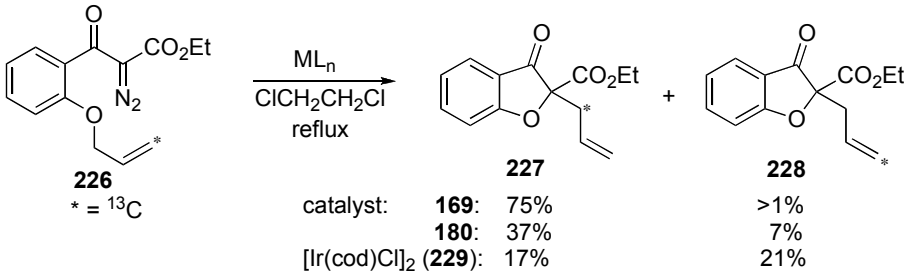


Scheme 79: Two mechanistic pathways

Recent studies with ^{13}C-labelled substrates have raised questions about these mechanisms (Scheme 80). Treatment of ^{13}C-labelled diazo keto ester **226** with various catalysts delivered mixture of the cyclic products **227** and **228**, which contain the ^{13}C label either at the terminal or internal position of the alkene.[82] The rhodium-catalysed reaction proceeds almost exclusively to give the product expected by [2,3] rearrangement of a free oxonium ylide intermediate i.e. that with the ^{13}C label at internal position. In those cases where copper (**180**) or iridium (**229**) complexes are used as catalysts, the reaction either does

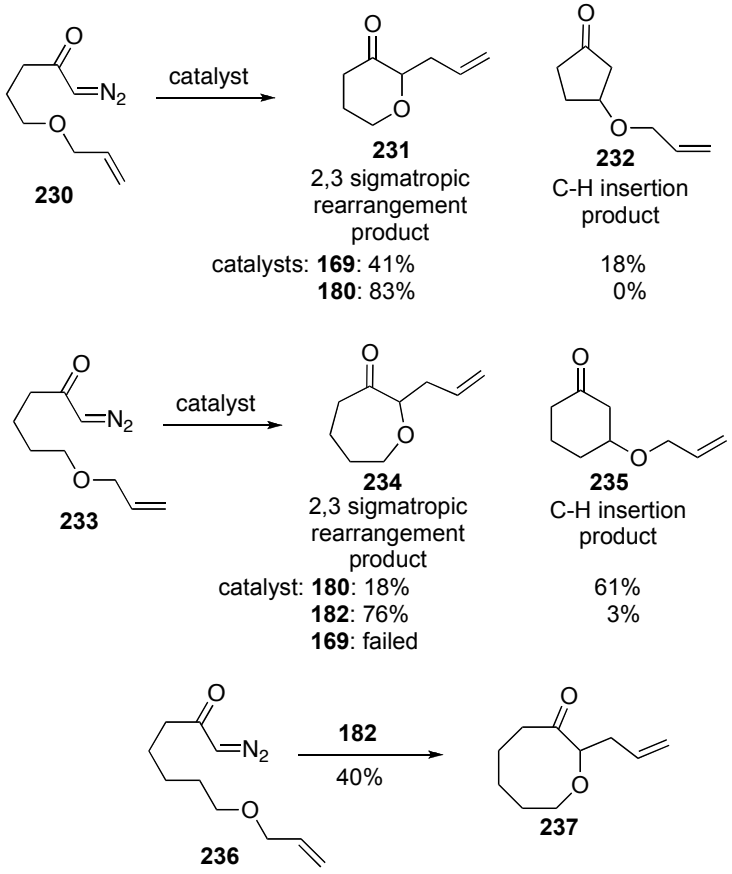
[80] Clark, J. S.; Whitlock, G. A.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578–2579.
[81] Lambert, J. B.; Johnson, D. H. *J. Am. Chem. Soc.* **1968**, *90*, 1349–1350.
[82] Clark, J. S.; Hansen, K. E. *Angew. Chem., Int. Ed.*, submitted.

not proceed *via* a free oxonium ylide at all or seems to follow a major competing non-ylide route, which afford mixtures of the products **227** and **228**.



Scheme 80: ^{13}C-labeled substrates experiments

Clark and co-workers explored the challenging cyclisations of six-membered (**231**), seven-membered (**234**) and eight-membered (**237**) cyclic ethers (Scheme 81).[83] Medium-ring ethers were particularly attractive targets due to the common occurrence of these systems in marine natural products.



Scheme 81: Scope extension of copper-catalysed cyclisation

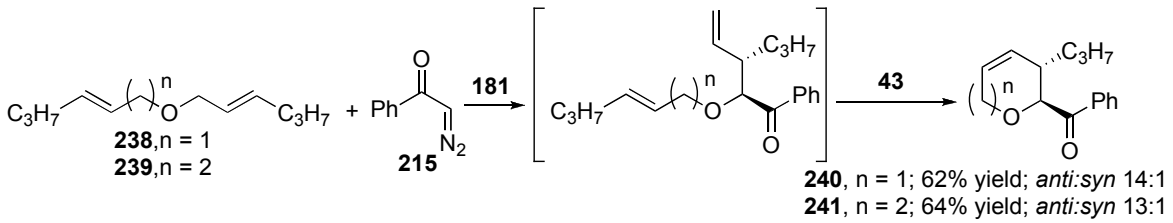
[83] Clark, J. S.; Krowiak, S. A. *Tetrahedron. Lett.* **1993**, *34*, 4385–4388.

This study revealed that for the synthesis of six-membered cyclic ether **231**, copper-mediated diazoketone **230** decomposition resulted in almost exclusive tandem oxonium ylide formation and [2,3] sigmatropic rearrangement. In comparison, the use of $Rh_2(OAc)_4$ **169** was less chemoselective and the competing C-H insertion product **232** was generated in significant amounts.

Rhodium-catalysed decomposition of the diazoketone **233** failed to deliver the corresponding seven-membered oxacycle **234**. Use of $Cu(acac)_2$ **180** as the catalyst resulted in the formation a significant amount of the C-H insertion product **235**, but switching to $Cu(hfacac)_2$ **182** generated the desired cyclic ether **234** with high chemoselectivity.

With regard to the synthesis of the eight-membered cyclic ether **237**, $Rh_2(OAc)_4$ **169**, $Cu(acac)_2$ **180** or $Cu(tfacac)_2$ **181**-catalysed reactions did not afford the expected oxacycle **237**. Only the use of $Cu(hfacac)_2$ **182** resulted in formation of the cyclic ether **237** in substantial amounts (40% yield). Consequently, altering the electron demand on the copper atom by introduction of an electron-withdrawing ligand favoured the [2,3] sigmatropic rearrangement pathway when $Rh_2(OAc)_4$ **169** was not chemoselective.

The flexibility of this method was demonstrated by Njardarson and co-workers who described a one pot-process involving intermolecular copper-mediated diazo carbonyl decomposition, ylide formation, sigmatropic rearrangment and subsequent ring closing metathesis reaction (Scheme 82).[84] Cyclic ethers with various ring sizes were obtained in moderate yield with high *cis:trans* ratios.



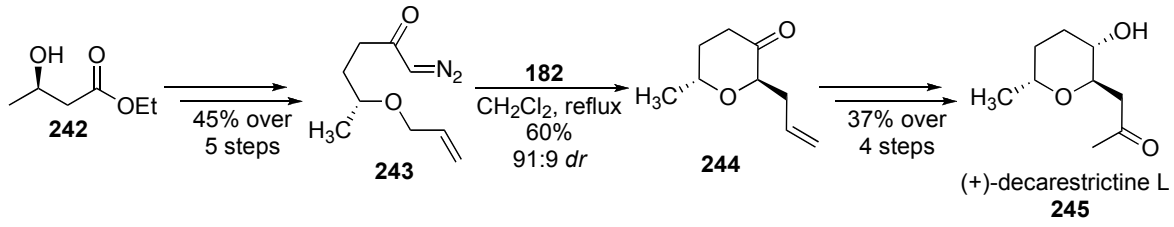
Scheme 82: Njardarson's intermolecular copper-mediated cyclisations

[84] Mack, D. J.; Batory, L. A.; Njardarson J. T. *Org. Lett.* **2012**, *14*, 378–381.

The copper-catalysed cyclisation provided a novel tool for organic chemists and the efficiency of the Clark's methodology has been demonstrated by numerous natural product total syntheses.

2.1.6 Applications in the Total Synthesis of Natural Products

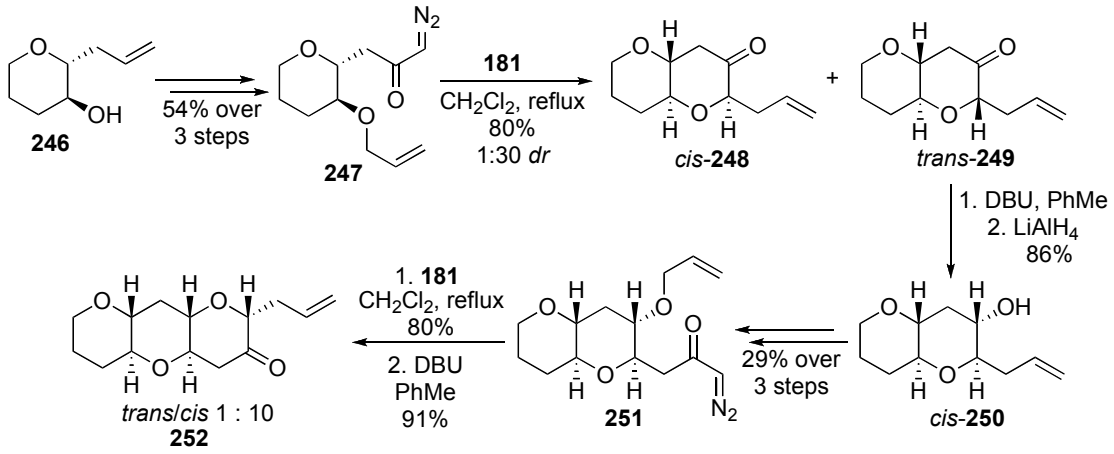
Clark and co-workers illustrated the effectiveness of this methodology by using it to complete the total synthesis of racemic and enantiopure (+)-descarestrictine L **245** (Scheme 83).[85,86] Diazoketone **242** was treated with Cu(hfacac)$_2$ complex **182** resulting in tandem oxonium ylide generation and [2,3] sigmatropic rearrangement to afford, preferentially, the *trans*-tetrahydropyran **244** in 60% yield and with an excellent diastereoisomeric ratio. The total synthesis of decarestrictine L **245** was completed in ten steps in an overall yield of 9%.



Scheme 83: Clark's decarestrictine L synthesis

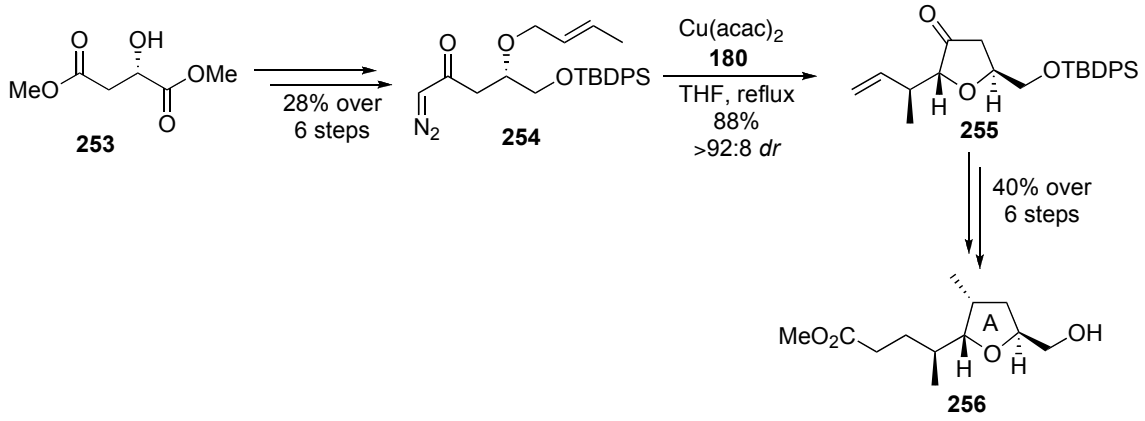
Following this, West and co-workers applied the methodology to the synthesis of fused cyclic ethers of the type found in marine polyether natural products (Scheme 84).[87] Starting from tetrahydropyran **246**, diazoketone **247** was prepared in a three-step sequence in good overall yield. Decomposition of the diazo compound **247** by Cu(tfacac)$_2$ **181** afforded almost exclusively the *trans* tetrahydropyran **249**, which was successfully epimerised and reduced to give the desired *cis* isomer **250**. The sequence was then repeated, resulting in formation of the tricyclic ether **252** in ten steps and in an overall yield of 9%.

[85] Clark, J. S.; Whitlock, G. A. *Tetrahedron Lett.* **1994**, *35*, 6381–6382.
[86] Clark, J. S.; Fessard, T. C.; Whitlock, G. A. *Tetrahedron* **2006**, *62*, 73–78.
[87] Marmsäter; F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144–5145.



Scheme 84: West's strategy to polycyclic ethers synthesis

The total synthesis of naturally fused polycyclic ethers is a challenging endeavour and the Clark group has been developing methods to allow rapid access to different sizes of cyclic ethers for many years. Gambieric acid A is one of the largest fused polyether natural products and Clark and co-workers have been dedicated to completing the total synthesis of this target.[88] The strategy for the synthesis of the A-ring fragment **256** involves oxonium ylide generation and subsequent [2,3] sigmatropic rearrangement (Scheme 85). Using the dimethyl ester of L-malic acid **253** as a chiral pool starting material, diazoketone **254** was prepared over six steps. Treatment of the diazo carbonyl compound **254** with $Cu(acac)_2$ **180** afforded the tetrahydrofuran **255** in an excellent yield and with high diastereoisomeric ratio. A further six-step sequence delivered the A-ring fragment **256** of gambieric acid A.

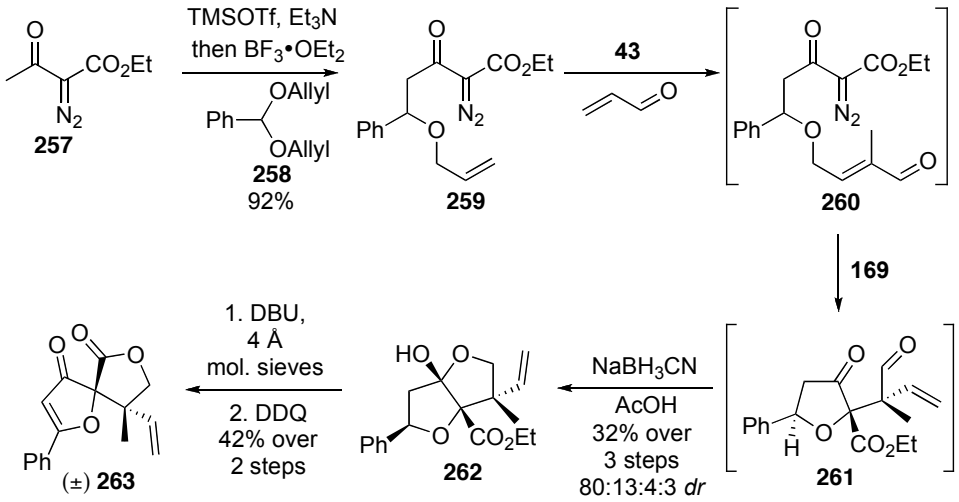


Scheme 85: Gambieric acid A-ring synthesis

[88] a) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773–1776; b) Clark, J. S.; Kimber, M. C.; Robertson, J.; McErlean, C. S. P.; Wilson, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 6157–6162.

The same approach is currently applied in the Clark group towards the synthesis of tetrahydrofuran-containing fragments of amphidinolide C.[89]

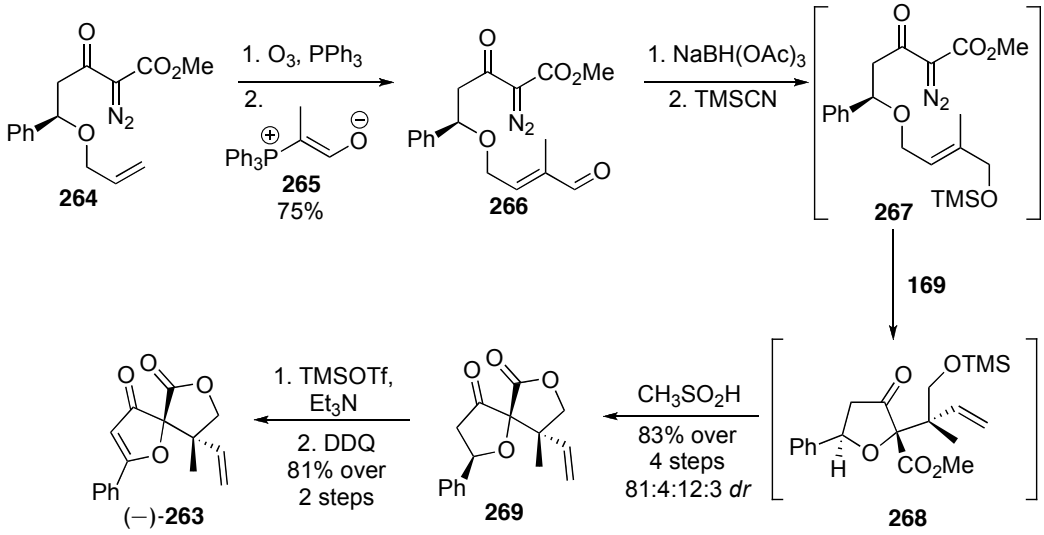
In 2008, an interesting strategy was reported by Hodgson for the total synthesis of the anti-HIV agent (±)-hyperolactone C **263**.[90] In order to generate a tetrasubstituted tetrahyrofuran **261**, a one-pot method consisting of cross metathesis and oxonium ylide rearrangement was explored (Scheme 86). The required precursor **259** was prepared by a Mukaiyama aldol reaction on diazo ester **257**. One-pot, *E*-selective cross-metathesis followed by tandem oxonium ylide formation and [2,3] sigmatropic rearrangement and subsequent chemoselective aldehyde reduction afforded the fused bicyclic ether **262** in 32% yield with 80% being the desired diastereoisomer. Lactonisation and dehydrogenation completed the very concise synthesis of (±)-hyperolactone C **263** consisting of a total of seven steps (three in one pot) and in 10% yield.



Scheme 86: Hodgson's racemic hyperolactone C synthesis

Further advances have delivered the enantiopure material (−)-**263**. In this case, a four-step sequence was carried out to prepare **269** with an overall yield of 67% and 81:19 diastereoisomeric ratio in favour of the desired isomer (Scheme 87).[91] The total synthesis of (−)-hyperolactone C **263** was performed in ten steps and with 15% overall yield.

[89] PhD projects of A. Osnowski and G. Yang are still ongoing.
[90] Hodgson, D.M.; Angrish, D.; Erickson, S.P.; Kloesges, J.; Lee, C.H. *Org. Lett.* **2008**, *10*, 5553–5556.
[91] Hodgson, D.M.; Man, D. M. *Chem. Eur. J.* **2011**, *17*, 9731–9737.



Scheme 87: Hodgson's synthesis of (—)-hyperolactone C

Clark and co-workers have focused their attentions on the total synthesis of complex terpenoids such as neoliacinic acid **270** and labiatin A **271** (Figure 8).

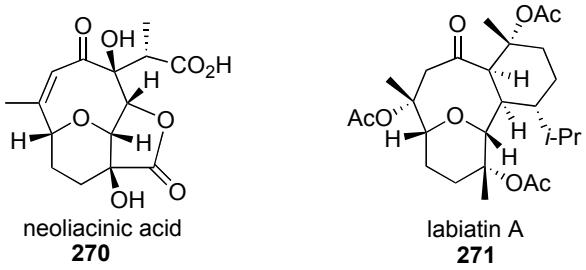
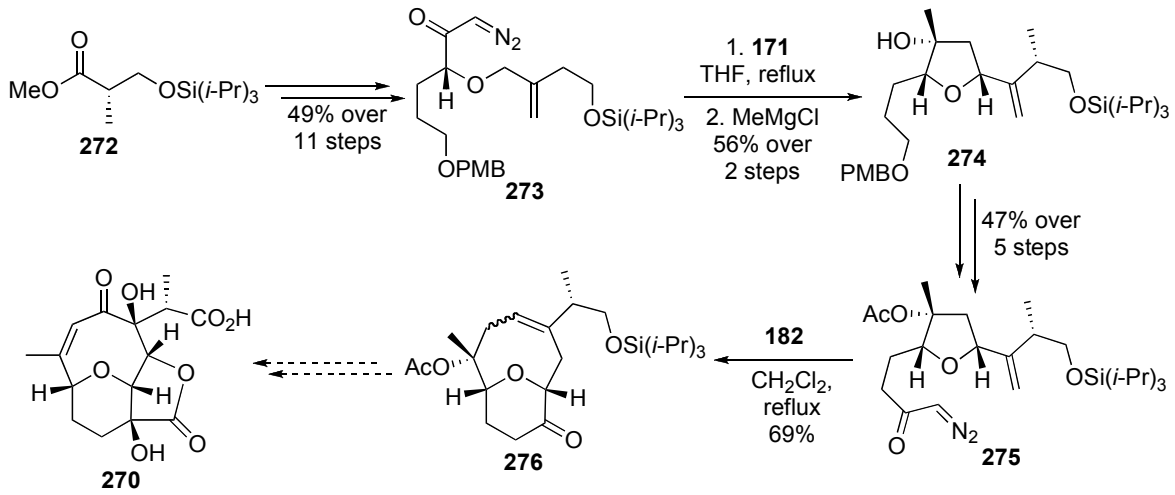


Figure 8: neoliacinic acid and labiatin A structures

The synthetic strategy used for the total synthesis of neoliacinic acid **270** involves two cyclisation reactions *via* metallocarbene intermediates (Scheme 88). The synthesis began with an extremely efficient eleven-step sequence converting the silyl-protected *R*-(—)-Roche ester **272** into the tetrahydrofuran ring precursor **273**. The diazoketone **273** was subjected to rhodium-catalysed decomposition followed by C-H insertion. Subsequent methylation delivered the cyclic ether **274** in a good yield over the two steps. Diazoketone **275**, fashioned from **274** in five steps, underwent tandem oxonium ylide formation followed by [2,3] sigmatropic rearrangement upon treatment with $Cu(hfacac)_2$ **182**. This transformation resulted in a mixture of 3:2 (*Z*:*E*) bridged cyclic ethers **276** in good yield. A similar approach has been adopted for the total synthesis of

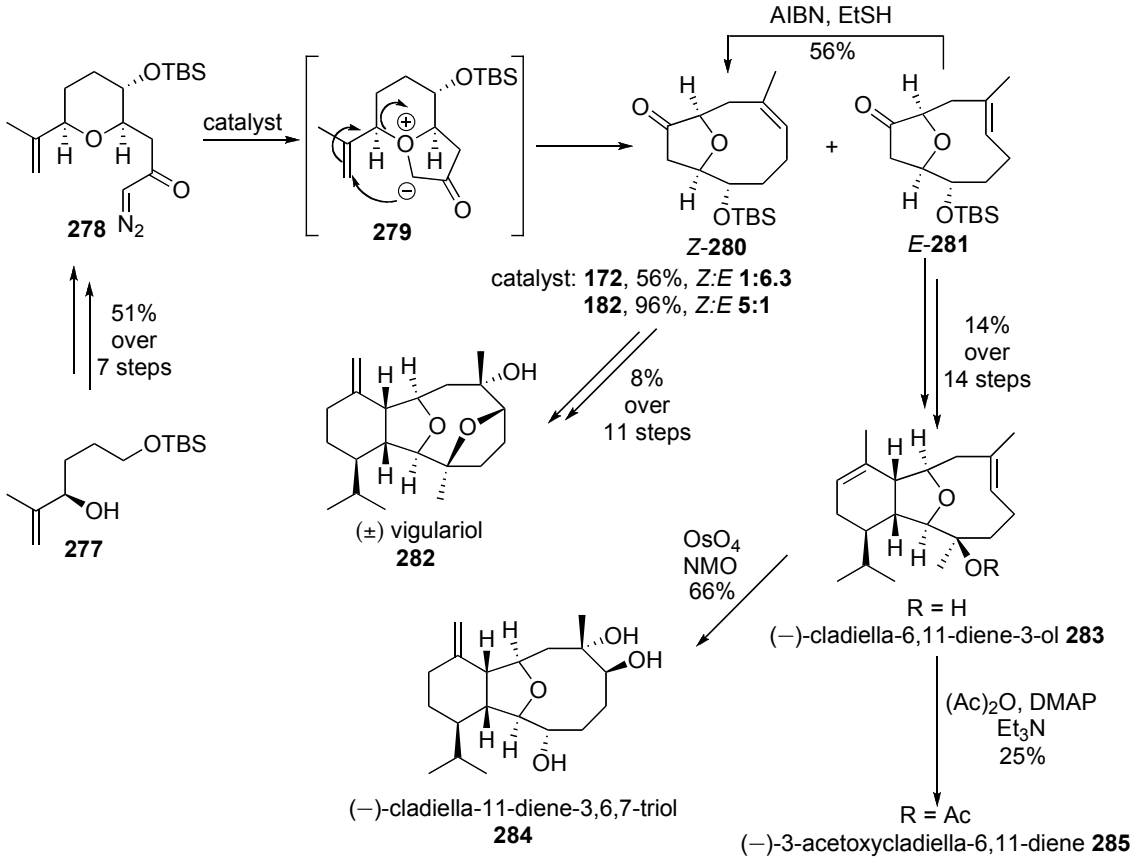
labiatin A **271** and synthetic studies concerning both natural products are still ongoing in the Clark group.[92,93]



Scheme 88: Clark's approach towards neoliacinic acid

In addition, a highly efficient total synthesis of vigulariol **282** has been completed in the Clark group using the copper-catalysed oxonium ylide generation and [2,3] sigmatropic rearrangement as the key step (Scheme 89).[94] The diazoketone **278** was prepared from the allylic alcohol **277** in seven steps with an excellent overall yield of 51%. Subsequent treatment with $Cu(hfacac)_2$ **182** afforded the bridged nine-membered cyclic ether *Z*-**280** in excellent yield along with the minor *E*-**281**. Fortunately, the undesired *E*-isomer could be isomerised to the *Z*-isomer by treatment with ethanethiol and AIBN. A further eleven steps were performed with an overall yield of 8%, which completed the synthesis of vigulariol **282**.

[92] Carosso, S. *PhD thesis*, University of Glasgow, **2011**.
[93] Nuter, F. *PhD thesis*, University of Glasgow, **2011**.
[94] Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 437–440.



Scheme 89: Racemic vigulariol and cladiellins total syntheses

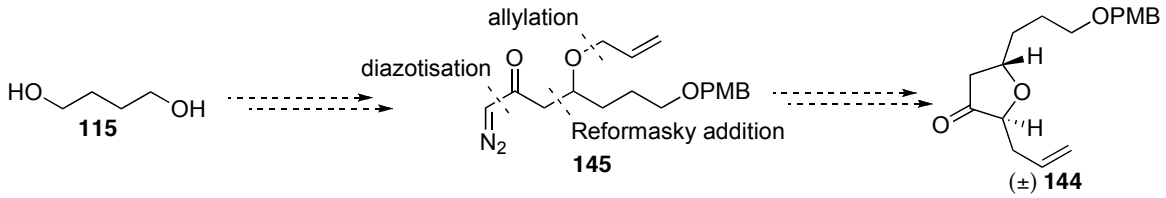
Using the same strategy as described above, the Clark group was able to access several members of the cladiellin family of diterpenoids (Scheme 89). The majority of the cladiellin natural products possess an *E*-alkene configuration or contain an anti-1,2-diol at the same position (C6 and C7) that could result from dihydroxylation of the *E*-alkene present on *E*-**281**. The main challenge, therefore, was to bias the rearrangement reaction in favour of the less-stable isomer *E*-**281** in order to allow access to the entire family.[95] Although copper-catalysed rearrangement reactions generally deliver higher yields than rhodium-mediated transformations, the use of rhodium catalysts did provide additional opportunities to tune the reaction towards the formation of the *E*-isomer **281** by varying the properties of the ligand. Treatment of **278** with dirhodium(II) triphenylacetate dimer **172** increased the proportion of the *E*-**281** to 6.3:1 and delivered a yield of 56%. Further transformations of the *E*-**281** completed the total synthesis of three *E*-cladiellin natural products **283**-**285**.[96]

[95] Clark, J. S.; Berger, R.; Hayes, S. T.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9867–9870.
[96] Berger, R. *PhD thesis*, University of Glasgow, **2011**.

Cyclisation by tandem oxonium ylide generation followed by [2,3] sigmatropic rearrangement has proven to be an efficient and valuable transformation as illustrated by the total syntheses described above.

2.2 Synthesis of the Tetrahydrofuran Fragment in Racemic Form

The common motif to all five members of the amphidinolide T family is a trisubstituted *trans*-tetrahydrofuran. Easy access to the five-membered cyclic ether is the key to an efficient total synthesis of members of this family of macrolides. Consequently, the first challenge was to identify a concise sequence for the preparation of the diazoketone **145**, the cyclisation precursor (Scheme 90). In order to define a viable route for the synthesis of our natural product targets, explorative work was conducted using racemic material, starting from 1,4-butanediol **115**. Most of the transformations in this project were first established using racemic material.



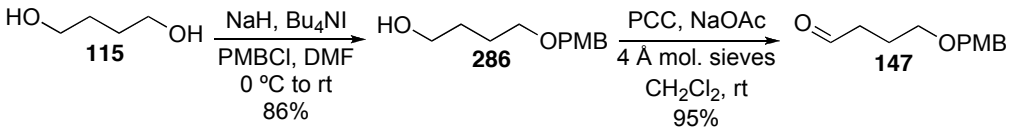
*Scheme 90: Towards the racemic tetrahydrofuran **144** synthesis*

The total syntheses raised specific experimental issues related to scale up, so efforts were focused on designing an efficient, convenient, practical and scalable pathway. The preparation of the diazoketone **145** started with a Reformatsky reaction.

2.2.1 Reformatsky Addition

The first step was the monoprotection of 1,4-butandiol **115** using *para*-methoxybenzyl chloride (PMBCl) (Scheme 91). Monoprotection of a symmetric diol can result in a statistical mixture of unprotected, monoprotected and

diprotected material.[97] The Condon group had developed a method that selectively protects only one hydroxyl groups of a symmetrical diol.[98] Initially, the process was developed for silyl ether formation but the reaction was adapted successfully to diol monoprotection by formation of a *para*-methoxybenzyl ether **286**.[99] Switching the solvent from DMF to THF did not improve the yield.

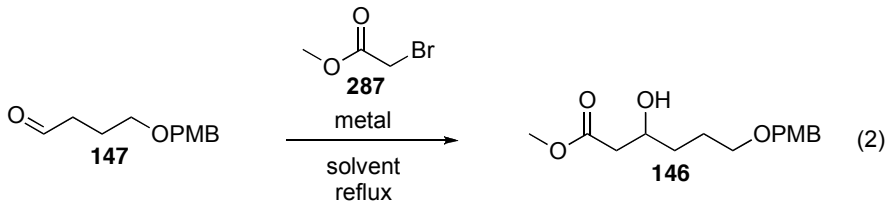


*Scheme 91: Aldehyde **147** preparation*

Oxidation of the primary alcohol **286** to give the aldehyde **147** had to be performed carefully because of the possibility of over-oxidation.[100] The combination of pyridinium chlorochromate (PCC) and 4 Å molecular sieves in dichloromethane delivered the aldehyde **147** in good yield. The drawback of this method was the formation of a sticky black residue containing chromium salts, which trapped the aldehyde **147** and lowered the yield to 85% on 10 mmol scale.

With the aldehyde **147** in hand, Reformatsky addition was conducted to form the β-hydroxyester **146** (Equation 2). The standard conditions were defined as using powdered *in situ* activated zinc and α-bromo acetate **287** in diethyl ether under reflux.[101] However, after several attempts to carry out the reaction, it was clear that there was a recurring issue of spontaneous agglomeration of the zinc powder reducing the number of active sites on the metal. This resulted in a slow reaction, moderate to good yields and poor reaction reproducibility, especially on large scale. Relevant assays in order to address the agglomeration issue are summarised in Table 2.

[97] Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327–333.
[98] McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51,* 3388–3390.
[99] Whitlock, G. A. *PhD Thesis* University of Nottingham, **1995**.
[100] Herscovici, J.; Egron, M. J.; Antonakis, K. *J. Chem. Soc. Perkin Trans. I* **1982**, 1967–1973.
[101] Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796–4798.

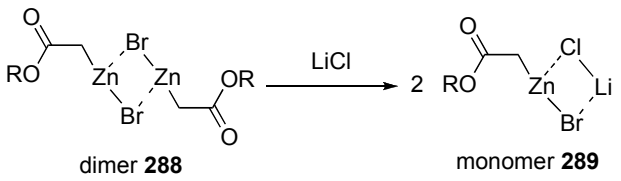


Entry	Metal[a]	Solvent	Reagent	Condition	Result[b]
1	Zn powder	Et_2O	–	reflux	69%
2	Zn powder	Et_2O	**LiCl**	reflux	72%
3	Zn powder	**THF**	LiCl	reflux	14%
4	Zn powder	Et_2O	LiCl, **Ac_2O**	reflux	No conversion
5	**Mn powder**	Et_2O	LiCl	reflux	No conversion
6	Zn powder	Et_2O	LiCl	reflux, **sonication**	No conversion
7	**Zn granulate +powder**	Et_2O	LiCl	reflux	**72%**

a) Zn powder was activated by treatment with TMSCl or HCl; b) isolated yield.

Table 2: Reformatsky optimisation

It seemed that increasing the solubility of the organometallic intermediate would address the issue of agglomeration. Knochel *et al*. noticed that the use of lithium chloride in organometallic reactions increased the solubility of the organometallic complex by breaking up organometallic dimers **288** (Scheme 92).[102] Monomeric species **289** increased the solubility and the reactivity of the organometallic species. In our case, addition of lithium chloride helped to keep the zinc as a powder in the slurry but precipitation still occurred regularly (Entry 2).



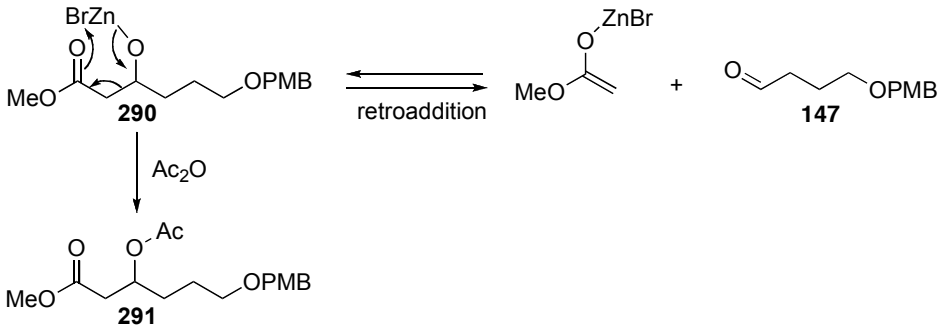
Scheme 92: Organometallic intermediate oligomer dismantling

Better solubility could also be obtained by changing solvent. Using THF was deemed likely to improve the solubility of the reagents and the reaction

[102] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336.

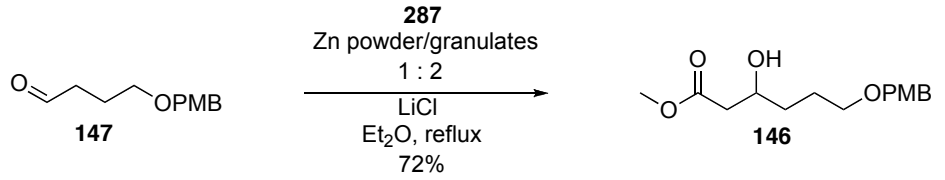
temperature could be increased (Entry 3). Unfortunately, solvent exchange resulted in a low yield.

After the nucleophilic attack, retro-addition was suspected to occur because of the Lewis acidic nature of the resulting zinc complex (Scheme 93).[103] To circumvent this problem, acetic anhydride was used to trap the alcoholate **290** (Entry 4). The newly formed acetate **291** could be hydrolysed to desired β-hydroxyester **146**. In our case, the reaction did not proceed either with acetic anhydride or with allyl bromide, so this procedure was abandoned.



Scheme 93: Retro-addition and trapping by acetic anhydride

Various attempts were carried out to perform the reaction using manganese powder instead of zinc and under sonication, but no conversion was observed (Entry 5–6). The best and most reproducible yields on large scale were obtained by using granulated zinc in combination with zinc powder, diethyl ether and lithium chloride (Scheme 94).

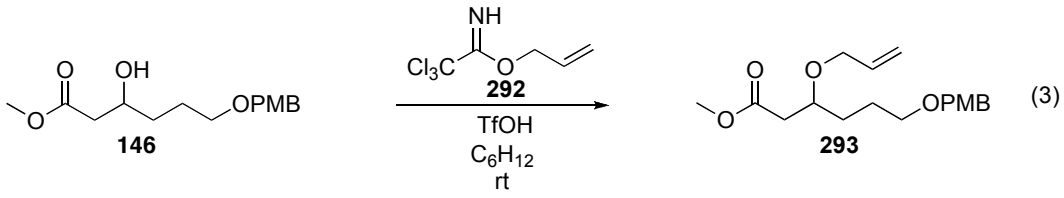


Scheme 94: Optimised conditions

[103] Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373–7376.

2.2.2 O-Allylation of β-Hydroxy Ester 146

O-Alkylation has been studied extensively and *O*-allylation can be performed under both acidic or basic conditions.[104,105] In our case, basic media were avoided due to the acidic hydrogen atoms on the α-position of ester **146** (Equation 3). The acid-mediated procedure combined allyl trichloroacetimidate **292** and catalytic amount of triflic acid (TfOH). First attempts of *O*-allylation were not successful in terms of yield and conversion. Various reaction conditions were screened and table 3 summarises the most relevant attempts.



(3)

Entry	Acid	Solvent	Concentration	Time	Result[a]
1	TfOH 0.2 eq	C_6H_{12}	0.1 M	14 h	23%
2	TfOH 0.2 eq	C_6H_{12} : CH_2Cl_2 2 : 1	0.1 M	14 h	21%
3	TfOH 0.2 eq	C_6H_{12} : CH_2Cl_2 2 : 1	**0.1 M, acid diluted: 0.01 M**	Acid addition: 1h then 3 days	31%
4	**TfOH 0.05 eq**	C_6H_{12}	0.1 M	14 h	22%
5	**TfOH 0.05 eq**	C_6H_{12}	**0.01 M**	14 h	11%
6	**BF_3•Et_2O 0.05 eq**	C_6H_{12}	0.1 M	14 h	44%
7	BF_3•Et_2O **0.2 eq**	C_6H_{12}	0.1 M	14 h	12%
8	BF_3•Et_2O 0.05 eq	C_6H_{12} : CH_2Cl_2 4 : 1	0.1 M	14 h	—[b]
9	BF_3•Et_2O 0.05 eq	C_6H_{12} : CH_2Cl_2 4 : 1	0.1 M	**5 min**	—[b]

a) isolated yield; b) decomposition without expected product.

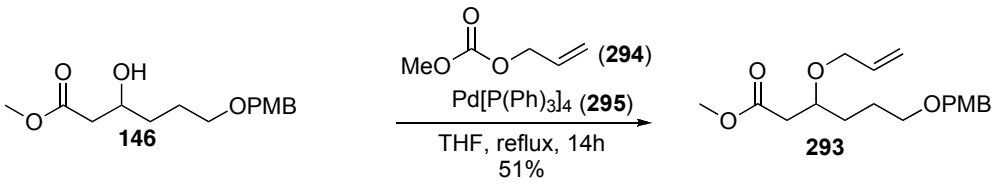
Table 3: Screening for O-allylation

[104] Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247–2250.
[105] Williamson, A *Philosophical Magazine* **1850**, *37*, 350–356.

Acid-mediated allylation resulted in decomposition and PMB deprotection was suspected to compete with the desired reaction. In order to switch to milder conditions, triflic acid was diluted in ether prior to addition, but the reaction was too slow and the conversion was not complete (Entry 3). Further attempts were conducted by modifying the solvent system, the concentration and the catalyst loading, but without success (Entry 2–5).

The main by-product observed was the deprotected alcohol: the PMB group proved to be unstable to protic acid.[106] The use of a Lewis acid instead of a protic acid offered a potential alternative procedure. Although the first attempt with boron trifluoride was promising, satisfactory results were not obtained (entries 6-9). Silver-mediated allylation was not attempted as it had been shown to be ineffective on a similar substrate.[107]

Schmidt and co-workers adapted a Tsuji-Trost palladium-catalysed *O*-allylation reaction to the synthesis of β-hydroxy carbonyl compounds.[108,109] Reactions conditions were established using an excess of alkyl allyl carbonate and a catalytic amount of palladium(0) complex in THF at reflux (Scheme 95). The first attempt was conducted using methyl allyl carbonate **294** and tetrakis(triphenylphosphine) palladium **295**.

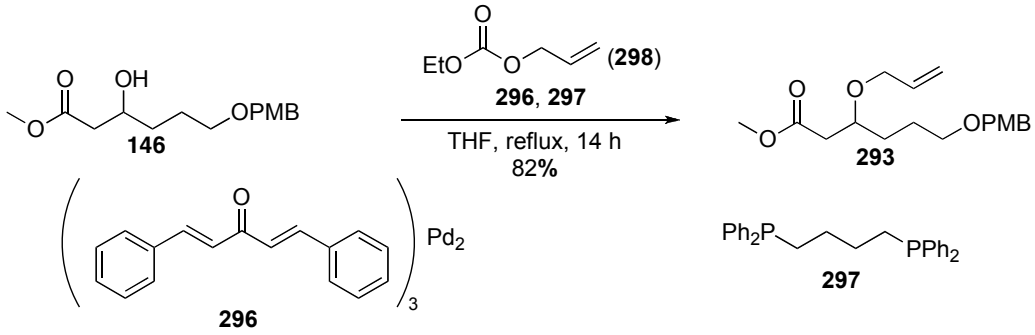


Scheme 95: Palladium catalysed O-allylation

The allylation reaction delivered the allyl ether **293** in moderate yield. However, this result was promising and encouraged us to examine further the palladium-catalysed *O*-allylation reaction. Other palladium complexes were screened: tris(dibenzylideneacetone) dipalladium **296** combined with *bis*(diphenylphosphino)butane **297** (dppb) delivered the product with an

[106] Yanand, L.; Kahne, D. *Synlett*. **1995**, *32*, 523–524.
[107] From studies towards the gambieric acid total synthesis, see chapter 2.1.6.
[108] Schmidt, B.; Nave, S. *Adv. Synth. Catal*. **2006**, *348*, 531–537.
[109] Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc*. **1973**, *95*, 292–294.

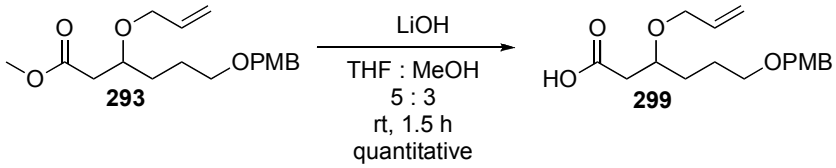
improved 71% yield. By switching from methyl allyl carbonate **294** to ethyl allyl carbonate **298**, the reaction proceeded in good yield (Scheme 96).



Scheme 96: Optimised conditions

2.2.3 Formation of the Tetrahydrofuran Ring

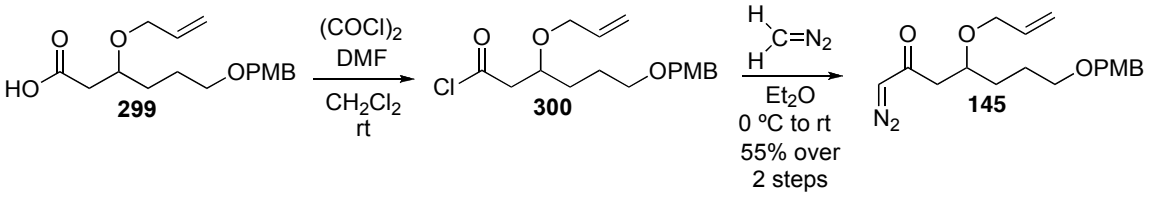
The next step was synthesis of the tetrahydrofuran **144** by [2,3] sigmatropic rearrangement of an oxonium ylide from a diazo-generated metallocarbenoid. The selected method for the terminal diazoketone synthesis was the nucleophilic addition of diazomethane to an activated carboxyl group. The ester **293** cannot be a direct precursor of the diazoketone because it is not electrophilic enough and so activation of the carboxyl group was required. To further functionlise the compound, basic hydrolysis of the ester **293** with lithium hydroxide was performed, which afforded the corresponding carboxylic acid **299** in quantitative yield (Scheme 97).



*Scheme 97: Ester **293** hydrolysis*

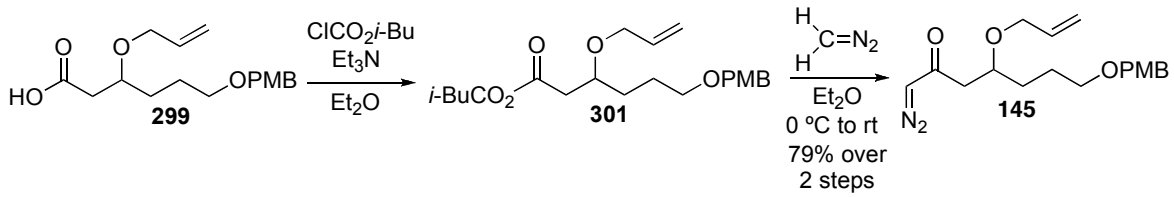
The acid **299** was converted into an acid chloride to generate the diazoketone precursor. Treatment of the acid with an excess of oxalyl chloride and a catalytic loading of DMF delivered acid chloride **300** (Scheme 98). Due to the very high sensitivity of the acyl chloride, the resulting mixture was transferred directly (cannula) into a freshly prepared solution of diazomethane in ether. Diazomethane is a very hazardous yellow gas and it is necessary to

keep it diluted in ether at low temperature and to avoid exposure to strong light.



*Scheme 98: From acid **299** to diazo ketone **145***

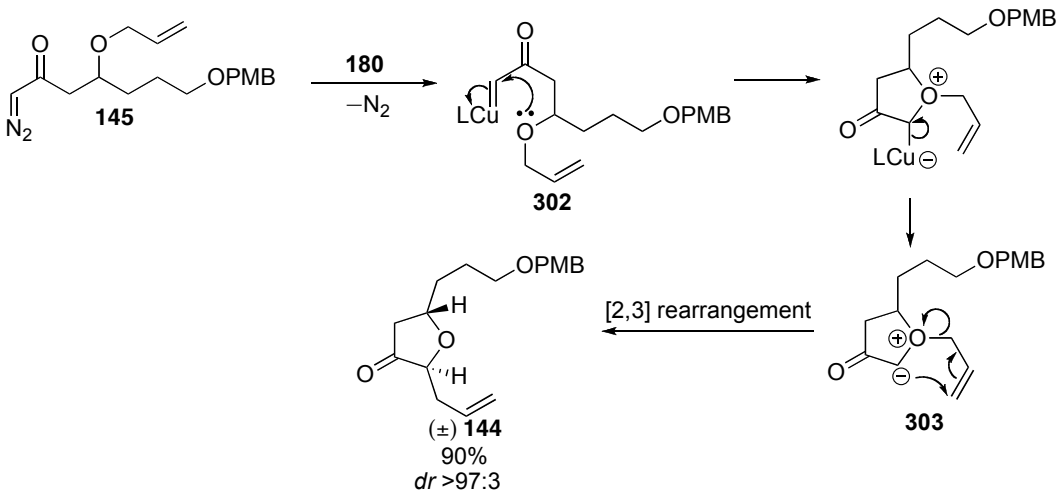
A modest yield of the required diazo ketone was obtained, probably due to hydrochloric acid generation.[110] Consequently, an alternative method was tested in an attempt to improve the yield. Conversion of acid **299** into the corresponding mixed anhydride **301** was performed by reaction with *iso*-butyl-chloroformate and triethylamine (Scheme 99). Pleasingly, the diazo ketone was obtained in 79% yield over two steps when these reaction conditions were employed.



*Scheme 99: From acid **299** to diazoketone **145** via mixed anhydride formation*

The diazoketone **145** was treated with $Cu(acac)_2$ **180** complex to generate the corresponding metal carbenoid **302** and formation of the tetrahydrofuran occurred by formation and [2,3] rearrangement of the oxonium ylide **303** (see chapter 2.1.5.2) (Scheme 100).

[110] Jenkins, D. J.; Riley, A. M.; Potter, B. V. L. *J. Org. Chem.* **1996**, *61*, 7719–7726.

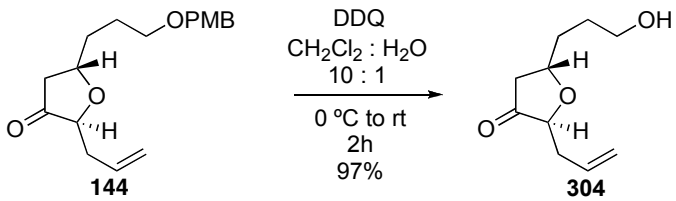


*Scheme 100: Tetrahydrofuran **144** formation*

Many transition metals and ligands had been screened for this rearrangement reaction and the Clark group has studied copper-based catalysts. Our first choice was to use copper(II) acetoacetonate **180** and the sequence proceeded selectively in good yield and with an excellent diastereoisomeric ratio to give the desired racemic *trans*-disubstituted tetrahydrofuranone **144**.

Starting from the ester **293**, the chosen route provided the tetrahydrofuranone **144** in up to 71% yield over four steps. Excellent diastereoselectivity was obtained from the key step, demonstrating the effectiveness of the methodology.

The last step in the synthesis of the fragment **304** was the cleavage of the PMB group. Deprotection of **144** was performed in a biphasic mixture of dichloromethane-water using a slight excess of DDQ. Removal of the protecting group delivered the alcohol **304** in excellent yield (Scheme 101).



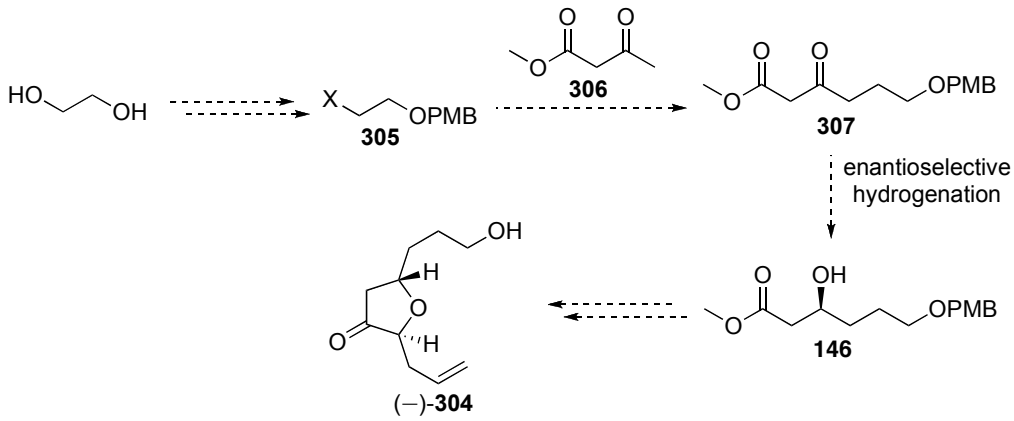
Scheme 101: PMB deprotection

This final step completed the synthesis of the first fragment **304** in racemic form. The synthesis of this amphidinolide T fragment was achieved in a

total of nine steps and with an overall yield of 34% (average yield per step: 88%). However, the moderate success of the Reformatsky reaction meant that better alternatives would have to be investigated for the enantioselective synthesis.

2.3 Enantioselective Pathway

A different strategy was required for the enantioselective synthesis of fragment **304**, in which the previously used Reformatsky reaction would be avoided (Scheme 90). Ethylene glycol would be converted to the corresponding electrophile **305** followed by coupling to the methyl acetoacetonate **306** (Scheme 102). Enantioselective hydrogenation of **307** would result in introduction of the stereocentre to give the alcohol **146** in high *ee*. A sequence similar to that used to prepare racemic material would be used to construct the enantiopure tetrahydrofuran **304**.

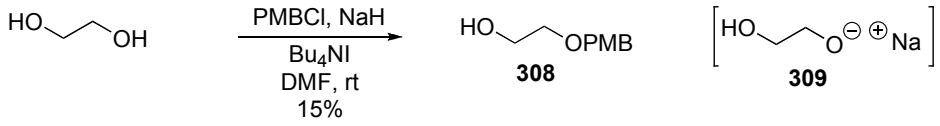


*Scheme 102: Overview of the enantioselective synthesis of **304***

2.3.1 Monoprotection of Ethylene Glycol and Dianion Coupling

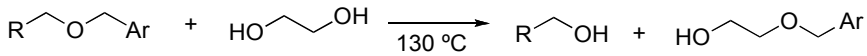
The synthesis of the tetrahydrofuran **304** commenced by PMB monoprotection of ethylene glycol. The first attempt to perform this reaction was carried out in the same way as in the racemic route: DMF as solvent at room temperature (Scheme 103 and 91). Low yields were obtained, even when THF was employed instead of DMF as solvent or when the reaction was performed at higher temperature. Ethylene glycol is a difficult diol to monoprotect and other research groups had already shown that it was difficult to obtain high yields,

probably due to the low solubility of the intermediate alkoxide **309** in an organic solvent.[111]



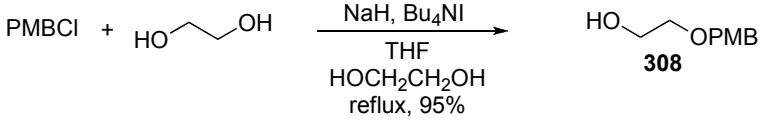
Scheme 103: Monoprotection of ethylene glycol

In 2006, Miyake and co-workers developed a deprotection of benzyl ether protecting group by solvolysis with ethylene glycol as solvent (Scheme 104).[112] The by-product of this reaction is the monoprotected ethylene glycol.



Scheme 104: Solvolysis by ethylene glycol

The result above inspired the next attempt to perform selective monoprotection. In this case, ethylene glycol was used as a co-solvent and the reaction mixture was heated to reflux in THF (Scheme 105). The protection reaction proceeded in excellent yield, even on large scale.

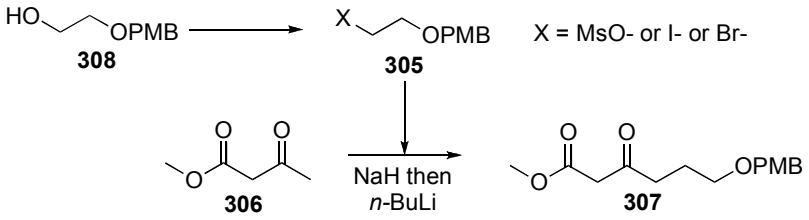


Scheme 105: Monoprotection with large excess of ethylene glycol

The next step was the coupling of methyl acetoacetonate **306** and the electrophile **305** derived from monoprotected alcohol **308** (Scheme 106).[113,114] To deprotonate acetoacetonate **306** at the terminal position, two bases are required. The proton at α-position of the ester is more acidic and sodium hydride was used to deprotonate at this site. The terminal proton is less acidic so a stronger base was necessary to deprotonate at the terminal position of the monoanion. *n*-Butyllithium is basic enough to deprotonate at the both sites and

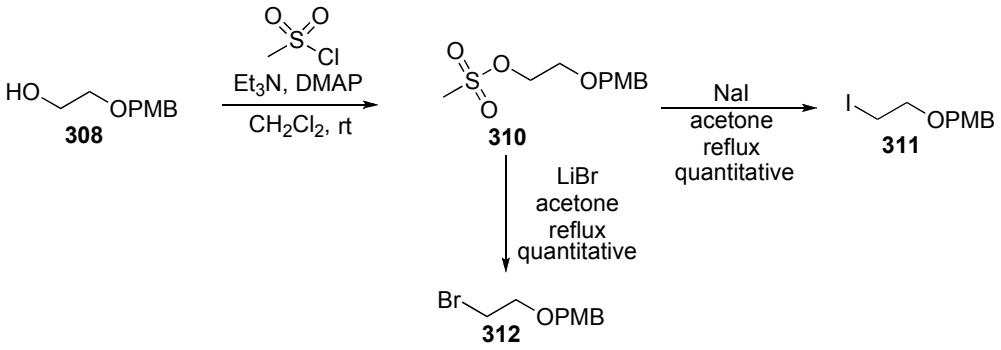
[111] Masutani, K.; Minowa, T.; Hagiwara, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106–1117.
[112] Miyake, H.; Fujimura, M.; Tsumura, T.; Sasaki, M. *Chem. Lett.* **2006**, *35*, 778–779.
[113] Heslin, J.; Moody, C. *J. Chem. Soc. Perkin Trans. I* **1988**, 1417–1423.
[114] Hoppen, S.; Bäurle, S.; Koert, U. *Chem. Eur. J.* **2000**, *6*, 2382–2396.

other alkyl lithium reagents could add to the ester. Consequently, a prior treatment with sodium hydride "locks" the ester and avoids any nucleophilic attack by butyl anion.[115]



Scheme 106: Dianion coupling

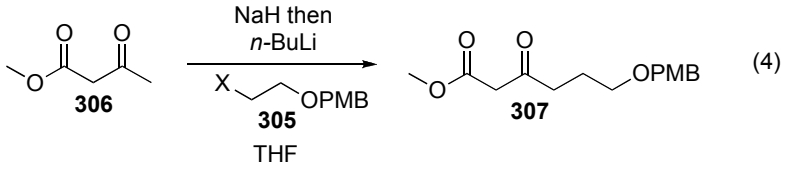
Three electrophiles were chosen for the reaction screening. Alcohol **308** was first converted into the corresponding methanesulfonate **310** (Scheme 107). Upon treatment with either sodium iodide or lithium bromide, iodide **311** and bromide **312** were obtained in quantitative yield.[116,117]



Scheme 107: Electrophiles syntheses

The three electrophiles were subjected to dianion coupling (Equation 4 and Table 4). Coupling using iodide **311** afforded ester **307** in good yield even on a gram-scale. The mesyl group and bromide were not suitable leaving groups.

[115] Weiler, L. *J.Am. Chem. Soc.* **1970**, *92*, 6702–6704.
[116] Coelho, F.; Diaz, G. *Tetrahedron* **2002**, *58*, 1647–1656.
[117] Honzawa, S.; Yamamoto, Y.; Yamashita, A.; Sugiura, T.; Kurihara, M.; Arai, M. A.; Kato, S.; Kittaka, A. *Bioorg. Med. Chem.* **2008**, *16*, 3002–3024.



(4)

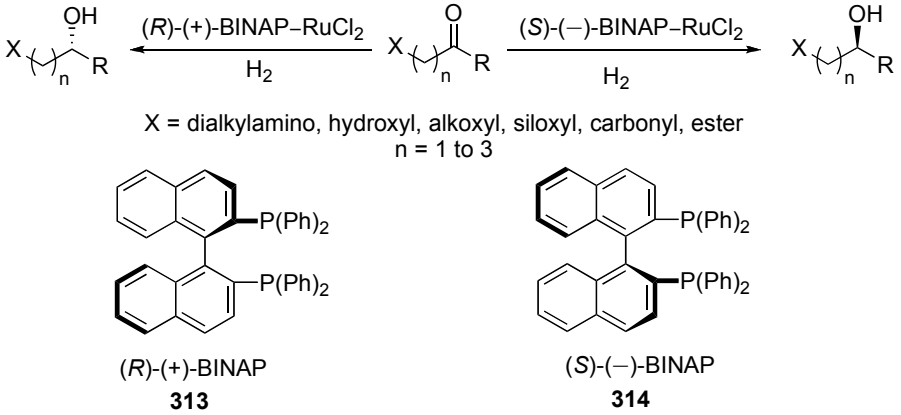
Entry	Electrophile	Temperature	Time	Result[a]
1	mesylate **310**	[b]	6 days	no conversion
2	iodide **311**	−25 °C	3 hours	88 % yield
3	bromide **312**	[b]	6 days	7 % yield

a) isolated yield; b) addition at −25 °C, low temperature kept for 3 h then rt.

Table 4: Coupling results

2.3.2 Noyori Enantioselective Hydrogenation

Noyori discovered that β-ketoesters can be reduced enantioselectively using chiral dichloro[2,2'-bis(diphenylphosphino)-1,1'-binaphtyl]ruthenium(II) **313** and **314** under a pressurised atmosphere of hydrogen (Scheme 108). They extended the concept on other functional groups and obtained excellent yields with exceptional enantioselectivities.[118] Following this breakthrough, Professor Ryoji Noyori shared the 2001 chemistry Nobel Prize with Professor William S. Knowles and Professor K. Barry Sharpless.[119]

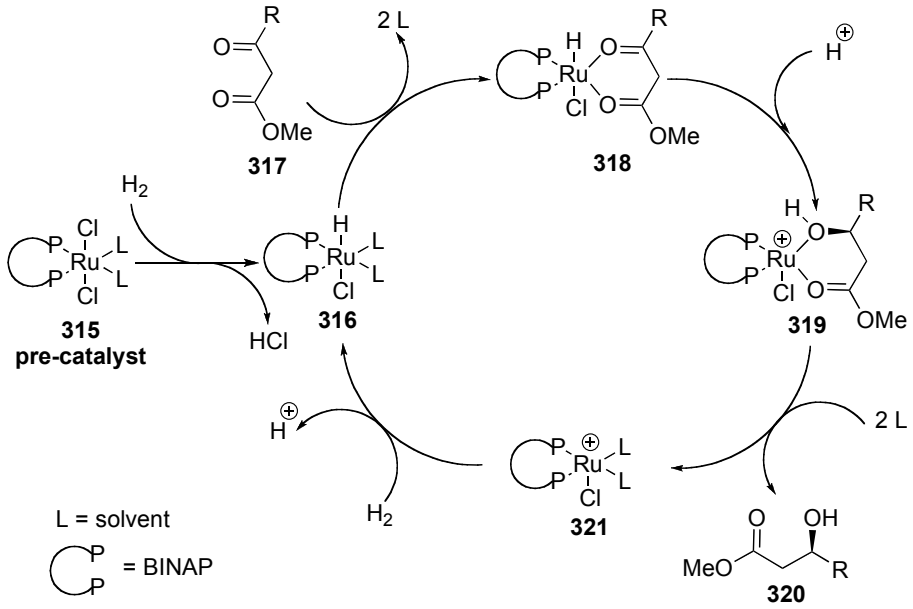


Scheme 108: Noyori enantioselective hydrogenation

The mechanism commences by hydride transfer to the ruthenium complex **315** releasing hydrochloric acid and activate the catalyst **316** (Scheme

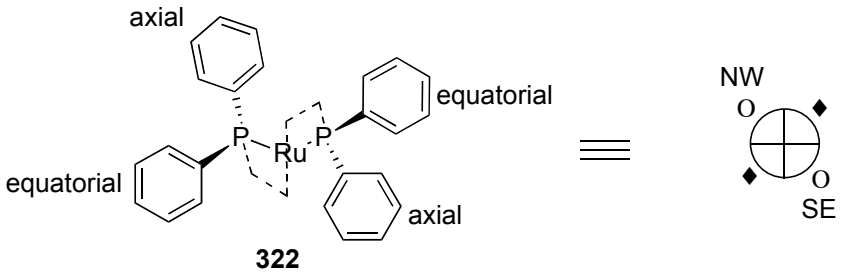
[118] Noyori, R. *Science* **1990**, *248*, 1194–1199.
[119] "The Nobel Prize in Chemistry 2001". Nobelprize.org. 10th March 2012 http://www.nobelprize.org/ nobel_prizes/chemistry/laureates/2001/

109).[120,121] Subsequent simultaneous coordination of the substrate **317** by both carbonyl groups to the ruthenium metal generates the 6-membered chelated ring **318**. Protonation with concomitant hydride transfer from the metal reduces the ketone moiety. Ligand exchange releases the β-hydroxyester **320** and hydride transfer from hydrogen regenerates the catalyst **316**.



Scheme 109: Catalytic circle

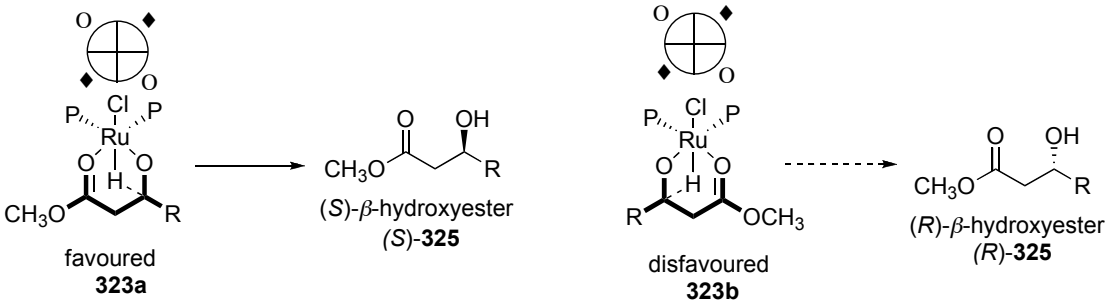
The X-ray crystal structure of $Ru(OCOCH_3)_2$[(*S*)-BINAP] **322** revealed that the rigid BINAP backbone forces the phenyl rings attached to the phosphorus atom to adopt an inflexible conformation (Scheme 110).[122] The equatorial phenyl groups allow coordination at specific sites in only two quadrants on the accessible face of the metal.[120] These chelating sites are represented by a circle with black diamonds (♦) where no coordination can occur and with white circle (O) on the northwest and southeast positions where chelation is possible.



*Scheme 110: Chiral environment of (S)-BINAP complex **322***

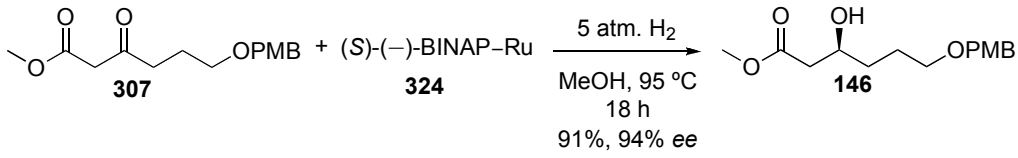
[120] Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56.
[121] Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, **1993**, 56–82.
[122] Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566–569.

The stereo-determining step is the coordination of the ruthenium complex and the β-ketoester **317** in such a way as to minimise the steric repulsion between the equatorial phenyl groups and the ketone moiety. Of the two possible transition states **323a** and **323b** for complexes with (*S*)-BINAP-Ru **324**, the favoured approach of the ketone at the unhindered southeast position leads to the (*S*)-β-hydroxyester (*S*)-**325** (Scheme 111).



Scheme 111: Enantioselective hydride addition

Noyori's methodology was successfully applied to the reduction of the β-ketoester **307** in excellent yield and with 94% *ee* on gram scale (Scheme 112).[123] The enantiomeric excess was determined by chiral HPLC and optical rotation was consistent with that reported in the literature.[124]



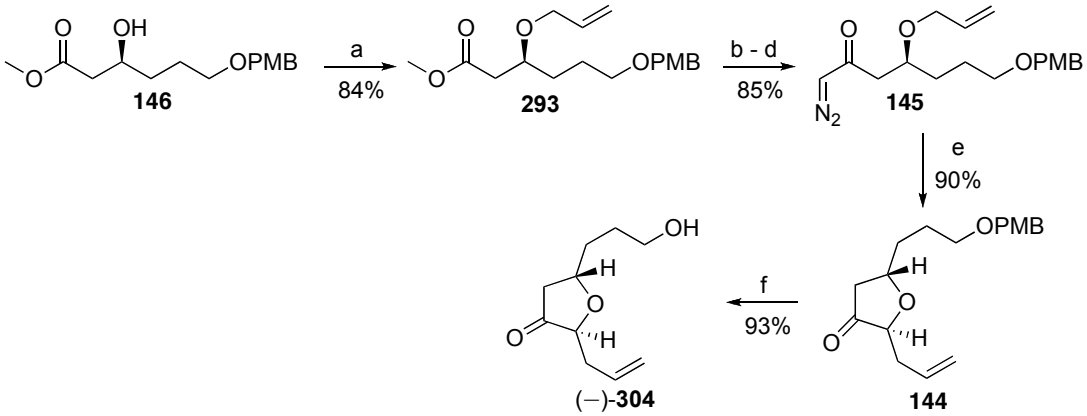
*Scheme 112: Enantioselective reduction of the ketoester **307***

It is noteworthy that the reaction was designed for large scale synthesis. The catalyst loading was low (5 mol%) and an excess of ruthenium complex resulted in racemisation of the alcohol **146** and PMB deprotection. Consequently, the reaction was more difficult to perform on a small scale.

[123] Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Organic Syntheses* **1993**, *71*, 1–11.
[124] a) Hoppen, S.; Baürle, S.; Koert, U. *Chem. Eur. J.* **2000**, *6*, 2382–2396; b) Herb, C.; Bayer, A.; Maier, M. E. *Chem. Eur. J.* **2004**, *10*, 5649–5660.

2.3.3 Completion of the Enantioselective Synthesis of Tetrahydrofuran 304

With the (+)-β-hydroxy-ester **146** in hand, the synthesis of the enantiopure tetrahydrofuran ring **304** was successfully conducted following the optimised route established using racemic material (Scheme 113).



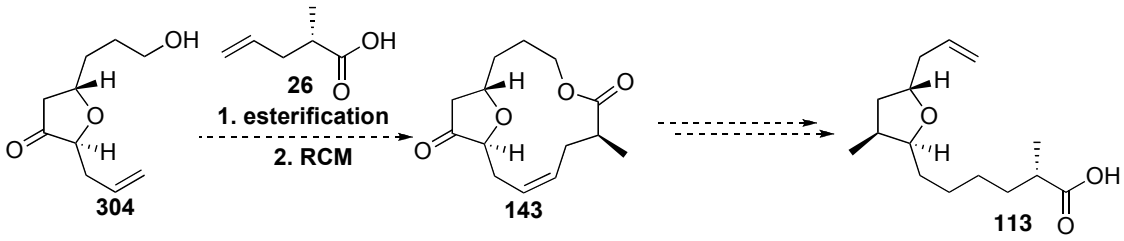
a) **296**, **297**, **298**, THF, reflux; b) LiOH, THF-MeOH (5:3), rt; c) *i*-BuOCOCl, Et_3N, Et_2O, rt; d) CH_2N_2, Et_2O, 0 ºC to rt; e) $Cu(acac)_2$, THF, reflux; f) DDQ, CH_2Cl_2-H_2O, (10:1), 0 ºC to rt.

*Scheme 113: Towards the (−)-tetrahydrofuran **304***

The fragment **(−)-304** was prepared in 45% yield over nine steps using a route that included high-yielding and diastereoselective tetrahydrofuran formation *via* [2,3] sigmatropic rearrangement of the oxonium ylide or metal-bound ylide equivalent generated from diazo-generated metal carbenoid. The average yield per step was 92% and the sequence was applicable on gram scale. The next challenge to be addressed was the coupling of the side chain **26** using a sequence of esterification and metathesis reaction.

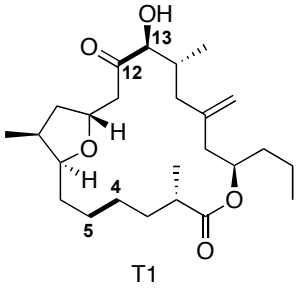
Chapter 3: Coupling of Fragments by RCM

First fragment union was envisaged by metathesis between tetrahydrofuran **304** and acid **26** (Scheme 114). Direct cross metathesis had been employed in Ghosh's strategy so an original alternative approach was envisaged (see chapt. 1.2.2). Esterification would couple the two fragments and RCM would form the expected C=C bond, delivering macrolactone **143**. Further transformations would complete the segment **113**, a common intermediate that would be required for the synthesis of the entire amphidinolide T family.



*Scheme 114: Fragment coupling and end game to key segment **113***

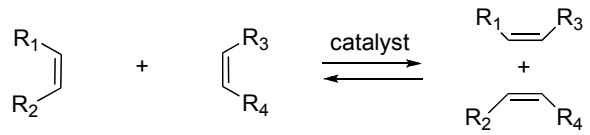
Since metathesis reactions are employed to form two carbon-carbon bonds in our approach, the process was a key step in the journey towards the total syntheses of members of the amphidinolide T family (Scheme 115).



Scheme 115: Bonds generated by RCM on Amphidinolide T1

3.1 Overview of Olefin Metathesis

The word metathesis is derived from the Greek *metatithenai,* which means literally "in an other place" (*meta*) and "to place" (*tithenai)*; therefore the process is transposing something to another site. In organic chemistry, metathesis reactions result in reorganisation of unsaturated carbon-carbon bonds in the presence of metal carbene complexes (Scheme 116).[125]



Scheme 116: Principle of olefin metathesis

This transformation has been known since the late 1950s with the fundamental discovery by Karl Ziegler that some transition metals promoted polymerisation of olefins under mild conditions. However, the main drawback of early metathesis catalysts was their high activity at the expense of compatibility with polar functional groups, due to their strong Lewis acidity and alkylating properties. Consequently, the process was generally inapplicable in disciplines other than polymer chemistry.

In the early 1980s, the discovery that metal alkylidene complexes can catalyse metathesis reactions led to dramatic advances in organic synthesis.[126] The development of efficient chemoselective single-component molybdenum and ruthenium carbene complexes as catalysts in the 1990s increased the scope of metathesis to include highly functionalised olefins. Over the last twenty years, this process has emerged as one of the most useful and powerful tools for the generation of C=C bonds. The reaction has revolutionised the design of synthetic routes and its success has been demonstrated by numerous elegant applications to the synthesis of complex molecular architectures and industrial processes.

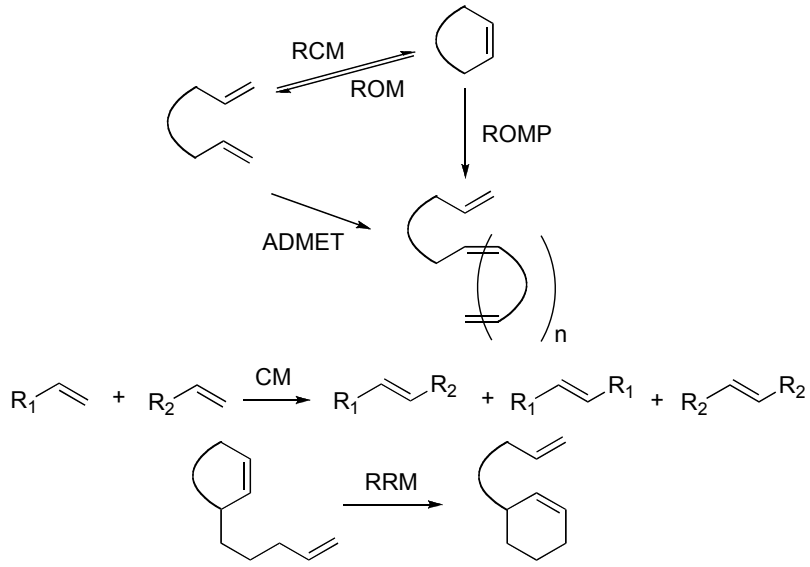
The scientific community recognised the value of olefin metathesis in 2005 through the award of the Nobel Price in Chemistry to Professors Yves

[125] Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.
[126] Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.

Chauvin, Robert H. Grubbs and Richard R. Schrock "for the development of the metathesis method in organic chemistry".[127]

3.1.1 Different Metatheses for Diverse Applications

Alkene metathesis reactions can be classified into five related categories. In the case of acyclic unsaturated systems, the reaction can be intramolecular (ring closing metathesis or RCM) or intermolecular (cross metathesis or CM) (Scheme 117).[128] In addition, polymerisation (acyclic diene metathesis or ADMET) may compete with the RCM process. Strained cyclic olefins can undergo ring opening metathesis (or ROM) followed by polymerisation through metathesis (ROMP). However, in some cases, strained cyclic olefins can undergo ROM followed by RCM with different olefinic functionalities to form a less strained cyclic structure in a process called ring-rearrangement metathesis (or RRM).

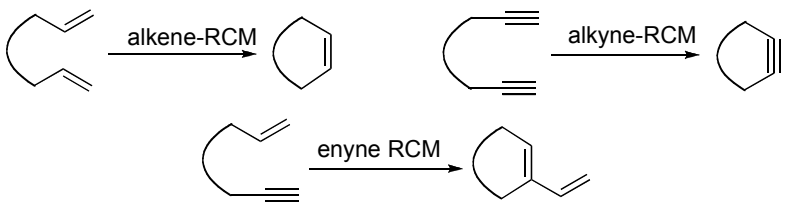


Scheme 117: Olefin metathesis reactions

Alkene-metathesis is the most commonly employed of the metathesis-based bond-forming reactions (Scheme 118). Recent years have witnessed the development of related processes applied to a broader range of unsaturated substrates, such as alkyne metathesis. The latter is a direct analogue of the alkene metathesis reaction and connects two alkyne groups. It is

[127] "The Nobel Prize in Chemistry 2005". Nobelprize.org. 10th April 2012 http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2005/
[128] Nicolaou, K. C.; Bulger, P. G.; Sarlah D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527.

also possible to perform enyne metathesis to unite an alkyne with an alkene and deliver a 1,3-diene.

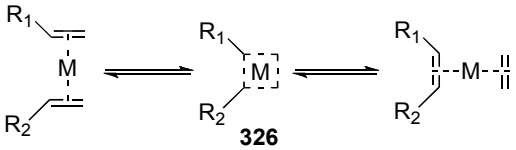


Scheme 118: Diverse unsaturated systems subjected to RCM

Different conditions applied to various substrates generate a wide variety of carbon scaffolds and so metathesis reactions are extensively used in synthetic organic chemistry. Initially, the mechanistic pathway was obscure to the scientific community and questions relating to the detailed reaction mechanism perplexed organic chemists for years.

3.1.2 Mechanism

The first proposed mechanism involved a pair-wise exchange of alkylidenes *via* a "quasicyclobutane" intermediate **326** in which two unsaturated C-C bonds coordinated to the metal and exchanged alkylidene groups (Scheme 119).[129] The mechanism could explain most of the transformations, but the direct thermal [2+2] cycloaddition of two alkenes is symmetry forbidden according to the Woodward-Hoffmann rules.[71]

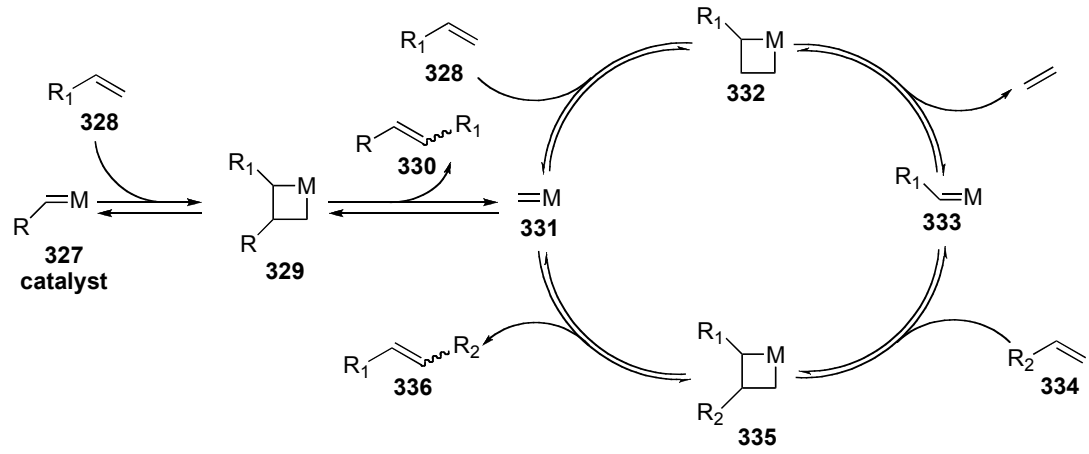


Scheme 119: Pair-wise exchange mechanism

In 1971, Chauvin and Hérisson proposed a new mechanism to explain the observation that in some cases, olefins resulting from cross products were formed at an early stage of the reaction rather than the two olefins resulting from the pair-wise exchange (Scheme 120).[130] This observation led Chauvin to propose a different mechanistic pathway consisting of a sequence of formal

[129] Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, *8*, 3327–3329.
[130] Hérisson, J.-L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161–167.

[2+2] cycloaddition/cycloreversion steps involving alkenes, metal alkylidenes and metallocyclobutane intermediates.



Scheme 120: Chauvin's mechanism

The first step is a [2+2] cycloaddition reaction between the metal carbene catalyst **327** the olefin **328** to afford the first metallocyclobutane **329**. This metal complex intermediate undergoes a [2+2] cycloreversion reaction releasing a highly active metal carbene **331**. Metallocycle **332** is generated by [2+2] cycloaddition with olefin **328** and further rearrangement delivers ethylene and the metal alkylidene **333**, which bears the R_1 group. Subsequent [2+2] cycloaddition occurs between the olefin **334** and the metal carbene **333** to form the metallocyclobutane **335**. After a further [2+2] cycloreversion reaction, the coupled product **336** is released and the catalyst **331** is regenerated to undergo further catalytic cycles.

All steps of this mechanism are reversible and so it is necessary to displace the equilibrium in favour of the desired product to avoid olefinic by-products.[131] In the case of RCM, the process is usually entropically favoured because a single starting diene is rearranged to give two olefinic products. If one of them is volatile (ethylene for example), gas evolution shifts the equilibrium towards the products. In some cases, RCM products can undergo retro-reaction because release of ring strain can provides a considerable driving force for ring-opening metathesis (ROM).

[131] Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043.

Substitution on the alkene substrates is the determining factor for the kinetics of the reaction and it is generally accepted that the more substituted the alkene is, the less reactive it is towards metathesis reactions. The choice of solvent, temperature, concentration, reaction time and especially catalyst are all crucial in metathesis processes.[132]

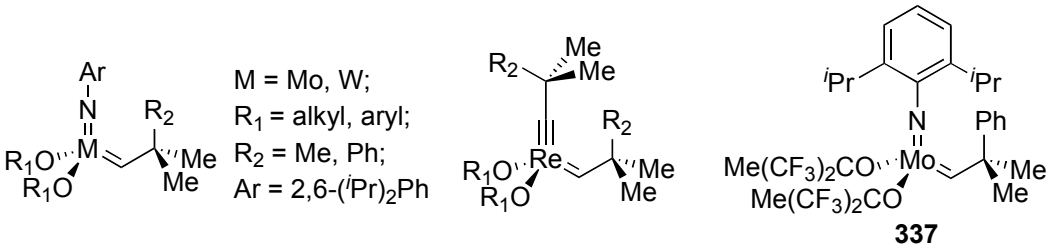
3.1.3 Catalysts

Numerous catalytic systems are able to promote alkene metathesis. Early catalysts were multicomponent, complex and hard to handle mixtures of inorganic compounds like $WCl_6/AlCl_3$ or ReO_7/Al_2O_3.[133] These metal complexes are highly reactive, resulting in poor selectivity and have very low tolerance for acid-sensitive functional groups due to their high Lewis acidity. A major breakthrough in the field was achieved with the discovery of higher oxidation state metal complexes of tungsten, rhenium, molybdenum and ruthenium, which provided a library of more tolerant, less sensitive and efficient metathesis catalysts.

3.1.3.1 Schrock's Catalysts

Schrock and co-workers developed a wide variety of metathesis catalysts based on tungsten, rhenium and molybdenum.[134] The most commonly used system is the molybdenum complex **337** because it exhibits high reactivity towards a broad range of substrates with differing steric and electronic environments (Scheme 121). The alkoxide group can be modified to adjust its reactivity: for example, when R_1 = *t*-Bu, the complex reacts preferentially with strained cyclic alkenes, creating an ideal ROMP catalyst. Unfortunately, molybdenum complexes also display many distinct disadvantages including poor functional group tolerance, thermal instability and high sensitivity to air, water and traces of impurities in solvent.

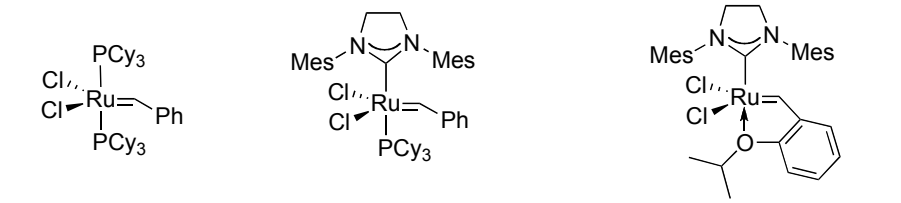
[132] Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783–3816.
[133] Calderon, N.; Ofstead, E. A.; Judy, W. A. *Angew. Chem. Int. Ed.* **1976**, *15*, 401–409.
[134] Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633.



Scheme 121: Schrock's catalysts

3.1.3.2 Grubbs Catalysts

During the 1990s, Grubbs *et al*. studied a series of ruthenium catalysts that promote olefin metathesis (Scheme 122).[135] These alkylidene catalysts are used extensively in organic synthesis for several practical reasons. For example, they exhibit high reactivity towards initiation of a variety of ROMP, cross-metathesis and RCM reactions. Furthermore, the ruthenium complexes show high tolerance with regard many functional groups.



Scheme 122: Most common Grubbs catalysts

The GII **43** and HGII **339** catalyst systems remain reactive and stable regards to exposure to air, moisture or solvent impurities. Although the Grubbs catalysts sometimes show relatively low reactivity toward sterically hindered substrates compared to Schrock's catalysts, their stability, ease of use and high functional group tolerance makes them the catalyst of choice for many alkene or enyne metathesis reactions.

The first generation catalyst **338** is the cheapest and the easiest to prepare, but it is thermally unstable and less reactive towards substituted olefins. Nolan *et al*. introduced *N*-heterocyclic carbenes (NHC) as ligands for

[135] Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.

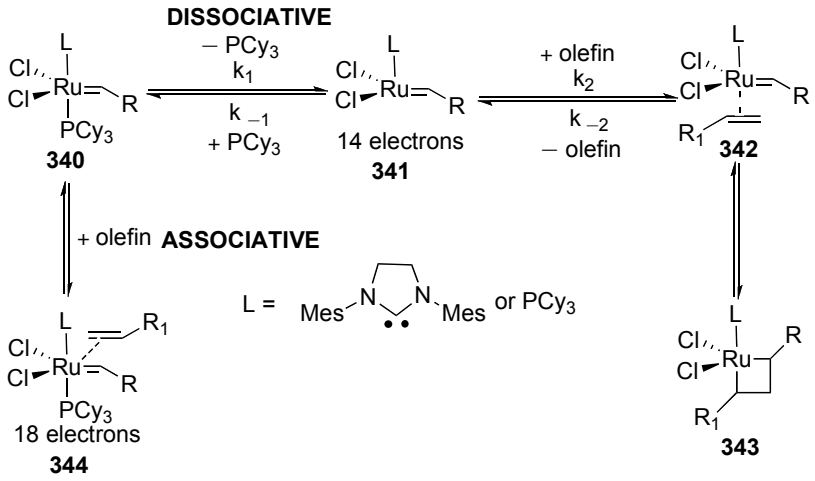
ruthenium-based metathesis catalysts. Dramatic improvements have been made by replacing one of the phosphine ligands by a NHC ligand to create the Grubbs second-generation catalyst **43**.[136,137] This ligand replacement improved the reactivity and the stability towards air, moisture and high temperature. The metal carbene complex **43** is also resistant to chromatography, which confers recyclable properties, in some cases.

A third-generation of ruthenium catalysts has been developed by Hoveyda and co-workers by alteration of the second phosphine group by an *iso*-propoxy group coordinated to the ruthenium and attached to the phenyl carbene unit (Scheme 122).[138] The Hoveyda-Grubbs catalyst **339** is generally accepted as the most reactive of those catalysts that are either readily accessible from complex **43** or commercially available.

In contrast to the Schrock's catalysts, the Grubbs catalyst systems are pre-catalysts and the active species are generated *in situ*.[139] Understanding the mechanism of the formation of the active catalyst was crucial for ligand design and two possible pathways have been established (Scheme 123). In the dissociative route, complex **340** undergoes exchange of a phosphine ligand with the olefin to form a 14-electron complex **341**. With regard to the associative pathway, the olefin coordinates first to the catalyst and forms an 18-electron complex **344**. Recent studies performed by the Grubbs group suggested the dissociative pathway is more likely to occur than the associative mechanism.[140] The dissociative mechanism is consistent with the observation that the Grubbs first-generation catalyst is less reactive than the others, because in the case of the GI, the rate of phosphine ligand loss is high (k_1 large) but recoordination of the ligand is faster than coordination of the olefin ($k_{-1}/k_2>>1$). Therefore the active species is formed rapidly but catalyst turnover is low. In the case of the NHC ligand, the dissociation of the phosphine is slow but so is the recoordination

[136] Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678.
[137] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
[138] Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
[139] Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
[140] Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749–750.

rate. Due to the strong sigma-donor effect of the NHC group, the metal complex **341** is more stable allowing a higher turnover of the active species.



Scheme 123: Ruthenium catalyst mechanism

Grubbs catalysts have been employed widely for the total syntheses of natural products as well as in materials chemistry. An interesting application is in the aerospace industry.[141] A spaceship's hull requires a particularly strong material to prevent formation of microcracks in the structure, which can form over time. A new material incorporates Grubbs catalyst as well as capsules of monomers, which can undergo ROMP. When a fissure forms in the hull, the capsules are ruptured, allowing the monomers to come in contact with the metathesis catalyst initiating polymerisation and sealing the crack. In our case, Grubbs catalysts were used to promote macrocyclisation through RCM, a process highlighted in many successful total syntheses of natural products.

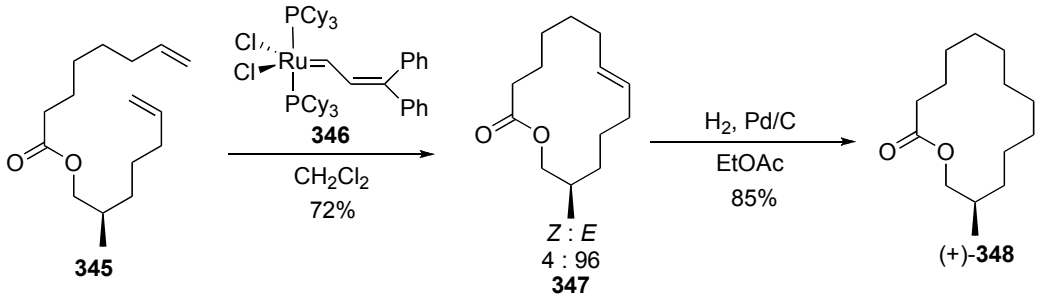
3.1.4 Alkene RCM in Macrocyclic Natural Products Total Synthesis

The RCM reactions of acyclic dienes can be used to form rings of many sizes, from 5-membered to macrocyclic. The construction of a macrocycle by RCM has often been employed as the key step during the synthesis of complex natural products containing large rings.[142,143,144] The reaction is synthetically

[141] White, S. R.; Sottos, N. R.; Geubelle, P. H.; Moore, J. S.; Kessler, M. R.; Sriram, S. R.; Brown, E. N.; Viswanathan S. *Nature* **2001**, *409*, 794–797.
[142] Borer, B. C.; Deeremberg, S.; Bierfugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191–3194.
[143] Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086–6101.
[144] Gradillas, A.; Pérez-Castells, J. *Metathesis in Natural Product Synthesis* Wiley-VCH: Weinheim; 1st edition **2010**, Chap. 5.

attractive because of the high functional group compatibility, which allows complex substrates to be assembled prior cyclisation. The main disadvantages involve the control of stereochemistry in the newly formed alkene and competition with intermolecular processes, resulting in polymers rather than macrocycles.

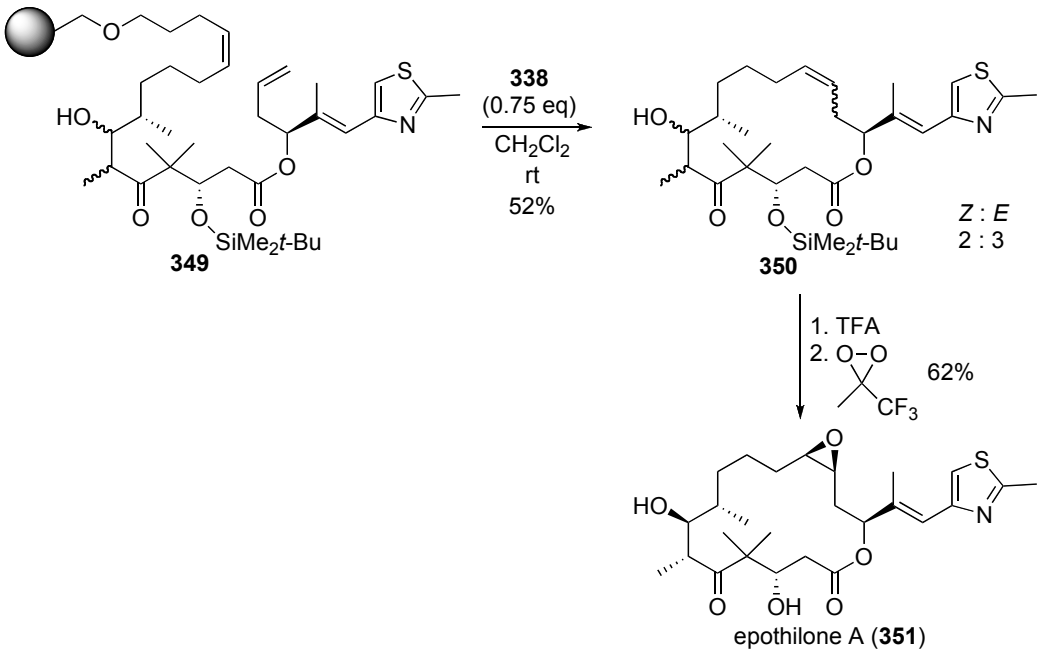
The compound (12*R*)-(+)-12-methyl-13-tridecanolide **348** was the first macrocyclic natural product to be synthesised using RCM as the key step (Scheme 124).[145] Fürstner *et al*. demonstrated the synthetic utility of RCM by formation of a 14-membered macrolactone **347**. Treatment of diene **345** with modified GI catalyst **346** afforded the expected macrocycle **347** in good yield and excellent stereoselectivity of the newly formed *E*-alkene. The macrolactone was reduced subsequently to the natural odorant **348**; the total synthesis was completed in five steps and in 33% overall yield.



Scheme 124: First total synthesis employing RCM-based approach

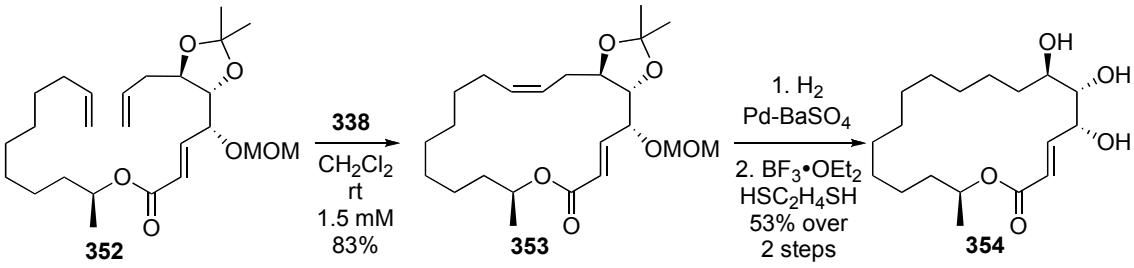
In the race towards the total synthesis of anti-cancer natural products, a RCM-based strategy was employed by Nicolaou and co-workers during construction of epothilone A **351** (Scheme 125).[146] The macrocycle **350** was formed with a high catalyst loading of GI **338**, in modest yield and poor stereoselectivity. This pioneering study opened this field to the whole synthetic chemistry community and RCM-based strategies for the total synthesis of the epothilone family natural products and analogues have been investigated extensively.[147]

[145] Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942–3943.
[146] Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, 387, 268–272.
[147] Rivkin, A.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 2838–2850.



Scheme 125: Total synthesis of epothilone A using RCM-based strategy

Hatakeyama *et al.* studied the enantioselective total synthesis of (+)-aspicilin **354** employing diene RCM as the key step (Scheme 126).[148] In this case, the 18-membered macrolactone core was formed smoothly in the presence of GI **338** under dilute conditions, delivering the *Z*-isomer **353** as the sole product in good yield. Hydrogenation and global deprotection afforded the macrolide (+)-aspicilin **354** in 10% yield over ten steps.

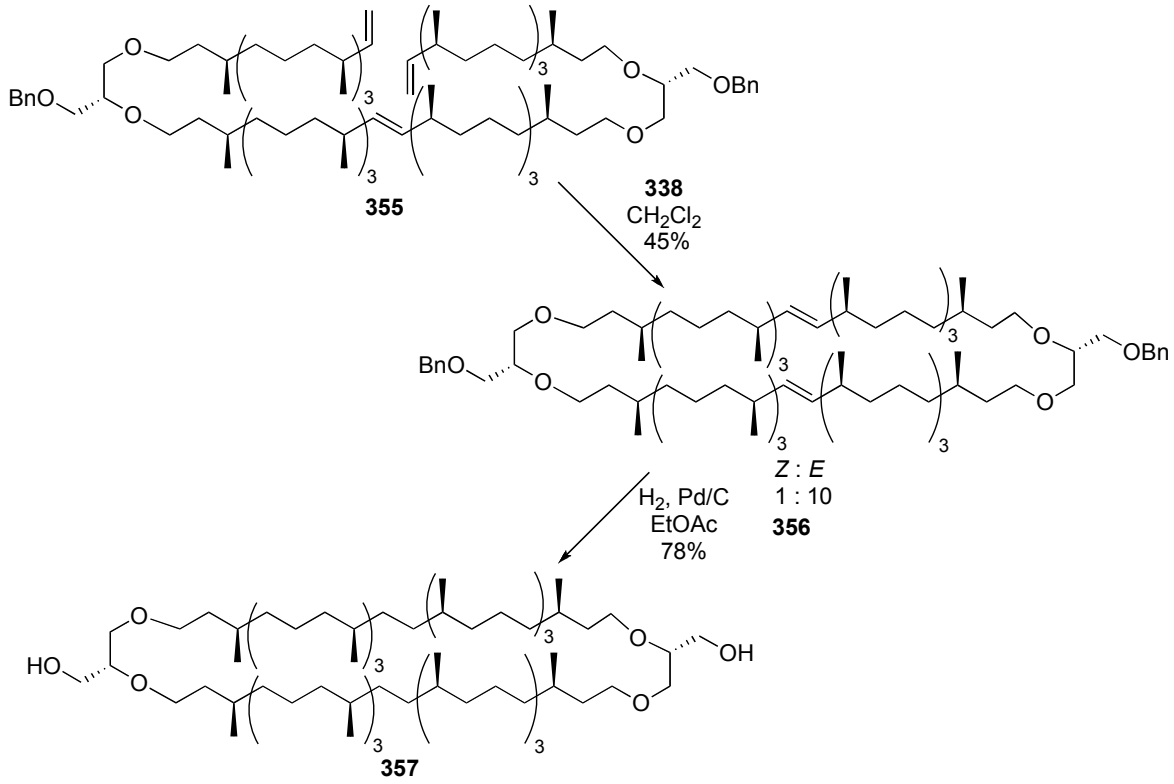


Scheme 126: Total synthesis of (+)-aspicilin

Diene RCM has been applied even to the formation of large macrocycles. Macrocyclic lipids are found rarely in nature, however 72-membered cyclic diol **357** was extracted from the membrane of *Archaebacteria* (Scheme 127).[149] An efficient metathesis-based synthetic approach was designed by Kakinuma and co-workers for the total synthesis of **357**. Triene **355** was cyclised using GI **338**

[148] Nishioka, T.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1998**, *39*, 5597–6000.
[149] Arakawa, K.; Eguchi, T.; Kakinuma, K. *J. Org. Chem.* **1998**, *63*, 4741–4745.

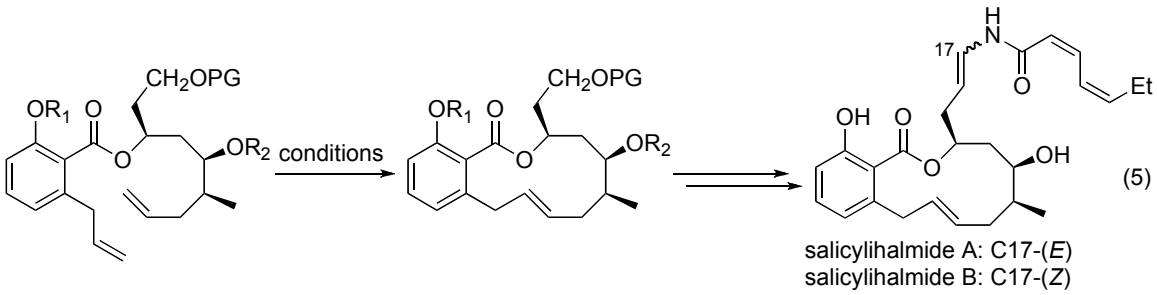
under dilute conditions to afford macrocycle **356** in moderate yield and with good stereocontrol of the *E*-alkene. Further double bond reductions with concomitant protecting group removal delivered target **357**.



Scheme 127: Total synthesis of large macrocycle

The presence of substituents on the macrocyclic precursor greatly influences the outcome of an RCM reaction. Studies concerning the total syntheses of salicylihalmide A and B highlighted the influence of remote functional groups (Equation 5 and Table 5). Obtaining the required *E*-stereochemistry for the newly-formed double bond was challenging using GI complex **338** because the presence of the remote phenolic hydroxyl group favoured the undesired *Z*-isomer (Entry 1).[150,151] Protection of both hydroxyl groups improved the yield and altered the stereochemical outcome significantly (Entries 2–3). However, altering the ligand on the metathesis catalyst did not enhance the stereoselectivity during macrocycle formation (Entries 4–5).[152,153]

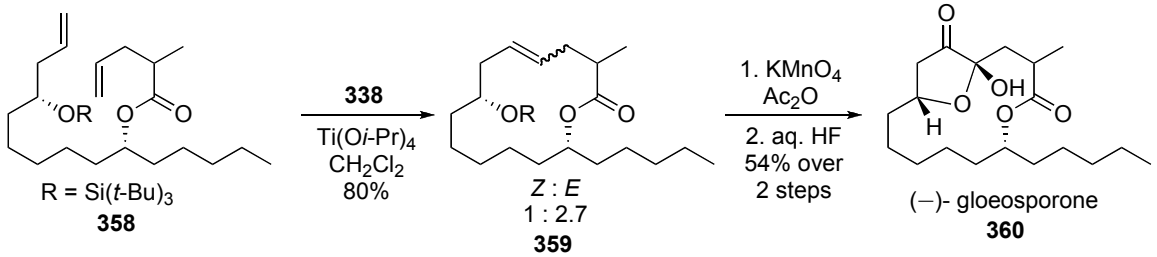
[150] Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817–1820.
[151] Smith, A. B. III; Zheng, J. *Tetrahedron* **2002**, *58*, 6455–6471.
[152] Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245–3253.
[153] Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286–5298.



Entry	R_1	R_2	Catalyst	Yield	*E*:*Z*
1	H	H	GI **338**	low	*Z*
2	TBS	H	GI **338**	57%	4:1
3	Me	TBS	GI **338**	85%	10:1
4	H	MOM	mod. GII **32**	69%	*Z*
5	MOM	MOM	GII **43**	98%	2:1

Table 5: Substrate substitution influences on salicylihalmide A and B total syntheses

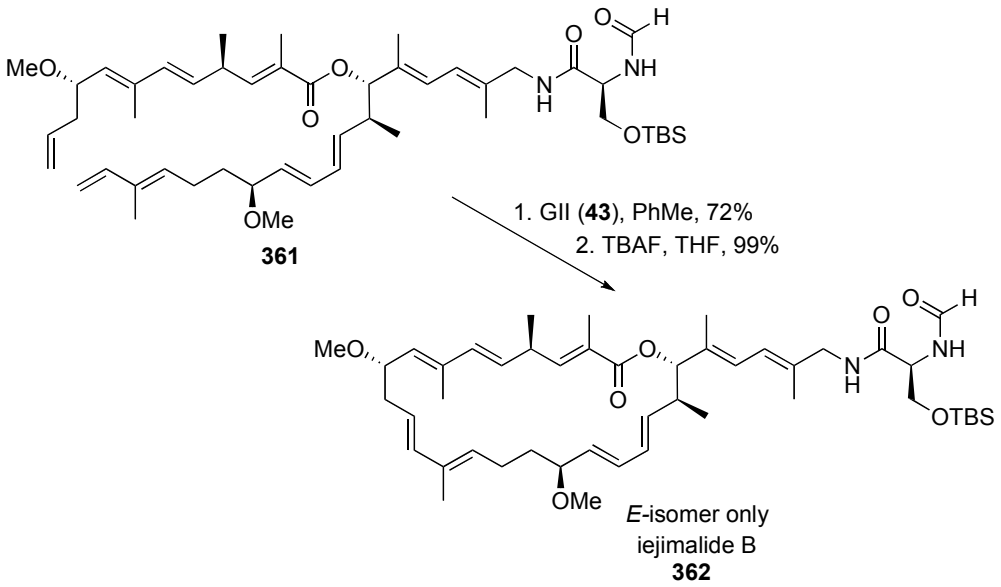
Fürstner and co-workers highlighted the effect of heteroatoms on the reactivity of the olefin under metathesis conditions.[154] Nitrogen-containing molecules are generally not suitable substrates except for non-basic functional groups such as tosylamides.[143] Oxygen-containing substrates can have either a positive or negative effect on the course of the RCM reaction. In some cases, negative influences can be overcome by the addition of Lewis acids to prevent coordination of the oxygen lone pair to the catalyst. During the studies concerning the total synthesis of (−)-gloeosporone **360**, diene **358** failed to cyclise when treated with GI catalyst **338** (Scheme 128). However, the use of Ti(O*i*-Pr)$_4$ as an additive enhanced the substrate reactivity and the macrocycle **359** was formed in good yield, although low stereoselectivity was obtained. Oxidation and lactol formation completed the highly enantioselective eight-step total synthesis of (-)-gloeosporone **360** in 18% yield.



Scheme 128: Total synthesis of (−)-gloeosporone

[154] Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

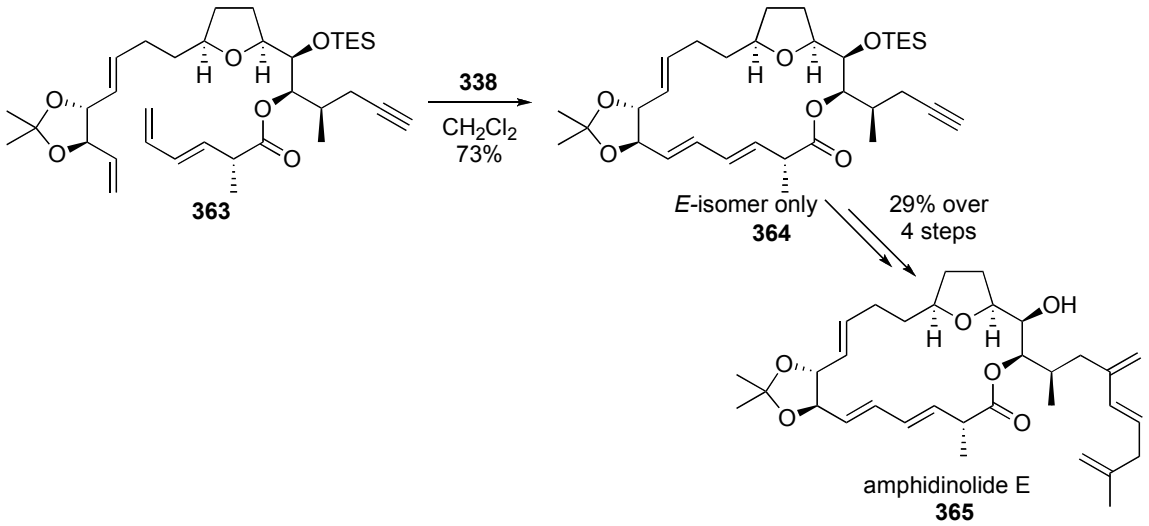
Over the past two decades, metathesis transformations have fascinated the research community and a large library of catalysts for various applications to diverse substrates has been generated. Since the introduction of NHC ligands on Grubbs complex, the GII **43** has been by far the most widely employed catalyst for diene RCM during natural product syntheses, thanks to its excellent functional group tolerance, high catalytic activity and stability. The GII catalyst **43** was employed recently during a gram-scale total synthesis of iejimalide B **362** (Scheme 129).[155] The 24-membered macrolactone **362** was forged by a remarkably selective GII-catalysed RCM reaction, in which two of the ten double bonds present in the cyclisation precursor were selectively activated. The gram-scale total synthesis of the macrolide **362** was accomplished in 16 steps (longest linear sequence) and in 7% overall yield.



Scheme 129: Gram-scale total synthesis of iejimalide B

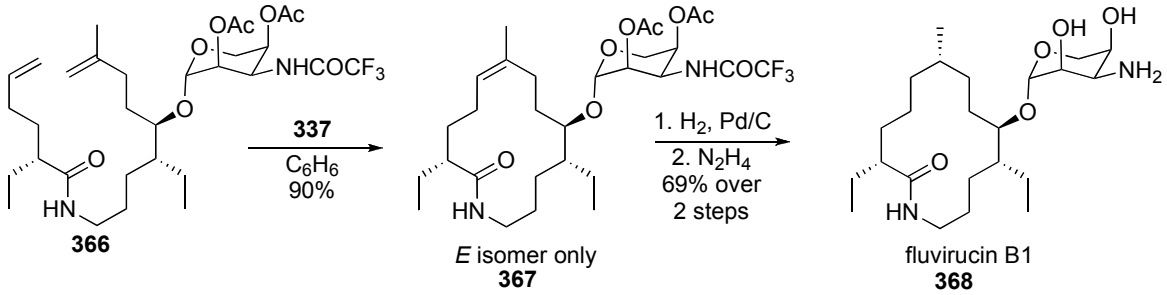
In certain cases, GII-catalysed metathesis reactions are not very chemoselective. In the course of the studies directed towards the total synthesis of amphidinolide E **365**, polyene **363** was found to undergo complete decomposition when exposed to GII **43** (Scheme 130).[156] However, smooth RCM using GI **338** catalyst afforded the macrocycle **364** in good yield and with total diastereocontrol.

[155] Gagnepain, J.; Moulin, E.; Fürstner A. *Chem. Eur. J.* **2011**, *17*, 6964–6972.
[156] Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960–15961.



Scheme 130: Total synthesis of amphidinolide E

Fluvirucin B1 **368** was one of the first natural macrolides to be synthesised by alkene RCM and of the synthesis includes one of the few examples in which Schrock's molybdenum catalyst **337** has been employed (Scheme 131).[157] The macrolactam **367** was obtained from a high yielding and totally stereoselective RCM reaction.

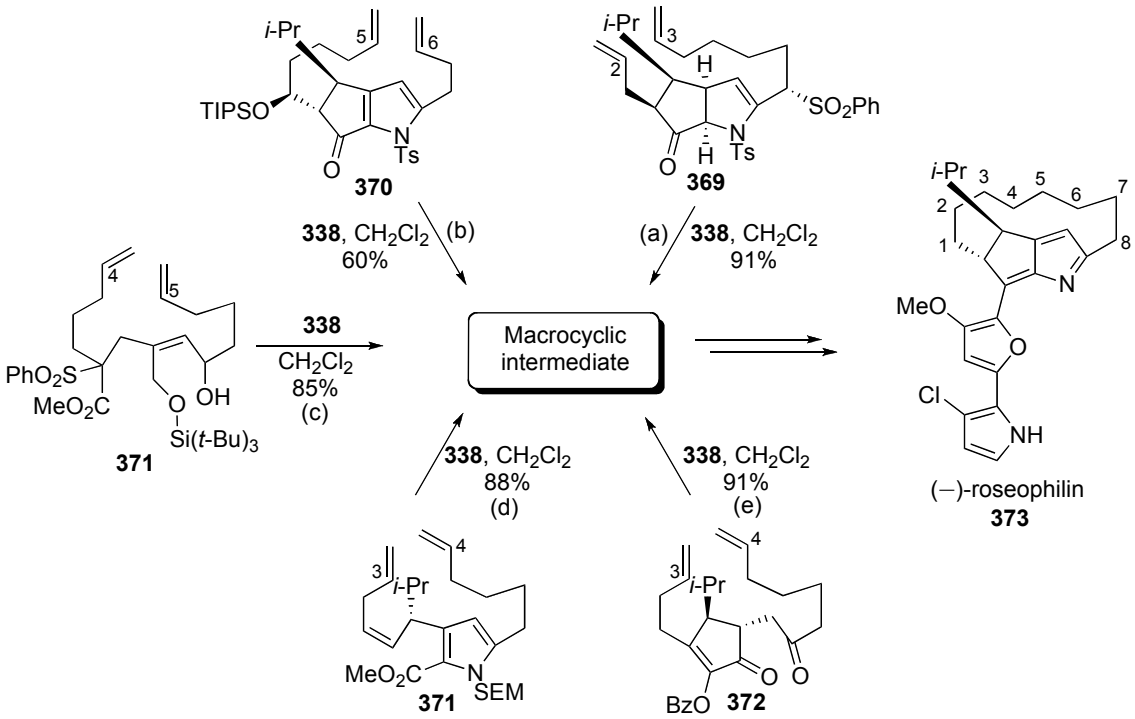


Scheme 131: Molybdenum catalyst-based RCM

The total synthesis of the natural product (−)-roseophilin **373** posed a challenge for synthetic research groups (Scheme 132). The main issue was the construction of the macrocycle and initial attempts to perform the diene RCM were performed on azafulvenes **369** and **370**, thereby generating connections at C2-C3 and C5-C6 on the macrocyclic frame (pathway a and b).[158,159] Unfortunately, these efforts led to the undesired isomer (route a) or to racemic product (route b). Better results were obtained when the *ansa*-macrocycle was

[157] Wu, Z.; Johannes, C. W.; Salman, S. S., Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926–10927.
[158] Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601–2604.
[159] Bamford, S. J.; Lucker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157–1160.

closed prior to the formation of the azafulvene moiety, because ring strain was partially avoided (pathway c and d).[160,161] An optimised synthetic route for the total synthesis of (−)-roseophilin **373** was established by Tius and co-workers through RCM bond creation at C3-C4 (pathway e).[162]



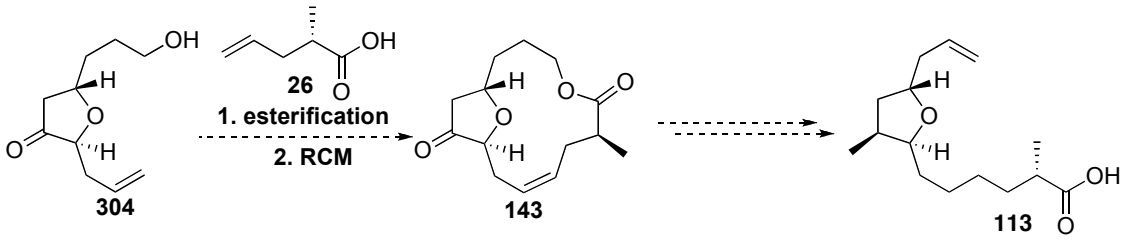
Scheme 132: RCM-based strategies towards (−)-roseophilin total synthesis

This case study highlighted the versatility of the RCM-based strategy, as RCM allowed diverse C=C bond formations at different positions on the macrocyclic framework. Consequently, various potential synthetic routes for the total synthesis of (−)-roseophilin **373** could be investigated.

[160] Fürstner A.; Gartner, T.; Weintritt, H *J. Org. Chem.* **1999**, *64*, 2361–2366.
[161] Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515–8519.
[162] Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514.

3.2 Completion of the Western Fragment 113 Synthesis

The synthetic sequence used to construct the key fragment **113** commenced with the coupling of the tetrahydrofuran **304** and carboxylic acid **26** (Scheme 133). Esterification would tether the two fragments and a subsequent RCM reaction would form the expected C=C bond connection to deliver macrolactone **143**. Further transformations would result in completion of the western fragment **113**, which is a common segment of the entire amphidinolide T family.

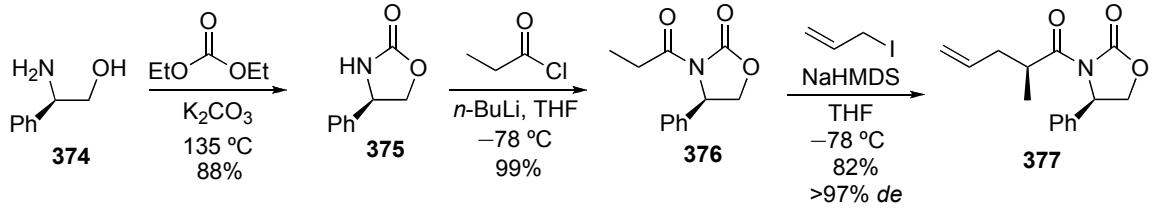


*Scheme 133: Fragments coupling and completion of **113** synthesis*

3.2.1 Preparation of Acid 26 and Coupling to Tetrahydrofuran 304

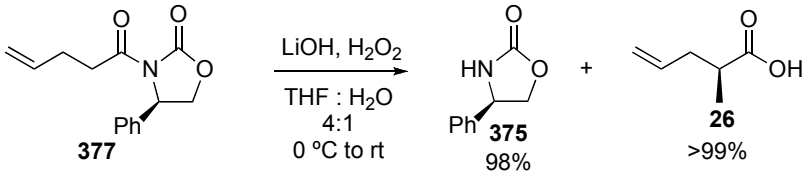
The next objective was the preparation of the carboxylic acid **26**.[163] The strategy for the synthesis of the acid **26** relied on the highly diastereoselective Evans alkylation reaction. The sequence started with the efficient preparation of oxazolidinone chiral auxiliary **375** by condensation between enantiopure D-(—)-α-phenylglycinol **374** and diethyl carbonate (Scheme 134).[164] Oxazolidinone formation proceeded in good yield and subsequent acylation by freshly distilled propionyl chloride delivered *N*-acyl oxazolidinone **376** in excellent yield.[165] Treatment of the acylated oxazolidinone **376** with sodium *bis*(trimethylsilyl)amide and allyl iodide produced **377** in good yield and in excellent diastereoselectivity; the diastereoisomers were separated by careful column chromatography.

[163] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
[164] Evans, D. A.; Gage, J. R. *Organic Synthesis* **1990**, *Coll. Vol. 68*, 83–91.
[165] Evans, D. A.; Gage, J. R. *Organic Synthesis* **1993**, *Coll. Vol. 8*, 528–531.



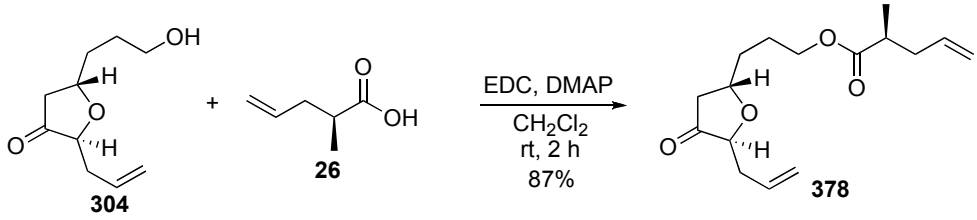
Scheme 134: Preparation of the side chain

Using freshly prepared LDA as base did not improve the yield of the alkylation reaction. The last step towards the preparation of the carboxylic acid **26** involved removal of the chiral auxiliary by hydrolysis with lithium hydroperoxide generated *in situ* (Scheme 135).[166] The carboxylic acid **26** was produced in quantitative yield and the oxazolidinone **375** was recycled efficiently. Quenching the peroxides was the critical point of the process due to the exothermic reaction and the requirement to use a precise amount of quenching agent (sodium sulfite) to avoid sulfur contamination. The gram-scale enantioselective preparation of the carboxylic acid **26** was performed in four straightforward steps and in 72% overall yield.



Scheme 135: Chiral auxiliary removal

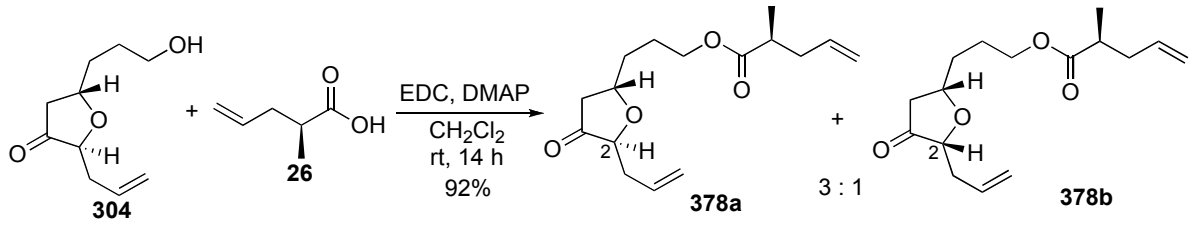
Union of the acid **26** and the alcohol **304** proceeded under mild conditions using the Steglich esterification procedure.[33] The condensation reaction was executed using an excess of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and DMAP in dry dichloromethane at room temperature (Scheme 136).



Scheme 136: Steglich esterification

[166] Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

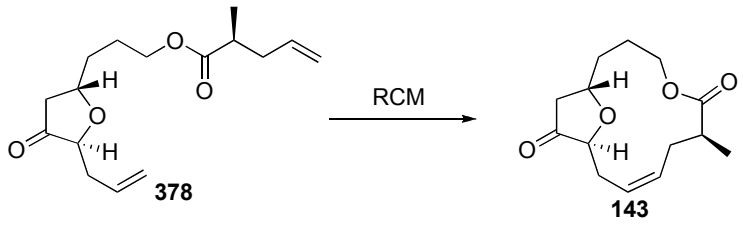
Fragments **26** and **304** were coupled efficiently, but prolonged reaction time resulted in epimerisation at the C2 stereocentre in the tetrahydrofuran ring due to proton acidity (Scheme 137). The resulting diene **378** was the precursor required for the key RCM macrocyclisation reaction.



Scheme 137: Epimerisation

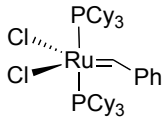
3.2.2 Macrocyclisation by Ring-Closing Metathesis

Cross metathesis and ring-closing metathesis reactions have emerged as powerful and convenient synthetic transformations to use in the total synthesis of macrocyclic natural products (*vide infra*).[143,144]

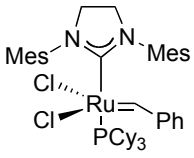


Scheme 138: Metathesis-mediated macrocycle formation

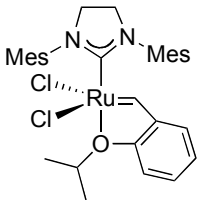
Numerous parameters influence diene metathesis reactions and there are no general conditions that guarantee the success of the process.[132] Various catalysts have been developed and the more common ones are metal complexes of molybdenum (Schrock's catalysts) or ruthenium (Grubbs catalysts). Schrock's catalysts are very sensitive and expensive so we focused on the on the use of Grubbs-type catalysts: Grubbs I **338** (GI), Grubbs II **43** (GII) to Hoveyda-Grubbs II **339** (HGII) (Scheme 139).



Grubbs 1st generation (GI)
338



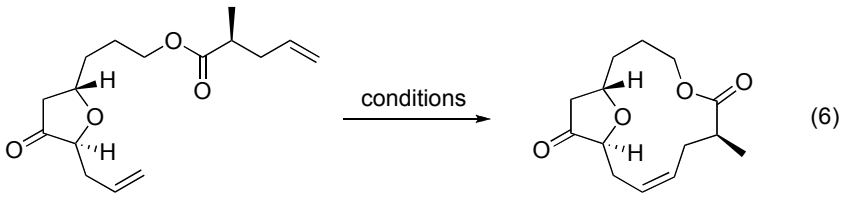
Grubbs 2nd generation (GII)
43



Hoveyda-Grubbs 2nd generation (HGII)
339

Scheme 139: Grubbs catalysts

Grubbs ruthenium complexes were screened as catalysts for the macrocyclisation of **378** using racemic material in dichloromethane. The reactions were performed at various temperatures and concentrations with or without addition of the Lewis acid, titanium(IV) *iso*-propoxide (Equation 6 and Table 6).



(±)-**378** (±)-**143** (6)

Entry	Catalyst	Temp.	Lewis acid	Conc.	Time	Results[a]
1	GII	reflux	—	50 mM	1 h	decomp.[b]
2	GII	rt	—	30 mM	4 h	21%
3	HGII	rt	—	30 mM	1 h	decomp.[b]
4	GII	reflux	—	3 mM	20 min	72%
5	GII	rt	—	3 mM	14 h	31%
6	GI	rt	—	3 mM	14 h	10%
7	GII	reflux	1 eq.	3 mM	20 min	65%

a) isolated yield, b) decomposition without detection of desired product.

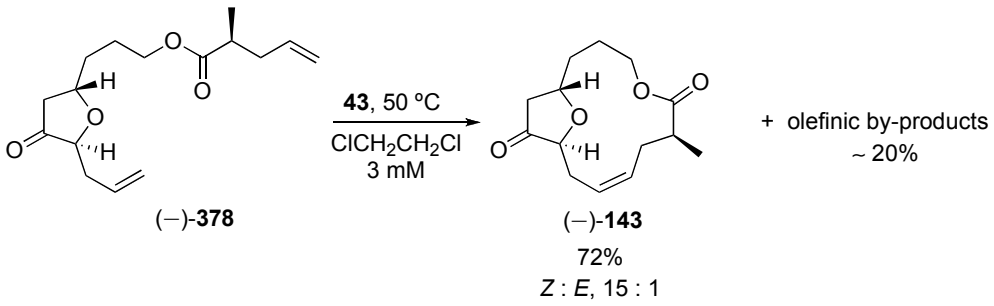
Table 6: RCM results

The substrate **378** and product **143** were both sensitive with regard to the metathesis catalyst and harsh conditions resulted in olefinic mixtures (Entry 1–3). Dilution diminished the catalyst activity greatly while maintaining complete conversion and the use of the GII **43** catalyst afforded the macrocycle

143 in good yield (Entry 4). Reactions were conducted at concentrations of less than 3mM, but in these cases the RCM reaction was slower than product decomposition. Therefore, more olefinic by-products were obtained than the attempt described in entry 4. Varying the catalyst loadings (from 5 to 20 mol%) did not affect the reaction kinetics.

With regard to identifying the optimum conditions, titanium(IV) *iso*-propoxide was added to complex the carboxyl groups of the diene **378** and prevent the RCM catalyst coordinating to the ester group (Entry 7).[154] The metal carbene intermediate could bind polar groups during the metathesis reaction and the selectivity could drop as a result (see chapter 3.1.4). However, the addition of a Lewis acid did not improve the RCM process.

Solvent exchange from dichloromethane to 1,2-dichloroethane allowed higher reaction temperatures and better reproducibility was achieved when the reaction mixture was heated to 50 °C over 15 minutes in the presence of GII **43** (Scheme 140). The optimised conditions were applied to enantiopure diene **378** and the macrocycle **143** was forged in good yield along with a significant amount of oligomers. RCM proceeded with excellent diastereocontrol of the endocyclic alkene formed.



Scheme 140: Optimised RCM conditions

After recrystallisation, the structure of the macrocycle **143** was confirmed using X-ray crystallography, validating the configuration of the stereogenic centres: the *trans*-tetrahydrofuran, the *Z*-alkene and the (*S*)-stereochemistry at C12 (Figure 9).

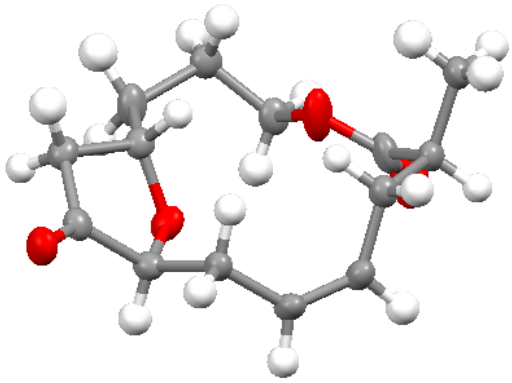
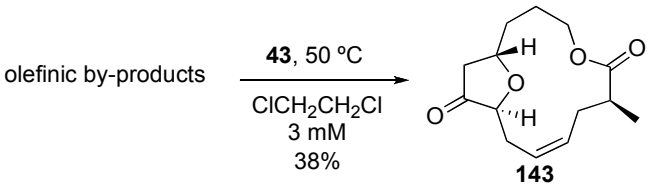


*Figure 9: Structure of **143** by X-Ray crystallography*

The metathesis mechanism consists of a sequence of reversible steps (see chapter 3.1.2) and so it was proposed that the olefinic by-products could be recycled to give the expected macrocycle **143**. Pleasingly, treatment of the by-products with the Grubbs II **43** catalyst delivered a significant quantity of the macrocyclic product **143** (Scheme 141).

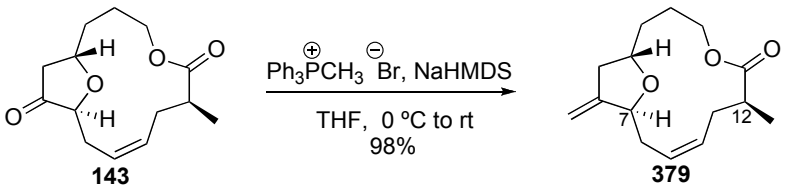


Scheme 141: By-products recycling

Thus, Grubbs second generation catalyst-mediated RCM successfully closed the 14-membered macrolactone **143** in a highly diastereoselective manner, the stereochemistry of which confirmed by X-ray crystallography. Optimised reactions conditions afforded an oligomeric by-product, which could be partially recycled to boost the yield. The next sequence involved ketone methylenation, alkene reduction and macrolactone opening.

3.2.3 Towards the Completion of Fragment 113

Wittig olefination, using an excess of phosphonium salt and NaHMDS as base, proceeded in high yield and converted the ketone **143** into the 1,1-disubstituted alkene **379** (Scheme 142). Using potassium *tert*-butoxide rather than NaHMDS resulted in epimerisation at the C7 stereogenic centre.



Scheme 142: Wittig olefination

Interestingly, NMR investigations revealed that the macrolactone **379** consisted of mixture of inseparable isomers. ^{1}H NMR spectra in deuterated chloroform displayed the methyl group on C12 as two doublets in a 3 : 1 ratio (Figure 10). However, similar NMR analysis was conducted in deuterated benzene and the ratio changed to 1.1 : 1 (Figure 11).

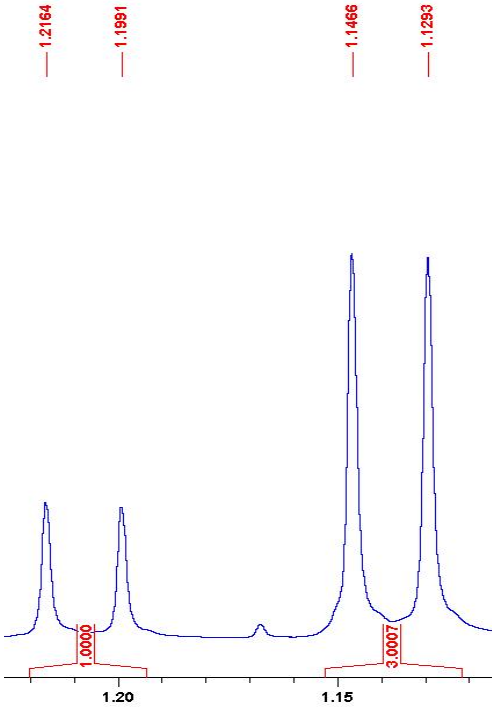


Figure 10: NMR experiment in $CDCl_3$

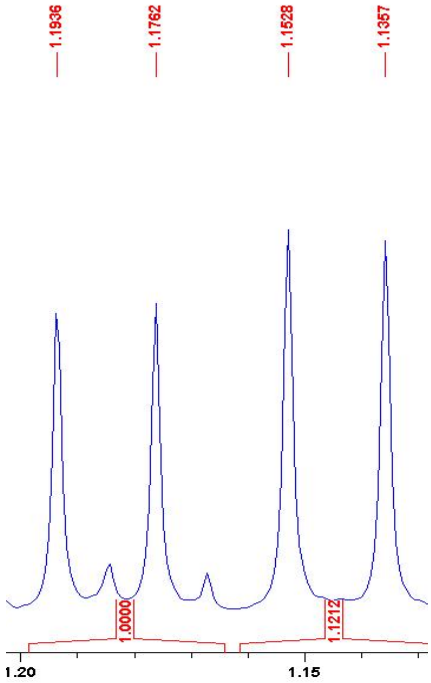
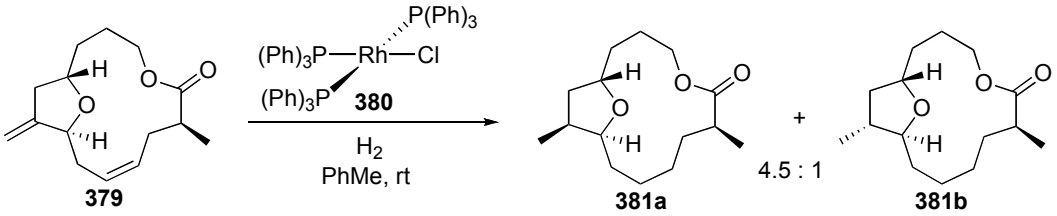


Figure 11: NMR experiment in C_6D_6

This observation suggested that the distribution between the two isomers depended on the environment, therefore it is proposed that the macrocyclic framework flips between two conformational isomers of different energies.

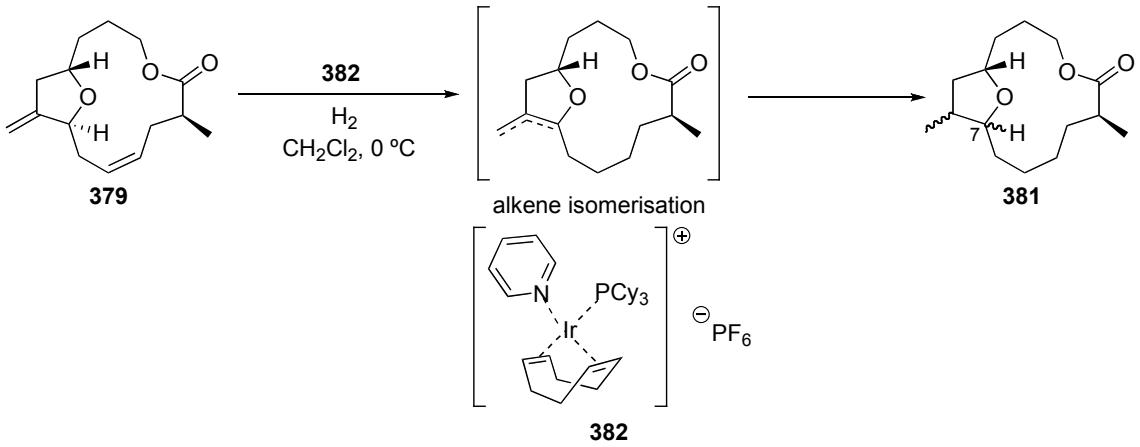
The next step in the strategy involved simultaneous reduction of both alkenes using Wilkinson's catalyst **380**, relying on substrate control to reduce the exocyclic double bond diastereoselectively (Scheme 143). With regard to the

geometry of the macrocycle **379**, the bottom face of the 14-membered ring was expected to be less sterically hindered and so hydrogen would add preferentially to this side. The desired diastereoisomer **381a** was obtained with moderate diastereocontrol using Wilkinson's catalyst **380**. The internal alkene was reduced concomitantly when Wilkinson's catalyst **380** that had been freshly purified was used.



Scheme 143: Alkene hydrogenation

Crabtree's catalyst **382** could be used to give efficient reduction of both alkenes but in this case no diastereoselectivity was observed. A mixture of four diastereoisomers was recovered, which could be explained by isomerisation of the exocyclic double bond by Crabtree's catalyst and scrambling of the stereocentre at C7 (Scheme 144).[167]

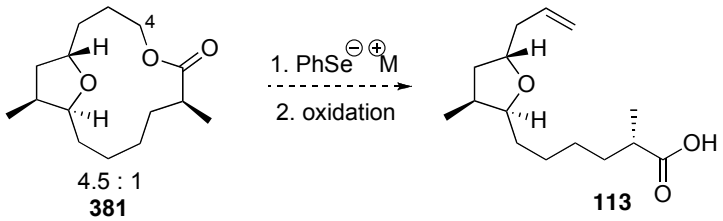


Scheme 144: Double bond isomerisation

It was anticipated that the synthesis of the western fragment could be completed *via* nucleophilic lactone opening by phenyl selenide anion followed by oxidation and selenoxide elimination (Equation 7). The Smith group developed this chemoselective nucleophilic cleavage of the C-O bond and used it to ring-

[167] Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*,14, 2655–2661.

open five- to fourteen-membered lactones.[168] Subsequent oxidation and elimination afforded the corresponding alkenyl carboxylic acid **113**. Metal phenyl selenoate salts were prepared by reduction of diphenyl diselenide to perform S_N2-type reactions on the carbinol carbon C4 instead of the carboxyl group (Equation 7 and Table 7).[169,170,171]



4.5 : 1
381 **113** (7)

Entry	Reducing agent	Chelating agent	Solvent	Temp.	ref.
1	$NaBH_4$	—	DMF	110 °C	[168]
2	Na	18-crown-6-ether	THF	reflux	[169]
3	$NaBH(OMe_3)$	—	DMF	110 °C	[170]
4	Zn	$AlCl_3$	MeCN	70 °C	[171]

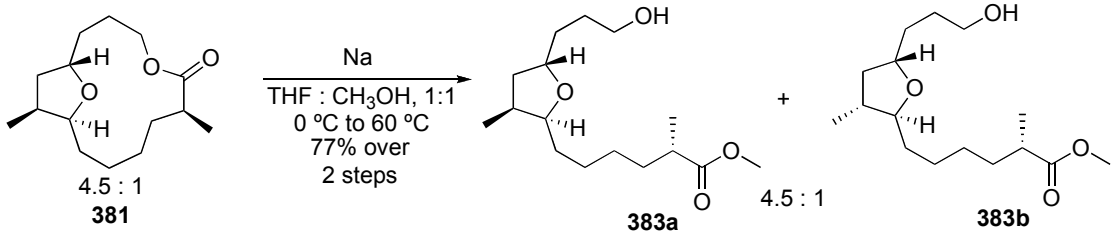
Table 7: Screening of lactone opening selenium reactions

Unfortunately, all these attempts to open the macrolactone **381** were unsuccessful due to what appeared to be the low reactivity of the organoselenium reagent to undergo a nucleophilic attack on the lactone **381**. Attempts were made to enhance the nucleophilicity of the selenide salt by the addition of chelating agents, but this did not lead to S_N2-type reaction at C4 (entries 2 and 4). Consequently, macrolactone opening using a selenium nucleophile was abandoned in favour of a classical reaction using sodium methoxide, an approach that would increase the length of the synthesis of the western fragment **113** by two steps.

Rather than attacking the unreactive carbinol carbon, various methods were developed to open lactones by nucleophilic attack on the carboxyl

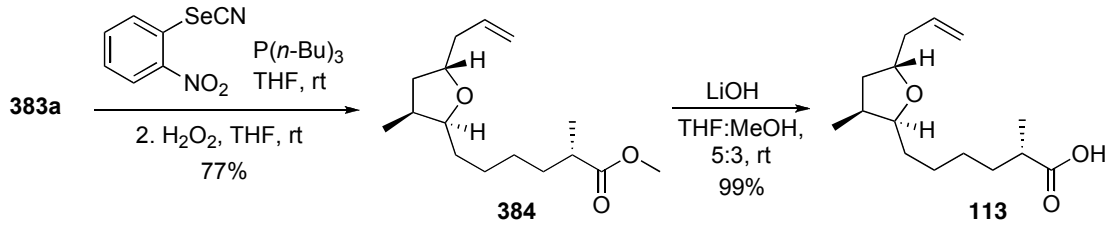
[168] Scarborough, R.; Smith, J.; Smith, A. B. *Tetrahedron Lett.* **1977**, *50*, 4361–4364.
[169] Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605–2610.
[170] Pedersen, M. L.; Berkowitz D. *Tetrahedron Lett.* **1992**, *33*, 7315–7318.
[171] Nazari, M.; Movassagh, B. *Tetrahedron Lett.* **2009**, *50*, 438–441.

group.[172] Macrolactone **381** was exposed to sodium methoxide and transesterification afforded the corresponding hydroxy esters **383a** and **383b** (Scheme 145). The sequence resulted in a satisfactory yield of the methyl ester over two steps from macrolactone **379**. Repeated careful chromatographic purifications were required to separate the two diastereoisomers.



Scheme 145: Lactone opening by sodium methoxide

Hydroxy ester **383a** was subjected to mild and non-basic Grieco-Sharpless elimination to afford the corresponding alkenyl ester **384** in good yield (Scheme 146).[173,174] The reagents are extremely sensitive to water and air, requiring freshly distilled tri-*n*-butylphosphine and carefully degassed solvent. The selenium source was crucial and elimination proceeded only if the *o*-nitrophenyl selenocyanate was purified using Bauer's process immediately before use.[175] The ester **384** was then hydrolysed to give the corresponding acid **113** in quantitative yield, completing the western fragment synthesis.



Scheme 146: Completion of the western fragment synthesis

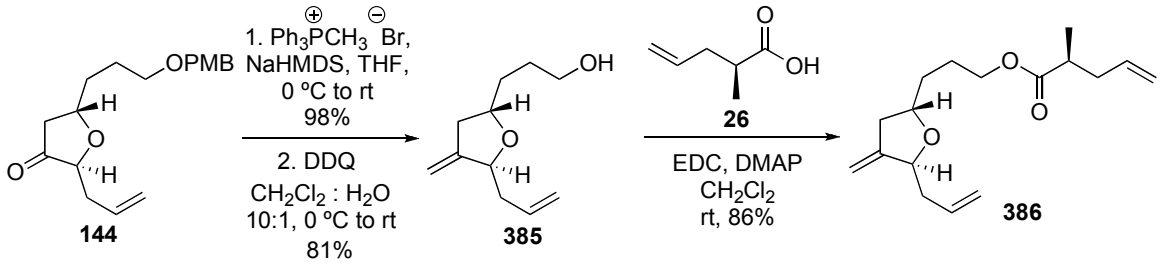
Gram-scale preparation of the key fragment **113** was performed in 16% yield over fifteen steps from ethylene glycol. The synthetic route included RCM and diastereoselective tetrahydrofuran formation *via* [2,3] sigmatropic

[172] McMurry, J. E. *Org. Reaction* **1976**, *24*, 187–224.
[173] Sharpless K. B.; Young M. W. *J. Org. Chem.* **1975**, *40*, 947–949.
[174] Grieco, P. A.; Gilman, S.; Nishizawa M. *J. Org. Chem.* **1976**, *41*, 1485–1486.
[175] Bauer, H. *Chem. Ber.* **1913**, *46*, 92–98.

rearrangement from a diazo-generated metal carbenoid as key steps.[176] Optical rotation and analytical data were in accordance with literature values.[14] An alternative pathway was studied to access the western fragment **113** by improvement of the RCM sequence.

3.2.4 Alternative RCM sequence

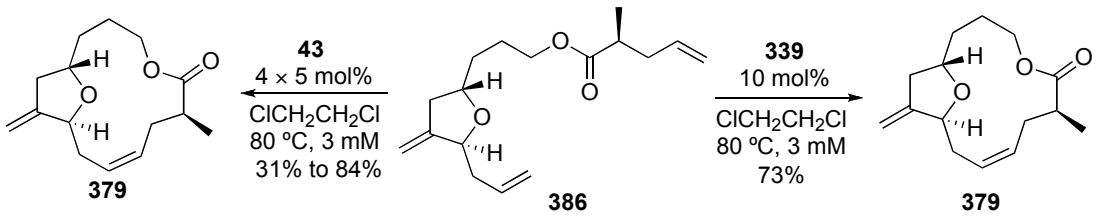
After completing the synthesis of **113**, we established that it was possible to increase the efficiency of the route by performing the RCM on the triene **386** and combining the metathesis and hydrogenation steps in a one-pot process (Scheme 147). Methylenation of ketone **144** followed by removal of the PMB group afforded alcohol **385**. Esterification of alcohol **385** with the carboxylic acid **26** delivered triene **386** as the macrocycle precursor.



*Scheme 147: Towards the triene **386** synthesis*

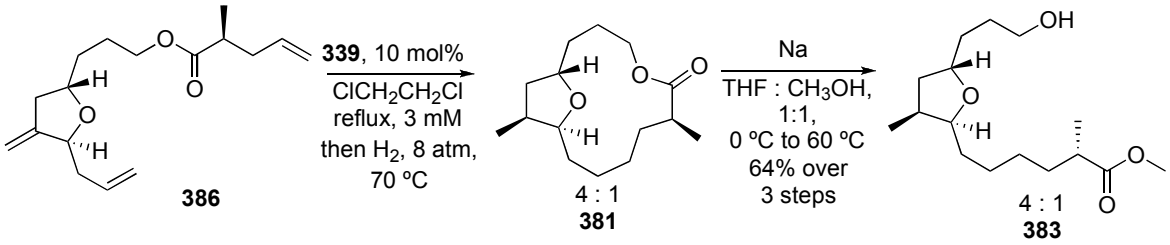
The RCM reaction of the triene **386** using the Grubbs second-generation catalyst afforded diene **379** in poor to good yield (Scheme 148). The triene **386** was less reactive than macrocycle precursor **378** with regard to metathesis reactions. The process required four portions of catalyst and the reaction mixture was heated at reflux for 14 hours rather than at 50 °C over 15 minutes, as described as the optimised conditions for RCM of the diene **378** (see chapter 3.2.2). In addition to exhibit low reactivity, the cyclisation reaction of the triene **386** using GII **43** was not reproducible. The use of HGII **339** shortened the reaction time to 45 minutes and the results were more consistent with similar yield (Scheme 148).

[176] Clark, J. S.; Labre, F.; Thomas, L. H. *Org. Biomol. Chem.* **2011,** *9*, 4823–4830.



Scheme 148: GII and HGII-catalysed RCM

Although ruthenium complexes have found extensive use in olefin metathesis, Grubbs catalysts have also been shown to be effective pre-catalysts for hydrogenation reactions.[177] One-pot metathesis and hydrogenation using the Hoveyda–Grubbs second-generation catalyst **339** followed by treatment of the resulting lactone with sodium methoxide delivered the esters **381a** and **381b** (4:1 ratio) in good yield (Scheme 149).



Scheme 149: One-pot RCM and hydrogenation reaction

The level of diastereocontrol during hydrogenation was similar to that obtained when the diene **379** was reduced using Wilkinson's catalyst **380**. The newly designed sequence afforded hydroxy ester **383** in 44% yield from alcohol **304** (40% previously) and is a step shorter than the initial route.[176] The western fragment **113** was achieved in fourteen steps from ethylene glycol, producing the target in 18% overall yield with the alternative route.

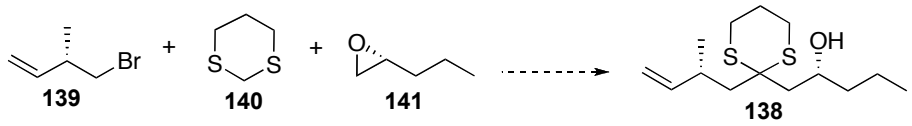
The successful synthesis of the western fragment **113** meant the synthesis of the eastern fragment **138** and macrocyclisation were the next objectives.

[177] Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312–1131.

Chapter 4: Eastern Fragment Synthesis, Macrocyclisation and Formal Synthesis

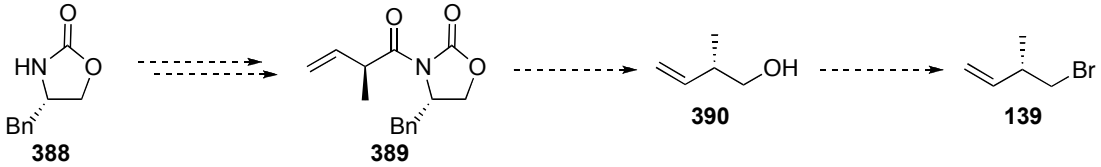
4.1 Initial and Revised Strategies

It was expected that the eastern fragment **138** could be constructed by joining the bromide **139**, dithiane **140** and the epoxide **141** (Scheme 150). Dithiane is commercially available and the epoxide **141** could be obtained in enantiopure form based on known procedures.[35,36]



*Scheme 150: Synthetic approach towards the eastern fragment **138***

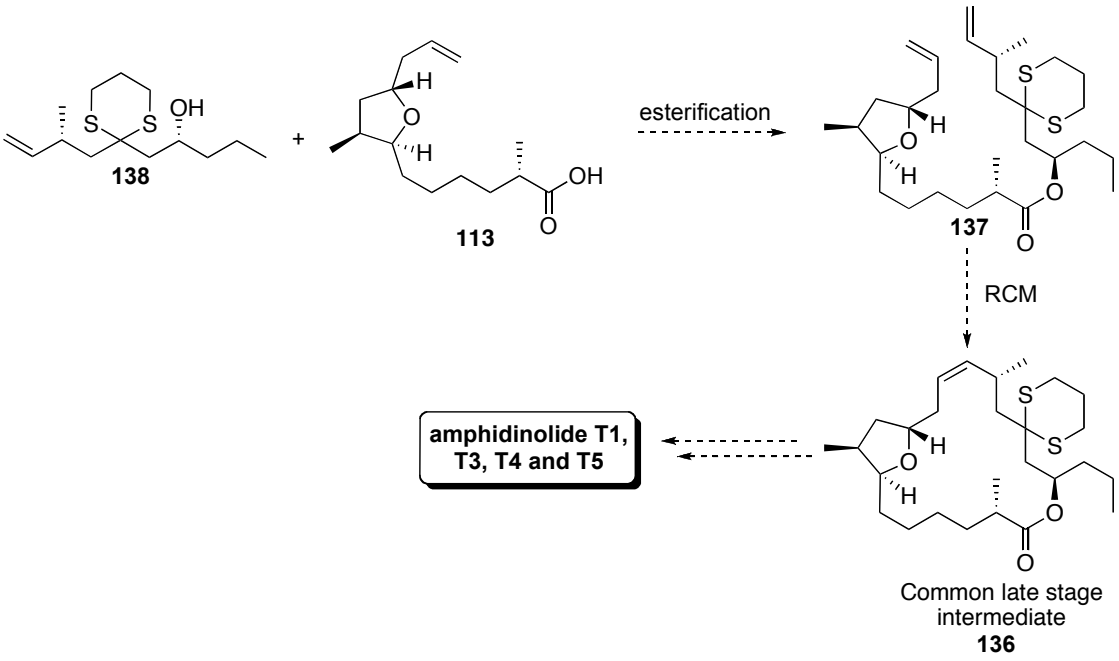
The bromide **139** would be derived from β,γ-unsaturated *N*-acyl-2-oxazolidinone **388** (Scheme 151).[178] Removal of the auxiliary followed by bromination would provide the bromide **139**.



*Scheme 151: Pathway towards the bromide **139** synthesis*

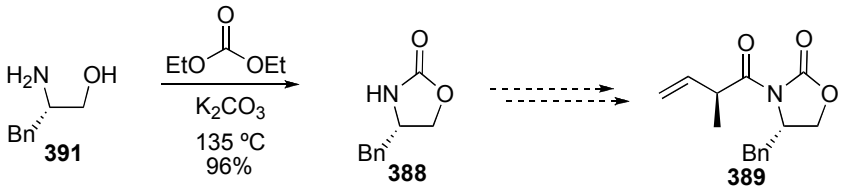
Following completion of the eastern fragment **138**, it was expected that coupling of the fragment **138** and the western fragment **113** would be performed by esterification and the 19-membered macrolactone would be closed by alkene RCM (Scheme **152**). The resulting macrocycle **136** would be the common late stage precursor to four of the natural product targets by functionalisation of the alkene generated during RCM.

[178] Dobarro, A.; Velasco, D. *Tetrahedron* **1996**, *52*, 13733–13738.



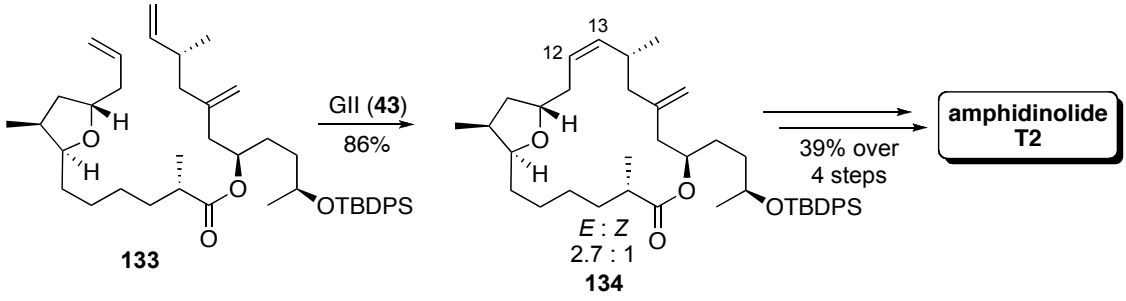
Scheme 152: Fragments coupling and alkene-RCM

The synthesis of the bromide **139** commenced with formation of the oxazolidinone **388** (Scheme 153). Condensation between L-phenylalaninol **391** and diethyl carbonate was achieved in excellent yield.



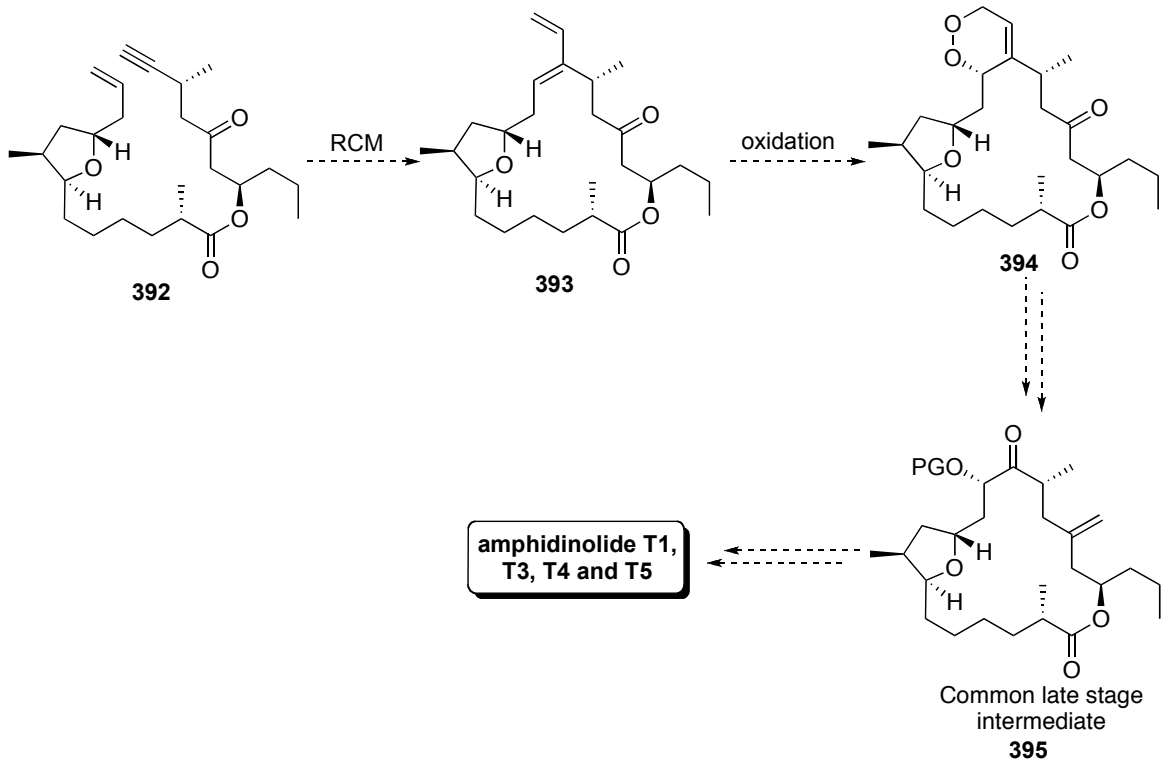
*Scheme 153: Towards the oxazolidinone **389** synthesis*

Concurrently with our own studies, the Dai group published the total synthesis of amphidinolide T2 using RCM to close the macrocycle at the C12-C13 bond (Scheme 154).[17] The same strategy was applied to the total synthesis of amphidinolide T3.[18]



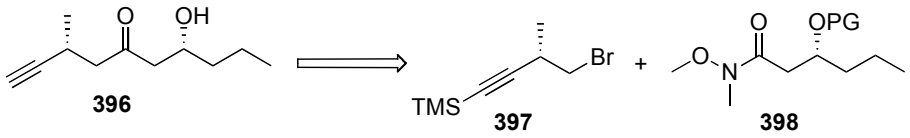
Scheme 154: Dai's approach to the amphidinolide T family

Although the publication of this work was disappointing, we undertook the challenge of designing a novel alternative route to the natural targets that might address some of the problems encountered by Dai and co-workers. We envisaged using enyne RCM as a promising alternative to alkene RCM because it might allow access to the hydroxy ketone functionality present in **395** in a more direct fashion *via* stereocontrolled photooxidation (Scheme 155).



Scheme 155: Alternative pathway

The synthetic route to the eastern fragment was redesigned to access hydroxy alkyne **396** (Scheme 156). Construction through dithiane chemistry was abandoned owing to the low-yielding dithiane addition to epoxide (Scheme 150).[179] The eastern fragment **396** was simply disconnected to give the bromide **397** and the Weinreb amide **398** which we envisaged coupling under Grignard conditions.



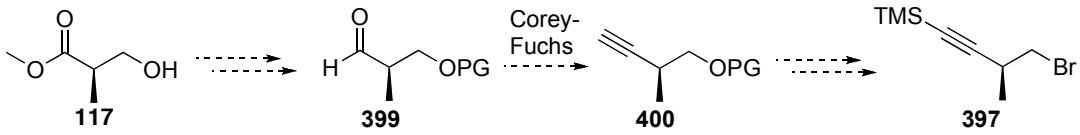
*Scheme 156: Retrosynthetic disconnection of the eastern fragment **396***

[179] Dreeßen, S.; Schabbert, S.; Schaumann, E. *Eur. J. Org. Chem.* **2001**, *2*, 245–251.

4.2 Toward Eastern Fragment Synthesis

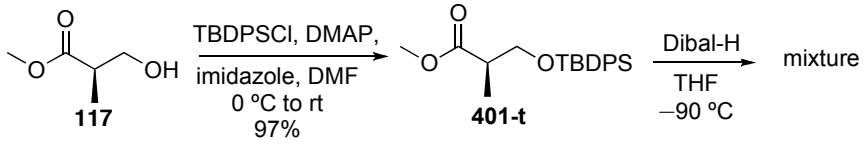
4.2.1 Bromide 397 Formation

The first objective was preparation of the bromide **397** using Corey-Fuchs methodology. We selected (*R*)-(−)-Roche ester **117** as a starting material, which would be converted into the aldehyde **399** (Scheme 157). Subsequent Corey-Fuchs homologation would produce alkyne **400**. Further steps would lead to the required bromide **397**.



*Scheme 157: Synthetic strategy towards bromide **397***

The β-Hydroxy ester **117** was silylated in good yield to afford the ester **401-t** (Scheme 158). Dibal-H reduction did not proceed selectively to give the aldehyde **399-t**, even at low temperature and with dropwise addition of just one equivalent of reducing agent. Instead, the reaction delivered a mixture of starting material **401-t**, desired aldehyde **399-t** and alcohol in approximately 1 : 1 : 1 ratio.

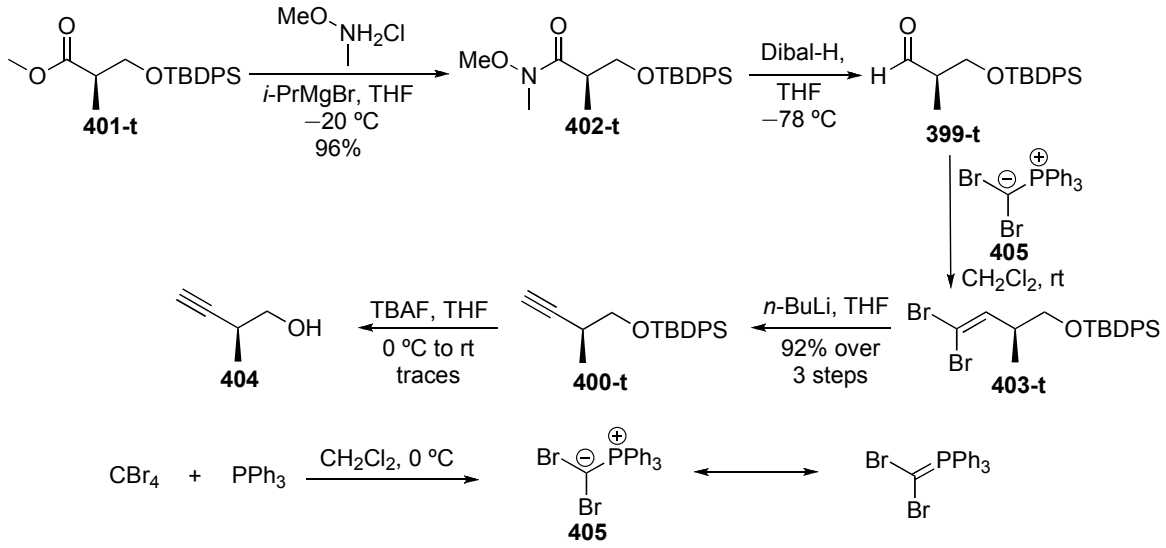


Scheme 158: Reduction attempt

A Weinreb amide is more versatile intermediate than a methyl ester with regard to aldehyde generation.[180] Ester **401-t** was converted into the corresponding Weinreb amide **402-t** in good yield using a Grignard reagent as the base (Scheme 159). Dibal-H reduction delivered the aldehyde **399-t** selectively, which was unstable and prone to spontaneous epimerisation. The first step of the Corey-Fuchs sequence afforded the unstable dibromoalkene **403-t** *via* Wittig-like addition of the *in situ* generated ylide **405**, a procedure known as Ramirez

[180] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

olefination (Scheme 159).[181,182] Treatment of the dibromide with *n*-butyllithium produced the terminal alkyne in excellent yield over three steps. However, subsequent deprotection afforded the alcohol **404** in low yield.



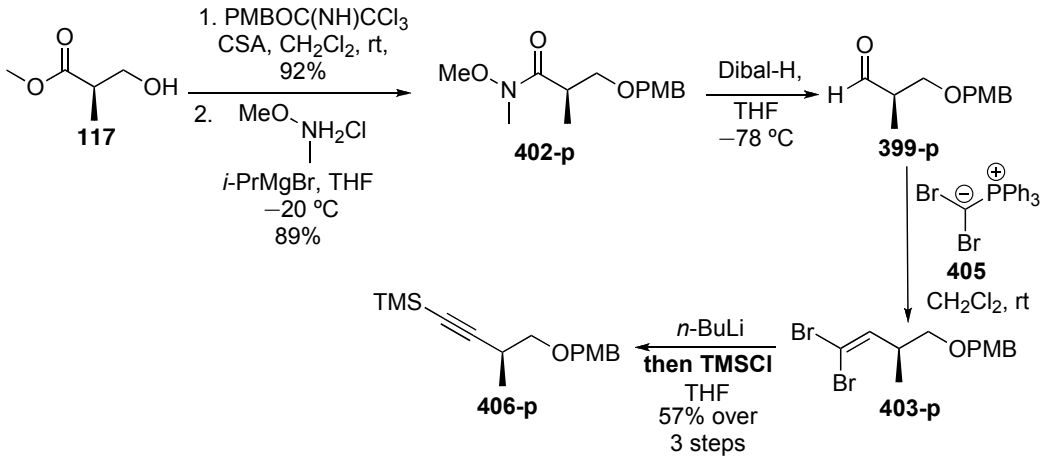
*Scheme 159: Sequence towards the alcohol **404***

The Corey-Fuchs sequence was effective on small scale, even if the aldehyde **399-t** and the dibromoalkene **403-t** intermediates were unstable. The reaction scale was limited to 15 mmol because dibromoalkene formation required an excess of triphenylphosphine and carbon tetrabromide, which generated substantial amounts of by-products. These side products were removed by filtration through a silica pad and rapid purification was necessary because of the instability of dibromoalkene **403-t** to silica gel. On a gram-scale, this operation was more time-consuming and prolonged exposure to silica gel resulted in more decomposition of the intermediate **403-t** ensuing a moderate yield. Thus, only a small amount of alcohol **404** was obtained and its low boiling point meant that purification by distillation was difficult to achieve without substantial loss of material.[183] To address the volatility issue, a different protecting group was used.

(*R*)-(−)-Roche ester **117** was protected as a PMB ether under acidic conditions and subsequent exposure to *N,O*-dimethylhydroxylamine hydrochloride and Grignard reagent delivered the Weinreb amide **402-p** in good

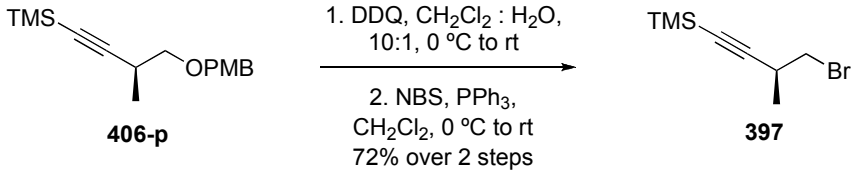
[181] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.
[182] Desai, N. B.; McKelvie, N.; Ramirez, F. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747.
[183] Gérard, F.; Miginiac, P. *Synth. Commun.* **1976**, *6,* 461–464.

yield over two steps (Scheme 160). Dibal-H reduction followed by a modified Corey-Fuchs sequence including a TMSCl quench afforded the TMS-protected terminal alkyne **406-p**. Unfortunately, the Corey-Fuchs methodology proved to be as difficult to adapt to large scale as the TBDPS-protected sequence had been.



*Scheme 160: Synthetic pathway to TMS-protected alkyne **406-p***

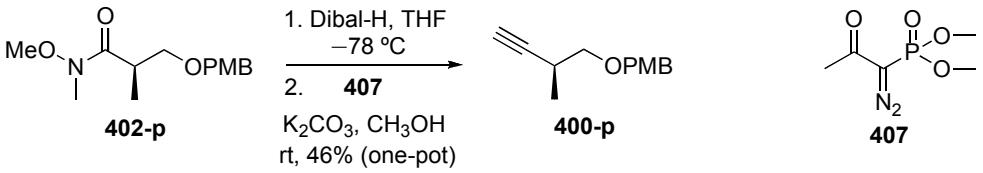
The PMB group was removed successfully under standard conditions and treatment with *N*-bromosuccinimide afforded the bromide **397** selectively and in good yield without affecting the alkyne (Scheme 161). It was noteworthy that the generated bromoalkyne **397** was both unstable and volatile.



*Scheme 161: Completion of the bromide **397** synthesis*

The synthesis of bromide **397** was completed in seven steps and 33% overall yield. The inherent instability of the intermediates was an interesting experimental challenge to overcome, especially on large scale. An improvement could be made by switching to the Ohira-Bestmann homologation reaction. This alternative allowed purification of the unstable dibromo alkene **403** to be avoided and delivered the unprotected terminal alkyne **400-p** (Scheme

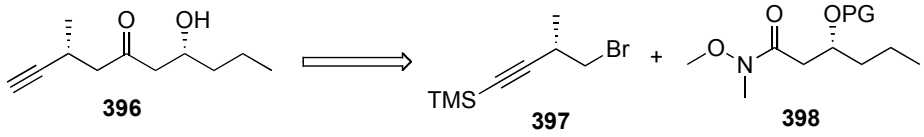
162).[184,185] The one-pot reduction/Ohira-Bestmann homologation reaction proceeded in moderate yield but was reproducible.



Scheme 162: Ohira-Bestmann homologation

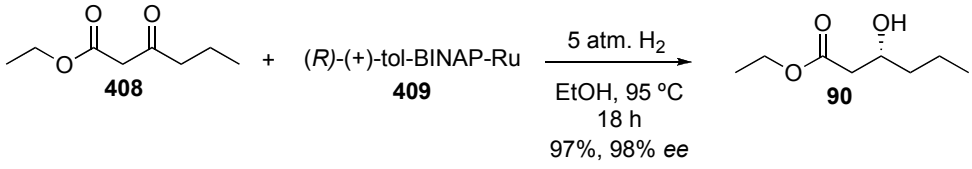
4.2.2 Grignard Coupling

Preparation of the eastern fragment **396** was envisaged by Grignard addition of bromide **397** to electrophile **398** (Scheme 163). We first focused on the synthesis of the Weinreb amide **398**, which could be obtained in enantiopure form following a literature procedure.[186]



*Scheme 163: Towards the eastern fragment **396** synthesis*

The sequence commenced with a Noyori reduction of ketoester **408** (Scheme 164 and Chapt 2.3.2)[120] Using the ruthenium complex of (*R*)-(+)-tol-BINAP **409** as the catalyst, the reduction reaction installed the stereocentre to give the β-hydroxy ester **90** in excellent yield and high enantiomeric excess.

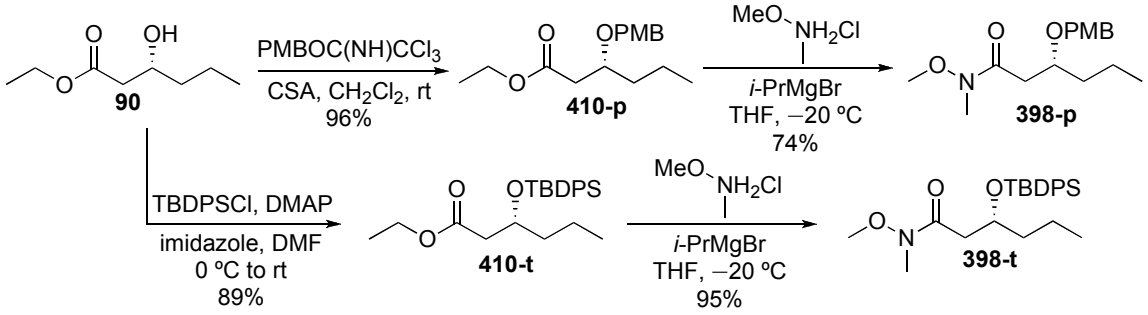


Scheme 164: Noyori enantioselective hydrogenation

The hydroxy ester **90** was protected as the corresponding PMB ether **410-p** under acidic conditions in good yield (Scheme 165). Alternatively, the hydroxyl

[184] Mueller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *6*, 521–522.
[185] Dickson, H. D.; Smith, S. C.; Hinkle, K. W. *Tetrahedron Lett.* **2004**, *45*, 5597–5599.
[186] Custar, D. W.; Zabawa, T. P.; Hines, J.; Crews, C. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 12406–12414.

functionality was silylated using TBDPSCl because protecting group selection was judged to be crucial for the success of the Grignard coupling reaction (*vide supra*). Resulting esters **410-p** and **410-t** were successfully converted into amides **398-p** and **398-t** in good to excellent yield.



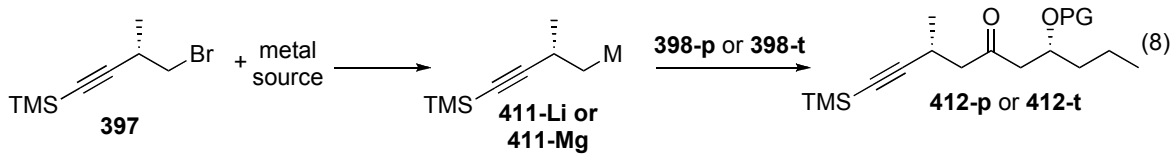
*Scheme 165: Preparation of amides **398-p** and **398-t***

We envisaged performing nucleophilic addition to the Weinreb amides **398-p**/**398-t** in order to deliver the ketone **412-p**/**412-t** selectively (Equation 8).[186] The alkylmagnesium species **411-Mg** was prepared *via* oxidative insertion of magnesium into the C-Br bond of the bromide **397**. The newly-generated Grignard reagent **411-Mg** was reacted with the amides **398-p** and **398-t** (Table 8). Treatment of bromide **397** with activated magnesium turnings produced the Grignard reagent **411-Mg**, but unfortunately the alkylmagnesium intermediate **411-Mg** precipitated in diethyl ether or THF ensuring no further reaction (Entries 1-4). Addition of a stoichiometric amount of lithium chloride greatly improved the solubility of the Grignard reagent **411-Mg** (*vide infra*) (Entry 5-6).[102] However, the alkylmagnesium species **411-Mg** was not reactive enough to undergo nucleophilic addition to amides **398-p** and **398-t**, even at high temperature, and only the Würtz coupling product **413** was obtained (Scheme 166).

Alkyllithium reagents tend to be more reactive than the corresponding alkylmagnesium complexes. Lithium-bromide exchange resulted in conversion of the bromide **397** into the corresponding lithium **411-Li** intermediate by treatment upon *tert*-butyllithium (Entry 7-8). The newly formed metal complex was too basic for the substrates **398-p** and **398-t** and deprotonation at the α-position of the amide resulted in elimination of the protected hydroxyl group to produce the α,β-unsaturated amide **414** (Scheme 166). It is noteworthy that the

PMB-protected hydroxyl group was more prone to elimination than the silyl-protected substrate **398-t**.

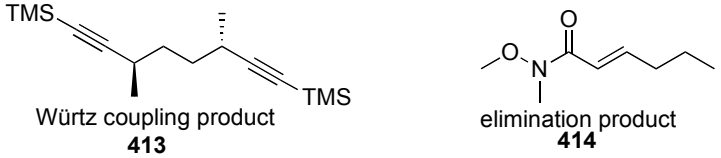
The Grignard reagent was prepared efficiently by transmetalation of the alkyllithium species using freshly prepared magnesium bromide etherate complex (Entry 9-10). The newly formed magnesium complex **411-Mg** did not undergo Würtz coupling but no reaction with the Weinreb amides **398-p** and **398-t** was observed.



Entry	Reagents	Solvent	Temperature	Protecting group	Result
1	Mg	Et_2O	0 °C to rt	PMB	precipitation[a]
2	Mg	Et_2O	0 °C to rt	TBDPS	precipitation[a]
3	Mg	THF	0 °C to rt	PMB	precipitation[a]
4	Mg	THF	0 °C to rt	TBDPS	precipitation[a]
5	Mg + LiCl	Et_2O	0 °C to 60 °C	PMB	Würtz coupling[b]
6	Mg + LiCl	Et_2O	0 °C to 60 °C	TBDPS	Würtz coupling[b]
7	*t*-BuLi	THF	−78 °C to rt	PMB	82% of elimination[b]
8	*t*-BuLi	THF	−78 °C to rt	TBDPS	60% of elimination[b]
9	*t*-BuLi then $MgBr_2 \bullet Et_2O$	Et_2O	−78 °C to rt	PMB	no conversion
10	*t*-BuLi then $MgBr_2 \bullet Et_2O$	Et_2O	−78 °C to rt	TBDPS	no conversion

a) precipitation and no conversion; b) see scheme 166 for structures.

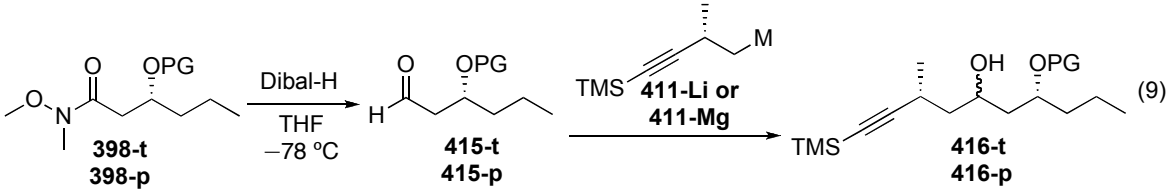
Table 8: Nucleophilic addition screening



Scheme 166: By-products formed during attempted Grignard addition

The unsuccessful attempts to perform Grignard addition clearly showed that electrophiles **398-p** and **398-t** were unsuitable substrates for direct nucleophilic addition. Apparently, Weinreb amides **398-p** and **398-t** are not electrophilic enough towards alkylation by alkylmagnesium salt **411-Mg**, or even the corresponding alkylcerium complex as mentioned by Scheidt and co workers.[186]

To address the problems outlined above, the amides **398-p** and **398-t** were reduced to the corresponding aldehydes **415-p** and **415-t** using Dibal-H (Equation 9). In order to address the problem of potential instability of the generated aldehydes **415-p** and **415-t**, the new electrophiles were used without purification and were exposed to the previously prepared nucleophiles (Table 9). Lithium chloride assisted generation of the Grignard reagent yielded the Würtz coupling product (Entries 1 and 2) and reaction with alkyllithium complex resulted in elimination with formation of traces of the coupled product **416-t** (Entry 4). Preparation of the Grignard reagent by transmetalation and reaction with the PMB-protected electrophile gave a low yield of the product **416-p** (Entry 5) and a moderate yield was obtained using the TBDPS-protected substrate (Entry 6).



398-t
398-p

415-t
415-p

416-t
416-p

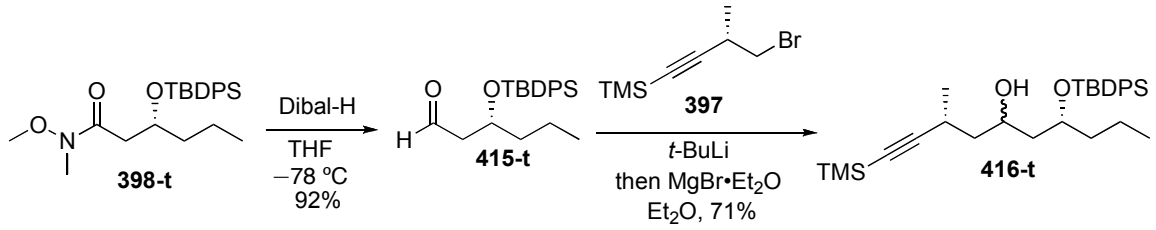
(9)

Entry	Reagents	Solvent	Temperature	Protective group	Result
1	Mg + LiCl	Et_2O	0 °C to rt	PMB	Würtz coupling
2	Mg + LiCl	Et_2O	0 °C to rt	TBDPS	Würtz coupling
3	*t*-BuLi	THF	−78 °C to rt	PMB	30% of elimination
4	*t*-BuLi	THF	−78 °C to rt	TBDPS	**8% yield**[a] + 23% of elimination
5	*t*-BuLi then $MgBr_2 \bullet Et_2O$	Et_2O	−78 °C to rt	PMB	**15% yield**[a]
6	*t*-BuLi then $MgBr_2 \bullet Et_2O$	Et_2O	−78 °C to rt	TBDPS	**45% yield**[a]

a) isolated yield.

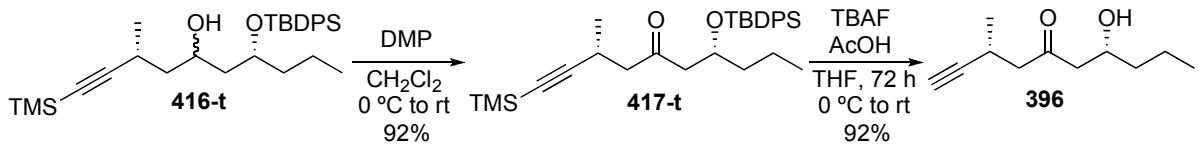
*Table 9: Nucleophilic addition on aldehydes **415-p** and **415-t***

Optimum conditions were accessed when the aldehyde **415-t** was purified prior to Grignard addition (Scheme 167). In this case, nucleophilic addition afforded the coupled product **416-t** in 65% yield over two steps. The Grignard reagent was prepared successfully *via* transmetalation of alkyllithium species and pre-cautions were required to keep the media anhydrous. Protecting group choice proved to be crucial and further investigations might improve the reaction yield.



Scheme 167: Grignard coupling optimised conditions

Subsequent Dess-Martin oxidation delivered the base-sensitive ketone **417-t** in excellent yield. Treatment of the ketone **417-t** with TBAF in acidic media resulted in smooth global desilylation to complete the synthesis of the eastern fragment **396** (Scheme 168).[187]



*Scheme 168: Completion of the eastern fragment **396** synthesis*

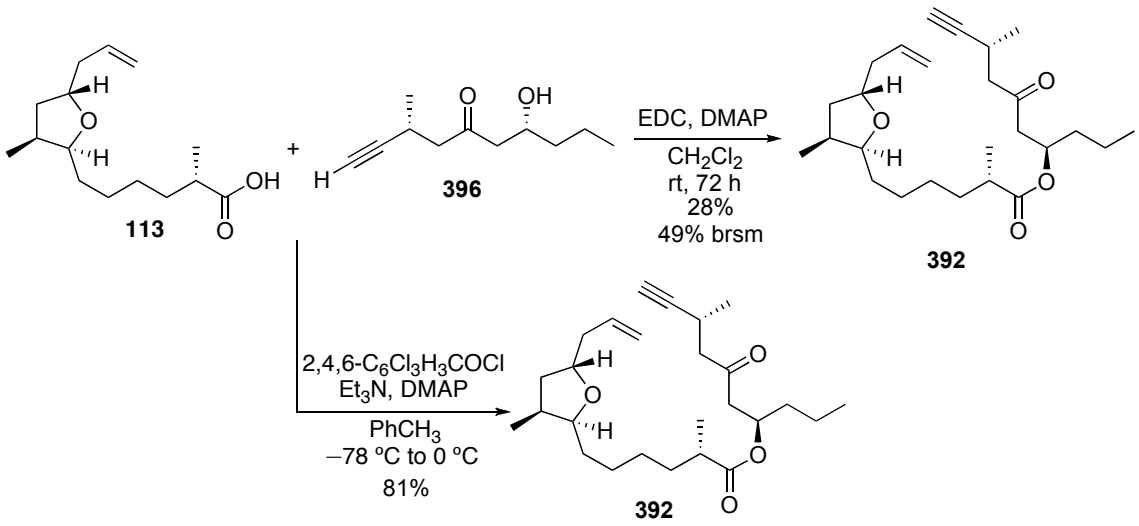
The eastern fragment **396** was prepared in 20% overall yield over ten steps from (*R*)-(−)-Roche ester **117**. Key reactions were Corey-Fuchs/Ohira-Bestmann homologation and Grignard addition to couple the fragments. Chiral centres were established using readily-available chiral pool starting materials and by using enantioselective Noyori hydrogenation. Further improvements to the route might possible using alternative protecting groups.

[187] Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**,*115*, 9345–9346.

4.3 Towards the Macrocycle Formation

4.3.1 Fragments Coupling

Completion of the western and the eastern fragments meant that fragment coupling and macrocyclisation to from the 19-membered ring could be explored. The first attempt to couple the alcohol **396** and the carboxylic acid **113** was conducted using an excess of EDC and DMAP in dry dichloromethane at room temperature (Scheme 169).[33] The coupling was sluggish and the reaction was not complete after three days. Alternatively, Yamaguchi protocol was tested and the fragment tethering was performed in 30 minutes at low temperature in good yield.[21]



Scheme 169: Coupling by Steglich and Yamaguchi esterification

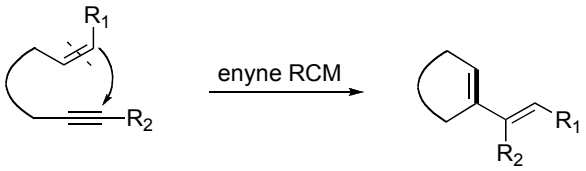
4.3.2 Macrocyclisation by Enyne-Ring Closing Metathesis

The next objective was to effect the key cyclisation by enyne RCM and thereby construct the complete macrocyclic core of the amphidinolide T series.

4.3.2.1 Enyne-Ring Closing Metathesis

The macrocycle formation was envisaged by ring-closing enyne metathesis (Scheme 170). This reaction involves cleavage of the alkene functionality, creation of a double bond between the unsaturated groups and migration of the

cleaved alkylidene part of the alkene onto the alkyne moiety.[188,189] Enyne bond reorganisation is atom economical and is driven by the enthalpic stability of the conjugated 1,3-diene.[190]

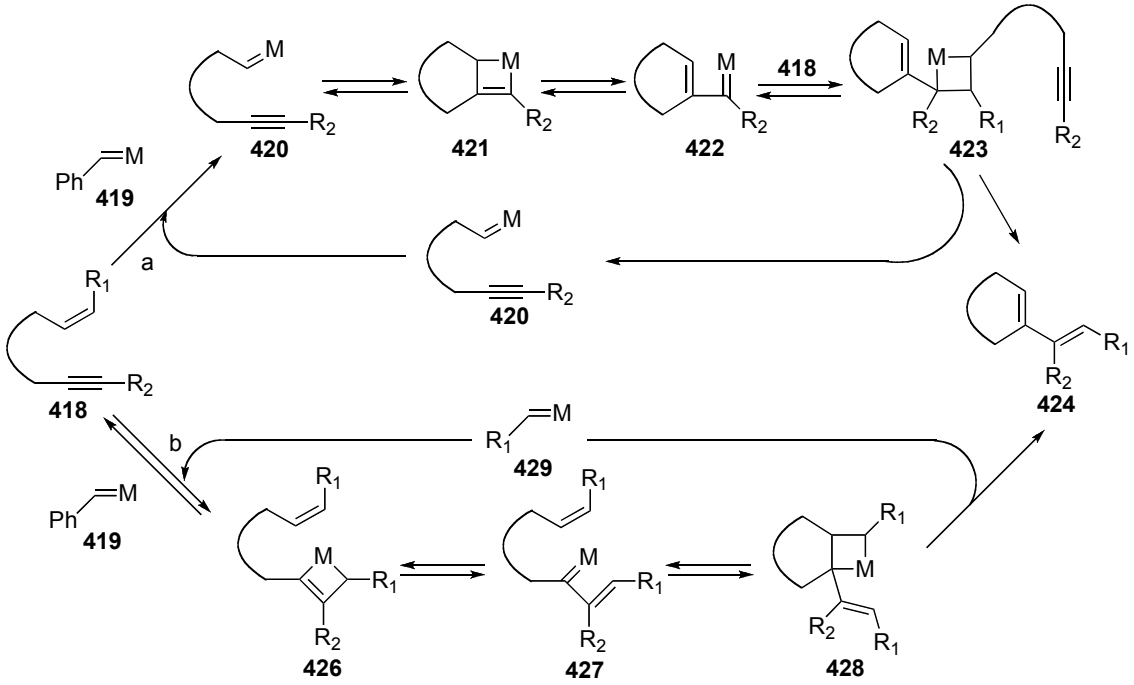


Scheme 170: Enyne-RCM principle

The proposed mechanism (pathway *a*) commences with reaction of metal carbene complex **419** with the **alkene** part of **418** to afford metallocarbene **420** (Scheme 171). Subsequent [2+2] cycloaddition with the alkyne group delivers the metallocyclobutene **421**, which then undergoes ring opening to yield the metal alkylidene complex **422**. The metal carbenoid **422** reacts with the alkene group of starting material **418** *via* [2+2] cycloaddition to afford metallocycle **423**. Subsequent [2+2] cycloreversion reaction releases the 1,3-diene **424** and the metal alkylidene **425** is regenerated to close the catalytic cycle.

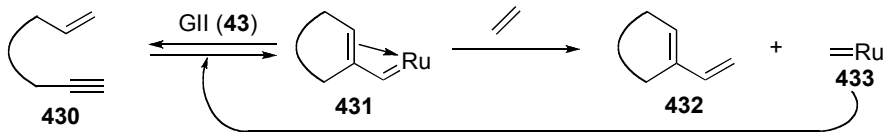
An alternative mechanism would proceed *via* [2+2] cycloaddition of the metal carbene complex **419** with the **alkyne** part of **418** to produce metallacyclobutene **426** (Scheme 171, pathway *b*). However, studies by Lippstreu *et al.* revealed that enyne metathesis would proceed *via* pathway *a* because the metallocycle **426** would not exist in the catalytic cycle.[191] The barrier of this intermolecular C-C-bond formation is disfavored by almost 100 kJ mol^{-1}, thus not competitive and not relevant for enyne metathesis.

[188] Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 121–135.
[189] Mori, M. *Metathesis in Natural Product Synthesis* Wiley-VCH: Weinheim; 1st edition **2010**, Chap. 6.
[190] Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.
[191] Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444–7457.



Scheme 171: Enyne-RCM mechanisms

Mori and co-workers discovered that enyne metathesis reactions are promoted by using an ethylene atmosphere.[192] The use of ethylene gas was justified by coordination of the alkene part to the metal carbene in the late stage of the catalytic cycle (Scheme 172). Catalytic activity is reduced but if the alkylidene metal complex **431** reacts with ethylene, the metal carbene **433** is regenerated.

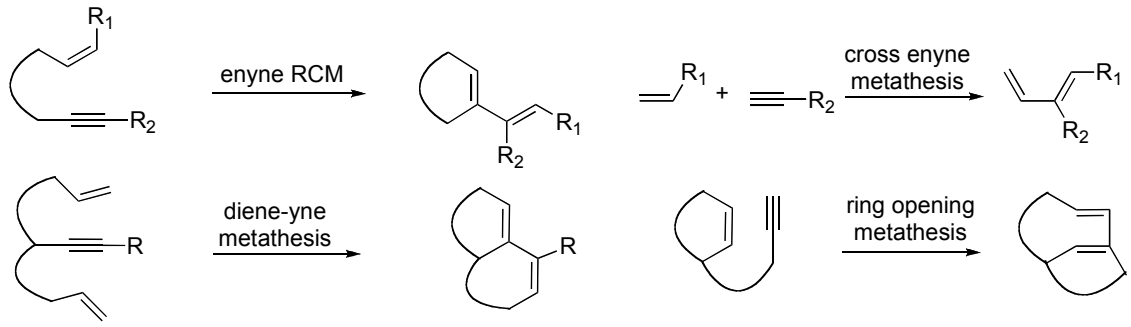


Scheme 172: Ethylene gas to improve catalyst activity

Metathesis conditions have been applied to a variety of enyne substrates resulting in various transformations such as enyne RCM, diene-yne metathesis, cross enyne metathesis and ring-opening metathesis (Scheme 173). Numerous natural products have been synthesised using these strategies, a fact that demonstrates the power of these transformations. However, macrocyclic enyne RCM has only been reported a handful of times.[189,193] Closing the 19-membered

[192] Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082–6083.
[193] Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773–775.

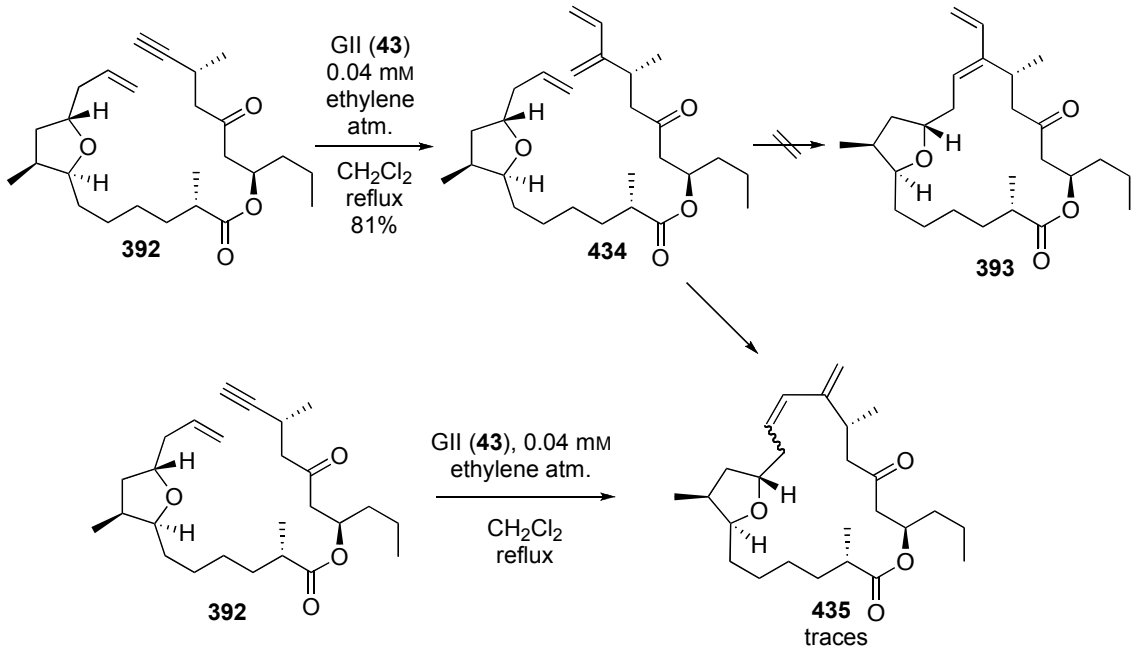
ring of our natural targets by macrocyclic enyne RCM would demonstrate the power of the enyne RCM process in this context.



Scheme 173: Various enyne metathesis rearrangements

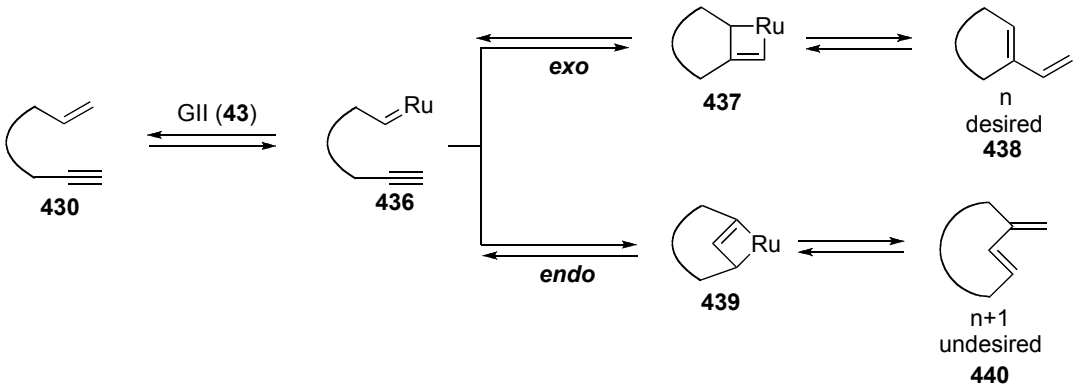
*4.3.2.2 Application to macrocyclisation of **392***

Macrocyclic precursor **392** was subjected to enyne RCM under Mori's conditions: GII **43**, high dilution and ethylene atmosphere (Scheme 174).[192] To our disappointment, none of the desired 19-membered macrolactone **393** was obtained and only the intermolecular enyne cross metathesis product **434** was produced in good yield. Increasing reaction time or re-exposing the intermediate **434** to the metathesis conditions failed to deliver the expected product **393** and only a mixture of olefins was obtained. Among the mixture of oligomers, traces of the 20-membered macrocycle **435** was detected (Scheme 174).



Scheme 174: Macrocyclic formation by enyne RCM

The formation of the by-product **435** was explained by the two possible macrocyclisation pathways (Scheme 175).[194] Mechanistically, enyne RCM could proceed *via* the initiation at the alkene part of **430** to form metal alkylidene **436**, which would then undergo [2+2] cycloaddition to afford either *exo*-metallocycle **437** and *endo*-metallocycle **439**. Ring opening of *exo*-**438** would yield the n-membered cyclic compound **438** and [2+2] cycloreversion of *endo*-**439** would deliver n+1-membered ring product **440**. The *exo*/*endo* selectivity would be driven by the difference in ring strain associated with the formation of the *exo*-metallocyclobutene **437** and *endo*-metallocyclobutene **439**. From small to medium-sized ring formation, the *exo*-pathway would be favoured. For macrocyclisation (higher than eleven-membered ring), the low ring strain should direct preferentially *via* the *endo*-pathway.[195]



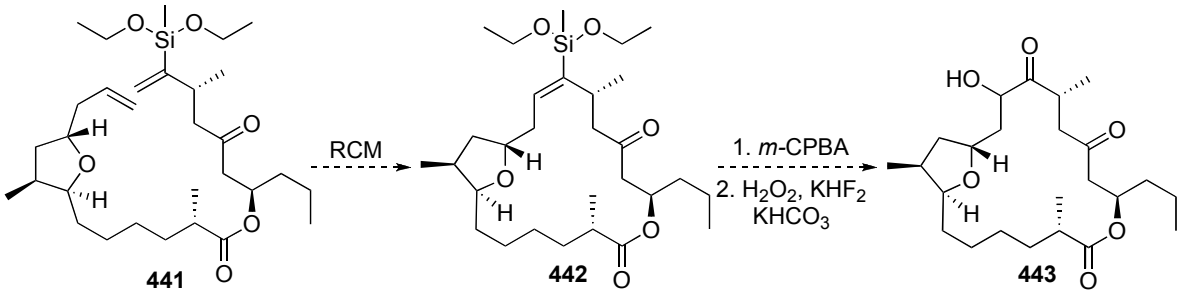
Scheme 175: Exo- and endo-pathways

Our aim was to forge the 19-membered macrocyclic alkene **393**, but enyne RCM proceeded *via* the *endo*-pathway and generated the undesired 20-membered macrolactone **435**. According to Hansen and co-workers, the use of an ethylene atmosphere favours the *endo*-pathway.[196] However, when enyne RCM of macrocyclic precursor **392** was conducted under an argon atmosphere, the experiment resulted in low conversion and decomposition of the starting material **392** was observed. Following this result, we decided that an alternative pathway was required in order to construct the macrocycle.

[194] Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582–9583.
[195] Grimwood, M. E.; Hansen, E. C. *Tetrahedron* **2009**, *65*, 8132–8138.
[196] Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 15074–15080.

4.3.3 Siloxane-Assisted Macrocyclic Alkene-RCM Strategy

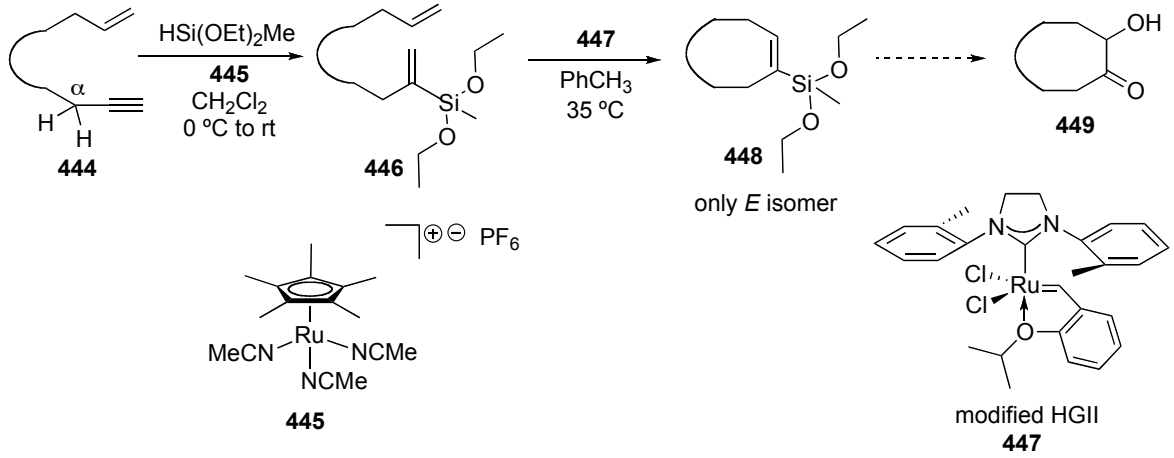
The strategy towards macrolactone formation was redesigned through alkene RCM (Scheme 176). Recently Young *et al*. have studied selective macrocyclic alkene-RCM using a removable silyl group.[197] The presence of a bulky silyl group on alkenyl functionality should favour the stereoselective formation of trisubstituted *E*-alkene, generating the desired 19-membered macrocycle **442**. Subsequent epoxidation and oxidative silyl group removal would deliver the hydroxy ketone **443** in only three steps.[198]



Scheme 176: Revised strategy

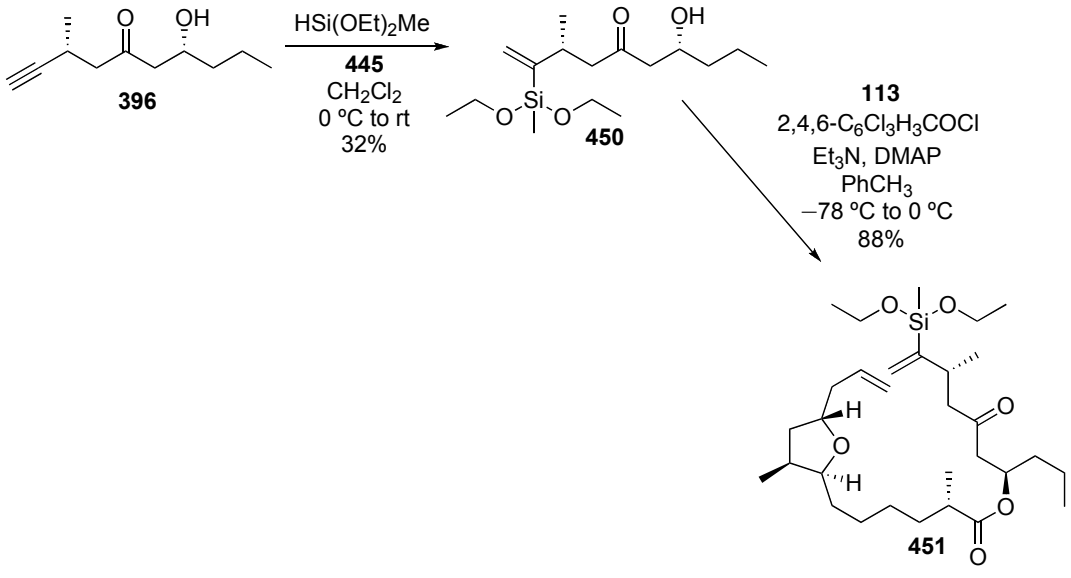
Controlling the stereochemical outcome of macrocyclic alkene RCM reactions remains a challenge in total synthesis. Silylated diene **446** underwent macrocyclic stereoselective RCM reaction when exposed to metathesis conditions (Scheme 177).[197] Starting from enyne **444**, reductive ruthenium catalysed hydrosilation added a siloxilane group regioselectively at the internal position of the terminal alkyne.[199] Subsequent alkene RCM using modified HGII catalyst **447** closed the macrocycle while affording the *E*-alkene **448**. The method was applied successfully to prepare 8- to 16-membered macrocycles when substitution was absent on α-position of the alkyne **444**.

[197] Wang, Y.; Jimenez, M.; Hansen, A. S.; Raiber, E.-A.; Schreiber, S. L.; Young, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 9196–9199.
[198] Tamao, K.; Maeda, K. *Tetrahedron Lett.* **1989**, *27*, 65–68.
[199] Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655.



Scheme 177: Young's approach to macrocyclic formation

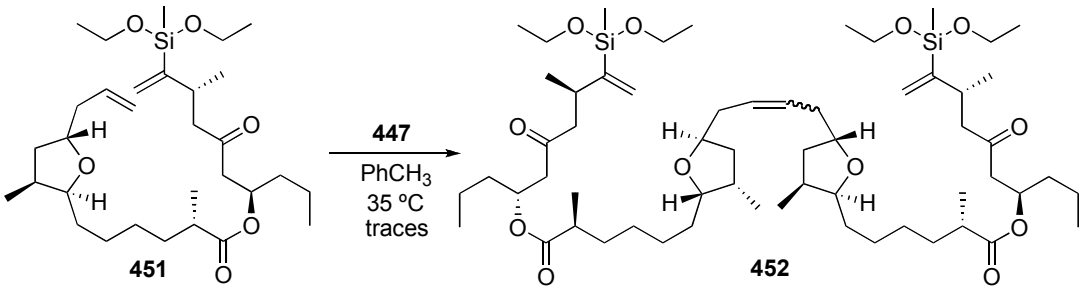
Trost and co-worker developed a method for the regioselective reductive hydrosilylation of a terminal alkynes.[199] When this reaction was applied to our substrate **396**, the ruthenium-catalysed reaction inserted a siloxyl group onto the internal position of the alkyne group (Scheme 178). A poor yield was obtained from the reaction, presumably due to the steric hindrance of the methyl group at the α-position of the alkyne group. Subsequently, hydroxyketone **450** and western fragment **113** were coupled *via* Yamaguchi esterification to afford diene **451** in good yield.



*Scheme 178: Preparation of the diene **451***

Diene **451** was subjected to diene RCM under Young's conditions using the modified HGII **447** catalyst (Scheme 179). Unfortunately, the desired macrocyclic compound was not obtained; a mixture of oligomers and traces of

dimer **452** were detected. It appeared that an intermolecular process was competing with the desired RCM reaction.[132] The siloxy-alkene part is probably too hindered to react further with the newly formed double bond and so would not proceed through the expected RCM process.



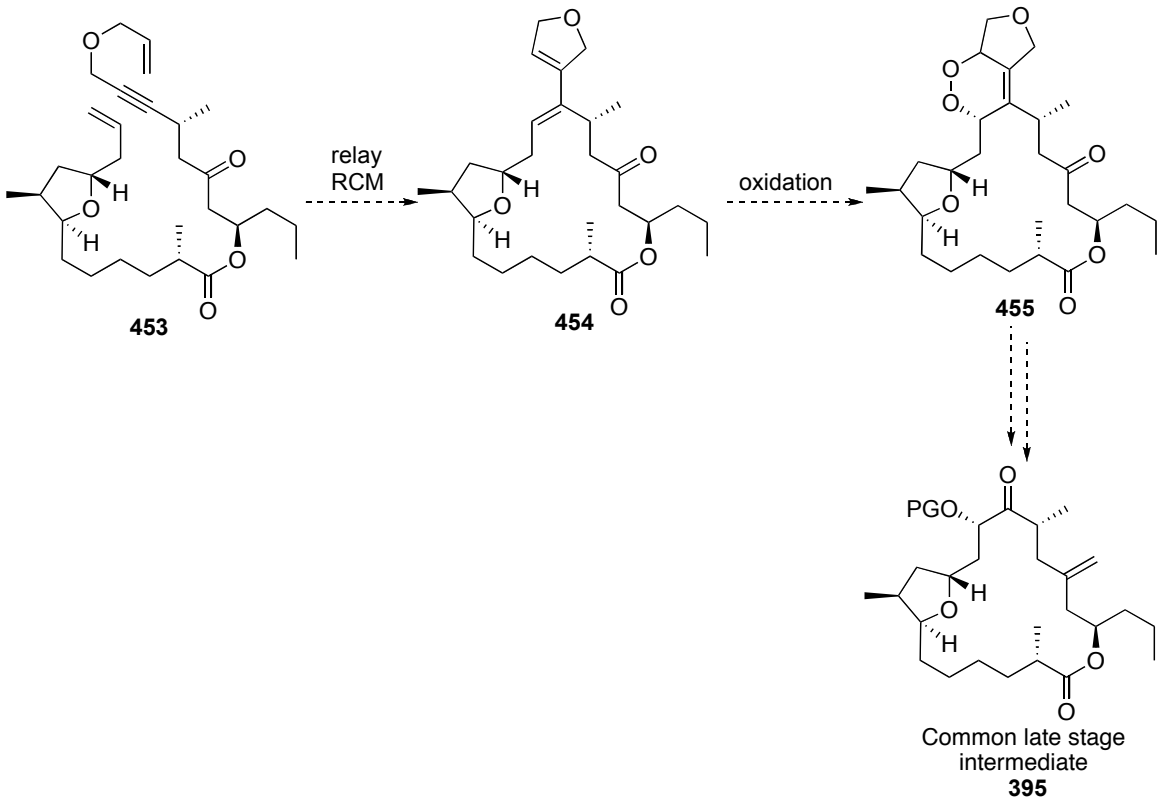
Scheme 179: Alkene RCM attempt

Young's strategy towards stereoselective alkene RCM using a removable silyl group did not proceed when applied to our synthesis. Low reactivity of the siloxy-alkene moiety was probably due to steric hindrance from the adjacent methyl group.

4.3.4 Relay Ring Closing Metathesis Approach

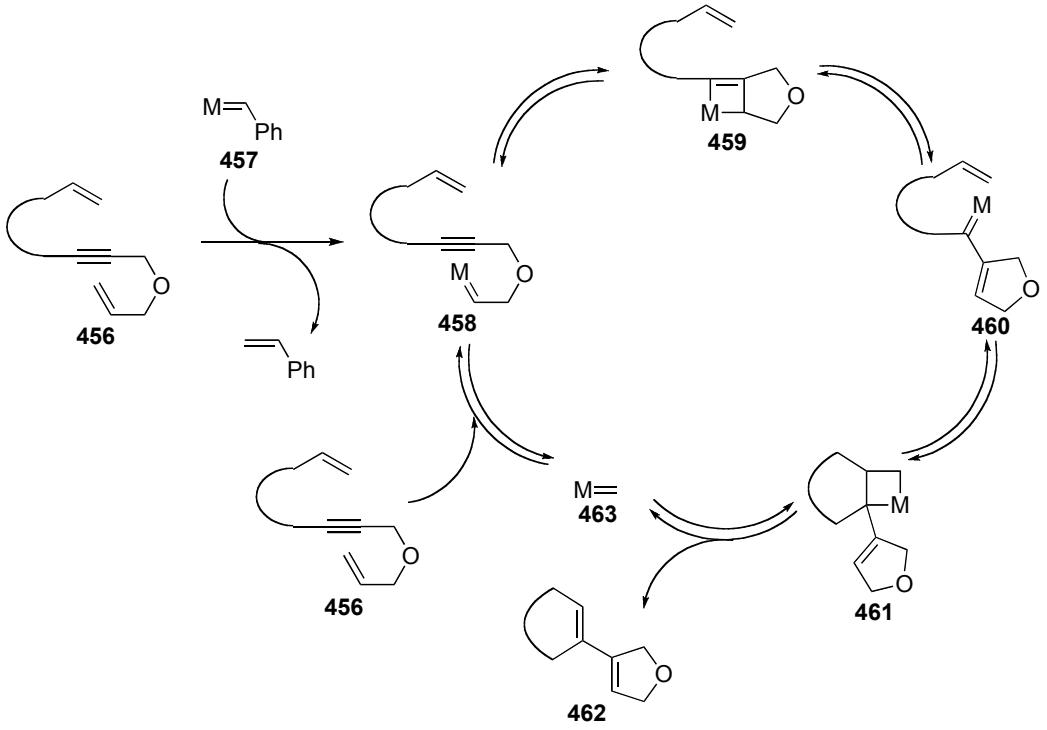
Introduction of a side chain at the terminal position of the alkyne group would direct the RCM towards formation of the expected macrocycle (Scheme 180).[200] Relay RCM of dienyne **453** would produce the desired 19-membered macrolactone **454** as well as the 5-membered cyclic ether moiety. The driving force for this metathesis reaction is favourable formation of dihydrofuran.[201,202] Subsequent stereocontrolled photooxidation would allow access to a common intermediate **395** from which the natural targets could be prepared readily.

[200] Wallace, D. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 1912–1915.
[201] Mori, M.; Kitamura, T.; Sato, Y. *Adv. Synth. Catal.* **2002**, *344*, 678–693.
[202] Lloyds-Jones, G. C.; Robinson, A. J.; Lefort, L.; De Vries, J. G. *Chem. Eur. J.* **2010**, *16*, 9449–9452.



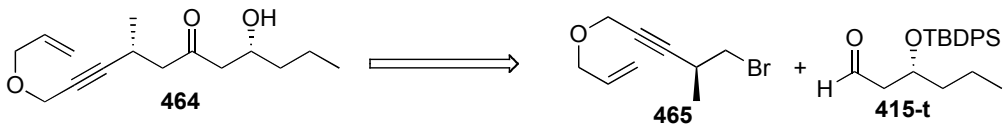
Scheme 180: Relay RCM strategy

Mechanistically, relay dienyne RCM proceeds by initiation at the alkene group of **456** to form metal alkylidene **458**, which subsequently undergoes [2+2] cycloaddition onto the alkyne functionality to afford bicyclic metallocyclobutene **459** (Scheme 181). Ring opening of the bicyclic intermediate **459** yields the metal carbene **460**, which reacts with the terminal alkene and affords the metallocycle **461**. [2+2] Cycloreversion of **461** delivers the bicyclic alkene **462** and regenerates the catalyst for further catalytic cycles.



Scheme 181: Relay dienyne RCM

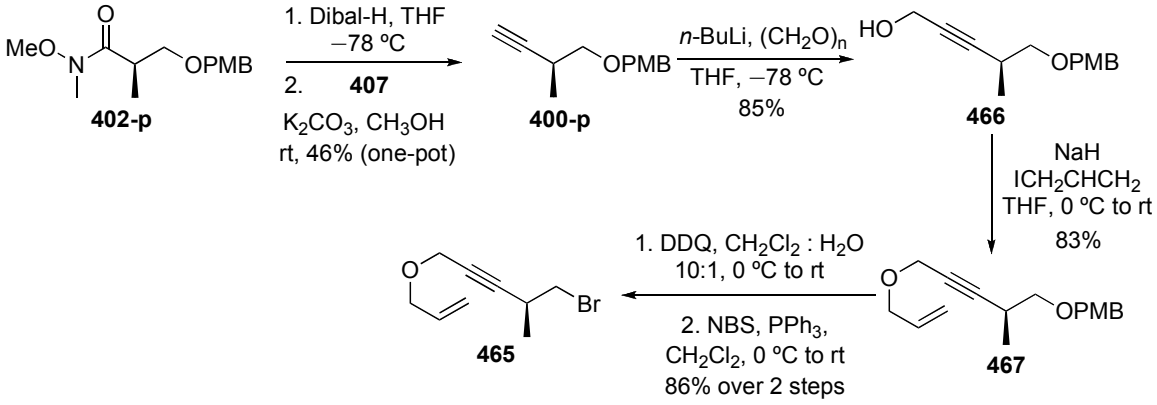
In order to implement this new strategy, the side chain was incorporated at the beginning of the eastern fragment **464** synthesis (Scheme 182).



Scheme 182: Approach towards side chain incorporation

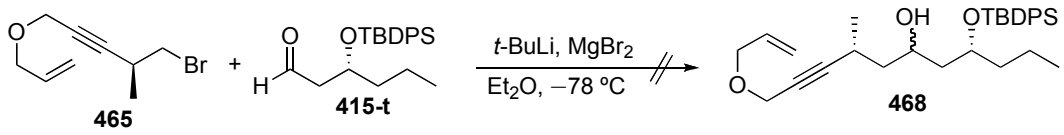
One-pot reduction/Ohira-Bestmann homologation on **402-p** proceeded in moderate yield but with good reproducibility (Scheme 183).[203,204] Isolation of the intermediate aldehyde would probably increase the yield of this reaction. Deprotonation of the terminal alkyne **400-p** with *n*-butyllithium and subsequent nucleophilic attack on formaldehyde afforded the alcohol **466** in good yield. *O*-Alkylation was performed under basic conditions, introducing the allyl moiety in good yield. A deprotection and bromination sequence delivered the required bromide **465** for Grignard addition.

[203] Mueller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *6*, 521–522.
[204] Dickson, H. D.; Smith, S. C.; Hinkle, K. W. *Tetrahedron Lett.* **2004**, *45*, 5597–5599.



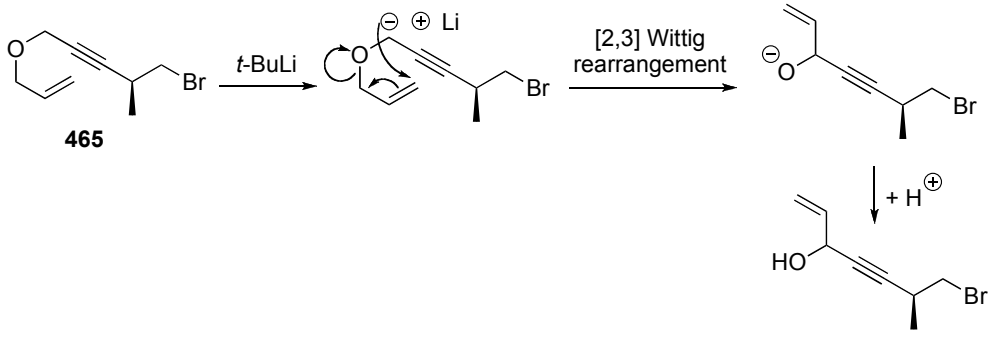
Scheme 183: Side chain introduction

The bromide **465** was then subjected to previously optimised Grignard addition conditions (Scheme 184). To our disappointment, the bromide **465** decomposed under basic conditions.



Scheme 184: Grignard addition failure

The detection of alcohol by-products led us to suspect deprotonation at the position adjacent to the alkyne and subsequent Wittig [2,3] sigmatropic rearrangement (Scheme 185).[205] Milder methods of Grignard reagent preparation failed to deliver the alkyl magnesium complex and so this approach was abandoned.

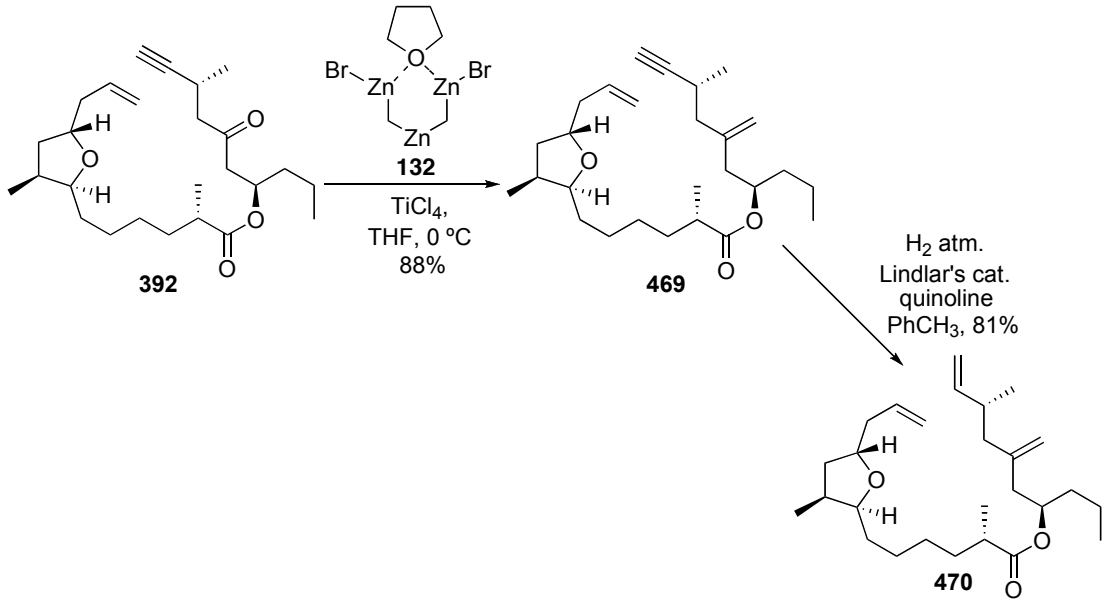


Scheme 185: Suspected decomposition pathway

[205] Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885–902.

4.4 Formal Synthesis of Amphidinolide T Family

To complete the project, transformations to intercept Dai's route were conducted, resulting in a formal synthesis of amphidinolide T family. Nysted methylenation was employed to accomplish smooth conversion of the ketone **392** into alkene **469** in good yield (Scheme 186). Subsequent partial reduction of the terminal alkyne functionality using Lindlar's catalyst afforded the triene **470**. Analytical data and optical rotation of triene **470** were in agreement to those provided by Dai and co-worker on amphidinolide T3 total synthesis.[18]



Scheme 186: Towards the formal synthesis of amphidinolide T series

In summary, the triene **469** was synthesised *via* a longest linear sequence of seventeen steps from ethylene glycol with 10% overall yield. In comparison, Dai's route delivered the RCM precursor **470** in 10% yield over thirteen steps.

Conclusion and Future Work

The aim of this project was the total synthesis of amphidinolide T family of natural products using a novel strategy by synthesising a common late stage intermediate allowing access to four members of the series.

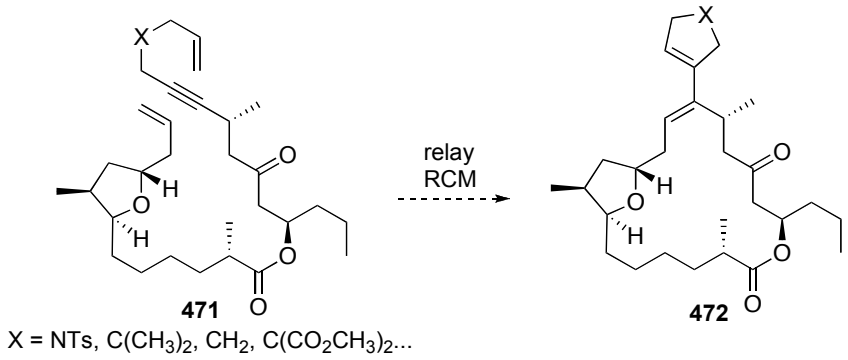
A stereoselective synthesis of the enantiopure western fragment **113** was achieved in fourteen steps from ethylene glycol, producing the target in 18% overall yield. Furthermore, the route was amenable to large-scale synthesis. The *trans*-tetrahydrofuran ring was forged efficiently *via* diastereoselective [2,3]-sigmatropic rearrangement of oxonium ylide from diazo-generated metal carbenoids. Coupling of the side chain **26** was achieved using a sequence of esterification and RCM reactions. Alternatively, a one-pot RCM followed by hydrogenation was developed to shorten the synthesis of the western fragment **113**. Enantioselective Noyori hydrogenation, Evans alkylation and substrate-controlled hydrogenation introduced the desired chirality of the stereocentres.

The eastern fragment **396** was prepared in 20% overall yield over ten steps. Key reactions included the Corey-Fuchs sequence and a Grignard addition to couple the fragments. Stereogenic centres were derived from the chiral pool and introduced by enantioselective Noyori hydrogenation.

Fragments **113** and **396** were coupled in excellent yield by Yamaguchi esterification and the final stages of the project focused on the closure of the 19-membered lactone. Various strategies were investigated, starting from enyne RCM, siloxane-assisted macrocyclic alkene RCM and relay dienyne RCM. Unfortunately, these strategies were unsuccessful for the synthesis of this complex structure.

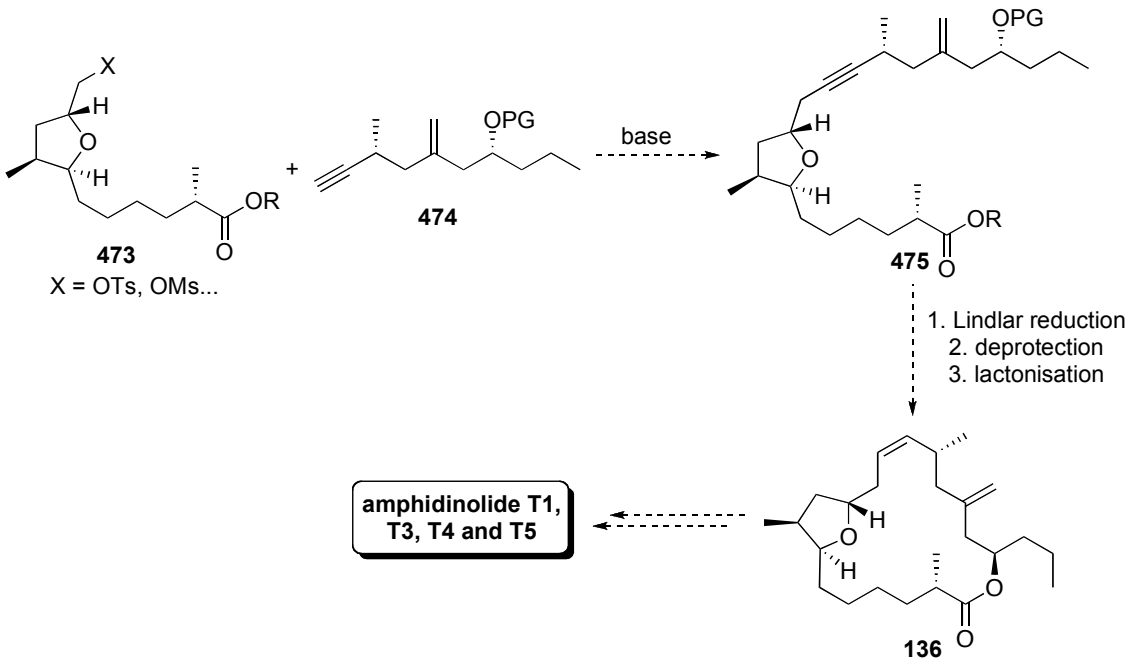
Finally, a formal synthesis of amphidinolide T3 was achieved by intercepting a late stage intermediate of the Dai's synthesis of members of the amphidinolide T family. Triene **470** was synthesised in seventeen steps and in 10% overall yield.

The relay dienyne RCM failed because of the low stability of the allyl ether side chain. Studies revealed effectiveness of enyne RCM with incorporation of either oxygen atom or nitrogen atom or diester functionality in the side chain to form 5-membered cyclic compounds.[201,202] Further efforts could be focused on the introduction of various functional groups with the expectation that relay RCM would give access to the desired 19-membered macrolactone (Scheme 187).



Scheme 187: Relay RCM optimisation

Studies towards the total syntheses of members of the amphidinolide T family of natural products are still in progress in the Clark group. The novel approach is based on the coupling of the main fragments **473** and **474** by displacement of a leaving group *via* nucleophilic attack of the deprotonated alkyne functionality (Scheme 188). Subsequent reduction, deprotection and lactonisation should lead to the desired common intermediate **136** in a straightforward manner.



Scheme 188: Revised strategy towards amphidinolide T family

Experimental Section

General Experimental

Air and/or moisture sensitive reactions were performed under an atmosphere of Argon in flame dried apparatus. Tetrahydrofuran, toluene, dichloromethane and diethyl ether were purified using a Pure-Solv^{TM} 500 Solvent Purification System. Other dry organic solvents and starting materials were obtained from commercial sources and used as received. Petroleum ether used for column chromatography was the 40-60 ºC fraction.

All reactions were monitored by thin layer chromatography using Merck silica gel 60 covered alumina plates F_{254}. Thin layer chromatography plates were viewed under UV light or were visualised using either potassium permanganate solution or acidic ethanolic anisaldehyde solution or phosphomolybdic acid solution. Flash column chromatography was performed on silica gel (Fluorochem 35-70 μm, 60A).

IR spectra were recorded at ambient temperature using a JASCO FT IR 410 instrument.

All ^{1}H NMR spectra were recorded on Bruker 400 MHz Spectrospin and Bruker 500 MHz Spectrospin spectrometers at ambient temperature. Data are reported as follows; chemical shift in ppm relative to $CDCl_3$ (7.26) or C_6D_6 (7.16) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app. = apparent or a combination of these), coupling constant(s) *J* (Hz) and assignment. All ^{13}C NMR spectra were recorded on a Bruker 400 MHz Spectrospin and Bruker 500 MHz Spectrospin spectrometers at 100 MHz and 125 MHz at ambient temperature and multiplicities were obtained using a DEPT sequence. Data are reported as follow; chemical shift in ppm relative to $CHCl_3$ (77.16) or C_6D_6 (128.1) on the δ scale and assignment.

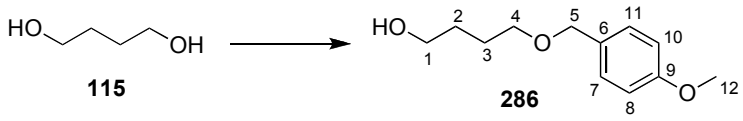
Optical rotations were recorded in chloroform or dichloromethane with an error of $\leq \pm 0.1$. The $[\alpha]_D$ values are given in 10^{-1} deg cm^3 g^{-1}.

Mass spectra were recorded using positive ion impact (EI+), positive or negative ion electrospray (ES+/ES-) and fast atom bombardment (FAB) techniques on Jeol MStation JMS-700 instrument. The intensity of each peak is quoted as a percentage of the largest, where this information was available. Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440.

Melting points were recorded with an Electrothermal IA 9100 apparatus.

Procedures and data

1-(*O*-*p*-Methoxybenzyl)butan-4-ol 286[99]



Sodium hydride (0.99 g of a 60% dispersion in oil, 25 mmol) was washed with petroleum ether (3 × 15 mL) and suspended in dry DMF (70 mL). To the suspension of NaH at 0 ºC, 1,4-butanediol **115** (2.00 mL, 22.6 mmol) in dry DMF (5.0 mL) was added dropwise and the reaction was stirred at rt for 1 h. Bu_4NI (0.45 g, 1.1 mmol) in dry DMF (10 mL) was then added, followed by *para*-methoxybenzyl chloride (3.00 mL, 22.6 mmol) and the reaction was stirred at rt for 19 h. Diethyl ether (150 mL) was added, followed by water (150 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (4 × 100 mL) and the combined organic extracts were washed with a saturated solution of ammonium chloride (4 × 100 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient from pure petroleum ether to petroleum ether - diethyl ether, 1:3) to give the alcohol **286** (4.02 g, 86%) as a colourless oil.

R_f = 0.41 (petroleum ether - diethyl ether, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65-1.72 (4H, m, CH_2-C2, CH_2-C3), 2.29 (1H, brs, OH), 3.50 (2H, t, *J* = 5.4 Hz, CH_2-C4), 3.64 (2H, dt, *J* = 5.8, 5.7 Hz, CH_2-C1), 3.80 (3H, s, CH_3-C12), 4.45 (2H, s, CH_2-C5), 6.89 (2H, d, *J* = 8.5 Hz, CH-C7, CH-C11), 7.26 (2H, d, *J* = 8.5 Hz, CH-C8, CH-C10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0 (CH_2-C3), 30.4 (CH_2-C2), 55.4 (CH_3-C12), 62.9 (CH_2-C1), 70.2 (CH_2-C4), 72.9 (CH_2-C5), 113.9 (CH-C7, CH-C11), 129.5 (CH-C8, CH-C10), 130.3 (C-C6), 159.3 (C-C9);

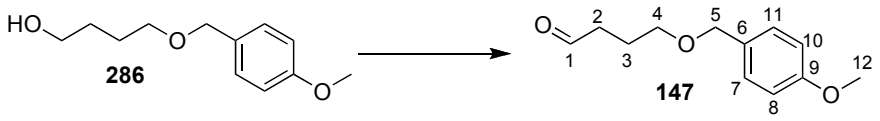
ν_{max} 3387, 2939, 2862, 1612, 1512, 1242, 1172, 1097, 1033, 817 cm^{-1};

LRMS (EI) *m/z* (intensity) 210 $[M]^+$ (22), 137 (100), 121 (100), 77 (32);

HRMS (EI) calcd for $C_{12}H_{18}O_3$ $[M]^+$ 210.1256, found 210.1254;

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55%; H, 8.62%. Found: C, 68.18%; H, 8.83% {Lit. C, 68.20%; H, 8.83%}.

4-(*O*-*p*-Methoxybenzyl)butanal 147[99]



To a suspension of pyridinium chlorochromate (PCC) (0.40 g, 1.9 mmol), 4 Å powdered activated molecular sieves (1.0 g) and sodium acetate (NaOAc) (0.16 g, 1.9 mmol) in dry dichloromethane (7.0 mL) at 0 ºC was added the alcohol **286** (0.20 g, 0.95 mmol) in dry dichloromethane (2.00 mL) and the reaction mixture was stirred at room temperature for 1 h. The mixture was eluted through a short pad of silica with dichloromethane (200 mL). The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient from pure petroleum ether to petroleum ether - diethyl ether, 1:1) to give the aldehyde **147** (0.19 g, 95%) as a pale yellow oil.

R_f = 0.73 (petroleum ether - diethyl ether, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91-1.98 (2H, m, CH_2-C3), 2.55 (2H, dt, *J* = 7.2, 1.5 Hz, CH_2-C2), 3.49 (2H, t, *J* = 6.0 Hz, CH_2-C4), 3.81 (3H, s, CH_3-C12), 4.43 (2H, s, CH_2-C5), 6.89 (2H, d, *J* = 8.5 Hz, CH-C7, CH-C11), 7.26 (2H, d, *J* = 8.5 Hz, CH-C8, CH-C10), 9.78 (1H, s, CH-C1);

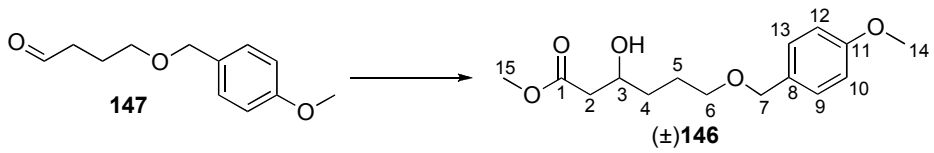
^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7 (CH_2-C3), 41.1 (CH_2-C2), 55.4 (CH_3-C12), 68.9 (CH_2-C4), 72.7 (CH_2-C5), 113.9 (CH-C7, CH-C11), 129.4 (CH-C8, CH-C10), 130.4 (C-C6), 159.3 (C-C9), 202.5 (CH-C1);

ν_{max} 2936, 2860, 1723, 1610, 1590, 1513, 1298, 1248, 1175, 1093, 1033, 821, 727 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 121.2 (100), 137.2 (12); 209.3 $[M+H]^+$ (3);

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21%; H, 7.74%. Found: C, 69.05%; H, 7.73% {Lit. C, 69.12%; H, 7.74%}.

(±)-Methyl 6-(*O*-*p*-methoxybenzyl)-3-hydroxy-hexanoate 146



To a suspension of dry zinc powder (64 mg, 1.0 mmol), granulated zinc (128 mg, 2.00 mmol) and dry lithium chloride (11 mg, 0.25 mmol) in dry diethyl ether (2.00 mL), trimethylsilyl chloride (0.20 mL) was added and the mixture was stirred for 15 minutes at rt. The suspension was concentrated by reduced pressure distillation, diethyl ether (5.00 mL) was added and the mixture was heated to 40 ºC. Over 1.5 h, the aldehyde **147** (100 mg, 0.49 mmol) and methyl bromoacetate (80 mg, 0.54 mmol) in diethyl ether (0.50 mL) were added simultaneously and the mixture was stirred for an additional 1 hour at 40 ºC. Diethyl ether (10 mL) was then added, followed by a solution of hydrochloric acid (10 mL, 1 M). The two phases were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with a saturated solution of sodium hydrogencarbonate (50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient from pure petroleum ether to petroleum ether - diethyl ether, 1:3) to give the ester (±) **146** (96 mg, 72%) as a colourless oil.

R_f = 0.34 (petroleum ether - diethyl ether, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.77 (4H, m, CH_2-C4, CH_2-C5), 2.44 (1H, dd, *J* = 16.3, 8.1 Hz, CH_2-C2), 2.49 (1H, dd, *J* = 16.3, 4.2 Hz, CH_2-C2), 3.28 (1H, d, *J* = 3.6 Hz, OH), 3.48 (2H, t, *J* = 6.0 Hz, CH_2-C6), 3.70 (3H, s, CH_3-C14), 3.80 (3H, s, CH_3-C15), 4.02 (1H, m, CH-C3), 4.44 (2H, s, CH_2-C7), 6.87 (2H, d, *J* = 8.3 Hz, CH-C9, CH-C13), 7.25 (2H, d, *J* = 8.3 Hz, CH-C10, CH-C12);

^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_2-C5), 33.9 (CH_2-C4), 41.4 (CH_2-C2), 51.8 (CH_3-C14), 55.4 (CH_3-C15), 68.0 (CH-C3), 70.0 (CH_2-C6), 72.8 (CH_2-C7), 113.9 (CH-C9, CH-C13), 129.4 (CH-C10, CH-C112), 130.3 (C-C8), 159.3 (C-C11), 173.4 (CH-C1);

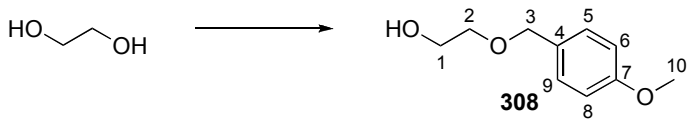
ν_{max} 3437, 2951, 2859, 1732, 1613, 1512, 1246, 1173, 1092, 1034, 818 cm^{-1};

LRMS (EI) *m/z* (intensity) 121.1 (100), 137.1 (78), 43.1 (29), 61.1 (13), 282.3 $[M]^+$ (3.1);

HRMS (EI) calcd for $C_{15}H_{22}O_5$ $[M]^+$ 282.1467, found 282.1463;

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81%; H, 7.85%. Found: C, 63.44%; H, 7.93%.

2-(4-Methoxybenzyloxy)ethanol 308



Sodium hydride (0.43 g of a 60% dispersion in oil, 11 mmol) was washed with petroleum ether (3 × 10 mL). To the suspension of NaH in dry THF (5.00 mL) at 0 ºC, 1,2-ethanediol (ethylene glycol) (5.00 mL, 87.9 mmol) in dry THF (5.0 mL) was added dropwise and the reaction was stirred at rt for 30 min. *Para*-methoxybenzyl chloride (1.20 mL, 8.79 mmol) was then added, followed by Bu_4NI (0.18 g, 0.44 mmol) in dry THF (5.00 mL) and the mixture was stirred at 70 ºC for 2.5 h. Diethyl ether (50 mL) was added, followed by water (50 mL) and the two phases were separated. The aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were washed with a saturated solution of ammonium chloride (2 × 50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient from pure petroleum ether to petroleum ether - diethyl ether, 1:3) to give the alcohol **308** (1.51 g, 95%) as a colourless oil.

R_f = 0.25 (petroleum ether - diethyl ether, 1:3);

^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (1H, t, *J* = 6.3 Hz, -OH), 3.57 (2H, t, *J* = 4.6 Hz, CH_2-C2), 3.75 (2H, dt, *J* = 6.3, 4.6 Hz, CH_2-C1), 3.80 (3H, s, CH_3-C10), 4.49 (2H, s, CH_2-C3), 6.89 (2H, d, *J* = 9.6 Hz, CH-C5, CH-C9), 7.28 (2H, d, *J* = 9.6 Hz, CH-C6, CH-C8);

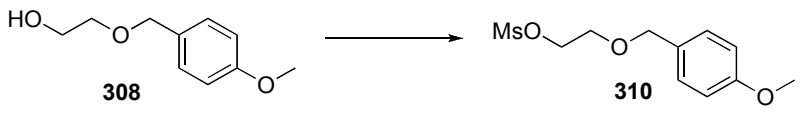
^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6 (CH_3-C10), 62.2 (CH_2-C1), 71.3 (CH_2-C2), 73.3 (CH_2-C3), 114.2 (CH-C5, CH-C9), 129.8 (CH-C6, CH-C8), 130.3 (C-C4), 159.6 (C-C7);

ν_{max} 3410, 2862, 1612, 1512, 1244, 1103, 1030, 812 cm^{-1};

LRMS (EI) *m/z* (intensity) 182 $[M]^+$ (60), 121 (100), 137 (51), 77 (26);

Anal. calcd for $C_{10}H_{14}O_3$ C, 65.91%; H, 7.74%. Found C, 65.51%; H, 7.86%.

2-(4-Methoxybenzyloxy)ethyl methanesulfonate 310



To a solution of the alcohol **308** (4.53 g, 24.9 mmol) in dry dichloromethane (160 mL) at 0 ºC was added triethylamine (4.50 mL, 31.4 mmol) and methanesulfonyl chloride (3.10 mL, 37.5 mmol). To the resulting mixture was added a solution of 4-dimethylaminopyridine (DMAP) (3.07 g, 24.9 mmol) in dry dichloromethane (10.0 mL) and the reaction mixture was stirred at room temperature for 2 h. Distilled water (50 mL) was added and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with 1 M hydrochloric acid solution (50 mL) and a saturated solution of sodium hydrogencarbonate (50 mL), dried over $MgSO_4$ and then filtered. The solvent was evaporated under reduced pressure and the mesylate **310** (6.22 g) was obtained as a pale yellow oil, which was used without further purification.
R_f = 0.42 (petroleum ether - diethyl ether, 1:3).

1-[(2-Iodoethoxy)methyl]-4-methoxybenzene 311

To a solution of the mesylate **310** (6.22 g, 24.9 mmol) in dry acetone (300 mL) at rt was added sodium iodide (18.0 g, 120 mmol) and the mixture was stirred at reflux for 18 h. After cooling the reaction mixture to room temperature, distilled water (100 mL) was added and the mixture was extracted with diethyl ether (3 × 300 mL). The combined organic extracts were washed with a saturated solution of sodium thiosulfate (500 mL) and a saturated solution of sodium chloride (500 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (pure

petroleum ether to petroleum ether - diethyl ether, 9:1) to give the iodide **311** (6.46 g, 99% over two steps) as a colourless oil.

R_f = 0.52 (petroleum ether - diethyl ether, 3:1);

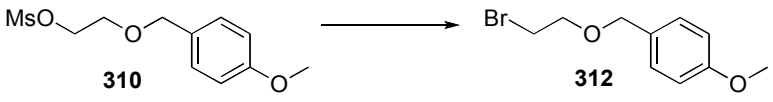
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (2H, t, *J* = 6.7 Hz, CH_2-C1), 3.75 (2H, t, *J* = 6.7 Hz, CH_2-C2), 3.81 (3H, s, CH_3-C10), 4.51 (2H, s, CH_2-C3), 6.88 (2H, d, *J* = 8.7 Hz, CH-C5, CH-C9), 7.27 (2H, d, *J* = 8.7 Hz, CH-C6, CH-C8);

^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9 (CH_2-C1), 55.6 (CH_3-C10), 70.8 (CH_2-C2), 72.9 (CH_2-C3), 114.2 (CH-C5, CH-C9), 129.8 (CH-C6, CH-C8), 130.2 (C-C4), 159.7 (C-C7);

ν_{max} 2854, 1612, 1510, 1244, 1172, 1103, 1031, 817, 512 cm^{-1};

LRMS (EI) *m/z* (intensity) 262 [M]$^+$ (21), 121.1 (100), 137 (72), 82 (28), 77 (16).

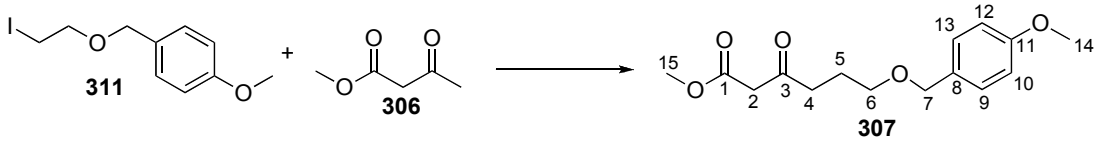
1-[(2-Bromoethoxy)methyl]-4-methoxybenzene 312



To a solution of the mesylate **310** (209 mg, 0.81 mmol) in dry acetone (5.0 mL) at rt was added lithium bromide (335 mg, 4.00 mmol) and the mixture was stirred at reflux for 18 h. After cooling the reaction mixture to room temperature, distilled water (2 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with a saturated solution of sodium chloride (50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the bromide **312** (181 mg) was obtained as a colorless oil, which was used without further purification.

R_f = 0.52 (petroleum ether - diethyl ether, 3:1).

Methyl 6-(4-methoxybenzyloxy)-3-oxohexanoate 307



Sodium hydride (2.00 g of a 60% dispersion in oil, 40.0 mmol) was washed with petroleum ether (2 × 100 mL). To the suspension of sodium hydride in dry THF (50 mL) at −25 ºC was added dropwise methyl acetoacetate **306** (4.00 mL, 37.1 mmol) and the mixture was stirred for 15 minutes. *n*-Butyl lithium (20 mL of a 2.5 M solution in hexanes, 50 mmol) was added dropwise. The mixture was stirred at −25 ºC for 15 min and the iodide **311** (7.91 g, 27.0 mmol) was then added dropwise. The resultant mixture was kept for 1 h at −25 ºC and then allowed to warm to rt over 30 minutes. Hydrochloric acid solution (100 mL, 1 M), diethyl ether (50 mL) and distilled water (20 mL) were added and the mixture was extracted by diethyl ether (3 × 100 mL). Combined organic phases were washed with a saturated solution of sodium hydrogencarbonate (300 mL) and a saturated solution of sodium chloride (200 mL), then dried over $MgSO_4$ and filtered. Concentrated under reduced pressure afforded a residue that was purified by flash chromatography on silica gel (pure petroleum ether to petroleum ether - diethyl ether, 3:1) to give the ester **307** (6.71 g, 89%) as a colourless oil.

R_f = 0.27 (petroleum ether - diethyl ether, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (2H, tt, *J* = 7.2, 5.9 Hz, CH_2-C5), 2.64 (2H, t, *J* = 7.2 Hz, CH_2-C4), 3.45 (2H, t, *J* = 5.9 Hz, CH_2-C6), 3.47 (2H, s, CH_2-C2), 3.72 (3H, s, CH_3-C15), 3.80 (3H, s, CH_3-C14), 4.40 (2H, s, CH_2-C7), 6.87 (2H, d, *J* = 8.9 Hz, CH-C9, CH-C13), 7.24 (2H, d, *J* = 8.9 Hz, CH-C10, CH-C12);

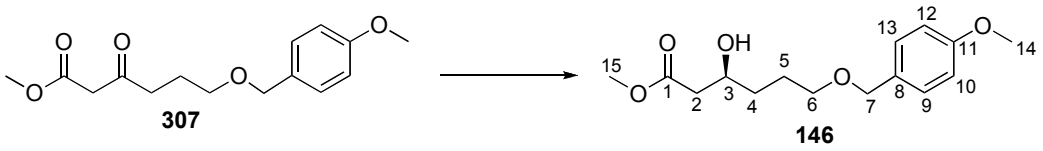
^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 (CH_2-C5), 40.0 (CH_2-C4), 49.2 (CH_2-C2), 52.5 (CH_3-C15), 55.4 (CH_3-C14), 68.8 (CH_2-C6), 72.7 (CH_2-C7), 113.9 (CH-C9, CH-C13), 129.4 (CH-C10, CH-C12), 130.5 (C-C8), 159.3 (C-C11), 167.8 (C-C1), 202.7 (C-C3)

ν_{max} 2955, 2858, 1743, 1712, 1612, 1512, 1246, 1091, 1030, 817 cm^{-1};

LRMS (EI) *m/z* (intensity) 280 $[M]^+$ (21), 121 (100), 141 (72), 262 (28), 203 (16);

Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27%; H, 7.19%. Found: C, 64.36%; H, 7.28%.

Methyl (*S*)-3-hydroxy-6-(4-methoxybenzyloxy)hexanoate 146



<u>Caution</u>: BINAP-Ru catalyst is extremely sensitive to water and oxygen therefore all the glassware has to be flame-dried and the solvents degassed by two freeze-thaw cycles.

The $[RuCl_2(benzene)]_2$ complex (5.4 mg, 1.1 μmol) and (*S*)-(−)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene or [(*S*)-BINAP] **314** (13.8 mg, 2.25 μmol) were dissolved in dry and degassed DMF (0.5 mL) in a 5 mL vial. The mixture was stirred at 110 ºC for 20 min and DMF was removed by vacuum distillation (50 ºC at 200 mbar). A solution of ester **307** (1.00 g, 3.57 mmol) in dry and degassed methanol (2.0 mL) was added. The vial was transferred to a hydrogenation autoclave and the vessel was purged three times with hydrogen. The reaction mixture was stirred at 95 ºC under an atmosphere of hydrogen (5 bar) for 18 h and then cooled to room temperature. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient from pure petroleum ether to petroleum ether - diethyl ether, 1:1) to give the ester **146** (912 mg, 91%) as a colourless oil. The enantiomeric excess was determined by chiral HPLC and found to be 94% *ee*.

R_f = 0.27 (petroleum ether - diethyl ether, 1:1);

HPLC: t_R (*S* enantiomer) = 15.0 min, t_R (*R* enantiomer) = 12.1 min (Chiracel OD-H, *n*-hexane - *iso*-propanol, 9:1, 1.00 mL × min^{-1}, oven: 25.0 ºC)

$[\alpha]^{25}_D$ +8.0 (c = 1.1, $CHCl_3$) {Lit.[124a] $[\alpha]^{26}_D$ +8.0 (c = 1.1, $CHCl_3$)};

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.80 (4H, m, CH_2-C4, CH_2-C5), 2.45 (2H, dd, *J* = 8.2, 4.3 Hz, CH_2-C2), 3.28 (1H, d, *J* = 3.7 Hz, -OH), 3.48 (2H, t, *J* = 6.0 Hz, CH_2-C6), 3.70 (3H, s, CH_3-C15), 3.80 (3H, s, CH_3-C14), 3.99-4.06 (1H, m, CH-C3), 4.43

(2H, s, CH_2-C7), 6.87 (2H, d, *J* = 8.7 Hz, CH-C9, CH-C13), 7.22 (2H, d, *J* = 8.7 Hz, CH-C10, CH-C12);

^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3 (CH_2-C5), 34.1 (CH_2-C4), 41.7 (CH_2-C2), 52.1 (CH_3-C15), 55.6 (CH_3-C14), 68.2 (CH-C3), 70.2 (CH_2-C6), 73.0 (CH_2-C7), 114.1 (CH-C9, CH-C13), 129.7 (CH-C10, CH-C12), 130.6 (C-C8), 159.4 (C-C11), 173.6 (C-C1);

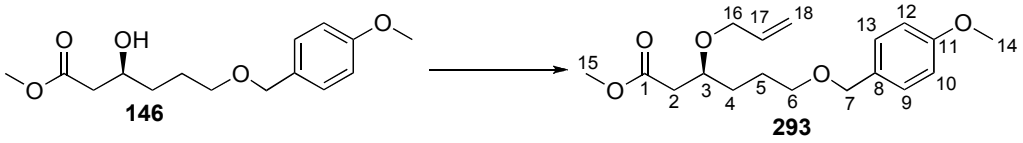
ν_{max} 3437, 2951, 2858, 1732, 1612, 1512, 1246, 1172, 1091, 1033, 817 cm^{-1};

LRMS (EI) *m/z* (intensity) 282 $[M]^+$ (6), 121 (100), 137 (78), 77 (25);

HRMS (EI) calcd for $C_{15}H_{22}O_5$ $[M]^+$ 282.1467, found 282.1464;

Anal. calcd for $C_{15}H_{22}O_5$: C, 63.81%; H, 7.85%. Found: C, 63.44%; H, 7.93%.

Methyl (*S*)-6-(4-methoxybenzyloxy)-3-(prop-2-en-1-yloxy)hexanoate 293



Boron trifluoride diethyl etherate (15 μL, 12 μmol) was added dropwise to a solution of ester **146** (26.0 mg, 92.2 μmol) and freshly prepared allyl trichloroacetimidate (71.2 mg, 352 μmol) in dry cyclohexane (10 mL). The mixture was stirred at room temperature for 16 h and then filtered through Celite. The reaction mixture was washed with a saturated solution of sodium carbonate (20 mL), water (20 mL) and a saturated solution of sodium chloride (20 mL). The mixture was dried over $MgSO_4$, filtered and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether - diethyl ether, 9:1) to give the allyl ether **293** (13.1 mg, 44%) as a colourless oil.

R_f = 0.21 (dichloromethane - methanol, 99.5:0.5); R_f = 0.75 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{27}_D$ +5.6 (*c* = 1.0, $CHCl_3$);

^1H NMR (400 MHz, $CDCl_3$) δ 1.57–1.75 (4H, m, CH_2-C4, CH_2-C5), 2.43 (1H, dd, *J* = 15.0, 5.8 Hz, CH_2-C2), 2.57 (1H, dd, *J* = 15.0, 7.3 Hz, CH_2-C2), 3.45 (2H, t, *J* = 5.5 Hz, CH_2-C6), 3.68 (3H, s, CH_3-C14), 3.77–3.84 (1H, m, CH-C3), 3.80 (3H, s,

CH_3-C15), 3.99 (2H, dddd, *J* = 5.6, 2.7, 1.6, 1.3, CH-C16), 4.43 (2H, s, CH_2-C7), 5.14 (1H, ddt, *J* = 10.3, 1.7, 1.3 Hz, CH_2-C18 *cis*), 5.24 (1H, ddt, *J* = 17.2, 1.7, 1.6 Hz, CH_2-C18 *trans*), 5.87 (1H, ddt, *J* = 17.2, 10.3, 5.6, CH-C17), 6.88 (2H, d, *J* = 9.1 Hz, CH-C9, CH-C13), 7.25 (2H, d, *J* = 9.1 Hz, CH-C10, CH-C12);

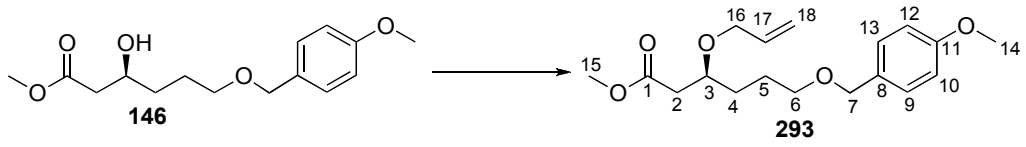
^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6 (CH_2-C5), 31.2 (CH_2-C4), 39.9 (CH_2-C2), 51.8 (CH_3-C15), 55.4 (CH-C14), 70.0 (CH_2-C6), 70.7 (CH_2-C16), 72.7 (CH_2-C7), 75.7 (CH-C3), 113.9 (CH-C9, CH-C13), 117.0 (CH_2-C18), 129.4 (CH-C10, CH-C12), 130.7 (C-C8), 135.1 (C-C17), 159.3 (C-C11), 172.3 (C-C1);

ν_{max} 2953, 2923, 2854, 1737, 1613, 1513, 1458, 1247, 1172, 1097, 1036, 819 cm^{-1};

LRMS (EI) *m/z* (intensity) 322.1 $[M]^+$ (20), 121 (100), 190 (91), 137 (88), 143.1 (86);

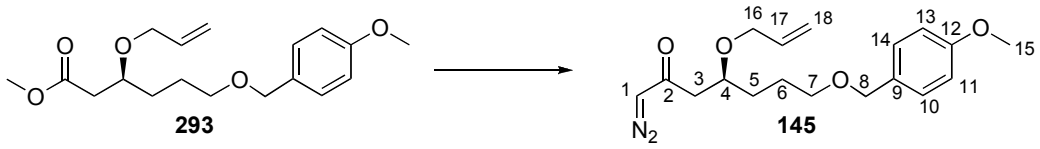
Anal. calcd for $C_{18}H_{26}O_5$: C, 67.06%; H, 8.13%. Found: C, 67.22%; H, 8.25%.

Methyl (*S*)-6-(4-methoxybenzyloxy)-3-(prop-2-en-1-yloxy)hexanoate 293



Tris(dibenzylideneacetone)dipalladium(0) **296** (8.50 mg, 9.28 μmol) and bis(diphenylphosphino)butane **297** (15.4 mg, 36.1 μmol) were dissolved in degassed anhydrous THF (1.0 mL), and allyl ethyl carbonate **298** (180 μL, 1.37 mmol) was added to the solution. To the green mixture was added a degassed solution of the ester **146** (106 mg, 0.34 mmol) in anhydrous THF (2.0 mL) and the mixture was then heated to reflux for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (dichloromethane - methanol, 99.5:0.5) to give the allyl ether **293** (102 mg, 84%) as a colourless oil.

(*S*)-1-Diazo-7-(4-methoxybenzyloxy)-4-(prop-2-en-1-yloxy)heptan-2-one 145



Methyl ester **293** (2.07 g, 6.40 mmol) was dissolved in a mixture of methanol (40 mL) and THF (60 mL). A solution of lithium hydroxide (3.78 g, 157 mmol) in water (25 mL) was added and the resulting mixture was stirred at rt for 1.5 h. The reaction was quenched by the addition of 1 M hydrochloric acid solution (200 mL) and diluted with EtOAc (150 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with a saturated solution of sodium chloride (300 mL) and dried over $MgSO_4$ then concentrated under reduced pressure to give the carboxylic acid **299** (2.02 g), which was used without further purification.

A portion of the carboxylic acid **299** (171 mg, 0.55 mmol) was dissolved in dry ether (6.0 mL) and *i*-butyl chloroformate (80.0 µL, 0.61 mmol) was added. Triethylamine (90 µL, 0.65 mmol) was added carefully to the reaction mixture and it was stirred at rt for 2 h. The resulting suspension was filtered and the filtrate was added directly to a freshly prepared ethereal solution of diazomethane (approximately 5 mmol in 20 mL of diethyl ether) at 0 ºC, with protection of the flask from light. The mixture was stirred at 0 ºC for 2 h and allowed to warm to rt then stirred for 14 h. Glacial acetic acid (0.60 mL, 8.25 mmol) was added dropwise. The excess of acetic acid was neutralised by the addition of a saturated solution of sodium hydrogencarbonate (10 mL) and the phases were separated. The aqueous phase was extracted with ether (2 × 10 mL) and the combined organic phases were washed sequentially with water (10 mL) and a saturated solution of sodium chloride (10 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether - EtOAc, 9:1 to 3:1) to give the diazoketone **145** (151 mg, 85%) as a bright yellow oil. R_f = 0.29 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{27}_{D}$ +19 (*c* = 1.2, $CHCl_3$);

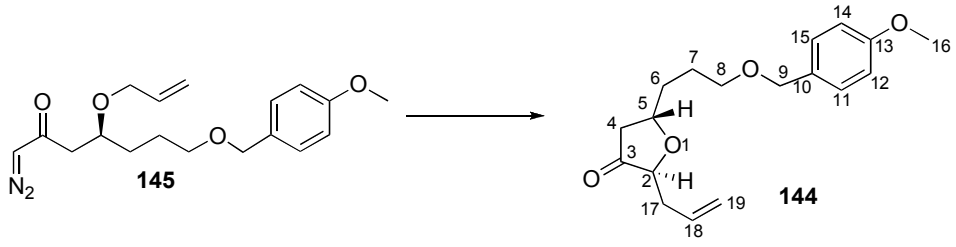
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56–1.75 (4H, m, CH_2-C5, CH_2-C6), 2.37–2.42 (1H, m, CH_2-C3), 2.50–2.60 (1H, m, CH_2-C3), 3.45 (2H, dd, *J* = 6.3, 5.8 Hz, CH_2-C7), 3.80 (3H, s, CH_3-C15), 3.77–3.86 (1H, m, CH-C4), 4.01 (2H, d, *J* = 5.2 Hz, CH_2-C16), 4.42 (2H, s, CH_2-C8), 5.14 (1H, dd, *J* = 10.6, 0.7 Hz, CH_2-C18 *cis*), 5.24 (1H, dd, *J* = 16.9, 0.7 Hz, CH_2-C18 *trans*), 5.33 (1H, brs, CH-C1), 5.87 (1H, ddt, *J* = 16.9, 10.6, 5.2 Hz, CH-C17), 6.87 (2H, d, *J* = 8.8 Hz, CH-C10, CH-C14), 7.23 (2H, d, *J* = 8.8 Hz, CH-C11, CH-C13);

^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6 (CH_2-C6), 31.2 (CH_2-C5), 46.2 (CH_2-C3), 55.4 (CH_3-C15), 55.6 (CH-C1), 70.0 (CH_2-C7), 70.7 (CH_2-C16), 72.7 (CH_2-C8), 76.0 (CH-C4), 113.9 (CH-C10, CH-C14), 117.0 (CH_2-C18), 129.4 (CH-C11, CH-C13), 130.7 (C-C9), 135.0 (CH-C17), 159.3 (C-C12), 193.3 (C-C2);

ν_{max} 2953, 2922, 2855, 2101, 1732, 1638, 1512, 1360, 1246, 1088, 1034, 924, 820 cm^{-1};

LRMS (FAB) *m/z* (intensity) 122 (100), 333.1 $[M+H]^+$ (12), 219 (8); HRMS (FAB) calcd for $C_{18}H_{25}O_4N_2$ $[M+H]^+$ 333.1814, found 333.1817.

(2*S*,5*S*)-5-[3-(4-Methoxybenzyloxy)propyl]-2-(prop-2-en-1-yl)dihydrofuran-3(2*H*)-one 144



Diazoketone **145** (440 mg, 1.32 mmol) in THF (25 mL) was added dropwise to a solution of copper acetylacetonate **180** (72.0 mg, 0.28 mmol) in THF (25 mL) at reflux. The mixture was stirred for 40 min at reflux, cooled to rt and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient from pure petroleum to ether petroleum

ether - EtOAc, 9:1) to give the furanone **144** (361 mg, 90%) as a colourless oil (single stereoisomer as judged by ^{1}H NMR and ^{13}C NMR analyses).

R_f = 0.52 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{28}_{D}$ −16 (*c* = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59–1.83 (4H, m, CH_2-C6, CH_2-C7), 2.22 (1H, dd, *J* = 18.0, 6.8 Hz, CH_2-C4), 2.26–2.37 (1H, m, CH_2-C17), 2.39–2.48 (1H, m, CH_2-C17), 2.55 (1H, dd, *J* = 18.0, 6.9 Hz, CH_2-C4), 3.44–3.52 (2H, m, CH_2-C8), 3.80 (3H, s, CH_3-C16), 4.00 (1H, dd, *J* = 7.2, 4.8 Hz, CH-C2), 4.33–4.40 (1H, m, CH-C5), 4.43 (2H, s, CH_2-C9), 5.11 (1H, d, *J* = 10.1 Hz, CH_2-C19 *cis*), 5.14 (1H, dd, *J* = 17.1, 1.4, CH_2-C19 *trans*), 5.80 (1H, dddd, *J* = 17.1, 10.1, 7.1, 6.8 Hz, CH-C18), 6.87 (2H, d, *J* = 8.5 Hz, CH-C11, CH-C15), 7.25 (2H, d, *J* = 8.5 Hz, CH-C12, CH-C13);

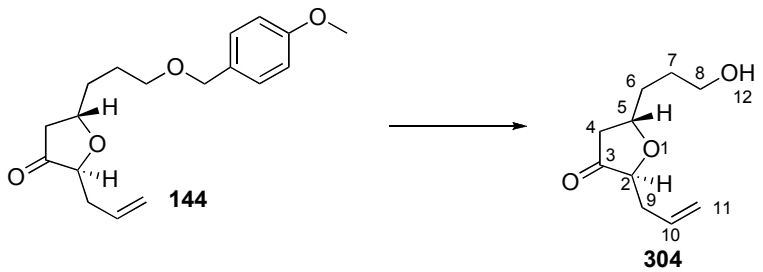
^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (CH_2-C6), 32.4 (CH_2-C7), 35.4 (CH_2-C17), 42.6 (CH_2-C4), 55.4 (CH_3-C16), 69.6 (CH_2-C8), 72.7 (CH_2-C9), 75.5 (CH-C5), 78.7 (CH-C2), 113.9 (CH-C11, CH-C15), 118.3 (CH_2-C19), 129.4 (CH-C12, CH-C14), 130.6 (C-C10), 133.2 (CH-C18), 159.3 (C-C13), 216.3 (C-C3);

ν_{max} 2936, 2917, 2855, 1756, 1729, 1613, 1513, 1249, 1172, 1094, 1034, 821 cm^{-1};

LRMS (EI) *m/z* (intensity) 304.2 $[M]^+$ (15), 121 (100), 137 (100), 190 (39); HRMS (EI) calcd for $C_{18}H_{24}O_4$ $[M]^+$ 304.1675, found 304.1672;

Anal. calcd for $C_{18}H_{24}O_4$: C, 71.03%; H, 7.95%. Found: C, 70.94%; H, 8.06%.

(2*S*,5*S*)-5-(3-Hydroxypropyl)-2-(prop-2-en-1-yl)dihydrofuran-3(2*H*)-one 304



To a solution of DDQ (131 mg, 0.577 mmol) in a 10:1 mixture of dichloromethane and water (13.2 mL) at 0 ºC, the furanone **144** (159 mg, 0.522 mmol) in dichloromethane (2.0 mL) was added in one portion. The reaction mixture was

stirred for 2 h at rt and then washed sequentially with a saturated solution of sodium carbonate (10 mL), water (10 mL) and a saturated solution of sodium chloride (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (petroleum ether - diethyl ether, 2:1 to 1:2) to give the alcohol **304** (89.5 mg, 93%) as a colourless oil.

R_f = 0.18 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{25}_D$ −48 (*c* = 1.1, $CHCl_3$);

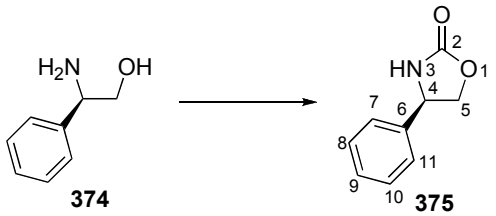
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.83 (4H, m, CH_2-C6, CH_2-C7), 1.97 (1H, brs, -OH), 2.26 (1H, dd, *J* = 18.0, 7.2 Hz, CH_2-C4), 2.30–2.37 (1H, m, CH_2-C9), 2.41–2.48 (1H, m, CH_2-C9), 2.58 (1H, dd, *J* = 18.0, 6.8 Hz, CH_2-C4), 3.69 (2H, m, CH_2-C8), 4.05 (1H, dd, *J* = 7.6, 4.6 Hz, CH-C2), 4.37–4.43 (1H, m, CH-C5), 5.12 (1H, dd, *J* = 10.1, 0.9 Hz, CH_2-C11 *cis*), 5.15 (1H, dd, *J* = 17.0, 1.0 Hz, CH_2-C11 *trans*), 5.81 (1H, ddt, *J* = 17.0, 10.1, 7.2, 6.8, CH-C10);

^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1 (CH_2-C7), 32.5 (CH_2-C6), 35.3 (CH_2-C9), 42.7 (CH_2-C4), 62.6 (CH_2-C8), 75.7 (CH-C5), 78.9 (CH-C2), 118.5 (CH_2-C11), 133.0 (CH-C10), 215.8 (C-C3);

ν_{max} 3406, 2925, 2868, 1754, 1642, 1434, 1173, 1062, 991, 920 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 185.3 $[M+H]^+$ (100), 167 (75), 71 (32); HRMS (CI, *iso*-butane) calcd for $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1178, found 185.1180.

(4*R*)-4-phenyloxazolidin-2-one, 375 [206]



Anhydrous potassium carbonate (0.54 g, 0.36 mmol) was added to a mixture of (*R*)-2-amino-2-phenylethanol **374** (5.00 g, 36.5 mmol) and diethylcarbonate (9.80 mL, 77.0 mmol). The mixture was heated to 135 ºC for 2.5 h. The mixture was allowed to cool to rt and water (50 mL) was added to quench the reaction.

[206] Janey, J. M.; Iwama, T.; Kozmin, A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059-9068.

The aqueous phase was extracted with dichloromethane (2 × 50 mL) and the combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by recrystallisation in diethyl ether to afford the oxazolidinone **375** (5.22 g, 88%) as a colourless crystalline solid.

R_f = 0.52 (diethyl ether);

$[\alpha]^{22}_D$ −46.9 (c = 1.5, $CHCl_3$) {Lit. $[\alpha]^{25}_D$ −48.4 (c = 1.0, $CHCl_3$)};

mp = 127-129 ºC {Lit. 129-131 ºC};

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (1H, dd, *J* = 8.6, 7.0 Hz, CH_2-C5), 4.74 (1H, t, *J* = 8.6 Hz, CH_2-C5), 4.96 (1H, dd, *J* = 8.6, 7.0 Hz, CH-C4), 5.71 (1H, brs, NH), 7.33-7.43 (5H, m, CH-C7, CH-C8, CH-C9, CH-C10, CH-C11);

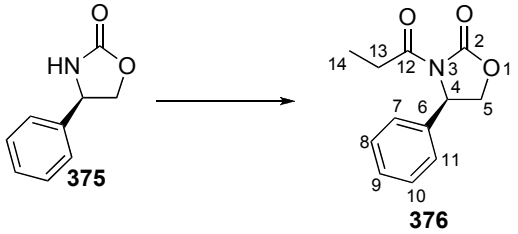
^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7 (CH-C4), 72.9 (CH_2-C5), 126.4 (CH-C7, CH-C11), 129.2 (CH-C9), 129.6 (CH-C8, CH-C10), 139.7 (C-C6), 159.9 (C-C2)

ν_{max} 3240, 1730, 1234, 1026, 924, 694 cm^{-1};

LRMS (EI) *m/z* (intensity) 163.1 $[M]^+$ (61), 105.1 (100), 104.0 (98), 133.0 (95), 161.1 (60); HRMS (EI) calcd for $C_9H_9O_2N$ $[M]^+$ 163.0633, found 163.0631;

Anal. calcd for $C_9H_9O_2N$: C, 66.25%; H, 5.56%; N, 8.58%. Found: C, 66.03%; H, 5.55%; N, 8.53%.

(*R*)-4-Phenyl-3-propionyl-oxazolidin-2-one 376[207]



Oxazolidinone **375** (5.2 g, 32 mmol) was dissolved in dry THF (60 mL) and the resulting solution was cooled to −78 ºC. *n*-Butyl lithium (1.0 mL of a 2.5 M solution in hexanes, 32 mmol) was added dropwise and the mixture was stirred for 30 min. Freshly distilled propionyl chloride (3.0 mL, 34 mmol) was added dropwise and the mixture was kept for 30 min at −78 ºC. The reaction mixture was allowed to warm to rt over 30 min. A saturated solution of ammonium

[207] Chiarotto, I.; Feeney, M. M. M.; Feroci, M.; Inesi, A. *Electrochimica Acta* **2009**, *54*, 1638-1644.

chloride (30 mL) was added and the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed successively with 1 M aqueous sodium hydroxide (30 mL) and a saturated solution of sodium chloride (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by trituration in petroleum ether to afford the oxazolidinone **376** (6.9 g, 99%) as a colourless powder.

R_f = 0.76 (diethyl ether);

$[\alpha]^{25}_D$ −21.5 (c = 10.7, $CHCl_3$) {Lit. $[\alpha]^{20}_D$ −82.8 (c = 0.93, EtOAc)};

mp = 77.5-79.0 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, t, *J* = 7.3 Hz, CH_3-C14), 2.94 (1H, q, *J* = 7.3 Hz, CH_2-C13), 2.96 (1H, q, *J* = 7.3 Hz, CH_2-C13), 4.28 (1H, dd, *J* = 9.0, 3.5 Hz, CH_2-C5), 4.69 (1H, t, *J* = 9.0 Hz, CH_2-C5), 5.42 (1H, dd, *J* = 9.0, 3.5 Hz, CH-C4), 7.29-7.41 (5H, m, CH-C7, CH-C8, CH-C9, CH-C10, CH-C11);

^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6 (CH_3-C14), 29.4 (CH_2-C13), 57.7 (CH-C4), 70.2 (CH_2-C5), 126.1 (CH-C7, CH-C11), 128.9 (CH-C9), 129.4 (CH-C8, CH-C10), 139.3 (C-C6), 153.9 (C-C2), 173.6 (C-C12);

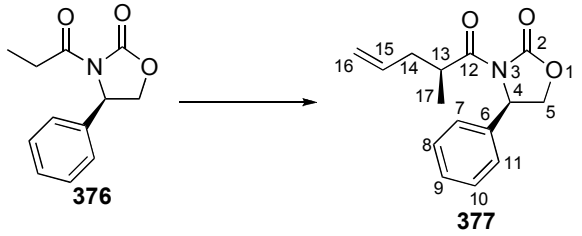
ν_{max} 2972, 1790, 1703, 1367, 1327, 1209, 1064, 939, 752, 700 cm^{-1};

LRMS (EI) *m/z* (intensity) 219.1 $[M]^+$ (10), 82.9 (100), 84.6 (92), 145.0 (30);

HRMS (EI) calcd for $C_{12}H_{13}O_3N$ $[M]^+$ 219.0895, found 219.0898;

Anal. calcd for $C_{12}H_{13}O_3N$: C, 65.74%; H, 5.98%; N, 6.39%. Found: C, 65.75%; H, 6.08%; N, 6.39%.

(*R*)-3-[(*S*)-2-methylpent-4-enoyl]-4-phenyloxazolidin-2-one 377



Oxazolidinone **376** (100 mg, 0.46 mmol) was dissolved in dry THF (1.00 mL) and the resulting solution was cooled to −78 °C. Sodium *bis*(trimethylsilyl)amide (480 μL of a 1 M solution in THF, 0.48 mmol) was added dropwise and the mixture was stirred for 1 h. Freshly distilled allyl iodide (170 μL, 1.38 mmol) was added

dropwise and the mixture was stirred at −78 °C for 4 h. The reaction mixture was allowed to warm to rt over 14 h. Water (1.0 mL) was added and the aqueous layer was extracted by dichloromethane (3 × 2.0 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride (2.0 mL) then dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - ether, 4:1) and then recrystallised (40 °C then −18 °C for two days, petroleum ether - EtOAc, 40:1) to give the oxazolidinone **377** (96.0 mg, 82%) as a colourless crystalline solid.

R_f = 0.18; (petroleum ether – diethyl ether, 1:3);

$[\alpha]^{25}_D$ −61.6 (c = 1.0, $CHCl_3$);

mp = 61.2-62.0 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, *J* = 6.7 Hz, CH_3-C17), 2.06-2.14 (1H, m, CH_2-C14), 2.36-2.43 (1H, m, CH_2-C14), 3.86 (1H, app. q, *J* = 6.7 Hz, CH-C13), 4.27 (1H, dd, *J* = 8.9, 3.9 Hz, CH_2-C5), 4.69 (1H, t, *J* = 8.9 Hz, CH_2-C5), 4.87-4.90 (1H, m, CH_2-C16), 4.91-4.93 (1H, m, CH_2-C16), 5.44 (1H, dd, *J* = 8.9, 3.9 Hz, CH-C4), 5.61 (1H, dddd, *J* = 17.3, 9.7, 7.1, 7.0 Hz, CH-C15), 7.28-7.39 (5H, m, CH-C7, CH-C8, CH-C9, CH-C10, CH-C11);

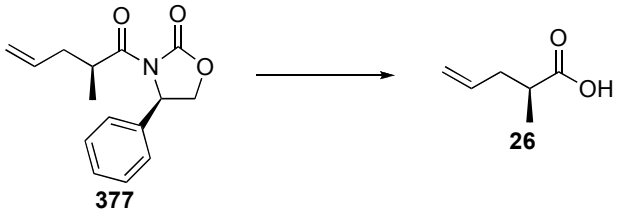
^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3-C17), 37.4 (CH-C13), 38.0 (CH_2-C14), 57.9 (CH-C4), 69.9 (CH_2-C5), 117.4 (CH_2-C16), 126.2 (CH-C7, CH-C11), 128.8 (CH-C9), 129.2 (CH-C8, CH-C10), 135.0 (CH-C15), 139.2 (C-C6), 153.5 (C-C2), 176.2 (C-C12);

ν_{max} 2983, 1776, 1712, 1388, 1330, 1217, 1084, 1062, 995, 927, 765, 700 cm^{-1};

LRMS (EI) *m/z* (intensity) 259.1 $[M]^+$ (32), 82.9 (100), 84.6 (79), 104.1 (47) HRMS (EI) calcd for $C_{15}H_{17}O_3N$ $[M]^+$ 259.1208, found 259.1212;

Anal. calcd for $C_{15}H_{17}O_3N$: C, 69.48%; H, 6.61%; N, 5.40%. Found: C, 69.42%; H, 6.69%; N, 5.53%.

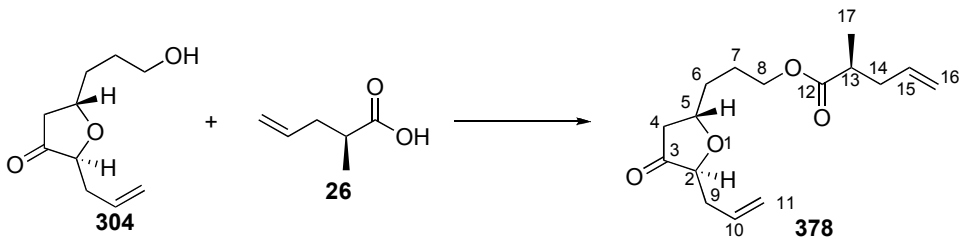
(*S*)-2-Methyl-4-pentenoic acid 26



To a solution of oxazolidinone **377** (388 mg, 1.50 mmol) in a 3:1 mixture of THF and water (10 mL) at 0 ºC, was added slowly hydrogen peroxide (0.80 mL of a 27% w/w solution in water, 5.95 mmol) followed by 2.1 M aqueous lithium hydroxide solution (1.00 mL, 2.10 mmol). The resulting mixture was stirred for one hour at 0 ºC before and the reaction was then quenched by the addition of 1.52 M aqueous sodium sulfite solution (4.30 mL, 6.54 mmol). The pH was adjusted to 12 by the addition of 1 M aqueous sodium hydroxide solution and the mixture was extracted with dichloromethane (3 × 5 mL) to recover the oxazolidinone **375** (238 mg, 98%) as a colourless crystalline solid.

The aqueous phase was acidified (pH = 2) by the addition of 2 M hydrochloric acid solution and the solution was then extracted with EtOAc (3 × 4 mL). The combined organic phases was washed with a saturated solution of sodium chloride (10 mL), then dried over $MgSO_4$ and filtered. The solution was concentrated under reduced pressure to afford the acid **26** (170 mg, 90%) as a colourless oil. The acid was used without further purification.

(*S*)-3-[(2*S*,5*S*)-4-Oxo-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]propyl 2-methylpent-4-enoate 378



N-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide (EDC) (447 mg, 2.88 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (303 mg, 2.48 mmol) were added to a solution of the carboxylic acid **26** (150 mg, 1.31 mmol) and (2*S*,5*S*)-2-allyl-5-(3-hydroxypropyl)dihydrofuran-3(2*H*)-one **304** (146 mg, 0.791 mmol) in dichloromethane (9 mL) at rt. The mixture was stirred for 2 h and the reaction was quenched by the addition of water (3 mL). The reaction mixture was extracted with dichloromethane (3 × 12 mL) and the organic phases were combined, washed with a saturated solution of sodium chloride (12 mL), dried over $MgSO_4$ and filtered. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether - diethyl ether, 9:1 to 4:1) to give the ester **378** (193 mg, 87%) as colourless oil.

R_f = 0.76 (petroleum ether - EtOAc, 3:2);

$[\alpha]^{26}_D$ −27 (*c* = 1.1, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, d, *J* = 6.9 Hz, CH_3-C17), 1.60–1.87 (4H, m, CH_2-C6, CH_2-C7), 2.13–2.21 (1H, m, CH_2-C14), 2.23 (1H, ddd, *J* = 18.0, 6.9, 0.9 Hz, CH_2-C4), 2.29–2.47 (3H, m, CH_2-C9, CH_2-C14), 2.51 (1H, q, *J* = 6.9 Hz, CH-C13), 2.57 (1H, ddd, *J* = 18.0, 6.9, 0.4 Hz, CH_2-C4), 4.01 (1H, dd, *J* = 7.4, 4.7 Hz, CH-C2), 4.11 (2H, t, *J* = 6.2 Hz, CH_2-C8), 4.34–4.41 (1H, m, CH-C5), 5.00–5.08 (2H, m, CH_2-C16), 5.09–5.18 (2H, m, CH_2-C11), 5.74 (1H, ddt, *J* = 17.0, 10.1, 6.9 Hz, CH-C15), 5.81 (1H, ddt, *J* = 17.1, 10.1, 7.0, CH-C10);

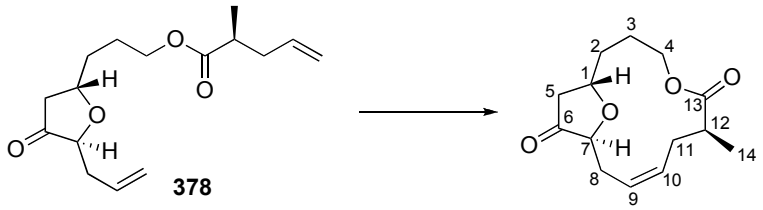
^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 (CH_3-C17), 25.0 (CH_2-C6), 32.1 (CH_2-C7), 35.4 (CH_2-C4), 37.9 (CH_2-C14), 39.4 (CH-C13), 42.5 (CH_2-C9), 63.9 (CH_2-C8), 75.2 (CH-C2), 78.8 (CH-C5), 117.0 (CH_2-C11), 118.4 (CH_2-C16), 133.1 (CH-C15), 135.6 (CH-C10), 176.2 (C-C12), 215.9 (C-C3);

ν_{max} 2975, 2937, 2918, 1756, 1730, 1642, 1177, 1076, 993, 916 cm^{-1};

LRMS (FAB) *m*/*z* (intensity) 281.2 $[M+H]^+$ (22), 69 (100), 73 (93);

HRMS (FAB) calcd for $C_{16}H_{25}O_4$ $[M+H]^+$ 281.1752, found 281.1753.

(1*S*,7*S*,12*S*)-7-Methyl-5,15-dioxabicyclo[10.2.1]pentadec-9-ene-6,13-dione 143



A solution of the diene **378** (79.2 mg, 0.282 mmol) in dry 1,2-dichloroethane (90 mL) was added slowly to a solution of the ruthenium complex **43** (21.1 mg, 24.9 μmol) in dry 1,2-dichloroethane (7 mL) at rt. The mixture was heated to 50 °C for 15 min then cooled to rt, silica (200 mg) was added and the mixture was stirred for 30 min. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether - diethyl ether, 9:1 to 4:1) to give the macrolactone **143** (51.0 mg, 72%) as colourless solid. Recrystallisation from pentane delivered crystals suitable for single X-ray diffraction.

R_f = 0.44 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{21}_D$ −28 (*c* = 1.0, $CHCl_3$);

mp = 73.8-74.8 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, d, *J* = 6.8 Hz, CH_3-C14), 1.70–1.89 (3H, m, CH_2-C2, CH_2-C3), 2.08–2.62 (8H, m, CH_2-C2, CH_2-C5, CH_2-C8, CH_2-C11, CH-C12), 4.04–4.13 (2H, m, CH_2-C4, CH-C7), 4.30–4.38 (1H, m, CH-C1), 4.43 (1H, ddd, *J* = 11.3, 9.9, 1.0 Hz, CH_2-C4), 5.25–5.34 (1H, m, CH-C10), 5.57–5.65 (1H, m, CH-C9);

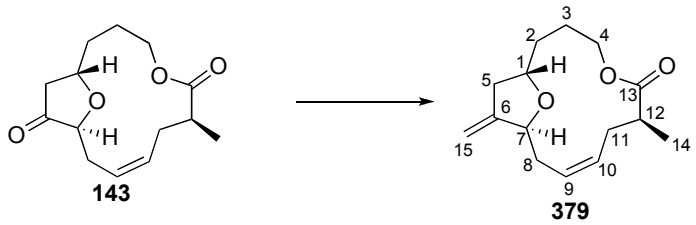
^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5 (CH_3-C14), 24.3 (CH_2-C2), 35.6 (CH_2-C3), 35.9 (CH_2-C8), 38.0 (CH_2-C11), 40.2 (CH_2-C12), 44.1 (CH_2-C5), 66.0 (CH_2-C4), 75.0 (CH-C1), 79.7 (CH-C7), 125.1 (CH-C9), 133.2 (CH-C10), 177.2 (C-C13), 217.4 (C-C6);

ν_{max} 2921, 2850, 1756, 1730, 1260, 1083, 801 cm^{-1};

LRMS (CI, *iso*-butane) *m*/*z* (intensity) 253.4 $[M+H]^+$ (100), 75 (92);

HRMS (CI, *iso*-butane) calcd for $C_{14}H_{21}O_4$ $[M+H]^+$ 253.1440, found 253.1438.

(1*S*,7*S*,12*S*,*Z*)-7-Methyl-13-methylene-5,15-dioxabicyclo[10.2.1]pentadec-9-en-6-one 379



To a suspension of methyltriphenylphosphonium bromide (212 mg, 593 µmol) in dry THF (5.00 mL) at 0 °C was added sodium bis(trimethylsilyl)amide (550 µL of a 1 M solution in THF, 550 µmol) and the mixture was allowed to warm to rt for 1 h. The ketone **143** (25.2 mg, 99.8 µmol) in dry THF (5.0 mL) was added to the solution of the ylide and the yellow mixture was stirred for 1 h at 0 °C. The reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL). The mixture was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with a saturated solution of sodium chloride (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient from pure petroleum ether to petroleum ether - diethyl ether, 9:1) to give the diene **379** (24.5 mg, 98%) as a colourless oil.

R_f = 0.80 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{21}_D$ −51 (*c* = 1.2, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) (~3:1 mixture of conformational isomers)

Major conformational isomer: δ 1.14 (3H, d, *J* = 7.2 Hz, CH_3-C14), 1.56–1.76 (3H, m, CH_2-C2, CH_2-C3), 1.97–2.29 (5H, m, CH_2-C2, CH_2-C5, CH_2-C11), 2.43–2.56 (2H, m, CH_2-C8), 2.57–2.60 (1H, m, CH-C12), 3.88–3.95 (1H, m, CH-C1), 3.96–4.02 (1H, m, CH_2-C4), 4.38–4.44 (1H, m, CH_2-C4), 4.54-4.59 (1H, m, CH-C7), 4.81–4.83 (1H, m, CH_2-C15), 4.99–5.01 (1H, m, CH_2-C15), 5.41–5.57 (2H, m, CH-C9, CH-C10);

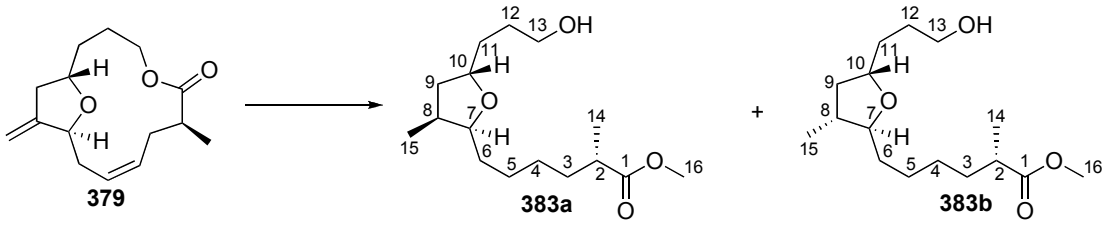
Minor conformational isomer: δ 1.21 (3H, d, *J* = 6.9 Hz, CH_3-C14), 1.56–1.76 (3H, m, CH_2-C2, CH_2-C3), 1.97–2.29 (5H, m, CH_2-C2, CH_2-C5, CH_2-C11), 2.43–2.56 (2H, m, CH_2-C8), 2.61–2.67 (1H, m, CH-C12), 3.88–3.95 (1H, m, CH-C1), 4.05–4.12

(1H, m, CH_2-C4), 4.38–4.44 (1H, m, CH_2-C4), 4.46-4.52 (1H, m, CH-C7), 4.83–4.85 (1H, m, CH_2-C15), 4.96–4.98 (1H, m, CH_2-C15), 5.41–5.57 (2H, m, CH-C9, CH-C10);

^{13}C NMR (100 MHz, $CDCl_3$) (~3:1 mixture of conformational isomers)
Major conformational isomer: δ 18.5 (CH_3-C14), 25.1 (CH_2-C2), 34.8 (CH_2-C3), 38.3 (CH_2-C5), 38.8 (CH_2-C8), 40.3 (CH-C12), 40.7 (CH_2-C11), 65.8 (CH_2-C4), 75.9 (CH-C1), 79.0 (CH-C7), 104.5 (CH_2-C15), 126.4 (CH-C10), 131.6 (CH-C9), 151.4 (C-C6), 177.3 (C-C13);

Minor conformational isomer: 18.4 (CH_3-C14), 25.7 (CH_2-C2), 31.8 (CH_2-C5), 34.0 (CH_2-C11), 35.4 (CH_2-C3), 40.6 (CH_2-C8), 41.4 (CH-C12), 66.4 (CH_2-C4), 75.3 (CH-C1), 79.9 (CH-C7), 104.3 (CH_2-C15), 127.4 (CH-C10), 128.9 (CH-C9), 152.3 (C-C6), 175.8 (C-C13);
ν_{max} 2954, 2924, 2898, 2853, 1730, 1463, 1188, 968 cm^{-1};
LRMS (CI, *iso*-butane) *m/z* (intensity) 251.4 $[M+H]^+$ (28), 75 (100), 81 (45);
HRMS (CI, *iso*-butane) calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1652.

Methyl (*S*)-6-[(2*S*,3*S*,5*S*)-5-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-yl]-2-methyl-hexanoate 383a and methyl (*S*)-6-[(2*S*,3*R*,5*S*)-5-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-yl]-2-methylhexanoate 383b



To a solution of alkene **379** (40 mg, 160 μmol) in dry toluene (6.0 mL) was added chlorotris(triphenylphosphine) rhodium(I) (Wilkinson's catalyst **380**) (26 mg, 28 μmol) at rt. The atmosphere was purged twice with hydrogen and the mixture was stirred for 6 h at rt under an atmosphere of hydrogen. The mixture was filtered through a short pad of silica (petroleum ether-diethyl ether, 4:1) and

the solvent was removed under reduced pressure to give the crude reduced lactone **381** as a pale yellow oil. R_f = 0.81 (petroleum ether-diethyl ether, 1:3).
Sodium in mineral oil (~10 mg, ~420 μmol) was added to dry methanol (4.0 mL) at 0 ºC and the resulting mixture was kept at 0 ºC until no further gas evolution was observed. The reduced lactone **381** was dissolved in a 2:1 mixture of methanol and THF (6.0 mL) and added to the solution of sodium methoxide. The mixture was heated at 60 ºC for 2 h and the reaction was quenched by the addition of a saturated solution of ammonium chloride (20 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic phases were washed with a saturated solution of sodium chloride (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 73:27) to give the esters **383a** (28.7 mg, 63%) and **383b** (7.6 mg, 14%) as colourless oils.
Data for **383a**: R_f = 0.18 (petroleum ether - diethyl ether, 1:3);
$[\alpha]^{24}_D$ +5.5 (*c* = 1.2, $CHCl_3$);
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.0 Hz, CH_3-C15), 1.13 (3H, d, *J* = 7.0 Hz, CH_3-C14), 1.21–1.77 (14H, m, CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C9, CH_2-C11, CH_2-C12), 2.17–2.27 (1H, m, CH-C8), 2.43 (1H, app. dq, *J* = 13.8, 7.0 Hz, CH-C2), 2.94 (1H, br s, OH), 3.57–3.72 (2H, m, CH_2-C13), 3.66 (3H, s, CH_3-C16), 3.84–3.89 (1H, m, CH-C7), 4.07 (1H, app. qd, *J* = 7.8, 3.6 Hz, CH-C10);
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3-C15), 17.2 (CH_3-C14), 26.7 (CH_2-C11), 27.6 (CH_2-C12), 30.3 (CH_2-C6), 30.5 (CH_2-C4) 33.9 (CH_2-C5), 34.3 (CH_2-C3), 36.1 (CH-C8), 39.6 (CH-C2), 40.5 (CH_2-C9), 51.6 (CH_3-C16), 63.2 (CH_2-C13), 77.0 (CH-C10), 81.4 (CH-C7), 177.5 (C-C1);
ν_{max} 3358, 2955, 2924, 2855, 2363, 1715, 1456, 1317 cm^{-1};
LRMS (CI, *iso*-butane) *m/z* (intensity) 287.5 $[M+H]^+$ (55), 69 (100), 81 (76); HRMS (CI, *iso*-butane) calcd for $C_{16}H_{31}O_4$ $[M+H]^+$ 287.2222, found 287.2220.

Data for **383b**: R_f = 0.18 (petroleum ether - diethyl ether, 1:3);
$[\alpha]^{24}_D$ −5.1 (*c* = 1.1, $CHCl_3$);
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, d, *J* = 7.0 Hz, CH_3-C15), 1.13 (3H, d, *J* = 7.0 Hz, CH_3-C14), 1.17–1.74 (13H, m, CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C9, CH_2-C11, CH_2-C12), 1.81–1.89 (1H, m, CH-C8), 2.11–2.17 (1H, m, CH_2-C9), 2.43 (1H,

app. dq, *J* = 13.8, 7.0 Hz, CH-C2), 3.15 (1H, br s, OH), 3.42 (1H, td, *J* = 8.2, 3.2 Hz, CH-C7), 3.58–3.69 (2H, m, CH_2-C13), 3.66 (3H, s, CH_3-C16), 3.91-3.97 (1H, m, CH-C10);

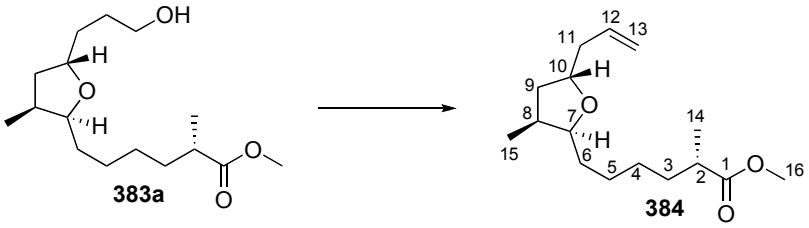
^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0 (CH_3-C15), 17.2 (CH_3-C14), 26.5 (CH_2-C11), 27.5 (CH_2-C12), 30.2 (CH_2-C6), 30.3 (CH_2-C4), 33.8 (CH_2-C5), 34.3 (CH_2-C3), 39.6 (CH-C2), 40.1 (CH-C8), 42.0 (CH_2-C9), 51.6 (CH_3-C16), 63.1 (CH_2-C13), 78.4 (CH-C10), 85.4 (CH-C7), 177.5 (C-C1);

ν_{max} 3379, 2932, 2862, 2337, 1735, 1458, 1373 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 287.4 $[M+H]^+$ (72), 121.2 (100), 73.1 (58);

HRMS (CI, *iso*-butane) calcd for $C_{16}H_{31}O_4$ $[M+H]^+$ 287.2222, found 287.2224.

Methyl (S)-6-[(2S,3S,5S)-3-methyl-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]-2-methylhexanoate 384



2-Nitrophenyl selenocyanate (88 mg, 0.39 mmol) and alcohol **383a** (40 mg, 0.14 mmol) were dissolved in degassed THF (2.0 mL) followed by addition of *n*-tributylphosphine (93 µL, 0.34 mmol). The solution was stirred at room temperature for 2 h then the resulting brown mixture was quenched by the addition of water (10 mL). The solution was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with a saturated solution of sodium chloride (10 mL) and dried over $MgSO_4$. The organic solution was concentrated under reduced pressure and the residue was diluted in THF (1.0 mL) and cooled to 0 ºC. To this solution was added hydrogen peroxide (0.20 mL of a 27% solution in water, 1.60 mmol) and the mixture was stirred for 2 h at room temperature. The mixture was diluted with water (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with a saturated solution of sodium chloride (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. Purification

by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) gave the alkene **384** (31.1 mg, 77%) as a pale yellow oil.

R_f = 0.93 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{25}_D$ +1.8 (*c* = 1.1, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.1 Hz, CH_3-C15), 1.14 (3H, d, *J* = 7.0 Hz, CH_3-C14), 1.23–1.50 (7H, m, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C9), 1.60–1.79 (3H, m, CH_2-C3, CH_2-C9), 2.15–2.24 (2H, m, CH-C8, CH_2-C11), 2.29–2.37 (1H, m, CH_2-C11), 2.43 (1H, app. dq, *J* = 13.7, 7.0 Hz, CH-C2), 3.66 (3H, s, CH_3-C16), 3.83 (1H, dt, *J* = 7.9, 5.1 Hz, CH-C7), 4.10 (1H, tt, *J* = 6.8, 6.8 Hz, CH-C10), 5.02–5.10 (2H, m, CH_2-C13), 5.80 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, CH-C12);

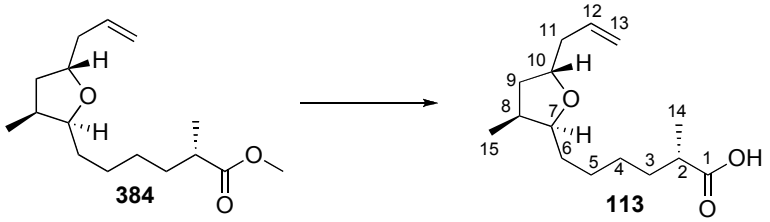
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3-C15), 17.2 (CH_3-C14), 26.7 (CH_2-C6), 27.6 (CH_2-C4), 30.4 (CH_2-C3), 33.9 (CH_2-C5), 36.0 (CH-C8), 39.4 (CH_2-C11), 39.5 (CH-C2), 41.2 (CH_2-C9), 51.6 (CH_3-C16), 76.1 (CH-C10), 81.4 (CH-C7), 116.9 (CH_2-C13), 135.2 (CH-C12), 177.5 (C-C1);

ν_{max} 2937, 2875, 2860, 1739, 1462, 1198, 1164, 913 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 269.5 $[M+H]^+$ (18), 89 (100), 69 (76);

HRMS (CI, *iso*-butane) calcd for $C_{16}H_{29}O_3$ $[M+H]^+$ 269.2117, found 269.2119.

(S)-6-[(2S,3S,5S)-3-Methyl-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]-2-methylhexanoic acid 113



Methyl ester **384** (71 mg, 0.26 mmol) was diluted in a 3:2 mixture of THF and methanol (5.0 mL). A solution of lithium hydroxide (300 mg, 11.1 mmol) in water (2.50 mL) was added and the resultant mixture was stirred at rt for 1.5 h. The reaction was quenched by addition of 1 M hydrochloric acid solution (10 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases

were washed with a saturated solution of sodium chloride (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the carboxylic acid **113** (67 mg, 99%) as a colourless oil, which was used in subsequent reactions without further purification.

R_f = 0.53 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{28}_D$ +10.2 (*c* = 3.1, CH_2Cl_2) {Lit.[14] $[\alpha]^{23}_D$ +8.4 (*c* = 4.5, CH_2Cl_2)};

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.0 Hz, CH_3-C15), 1.17 (3H, d, *J* = 7.0 Hz, CH_3-C14), 1.27–1.52 (7H, m, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C9), 1.66–1.80 (3H, m, CH_2-C3, CH_2-C9), 2.16–2.25 (2H, m, CH-C8, CH_2-C11), 2.33 (1H, ddd, *J* = 13.8, 7.0, 5.9 Hz, CH_2-C11), 2.46 (1H, app. dq, *J* = 13.8, 7.0 Hz, CH-C2), 3.85 (1H, dt, *J* = 7.9, 5.1 Hz, CH-C7), 4.11 (1H, app. tt, *J* = 7.0, 6.8 Hz, CH-C10), 5.01–5.10 (2H, m, CH_2-C13), 5.78 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, CH-C12);

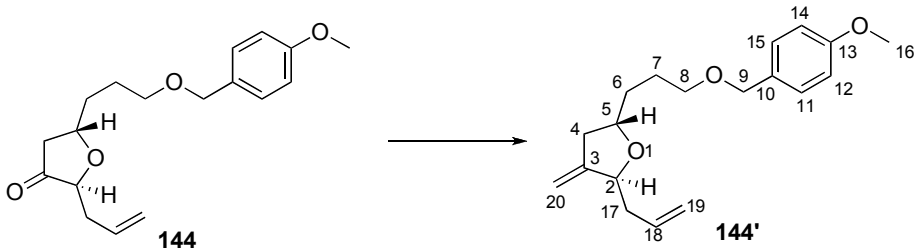
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3-C15), 17.0 (CH_3-C14), 26.6 (CH_2-C6), 27.5 (CH_2-C4), 30.4 (CH_2-C3), 33.6 (CH_2-C5), 36.0 (CH-C8), 39.3 (CH_2-C11), 39.4 (CH-C2), 41.1 (CH_2-C9), 76.2 (CH-C10), 81.4 (CH_2-C7), 116.9 (CH_2-C13), 135.2 (CH-C12), 182.2 (C-C1);

ν_{max} 2932, 2862, 1735, 1705, 1643, 1458, 1180, 918 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 255.4 $[M+H]^+$ (68), 75 (100), 81 (32);

HRMS (CI, *iso*-butane) calcd for $C_{15}H_{27}O_3$ $[M+H]^+$ 255.1960, found 255.1958.

(2*S*,5*S*)-5-[3-(4-Methoxybenzyloxy)propyl]-3-methylene-2-(prop-2-en-1-yl)tetrahydrofuran 144'



Methyltriphenylphosphonium bromide (4.40 g, 13.0 mmol) was suspended in dry THF (125 mL) and the solution was cooled to 0 ºC. Sodium bis(trimethylsilyl)amide (12.0 mL of a 1 M solution in THF, 12.0 mmol) was

added and the mixture was allowed to warm to rt for 1 h. A solution of the dihydrofuranone **144** (0.81 g, 2.7 mmol) in dry THF (100 mL) was added to the solution of the ylide and the yellow mixture was stirred for 1 h at 0 ºC. The reaction was quenched by the addition of a saturated solution of ammonium chloride (100 mL) and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 9:1) to give the diene **144'** (0.79 g, 98%) as a colourless oil.

R_f = 0.43 (petroleum ether - diethyl ether, 3:1);

$[\alpha]^{25}_D$ −55 (*c* = 0.95, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.76 (4H, m, CH_2-C6, CH_2-C7), 2.24–2.36 (3H, m, CH_2-C4, CH_2-C17), 2.66 (1H, ddtd, *J* = 15.5, 6.5, 2.0, 1.8 Hz, CH_2-C4), 3.43–3.51 (2H, m, CH_2-C8), 3.81 (3H, s, CH_3-C16), 4.06 (1H, tt, *J* = 6.5, 6.3 Hz, CH-C5), 4.43-4.47 (3H, m, CH-C2, CH_2-C9), 4.87 (1H, dt, *J* = 2.1, 2.1 Hz, CH_2-C20), 5.00 (1H, dt, *J* = 2.1, 2.1 Hz, CH_2-C20), 5.08 (1H, ddt, *J* = 10.2, 2.1, 1.1 Hz, CH_2-C19 *cis*), 5.12 (1H, ddt, *J* = 17.2, 2.1, 1.5 Hz, CH_2-C19 *trans*), 5.87 (1H, ddt, *J* = 17.2, 10.2, 6.9 Hz, CH-C18), 6.88 (2H, d, *J* = 8.7 Hz, CH-C11, CH-C15), 7.26 (2H, d, *J* = 8.1 Hz, CH-C12, CH-C14);

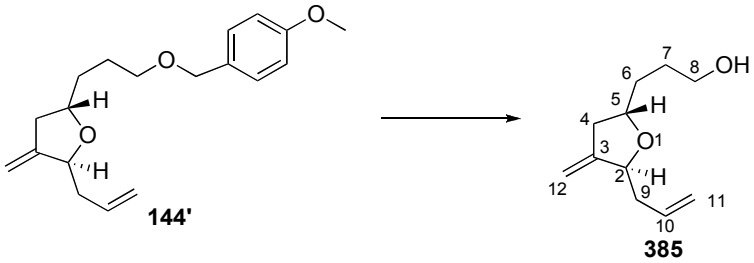
^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3 (CH_2-C6), 31.9 (CH_2-C7), 38.8 (CH_2-C4), 40.0 (CH_2-C17), 55.4 (CH_3-C16), 70.0 (CH_2-C8), 72.6 (CH_2-C9), 77.4 (CH-C5), 79.2 (CH-C2), 105.2 (CH_2-C20), 113.9 (CH-C11, CH-C15), 117.1 (CH_2-C19), 129.3 (CH-C12, CH-C14), 130.8 (C-C10), 134.9 (CH-C18), 151.3 (C-C3), 159.2 (C-C13);

ν_{max} 2933, 2854, 1612, 1512, 1440, 1246, 1172, 1094, 1036, 820 cm^{-1};

LRMS (EI) *m/z* (intensity) 302.2 $[M]^+$ (5), 121.1 (100), 82.9 (35);

HRMS (EI) calcd for $C_{19}H_{26}O_3$ $[M]^+$ 302.1880, found 302.1882.

(2S,5S)-5-(3-Hydroxypropyl)-3-methylene-2-(prop-2-en-1-yl)tetrahydrofuran 385



To a solution of DDQ (793 mg, 3.49 mmol) in a 10:1 mixture of dichloromethane and water (82.5 mL) at 0 ºC, the diene **144'** (960 mg, 3.17 mmol) in dichloromethane (5.0 mL) was added in one portion. The reaction mixture was stirred for 2 h at rt and then washed sequentially with saturated sodium carbonate solution (50 mL), water (50 mL) and a saturated solution of sodium chloride (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a residue which was purified by flash chromatography on silica gel (petroleum ether - diethyl ether, 2:1 to 1:2) to give the alcohol **385** (471 mg, 81%) as a colourless oil.

R_f = 0.45 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{25}_D$ −53.6 (*c* = 1.00, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56–1.70 (4H, m, CH_2-C6, CH_2-C7), 2.25–2.35 (3H, m CH_2-C4, CH_2-C9), 2.61–2.63 (1H, m, -OH), 2.67 (1H, ddtd, *J* = 15.5, 8.3, 2.0, 1.8 Hz, CH_2-C4), 3.60–3.69 (2H, m, CH_2-C8), 4.04–4.10 (1H, m, CH-C5), 4.46–4.50 (1H, m, CH-C2), 4.86 (1H, dt, *J* = 2.2, 2.0 Hz, CH_2-C12), 5.00 (1H, dt, *J* = 2.2, 2.0 Hz, CH_2-C12), 5.07 (1H, ddt, *J* = 10.2, 2.0, 1.1 Hz, CH_2-C11 *cis*), 5.11 (1H, ddt, *J* = 17.1, 1.9, 1.6 Hz, CH_2-C11 *trans*), 5.84 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, CH-C10);

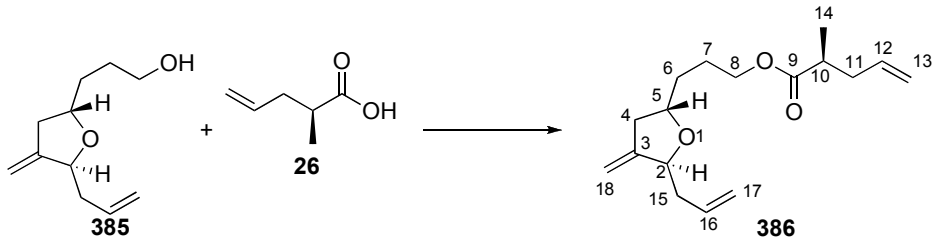
^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1 (CH_2-C6), 32.7 (CH_2-C7), 39.3 (CH_2-C4), 40.1 (CH_2-C9), 63.2 (CH_2-C8), 77.9 (CH-C5), 79.8 (CH-C2), 105.6 (CH_2-C12), 117.6 (CH_2-C11), 134.9 (CH-C10), 151.0 (C-C3);

ν_{max} 3356, 2933, 1714, 1641, 1433, 1375, 1238, 1110, 1056, 995, 914 cm^{-1};

LRMS (CI, *iso*-butane) *m*/*z* (intensity) 183.3 $[M+H]^+$ (100), 121.1 (100), 71.1 (35);

HRMS (*iso*-butane) calcd for $C_{11}H_{19}O_2$ $[M+H]^+$ 183.1387, found 183.1385.

(*S*)-3-[(2*S*,5*S*)-4-Methylene-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]propyl 2-methylpent-4-enoate 386



N-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDC) (1.10 g, 7.1 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (0.70 mg, 5.7 mmol) were added to a solution of the carboxylic acid **26** (0.34 g, 2.3 mmol) and alcohol **385** (0.33 g, 1.9 mmol) in dichloromethane (17 mL) at rt. The mixture was stirred for 1.5 h and quenched with water (5 mL). The solution was extracted with dichloromethane (3 × 10 mL) and the organic phases were combined, washed with a saturated solution of sodium chloride (20 mL), dried over $MgSO_4$ and filtered. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether then petroleum ether - diethyl ether, 19:1) to give the ester **386** (0.51 g, 98%) as colourless oil.

R_f = 0.62 (petroleum ether - diethyl ether, 9:1);

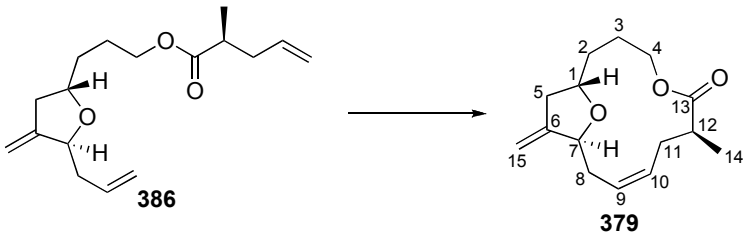
$[\alpha]^{26}_D$ −23 (*c* = 1.2, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, d, *J* = 7.0 Hz, CH_3-C14), 1.44–1.80 (4H, m, CH_2-C6, CH_2-C7), 2.12–2.20 (1H, m, CH_2-C11), 2.22–2.28 (1H, m, CH_2-C4), 2.30–2.36 (2H, m, CH_2-C15), 2.4 (1H, ddt, *J* = 14.1, 7.0, 1.2 Hz, CH_2-C11), 2.50 (1H, qt, *J* = 7.0, 6.9 Hz, CH-C10), 2.67 (1H, ddtd, *J* = 15.5, 6.2, 2.0, 1.9 Hz, CH_2-C4), 4.02–4.09 (3H, m, CH-C2, CH_2-C8), 4.42–4.45 (1H, m, CH-C5), 4.87 (1H, dt, *J* = 2.2, 2.2 Hz, CH_2-C18), 4.99–5.13 (5H, m, CH_2-C13, CH_2-C17, CH_2-C18), 5.73 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, CH-C12), 5.85 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, CH-C16);

^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7 (CH_3-C14), 25.4 (CH_2-C6), 31.7 (CH_2-C7), 37.9 (CH_2-C11), 38.8 (CH_2-C4), 39.4 (CH-C10), 40.0 (CH_2-C15), 64.3 (CH_2-C8), 77.1 (CH-C5), 79.3 (CH_2-C2), 105.4 (CH_2-C18), 117.0 (CH_2-C13), 117.2 (CH_2-C17), 134.8 (CH-C16), 135.7 (CH-C12), 151.0 (C-C3), 176.2 (C-C9);

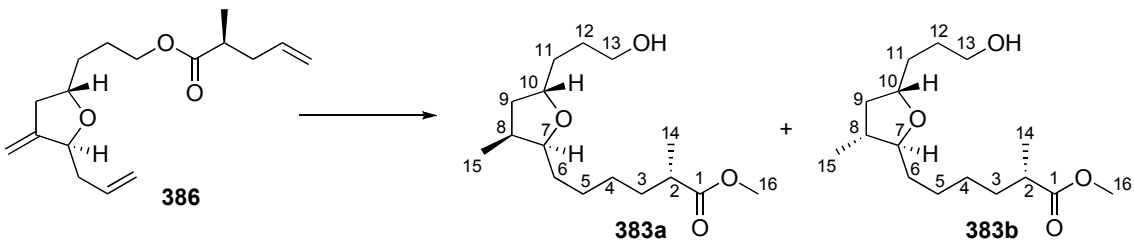
ν_{max} 2978, 2935, 2914, 1733, 1641, 1460, 1239, 1179, 1069, 991, 912 cm^{-1};
LRMS (CI, *iso*-butane) *m/z* (intensity) 279.4 $[M+H]^+$ (40), 69.1 (100), 85.2 (87);
HRMS (CI, *iso*-butane) calcd for $C_{17}H_{27}O_3$ $[M+H]^+$ 279.1958, found 279.1960.

(1*S*,7*S*,12*S*,*Z*)-7-Methyl-13-methylene-5,15-dioxabicyclo-[10.2.1]pentadec-9-en-6-one 379



A solution of the triene **389** (20.1 mg, 72.2 µmol) in dry 1,2-dichloroethane (10 mL) was added slowly to a solution of the ruthenium complex **43** (3.0 mg, 3.5 µmol) in dry 1,2-dichloroethane (2.0 mL) at reflux. Three extra portions of complex **43** (3 × 3.0 mg, 3 × 3.5 µmol) were added every two hours and the mixture was stirred at reflux for 14 hours. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient from pure petroleum ether - diethyl ether, 9:1 to 4:1) to give the macrolactone **379** (15.1 mg, 84%) as a colourless oil.
Analytical data match those of macrolactone **379**.

Methyl (*S*)-6-[(2*S*,3*S*,5*S*)-5-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-yl]-2-methyl-hexanoate 383a and methyl (*S*)-6-[(2*S*,3*R*,5*S*)-5-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-yl]-2-methylhexanoate 383b



A solution of the triene **386** (21.0 mg, 72.2 µmol) in dry 1,2-dichloroethane (10 mL) was added slowly to a solution of the ruthenium complex **339** (Hoveyda Grubbs 2 catalyst) (4.5 mg, 7.2 µmol) in dry 1,2-dichloroethane (2 mL) at rt. The

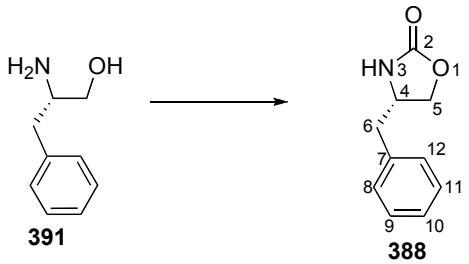
mixture was heated to reflux and stirred at this temperature for 45 min. The mixture was transferred by cannula to a hydrogenation autoclave and this was then purged three times with hydrogen. The reaction mixture was stirred at 70 ºC under hydrogen (100 PSI) for 14 h and then cooled to room temperature. The mixture was filtered through a short pad of silica (petroleum ether-diethyl ether, 95:5) and the solvent was evaporated under reduced pressure to give the crude lactone **381** as a pale yellow oil.

R_f = 0.81 (petroleum ether-diethyl ether, 1:3).

Sodium in mineral oil (~5 mg, ~210 µmol) was added to dry methanol (2.0 mL) at 0 ºC and the resulting mixture was kept at 0 ºC until no further gas evolution was observed. The reduced lactone **381** was dissolved in a mixture of methanol (1.0 mL) and THF (2.0 mL) and then added to the solution of sodium methoxide. The reaction mixture was heated for 1 h at 60 ºC and then quenched by the addition of a saturated solution of ammonium chloride (10 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL) and then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 73:27) to give a 4:1 mixture of the esters **383a** and **383b** (13.2 mg, 64%) as a colourless oil.

Spectroscopic data match those for esters **383a** and **383b**.

(S)-4-Benzyl-oxazolidin-2-one 388



Anhydrous potassium carbonate (0.98 g, 6.6 mmol) was added to a mixture of L-phenylalaninol **391** (10 g, 66 mmol) and diethylcarbonate (17.0 mL, 133 mmol). The mixture was heated to 135 ºC for 2.5 h. The mixture was allowed to cool to rt and water (50 mL) was added to quench the reaction. The aqueous phase was extracted with dichloromethane (2 × 50 mL) and the combined organic layer was

dried over $MgSO_4$, filtered, concentrated under reduced pressure. The solid residue was purified by recrystallisation from diethyl ether to afford the oxazolidinone **388** (11.2 g, 96%) as a colourless crystalline solid.

R_f = 0.12 (petroleum ether-diethyl ether, 1:3);

$[\alpha]^{21}_D$ −55.0 (c = 1.25, $CHCl_3$) {Lit.[208] $[\alpha]^{25}_D$ −62 (c = 1.0, $CHCl_3$)};

mp = 85.1-86.0 °C {Lit.[164] 84.5-86.5 °C};

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90-3.00 (2H, m, CH_2-C6), 4.13-4.22 (1H, m, CH-C4), 4.22 (1H, ddd, *J* = 8.1, 5.6, 1.5 Hz, CH_2-C5), 4.74 (1H, ddd, *J* = 8.1, 8.1, 4.0 Hz, CH_2-C5), 5.96 (1H, brs, NH), 7.24-7.43 (5H, m, CH-C8, CH-C9, CH-C10, CH-C11, CH-C12);

^{13}C NMR (100 MHz, $CDCl_3$) δ 41.5 (CH_2-C6), 53.9 (CH-C4), 69.7 (CH_2-C5), 127.3 (CH-C8, CH-C12), 129.1 (CH-C9, CH-C11), 129.1 (CH-C10), 136.0 (C-C7), 159.5 (C-C2);

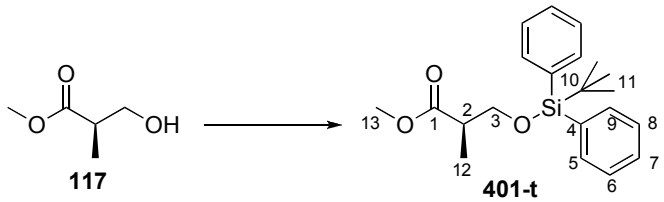
ν_{max} 3271, 1743, 1705, 1242, 1018, 941, 617 cm^{-1};

LRMS (EI) *m/z* (intensity) 177.1 $[M]^+$, 128.0, 117.0, 104.1;

HRMS (EI) calcd for $C_{10}H_{11}O_2N$ $[M]^+$ 177.0790, found 177.0789;

Anal. calcd for $C_{10}H_{11}O_2N$: C, 67.78%; H, 6.26%; N, 7.90%. Found: C, 67.72%; H, 6.26%; N, 7.89%.

Methyl (*R*)-3-(*tert*-butyl-diphenyl-silanyloxy)-2-methyl-propionoate 401-t



To a solution of hydroxyester **117** (1.00 g, 8.41 mmol) in DMF (15 mL) was added sequentially DMAP (0.20 g, 1.6 mmol), imidazole (0.69 g, 10 mmol) then *t*-butyldiphenylsilyl chloride (2.36 mL, 9.19 mmol) at 0 °C and the resulting mixture was allowed to warm to rt over 14h. The reaction was quenched by the addition of a solution of 1 M hydrochloric acid (5 mL), and the mixture was diluted with diethyl ether (10 mL). The phases were separated and the organic

[208] Pridgen, L. N.; Prol, J., Jr.; Alexander, B.; Gillyard, L. *J. Org. Chem.* **1989**, *54*, 13, 3231-3233.

phase was washed with a saturated aqueous solution of sodium hydrogencarbonate (3 × 10 mL) and a saturated aqueous solution of sodium chloride (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) to yield the ester **401-t** (2.90 g, 97%) as a colourless oil. R_f = 0.72 (petroleum ether - diethyl ether, 2:1);

$[\alpha]^{26}_D$ −15.9 (c = 1.0, $CHCl_3$), {Lit.[209] $[\alpha]^{22}_D$ −11.0 (c = 1.1, $CHCl_3$)};

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (9H, s, CH_3-C11), 1.15 (3H, d, *J* = 7.0 Hz, CH_3-C12), 2.71 (1H, qdd, *J* = 7.0, 7.0, 5.8 Hz, CH-C2), 3.68 (3H, s, CH_3-C13), 3.72 (1H, dd, *J* = 9.8, 5.8 Hz, CH_2-C3), 3.82 (1H, dd, *J* = 9.8, 7.0 Hz, CH_2-C3), 7.37-7.45 (6H, m, CH-C6, CH-C7, CH-C8), 7.64-7.66 (4H, m, CH-C5, CH-C9);

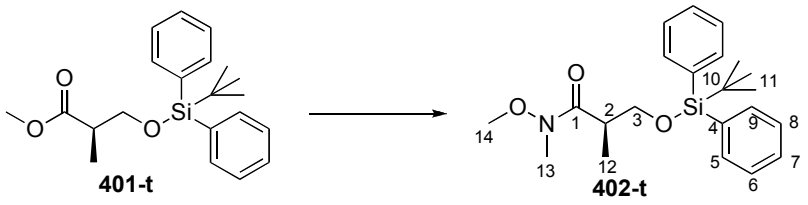
^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6 (CH_3-C12), 19.4 (C-C10), 26.8 (CH_3-C11), 42.5 (CH-C2), 51.7 (CH_3-C13), 66.0 (CH_2-C3), 127.8 (CH-C6, CH-C8), 129.8 (CH-C7), 133.6 (C-C4), 135.7 (CH-C5, CH-C9), 175.5 (C-C1);

ν_{max} 2947, 1744, 1466, 1427, 1258, 1196, 1111, 1026, 702 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 357.4 $[M+H]^+$ (12), 279.4 (100), 75.2 (46);

HRMS (CI, *iso*-butane) calcd for $C_{21}H_{29}O_3Si$ $[M+H]^+$ 357.1886, found 357.1888.

_N_-Methoxy-_N'_-methyl-(_R_)-3-(_tert_-butyl-diphenyl-silanyloxy)-2-methyl-propionamide 402-t



To a solution of *N,O*-dimethylhydroxylamine hydrochloride (1.18 g, 12.1 mmol) and ester **401-t** (2.60 g, 7.28 mmol) in THF (7 mL) at −15 °C was added dropwise *iso*-propylmagnesium bromide (11.3 mL of a 2 M solution in THF, 22.6 mmol) and the mixture was allowed to warm to rt over 1 h. The reaction was quenched by

[209] Clough, J. M.; Dube, H.; Martin, B. J.; Pattenden, G.; Reddy, K. S.; Waldron, Ian R. *Org. Biomol. Chem.* **2006**, *4*, 2906-2911.

the addition of a saturated solution of ammonium chloride (10 mL) and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 3:1) to give the Weinreb amide **402-t** (2.72 g, 96%) as a colourless crystalline solid.

R_f = 0.61 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{23}_D$ −19.2 (c = 1.1, $CHCl_3$);

mp = 53.6-55.1 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (9H, s, CH_3-C11), 1.08 (3H, d, *J* = 6.9 Hz, CH_3-C12), 3.17-3.24 (4H, m, CH-C2, CH_3-C13), 3.59 (1H, dd, *J* = 9.4, 6.3 Hz, CH_2-C3), 3.66 (3H, s, CH_3-C14), 3.93 (1H, dd, *J* = 9.4, 8.1 Hz, CH_2-C3), 7.36-7.43 (6H, m, CH-C6, CH-C7, CH-C8), 7.65-7.68 (4H, m, CH-C5, CH-C9);

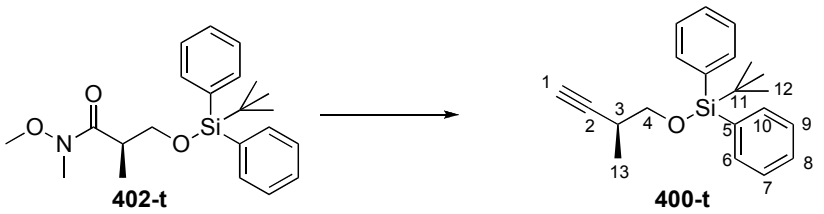
^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8 (CH_3-C12), 19.2 (C-C10), 26.8 (CH_3-C11), 32.1 (CH_3-C13), 38.0 (CH-C2), 61.9 (CH_3-C14), 66.3 (CH_2-C3), 127.6 (CH-C6, CH-C8), 129.6 (CH-C7), 133.8 (C-C4), 135.7 (CH-C5, CH-C9), 175.0 (C-C1);

ν_{max} 2961, 2937, 2357, 1661, 1471, 1427, 1111, 997, 702 cm^{-1};

LRMS (CI, *iso*-butane) *m*/*z* (intensity) 386.4 $[M+H]^+$ (92), 308.4 (100), 328.3 (49);

HRMS (CI, *iso*-butane) calcd for $C_{22}H_{32}O_3NSi$ $[M+H]^+$ 386.2151, found 386.2155.

tert-Butyl-[(*S*)-2-methyl-but-3-ynyloxy]-diphenyl-silane 400-t



402-t **400-t**

Diisobutylaluminium hydride (7.0 mL of a 1 M solution in toluene, 7.0 mmol) was added over 10 min to the Weinreb amide **402-t** (2.29 g, 6.39 mmol) in THF (25 mL) at −78 °C and the mixture was stirred at this temperature for 1 h. The reaction was quenched carefully by the addition of methanol (3 mL) and the resulting mixture was stirred for 15 min and then allowed to warm to 0 °C. A

saturated aqueous solution of potassium sodium tartrate (40 mL) was added and the mixture was stirred vigorously at rt until two clear phases were obtained (1 h). The phases where separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (100 mL), dried over MgSO4, filtered and concentrated under reduced pressure to yield the crude aldehyde as a colourless oil. The residue was dissolved in toluene (5 mL) and concentrated once more under reduced pressure. Residual material was used without any further purification.

To a solution of carbon tetrabromide (6.36 g, 19.2 mmol) in dichloromethane (50 mL) at 0 ºC was added portionwise triphenylphosphine (10.1 g, 38.3 mmol) and the resulting suspension was stirred for 1 h at 0 ºC. To the yellow suspension was added a solution of the aldehyde in dichloromethane (10 mL) at −78 ºC and the resulting slurry was allowed to warm to rt over 1.5 h. The suspension was poured onto petroleum ether (1 L) and the mixture was filtered quickly through a short pad of silica (petroleum ether - diethyl ether, 9:1). The filtrate was concentrated under reduced pressure and the resulting dibromoalkene was used without further purification.

To a solution of the dibromoalkene in THF (50 mL) at −78 ºC was added dropwise *n*-butyllithium (8.0 mL of a 2.5 M solution in hexanes, 20 mmol) over 30 min and the mixture was stirred at −78 ºC for 1.5 h. The reaction was quenched at −78 ºC by the addition of a saturated aqueous solution of ammonium chloride (30 mL) and the resulting mixture was extracted with diethyl ether (3 × 70 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 9:1) to give the alkyne **400-t** (1.90 g, 92%) as a colourless oil.

R_f = 0.75 (petroleum ether - diethyl ether, 4:1);

$[\alpha]^{24}_D$ −3.3 (c = 1.2, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (9H, s, CH_3-C12), 1.23 (3H, d, *J* = 6.9 Hz, CH_3-C13), 2.03 (1H, d, *J* = 2.4 Hz, CH-C1), 2.62-2.70 (1H, m, CH-C3), 3.54 (1H, dd, *J* = 9.6, 7.6 Hz, CH_2-C4), 3.73 (1H, dd, *J* = 9.6, 5.7 Hz, CH_2-C4), 7.36-7.45 (6H, m, CH-C7, CH-C8, CH-C9), 7.67-7.69 (4H, m, CH-C6, CH-C10);

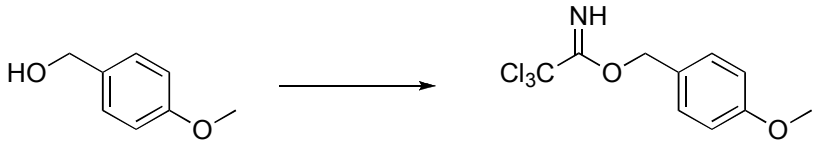
^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5 (C-C13), 19.4 (CH_3-C11), 26.9 (CH_3-C12), 28.9 (CH-C3), 67.6 (CH_2-C4), 69.1 (CH-C1), 89.7 (C-C2), 127.8 (CH-C7, CH-C9), 129.8 (CH-C8), 132.2 (C-C5), 135.7 (CH-C6, CH-C10);

ν_{max} 3297, 2931, 2857, 1792, 1427, 1111, 1087, 694 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 323.5 $[M+H]^+$ (4), 279.3 (100), 263.3 (92), 262.3 (31);

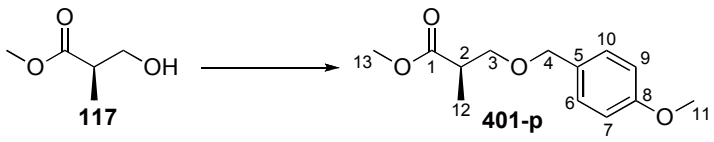
HRMS (CI, *iso*-butane) calcd for $C_{21}H_{27}OSi$ $[M+H]^+$ 323.1831, found 323.1838.

4-Methoxybenzyl-2,2,2-trichloroacetimidate



To a suspension of sodium hydride (1.0 g of a 60% dispersion in oil, 24 mmol) in diethyl ether (100 mL) was added carefully *p*-methoxybenzyl alcohol (30.0 mL, 241 mmol) in diethyl ether (300 mL) at 0 ºC and the mixture was stirred for 1 h at 0 ºC. Trichloroacetonitrile (26.5 mL, 265 mmol) was added slowly and the mixture was allowed to warm to rt for 1 h. The crude mixture was washed sequentially with saturated aqueous sodium hydrogencarbonate solution (300 mL) and a saturated aqueous solution of sodium chloride (300 mL). The organic phase was dried over $MgSO_4$, filtrated and concentrated under reduced pressure to yield the crude 4-methoxybenzyl-2,2,2-trichloroacetimidate, which was used without any further purification.

Methyl (*R*)-3-(4-methoxy-benzyloxy)-2-methyl-propionoate 401-p



PMB acetimidate (31.2 g, 111 mmol) was added to a solution of hydroxyester **117** (10.0 g, 84.6 mmol) in dichloromethane (150 mL) at rt, followed by addition of (1*S*)-(+)-10-camphorsulfonic acid (2.0 g, 8.6 mmol). The mixture was stirred for 14 h then diluted with petroleum ether (1 L), filtered, washed with a

saturated aqueous solution of sodium hydrogencarbonate (200 mL) and a saturated aqueous solution sodium chloride (200 mL). The organic phase was dried over $MgSO_4$, filtrated, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) to give the ester **401-p** (18.5 g, 92%) as a colourless oil.

R_f = 0.37 (petroleum ether - diethyl ether, 2:1);

$[\alpha]^{24}_D$ −8.1 (c = 1.5, $CHCl_3$), {Lit.[210] $[\alpha]^{20}_D$ −8.0 (c = 0.9, $CHCl_3$)};

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (3H, d, *J* = 7.1 Hz, CH_3-C12), 2.76 (1H, qdd, *J* = 7.3, 7.1, 6.0 Hz, CH-C2), 3.45 (1H, dd, *J* = 9.2, 6.0 Hz, CH_2-C3), 3.62 (1H, dd, *J* = 9.2, 7.3 Hz, CH_2-C3), 3.69 (3H, s, CH_3-C13), 3.80 (3H, s, CH_3-C11), 4.45 (2H, d, *J* = 2.5 Hz, CH_2-C4), 6.87 (2H, d, *J* = 8.7 Hz, CH-C6, CH-C10), 7.23 (2H, d, *J* = 8.7 Hz, CH-C7, CH-C9);

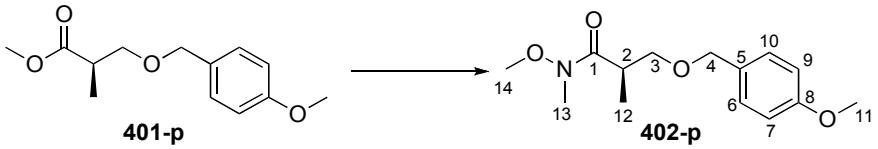
^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (CH_3-C12), 40.3 (CH-C2), 51.8 (CH_3-C13), 55.4 (CH_3-C11), 71.8 (CH_2-C3), 72.9 (CH_2-C4), 113.9 (CH-C6, CH-C10), 129.3 (CH-C7, CH-C9), 130.4 (C-C5), 159.3 (C-C8), 175.5 (C-C1);

ν_{max} 2949, 2357, 1738, 1612, 1514, 1248, 1174, 1089, 1036, 820 cm^{-1};

LRMS (EI) *m/z* (intensity) 238.1 $[M]^+$ (16), 137.1 (100), 121.1 (95), 77.0 (33);

HRMS (EI) calcd for $C_{13}H_{18}O_4$ $[M]^+$ 238.1205, found 238.1208.

N-Methoxy-*N'*-methyl (*R*)-3-(4-methoxy-benzyloxy)-2-methyl-propionamide 402-p



To a suspension of magnesium turnings (5.90 g, 245 mmol) in THF (10 mL) was added 2-bromopropane (1.0 mL, 11 mmol) in one portion. The suspension was stirred as soon as THF reflux was obtained and 2-bromopropane (20.3 mL, 214 mmol) in THF (120 mL) was added carefully in order to maintain reflux. After addition, the grey mixture was allowed to cool to rt. The resulting mixture was added to a solution of *N,O*-dimethylhydroxylamine hydrochloride (11.0 g, 112

[210] Lorenz, M.; Kalesse, M. *Org. Let.* **2008**, *10*, 19, 4371-4374.

mmol) and ester **401-p** (18.5 g, 77.8 mmol) in THF (50 mL) at −15 ºC and the mixture was allowed to warm to rt over 4 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (100 mL) and extracted with diethyl ether (3 × 300 mL). The combined organic extracts were washed with saturated sodium chloride solution (500 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 1:3) to give the Weinreb amide **402-p** (18.6 g, 89%) as a colourless thick oil.

R_f = 0.46 (petroleum ether - diethyl ether, 1:3);

$[\alpha]^{24}_D$ −3.5 (c = 1.0, $CHCl_3$), {Lit.[211] $[\alpha]^{23}_D$ −3.0 (c = 1.0, $CHCl_3$)};

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, d, *J* = 6.9 Hz, CH_3-C12), 3.19-3.29 (4H, m, CH-C2, CH_3-C13), 3.39 (1H, dd, *J* = 8.8, 6.0 Hz, CH_2-C3), 3.66-3.70 (4H, m, CH_2-C3, CH_3-C14), 3.80 (3H, s, CH_3-C11), 4.42-4.46 (2H, m, CH_2-C4), 6.86 (2H, d, *J* = 8.5 Hz, CH-C6, CH-C10), 7.23 (2H, d, *J* = 8.5 Hz, CH-C7, CH-C9);

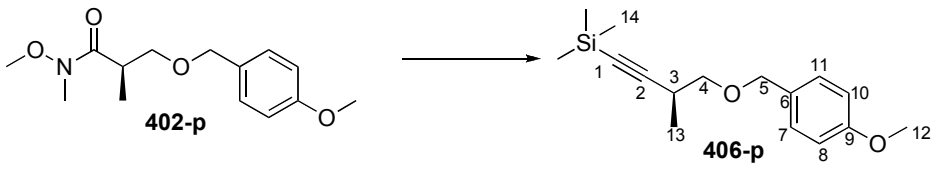
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (CH_3-C12), 32.3 (CH_3-C13), 36.0 (CH-C2), 55.4 (CH_3-C11), 61.7 (CH_3-C14), 72.5 (CH_2-C3), 73.0 (CH_2-C4), 113.8 (CH-C6, CH-C10), 129.3 (CH-C7, CH-C9), 130.7 (C-C5), 159.2 (C-C8), 173.3 (C-C1);

ν_{max} 2936, 1655, 1612, 1512, 1246, 1175, 1096, 1032, 818 cm^{-1};

LRMS (CI, *iso*-butane) *m*/*z* (intensity) 268.3 $[M+H]^+$ (16), 121.2 (100), 148.2 (20), 75.2 (18);

HRMS (CI, *iso*-butane) calcd for $C_{14}H_{22}O_4N$ $[M+H]^+$ 268.1549, found 268.1555.

[(*S*)-4-(4-Methoxy-benzyloxy)-3-methyl-but-1-ynyl]-trimethyl-silane 406-p



Diisobutylaluminium hydride (32.0 mL of a 1 M solution in toluene, 32.0 mmol) was added over 30 min to a solution of the Weinreb amide **402-p** (4.0 g, 15

[211] Handa, M.; Scheidt, K. A.; Bossart, M.; Zheng, N.; Roush, W. R. *J. Org. Chem*. **2008**, *73*, 3, 1031-1035.

mmol) in THF (70 mL) at −78 °C and the mixture was stirred for 1 h. The reaction was quenched carefully with methanol (5 mL) and the mixture was stirred for 15 min then allowed to warm to 0 °C. A saturated aqueous solution of potassium sodium tartrate (100 mL) was added and the mixture was stirred vigorously at rt until two clear phases were obtained (2 h). The aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with a saturated solution of sodium chloride (200 mL), dried over MgSO4, filtered and concentrated under reduced pressure to yield the crude aldehyde as a colourless oil. The residue was concentrated once more under reduced pressure after addition of toluene (5 mL) and used without further purification.

To a solution of carbon tetrabromide (15.2 g, 45.8 mmol) in dichloromethane (80 mL) at 0 °C was added portionwise triphenylphosphine (24.1 g, 91.9 mmol) and the suspension was stirred at 0 °C for 1 h. To the yellow suspension was added a solution of the aldehyde in dichloromethane (25 mL) at −78 °C and the resulting slurry was allowed to warm to rt over 1.5 h. The suspension was poured onto petroleum ether (2 L) and filtrated quickly through a short pad of silica (petroleum ether - diethyl ether, 9:1). The filtrate was concentrated under reduced pressure and the resulting dibromoalkene was used without further purification.

To a solution of the dibromoalkene in THF (200 mL) at −78 °C was added dropwise *n*-butyllithium (18.5 mL of a 2.5 M solution in hexanes, 46.2 mmol) over 30 min and the mixture was stirred at −78 °C for 1.5 h. The reaction was quenched carefully at −78 °C by the addition of freshly distilled trimethylsilyl chloride (12.0 mL, 94.5 mmol) in THF (40 mL) and the mixture was allowed to warm to rt over 2 h. Water was added (200 mL) and the aqueous phase was extracted with diethyl ether (3 × 200 mL). The combined organic phases were washed with saturated aqueous sodium chloride solution (300 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 9:1) to give the alkyne **406-p** (2.4 g, 57%) as a colourless oil.

R_f = 0.72 (petroleum ether - diethyl ether, 4:1);

$[\alpha]^{23}_D$ −4.6 (c = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (9H, s, CH_3-C14), 1.19 (3H, d, *J* = 6.9 Hz, CH_3-C13), 2.75 (1H, dqd, *J* = 7.8, 6.9, 5.9 Hz, CH-C3), 3.33 (1H, dd, *J* = 9.2, 7.8 Hz, CH_2-C4), 3.51 (1H, dd, *J* = 9.2, 5.9 Hz, CH_2-C4), 3.81 (3H, s, CH_3-C12), 4.49 (2H, s, CH_2-C5), 6.88 (2H, d, *J* = 8.6 Hz, CH-C7, CH-C11), 7.23 (2H, d, *J* = 8.6 Hz, CH-C8, CH-C10);

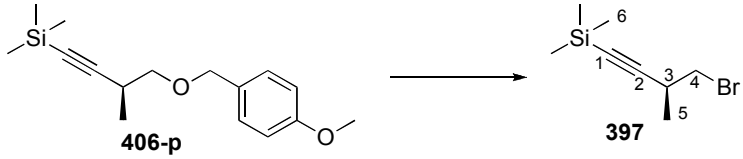
^{13}C NMR (100 MHz, $CDCl_3$) δ 0.3 (CH_3-C14), 18.0 (CH_3-C13), 27.8 (CH-C3), 55.4 (CH_3-C12), 72.8 (CH_2-C4), 73.9 (CH_2-C5), 85.1 (C-C2), 109.2 (C-C1), 113.9 (CH-C7, CH-C11), 129.3 (CH-C8, CH-C10), 130.6 (C-C6), 159.3 (C-C9);

ν_{max} 2959, 2872, 2170, 1612, 1514, 1248, 1092, 1037, 841 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 277.4 $[M+H]^+$ (11), 121.2 (100), 75.2 (24), 261.3 (12);

HRMS (CI, *iso*-butane) calcd for $C_{16}H_{25}O_2Si$ $[M+H]^+$ 277.1624, found 277.1620.

[(*S*)-4-Bromo-3-methyl-but-1-ynyl]-trimethyl-silane 397



To a solution of DDQ (540 mg, 2.38 mmol) in a 10:1 mixture of dichloromethane and water (44 mL) at 0 ºC, a solution of the alkyne **406-p** (600 mg, 2.15 mmol) in dichloromethane (5.0 mL) was added in one portion. The reaction mixture was stirred at rt for 2 h and then washed sequentially with saturated sodium carbonate solution (50 mL), water (50 mL) and a saturated solution of sodium chloride (50 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated and filtered through a short pad of silica gel (petroleum ether - diethyl ether, 9:1) to give the crude alcohol, which was used without any further purification.

To a solution of the crude alcohol and triphenylphosphine (677 mg, 2.58 mmol) in dichloromethane (15 mL) at 0 ºC was added, portionwise, recrystallised *N*-bromosuccinimide (440 mg, 2.47 mmol) and the mixture was allowed to warm to rt for 14 h. The mixture was purified by flash chromatography on silica gel (petroleum ether) to give the bromide **397** (341 mg, 72%) as a colourless oil.

R_f = 0.82 (dichloromethane);

$[\alpha]^{25}_D$ +3.6 (c = 0.36, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (9H, s, CH_3-C6), 1.30 (3H, d, *J* = 6.8 Hz, CH_3-C5), 2.83 (1H, dqd, *J* = 7.9, 6.8, 5.3 Hz, CH-C3), 3.30 (1H, dd, *J* = 9.8, 7.9 Hz, CH_2-C4), 3.80 (1H, dd, *J* = 9.8, 5.3 Hz, CH_2-C4);

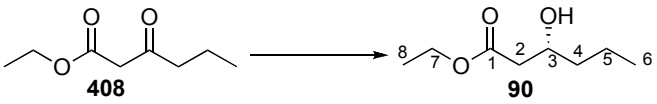
^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2 (CH_3-C6), 19.7 (CH_3-C5), 29.8 (CH-C3), 37.3 (CH_2-C4), 86.7 (C-C2), 107.6 (C-C1);

ν_{max} 2924, 1427, 1250, 1026, 841 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 221.2 $[M+H]^+$ (46), 219.2 $[M+H]^+$ (43), 75.1 (100), 123.3 (95), 165.3 (58);

HRMS (CI, *iso*-butane) calcd for $C_8H_{16}Si^{81}Br$ $[M+H]^+$ 221.0184, $C_8H_{16}Si^{79}Br$ $[M+H]^+$ 219.0205, found 221.0171, 219.0206.

Ethyl (*R*)-3-hydroxy-hexanoate 90



<u>Caution</u>: [tol-BINAP-Ru] catalyst is extremely sensitive to water and oxygen therefore all the glassware has to be flame-dried and the solvents degassed by two freeze-thaw cycles.

The $[RuCl_2(benzene)]_2$ complex (0.16 g, 0.32 mmol) and (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphtalene **409** or [(*R*)-tol-BINAP] (0.47 g, 0.70 mmol) were dissolved in dry and degassed DMF (9.0 mL) in a 100 mL vial. The mixture was stirred at 110 ºC for 20 min and DMF was removed by vacuum distillation (200 mbar) at 50 ºC. A solution of ester **408** (10.0 g, 63.6 mmol) in dry and degassed ethanol (35 mL) was added. The vial was transferred to a hydrogenation autoclave and the vessel was purged three times with hydrogen. The reaction mixture was stirred at 95 ºC under an atmosphere of hydrogen (5 bar) for 18 h and then cooled to room temperature. The mixture was concentrated under reduced pressure and the residue was purified by vacuum

distillation (62 °C, 1 mmHg) to give the ester **90** (9.9 g, 97%) as a colourless oil. The enantiomeric excess was determined by chiral HPLC and found to be 98% ee.

R_f = 0.66 (petroleum ether - diethyl ether, 1:3);

HPLC: t_R (*R* enantiomer) = 7.2 min, t_R (*S* enantiomer) = 9.4 min (Chiracel OD-H, *n*-hexane - *iso*-propanol, 95:5, 1.00 mL × min^{-1}, detection: 215 nm, oven: 25.0 °C);

$[\alpha]^{21}_D$ −25.6 (c = 1.1, $CHCl_3$) {Lit.[212] $[\alpha]^{26}_D$ −26.9 (c = 1.1, $CHCl_3$)};

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.0 Hz, CH_3-C6), 1.27 (3H, t, *J* = 7.2 Hz, CH_3-C8), 1.36-1.54 (4H, m, CH_2-C4, CH_2-C5), 2.39 (1H, dd, *J* = 16.4, 4.9 Hz, CH_2-C2), 2.49 (1H, dd, *J* = 16.4, 3.1 Hz, CH_2-C2), 2.92 (1H, d, *J* = 4.0 Hz, OH), 3.97-4.04 (1H, m, CH-C3), 4.17 (2H, q, *J* = 7.2 Hz, CH_2-C7);

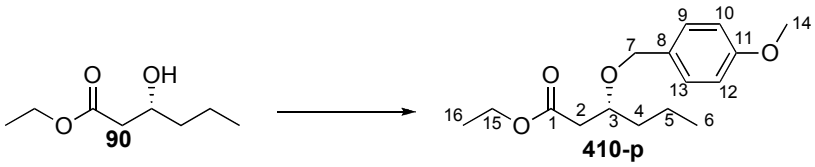
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3-C6), 14.3 (CH_3-C8), 18.8 (CH_2-C5), 38.8 (CH_2-C4), 41.5 (CH_2-C2), 60.8 (CH_2-C7), 67.9 (CH-C3), 173.3 (C-C1);

ν_{max} 3449, 2963, 2877, 1720, 1458, 1303, 1173, 1103, 1018, 848 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 161 $[M+H]^+$ (100), 143 (38), 115 (9);

HRMS (CI, *iso*-butane) calcd for $C_8H_{17}O_3$ $[M+H]^+$ 161.1178, found 161.1182.

Ethyl (*R*)-3-(4-methoxy-benzyloxy)-hexanoate 410-p



The PMB-acetimidate (1.74 g, 6.15 mmol) was added to a solution of hydroxyester **90** (0.90 g, 5.6 mmol) in dichloromethane (7 mL) at rt, followed by addition of (1*S*)-(+)-10-camphorsulfonic acid (0.14 g, 0.62 mmol). The mixture was stirred for 14 h, diluted with petroleum ether (15 mL), filtered through a short pad of Celite (10 g), washed with saturated aqueous sodium hydrogencarbonate solution (30 mL) and a saturated aqueous solution of sodium chloride (30 mL). The organic phase was dried over $MgSO_4$, filtrated, concentrated under reduced pressure and the residue was purified by flash

[212] Roche, C.; Desroy, N.; Haddad, M.; Phansavath, P.; Genet, J.-P. *Org. Let.* **2008**, *10*, 17, 3911-3914.

chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) to give the ester **410-p** (1.51 g, 96%) as a colourless oil.

R_f = 0.60 (petroleum ether - diethyl ether, 3:2);

$[\alpha]^{24}_D$ −0.5 (c = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.2 Hz, CH_3-C6), 1.25 (3H, t, *J* = 7.1 Hz, CH_3-C16), 1.33-1.61 (4H, m, CH_2-C4, CH_2-C5), 2.44 (1H, dd, *J* = 15.0, 5.3 Hz, CH_2-C2), 2.59 (1H, dd, *J* = 15.0, 7.3 Hz, CH_2-C2), 3.80 (3H, s, CH_3-C14), 3.87 (1H, tt, *J* = 7.0, 5.3 Hz, CH-C3), 4.14 (2H, qd, *J* = 7.2, 1.2 Hz, CH_2-C15), 4.47 (2H, d, *J* = 11.0 Hz, CH_2-C7), 6.86 (2H, d, *J* = 8.6 Hz, CH-C9, CH-C13), 7.25 (2H, d, *J* = 8.6 Hz, CH-C10, CH-C12);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3-C6), 14.4 (CH_3-C16), 18.6 (CH_2-C5), 36.9 (CH_2-C4), 40.2 (CH_2-C2), 55.4 (CH_3-C14), 60.5 (CH_2-C15), 71.3 (CH_2-C7), 75.8 (CH-C3), 113.9 (CH-C9, CH-C13), 129.5 (CH-C10, CH-C12), 130.9 (C-C8), 159.3 (C-C11), 173.3 (C-C1);

ν_{max} 2955, 1736, 1612, 1512, 1466, 1304, 1250, 1180, 1080, 1034, 817 cm^{-1};

LRMS (EI) *m/z* (intensity) 280.2 $[M]^+$ (12), 137.0 (100), 82.9 (88);

HRMS (EI) calcd for $C_{16}H_{24}O_4$ $[M]^+$ 280.1675, found 280.1671.

N-Methoxy-*N'*-methyl (*R*)-3-(4-methoxy-benzyloxy)-hexanamide 398-p

To a solution of *N,O*-dimethylhydroxylamine hydrochloride (0.80 g, 8.2 mmol) and ester **410-p** (1.51 g, 5.4 mmol) in THF (5 mL) at −15 ºC was added dropwise *iso*-propylmagnesium bromide (8.0 mL of a 2 M solution in THF, 16 mmol) and the mixture was allowed to warm to rt over 14 h. The reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride (30

mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 1:1) to give the Weinreb amide **398-p** (1.18 g, 74%) as a colourless gum.

R_f = 0.71 (diethyl ether);

$[\alpha]^{24}_D$ +9.3 (c = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.2 Hz, CH_3-C6), 1.42-1.61 (4H, m, CH_2-C4, CH_2-C5), 2.46 (1H, dd, *J* = 15.1, 5.2 Hz, CH_2-C2), 2.84 (1H, dd, *J* = 15.1, 6.6 Hz, CH_2-C2), 3.19 (3H, s, CH_3-C15), 3.66 (3H, s, CH_3-C16), 3.79 (3H, s, CH_3-C14), 3.97 (1H, tt, *J* = 7.1, 5.2 Hz, CH-C3), 4.47 (1H, s, CH_2-C7), 4.49 (1H, s, CH_2-C7), 6.85 (2H, d, *J* = 8.8 Hz, CH-C9, CH-C13), 7.25 (2H, d, *J* = 8.8 Hz, CH-C10, CH-C12);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (CH_3-C6), 18.8 (CH_2-C5), 32.2 (CH_3-C15), 37.3 (CH_2-C4), 37.4 (CH_2-C2), 55.4 (CH_3-C14), 61.4 (CH_3-C16), 71.7 (CH_2-C7), 76.0 (CH-C3), 113.8 (CH-C9, CH-C13), 129.5 (CH-C10, CH-C12), 131.1 (C-C8), 159.2 (C-C11), 172.8 (C-C1);

ν_{max} 2955, 2932, 1659, 1512, 1458, 1318, 1242, 1173, 1072, 1034, 818 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 296.3 $[M+H]^+$ (42), 121.2 (100), 75.1 (90);

HRMS (CI, *iso*-butane) calcd for $C_{16}H_{26}O_4N$ $[M+H]^+$ 296.1862, found 296.1861.

Ethyl (*R*)-3-(*tert*-butyl-diphenyl-silanyloxy)-hexanoate 410-t

To a solution of hydroxy ester **90** (1.00 g, 6.44 mmol) in DMF (10 mL) was added sequentially DMAP (0.16 g, 1.3 mmol), imidazole (0.52 g, 7.7 mmol) and then *t*-butyldiphenylsilyl chloride (1.80 mL, 6.92 mmol) at 0 ºC and the resulting mixture was allowed to warm to rt over 14h. The reaction mixture was quenched by the addition of a solution of 1 M hydrochloric acid (5 mL), diluted with diethyl ether (10 mL) and the phases were separated. The organic phase was washed

with a saturated aqueous solution of sodium hydrogencarbonate (3 × 10 mL) and a saturated solution aqueous sodium chloride (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) to yield the ester **410-t** (2.25 g, 89%) as a colourless oil.

R_f = 0.81 (petroleum ether - diethyl ether, 3:2);

$[\alpha]^{25}_D$ −8.4 (c = 1.5, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (3H, t, *J* = 7.3 Hz, CH_3-C6), 1.03 (9H, s, CH_3-C14), 1.85 (3H, t, *J* = 7.1 Hz, CH_3-C16), 1.21-1.30 (2H, m, CH_2-C5), 1.40-1.46 (2H, m, CH_2-C4), 2.41 (1H, dd, *J* = 14.7, 5.8 Hz, CH_2-C2), 2.48 (1H, dd, *J* = 14.7, 6.8 Hz, CH_2-C2), 4.01 (2H, q, *J* = 7.3, 4.2 Hz, CH_2-C15), 4.17-4.23 (1H, m, CH-C3), 7.34-7.44 (6H, m, CH-C9, CH-C10, CH-C11), 7.65-7.71 (4H, m, CH-C8, CH-C12);

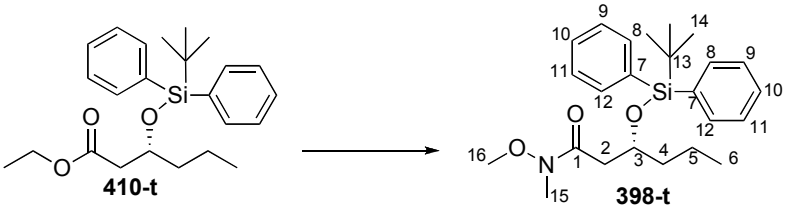
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3-C6), 14.2 (CH_3-C16), 18.1 (CH_2-C5), 19.5 (C-C13), 27.1 (CH_3-C14), 36.4 (CH_2-C4), 42.3 (CH_2-C2), 60.4 (CH_2-C15), 70.4 (CH-C3), 127.6 (CH-C9, CH-C11), 129.7 (CH-C10), 134.4 (C-C7), 136.1 (CH-C8, CH-C12), 171.8 (C-C1);

ν_{max} 2931, 1736, 1466, 1427, 1312, 1258, 1103, 1034, 702 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 399.3 $[M+H]^+$ (9), 321.3 (100), 75.1 (55);

HRMS (CI, *iso*-butane) calcd for $C_{24}H_{35}O_3Si$ $[M+H]^+$ 399.2355, found 399.2357.

_N_-Methoxy-_N'_-methyl (_R_)-3-(_tert_-butyl-diphenyl-silanyloxy)-hexanamide 398-t



To a solution of *N,O*-dimethylhydroxylamine hydrochloride (0.80 g, 8.2 mmol) and ester **410-t** (2.03 g, 5.10 mmol) in THF (5 mL) at −15 °C was added dropwise *iso*-propylmagnesium bromide (8.0 mL of a 2 M solution in THF, 16 mmol) and

the mixture was allowed to warm to rt over 14 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (5 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with a saturated solution of sodium chloride (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 3:1) to give the Weinreb amide **398-t** (2.02 g, 95%) as a colourless thick oil.

R_f = 0.83 (diethyl ether);

$[\alpha]^{24}_D$ −14.4 (c = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (3H, t, *J* = 7.3 Hz, CH_3-C6), 1.03 (9H, s, CH_3-C14), 1.25-1.32 (2H, m, CH_2-C5), 1.41-1.47 (2H, m, CH_2-C4), 2.46 (1H, dd, *J* = 14.8, 6.4 Hz, CH_2-C2), 2.70 (1H, dd, *J* = 14.8, 6.1 Hz, CH_2-C2), 3.09 (3H, s, CH_3-C15), 3.54 (3H, s, CH_3-C16), 4.31-4.37 (1H, m, CH-C3), 7.33-7.43 (6H, m, CH-C9, CH-C10, CH-C11), 7.68-7.72 (4H, m, CH-C8, CH-C12);

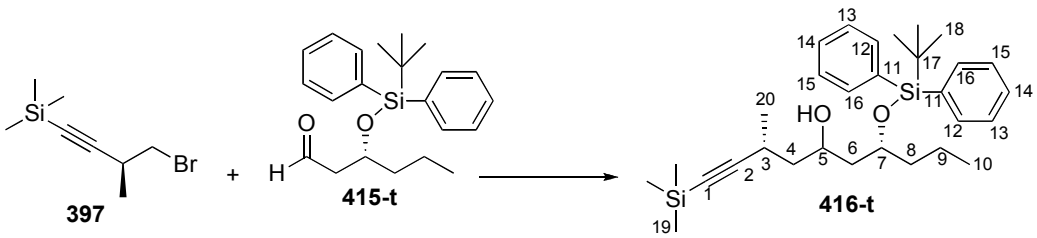
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3-C6), 18.2 (CH_2-C5), 19.6 (C-C13), 27.1 (CH_3-C14), 29.2 (CH_3-C15), 39.6 (CH_2-C2), 39.7 (CH_2-C4), 61.3 (CH_3-C16), 70.4 (CH-C3), 127.6 (CH-C9, CH-C11), 129.6 (CH-C10), 134.4 (C-C7), 136.1 (CH-C8, CH-C12), 172.3 (C-C1);

ν_{max} 2922, 2853, 1672, 1460, 1427, 1377, 1111, 1076, 702 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 414.0 $[M+H]^+$ (5), 75.1 (100), 336.1 (35);

HRMS (CI, *iso*-butane) calcd for $C_{24}H_{36}O_3NSi$ $[M+H]^+$ 414.2464, found 414.2459.

(3*R*,7*R*)-7-(*tert*-Butyl-diphenyl-silanyloxy)-3-methyl-1-trimethylsilanyl-dec-1-yn-5-ol 416-t



To a suspension of magnesium turnings (102 mg, 4.00 mmol) in a 3:1 mixture of diethyl ether and benzene (4 mL) was added dropwise 1,2-dibromoethane (0.35

mL, 4.00 mmol) and the suspension was stirred until no further gas evolution was observed. The mixture was heated to 50 ºC for 1 h and allowed to cool to rt.
To a solution of bromide **397** (340 mg, 1.56 mmol) in diethyl ether (8 mL) was added dropwise at −78 ºC *t*-butyllithium (1.95 mL of a 1.6 M solution in hexanes, 3.1 mmol). The mixture was stirred at −78 ºC for 0.5 h and then allowed to warm to −40 ºC over 30 min. To the resulting yellow mixture was added at −78 ºC a freshly prepared solution of magnesium bromide diethyl etherate complex (2.00 mL of 1 M solution, 2.00 mmol), the mixture was stirred at −78 ºC over 30 min then allowed to warm to −40 ºC for 30 min. To the resulting cloudy mixture was added at −40 ºC the aldehyde **415-t** (226 mg, 0.63 mmol) in diethyl ether (1.6 mL). The mixture was stirred at −40 ºC over 30 min then allowed to warm to rt for 30 min. The reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with saturated sodium chloride solution (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) to give alcohol **416-t** (220 mg, 71%) as a colourless oil.
R_f = 0.43 (petroleum ether - diethyl ether, 4:1);
$[\alpha]^{24}_D$ −9.3 (*c* = 1.1, $CHCl_3$);
^{1}H NMR (400 MHz, $CDCl_3$) (~1:1 mixture of diastereoisomers)
Diastereoisomer **416-ta** δ 0.14 (9H, s, CH_3-C19), 0.62 (3H, t, *J* = 7.3 Hz, CH_3-C10), 1.05 (9H, s, CH_3-C18), 1.15 (3H, d, *J* = 7.0 Hz, CH_3-C20), 1.18–1.40 (4H, m, CH_2-C8, CH_2-C9), 1.41–1.45 (2H, m, CH_2-C4), 1.61–1.65 (2H, m, CH_2-C6), 2.65 (1H, brs, OH), 2.70 (1H, qt, *J* = 7.1, 7.0 Hz, CH-C3), 3.96–4.00 (1H, m, CH-C7), 4.01–4.07 (1H, m, CH-C5), 7.37-7.43 (6H, m, CH-C13, CH-C14, CH-C15), 7.69-7.72 (4H, m, CH-C12, CH-C16);

Diastereoisomer **416-tb** δ 0.14 (9H, s, CH_3-C19), 0.62 (3H, t, *J* = 7.3 Hz, CH_3-C10), 1.05 (9H, s, CH_3-C18), 1.15 (3H, d, *J* = 7.0 Hz, CH_3-C20), 1.18–1.40 (4H, m, CH_2-C8, CH_2-C9), 1.41–1.45 (2H, m, CH_2-C4), 1.61–1.65 (2H, m, CH_2-C6), 2.66 (1H, brs, OH), 2.70 (1H, qt, *J* = 7.1, 7.0 Hz, CH-C3), 3.96–4.00 (1H, m, CH-C7),

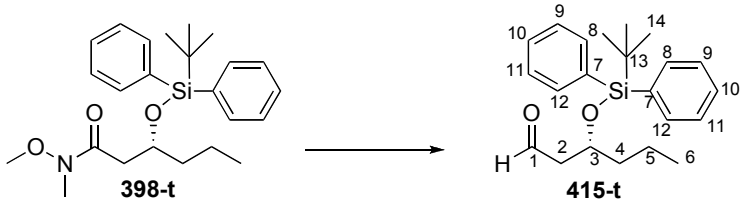
4.01–4.07 (1H, m, CH-C5), 7.37-7.43 (6H, m, CH-C13, CH-C14, CH-C15), 7.69-7.72 (4H, m, CH-C12, CH-C16);

^{13}C NMR (100 MHz, $CDCl_3$) (~1:1 mixture of diastereoisomers)
Diastereoisomer **416-ta** δ 0.4 (CH_3-C19), 14.0 (CH_3-C10), 18.1 (CH_2-C9), 19.5 (C-C17), 21.6 (CH_3-C20), 23.6 (CH-C3), 27.2 (CH_3-C18), 39.4 (CH_2-C8), 43.8 (CH_2-C6), 45.0 (CH_2-C4), 68.6 (CH-C5), 73.4 (CH-C7), 84.9 (C-C2), 111.6 (C-C1), 127.6 (CH-C13, CH-C15), 129.7 (CH-C14), 133.9 (C-C11), 136.0 (CH-C12, CH-C16);

Diastereoisomer **416-tb** δ 0.4 (CH_3-C19), 14.0 (CH_3-C10), 18.1 (CH_2-C9), 19.5 (C-C17), 21.6 (CH_3-C20), 23.6 (CH-C3), 27.2 (CH_3-C18), 39.4 (CH_2-C8), 43.8 (CH_2-C6), 45.0 (CH_2-C4), 68.6 (CH-C5), 73.4 (CH-C7), 84.9 (C-C2), 111.6 (C-C1), 127.8 (CH-C13, CH-C15), 129.8 (CH-C14), 134.6 (C-C11), 136.1 (CH-C12, CH-C16);

ν_{max} 3389, 2916, 2166, 1719, 1464, 1427, 1250, 1113, 1040, 843 cm^{-1};
LRMS (CI, *iso*-butane) *m/z* (intensity) 495.5 $[M+H]^+$ (8), 75.1 (100), 85.2 (67), 257.3 (20);
HRMS (CI, *iso*-butane) calcd for $C_{30}H_{47}O_2Si_2$ $[M+H]^+$ 495.3115, found 495.3115.

(*R*)-3-(*tert*-Butyl-diphenyl-silanyloxy)-hexanal 415-t



Diisobutylaluminium hydride (1.52 mL of a 1.0 M solution in toluene, 1.5 mmol) was added over 10 min to the Weinreb amide **398-t** (285 mg, 0.69 mmol) in THF (3 mL) at −78 °C and the mixture was stirred for 1 h. The reaction was quenched carefully with methanol (1 mL) and the mixture was stirred for 15 min then allowed to warm to 0 °C. A saturated solution of potassium sodium tartrate (4 mL) was added and the mixture was stirred vigorously at rt until two clear phases were obtained (1 h). The aqueous phase was extracted with diethyl ether

(3 × 5 mL) and the combined organic extracts were washed with a saturated solution of sodium chloride (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The mixture was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) to give the aldehyde **415-t** (226 mg, 92%) as a colourless oil.

R_f = 0.47 (petroleum ether - diethyl ether, 4:1);

$[\alpha]^{23}_D$ −2.6 (c = 0.3, $CHCl_3$);

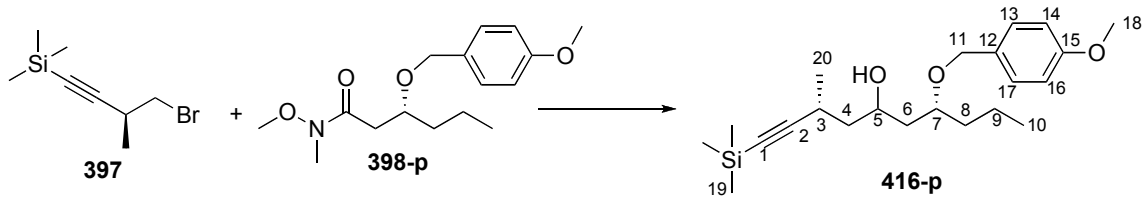
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (3H, t, *J* = 7.3 Hz, CH_3-C6), 1.04 (9H, s, CH_3-C14), 1.17-1.31 (2H, m, CH_2-C5), 1.47-1.53 (2H, m, CH_2-C4), 2.47 (2H, dd, *J* = 5.7, 2.5 Hz, CH_2-C2), 4.18-4.23 (1H, m, CH-C3), 7.36-7.46 (6H, m, CH-C9, CH-C10, CH-C11), 7.65-7.68 (4H, m, CH-C8, CH-C12), 9.71 (1H, t, *J* = 2.5 Hz, CH-C1);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3-C6), 18.3 (CH_2-C5), 19.4 (C-C13), 27.1 (CH_3-C14), 39.7 (CH_2-C4), 50.3 (CH-C2), 69.2 (CH_2-C3), 127.7 (CH-C9, CH-C11), 129.9 (CH-C10), 133.8 (C-C7), 136.0 (CH-C8, CH-C12), 202.5 (CH-C1);

ν_{max} 2955, 2931, 2862, 1728, 1465, 1427, 1111, 1042, 702 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 355.4 $[M+H]^+$ (16), 311.4 (100), 277.4 (72), 251.3 (20); HRMS (CI, *iso*-butane) calcd for $C_{22}H_{31}O_2Si$ $[M+H]^+$ 355.2093, found 355.2094.

(3*R*,7*R*)-7-(4-Methoxy-benzyloxy)-3-methyl-1-trimethylsilanyl-dec-1-yn-5-ol 416-p



Diisobutylaluminium hydride (1.1 mL of a 1 M solution in toluene, 1.1 mmol) was added over 10 min to the Weinreb amide **398-p** (150 mg, 0.51 mmol) in THF (3.0 mL) at −78 °C and the mixture was stirred for 1 h. The reaction was quenched carefully with methanol (1 mL) and the mixture was stirred for 15 min then allowed to warm to 0 °C. A saturated aqueous solution of potassium sodium

tartrate (4 mL) was added and the mixture was stirred vigorously at rt until two clear phases were obtained (1 h). The aqueous layer phase was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with a saturated solution of sodium chloride (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude aldehyde as a colourless oil. The residue was concentrated once more under reduced pressure after addition of toluene (5 mL) and used without any further purification.

To a suspension of magnesium turnings (102 mg, 4.00 mmol) in a 3:1 mixture of diethyl ether and benzene (4 mL) was added dropwise 1,2-dibromoethane (0.35 mL, 4.0 mmol) at rt and the suspension was stirred until no further gas evolution was observed. The mixture was warmed to 50 ºC and stirred at this temperature for 1 h and then allowed to cool to rt.

To a solution of bromide **397** (153 mg, 0.65 mmol) in diethyl ether (4 mL) was added dropwise at −78 ºC *t*-butyllithium (0.81 mL of a 1.6 M solution in hexanes, 1.3 mmol), the mixture was stirred at −78 ºC for 30 min then allowed to warm to −40 ºC for 30 min. To the resulting yellow mixture was added at −78 ºC a freshly prepared solution of magnesium bromide diethyl etherate complex (1.0 mL of 1 M solution, 1.0- mmol), the mixture was stirred at −78 ºC for 30 min then allowed to warm to −40 ºC over 30 min. To the resulting cloudy mixture was added at −40 ºC the aldehyde in diethyl ether (1.0 mL), the mixture was stirred at −40 ºC for 30 min then allowed to warm to rt over 30 min. The reaction mixture was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with sodium chloride saturated solution (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 9:1) to give the alcohol **416-p** (29 mg, 15%) as a colourless oil.

R_f = 0.39 (petroleum ether - diethyl ether, 4:1);

$[\alpha]^{26}_D$ −34.9 (*c* = 1.1, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) (~1:1 mixture of diastereoisomers)

Diastereoisomer **416-pa** δ 0.14 (9H, s, CH_3-C19), 0.94 (3H, t, *J* = 7.4 Hz, CH_3-C10), 1.17 (3H, d, *J* = 7.0 Hz, CH_3-C20), 1.45–1.72 (8H, m, CH_2-C4, CH_2-C6, CH_2-C8, CH_2-C9), 2.57 (1H, brs, OH), 2.69-2.78 (1H, m, CH-C3), 3.66–3.72 (1H, m,

CH-C7), 3.80 (3H, s, CH_3-C18), 3.97–4.04 (1H, m, CH-C5), 4.39 (1H, s, CH_2-C11), 4.41 (1H, s, CH_2-C11), 6.86 (2H, d, 8.6 Hz, CH-C13, CH-C17), 7.26 (2H, d, 8.6 Hz, CH-C14, CH-C16);

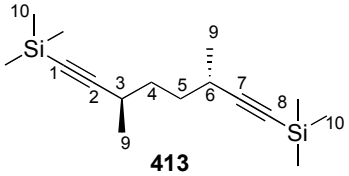
Diastereoisomer **416-pb** δ 0.14 (9H, s, CH_3-C19), 0.94 (3H, t, *J* = 7.4 Hz, CH_3-C10), 1.17 (3H, d, *J* = 7.0 Hz, CH_3-C20), 1.45–1.72 (8H, m, CH_2-C4, CH_2-C6, CH_2-C8, CH_2-C9), 2.58 (1H, brs, OH), 2.69-2.78 (1H, m, CH-C3), 3.66–3.72 (1H, m, CH-C7), 3.79 (3H, s, CH_3-C18), 3.97–4.04 (1H, m, CH-C5), 4.55 (1H, s, CH_2-C11), 4.58 (1H, s, CH_2-C11), 6.85 (2H, d, 8.6 Hz, CH-C13, CH-C17), 7.27 (2H, d, 8.6 Hz, CH-C14, CH-C16);

^{13}C NMR (100 MHz, $CDCl_3$) (~1:1 mixture of diastereoisomers)
Diastereoisomer **416-pa** δ 0.4 (CH_3-C19), 14.5 (CH_3-C10), 18.1 (CH_2-C9), 21.8 (CH_3-C20), 23.7 (CH-C3), 35.9 (CH_2-C8), 41.6 (CH_2-C6), 45.1 (CH_2-C4), 55.4 (CH_3-C18), 69.9 (CH-C5), 70.3 (CH_2-C11), 77.5 (CH-C7), 84.7 (C-C2), 111.8 (C-C1), 114.1 (CH-C13, CH-17), 129.5 (CH-C14, CH-16), 130.4 (C-C12), 159.4 (C-C15);

Diastereoisomer **416-pb** δ 0.4 (CH_3-C19), 14.5 (CH_3-C10), 18.1 (CH_2-C9), 21.8 (CH_3-C20), 23.7 (CH-C3), 35.9 (CH_2-C8), 41.6 (CH_2-C6), 45.2 (CH_2-C4), 55.4 (CH_3-C18), 69.9 (CH-C5), 70.4 (CH_2-C11), 77.5 (CH-C7), 84.7 (C-C2), 111.8 (C-C1), 114.0 (CH-C13, CH-17), 129.6 (CH-C14, CH-16), 130.4 (C-C12), 159.4 (C-C15);

ν_{max} 3426, 2932, 2361, 2160, 1512, 1458, 1366, 1250, 1042, 841 cm^{-1};
LRMS (CI, *iso*-butane) *m/z* (intensity) 377.4 $[M+H]^+$ (14), 121.2 (100), 75.2 (92), 269.3 (16);
HRMS (CI, *iso*-butane) calcd for $C_{22}H_{37}O_3Si$ $[M+H]^+$ 377.2512, found 377.2513.

Data for by-products 413 and 414:
(3*R*,6*S*)-3,6-Dimethyl-1,8-bis-trimethylsilanyl-octa-1,7-diyne 413



413

R_f = 0.95 (dichloromethane);

$[\alpha]^{26}_D$ −19.2 (c = 0.95, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (18H, s, CH_3-C10), 1.16 (6H, d, *J* = 6.9 Hz, CH_3-C9), 1.54-1.56 (4H, m, CH_2-C4, CH_2-C5), 2.45-2.50 (2H, m, CH-C3, CH-C6);

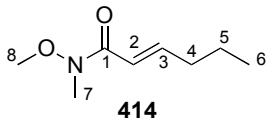
^{13}C NMR (100 MHz, $CDCl_3$) δ 0.4 (CH_3-C10), 21.17 (CH_3-C9), 26.5 (CH-C3, CH-C6), 37.4 (CH_2-C4, CH_2-C5), 84.4 (C-C2, C-C7), 111.9 (C-C1, C-C8);

ν_{max} 2924, 2168, 1458, 1250, 1026, 841 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 279.3 $[M+H]^+$ (14), 69.1 (100), 97.2 (25);

HRMS (CI, *iso*-butane) calcd for $C_{16}H_{31}Si_2$ $[M+H]^+$ 279.1964, found 279.1960.

_N_-Methoxy-_N_-methyl-(E)-hex-2-enamide 414



414

R_f = 0.31 (petroleum ether - diethyl ether, 4:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.4 Hz, CH_3-C6), 1.45-1.55 (2H, m, CH_2-C5), 2.18-2.23 (2H, m, CH_2-C4), 3.23 (3H, s, CH_3-C7), 3.69 (3H, s, CH_3-C8), 6.38 (1H, d, *J* = 15.4 Hz, CH-C2), 6.99 (1H, dt, *J* = 15.4, 7.0 Hz, CH-C3);

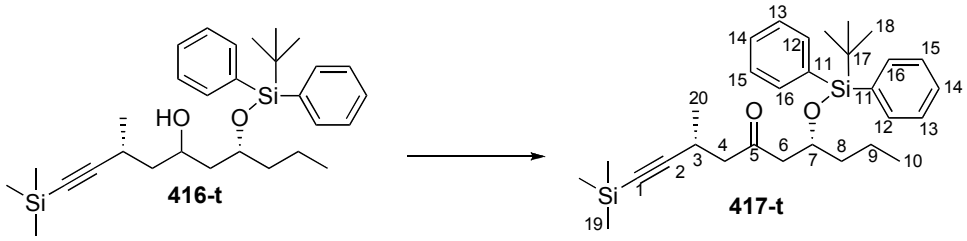
^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3-C6), 21.7 (CH_2-C5), 34.7 (CH_2-C4), 35.1 (CH_3-C7), 61.8 (CH_3-C8), 118.9 (CH-C3), 147.9 (CH-C2), 167.2 (C-C1);

ν_{max} 2932, 2839, 2361, 1658, 1458, 1250, 1173, 1034, 818 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 158.2 $[M+H]^+$ (39), 121.2 (100), 75.1 (48), 137.2 (36);

HRMS (CI, *iso*-butane) calcd for $C_8H_{16}NO_2$ $[M+H]^+$ 158.1181, found 158.1178.

(3*R*,7*R*)-7-(*tert*-Butyl-diphenyl-silanyloxy)-3-methyl-1-trimethylsilanyl-dec-1-yn-5-one 417-t



A solution of the alcohol **416-t** (290 mg, 0.57 mmol) in dichloromethane (15 mL) was added to Dess-Martin periodinane (373 mg, 0.88 mmol) at rt and the suspension was stirred for 1 h. To the reaction mixture was added a mixture (1:3) of sodium hydrogencarbonate solution and saturated sodium persulfate solution (12 mL) and diethyl ether (20 mL) then the mixture was stirred vigorously at rt until two clear phases were obtained (30 min). The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were then washed with a saturated solution of sodium chloride (60 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The mixture was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) to give the ketone **417-t** (259 mg, 92%) as a colourless oil.

R_f = 0.58 (petroleum ether - diethyl ether, 9:1);

$[\alpha]^{25}_D$ −5.2 (*c* = 1.1, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (9H, s, CH_3-C19), 0.73 (3H, t, *J* = 7.3 Hz, CH_3-C10), 1.03 (9H, s, CH_3-C18), 1.07 (3H, d, *J* = 6.9 Hz, CH_3-C20), 1.21–1.28 (2H, m, CH_2-C9), 1.38–1.43 (2H, m, CH_2-C8), 2.24 (1H, dd, *J* = 16.7, 7.4 Hz, CH_2-C4), 2.52 (2H, d, *J* = 6.2 Hz, CH_2-C6), 2.54 (1H, dd, *J* = 16.7, 6.6 Hz, CH_2-C4), 2.85 (1H, app. q, 6.9 Hz, CH-C3), 4.19–4.25 (1H, m, CH-C7), 7.36-7.43 (6H, m, CH-C13, CH-C14, CH-C15), 7.66-7.69 (4H, m, CH-C12, CH-C16);

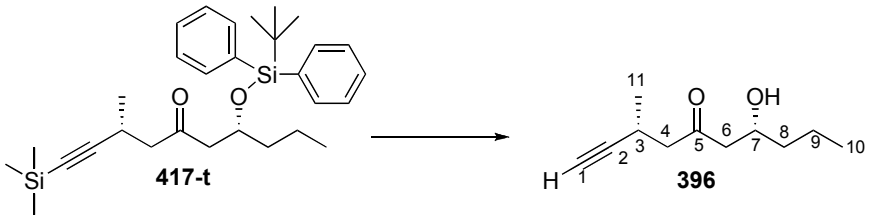
^{13}C NMR (100 MHz, $CDCl_3$) δ 0.3 (CH_3-C19), 14.1 (CH_3-C10), 18.2 (CH_2-C9), 19.5 (C-C17), 20.9 (CH_3-C20), 22.3 (CH-C3), 27.1 (CH_3-C18), 39.5 (CH_2-C8), 50.5 (CH_2-C4), 50.7 (CH_2-C6), 69.7 (CH-C7), 84.3 (C-C2), 110.6 (C-C1), 127.7 (CH-C13, CH-C15), 129.8 (CH-C14), 134.3 (C-C11), 136.0 (CH-C12, CH-C16), 207.1 (C-C5);

ν_{max} 2962, 2862, 2330, 2168, 1713, 1373, 1250, 1111, 1042, 841, 702 cm^{-1};

LRMS (CI, *iso*-butane) *m*/*z* (intensity) 493.4 $[M+H]^+$ (10), 311.3 (100), 415.4 (71), 237.3 (18);

HRMS (CI, *iso*-butane) calcd for $C_{30}H_{45}O_2Si_2$ $[M+H]^+$ 493.2958, found 493.2964.

(3*R*,7*R*)-7-Hydroxy-3-methyl-dec-1-yn-5-one 396



To a solution of ketone **417-t** (90.0 mg, 183 µmol) and acetic acid (20 µl, 0.35 mmol) in THF (24 mL) was added dropwise TBAF (720 µl of a 1 M solution in THF, 720 µmol) at 0 ºC and the mixture was stirred and allowed to warm to rt and stirred for 72 h. Water was added (5 mL) and the solution was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with saturated sodium chloride solution (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 4:1) to give the alcohol **396** (31 mg, 92%) as a colourless oil.

R_f = 0.38 (petroleum ether - diethyl ether, 3:2);

$[\alpha]^{25}_D$ −30.8 (*c* = 0.9, $CHCl_3$);

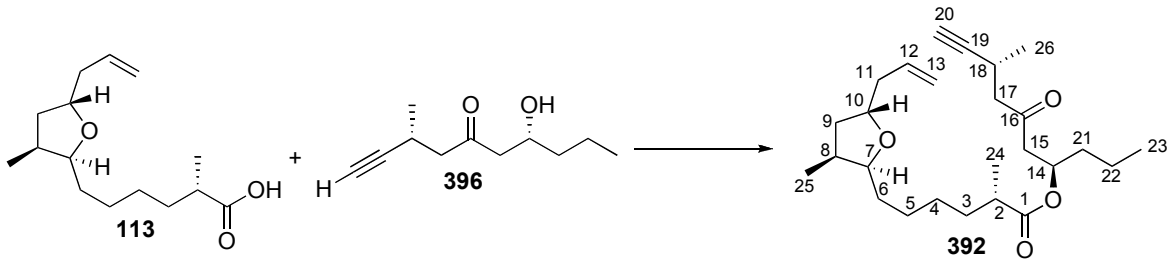
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 6.9 Hz, CH_3-C10), 1.21 (3H, d, *J* = 6.9 Hz, CH_3-C11), 1.33–1.53 (4H, m, CH_2-C8, CH_2-C9), 2.05 (1H, d, *J* = 2.4 Hz, CH-C1), 2.51 (1H, dd, *J* = 16.6, 6.5 Hz, CH_2-C4), 2.52 (1H, dd, *J* = 17.5, 9.0 Hz, CH_2-C6), 2.63 (1H, dd, *J* = 17.5, 2.8 Hz, CH_2-C6), 2.70 (1H, dd, *J* = 16.6, 7.5 Hz, CH_2-C4), 2.87 (1H, d, *J* = 3.5 Hz, OH), 2.98 (1H, app. dqdd, *J* = 7.5, 6.9, 6.5, 2.4 Hz, CH-C3), 4.04–4.11 (1H, m, CH-C7);

^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3-C10), 18.8 (CH_2-C9), 20.8 (CH_3-C11), 21.3 (CH-C3), 38.7 (CH_2-C8), 49.9 (CH_2-C6), 50.1 (CH_2-C4), 67.4 (CH-C7), 68.9 (CH-C1), 87.6 (C-C2), 209.8 (C-C5);

ν_{max} 3426, 3302, 2338, 1705, 1458, 1373, 1118, 1018 cm^{-1};

LRMS (CI, *iso*-butane) *m*/*z* (intensity) 183.3 $[M+H]^+$ (12), 165.3 (100), 111.2 (63); HRMS (CI, *iso*-butane) calcd for $C_{11}H_{19}O_2$ $[M+H]^+$ 183.1385, found 183.1387.

(1*R*,5*R*)-5-Methyl-3-oxo-1-propyl-hept-6-ynyl (S)-6-((2S,3S,5S)-5-prop-2-en-1-yl-3-methyl-tetrahydro-furan-2-yl)-2-methyl-hexanoate 392



To a solution of acid **113** (5.3 mg, 21 µmol), hydroxyketone **396** (5.0 mg, 27 µmol), DMAP (26.0 mg, 210 µmol) and triethylamine (14 µL, 0.11 mmol) in toluene (1 mL) was added 2,4,6-trichlorobenzoyl chloride (20 µl, 84 µmol) at −78 °C, the mixture was stirred for 30 min then allowed to warm to 0 °C. Saturated sodium hydrogencarbonate solution (2 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with saturated sodium chloride solution (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 9:1) to give the ester **392** (7.1 mg, 81%) as a colourless oil.

R_f = 0.76 (petroleum ether - diethyl ether, 6:4);

$[\alpha]^{25}_D$ +3.3 (*c* = 1.5, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.0 Hz, CH_3-C24), 0.91 (3H, t, *J* = 7.2 Hz, CH_3-C23), 1.11 (3H, d, *J* = 6.9 Hz, CH_3-C25), 1.19 (3H, d, *J* = 6.9 Hz, CH_3-C26), 1.25–1.80 (14H, m, CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C9, CH_2-C21, CH_2-C22), 2.04 (1H, d, *J* = 2.4 Hz, CH-C20), 2.15–2.24 (2H, m, CH-C2, CH_2-C11), 2.29–2.42 (2H, m, CH-C8, CH_2-C11), 2.49 (1H, dd, *J* = 16.9, 6.9 Hz, CH_2-C17), 2.60 (1H, dd, *J* = 16.2, 5.7 Hz, CH_2-C15), 2.69 (1H, dd, *J* = 16.9, 6.9 Hz, CH_2-C17), 2.72 (1H, dd, *J* = 16.2, 7.0 Hz, CH_2-C15), 2.96 (1H, qddd, *J* = 6.9, 6.9, 6.9, 2.4 Hz, CH-C18), 3.83 (1H, dt, *J* = 7.7, 5.2 Hz, CH-C7), 4.10 (1H, app. tt, *J* = 6.8, 6.8

Hz, CH-C10), 5.03–5.10 (2H, m, CH_2-C13), 5.20–5.26 (1H, m, CH-C14), 5.80 (1H, ddt, *J* = 17.1, 10.2, 7.0 Hz, CH-C12);

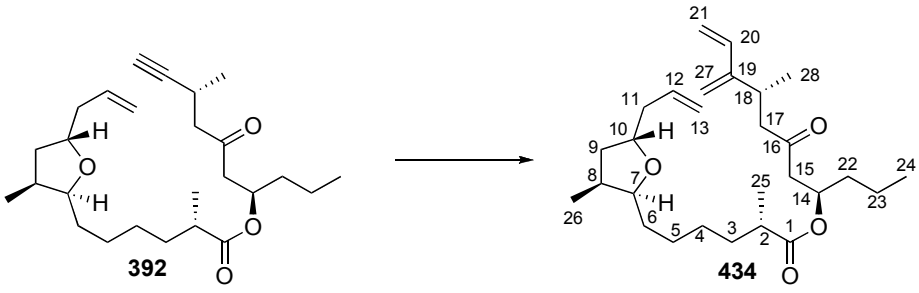
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3-C23), 14.1 (CH_3-C24), 17.1 (CH_3-C25), 18.6 (CH_2-C22), 20.8 (CH_3-C26), 21.3 (CH-C18), 26.6 (CH_2-C5), 27.6 (CH_2-C4), 30.5 (CH_2-C3), 33.8 (CH_2-C6), 36.0 (CH-C2), 36.4 (CH_2-C21), 39.4 (CH_2-C9), 39.8 (CH-C8), 41.2 (CH_2-C11), 47.7 (CH_2-C15), 49.8 (CH_2-C17), 68.7 (CH-C20), 69.8 (CH-C14), 76.1 (CH-C10), 81.4 (CH-C7), 87.7 (C-C19), 116.9 (CH_2-C13), 135.2 (CH-C12), 176.3 (C-C1), 205.4 (C-C16);

ν_{max} 3309, 2931, 2870, 2338, 1728, 1643, 1458, 1373, 1165, 1088, 1026, 918 cm^{-1};

LRMS (FAB/NOBA) *m/z* (intensity) 419.3 $[M+H]^+$ (29), 43.9 (100), 69.9 (79), 164.9 (58);

HRMS (FAB/NOBA) calcd for $C_{26}H_{42}O_4$ $[M+H]^+$ 419.3161, found 419.3156.

(1*R*,5*R*)-5-methyl-6-methylene-3-oxo-1-propyl-oct-7-enyl (*S*)-6-[(2S,3S,5S)-5-prop-2-en-1-yl-3-methyl-tetrahydro-furan-2-yl]-2-methyl-hexanoate 434



Ethylene was bubbled through a solution of the enyne **392** (5.0 mg, 12 µmol) in dichloromethane (30 mL) for 5 min and the solution was then heated to reflux and. A solution of the ruthenium complex **43** (0.5 mg, 1.2 µmol) in dichloromethane (1 mL) was added to the solution of the enyne. The mixture was heated at reflux for 15 min under ethylene atmosphere then allowed to cool to rt, silica (100 mg) was added, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (pure petroleum ether to petroleum ether - diethyl ether, 9:1) to give the triene **434** (4.3 mg, 81%) as colourless oil.

R_f = 0.81 (petroleum ether - diethyl ether, 6:4);

$[\alpha]^{25}_D$ +4.3 (*c* = 1.6, $CHCl_3$);

^{1}H NMR (500 MHz, C_6D_6) δ 0.77 (3H, d, *J* = 7.1 Hz, CH_3-C25), 0.83 (3H, t, *J* = 7.5 Hz, CH_3-C24), 1.06 (3H, d, *J* = 6.8 Hz, CH_3-C28), 1.14 (3H, d, *J* = 7.0 Hz, CH_3-C26), 1.40–1.64 (14H, m, CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C9, CH_2-C22, CH_2-C23), 1.93-2.00 (1H, m, CH-C2), 2.09–2.49 (7H, m, CH-C8, CH_2-C11, CH_2-C15, CH_2-C17), 3.21-3.16 (1H, m, CH-C18), 3.82 (1H, dt, *J* = 8.4, 4.8 Hz, CH-C7), 4.06 (1H, app. tt, *J* = 6.8, 6.5 Hz, CH-C10), 4.87 (1H, brs, CH_2-C27), 4.94–4.99 (2H, m, CH_2-C21, CH_2-C27), 5.04-5.11 (2H, m, CH_2-C13), 5.32 (1H, d, *J* = 17.6 Hz, CH_2-C21), 5.32 (1H, tt, *J* = 7.3, 5.2 Hz, CH-C14), 5.89 (1H, ddt, *J* = 17.3, 10.3, 6.9 Hz, CH-C12), 6.26 (1H, dd, *J* = 17.6, 10.7 Hz, CH-C20);

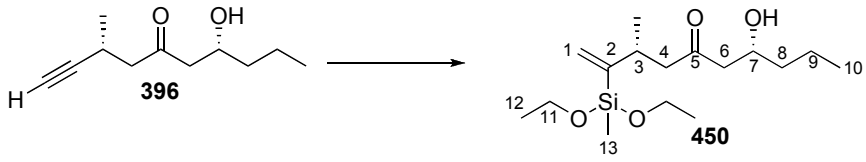
^{13}C NMR (125 MHz, C_6D_6) δ 14.0 (CH_3-C24), 14.2 (CH_3-C25), 17.5 (CH_2-C23), 18.8 (CH_3-C26), 20.0 (CH_3-C28), 27.1 (CH_2-C5), 27.4 (CH_2-C4), 29.7 (CH-C18), 30.2 (CH_2-C3), 30.8 (CH_2-C6), 36.3 (CH-C2), 36.7 (CH_2-C22), 39.6 (CH_2-C9), 40.1 (CH-C8), 41.6 (CH_2-C11), 47.8 (CH_2-C15), 49.7 (CH_2-C17), 69.8 (CH-C14), 76.1 (CH-C10), 81.3 (CH-C7), 113.5 (CH_2-C27), 113.8 (CH_2-C21), 116.6 (CH_2-C13), 135.8 (CH-C12), 135.8 (CH-C20), 151.3 (C-C19), 180.7 (C-C1), 205.3 (C-C16);

ν_{max} 2932, 2862, 2361, 1728, 1458, 1381, 1258, 1165, 1088, 1026, 910 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 447.5 $[M+H]^+$ (11), 75.1 (100), 193.3 (33);

HRMS (CI, *iso*-butane) calcd for $C_{28}H_{47}O_4$ $[M+H]^+$ 447.3474, found 44734.70.

(3*R*,7*R*)-2-(Diethoxy-methyl-silanyl)-7-hydroxy-3-methyl-dec-1-en-5-one 450



To a solution of hydroxyketone **396** (9.5 mg, 52 μmol) and diethoxymethylsilane (10 μl, 62 μmol) in dichloromethane (100 μl) was added $[Cp^*Ru(MeCN)_3]PF_6$ (1.2 mg, 2.4 μmol) in dichloromethane (50 μl) at 0 ºC and the mixture was allowed to warm to rt for 30 min. The resulting mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 5:1) to give the alcohol **450** (5.2 mg, 32%) as a colourless oil.

R_f = 0.40 (petroleum ether - diethyl ether, 6:4);

$[\alpha]^{26}_D$ −5.1 (*c* = 1.2, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.22 (3H, s, CH_3-C14), 0.92 (3H, t, *J* = 7.0 Hz, CH_3-C10), 1.06 (3H, d, *J* = 6.9 Hz, CH_3-C11), 1.21 (3H, t, *J* = 7.0 Hz, CH_3-C13), 1.22 (3H, t, *J* = 7.0 Hz, CH_3-C13), 1.29–1.52 (4H, m, CH_2-C8, CH_2-C9), 2.39 (1H, dd, *J* = 16.1, 8.1 Hz, CH_2-C4), 2.46 (1H, dd, *J* = 17.6, 9.3 Hz, CH_2-C6), 2.60 (1H, dd, *J* = 17.6, 2.6 Hz, CH_2-C6), 2.74 (1H, dd, *J* = 16.1, 6.0 Hz, CH_2-C4), 2.91 (1H, app. dqd, *J* = 8.0, 6.9, 6.0 Hz, CH-C3), 3.10 (1H, d, *J* = 3.2 Hz, -OH), 3.76 (2H, q, *J* = 7.0 Hz, CH_2-C12), 3.77 (2H, t, *J* = 7.0 Hz, CH_2-C12), 3.99–4.06 (1H, m, CH-C7), 5.55 (1H, d, *J* = 2.2 Hz, CH_2-C1 *cis*), 5.70 (1H, dd, *J* = 2.2 , 1.1 Hz, CH_2-C1 *trans*);

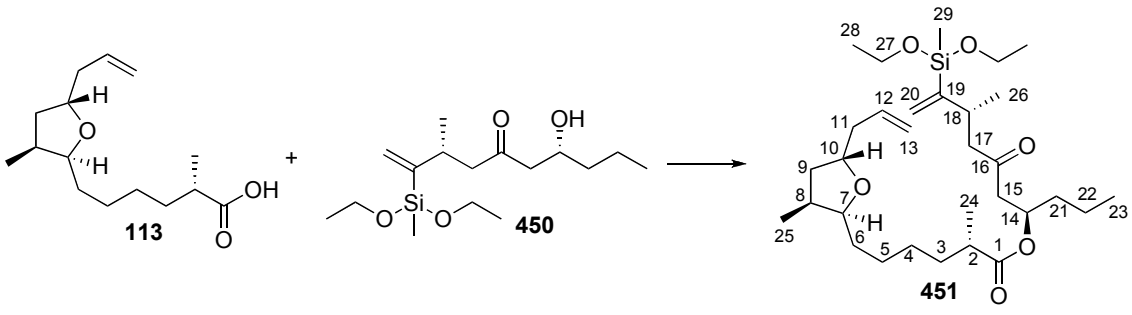
^{13}C NMR (125 MHz, $CDCl_3$) δ 1.2 (CH_3-C14), 14.1 (CH_3-C10), 18.4 (CH_3-C13), 18.8 (CH_2-C9), 20.6 (CH_3-C11), 35.0 (CH-C3), 38.7 (CH_2-C8), 49.6 (CH_2-C4), 50.2 (CH_2-C6), 58.4 (CH_2-C12), 67.5 (CH-C7), 126.8 (CH_2-C1), 151.8 (C-C2), 212.0 (C-C5);

ν_{max} 3464, 2963, 2924, 2360, 1712, 1443, 1257, 1080, 949 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 271.3 $[M-OCH_2CH_3]^+$ (7), 89.1 (100), 97.2 (9);

HRMS (CI, *iso*-butane) calcd for $C_{14}H_{27}O_3Si$ $[M-OCH_2CH_3]^+$ 217.1729, found 217.1732.

(1*R*,5*R*)-6-(Diethoxy-methyl-silanyl)-5-methyl-3-oxo-1-propyl-hept-6-enyl (*S*)-6-[(2*S*,3*S*,5*S*)-5-prop-2-en-1-yl-3-methyl-tetrahydro-furan-2-yl]-2-methyl-hexanoate 451



To a solution of acid **113** (4.0 mg, 16 μmol), hydroxyketone **450** (4.0 mg, 13 μmol), DMAP (13.0 mg, 105 μmol) and triethylamine (7.0 μL, 52 μmol) in toluene (0.8 mL) was added 2,4,6-trichlorobenzoyl chloride (10 μl, 42 μmol) at −78 ºC, the mixture was stirred for 30 min then allowed to warm to 0 ºC. Saturated

sodium hydrogencarbonate solution (2 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 3 mL). The combined organic phases were washed with saturated sodium chloride solution (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 9:1) to give the ester **451** (6.3 mg, 88%) as a colourless oil.

R_f = 0.81 (petroleum ether - diethyl ether, 6:4);

$[\alpha]^{24}_D$ +2.7 (*c* = 1.5, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.21 (3H, s, CH_3-C29), 0.89 (3H, d, *J* = 7.0 Hz, CH_3-C24), 0.90 (3H, t, *J* = 7.2 Hz, CH_3-C23), 1.04 (3H, d, *J* = 6.9 Hz, CH_3-C26), 1.10 (3H, d, *J* = 6.9 Hz, CH_3-C25), 1.21 (3H, t, *J* = 7.0 Hz, CH_3-C28), 1.22 (3H, t, *J* = 7.0 Hz, CH_2-C28), 1.24–1.49 (12H, m, CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C9, CH_2-C22), 1.69–1.78 (2H, m, CH_2-C21), 2.15–2.25 (2H, m, CH-C8, CH_2-C11), 2.30–2.42 (3H, m, CH-C2, CH_2-C11, CH_2-C17), 2.55 (1H, dd, *J* = 16.2, 5.9 Hz, CH_2-C15), 2.68 (1H, dd, *J* = 16.2, 6.1 Hz, CH_2-C17), 2.69 (1H, dd, *J* = 16.2, 7.7 Hz, CH_2-C15), 2.89 (1H, app. q, *J* = 6.9 Hz, CH-C18), 3.75 (2H, q, *J* = 7.0 Hz, CH_2-C27), 3.76 (2H, q, *J* = 7.0 Hz, CH_2-C27), 3.83 (1H, dt, *J* = 7.9, 5.1 Hz, CH-C7), 4.10 (1H, app. tt, *J* = 6.8, 6.8 Hz, CH-C10), 5.02–5.10 (2H, m, CH_2-C13), 5.23 (1H, dtd, *J* = 7.7, 6.6, 5.9 Hz, CH-C14), 5.54 (1H, d, *J* = 2.3 Hz, CH_2-C20), 5.69 (1H, d, *J* = 1.1 Hz, CH_2-C20), 5.80 (1H, ddt, *J* = 17.2, 10.2, 6.9 Hz, CH-C12);

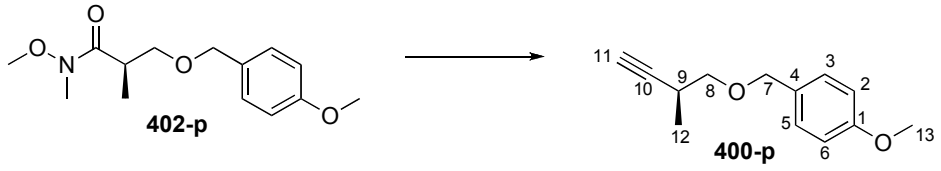
^{13}C NMR (125 MHz, $CDCl_3$) δ 1.0 (CH_3-C29), 14.0 (CH_3-C23), 14.1 (CH_3-C24), 17.1 (CH_2-C22), 18.5 (CH_3-C28), 18.6 (CH_3-C25), 20.5 (CH_3-C26), 29.2 (CH_2-C5), 29.9 (CH_2-C4), 30.4 (CH_2-C3), 33.2 (CH_2-C6), 34.7 (CH-C18), 36.0 (CH-C2), 36.4 (CH_2-C9), 39.4 (CH_2-C21), 39.8 (CH-C8), 41.2 (CH_2-C11), 47.6 (CH_2-C15), 50.0 (CH_2-C17), 58.4 (CH_2-C27), 69.9 (CH-C14), 74.9 (CH-C10), 81.4 (CH-C7), 116.9 (CH_2-C13), 126.7 (CH_2-C20), 135.3 (CH-C12), 147.0 (C-C19), 170.9 (C-C1), 210.4 (C-C16);

ν_{max} 2924, 2854, 2361, 1736, 1458, 1373, 1258, 1165, 1080, 1026, 802 cm^{-1};

LRMS (FAB) *m/z* (intensity) 575.4 $[M+Na]^+$ (38), 252.9 (100), 59.7 (46), 132.9 (33);

HRMS (FAB) calcd for $C_{31}H_{56}O_6SiNa$ $[M+Na]^+$ 575.3751, found 575.3744.

1-Methoxy-4-[(*S*)-2-methyl-but-3-ynyloxymethyl]-benzene 400-p



Diisobutylaluminium hydride (32 mL of a 1 M solution in dichloromethane, 32 mmol) was added over 30 min to the Weinreb amide **402-p** (4.0 g, 15 mmol) in THF (70 mL) at −78 °C and the mixture was stirred for 1 h. The reaction was quenched carefully with methanol (25 mL) and the mixture was stirred for 15 min and then allowed to warm to 0 °C. Potassium carbonate (4.3 g, 31 mmol) was added followed by a solution of Ohira-Bestmann reagent **407** (4.0 g, 21 mmol) in methanol (10 mL) and the resulting slurry was allowed to warm to rt and stirred for 14 h. A saturated solution of potassium sodium tartrate (100 mL) was added and the mixture was stirred vigorously at rt until two clear phases were obtained (2 h). The aqueous phase was extracted with diethyl ether (3 × 200 mL) and the combined organic extracts were then washed with saturated sodium chloride solution (300 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient from pure petroleum ether to petroleum ether - diethyl ether, 30:1) to give the alkyne **400-p** (1.4 g, 46%) as a colourless oil.

R_f = 0.62 (petroleum ether - diethyl ether, 4:1);

$[\alpha]^{25}_D$ +3.1 (c = 0.9, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, d, *J* = 6.9 Hz, CH_3-C12), 2.07 (1H, d, *J* = 2.4 Hz, CH-C11), 2.73 (1H, dqdd, *J* = 7.2, 6.9, 6.3, 2.4 Hz, CH-C9), 3.35 (1H, dd, *J* = 9.1, 7.2 Hz, CH_2-C8), 3.51 (1H, dd, *J* = 9.1, 6.3 Hz, CH_2-C8), 3.81 (3H, s, CH_3-C13), 4.49 (1H, s, CH_2-C7), 4.50 (1H, s, CH_2-C7), 6.88 (2H, d, *J* = 8.7 Hz, CH-C3, CH-C5), 7.27 (2H, d, *J* = 8.6 Hz, CH-C2, CH-C6);

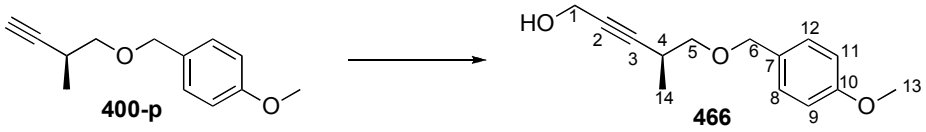
^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (CH_3-C12), 26.7 (CH-C9), 55.4 (CH_3-C13), 69.1 (CH-C11), 72.8 (CH_2-C7), 73.6 (CH_2-C8), 86.6 (C-C10), 113.9 (CH-C3, CH-C5), 129.4 (CH-C2, CH-C6), 130.4 (C-C4), 159.3 (C-C1);

ν_{max} 3294, 2909, 2855, 2338, 1612, 1512, 1458, 1250, 1088, 1034, 818 cm^{-1};

LRMS (EI) *m/z* (intensity) 204.1 $[M]^+$, 121.0, 84.9, 82.9;

HRMS (EI) calcd for $C_{13}H_{16}O_2$ $[M]^+$ 204.1150, found 204.1146.

(*S*)-5-(4-Methoxy-benzyloxy)-4-methyl-pent-2-yn-1-ol 466



n-Butyllithium (1.5 mL of a 2.5 M solution in hexanes, 3.7 mmol) was added over 10 min to a solution of the alkyne **400-p** (0.48 g, 2.3 mmol) in THF (10 mL) at −78 °C and the mixture was stirred for 1 h. To the reaction mixture was added a suspension of paraformaldehyde (0.29 g, 9.8 mmol) in THF (2 mL) and the mixture was stirred for a further 1.5 h, then allowed to warm to rt. Saturated ammonium chloride solution (5 mL) was added and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with saturated sodium chloride solution (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 3:1) to give the alkyne **466** (0.46 g, 85%) as a colourless oil.

R_f = 0.25 (petroleum ether - diethyl ether, 3:2);

$[\alpha]^{25}_D$ −4.6 (c = 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (3H, d, *J* = 6.9 Hz, CH_3-C14), 1.91 (1H, brs, OH), 2.75 (1H, dqdt, *J* = 7.2, 6.9, 6.4, 2.0 Hz, CH-C4), 3.33 (1H, dd, *J* = 9.0, 7.2 Hz, CH_2-C5), 3.47 (1H, dd, *J* = 9.0, 6.4 Hz, CH_2-C5), 3.80 (3H, s, CH_3-C13), 4.23 (2H, d, *J* = 3.5 Hz, CH_2-C1), 4.48 (2H, s, CH_2-C6), 6.88 (2H, d, *J* = 8.8 Hz, CH-C8, CH-C12), 7.26 (2H, d, *J* = 8.8 Hz, CH-C9, CH-C11);

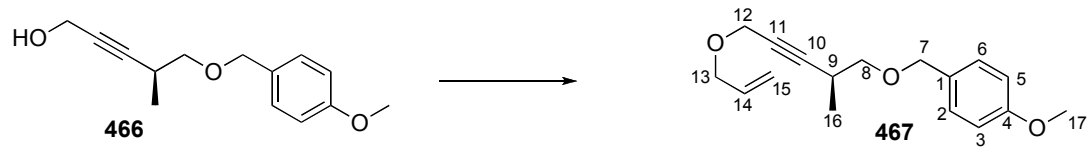
^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7 (CH_3-C14), 26.8 (CH-C4), 51.4 (CH_2-C1), 55.4 (CH_3-C13), 72.8 (CH_2-C6), 73.7 (CH_2-C5), 79.4 (C-C2), 88.2 (C-C3), 113.9 (CH-C8, CH-C12), 129.4 (CH-C9, CH-C11), 130.3 (C-C7), 159.3 (C-C10);

ν_{max} 3387, 2963, 2862, 1612, 1512, 1456, 1246, 1088, 1032, 810 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 217.3 $[M-OH]^+$ (7), 121.2 (100), 122.2 (40), 203.3 (12);

HRMS (EI) calcd for $C_{14}H_{17}O_2$ $[M-OH]^+$ 217.1229, found 217.1234.

4-Methoxy-1-[(*S*)-5-prop-2-en-1-yloxy-2-methyl-pent-3-ynyloxymethyl]-benzene 467



Sodium hydride (85 mg of a 60% dispersion in oil, 0.22 mmol) was washed with petroleum ether (3 × 1 mL). To the suspension of NaH in THF (0.5 mL) at 0 ºC, the alcohol **466** (0.42 g, 0.18 mmol) in THF (1 mL) was added over 5 min and the mixture was stirred for 1 h. To the reaction mixture was added 3-iodo-1-propene (35 µL, 0.36 mmol) and the reaction mixture was allowed to warm to rt over 2 h. A saturated solution of ammonium chloride (1 mL) was added and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic phases were washed with saturated sodium chloride solution (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 9:1) to give the alkyne **467** (41 mg, 83%) as a colourless oil.

R_f = 0.65 (petroleum ether - diethyl ether, 3:2);

$[\alpha]^{25}_D$ −3.9 (c = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, d, *J* = 6.9 Hz, CH_3-C16), 2.77 (1H, dqd, *J* = 7.5, 6.9, 6.1 Hz, CH-C9), 3.34 (1H, dd, *J* = 9.1, 7.5 Hz, CH_2-C8), 3.50 (1H, dd, *J* = 9.1, 6.1 Hz, CH_2-C8), 3.81 (3H, s, CH_3-C17), 4.04 (2H, dt, *J* = 5.8, 1.3 Hz, CH_2-C13), 4.14 (2H, d, *J* = 2.0 Hz, CH_2-C12), 4.48 (2H, d, *J* = 1.6 Hz, CH_2-C7), 5.20 (1H, d, *J* = 10.4 Hz, CH_2-C15 *cis*), 5.29 (1H, d, *J* = 17.2 Hz, CH_2-C15 *trans*), 5.91 (1H, ddt, *J* = 17.2, 10.4, 5.8 Hz, CH-C14), 6.87 (2H, d, *J* = 8.6 Hz, CH-C2, CH-C6), 7.26 (2H, d, *J* = 8.6 Hz, CH-C3, CH-C5);

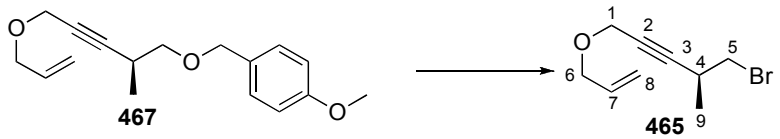
^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (CH_3-C16), 26.9 (CH-C9), 57.8 (CH_3-C17), 58.7 (CH_2-C13), 70.6 (CH_2-C7), 71.2 (CH_2-C12), 72.8 (CH_2-C8), 73.8 (C-C11), 88.9 (C-C10), 113.6 (CH-C2, CH-C6), 117.8 (CH_2-C15), 129.4 (CH-C3, CH-C5), 130.4 (C-C1), 134.3 (CH-C14), 159.3 (C-C4);

ν_{max} 2853, 1612, 1514, 1458, 1248, 1173, 1086, 1036, 820 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 275.3 $[M+H]^+$ (3), 121.2 (100), 122.2 (38), 217.3 (27);

HRMS (EI) calcd for $C_{17}H_{23}O_3$ $[M+H]^+$ 275.1647, found 275.1654.

(*S*)-1-(Prop-2-en-1-yloxy)-5-bromo-4-methyl-pent-2-yne 465



To a solution of DDQ (0.54 g, 2.38 mmol) in a 10:1 mixture of dichloromethane and water (44 mL) at 0 ºC, the alkyne **467** (0.55 g, 2.0 mmol) in dichloromethane (5.0 mL) was added in one portion. The reaction mixture was stirred for 2 h at rt and then washed sequentially with saturated sodium carbonate solution (50 mL), water (50 mL) and a saturated solution of sodium chloride (50 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated and filtered through a short pad of silica gel (petroleum ether - diethyl ether, 6:1) to give the crude alcohol, which was used without any further purification.

To a solution of the crude alcohol and triphenylphosphine (0.63 g, 2.4 mmol) in dichloromethane (15 mL) at 0 ºC was added, portionwise, recrystallised *N*-bromosuccinimide (0.44 g, 2.3 mmol) and the mixture was stirred and allowed to warm to rt and stirred for 14 h. The mixture was purified by flash chromatography on silica gel (petroleum ether) to give the bromide **465** (0.37 g, 86%) as a colourless oil.

R_f = 0.49 (petroleum ether - diethyl ether, 9:1);

$[\alpha]^{24}_D$ −2.5 (c = 1.2, $CHCl_3$);

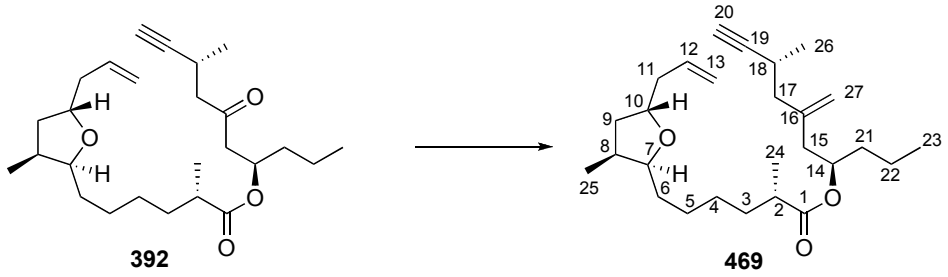
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (3H, d, *J* = 6.9 Hz, CH_3-C9), 2.89 (1H, dqd, *J* = 7.1, 6.9, 5.7 Hz, CH-C4), 3.35 (1H, dd, *J* = 9.8, 7.1 Hz, CH_2-C5), 3.47 (1H, dd, *J* = 9.8, 5.7 Hz, CH_2-C5), 4.06 (2H, dt, *J* = 5.8, 1.2 Hz, CH_2-C6), 4.15 (1H, s, CH_2-C1), 4.16 (1H, s, CH_2-C1), 5.21 (1H, d, *J* = 10.4 Hz, CH_2-C8 *cis*), 5.31 (1H, d, *J* = 17.2 Hz, CH_2-C8 *trans*), 5.91 (1H, ddt, *J* = 17.2, 10.4, 5.8 Hz, CH-C7);

^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8 (CH_3-C9), 29.0 (CH-C4), 37.5 (CH_2-C5), 57.6 (CH_2-C6), 70.7 (CH_2-C1), 78.1 (C-C2), 87.8 (C-C3), 118.0 (CH_2-C8), 134.2 (CH-C7); ν_{max} 2932, 2855, 2345, 1450, 1358, 1088, 494 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 217.2 $[M+H]^+$ (22), 219.2 $[M+H]^+$ (20), 75.1 (100), 69.1 (32);

HRMS (EI) calcd for $C_9H_{14}O^{79}Br$ $[M+H]^+$ 217.0228, $C_9H_{14}O^{81}Br$ $[M+H]^+$ 219.0208, found 217.0226, 217.0209.

(1*R*,5*R*)-5-methyl-3-methylene-1-propyl-hept-6-ynyl (*S*)-6-[(2*S*,3*S*,5*S*)-5-prop-2-en-1-yl-3-methyl-tetrahydro-furan-2-yl]-2-methyl-hexanoate 469



To the suspension of Nysted reagent **132** (325 mg of a 20% w/w suspension in THF, 143 μmol) in THF (0.5 mL) at 0 ºC, was added titanium(IV) chloride (2 drops) and the resulting slurry was stirred for 30 min at 0 ºC. Ketone **392** (5.0 mg, 12 μmol) in THF (0.5 mL) was added and the suspension was stirred for 1 h at 0 ºC. The resulting slurry was filtered through a short pad of wet alumina (10 g alumina for 10% w/w of water) and the resulting solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) to give the alkyne **469** (4.4 mg, 88%) as a colourless oil.

R_f = 0.81 (petroleum ether - diethyl ether, 7:3);

$[\alpha]^{26}_D$ +6.4 (*c* = 1.1, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.0 Hz, CH_3-C24), 0.90 (3H, t, *J* = 7.3 Hz, CH_3-C23), 1.11 (3H, d, *J* = 6.8 Hz, CH_3-C25), 1.18 (3H, d, *J* = 6.8 Hz, CH_3-C26), 1.27–1.80 (14H, m, CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C9, CH_2-C21, CH_2-C22), 2.04 (1H, d, *J* = 2.4 Hz, CH-C20), 2.14–2.23 (4H, m, CH-C2, CH_2-C15, CH_2-C17), 2.25–2.29 (2H, m, CH-C11, CH_2-C15), 2.30–2.42 (2H, m, CH-C8, CH_2-C11),

2.62 (1H, app. qd, *J* = 6.8, 2.4 Hz, CH-C18), 3.82 (1H, dt, *J* = 7.9, 5.1 Hz, CH-C7), 4.10 (1H, app. tt, *J* = 6.8, 6.8 Hz, CH-C10), 4.87 (1H, s, CH_2-C27), 4.88 (1H, s, CH_2-C27), 4.98–5.11 (3H, m, CH_2-C13, CH-C14), 5.80 (1H, ddt, *J* = 17.1, 10.3, 7.0 Hz, CH-C12);

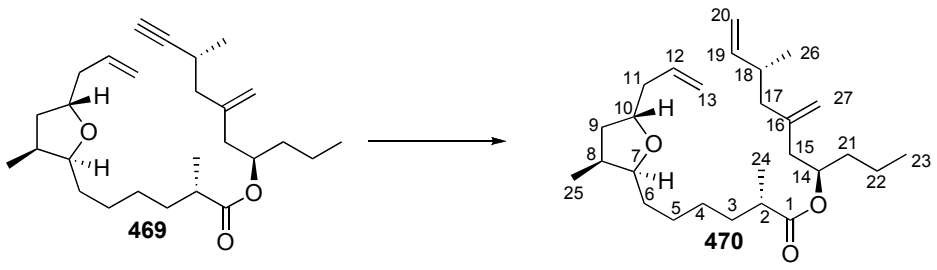
^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (CH_3-C23), 14.1 (CH_3-C24), 17.4 (CH_2-C22), 18.8 (CH_3-C25), 20.9 (CH_3-C26), 24.3 (CH-C18), 26.7 (CH_2-C5), 27.7 (CH_2-C4), 30.4 (CH_2-C3), 33.9 (CH_2-C6), 35.9 (CH-C2), 36.5 (CH_2-C21), 39.4 (CH_2-C9), 40.0 (CH-C8), 41.0 (CH_2-C11), 41.2 (CH_2-C15), 43.1 (CH_2-C17), 68.7 (CH-C20), 71.5 (CH-C14), 76.1 (CH-C10), 81.4 (CH-C7), 90.0 (C-C19), 114.9 (CH_2-C27), 116.9 (CH_2-C13), 135.2 (CH-C12), 142.8 (C-C16), 176.8 (C-C1);

ν_{max} 3307, 2916, 2849, 2362, 1730, 1463, 1379, 1260, 1169, 1092, 1002, 910 cm^{-1};

LRMS (CI, *iso*-butane) *m/z* (intensity) 417.5 $[M+H]^+$ (12), 121.2 (100), 87.1 (42);

HRMS (CI, *iso*-butane) calcd for $C_{27}H_{45}O_3$ $[M+H]^+$ 417.3369, found 417.3358.

(1*R*,5*R*)-5-methyl-3-methylene-1-propyl-hept-6-enyl (*S*)-6-[(2*S*,3*S*,5*S*)-5-prop-2-en-1-yl-3-methyl-tetrahydro-furan-2-yl]-2-methyl-hexanoate 470



To a solution of alkyne **469** (4 mg, 9.6 μmol) and quinoline (30 μg, 0.23 μmol) in toluene (1.5 mL) was added Lindlar catalyst (1.0 mg of 5% w/w supported on $CaCO_3$, 0.47 μmol) at rt. The atmosphere was purged twice with hydrogen and the mixture was stirred for 4 h at rt under an atmosphere of hydrogen. The suspension was filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient elution from pure petroleum ether to petroleum ether - diethyl ether, 19:1) to give the

triene **470** (3.3 mg, 81%) as a colourless oil. NMR data are matching the literature.[213]

R_f = 0.85 (petroleum ether - diethyl ether, 3:2);

$[\alpha]^{26}_D$ +7.0 (*c* = 1.0, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.0 Hz, CH_3-C24), 0.90 (3H, t, *J* = 7.2 Hz, CH_3-C23), 0.98 (3H, d, *J* = 6.7 Hz, CH_3-C26), 1.11 (3H, d, *J* = 6.8 Hz, CH_3-C25), 1.32–1.52 (10H, m, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C21, CH_2-C22), 1.63–1.78 (4H, m, CH_2-C3, CH_2-C9), 2.02 (1H, dd, *J* = 14.2, 7.7 Hz, CH_2-C17), 2.05 (1H, dd, *J* = 14.2, 7.2 Hz, CH_2-C17), 2.15–2.23 (3H, m, CH-C2, CH_2-C11, CH_2-C15), 2.26 (1H, dd, *J* = 14.5, 7.8 Hz, CH-C15), 2.29–2.40 (3H, m, CH-C8, CH_2-C11, CH-C18), 3.83 (1H, dt, *J* = 7.8, 5.1 Hz, CH-C7), 4.10 (1H, app. tt, *J* = 6.9, 6.9 Hz, CH-C10), 4.77 (1H, s, CH-C27), 4.79 (1H, s, CH-C27), 4.91 (1H, d, *J* = 10.3 Hz, CH_2-C20), 4.96 (1H, d, *J* = 17.4 Hz, CH-C20), 5.00–5.10 (3H, m, CH_2-C13, CH-C14), 5.80 (1H, ddd, *J* = 17.4, 10.4, 7.1 Hz, CH-C19), 5.80 (1H, ddt, *J* = 17.2, 10.3, 7.0 Hz, CH-C12);

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 (CH_3-C23), 14.1 (CH_3-C24), 17.4 (CH_3-C26), 18.8 (CH_3-C22), 20.0 (CH_3-C25), 26.7 (CH_2-C5), 27.7 (CH_2-C4), 30.4 (CH_2-C3), 34.0 (CH_2-C6), 35.7 (CH-C2), 36.0 (CH-C18), 36.5 (CH_2-C21), 39.4 (CH_2-C9), 40.0 (CH-C8), 41.1 (CH_2-C15), 41.2 (CH_2-C11), 43.0 (CH_2-C17), 71.6 (CH-C14), 76.2 (CH-C10), 81.5 (CH-C7), 112.7 (CH_2-C20), 114.1 (CH_2-C27), 116.9 (CH_2-C13), 135.2 (CH-C12), 143.9 (C-C16), 144.3 (CH-C19), 176.7 (C-C1);

ν_{max} 2957, 2917, 2848, 1734, 1459, 1277, 1167, 912 cm^{-1};

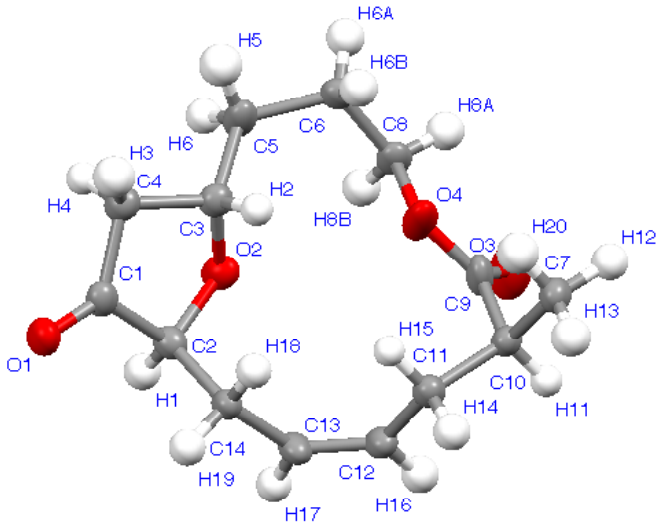
LRMS (CI, *iso*-butane) *m*/*z* (intensity) 419.5 $[M+H]^+$ (8), 75.1 (100), 85.2 (18);

HRMS (CI, *iso*-butane) calcd for $C_{27}H_{47}O_3$ $[M+H]^+$ 419.3525, found 419.3527.

[213] Wu, D.; Li, H.; Jing, J.; Wu, J.; Dai, W.-M. *Synlett* **2011**, *7*, 895–898.

Appendices

X-ray crystallography of compound 143



Chemical Data

Identification name: fl-ii-194 final

Chemical formula: $C_{14}H_{20}O_4$

Chemical formula weight: 252.3

Crystal Data and structure refinement

symmetry cell setting: monoclinic

symmetry space group name H-M: P21

cell length a: 5.28510(10) Å

cell length b: 15.1376(4) Å

cell length c: 8.2950(2) Å

cell angle alpha: 90°

cell angle beta: 94.6100(10)°

cell angle gamma: 90°

cell volume: 661.48(3) $Å^3$

Z: 2

Experimental crystal density diffrn: 1.267 mg/m^3

Cell measurement temperature: 100(2)

Cell measurement reflections used: 21401

Cell measurement theta min: 1.000°

Cell measurement theta max: 27.485°
Experimental crystal size max: 0.2 mm
Experimental crystal size mid: 0.1 mm
Experimental crystal size min: 0.05 mm

Experimental crystal density method: 'not measured'
Experimental crystal F(000): 272
Experimental absorption coefficient mu: 0.092 mm^{-1}
Experimental absorption correction type: 'multi-scan'
Experimental absorption process details: 'SADABS, Bruker(2001)'
Experimental absorption correction T min: 0.8779
Experimental absorption correction T max: 1.00

Experimental data
Diffraction ambient temperature: 100(2)
Diffraction radiation type: MoK\a
Diffraction radiation wavelength: 0.71073
Diffraction radiation monochromator: graphite
Diffraction measurement device type: KappaCCD
Diffraction measurement method: 'CCD; rotation images'
Diffraction reflections number: 8733
Diffraction reflections R equivalents: 0.0316
Diffraction theta min: 2.69°
Diffraction theta max: 27.51°
Diffraction theta full: 27.51°
Diffraction measured fraction theta max: 0.987
Diffraction measured fraction theta full: 0.987
Diffraction limit h min: −6
Diffraction limit h max: 6
Diffraction limit k min: −19
Diffraction limit k max: 19
Diffraction limit l min: −10
Diffraction limit l max: 10

Refinement data

Refinement of F^2 against all reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2>2\s(F^2)$ is used only for calculating R-factors (gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger. There is disorder of the ring at the C6 and C8 positions (C6A and C8A) with a 60:40 occupancy. The hydrogen atoms on these atoms are inserted at calculated positions whilst all other hydrogen atoms are located in the difference Fourier maps and their respective positions and isotropic thermal paramaters refined independantly.

Reflections number total: 2933

Reflections number gt: 2389

Reflections threshold expression: >2\s(I)

Refine ls structure factor coef: Fsqd

Refine ls matrix type: full

Refine ls R factor all: 0.0577

Refine ls R factor gt: 0.0392

Refine ls wR factor ref: 0.0866

Refine ls goodness of fit ref: 0.939

Refine ls restrained S all: 0.939

Refine ls number reflections: 2933

Refine ls number parameters: 245

Refine ls number restraints: 1

Refine ls hydrogen treatment: mixed

Refine ls weighting scheme: calculated

Refine ls weighting details calculation: $w=1/[\s^2(Fo^2)+(0.0415P^2+0.1371P]$ where $P=(Fo^2+2Fc^2)/3$

Refine ls shift/su max: 0.034

Refine ls shift/su mean: 0.006

Refine diff. density max: 0.162

Refine diff. density min: −0.165

Refine diff. density rms: 0.031

Refine ls extinction method: none

Atomic coordinates and displacement parameters

	x	y	z	U(iso/eq)
O1	0.0101(2)	0.88133(8)	0.36081(16)	0.0368(3)
O2	0.3754(2)	1.02523(8)	0.14311(14)	0.0325(3)
O3	0.7599(3)	1.29046(12)	0.07768(19)	0.0616(5)
O4	0.3690(3)	1.23432(10)	0.07743(16)	0.0505(4)
C1	0.0938(3)	0.93189(11)	0.2647(2)	0.0278(4)
C2	0.3470(3)	0.97901(12)	0.2912(2)	0.0281(4)
C3	0.1233(3)	1.04393(13)	0.0689(2)	0.0282(4)
C4	−0.0273(3)	0.96162(13)	0.1050(2)	0.0299(4)
C5	0.1418(4)	1.06334(14)	−0.1091(2)	0.0367(5)
C6	0.1856(6)	1.1613(2)	−0.1551(4)	0.0309(7)
C6A	0.3725(9)	1.1295(3)	−0.1360(5)	0.0270(9)
C7	0.3149(4)	1.38714(13)	0.2858(2)	0.0322(4)
C8	0.4342(8)	1.1965(3)	−0.0842(4)	0.0312(7)
C8A	0.2927(15)	1.2232(4)	−0.0970(6)	0.0382(13)
C9	0.5676(4)	1.27863(12)	0.1436(2)	0.0359(5)
C10	0.5193(4)	1.31558(11)	0.3067(2)	0.0278(4)
C11	0.4379(4)	1.24511(12)	0.4251(2)	0.0301(4)
C12	0.6357(4)	1.17585(13)	0.4615(2)	0.0313(4)
C13	0.6001(4)	1.08920(12)	0.4662(2)	0.0321(4)
C14	0.3515(3)	1.04149(12)	0.4368(2)	0.0275(4)
H1	0.483(4)	0.9362(13)	0.304(2)	0.035(5)
H2	0.054(3)	1.0953(12)	0.121(2)	0.027(5)
H3	−0.214(4)	0.9719(15)	0.106(3)	0.045(6)
H4	0.009(3)	0.9147(13)	0.029(2)	0.028(5)
H5	−0.046(5)	1.0605(16)	−0.167(3)	0.047(6)
H6	0.233(4)	1.0148(14)	−0.152(2)	0.033(5)
H6A	0.1789	1.1664	−0.272	0.037
H6B	0.0496	1.1971	−0.1179	0.037

H6A1	0.5208	1.1128	−0.0661	0.032
H6B1	0.4159	1.1262	−0.2472	0.032
H8A	0.4982	1.2421	−0.1524	0.037
H8B	0.5595	1.1498	−0.0691	0.037
H8A1	0.3784	1.2659	−0.1607	0.046
H8B1	0.1107	1.2305	−0.1184	0.046
H11	0.677(4)	1.3426(13)	0.350(2)	0.027(5)
H12	0.363(3)	1.4378(14)	0.211(2)	0.034(5)
H13	0.276(4)	1.4099(14)	0.392(3)	0.040(5)
H14	0.404(3)	1.2751(14)	0.530(2)	0.035(5)
H15	0.276(4)	1.2185(12)	0.382(2)	0.025(5)
H16	0.811(4)	1.1994(14)	0.480(2)	0.036(5)
H17	0.747(4)	1.0524(14)	0.490(2)	0.032(5)
H18	0.205(4)	1.0841(13)	0.418(2)	0.032(5)
H19	0.315(4)	1.0059(13)	0.533(2)	0.034(5)
H20	0.158(4)	1.3625(15)	0.239(3)	0.045(6)

Table 10: Atomic coordinates and equivalent isotropic displacement parameters

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11}+ ...+ 2\ h\ k\ a^*\ b^*\ U^{23}\ ]$

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0431(8)	0.0339(7)	0.0341(7)	−0.010(6)	0.0066(6)	0.0037(6)
O2	0.0281(7)	0.0420(8)	0.0280(6)	−0.007(6)	0.0065(5)	0.0005(6)
O3	0.0760(12)	0.0576(10)	0.0563(10)	−0.022(9)	0.0379(9)	−0.013(8)
O4	0.0865(12)	0.0422(8)	0.0233(7)	−0.026(8)	0.0074(7)	−0.007(6)
C1	0.0325(9)	0.0253(9)	0.0264(8)	−0.001(7)	0.0075(7)	−0.003(8)
C2	0.0254(9)	0.0301(9)	0.0291(9)	0.0015(8)	0.0046(7)	0.0026(8)
C3	0.0290(9)	0.0304(9)	0.0258(8)	−0.003(8)	0.0055(7)	−0.003(8)
C4	0.0266(9)	0.0351(10)	0.0285(9)	−0.003(8)	0.0054(7)	−0.002(8)
C5	0.0533(13)	0.0340(11)	0.0240(9)	−0.001(10)	0.0094(9)	−0.006(8)
C6	0.0370(18)	0.0346(18)	0.0212(15)	−0.001(15)	0.0032(12)	−0.01(12)
C6A	0.036(3)	0.029(2)	0.017(2)	0.002(2)	0.0063(17)	0.0025(19)
C7	0.0363(11)	0.0265(9)	0.0334(10)	−0.002(8)	−0.0007(8)	−0.0011(9)
C8	0.043(2) −	0.033(2)	0.0186(15)	−0.04(17)	0.0079(14)	0.0032(14)
C8A	0.066(4)	0.024(3)	0.023(3)	0.011(3)	−0.0002(3)	−0.005(2)

C9	0.0524(12)	0.0224(9)	0.0342(10)	−0.009(9)	0.0107(9)	−0.0001(8)
C10	0.0321(10)	0.0244(9)	0.0263(9)	−0.002(8)	−0.0002(7)	−0.0025(7)
C11	0.0348(11)	0.0296(10)	0.0258(9)	−0.003(8)	0.0022(8)	−0.0005(8)
C12	0.0305(10)	0.0319(9)	0.0305(9)	−0.006(8)	−0.0043(7)	0.0036(8)
C13	0.0285(10)	0.0310(10)	0.0355(10)	−0.0007(8)	−0.0057(8)	0.0078(8)
C14	0.0299(9)	0.0259(9)	0.0263(9)	−0.0030(8)	0.0003(7)	0.0033(8)

Table 11: Anisotropic displacement parameters ($Å^2$ x 10^3)

Molecular geometry

All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell s.u.'s are taken into account individually in the estimation of s.u.'s in distances, angles and torsion angles; correlations between s.u.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell s.u.'s is used for estimating s.u.'s involving l.s..

Bonds lengths (Å)

O1-C1 1.214(2)	C4-C1 1.493(3)
O2-C2 1.432(2)	C4-C3 1.521(3)
O2-C3 1.450(2)	C4-H3 1.00(2)
C2-C1 1.517(2)	C4-H4 0.981(19)
C2-C14 1.533(3)	C9-C10 1.505(2)
C2-H1 0.97(2)	C3-C5 1.517(2)
O4-C9 1.327(2)	C3-H2 0.972(19)
O4-C8A 1.480(5)	C13-H17 0.96(2)
O4-C8 1.522(4)	C5-C6 1.554(4)
C14-C13 1.502(2)	C5-C6A 1.607(5)
C14-H19 1.00(2)	C5-H5 1.07(2)
C14-H18 1.01(2)	C5-H6 0.96(2)
C11-C12 1.494(3)	C10-H11 0.97(2)
C11-C10 1.535(2)	C8-C6 1.494(5)
C11-H14 1.01(2)	C8-H8A 0.97
C11-H15 0.984(19)	C8-H8B 0.97
C7-C10 1.530(3)	C6-H6A 0.97

C7-H13 0.98(2)
C7-H12 1.03(2)
C7-H20 0.96(2)
C12-C13 1.326(3)
C12-H16 1.00(2)
O3-C9 1.206(2)
C6-H6B 0.97
C6A-C8A 1.523(7)
C6A-H6A1 0.97
C6A-H6B1 0.97
C8A-H8A1 0.97
C8A-H8B1 0.97

Bonds angles (°)

C2 O2 C3 107.66(12)
O2 C2 C1 104.92(13)
O2 C2 C14 112.25(14)
C1 C2 C14 111.22(14)
O2 C2 H1 106.9(11)
C1 C2 H1 109.9(11)
C14 C2 H1 111.4(11)
C9 O4 C8A 127.3(3)
C9 O4 C8 109.1(2)
C8A O4 C8 32.8(2)
C13 C14 C2 112.47(15)
C13 C14 H19 110.8(11)
C2 C14 H19 107.9(11)
C13 C14 H18 111.6(11)
C2 C14 H18 107.9(11)
H19 C14 H18 105.9(16)
C12 C11 C10 112.93(15)
C12 C11 H14 108.0(11)
C10 C11 H14 108.6(11)
C12 C11 H15 111.0(11)
C10 C11 H15 109.6(10)
H14 C11 H15 106.4(14)
C10 C7 H13 110.1(12)
C10 C7 H12 112.8(10)
H13 C7 H12 111.1(16)
C10 C7 H20 110.4(13)
H13 C7 H20 105.3(17)
O2 C3 C4 103.53(14)
C5 C3 C4 115.22(15)
O2 C3 H2 109.4(11)
C5 C3 H2 109.3(11)
C4 C3 H2 110.3(11)
C12 C13 C14 126.53(18)
C12 C13 H17 117.6(12)
C14 C13 H17 115.9(12)
C3 C5 C6 116.53(19)
C3 C5 C6A 111.4(2)
C6 C5 C6A 40.66(19)
C3 C5 H5 107.4(12)
C6 C5 H5 94.6(13)
C6A C5 H5 130.6(13)
C3 C5 H6 106.6(12)
C6 C5 H6 123.3(12)
C6A C5 H6 90.9(12)
H5 C5 H6 106.1(18)
C9 C10 C11 113.17(15)
C9 C10 C7 109.31(15)
C11 C10 C7 109.44(15)
C9 C10 H11 106.5(11)
C11 C10 H11 109.6(11)
C7 C10 H11 108.7(11)
C6 C8 O4 103.1(3)
C6 C8 H8A 111.1
O4 C8 H8A 111.1

H12 C7 H20 106.8(17)
C13 C12 C11 126.96(18)
C13 C12 H16 118.9(12)
C11 C12 H16 114.1(12)
C1 C4 C3 103.16(14)
C1 C4 H3 113.0(12)
C3 C4 H3 114.0(14)
C1 C4 H4 105.3(11)
C3 C4 H4 109.5(11)
H3 C4 H4 111.3(17)
O1 C1 C4 128.28(17)
O1 C1 C2 124.40(16)
C4 C1 C2 107.29(14)
O3 C9 O4 123.72(18)
O3 C9 C10 124.24(18)
O4 C9 C10 111.99(16)
O2 C3 C5 108.81(14)
C6A C8A H8B1 110.8
H8A1 C8A H8B1 108.9
C6 C8 H8B 111.1
O4 C8 H8B 111.1
H8A C8 H8B 109.1
C8 C6 C5 112.8(3)
C8 C6 H6A 109
C5 C6 H6A 109
C8 C6 H6B 109
C5 C6 H6B 109
H6A C6 H6B 107.8
C8A C6A C5 108.9(4)
C8A C6A H6A1 109.9
C5 C6A H6A1 109.9
C8A C6A H6B1 109.9
C5 C6A H6B1 109.9
H6A1 C6A H6B1 108.3
O4 C8A C6A 104.8(4)
O4 C8A H8A1 110.8
C6A C8A H8A1 110.8
O4 C8A H8B1 110.8

Torsion angles (°)

C3 O2 C2 C1 27.37(17)
C3 O2 C2 C14 −93.55(16)
O2 C2 C14 C13 −62.77(19)
C1 C2 C14 C13 −179.99(15)
C10 C11 C12 C13 −135.0(2)
C3 C4 C1 O1 162.42(17)
C3 C4 C1 C2 −15.97(18)
O2 C2 C1 O1 175.48(16)
C14 C2 C1 O1 -62.9(2)
O2 C2 C1 C4 −6.05(18)
C14 C2 C1 C4 115.54(16)
C8A O4 C9 O3 −27.0(5)
C8 O4 C9 O3 4.3(3)
C8A O4 C9 C10 150.5(3)
C11 C12 C13 C14 −0.4(3)
C2 C14 C13 C12 118.4(2)
O2 C3 C5 C6 −89.8(2)
C4 C3 C5 C6 154.5(2)
O2 C3 C5 C6A −45.4(3)
C4 C3 C5 C6A −161.1(2)
O3 C9 C10 C11 −127.4(2)
O4 C9 C10 C11 55.1(2)
O3 C9 C10 C7 110.3(2)
O4 C9 C10 C7 −67.10(19)
C12 C11 C10 C9 61.9(2)
C12 C11 C10 C7 −175.92(15)
C9 O4 C8 C6 −171.6(2)
C8A O4 C8 C6 −41.2(5)

C8 O4 C9 C10 −178.2(2)

C2 O2 C3 C5 −160.75(15)

C2 O2 C3 C4 −37.73(17)

C1 C4 C3 O2 32.04(17)

C1 C4 C3 C5 150.72(16)

C8 O4 C8A C6A 38.7(4)

C5 C6A C8A O4 90.2(5)

O4 C8 C6 C5 −90.4(3)

C3 C5 C6 C8 63.8(3)

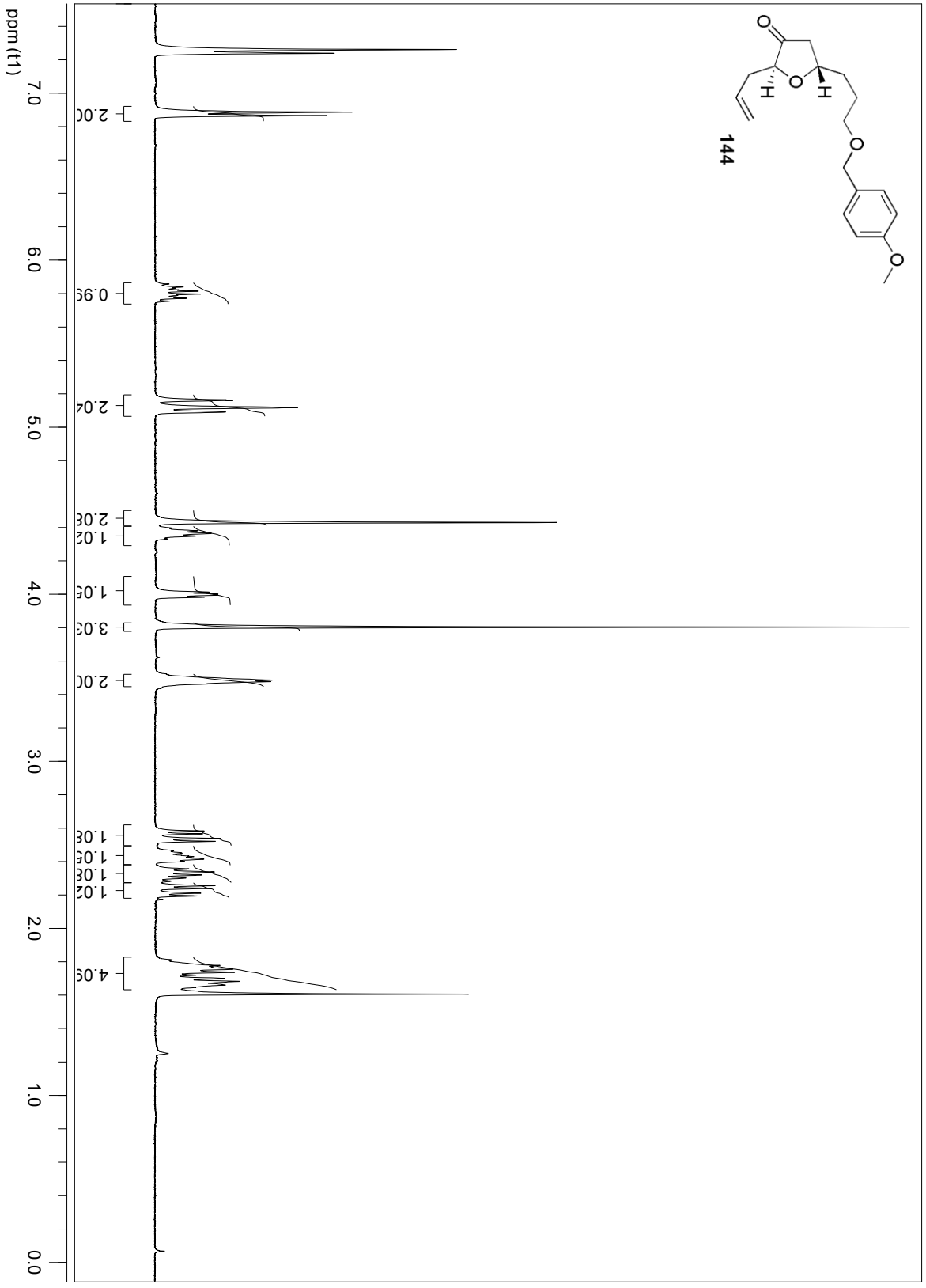
C6A C5 C6 C8 −28.7(3)

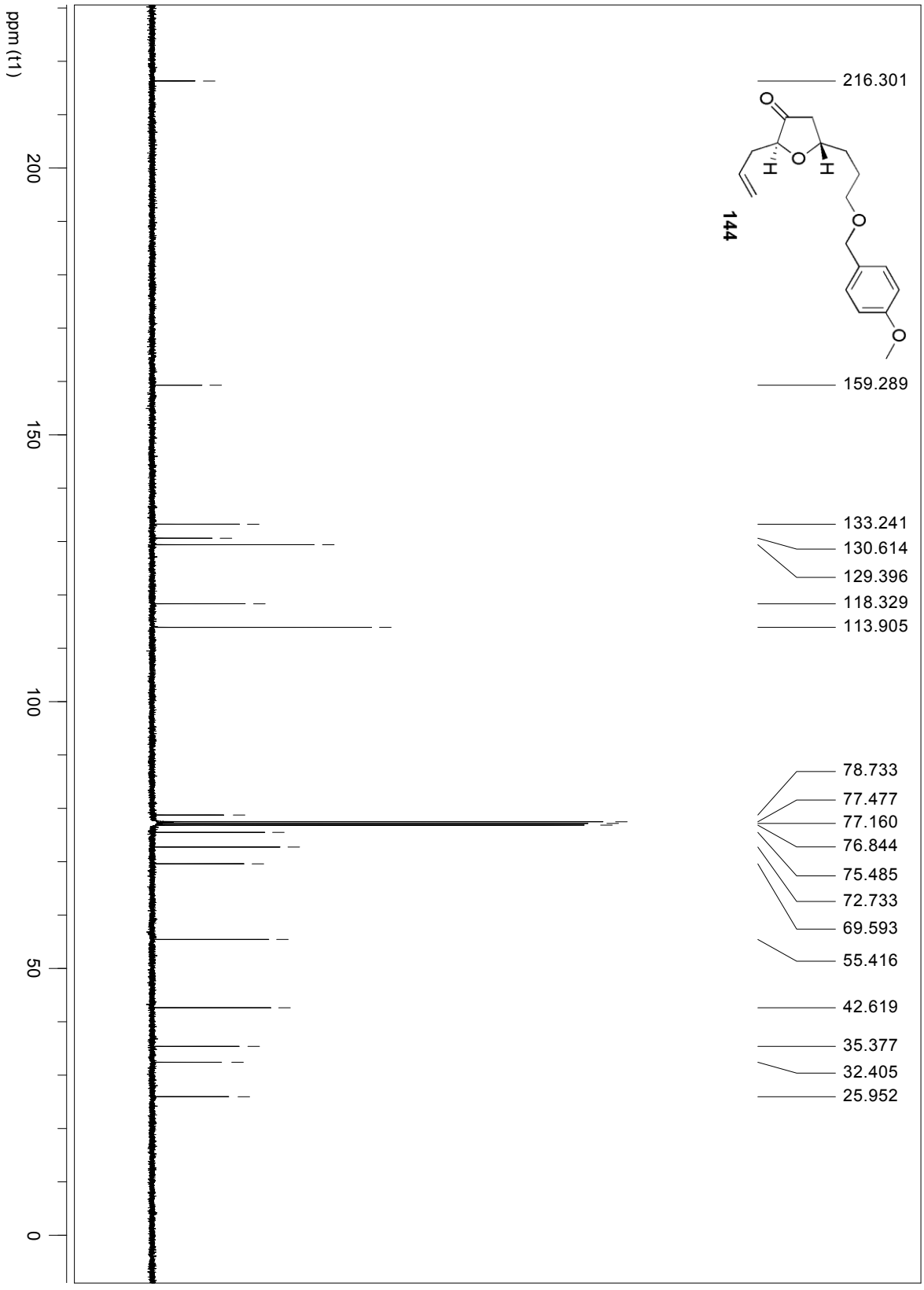
C3 C5 C6A C8A −77.8(4)

C6 C5 C6A C8A 28.4(3)

C9 O4 C8A C6A 103.6(4)

Spectra of main compounds

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77.160
76.844
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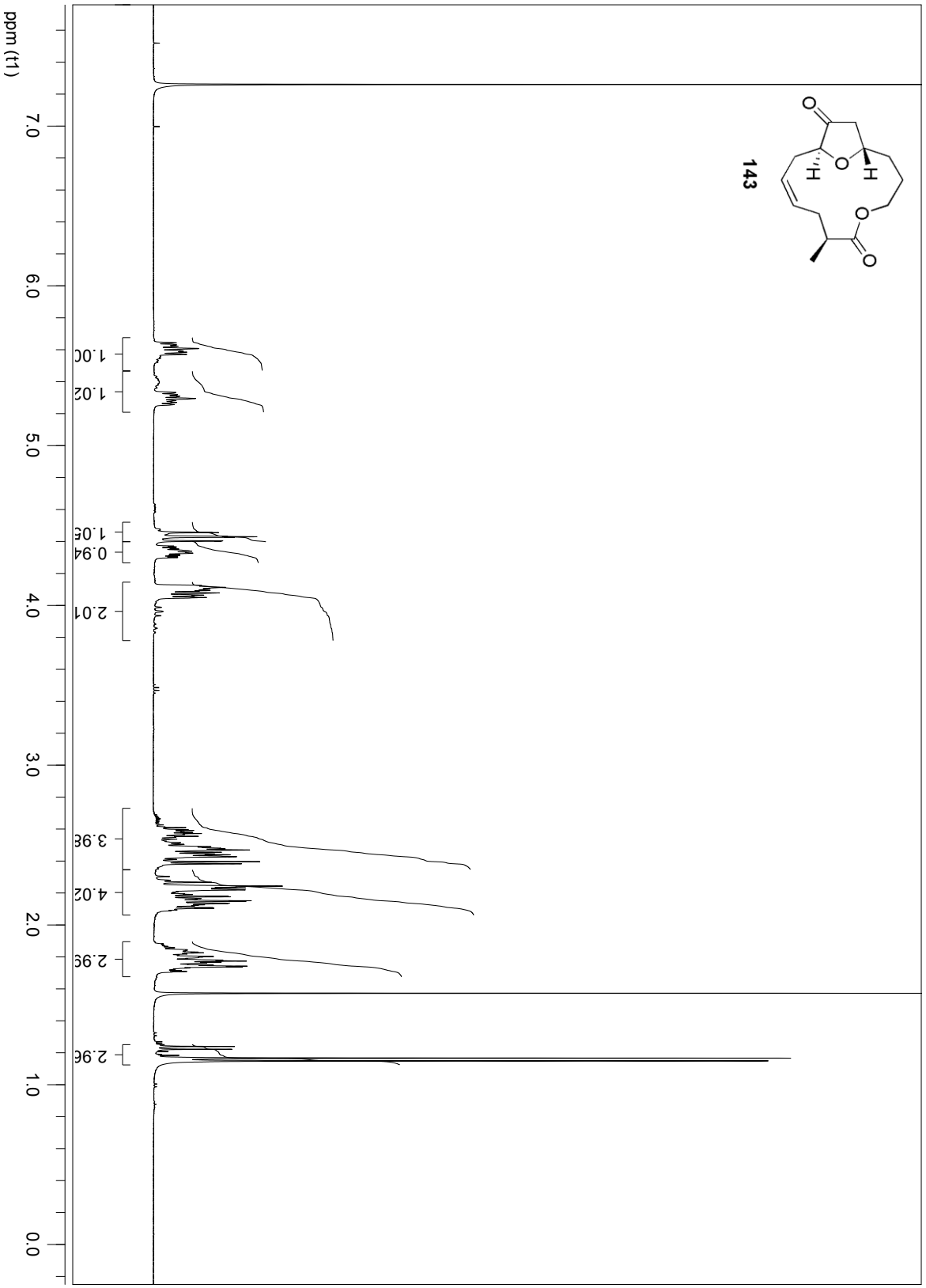
72.733
69.593
55.416
42.619
35.377
32.405
25.952
144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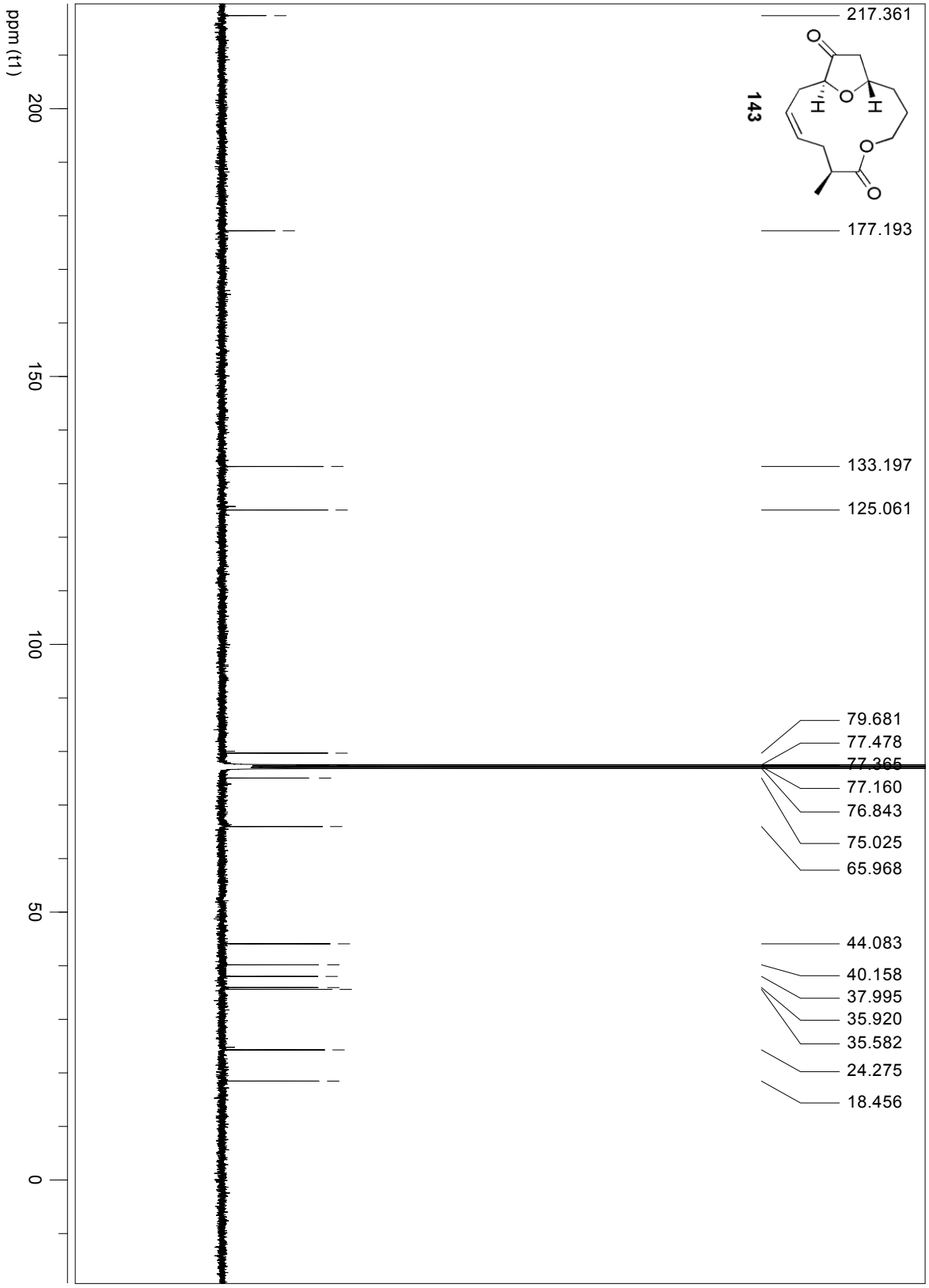
1.02
1.05
0.94
2.01
3.98
4.02
2.99
2.96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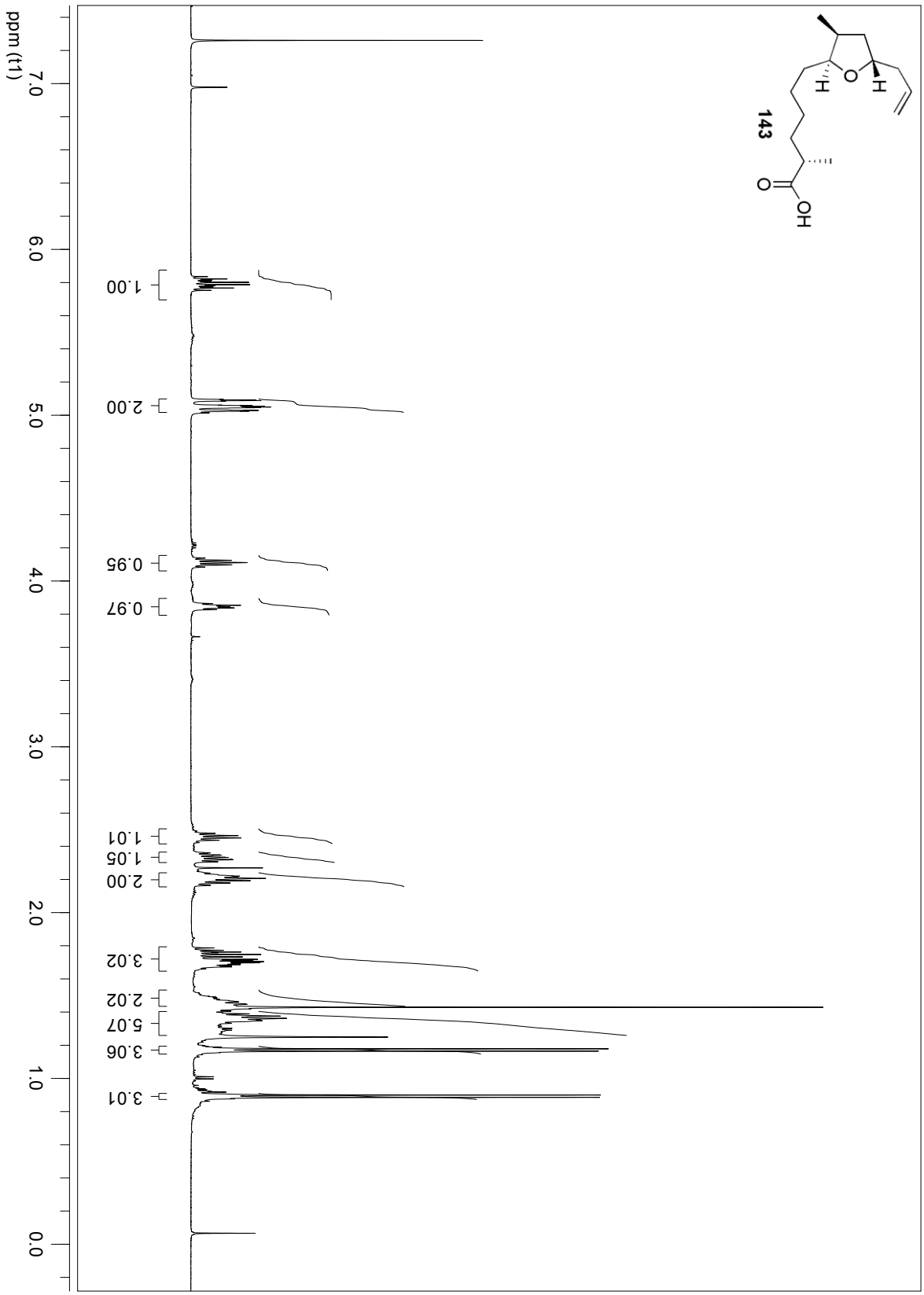
40.158
37.995
35.920
35.582
24.275
18.456
143


143
O
OH
H
H
O
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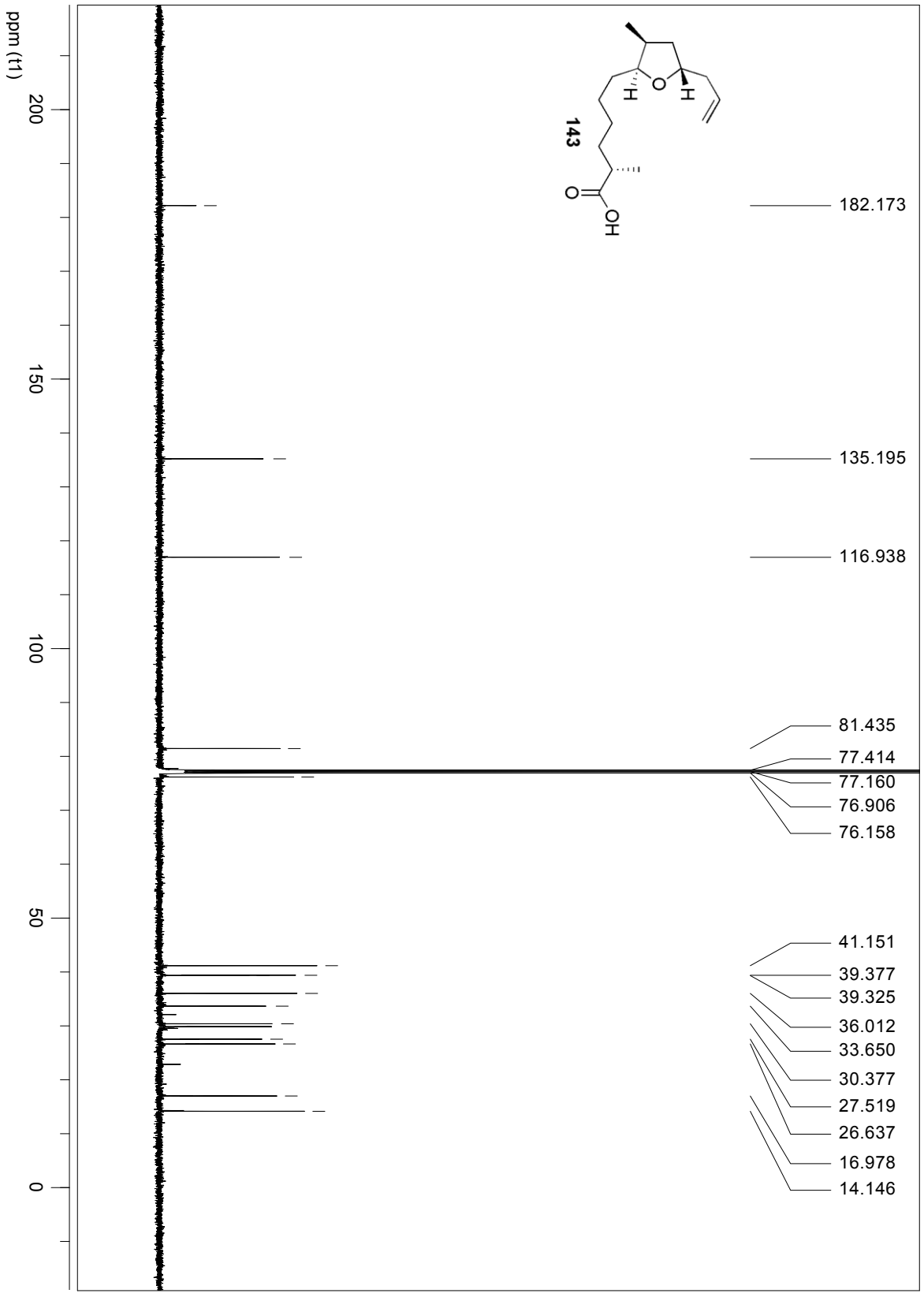
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.00
2.00
0.95
0.97
1.01
1.05
2.00
3.02
2.02
5.07
3.06
3.01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OH
H
O
H
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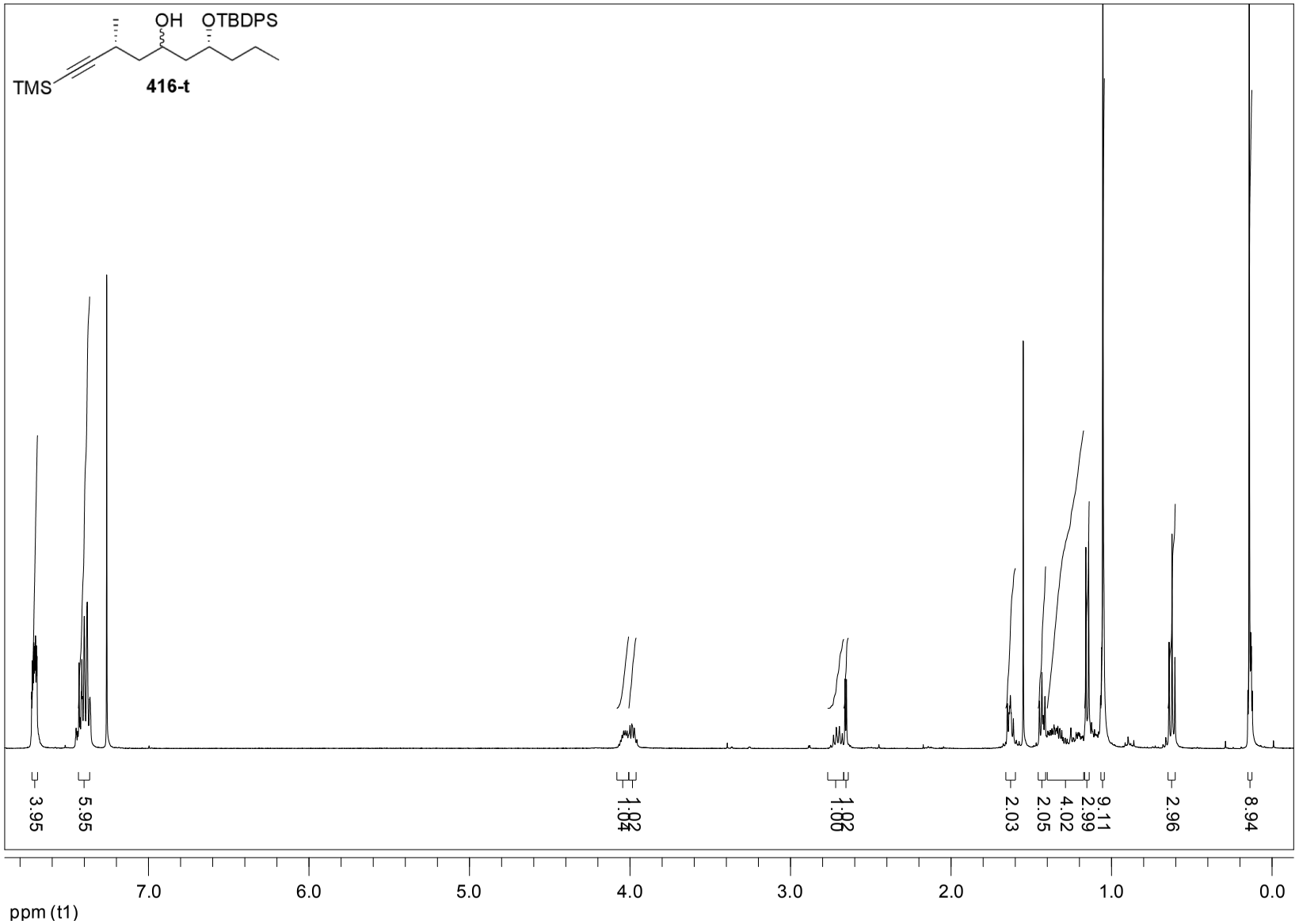
77.414
77.160
76.906
76.158
41.151
39.377
39.325
36.012
33.650
30.377
27.519
26.637
16.978
14.146


OH
OTBDPS
TMS
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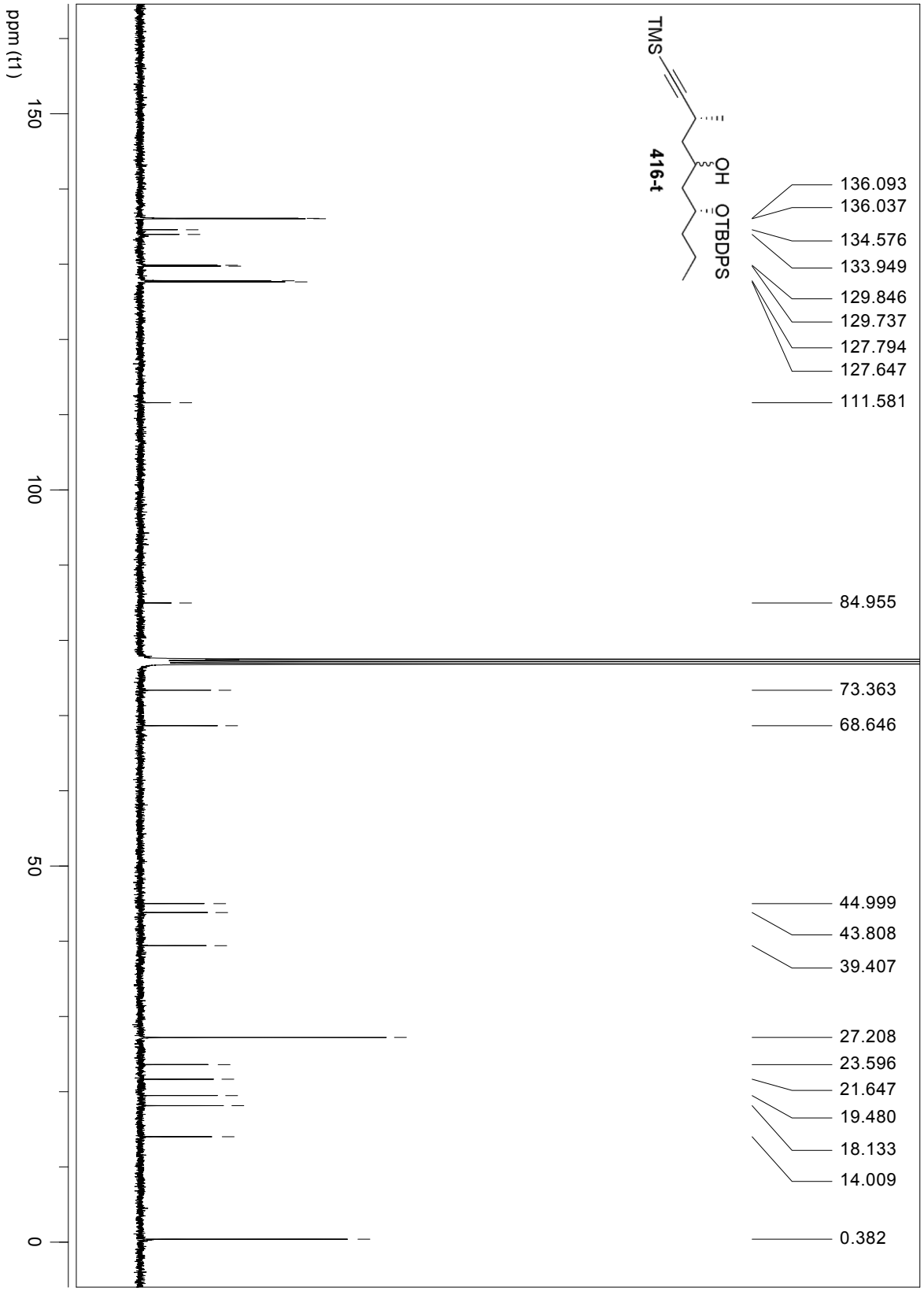
5.95
1.04
1.02
1.00
1.02
2.03
2.05
4.02
2.99
9.11
2.96
8.94
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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100
50
0
TMS
OH
OTBDPS
416-t
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136.037
134.576
133.949
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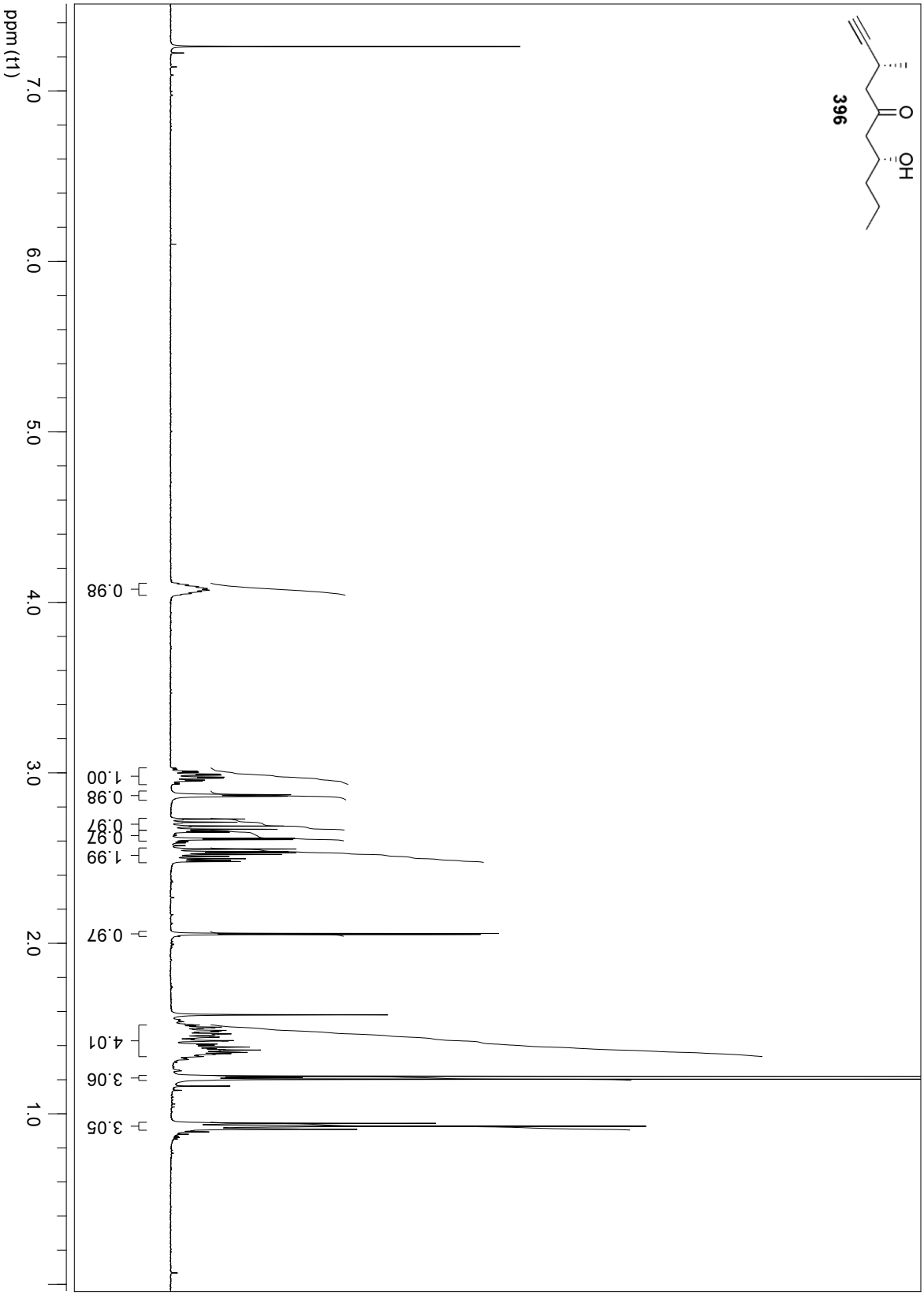
127.794
127.647
111.581
84.955
73.363
68.646
44.999
43.808
39.407
27.208
23.596
21.647
19.480
18.133
14.009
0.382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OH
O
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5.0
4.0
3.0
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1.00
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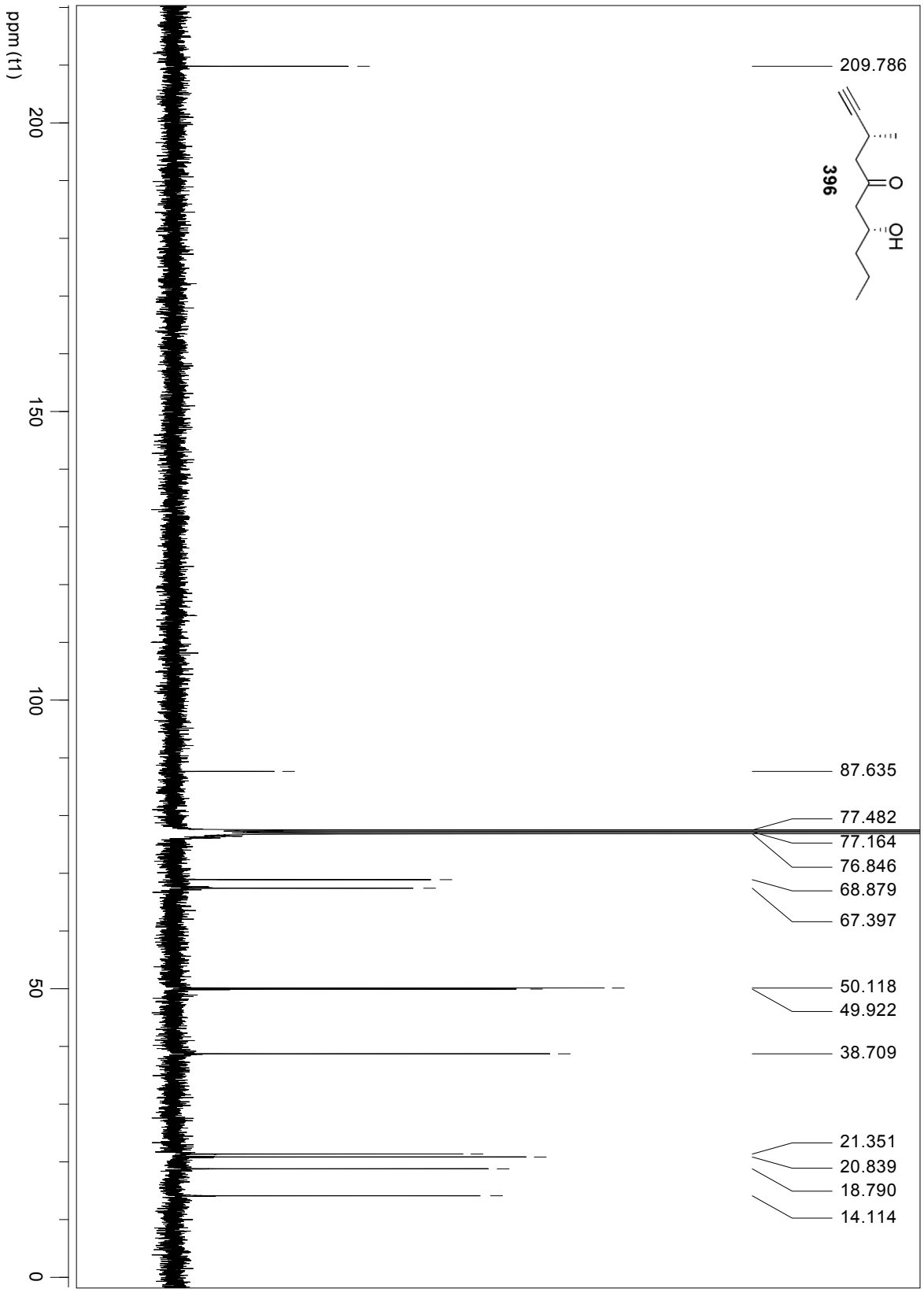
0.97
0.97
1.99
0.97
4.01
3.06
3.05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100
50
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396
O
OH
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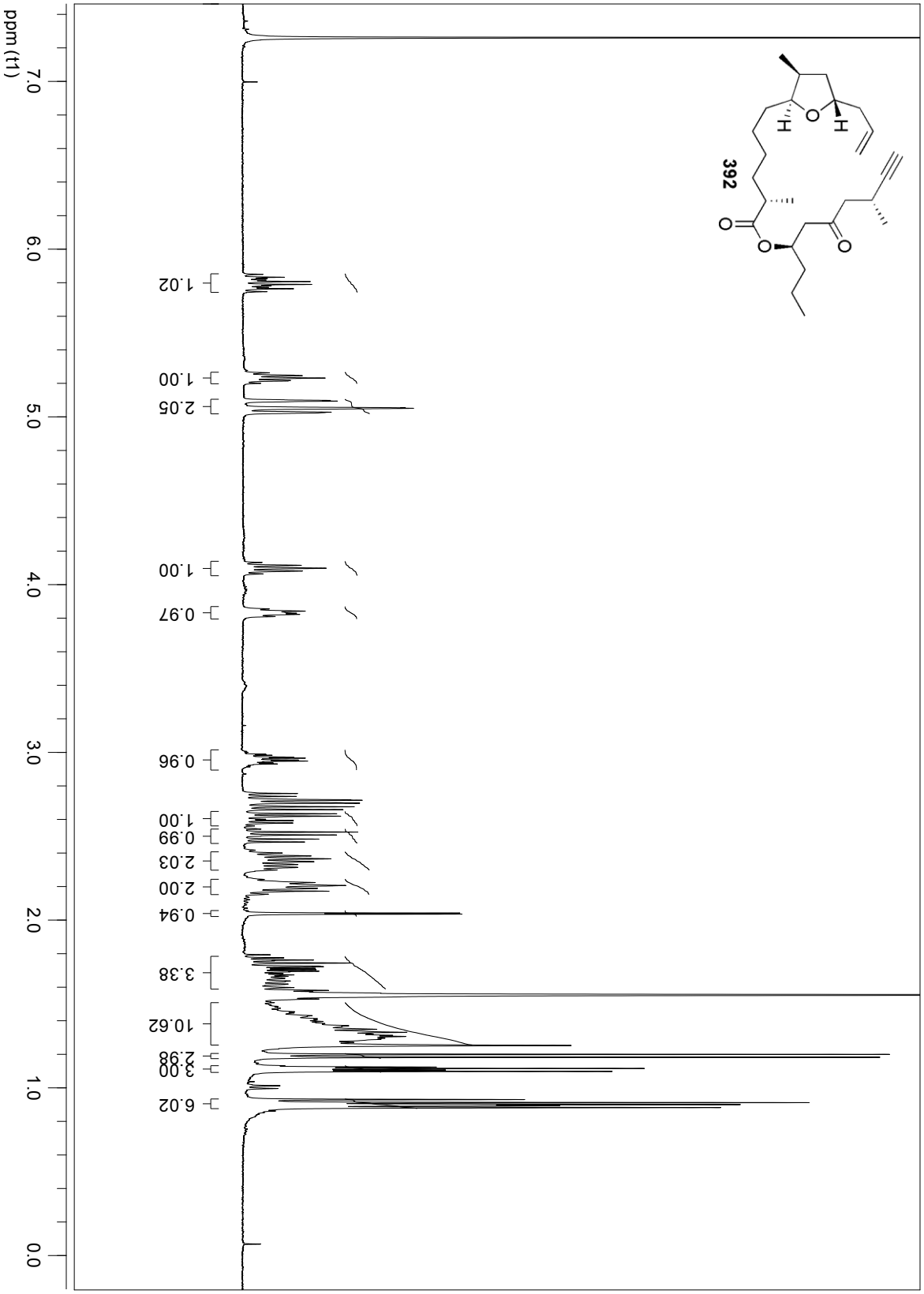
67.397
50.118
49.922
38.709
21.351
20.839
18.790
14.114


392
O
O
O
O
H
H
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6.0
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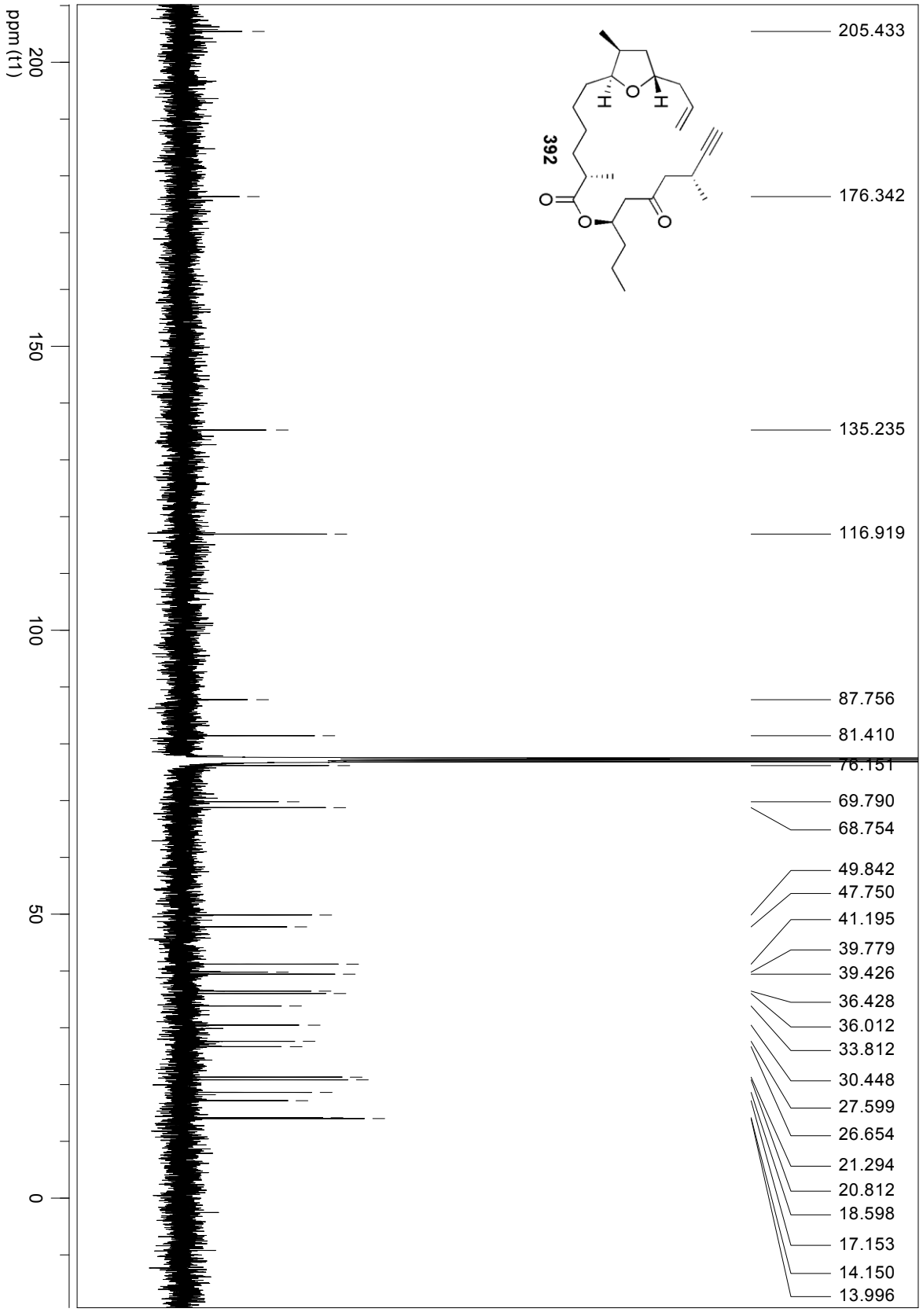
4.0
3.0
2.0
1.0
0.0
1.02
1.00
2.05
1.00
0.97
0.96
1.00
0.99
2.03
2.00
0.94
3.38
10.62
2.98
3.00
6.02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69.790
68.754
49.842
47.750
41.195
39.779
39.426
36.428
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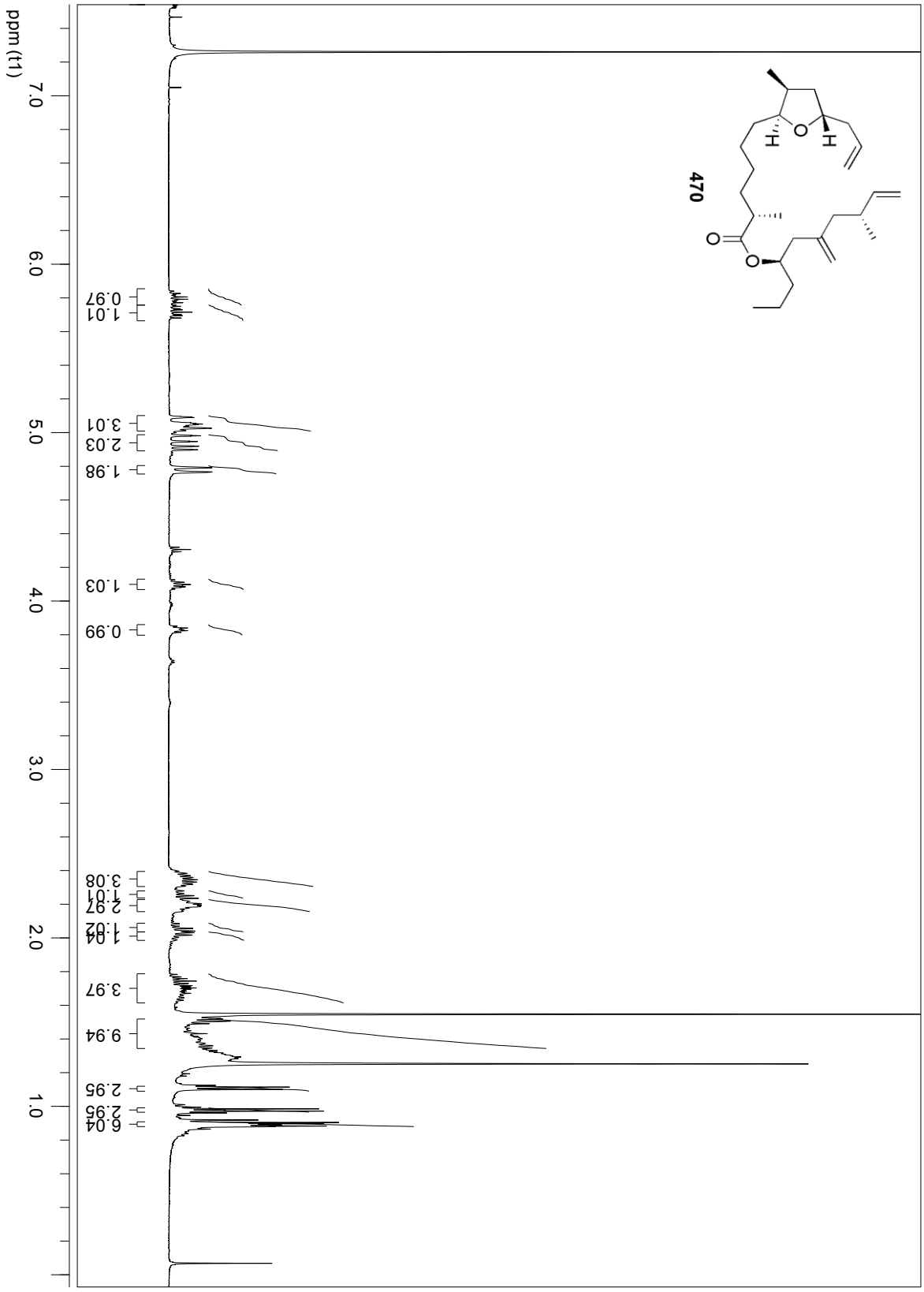
14.150
13.996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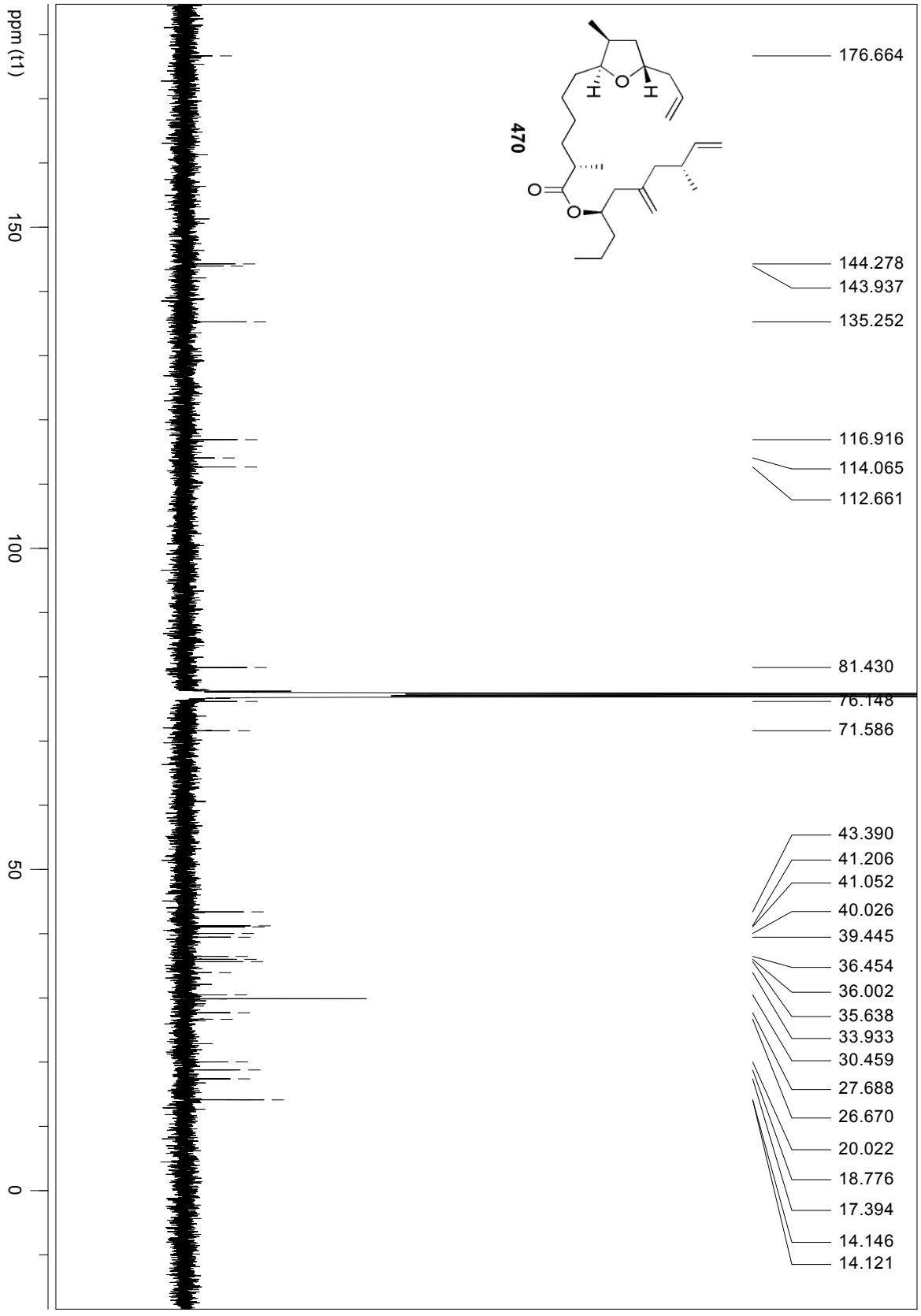
6.0
5.0
4.0
3.0
2.0
1.0
0.97
1.01
3.01
2.03
1.98
1.03
0.99
3.08
1.01
2.97
1.02
1.04
3.97
9.94
2.95
2.95
6.04
470
O
O
H
O
H


ppm (t1)
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100
50
0
470
O
O
H
O
H
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116.916
114.065
112.661
81.430
76.148
71.586
43.390
41.206
41.052
40.026
39.445
36.454
36.002
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20.022
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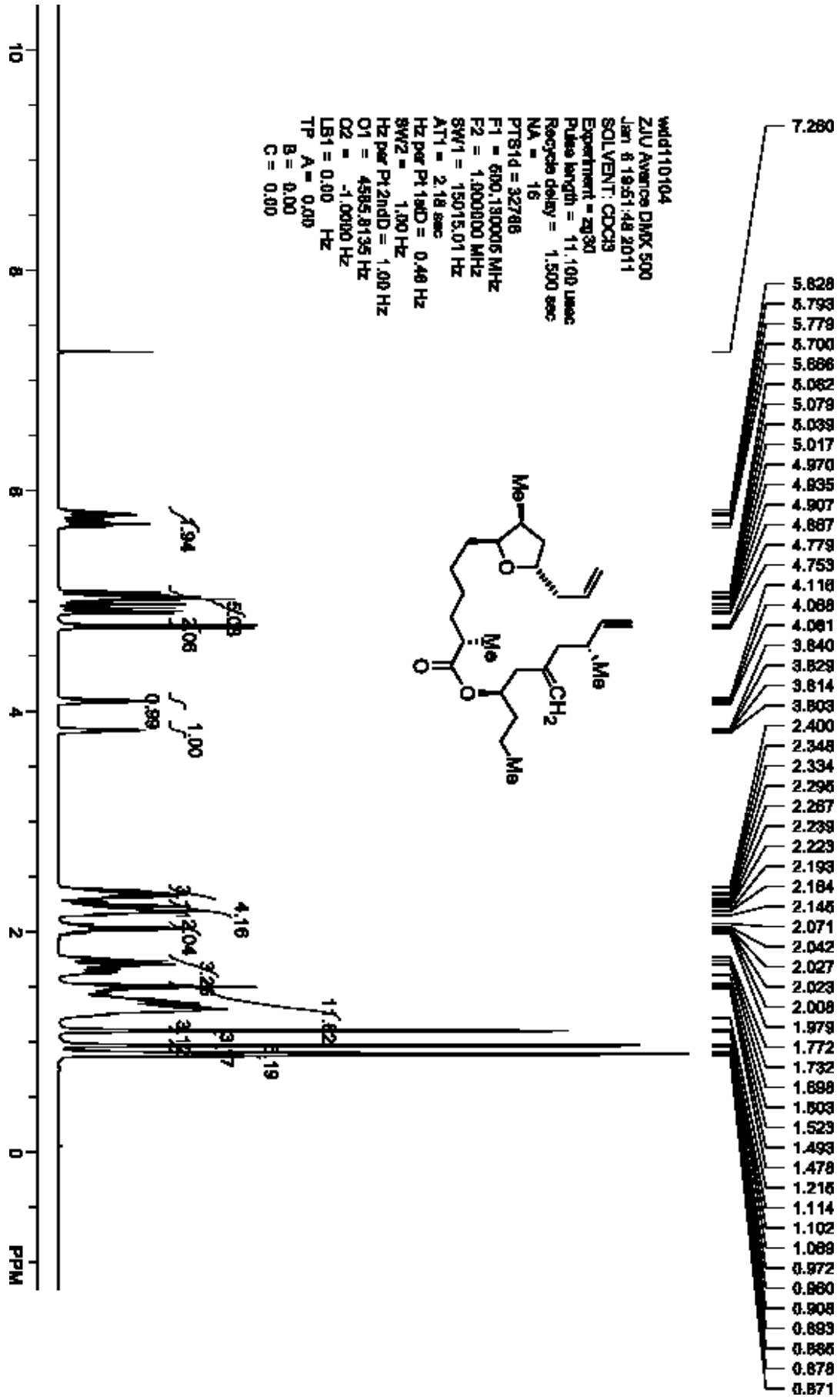
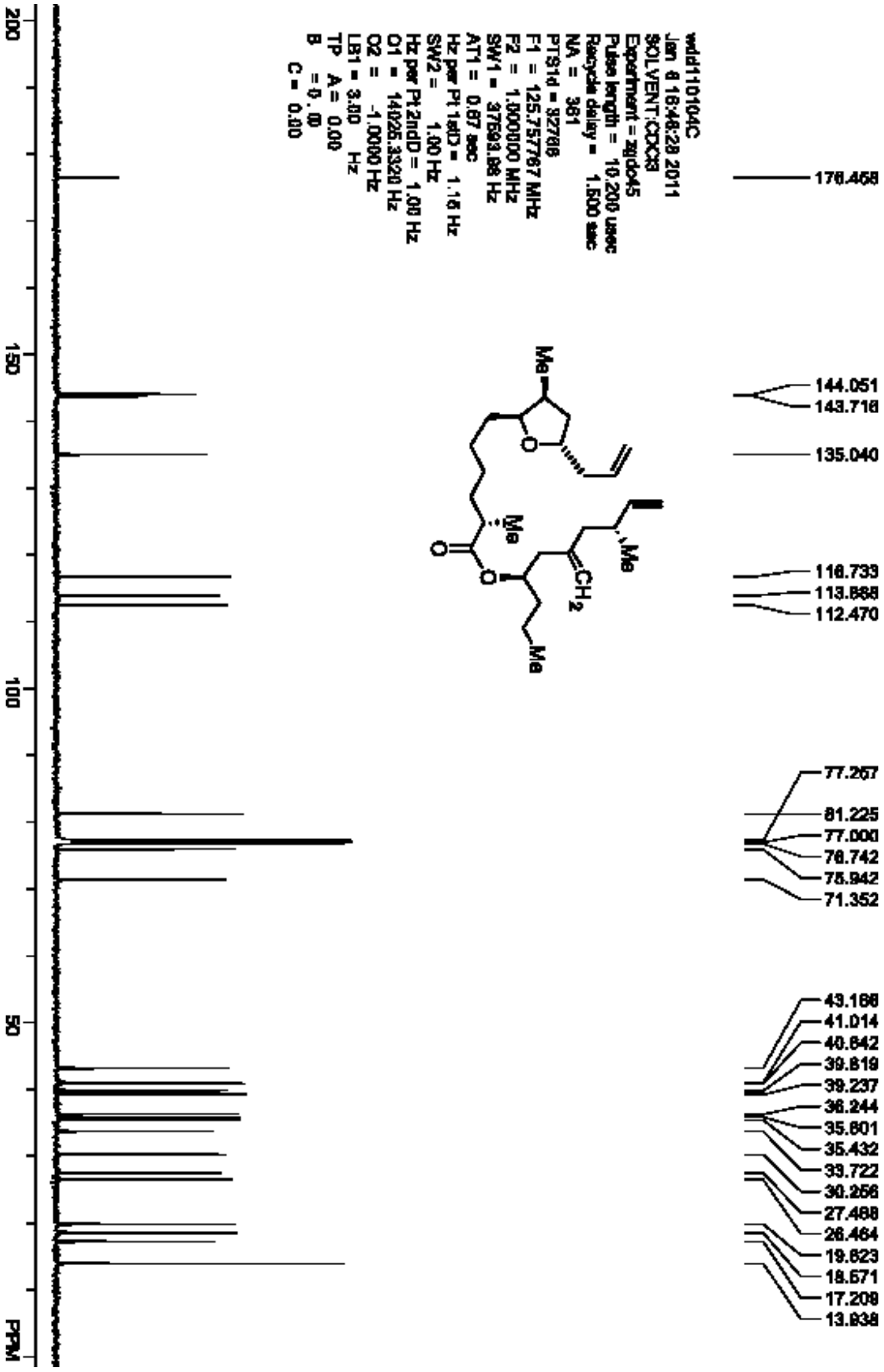
17.394
14.146
14.121

Spectra of 470 from the Dai's group




wdd110104C
Jan 6 16:48:28 2011
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Experiment = zgdc45
Pulse length = 10.200 usec
Recycle delay = 1.500 sec
NA = 381
PTS1d = 32768
F1 = 125.757767 MHz
F2 = 1.000000 MHz
SW1 = 37593.98 Hz
AT1 = 0.87 sec
Hz per Pt 1stD = 1.15 Hz
SW2 = 1.00 Hz
Hz per Pt 2ndD = 1.00 Hz
O1 = 14025.3320 Hz
O2 = -1.0000 Hz
LB1 = 3.00 Hz
TP A = 0.00
B = 0.0
C = 0.00
Me
Me
Me
CH2
O
O
O
170.458
144.051
143.716
135.040
116.733
113.888
112.470
77.257
81.225
77.000
76.742
75.942
71.352
43.186
41.014
40.642
39.819
39.237
36.244
35.801
35.432
33.722
30.256
27.488
26.464
19.823
18.671
17.209
13.938
200
150
100
50
PPM