DEPARTMENT OF CHEMISTRY, UNIVERSITY OF JYVÄSKYLÄ
RESEARCH REPORT No. 172

MUKAIYAMA–MICHAEL REACTIONS WITH α-SUBSTITUTED ACROLEINS – A USEFUL TOOL FOR THE SYNTHESIS OF THE PECTENOTOXINS AND OTHER NATURAL PRODUCT TARGETS

BY

EEVA K. KEMPPAINEN

Academic Dissertation for the Degree of
Doctor of Philosophy

To be presented, by permission of the Faculty of Mathematics and Science of the University of Jyväskylä, for public examination in Auditorium FYS1, on September 21st, 2013 at 12 noon.

UNIVERSITY OF JYVÄSKYLÄ

Jyväskylä, Finland
ISBN 978-951-39-5369-0
ISSN 0357-346X

ABSTRACT

Kemppainen, Eeva
Mukaiyama–Michael reactions with α-substituted acroleins – a useful tool for the synthesis of the pectenotoxins and other natural product targets
Jyväskylä: University of Jyväskylä, 2013, 201 p.
Department of Chemistry, University of Jyväskylä, Research report Series
ISSN 0357-346X
ISBN 978-951-39-5369-0

The first chapter of this thesis comprises the literature review of the discovery of pectenotoxins, a family of complex natural products with interesting biological activity, and a brief look at the synthetical approaches towards these compounds. Including us, several groups are aiming towards the total synthesis of pectenotoxin-2 or some other member of the family. Herein are presented the published approaches towards the synthesis of fragments containing the F-ring moiety. In relation to this, a more detailed description of our own efforts towards the synthesis of this segment will be discussed in chapter three.
The second chapter of this thesis focuses on the vinylogous Mukaiyama–Michael reaction employing silyloxyfurans. The literature review concentrates in particular on the asymmetric methodologies, developed by several groups. Additionally, selected examples of applications for these methodologies are presented in the form of diverse natural product total syntheses.
The experimental results of this thesis are discussed in the third and fourth chapters, beginning with studies towards the synthesis of the C17–C28 fragment of pectenotoxin-2. The final route towards this fragment employed as a key step a Mukaiyama–Michael reaction variant of our own design. The development of this organocatalytic Mukaiyama–Michael reaction, including studies towards understanding the unique mode of action of the diphenylpyrrolidine catalyst on a deeper level, are also presented.

Keywords: pectenotoxin, total synthesis, Mukaiyama–Michael reaction, organocatalysis, 2,5-diphenylpyrrolidine

Author's address

Eeva Kemppainen
Department of Chemistry
University of Jyväskylä
P.O. Box 35
FI-40014 University of Jyväskylä
Finland
eeva.k.kemppainen@jyu.fi

Supervisor

Professor Petri Pihko
Department of Chemistry
University of Jyväskylä
P.O. Box 35
FI-40014 University of Jyväskylä
Finland

Reviewers

Dr. Marco Bella
Università "Sapienza" di Roma
P.le Aldo Moro 5
00185 Roma
Italy

Professor Andrei V. Malkov
Department of Chemistry
Loughborough University
Loughborough LE11 3TU
United Kingdom

Opponent

Professor Darren J. Dixon
Department of Chemistry
Chemistry Research Laboratory
University of Oxford
Mansfield Road
Oxford OX1 3TA
United Kingdom

ACKNOWLEDGEMENTS

The work reported in this thesis was carried out in the Department of Chemistry, University of Jyväskylä, during 08/2008–09/2013. A part of the work was done in the Department of Chemistry, University of Glasgow, during 08–09/2012. The work was financially supported by the Academy of Finland until the end of 2012. In 2013, the financial support came from the University of Jyväskylä and the Eemil Aaltonen foundation. I would like to thank all these organisations for their support. In addition, I am grateful to the COST (European Co-operation in Science and Technology) action CM0804 for enabling me to visit the University of Glasgow, and GSOCCB (Graduate School of Organic Chemistry and Chemical Biology) for the travel grants which allowed me to participate in various conferences during these years.

I would like to express my gratitude to my supervisor Professor Petri Pihko for giving me the opportunity to do my Ph.D. in his group. I thank Professor J. Stephen Clark for the opportunity to work in his laboratory, and his whole research group for the interesting and memorable experience.

I also thank Dr. Marco Bella and Professor Andrei V. Malkov for careful revision of my manuscript. Mr. Antti Piisola is kindly thanked for revision of the language of the manuscript.

I would like to thank all the current and past members of Pihko group: Dr. K. Syam Krishnan, Dr. Hasibur Rahaman, Dr. Meryem Benohoud, Dr. Antti Pohjakallio, Dr. Jun Liu, Dr. Kai-Tai (Billy) Yip, Dr. Roshan Y. Nimje, Dr. Nicolas Probst, Dr. Jatta Himanen, Dr. Gokarneswar Sahoo, Dr. Rosy Mallik, Dr. Aurélie Claraz, Ms. Sanna Yliniemelä–Sipari, Mr. Mikko Leskinen, Mr. Antti Piisola, Mr. Antti Neuvonen, Mr. Sakari Tuokko, Mr. Mikko Melarto, Mr. Toni Metsänen, Ms. Laura Pitkäjärvi, Ms. Aini Vuorinen, Mr. Juha Siitonen, Ms. Minna kortelainen and Ms. Ulla Laitinen. I would also like to thank other personel in the department for their co-operation and assistance, particularly Dr. Arto Valkonen, Ms. Mirja Lahtiperä, Mr. Esa Haapaniemi, Mr. Reijo Kauppinen, Mr. Pekka Juhani Salovaara, Mr. Jarno Törn, Ms. Leena Koskela, Ms. Pia Petriläinen, Ms. Elina Hautakangas, Ms. Ritva Watia, Ms. Satu Rautiainen, Mr. Hannu Salo, Ms. Marja Salo, Ms. Leena Mattila, Ms. Ritva Kaski, Ms. Maritta Leinonen and Ms. Tuula Paukama.

I would like to thank my parents Sirpa and Juhani, my brother Kalle and his family Janita, Anna, Emma and Justus, my friends, and my Mikko, Rino and Oomi for bringing joy to my everyday life.

Jyväskylä, August 22nd 2013
Eeva Kemppainen

AUTHOR'S CONTRIBUTION

The author has designed and carried out the experiments and analyses, and interpreted the results that are presented in this work. This work is also written by the author.

Certain parts of the presented work were done by other collaborating researchers. More specifically, Dr. Arto Valkonen has determined the crystal structure of compound **248** (**Scheme 43**b on page 81 and crystal data on page 151). Dr. Gokarneswar Sahoo is responsible for the epimerisation studies and Luche reduction studies, the results presented in **Schemes 36** (on page 76) and **39** (on page 78), and **Table 14** (on page 83) on the preliminary scope of the Mukaiyama–Michael reaction. Dr. Imre Pápai has performed all the computational modeling studies (presented in **Figures 17** and **18** on pages 102 and 103).

The publication related to this work has been written by the author together with co-authors.[97]

ACRONYMS, ABBREVIATIONS, SYMBOLS AND DEFINITIONS

9BBN	9-borabicyclo[3.3.1]nonane
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
AB	strongly coupled two-spin-½ system
ABX	a special type of three-spin system in which two nonequivalent nuclei are strongly coupled and each is weakly coupled to a third nonequivalent nucleus
Ac	acetyl
acac	acetylacetonyl
acetaldehyde	ethanal
ACN	acetonitrile
AcO	acetoxy
acrolein	propenal/prop-2-enal
AD	asymmetric dihydroxylation
AD-mix α	$K_2OsO_4 \bullet 2H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3
AD-mix β	$K_2OsO_4 \bullet 2H_2O$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3
AIBN	2,2′-azo bisisobutyronitrile
α-angelica lactone	5-methyl-2(3*H*)-furanone
β-angelica lactone	5-methyl-2(5*H*)-furanone
anisaldehyde	4-methoxybenzaldehyde
anti	alignment of two substituents on the opposite sides/faces of a compound
app.	apparent
aq.	aqueous
Ar	aromatic group
(–)-aromadendranediol	(1a*R*,4*R*,4a*R*,7*R*,7a*S*,7b*R*)-1,1,4,7-tetramethyldecahydro-4a*H*-cyclopropa[*e*]azulene-4a,5-diol
ax	axial
AX	weakly coupled two-spin-½ system
bar	unit of pressure
BINIM	*N*,*N*′-bis(2-quinolylmethylene)-1,1′-binaphthyl-2,2′-diamine
BINOL	1,1′-bi(2-naphthol)
Bn	benzyl
BOX	bis(oxazoline)
Bu	butyl
γ-butenolide	2(5*H*)-furanone/γ-crotonolactone/2-buten-1,4-olide
γ-butyrolactone	dihydrofuran-2(3*H*)-one
br.	broad
brine	saturated aqueous NaCl solution
BRSM	based on recovered starting material
Bz	benzoyl
c	concentration (g/100 mL)
c	prefix centi (10^{-2})
ca.	*circa*, approximately
cal	unit of energy
calcd	calculated
cat.	catalytic amount
chalcone	benzylideneacetophenone/1,3-diphenyl-2-propen-1-one
CHP	cumene hydroperoxide

cis	prefix that describes the position of functional groups attached "on the same side" of the molecule
CNS	central nervous system
(+)–compactin	mevastatin/ML-236B/(1*S*,7*R*,8*S*,8a*R*)-8-{2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-7-methyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid/ (7,7-dimethyl-2-oxobicyclo-[2.2.1]heptan-1-yl)methanesulfonic acid
d	day(s)
d	doublet
D	dextrorotation, *i.e.* rotating plane-polarised light clockwise
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
ddt	doublet of doublet of triplets
(–)-DET	(-)-diethyl D -tartrate
DFT	density functional theory (molecular modeling term)
dia	diastereomer
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutyl aluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMPS	dimethylphenylsilyl
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNBA	dinitrobenzoic acid
DPGFSE-NOE	double pulsed field gradient spin echo 1D NOE
DPMS	diphenylmethylsilyl
dppe	ethylenebis(diphenylphosphine)
dppf	1,1′-bis(diphenylphosphino)ferrocene
dq	doublet of quartets
dr	diastereomeric ratio
Dr.	doctor
dt	doublet of triplets
dtdd	doublet of triplet of doublet of doublets
E	entgegen (opposite, *trans*)
ee	enantiomeric excess
Et	ethyl

EtO	ethoxy
(–)-ephedrine	(1*R*,2*S*)-(−)-2-methylamino-1-phenyl-1-propanol
epi-	epimer (epimers are stereoisomers that differ in configuration of only one stereogenic centre)
eq	equatorial
eq./equiv	equivalent
er	enantiomeric ratio
ESI	electrospray ionisation
F-actin	filamentous actin
formaldehyde	methanal
formic acid	methanoic acid
FT-IR	fourier transform infrared spectroscopy
G-actin	globular actin
GC	gas chromatography
gen.	generation
geraniol	*trans*-3,7-dimethyl-2,6-octadien-1-ol
glycidol	2,3-epoxy-1-propanol
glysine	aminoacetic acid
Grubbs 2nd gen. cat.	(1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexyl phosphine)ruthenium
h	hour(s)
[H]	reduction/hydrogenation
HFIP	hexafluoroisopropanol
H–G	Hoveyda–Grubbs
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HMPA	hexamethylphosphoramide/hexamethylphosphoric triamide
Homocitric acid lactone	3-carboxy-3-hydroxyhexanedioic acid 6,3-lactone/ 3-carboxyhexano-6,4-lactone
Hoveyda–Grubbs 2nd gen. cat.	(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)-ruthenium
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
hydroquinone	benzene-1,4-diol
Hz	unit of frequency
i-	iso-
i.e.	*id est*/that is
i.p.	intraperitoneal injection
IBCF	isobutyl chloroformate
IEFPCM	the integral equation formalism variant of the polarisable continuum model
imid.	imidazole
in situ	in position/in the reaction mixture
in vacuo	under reduced pressure
Ipc	isopinocamphenyl
IR	infrared
J	coupling constant (spin-spin coupling in NMR spectroscopy, unit Hz)
k	prefix kilo (10^3)
KHMDS	potassium bis(trimethylsilyl)amide
L	levorotation, *i.e.* rotating plane-polarised light counterclockwise
LA	Lewis acid

Lactic acid	2-hydroxypropionic acid
LB	Lewis base
LDA	lithium diisopropylamide
LD_{min}	minimum lethal dose
LiHMDS	lithium bis(trimethylsilyl)amide
linalool	3,7-dimethyl-1,6-octadien-3-ol
lit.	literature
L/Ln	ligand
logP/logD	partition coefficient/distribution coefficient
LRMS	low resolution mass spectrometry
2,6-lutidine	2,6-dimethylpyridine
M	prefix mega (10^6)
M	mol/L (concentration unit)
m	prefix milli (10^{-3})
m	multiplet
MacMillan 2nd generation catalyst	(2*S*,5*S*)-(−)-2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolidinone
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
Meerwein's salt	trimethyloxonium tetrafluoroborate (methylation agent)
methacrolein	methacrylaldehyde/α-methyl acrolein/2-methylprop-2-enal
MMFF	Merck Molecular Force Field
min	minute(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	molecular sieve
MW	molecular weight
m/z	mass-to-charge ratio
n-	"normal" (linear carbon chain)
NaHMDS	sodium bis(trimethylsilyl)amide
NBA	nitrobenzoic acid
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhouser effect
NOESY	nuclear Overhouser effect spectroscopy
[O]	oxidation
obs.	obscure
OH	hydroxyl
OXONE®	potassium peroxymonosulfate/$KHSO_5$• ½$KHSO_4$ •½K_2SO_4
p-	*para*-
p.a.	pro analysi (purity of reagent/solvent, which is suitable for the stated analytical application)
PBS	phosphate buffer solution
PDB	protein data bank
Pd/C	palladium on charcoal
PEG	polyethylene glycol
PFP	pentafluorophenol
P/Pg	protecting group
PGME	phenylglycine methyl ester
Ph	phenyl

pH	the decimal logarithm of hydrogen ion concentration in an aqueous solution (measure of the acidity/basicity)
Piv	pivaloyl/trimethylacetyl
pK_a	acid dissociation constant/acidity constant/acid-ionisation constant/negative logarithm of K_a; –log K_a
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
L-proline	(*S*)-pyrrolidine-2-carboxylic acid
propionic acid	propanoic acid
PTSH	1-phenyl-1*H*-tetrazole-5-thiol
PTX	pectenotoxin
pyBOX	pyridine bis(oxazoline)
pyruvate	α-ketopropionate/CH_3COCOO^-
q	quartet
R	arbitrary substituent
R-	*Rectus* (Latin for right, used in the nomenclature of enantiomers)
RCM	ring-closing metathesis
re	refers to the face of a trigonal centre where the substituents are positioned in a clockwise order (according to Cahn–Ingold–Prelog-priority rules)
Red-Al®	sodium bis(2-methoxyethoxy)aluminum hydride solution (≥ 60 wt. % in toluene)
Ref.	reference
R_f	retardation factor (ratio of the distance traveled by the centre of a spot to the distance traveled by the solvent front in TLC)
Roche ester	3-hydroxy-2-methylpropionic acid methyl ester
Rochelle's salt	potassium sodium tartrate
Rongalite	sodium hydroxymethanesulfinate hydrate/ ($HOCH_2SO_2Na \bullet xH_2O$)
rt	room temperature
s	singlet
S-	*Sinister* (Latin for left, used in the nomenclature of enantiomers)
(*R*,*R*)-Salen	(*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine
sat.	saturated
SDS	sodium dodecyl sulfate
sept.	septet
sext.	sextet
si	refers to the face of a trigonal centre where the substituents are positioned in a counterclockwise order (according to Cahn–Ingold–Prelog-priority rules)
SM	starting material
sol.	solution
spiculisporic acid	2-(1-carboxyundecyl)-5-oxooxolane-2-carboxylic acid
Sudan red	1-(2-methoxyphenylazo)-2-naphthol/amethoxybenzenazo-β-naphthol
syn	alignment of two substituents on the same side/face of a compound

t-	*tert*-
t	triplet
T/Temp.	temperature
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
tddd	triplet of doublet of doublet of doublets
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TfO	trifluoromethanesulfonate/triflate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
toluene	methylbenzene
TPAP	tetrapropylammonium perruthenate
tq	triplet of quartets
trans	prefix that describes the position of functional groups attached "on the opposite sides" of the molecule
TS	transition state
p-TsOH	*para*-toluenesulfonic acid
tt	triplet of triplets
ttq	triplet of triplet of quartets
UV-light	ultraviolet light (400-10 nm wavelength)
valeraldehyde	pentanal
vanillin	4-hydroxy-3-methoxybenzaldehyde
via	by way of/by means of
vide infra	see below
v/v	volume/volume (volume concentration)
whisky lactone	5-butyl-4-methyloxolan-2-one
Wilkinson's catalyst	tris(triphenylphosphine)rhodium(I) chloride
wt-%	weight percent
Z	zusammen (together, *cis*)
Å	Ångström (unit of length; 10^{-10} m = 0.1 nm)
α	referring to the position of the carbon in relation to a functional group, α is the position adjacent to the functionalised carbon
$[\alpha]_D$	optical rotation
β	referring to the position of the carbon in relation to a functional group, β is the position one carbon further than α
γ	referring to the position of the carbon in relation to a functional group, γ is the position one carbon further than β
δ	chemical shift in parts per million downfield from TMS
ø	diameter
Δ	difference
Δν	the relative chemical shift difference in higher-order splitting pattern (unit Hz)
μ	prefix micro (10^{-6})

CONTENTS

1 INTRODUCTION: PECTENOTOXINS

This thesis contains my work in two connected projects: Studies towards the total synthesis of pectenotoxin-2, a complex natural product of marine origin, and studies on an organocatalytic Mukaiyama–Michael reaction that was initially developed in the course of the work on the pectenotoxin-2, but subsequently expanded on. The thesis begins with short literature reviews on both of the main topics, followed by the description of my own research.

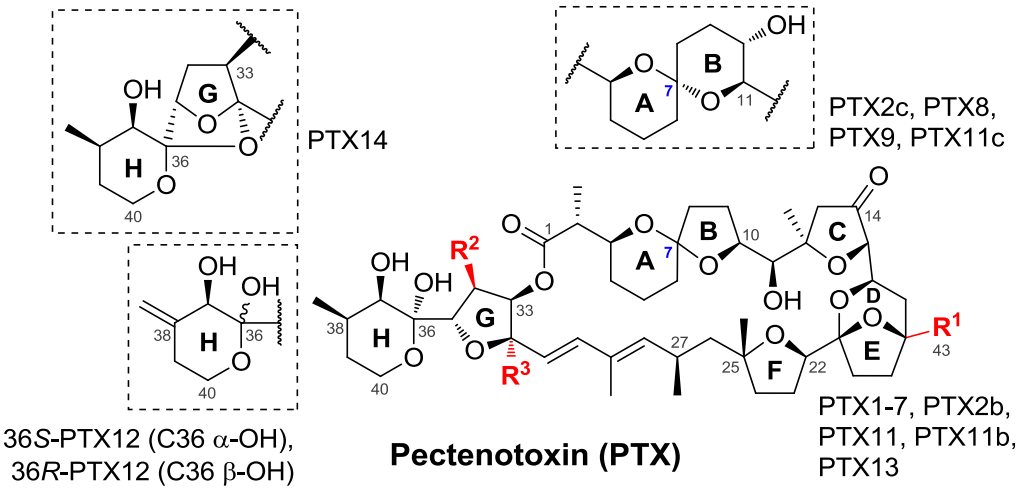
1.1 The Discovery and Activity of Pectenotoxins

In 1985, Yasumoto and co-workers reported the discovery of a novel polyether macrolactone family which was named the pectenotoxins (PTXs). The name is derived from the genus name of scallops named *Patinopecten yessoensis*. The digestive glands of these mollusks were the original source of the toxins.[1] It was soon discovered that PTXs were actually produced by the toxic dinoflagellate genus *Dinophysis*, which were part of the diet of the scallops. These dinoflagellates can be found in marine environments worldwide.[2]

The PTX family has slowly grown during the last three decades. The family comprises many complex structurally related macrolactones and "open chain" carboxylic acid analogues (**Table 1** and **Table 2**). The molecules can be divided in to three groups based on their origin: naturally occurring biosynthesis

products, shellfish metabolites (typically products further oxidised at the C43 position) or artificial products (mainly generated during isolation and purification, but also synthetical derivatives).

Table 1. Structure and toxicity information of PTXs. Blue: shellfish metabolism products, orange: biosynthesis products, white: artificial products (formed mainly by acid catalysis).



	R¹	R²	R³	C7	Formula	MW [g/mol]	LD_{min} [µg/kg] (i.p.)	Ref.
PTX1 (**1a**)	CH_2OH	H	H	*R*	$C_{47}H_{70}O_{15}$	874.5	250	1
PTX2 (**1b**)	CH_3	H	H	*R*	$C_{47}H_{70}O_{14}$	858.5	230	1
PTX2b (**1c**)	CH_3	H	H	*S*	$C_{47}H_{70}O_{14}$	858.5	-	3
PTX2c (**1d**)	CH_3	H	H	*S*	$C_{47}H_{70}O_{14}$	858.5	-	3
PTX3 (**1e**)	CHO	H	H	*R*	$C_{47}H_{68}O_{15}$	872.5	350	1, 4
PTX4 (**1f**)	CH_2OH	H	H	*S*	$C_{47}H_{70}O_{15}$	874.5	770	1, 5, 6
PTX5 (**1g**)	*Structure unidentified*				$C_{47}H_{72}O_{15}$	876.5	-	1
PTX6 (**1h**)	COOH	H	H	*R*	$C_{47}H_{68}O_{16}$	888.5	500	7, 8
PTX7 (**1i**)	COOH	H	H	*S*	$C_{47}H_{68}O_{16}$	888.5	>5000	5, 7
PTX8 (**1j**)	CH_2OH	H	H	*S*	$C_{47}H_{70}O_{15}$	874.5	>5000	5
PTX9 (**1k**)	COOH	H	H	*S*	$C_{47}H_{68}O_{16}$	888.5	>5000	5
PTX10 (**1l**)	*Structure unidentified*				-	-	-	5
PTX11 (**1m**)	CH_3	OH	H	*R*	$C_{47}H_{70}O_{15}$	874.5	250	3, 9
PTX11b (**1n**)	CH_3	OH	H	*S*	$C_{47}H_{70}O_{15}$	874.5	-	3, 9
PTX11c (**1o**)	CH_3	OH	H	*S*	$C_{47}H_{70}O_{15}$	874.5	-	3, 9
36*S*-PTX12 (**1p**)	CH_3	H	H	*R*	$C_{47}H_{68}O_{14}$	856.5	-	10
36*R*-PTX12 (**1q**)	CH_3	H	H	*R*	$C_{47}H_{68}O_{14}$	856.5	-	10
PTX13 (**1r**)	CH_3	H	OH	*R*	$C_{47}H_{70}O_{15}$	874.5	-	11
PTX14 (**1s**)	CH_3	H	-	*R*	$C_{47}H_{68}O_{14}$	856.5	-	11

The first isolated family members were PTX1–5 (excluding the PTX2 spiroketal isomers PTX2b and PTX2c, which were discovered later, **Table 1**). The Yasumoto group managed to determine the relative stereochemistry of PTX1 by using single crystal X-ray diffraction techniques combined with spectral data

analysis. The structure of PTX2 was also determined in the paper, and it was identified to be "C43-deoxy PTX1" based on spectral data comparison between PTX1 and PTX2. In addition to these characterisations, some data was gathered for PTX3-5. The mass spectrum of PTX5 indicated that the compound was a dihydro derivative of either PTX1 or PTX4, being two mass units heavier than either of these congeners. The lack of an IR absorption band at the 1760 cm^{-1} region, characteristic for the C14 carbonyl of PTXs, suggested the reduction of the carbonyl moiety and further defined the structure. However, no conclusive structural elucidation has been performed, and the actual structure of PTX5 remains undetermined.[1] Further analysis of PTX3 confirmed it to be a C43 aldehyde derivative of PTX2, based on the spectral data.[1,4] The exact structure of PTX4 was not determined until later (*vide infra*).

PTX6 (**Table 1**) was determined to be a further oxidised derivative of PTX3, with a carboxylic acid moiety at C43 (based on the comparison of spectral data). A similar comparison between PTX7 and PTX4 suggested an analogous relation between the two compounds, but their exact structures remained undetermined. As PTX2 was the only pectenotoxin isolated from dinoflagellates, it was reasoned that oxidation of PTX2 in the hepatopancreas of shellfish generated PTX1, PTX3 and finally PTX6 (**Figure 1**).[7]

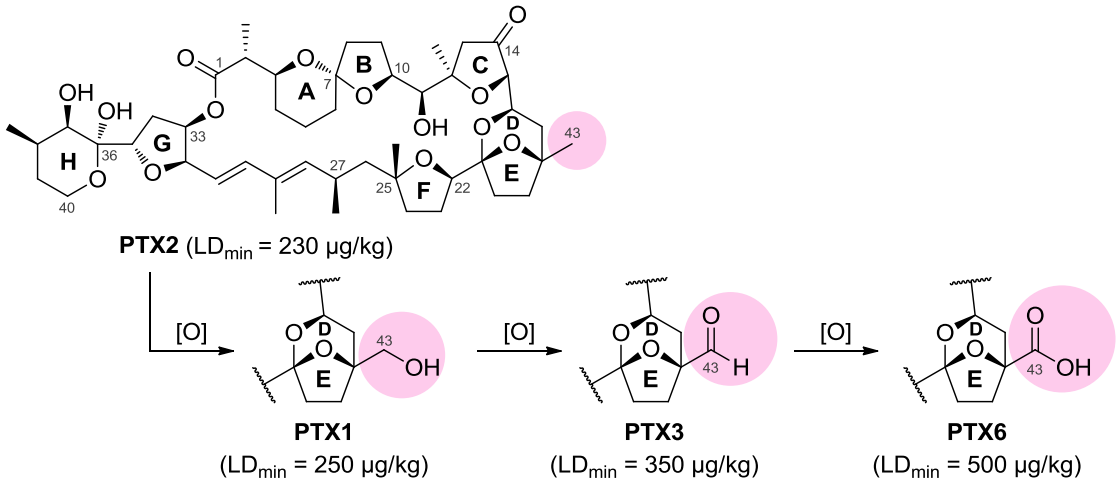


Figure 1. Biological oxidation of the C43 methyl group of PTX2 in the shellfish.[7]

In 1997, the absolute stereochemistry of PTX6 (as well as other PTXs by analogy) was finally confirmed employing a chiral auxiliary. The assignment was performed using (*R*)- and (*S*)-phenylglycine methyl ester (PGME) derivatives of PTX6. The stereochemistry of the C18-stereocentre was assigned on the basis of the anisotropic effect caused by the phenyl group of the chiral auxiliary connected to C43 of PTX6. The conformation of the amide group of the PGME-chain was first determined with NOE experiments (**Figure 2**a).[8] Using this information, the positioning of the phenyl group of the chiral auxiliary could be unambiguously determined. The anisotropic effect caused by the phenyl group to the protons in near proximity, *i.e.* the upfield shift of the affected protons due to the changed electrochemical shielding, was clearly observed (**Figure 2**b).[8,12] Calculating the differences between the proton chemical shifts of the (*S*)-PGME and (*R*)-PGME derivatives showed a clear trend and confirmed the absolute stereochemistry of the C18-stereocentre to be *S*. The absolute stereochemistries of the other members of the PTX family were determined by analogy, based on the previously determined relative stereochemistries and optical rotation values.[8]

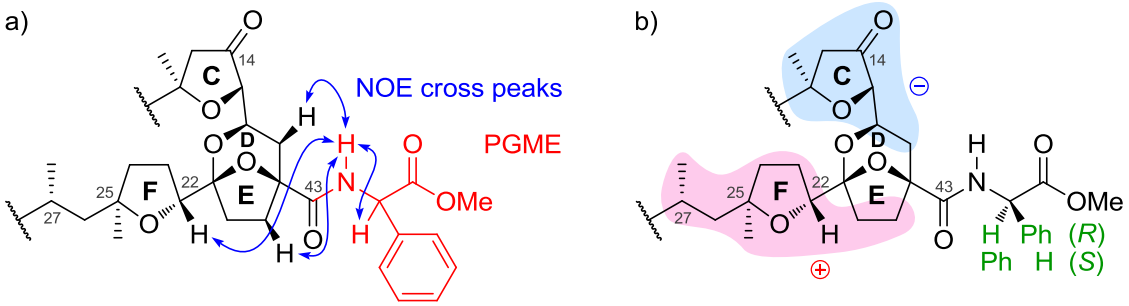


Figure 2. a) The partial PTX6-PGME structure and NOE cross peaks. b) The structures of (*R*)- and (*S*)-PGME derivatives with the information of the NMR shift differences [$\Delta\delta = \delta_{(S)} - \delta_{(R)}$]. Blue areas indicate negative $\Delta\delta$ and red areas positive $\Delta\delta$ values.[8]

The exact structures of PTX4 and PTX7 were reported in 1998 (**Table 1**). A comparison of NMR data between the different PTX family members led the researchers to the conclusion that PTX7 is the C7 stereoisomer of PTX6, and PTX4 is the C7 stereoisomer of PTX1. It was also observed that acidic treatment of PTX7 led to the formation of PTX6 and additionally to the formation of a new

spiroketal stereoisomer, which was named PTX9 (**Figure 3**).[5] Similarly, PTX8 was found to form from the acidic treatment of PTX1 and PTX4. Neither PTX8 nor PTX9 have been isolated from Nature, and are considered to be artefacts from the extraction process.[5]

More recently, similar equilibrium mixtures of the three spiroketal isomers (7*R*-, 7*S*- and the 6-membered B-ring-isomers) were observed for other PTX family members.[3,9b] In 2003, Suzuki and co-workers exposed PTX2 to acidic conditions and discovered the formation of PTX2b and PTX2c.[3] In 2006, the same group reported an analogous equilibrium between the newly discovered PTX11, a novel C34-hydroxyderivative of PTX2, and its isomers PTX11b and PTX11c.[3,9b]

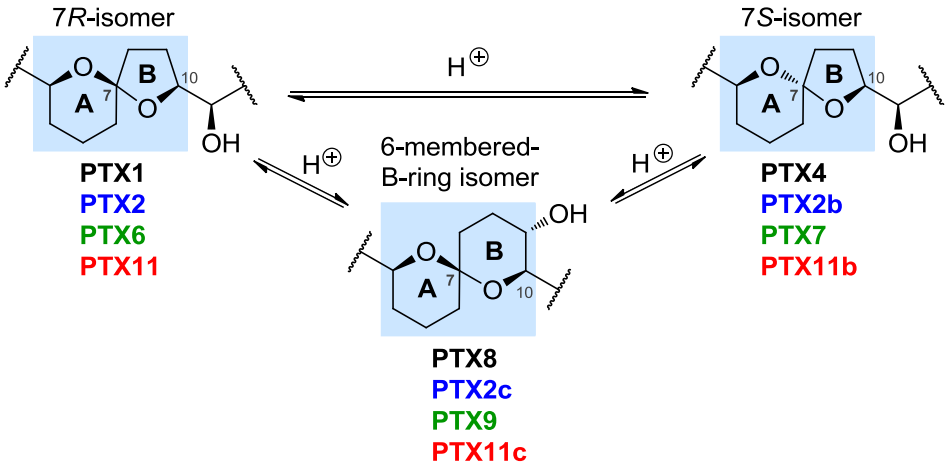


Figure 3. Acid-catalysed spiroketal isomerisation of PTXs. All the 6-membered-B-ring PTXs are considered artefacts.[3,5,9b]

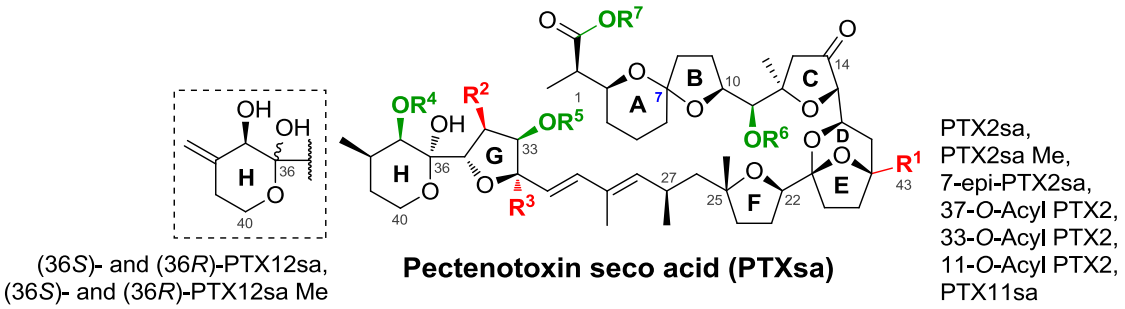
In 2002, the Evans group reported the total synthesis of PTX4, whose ^{1}H NMR and optical rotation were identical to natural PTX4. Subjecting the synthetic material to acidic conditions generated PTX8, corresponding with the previously detected artificial material (**Figure 3**). These results confirmed the correctness of the previously assigned absolute stereochemistry.[6]

Miles and co-workers reported the structures of two new PTX derivatives in 2004: an equilibrating pair of 36*S*- and 36*R*- isomers they named PTX12 (**Table 1**). PTX12 differed from PTX2 in that the methyl at C38 was oxidised to methylene.[10] In 2006, the same group published the characterisation of PTX13

(originally called PTX11x), and PTX14. PTX13 was the C32-hydroxy derivative of PTX2, and PTX14 was determined to be a 32,36-dehydration product of PTX13. PTX14 was isolated from the same sample as PTX13, but this compound was suspected to be of artificial origin.[11]

The structure of PTX10 is still unknown. Although this compound has been mentioned occasionally in the literature,[2,5] no characterisation information is available.

Table 2. Structures of PTX seco acids. Blue: shellfish metabolism products, white: artificial products.



	R¹	R²	R³	C7	R⁴	R⁵	R⁶	R⁷	Ref.
PTX2sa (**2a**)	CH_3	H	H	*R*	H	H	H	H	13
PTX2sa Me (**2b**)	CH_3	H	H	*R*	H	H	H	CH_3	14
7-epi-PTX2sa (**2c**)	CH_3	H	H	*S*	H	H	H	H	13
37-*O*-Acyl PTX2sa (**2d**)	CH_3	H	H	*R/S*	Acyl	H	H	H	15
33-*O*-Acyl PTX2sa (**2e**)	CH_3	H	H	*R/S*	H	Acyl	H	H	15
11-*O*-Acyl PTX2sa (**2f**)	CH_3	H	H	*R/S*	H	H	Acyl	H	15
PTX11sa (**2g**)	CH_3	OH	H	*R*	H	H	H	H	6
36*S*-PTX12sa (**2h**)	CH_3	H	H	*R*	-	H	H	H	10, 15b
36*R*-PTX12sa (**2i**)	CH_3	H	H	*R*	-	H	H	H	10, 15b
36*S*-PTX12sa Me (**2j**)	CH_3	H	H	*R*	-	H	H	CH_3	10
36*R*-PTX12sa Me (**2k**)	CH_3	H	H	*R*	-	H	H	CH_3	10

It was observed that the lactone moiety of PTX2 undergoes enzymatic hydrolysis to form PTX2 seco acids (PTXsas, **Table 2**) in some scallop and mussel species (**Figure 4**a).[14] Two of these open chain PTXs were isolated and characterised in 1998 by Yasumoto and co-workers. NMR and mass spectrometric analyses confirmed the structures of PTX2sa and 7-*epi*-PTX2sa by comparison with the data of PTX2.[13] It was later observed that while similar

seco acid forms have also been detected for PTX11 and PTX12, these macrocyclic lactones are more resistant to enzymatic hydrolysis than PTX2.[6,10]

Miles and co-workers detected a PTX2sa methyl ester (PTX2sa Me) during the isolation and purification process of PTX2 in 2004, when they reported a new isolation method for PTX2 from *Dinophysis* cells.[14] In the same year they reported the use of PTX12sa methyl ester (PTX12sa Me) derivatives to demonstrate the presence of a carboxylic acid group in their PTX12 samples.[10] To date all methyl ester derivatives of PTXsas have been artificially produced.

In 2006, different *O*-Acyl PTX2sa derivatives (**Table 2**) were detected in mass spectrometric analyses of the mussel samples. Presumably these esters are further metabolites produced by acyl transferases in the shellfish (**Figure 4**b).[15]

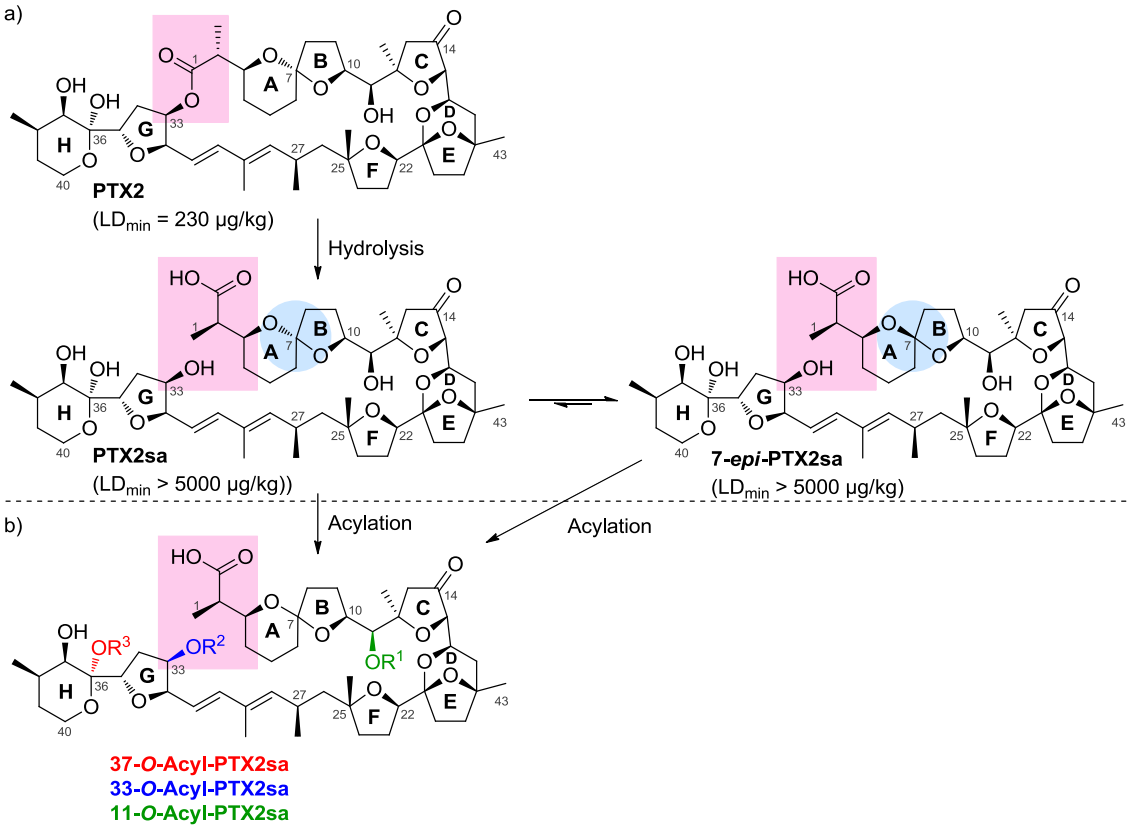


Figure 4. The metabolism of PTX2 in shellfish: a) enzymatic hydrolysis step and epimerisation of PTX2sa to 7-*epi*-PTX2sa, and b) enzymatic acylation.

PTX2 has been suggested as the parent compound of other PTXs.[7] According to the reported minimum lethal doses (LD_{min}) determined by intraperitoneal (i.p.)

injections to mice (**Table 1**), PTX2 is the most toxic pectenotoxin (LD_{min} = 230 μg/kg). The metabolites of PTX2 (**Figure 1** and **Figure 4**) are less toxic, suggesting a kind of detoxification of PTX2 in the scallops. Additionally, 7*S*-PTX isomers (PTX4, PTX7–9) are less toxic than their 7*R*-counterparts with LD_{min} values from 770 to >5000 μg/kg.[5] PTX11 (LD_{min} = 250 μg/kg) is among the most toxic variants of PTXs, so the additional OH in C34 position does not decrease the toxicity of the molecule.[9b] It has been determined that PTXs are hepatotoxic compounds, as intraperitoneal injections have caused severe liver damage to mice.[16] By oral route, PTXs are nontoxic.[14,17,18]

PTX2 has shown cytotoxic activity against certain human cancer cell lines in *in vitro* culture assays. Studies have shown potent cytotoxicity towards some human colon, lung, ovarian, renal, and breast cancers, as well as central nervous system (CNS) tumors and melanoma.[19] Based on these results, PTX2 can be classified as a potential antitumor drug. PTX2 has been observed to interact with the actin cytoskeleton of a cell. Actin is largely responsible for the cell's motility, shape, division and adhesion.[20] The co-crystal structure of PTX2 with G-actin, published by Miles and co-workers in 2007, revealed that PTX2 binds to the barbed end of an actin filament (**Figure 5**), thus capping it and inhibiting its polymerisation.[21] This crystal structure (PDB code 2Q0R, at 1.7Å resolution) also unambiguously confirms the stereochemistry of PTX2. The cyclic structure of PTX2 is essential for this interaction process, as it has been observed that the open form (PTX2sa) no longer has any visible effect on the F-actin or the shape of the cells even at substantially higher (5-fold) concentrations.[22]

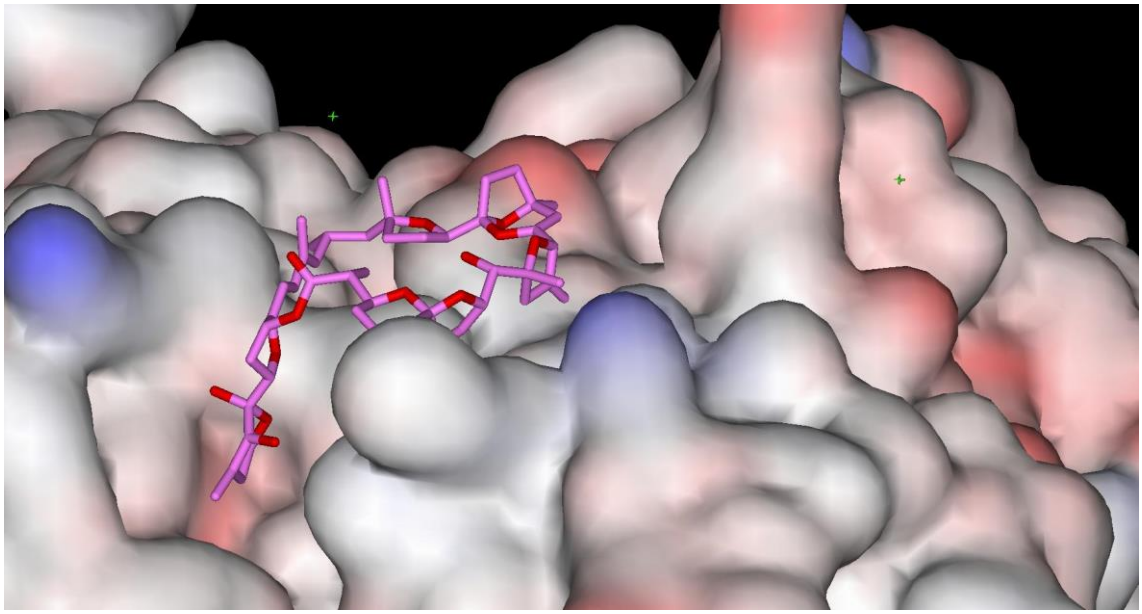


Figure 5. The PTX2-actin complex (PDB: 2Q0R).[21]

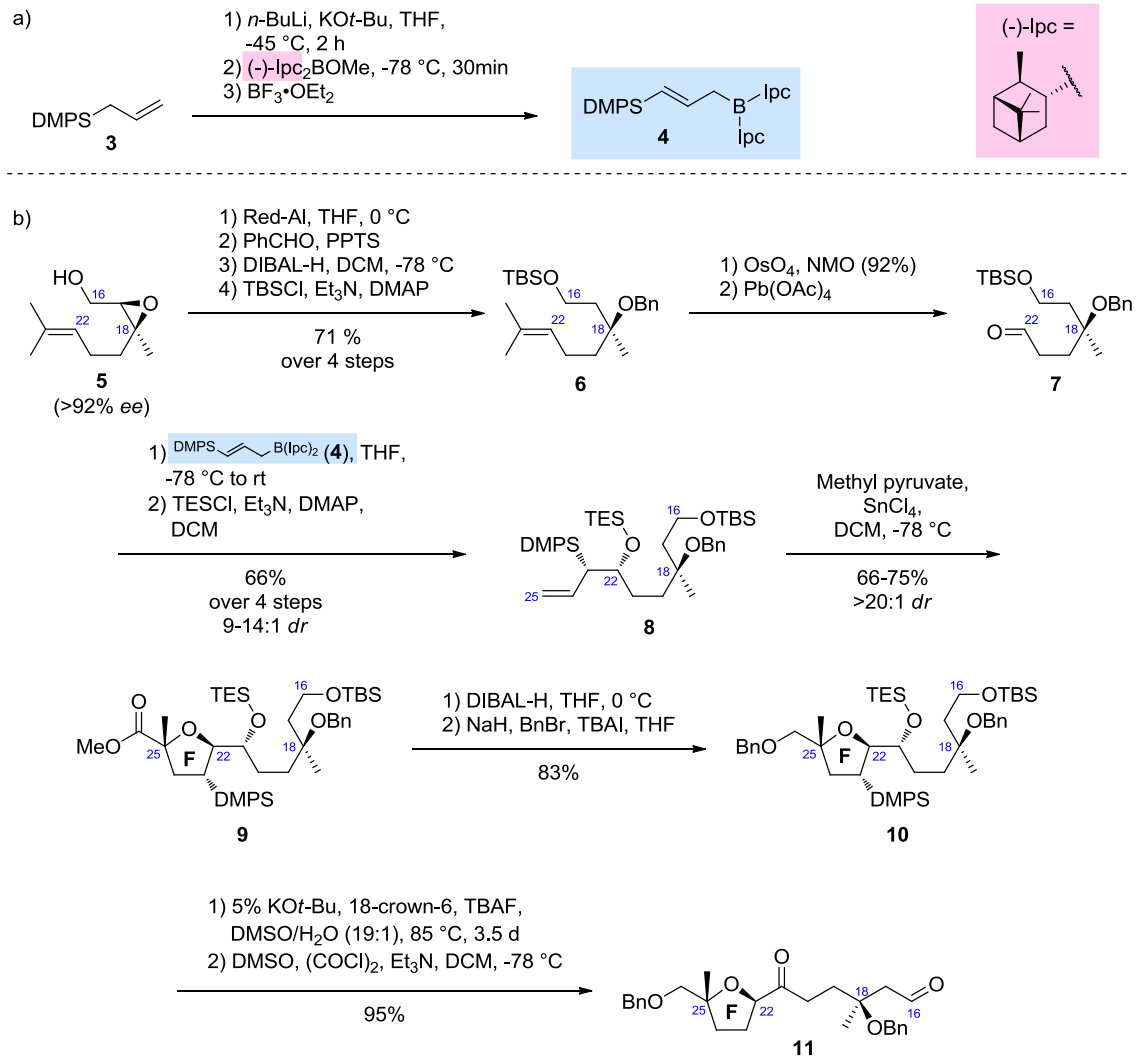
The biological activity profile of PTX2 makes it the most interesting member of the whole PTX family. The total synthesis of PTX2 still remains an unobtainable dream for several research groups who are aiming for this target all around the world. Isolation and purification of large quantities of PTX2 from natural sources is highly challenging. There is therefore need for a total synthesis, as it is the only viable way to produce sufficient amounts of the compound for further biological, toxicological and medical studies.

1.2 Syntheses of the F-ring Fragment of the Pectenotoxins

Only a single total synthesis of pectenotoxins has been reported: the total synthesis of PTX4 (and its isomerisation to PTX8) by Evans and co-workers, in 2002.[6] Still today, many groups are aiming towards the total synthesis of other PTXs, mainly PTX2.[23,24] The "F-ring" moiety is identical for all known PTXs (**Table 1** and **Table 2**). As a major part of my Ph.D. studies is related to the synthesis of the C17–C28 fragment of the pectenotoxins (discussed in detail in Chapter 3), which contains the F-ring, a brief review of other research groups' approaches towards the synthesis of F-ring fragments has been included in this chapter.

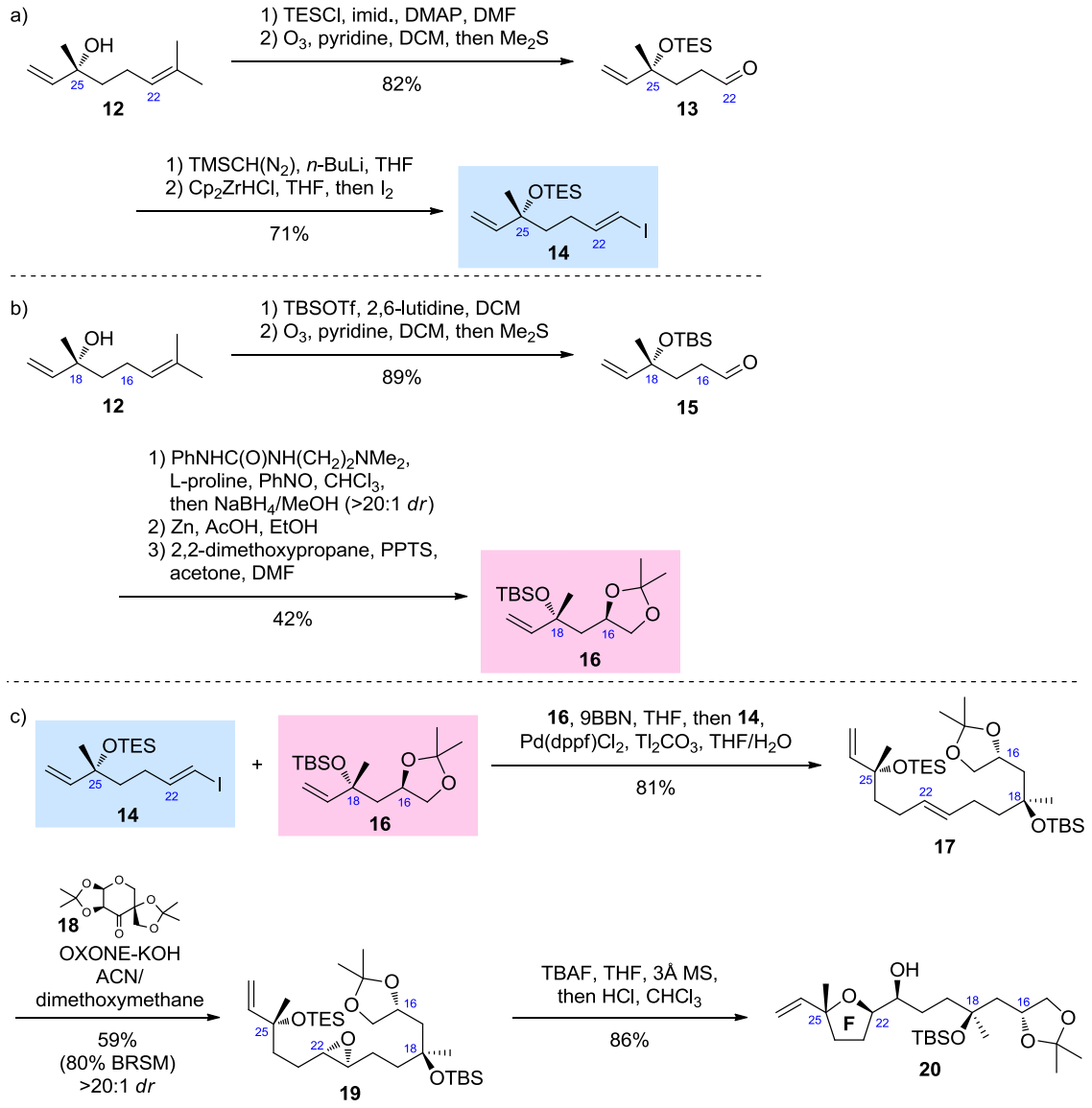
1.2.1 Micalizio's Approaches

In 2001, Micalizio and Roush reported the synthesis of a C11–C26 fragment of PTX2.[25] The route began from geraniol epoxide (**5**, **Scheme 1**), which could be prepared from geraniol by Sharpless asymmetric epoxidation.[26] The starting material **5** contained the correct C18 stereochemistry. The key steps in the synthetic route were: 1) the formation of the C22 stereocentre in an asymmetric silylallylboration [27] reaction with aldehyde **7** to afford the *anti*-β-hydroxyallylsilane (**8**) as an inseparable 9–14:1 mixture of diastereomers and 2) the formation of C25 stereochemistry in an $SnCl_4$–promoted [3+2] annulation[28] reaction of compound **8** with methyl pyruvate, which afforded the desired THF-ring product **9** in >20:1 diastereomeric ratio. This F-ring unit (**11**, the whole C16–C26 fragment) synthesis route contained 13 steps in total.



Scheme 1. Roush's and Micalizio's synthesis of the F-ring moiety (**11**) of PTX2. a) Preparation of the [(*E*)-γ-(dimethylphenylsilyl)allyl]diisopinocampheylborane (**4**)[27] and b) synthesis of the C16–C26 fragment (**11**) of PTX2.[25]

A decade later, in 2011, Micalizio and co-workers published a convergent synthetic pathway to the C15–C26 fragment (**20**, **Scheme 2**), which encompassed only 8 linear steps.[24b,m] Commercial (–)-linalool (**12**) was used as the starting material for two separate subcomponents, utilising its chiral centre as both the C18 and C25 stereocentres of PTX2 (**Scheme 2**a and b). The key steps in this route were 1) Suzuki coupling[29] of two different linalool derivatives **14** and **16** in high yield, 2) Shi epoxidation[30] to form the C22 stereocentre with high diastereoselectivity (>20:1 *dr*) and moderate yield, and 3) acidic treatment to form the THF ring **20** as a single diastereomer.



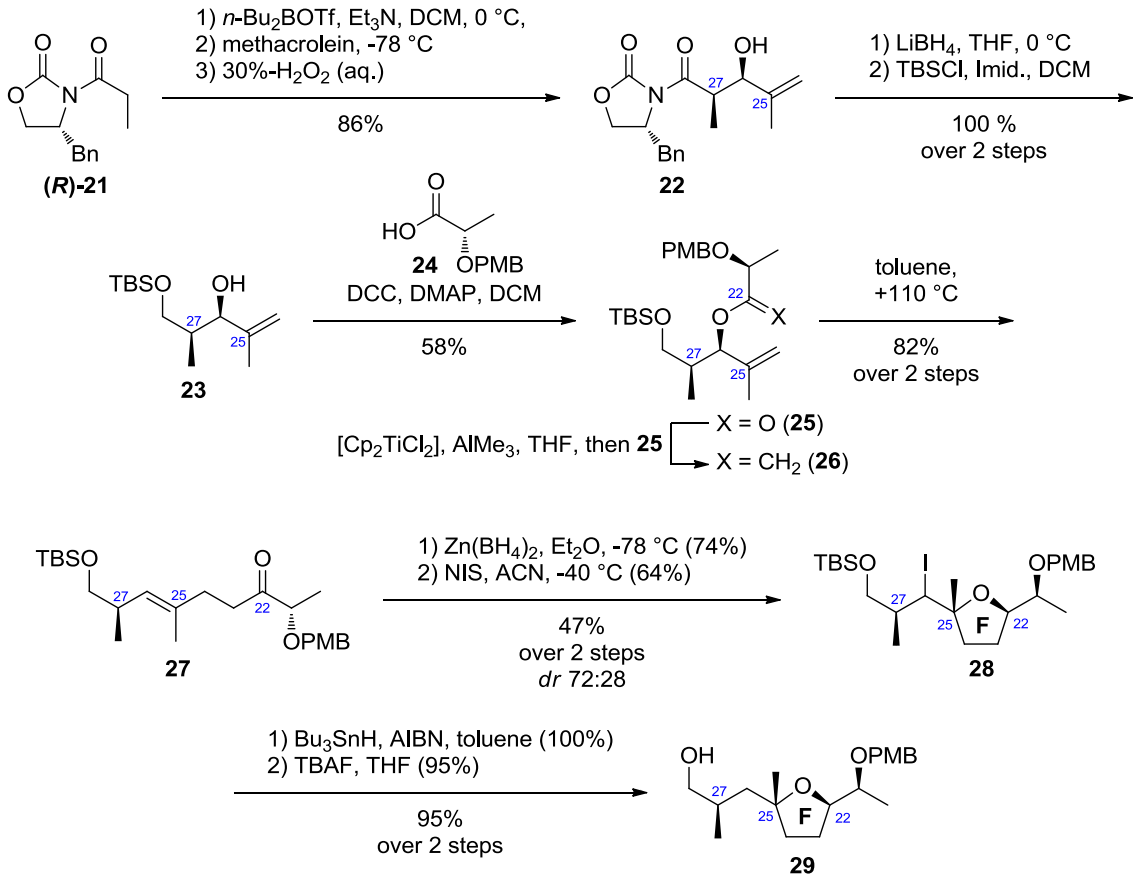
Scheme 2. Micalizio's improved synthesis for the F-ring fragment (**20**, C15–C26). a) Synthesis of the C25 stereocentre containing building block **14**. b) Synthesis of the C18 stereocentre containg building block **16**. c) The synthesis of fragment **20**.

Both routes (**Scheme 1** and **Scheme 2**) utilised naturally occuring terpenes as their starting materials. However, neither of the fragments contained the tertiary stereocentre C27, located next to the THF ring. Its installation in a stereoselective manner in later steps could be challenging.

1.2.2 Evans' Approach

Evans and co-workers published the total synthesis of PTX4 and PTX8 in 2002.[6] Their approach to the synthesis of the F-ring fragment (**29**, C20–C28) they used

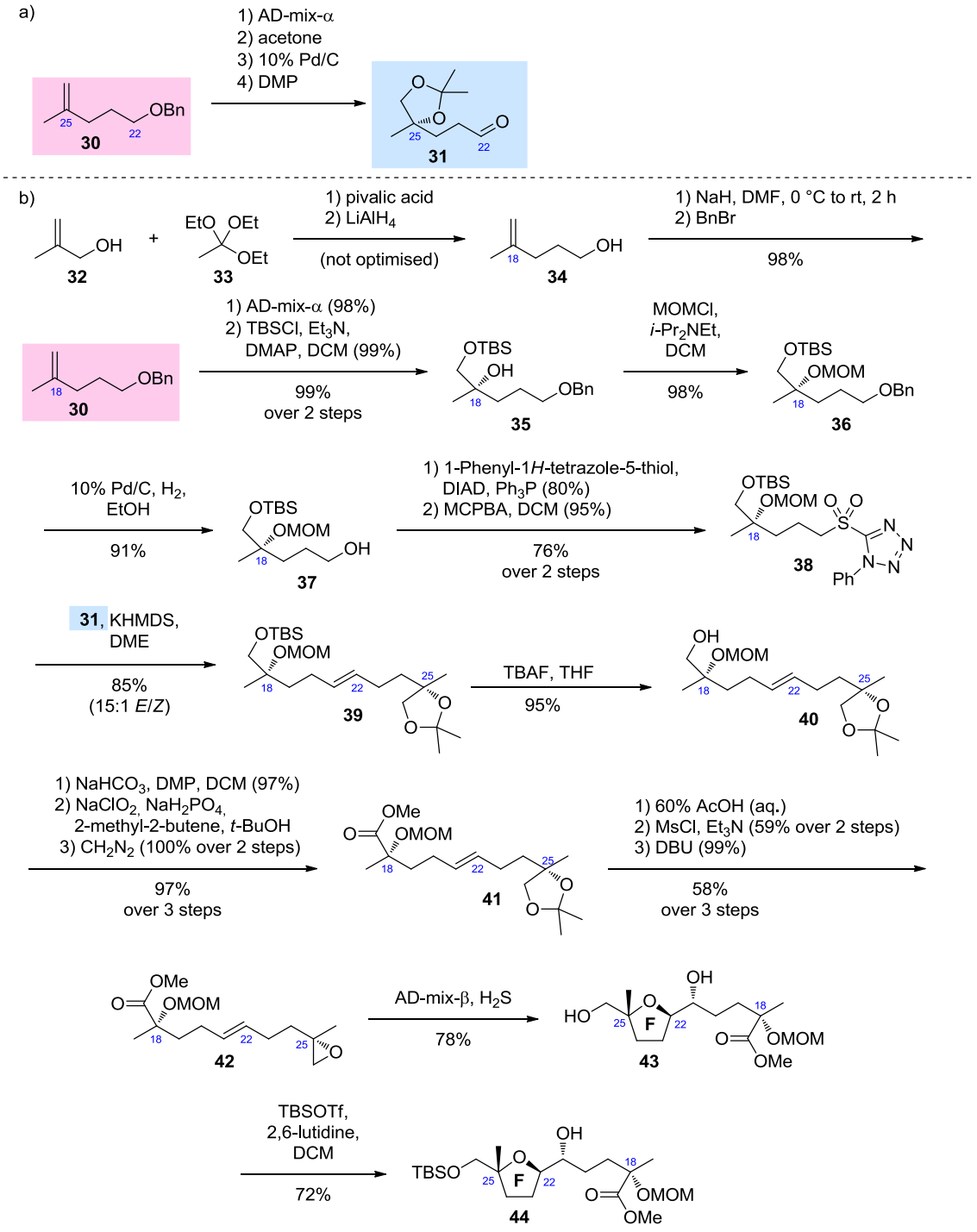
for the total synthesis (**Scheme 3**) began from the commercially available carboximide **(*R*)-21**, which could also be prepared in 3 steps starting from D-phenylalanine.[31] In the first step in this reaction route a boron enolate was generated from carboximide **(*R*)-21** and the addition of methacrolein formed the stereocentre at the C27 position of compound **22**.[32] Later key steps included the esterification of a secondary alcohol **23** with PMB protected lactic acid (**24**),[33] followed by Tebbe olefination[34] and Claisen rearrangement.[35] The formed ketone **27** was subsequently reduced in chelation-controlled manner with $Zn(BH_4)_2$ to generate the C22 stereocentre. The THF-ring closure was achieved *via* iodoetherification, affording the desired product **28** as a 72:28 mixture of C25-diastereomers in moderate yield. Evans' approach was 10 steps long, beginning from the carboximide **(*R*)-21**.



Scheme 3. Evans' synthesis of the F-ring fragment **29** (C20–C28).

1.2.3 Paquette's Approaches

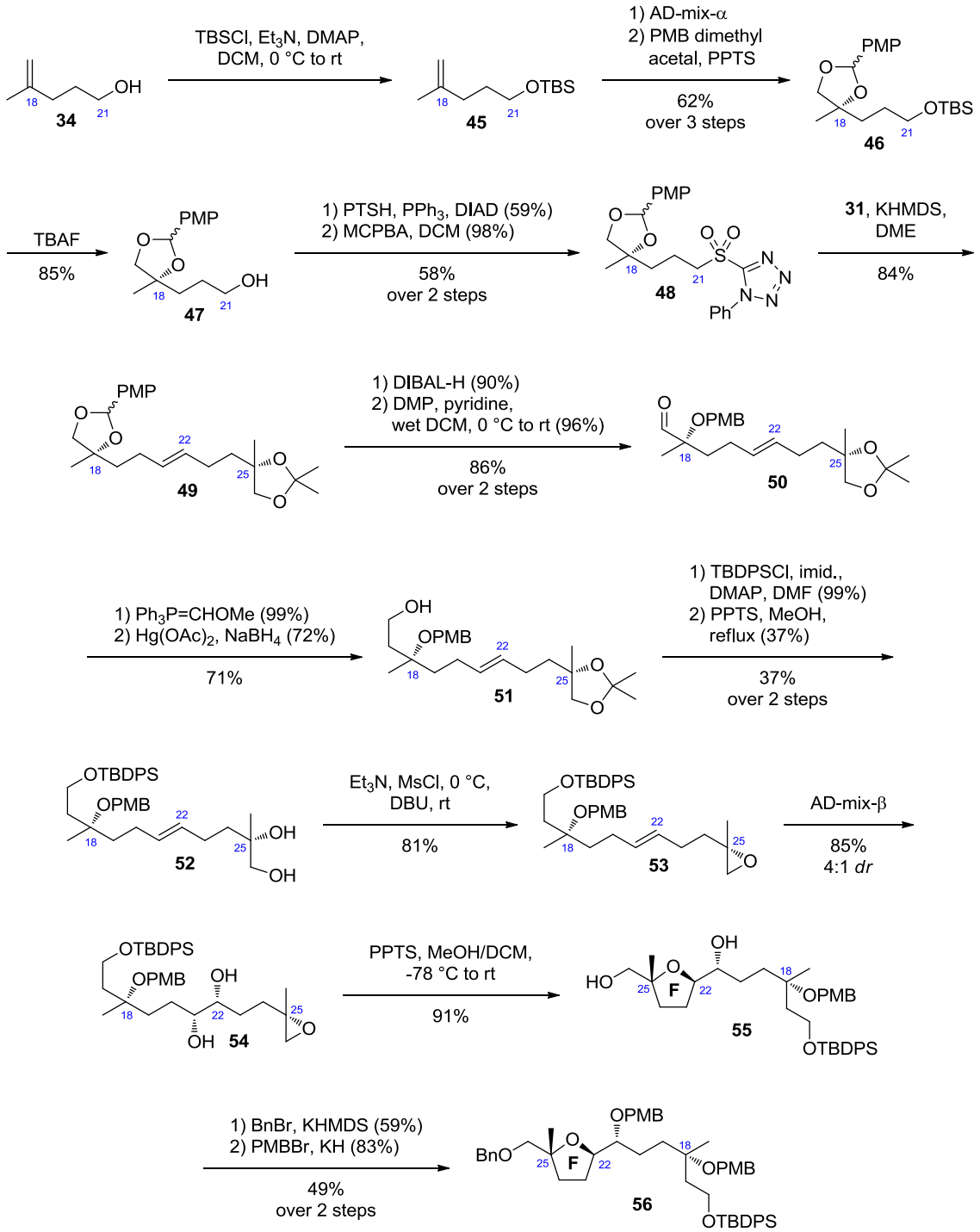
In 2005, Paquette and co-workers published the synthesis of an A–F (C1–C26) fragment precursor of PTX2.[36] The synthesis of the C17–C26 subfragment is presented in **Scheme 4**. The route began from compound **30** (which was in turn prepared from methallyl alcohol (**32**) and triethyl ortho acetate (**33**) by Johnson–Claisen rearrangement[37] reaction, followed by reduction and benzyl protection). The group prepared all the critical stereocentres, C18, C22 and C25 using Sharpless asymmetric dihydroxylation. [38] Neither the diastereo- nor the enantioselectivities are reported in the publication. A key step in this convergent approach was the coupling of compounds **31** and **38** together employing the Julia–Lythgoe coupling reaction,[39] obtaining the desired *trans*-isomer in a 15:1 stereoisomeric ratio. The group used acid catalysed cyclisation, promoted by H_2S (which was used in the place of standard workup conditions directly after the AD reaction), to achieve a selective THF-ring closure. The route contained 16 steps in total (beginning from the **30**) to afford the fragment **44** (C17–C26).



Scheme 4. The synthesis of the F-ring fragment in Paquette's approach towards PTX2: a) preparation of compound **31** and b) the whole synthetic route of the F-ring fragment **44** (C17–26).

Paquette's group reported a second generation synthesis for the F-ring fragment (**Scheme 5**), in 2007. [24a] The route was strategically highly similar to the previous one, and the beginning of the route was identical in both (compare **Scheme 4** and **Scheme 5**). The main difference in the 2nd generation synthesis

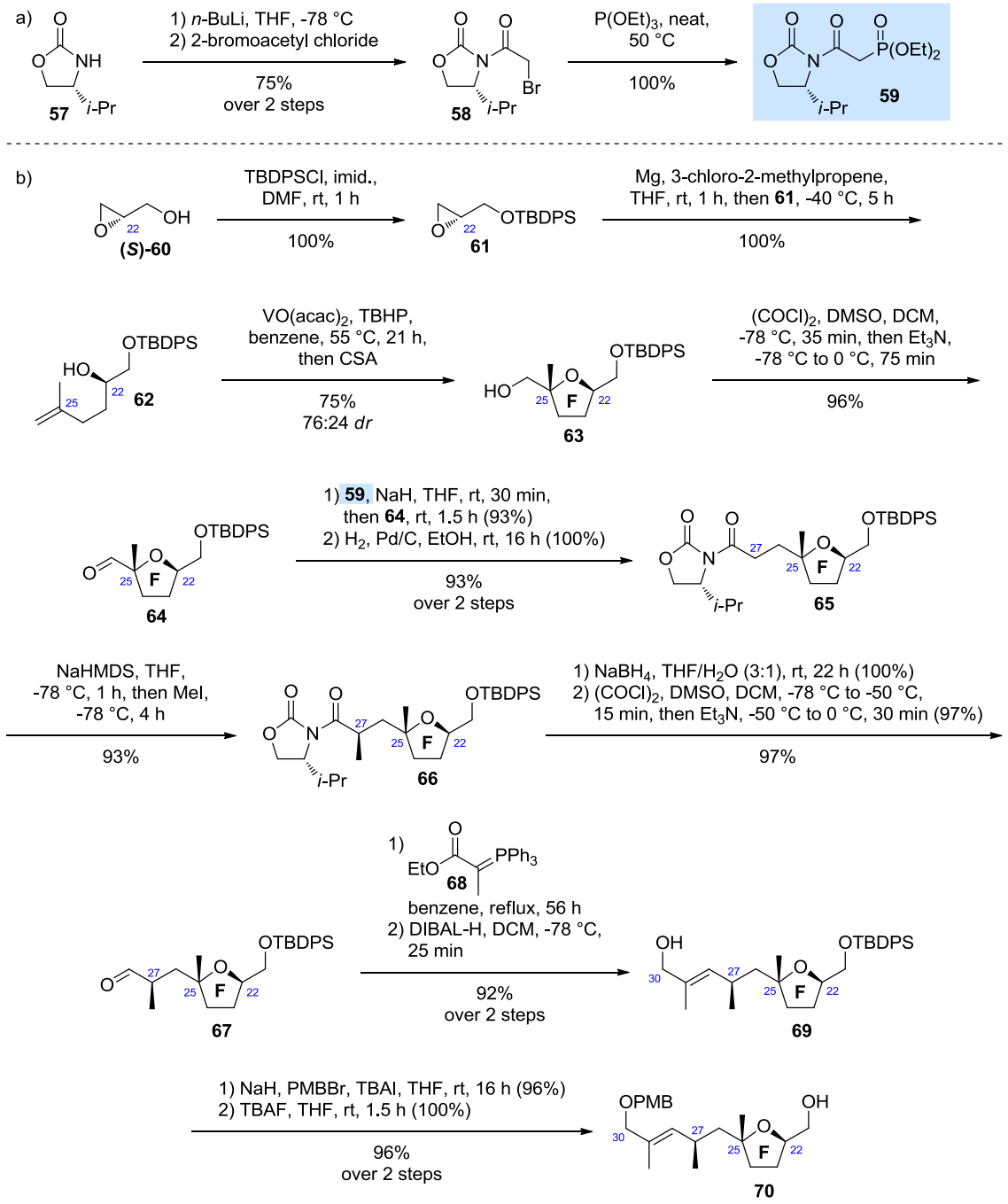
came from the use of different protecting groups and an improved procedure for the stereocontrolled acid catalysed THF-ring closure. In the end they could not reduce the total number of steps, but the product fragment **56** (C16–C26) was more readily usable in the subsequent reactions.



Scheme 5. Paquette's second generation synthesis of the F-ring fragment **56** (C16–C26).

1.2.4 Fujiwara's Approach

In 2007, Fujiwara and co-workers published the synthesis of the C21–C30 sequence **70** of PTX (**Scheme 6**).[24k] The group used (*S*)-glycidol (**(*S*)-60**) as the starting material in their approach. **(*S*)-60** could be prepared from 2-propenol by asymmetric epoxidation. The starting material itself contained the C22 stereocentre, and it was used to control the stereoselectivity of C25 in the $VO(acac)_2$ catalysed epoxidation step. This was followed by *in situ* acid catalysed THF-ring formation to afford the desired compound **63** in 57% yield and 76:24 diastereomeric ratio. Phosphonate ester **59**, containing an Evans' auxiliary, is coupled to fragment **64** by Horner–Wadsworth–Emmons olefination[40] reaction, and the C27 methyl was inserted in a stereoselective manner utilising the chiral auxiliary to afford **66** (the diastereomeric ratio is not reported in the publication). Wittig reaction was used to connect **67** and **68**, and 12 steps in total were used for the synthesis of the F-ring fragment **70** (C21–C30).

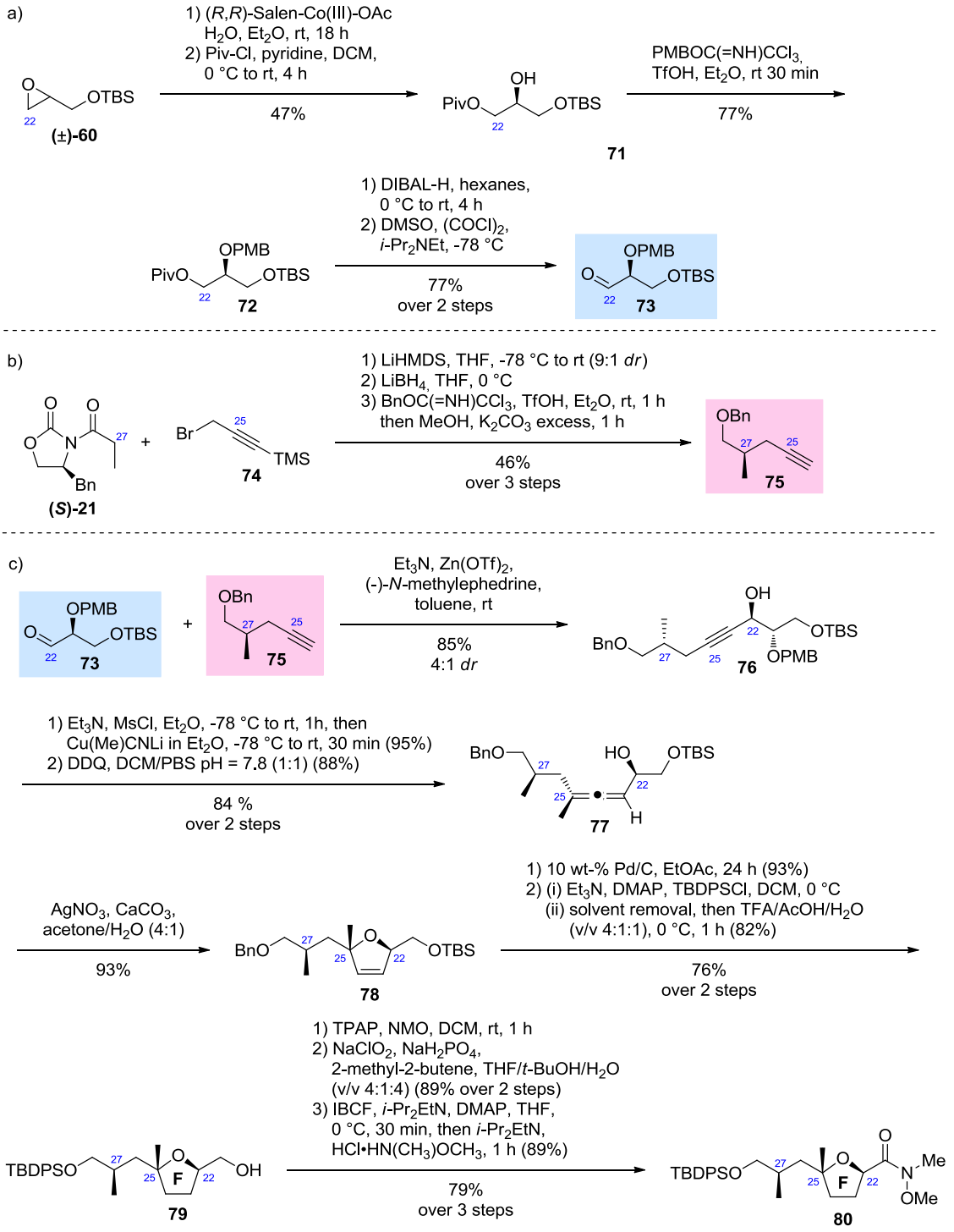


Scheme 6. Fujiwara's approach: a) preparation of the Horner–Wadsworth–Emmons reagent **59** and b) synthetic pathway to the F-ring fragment **70** (C21–30).

1.2.5 Williams' Approach

Williams and co-workers published the synthesis of a C21–C28 building block of PTX (**Scheme 7**) in 2007.[24n] The group used Jacobsen's hydrolytic kinetic resolution [41] on TBS-protected (±)-glycidol (**(±)-60**), followed by selective protection of the formed primary hydroxyl group with pivaloyl chloride to

access the enantiopure compound **71**. After PMB-protection of the secondary hydroxyl group, reduction and Swern oxidation[42] they obtained aldehyde **73**. Evans' auxiliary was employed to generate the subcomponent **75** with the C27 stereocentre. Other key steps in their synthetic route were 1) Carreira alkynylation[43] of **73** with **75** to generate the desired C22 stereocentre, forming alkyne **76** with 4:1 diastereoselectivity, 2) formation of allene **77** by one-pot mesylation and methyl cuprate addition, followed by PMB cleavage with DDQ, and 3) the use of Marshall cyclisation[44] conditions to form the dihydrofurane **78**. The F-ring fragment **80** (C21–C28) was synthesised in 14 steps in total.

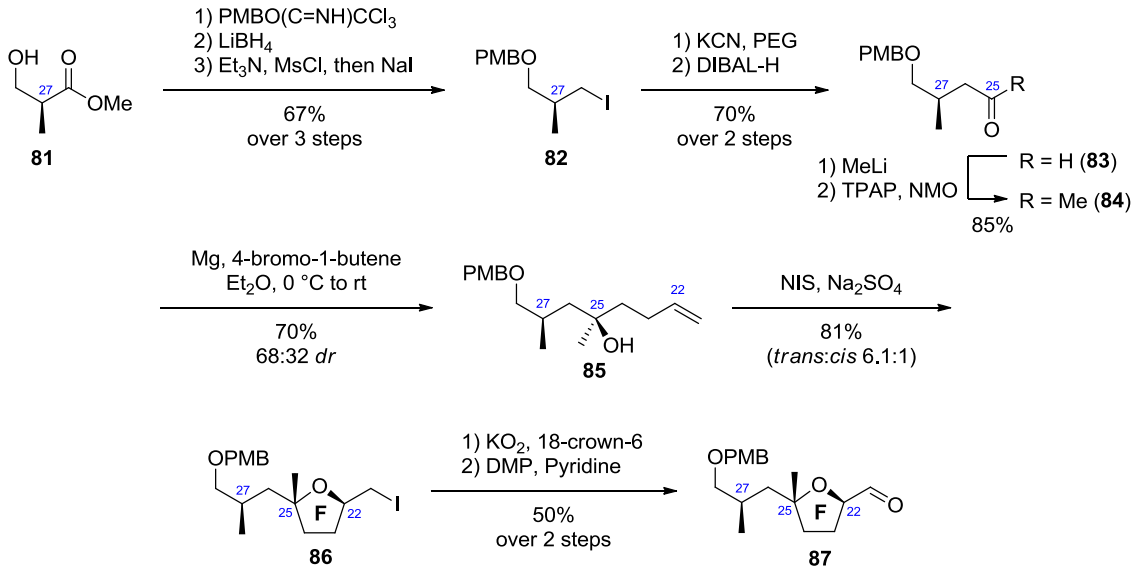


Scheme 7. Williams' convergent approach: a) preparation of aldehyde **73**, b) preparation of alkyne **75** and c) the synthetic route for the preparation of the complete F-ring fragment **80** (C21–C28).

1.2.6 Brimble's Approach

In 2009, Brimble and co-workers reported the synthesis of the C21–C28 fragment **87** of PTX (**Scheme 8**).[241] The group used enantiopure (+)-Roche ester

(**81**) as their starting material. The C25 stereocentre was formed by Grignard reaction, affording the desired alcohol **85** in moderate 68:32 diastereomeric ratio, and the C22 stereocentre in an iodoetherification reaction that generated the THF-ring, affording **86** in 6.1:1 diastereomeric ratio. The route contained 10 steps in total and afforded the F-ring fragment **87** (C21–C28).



Scheme 8. Brimble's synthetic approach to the F-ring fragment **87** (C21–C28).

The direct comparison of these different approaches is difficult, because the individual target fragments differ significantly. Among the strategically most important methods are the use of Evans' auxiliaries, asymmetric epoxidation and Sharpless asymmetric dihydroxylation, mainly due to their high reliability and compatibility. Most of the groups utilised some or several of these methods in their synthetic approaches. The C27 stereocentre is commonly created employing Evans' auxiliary. An exception to this strategy is the Brimble group's approach, in which the important centre is already installed in their starting material. The C27 centre is not included in the fragment targets of Micalizio and Paquette. Practical methods for the insertion of the C27 methyl are limited, which highlights the importance of the development of new reaction methodologies that can be employed for complex and highly functionalised molecules. This development would likely enable the design of more efficient synthetic routes.

2 VINYLOGOUS MUKAIYAMA–MICHAEL REACTIONS WITH SILYLOXYFURANS

In 1974, Mukaiyama and co-workers reported a Lewis acid-catalysed Michael type reaction between silyl enol ethers and α,β–conjugated carbonyl compounds.[45] This reaction, which essentially combined the Mukaiyama aldol[46] reaction and the Michael reaction,[47] came to be known as the Mukaiyama–Michael reaction (**Figure 6**). Compared to the original Michael reaction, the Mukaiyama variant can be performed in milder conditions and some of the selectivity issues have been eliminated. Over the course of the following decades of development, the reaction has become a staple method for C–C bond formation. Several groups have also published asymmetric variations of the reaction, using either Lewis acids with chiral ligands, or organocatalysis to achieve the enantioselectivity. This chapter focuses on the vinylogous Mukaiyama–Michael reaction[48] variants and particularly on the asymmetric reactions employing silyloxyfuran nucleophiles, which are closely related to my Ph.D. research described in detail in chapter 4.

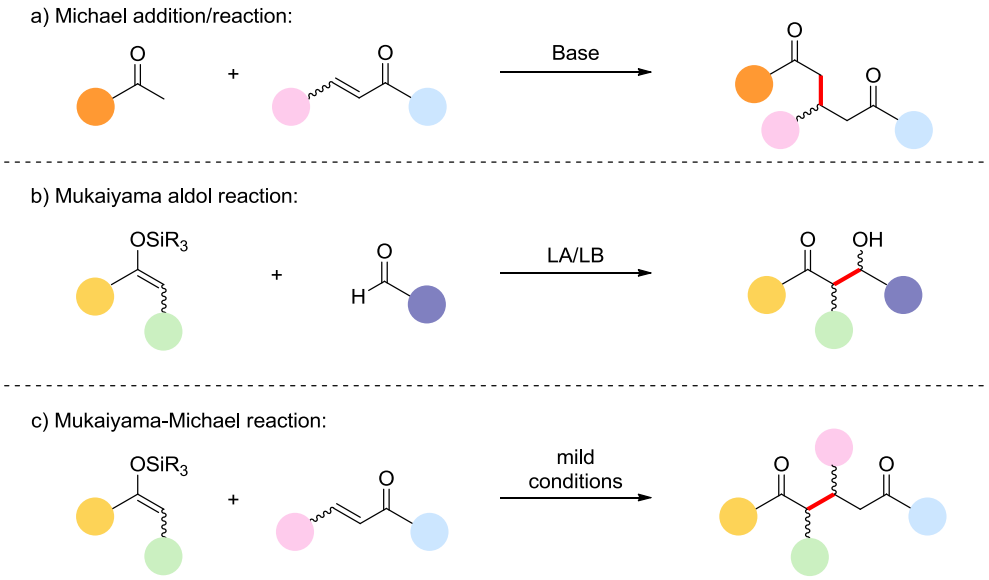


Figure 6. Simplified examples of a) Michael, b) Mukaiyama–aldol and c) Mukaiyama–Michael reactions.

2.1 Asymmetric Variants

γ-Butenolide (**Figure 7**) – the product of the vinylogous Mukaiyama–Michael reaction when a silyloxyfuran is used as the Michael donor (nucleophile) – is a subunit that can be found in thousands of natural products and biologically active compounds.[49] It is for this reason that its derivatives are popular targets in method development. Several asymmetric methods (e.g. aldol reaction[50,51]) for the preparation of γ-butenolide structures exist, but the focus of this review is on the vinylogous Mukaiyama–Michael reaction. The following examples highlight the current state of this approach towards these valuable subunits. The reaction methodologies can be divided in two subgroups depending on the mode of activation of the electrophile: transition metal catalysis (Lewis acid catalysis) utilising chiral ligands, and metal-free iminium catalysis (which has also been classified as a type of Lewis base catalysis[52]).

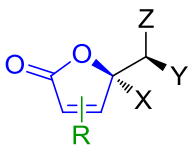
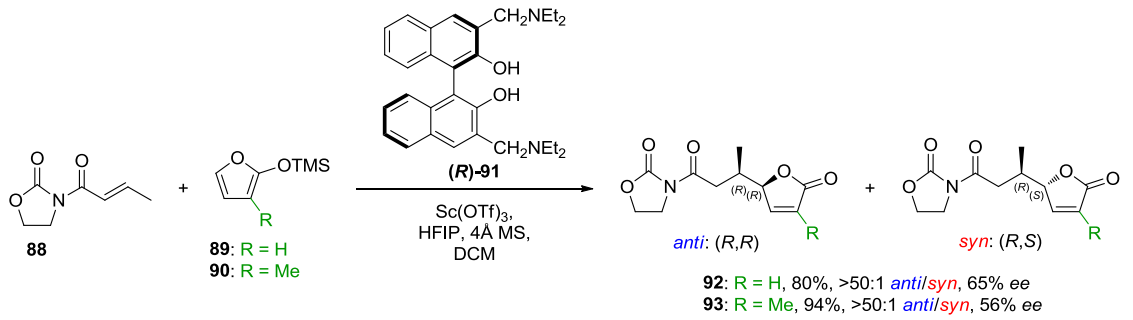


Figure 7. The general structure of substituted γ-butenolides.

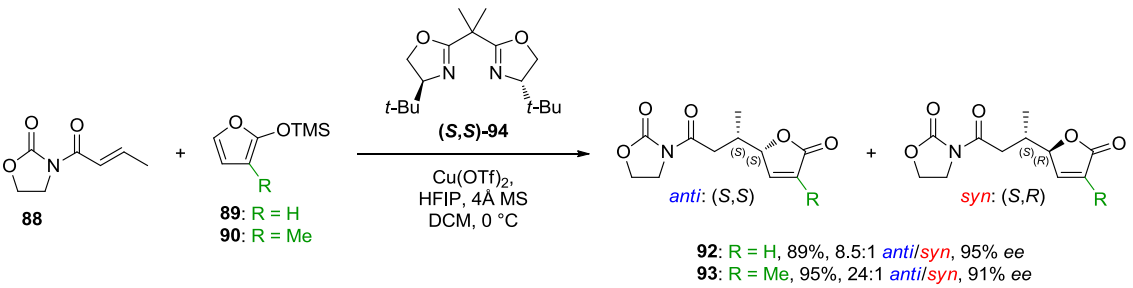
2.1.1 Applications Based on Chiral BINOL and BOX-Ligands

Katsuki and co-workers were the first group to report on a chiral Lewis acid promoted asymmetric Mukaiyama–Michael reaction, in 1997.[53] They studied the use of 1,1-bi-2-naphthol-ligands (BINOL) combined with $Sc(OTf)_3$ in the reaction between 2-silyloxyfurans **89**/ **90** and 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one (**88**) (**Scheme 9**). Their optimised reaction conditions afforded products with excellent diastereoselectivity (>50:1 *anti*/*syn*), but the enantioselectivities ranged from neglible to moderate (≤73% *ee*).



Scheme 9. Two example reactions of the $Sc(OTf)_3$-BINOL catalysed Mukaiyama–Michael reactions by Katsuki and co-workers.

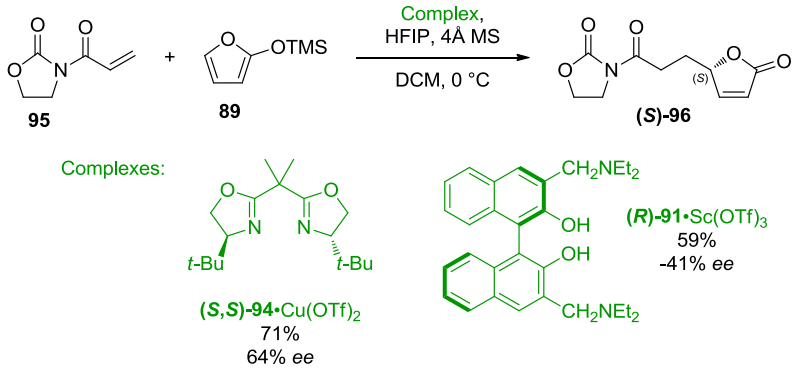
The group also studied the use of $Cu(OTf)_2$ with bis(oxazoline)-ligand[54] **94** (BOX), obtaining products with reduced (though still good) diastereoselectivity (8.5-24:1 *anti*/*syn*), but significantly improved enantioselectivity (89-95% *ee*) (**Scheme 10**).



Scheme 10. Two examples of reactions of the $Cu(OTf)_2$-BOX catalysed Mukaiyama–Michael reactions by Katsuki and co-workers.

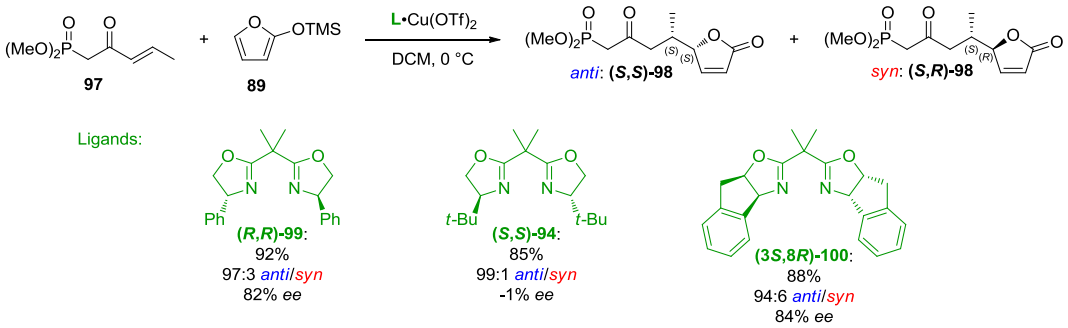
The substrate scope, as reported by Katsuki and co-workers, was limited to the use of two different silyloxyfurans (reactions presented in **Scheme 9** and

Scheme 10) and two different enone derivatives, which contained Me (**90**) or H (**89**) in the β-position (**Scheme 11**).



Scheme 11. Two examples of Mukaiyama–Michael reactions employing 3-acryloyloxazolidin-2-one (**95**) as the Michael acceptor.

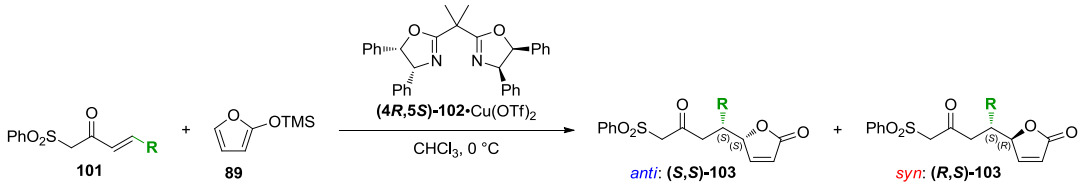
In 2008, Kim and Yang reported on similar studies, combining chiral BOX ligands with $Cu(OTf)_2$. [55] In the reaction between unsaturated β-ketophosphonate **97** and 2-(trimethylsilyloxy)furan (**89**), the catalyst complex afforded excellent diastereoselectivity (95:6 to 99:1 *anti*/*syn*), high yields (85-92%) and enantioselectivity ranging from racemic to good (-1% or 82-84% *ee*) (**Scheme 12**).



Scheme 12. Examples of $Cu(OTf)_2$-catalysed Mukaiyama–Michael reactions with various BOX-ligands.

In optimised reaction conditions employing α'-phenylsulfonyl enones as the electrophiles, the group obtained products with excellent enantiopurity (95–99% *ee*) and diastereoselectivity (95:5–>99:1 *anti*/*syn*). The substrate scope of the reactions included various β-substituted α'-phenylsulfonyl enones (**Table 3**).

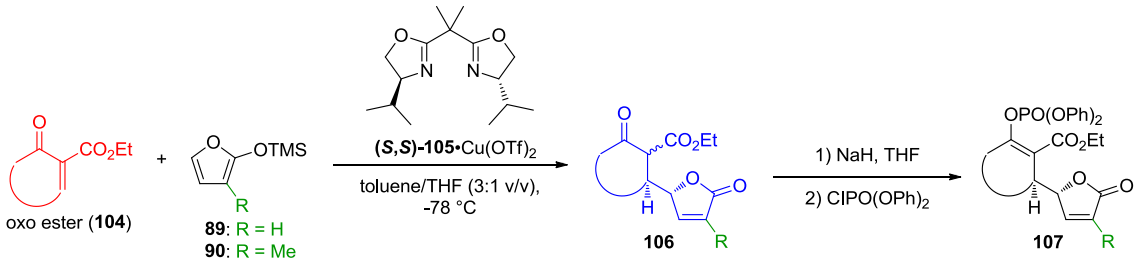
Table 3. Substrate scope of the Mukaiyama–Michael reaction with α′-phenylsulfonyl enones.

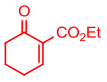
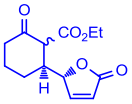
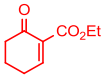
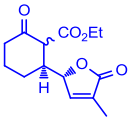
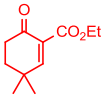
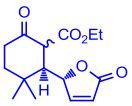
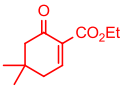
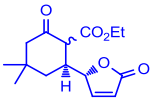
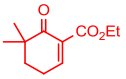
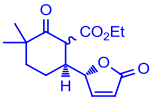
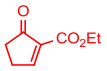
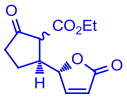
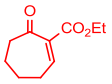
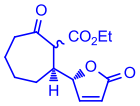


Entry	R	Product	Yield (%)	*ee* (%)	*anti*/*syn*
1	H (**101a**)	**103a**	91	95	-
2	Me (**101b**)	**103b**	95	99	>99:1
3	Et (**101c**)	**103c**	79	99	98:2
4	*n*-Pr (**101d**)	**103d**	92	98	>99:1
5	*i*-Pr (**101e**)	**103e**	28	97	95:5
6	CH_2CH_2Ph (**101f**)	**103f**	88	97	>99:1
7	Ph (**101g**)	**103g**	>99	99	>99:1

Recently, Guillou and co-workers reported a $Cu(OTf)_2$-BOX complex catalysed Mukaiyama–Michael reaction, where cyclic unsaturated oxo esters were employed as electrophiles.[56] The products were obtained with fair to excellent diastereoselectivities (78:22–>99:1 *dr*) and modest to high enantioselectivities (59–91% *ee*).

Table 4. Substrate scope of the Mukaiyama–Michael reaction with various unsaturated oxoesters.



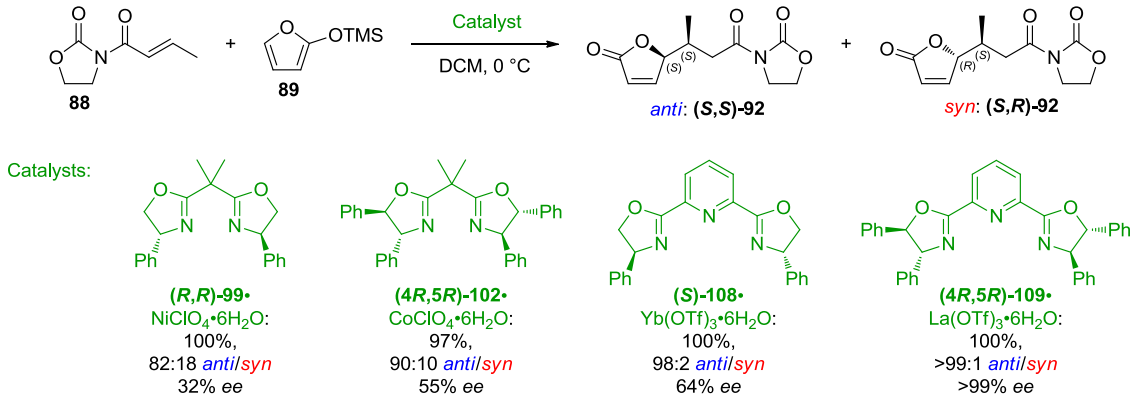
Entry	Oxo ester		R	Product		Yield (%)[a]	*dr*[b] [(*S*,*R*):(*S*,*S*)]	*ee* (%)[b]
1		**104a**	H		**106a**	81	>99:1	91
2		**104b**	Me		**106b**	69	99:1	59
3		**104c**	H		**106c**	74	>99:1	96
4		**104d**	H		**106d**	79	>99:1	90
5		**104e**	H		**106e**	82	99:1	60
6		**104f**	H		**106f**	63	78:22	84/88[c]
7		**104g**	H		**106g**	72	>99:1	79

[a] Isolated yield. [b] Determined from corresponding enol phosphates. [c] The *ee* of the major and minor diastereomers, respectively.

2.1.2 Applications Based on Chiral pyBOX-Ligands

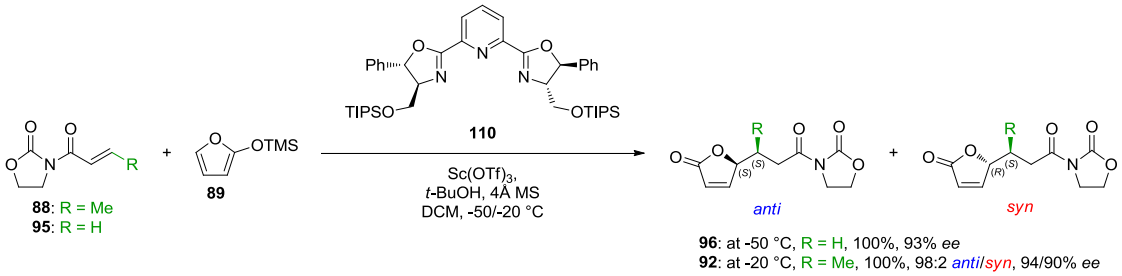
In 2001, Desimoni and co-workers reported Mukaiyama–Michael reaction studies between silyloxyfuran **89** and and 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one (**88**), catalysed by various chiral Lewis acid complexes (**Scheme 13**).[57] The group obtained their best results when pyridine-2,6-bis(oxazoline)–ligands (pyBOX)[58] were complexed with various lanthanide triflates. The reactions

afforded quantitative yields with excellent diastereo- (>99:1 *anti*/*syn*) and enantioselectivity (92–>99% *ee*).



Scheme 13. Mukaiyama–Michael reactions with various chiral Lewis acidic complexes.

Their later report on Mukaiyama–Michael reactions performed employing a modified pyBOX-ligand (**Scheme 14**) showed no improvement compared to their earlier results.

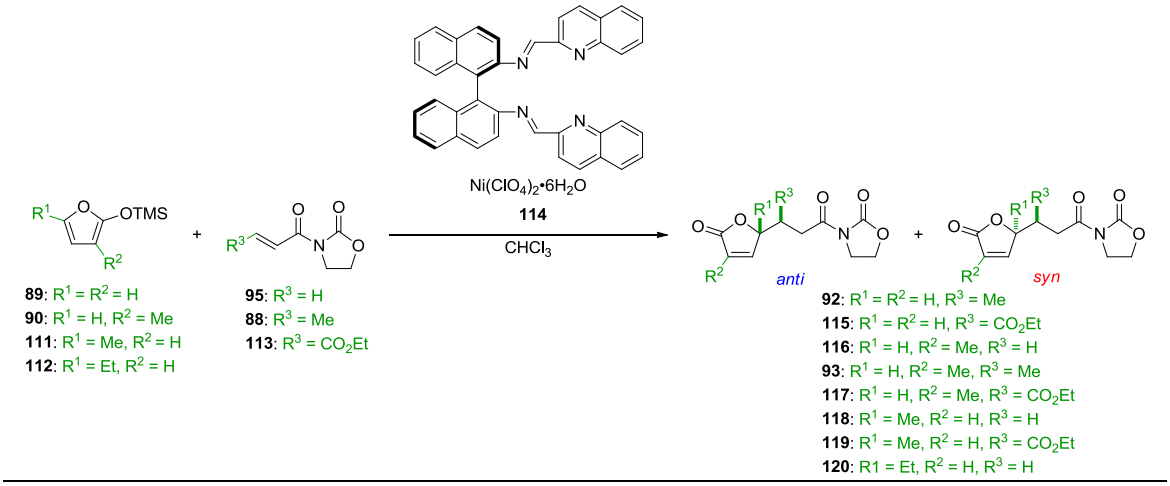


Scheme 14. Enantioselective Mukaiyama–Michael reactions catalysed by a Lewis acidic $Sc(OTf)_3$-pyBOX (**110**) complex.

2.1.3 Applications Based on Chiral BINIM-Ligands

In 2004, Suga and co-workers reported on studies where they used their *N*,*N*′-bis(2-quinolylmethylene)-1,1′-binaphtyl-2,2′-diamine-Ni(II)–complexes (**114**) (BINIM)[59] as chiral Lewis acid catalysts in the Mukaiyama–Michael reaction between silyloxyfurans and 3-alkenoyl-2-oxazolidinones (**Table 5**).[60] The substrate scope was diverse and the products were obtained in good to quantitative yields (82-100%), up to 97% enantioselectivities and good to excellent diastereoselectivities (91:9–>99:1 *anti*/*syn*).

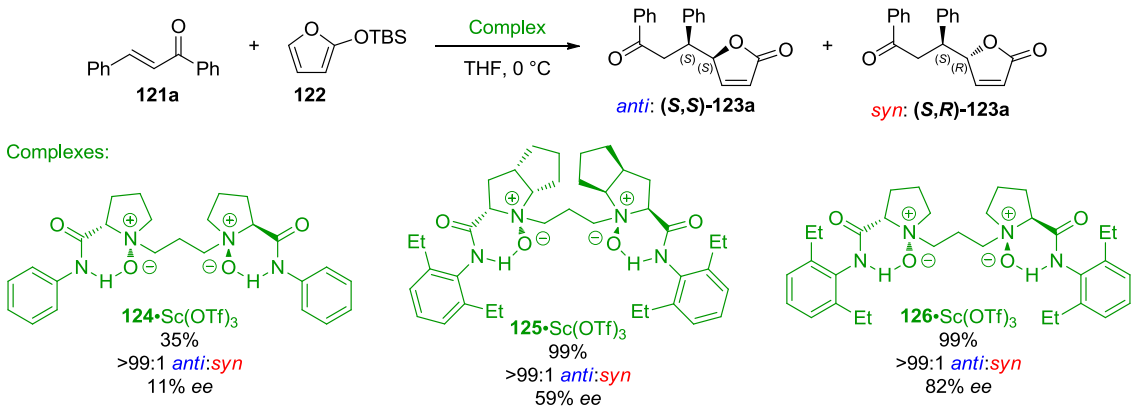
Table 5. Substrates used in BINIM-Ni(II) catalysed reactions.



Entry	R^1	R^2	R^3	Additive	Temp (°C)	Yield (%)	*anti*/*syn*	*ee* (%)
1	H	H	Me	HFIP	-25	100	98:2	88
2	H	H	CO_2Et	PFP	-40	97	>99:1	93
3	H	Me	H	PFP	-25	84	-	97
4	H	Me	Me	HFIP	-25	82	99:1	93
5	H	Me	CO_2Et	HFIP	-25	95	>99:1	97
6	Me	H	H	PFP	-25	100	-	88
7	Me	H	CO_2Et	HFIP	-40	95	91:9	78
8	Et	H	H	HFIP	-25	89	-	86

2.1.4 Applications Based on Chiral *N,N*-Dioxide–Ligands

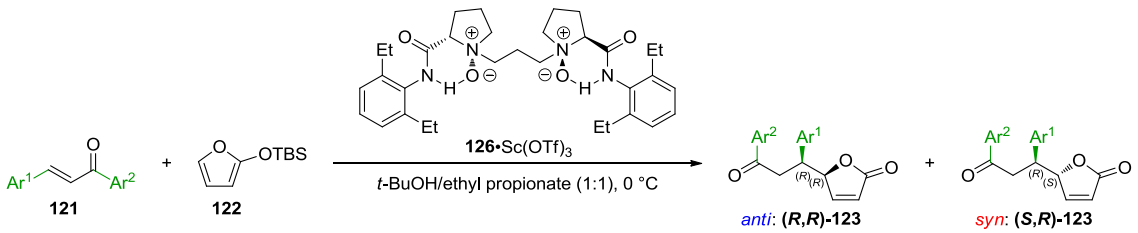
In 2011, Feng and co-workers reported a method based on the Lewis acidic *N,N'*-dioxide–Sc(III)[61] complexes **124–126**, which were used in the reaction between silyloxyfuran (**122**) and various chalcone derivatives.[62] A variety of catalysts were screened (**Scheme 15**).



Scheme 15. Chiral Lewis acid complexes studied in the Mukaiyama–Michael reaction with chalcone **121** and silyloxyfuran **122**.

The optimised reaction conditions employing the most suitable Sc-ligand–complex (**Table 6**) were then used to probe the scope of the methodology. The reaction afforded excellent yields (92-99%) and diastereomeric ratios (>99:1 *anti*:*syn* in all the examples). Additionally, good enantioselectivities were obtained (82-94% *ee*), and they were improved after recrystallisation (up to >99% *ee*).

Table 6. Some chalcone substrates used in the studies.



Entry	Ar^1	Ar^2	Chalcone	Product	Yield (%)	*ee* (%)
1	Ph	Ph	**121a**	**123a**	99	90
2	2-MeC_6H_4	Ph	**121b**	**123b**	99	90
3	4-$MeOC_6H_4$	Ph	**121c**	**123c**	98	90
4	4-ClC_6H_4	Ph	**121d**	**123d**	92	90
5	3-$CF_3C_6H_4$	Ph	**121e**	**123e**	98	94
8	Ph	4-MeC_6H_4	**121f**	**123f**	99	88
6	Ph	4-$MeOC_6H_4$	**121g**	**123g**	99	83
7	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**121h**	**123h**	92	82
8	3-$CF_3C_6H_4$	4-MeC_6H_4	**121i**	**123i**	99	89

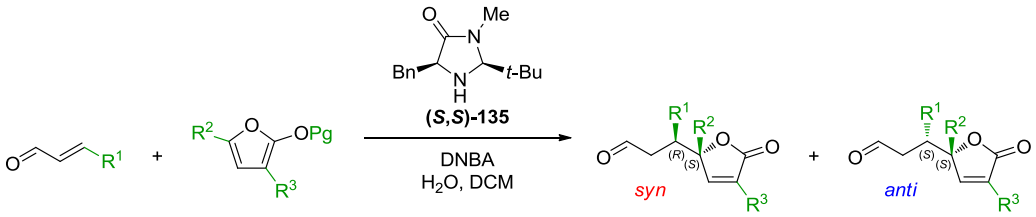
Since the discovery of the asymmetric Mukaiyama–Michael reaction, many groups have applied it for their own purposes, used various different catalysts, and expanded the electrophile substrate scope. The main problem with the use of C2-symmetrical chiral Lewis acids as catalysts is the fact that most of the methodologies require electrophiles capable of chelation with the chiral Lewis acidic metal centre. For example, the typical electrophiles contain oxygens at 1,3-positions. This limits the substrate scope significantly. Fang and co-workers do not have that problem, but their electrophile scope is limited to only aromatic substituents.

2.1.5 Applications Based on Organocatalysts

In 2003, MacMillan and co-workers were the first group to publish an organocatalytic method for the Mukaiyama–Michael reaction.[63] The group used imidazolidinone catalyst **135** for their studies (**Table 7**), obtaining products in good yields (73-86%), high enantioselectivities (84-99%) and diastereoselectivities ranging from moderate to excellent (6:1 to 31:1 *syn*/*anti*) with various silyloxyfurans and β-substituted acroleins (**127–132**).

The MacMillan method is an extension of their iminium-catalysed[64] Friedel-Crafts methodologies, where they previously had utilised electron-rich arenes and heteroarenes such as pyrroles, indoles and furans.[65] In all of these cases, only β-substituted enals were used as substrates.

Table 7. Substrate scope of the imidazolidinone catalysed Mukaiyama–Michael reaction.



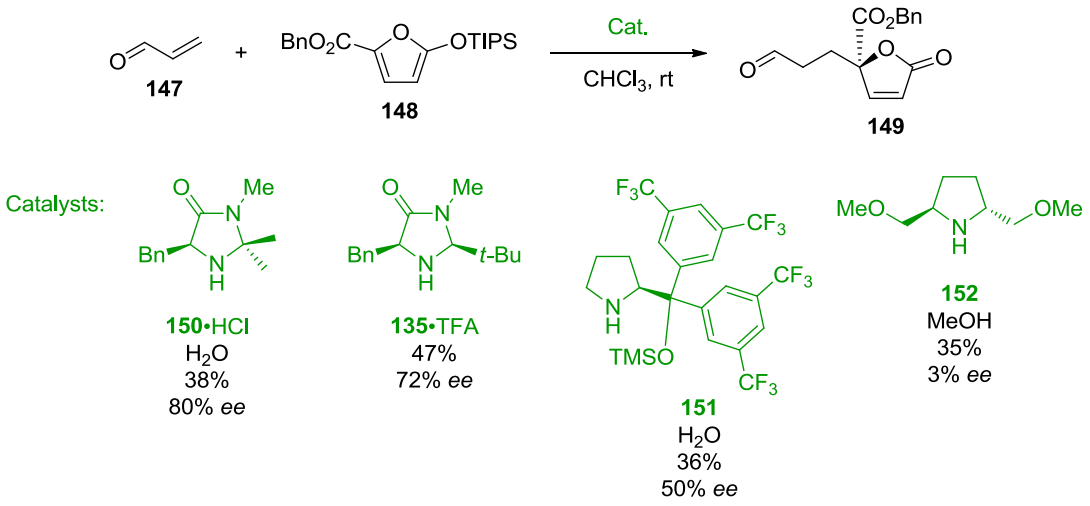
127: R^1 = Me
128: R^1 = Pr
129: R^1 = *i*-Pr
130: R^1 = Ph
131: R^1 = CH_2OBz
132: R^1 = CO_2Me

111: R^2 = Me, R^3 = H, Pg = TMS
89: R^2 = R^3 = H, Pg = TMS
112: R^2 = Et, R^3 = H, Pg = TMS
133: R^2 = CO_2Me, R^3 H, Pg = TIPS
134: R^2 = R^3 = Me, Pg = TMS

136: R^1 = R^2 = Me, R^3 = H
137: R^1 = Pr, R^2 = Me, R^3 = H
138: R^1 = *i*-Pr, R^2 = Me, R^3 = H
139: R^1 = Ph, R^2 = Me, R^3 = H
140: R^1 = CH_2OBz, R^2 = Me, R^3 = H
141: R^1 = CO_2Me, R^2 = Me, R^3 = H
142: R^1 = Me, R^2 = H, R^3 = H
143: R^1 = Me, R^2 = Me, R^3 = H
144: R^1 = Me, R^2 = Et, R^3 = H
145: R^1 = Me, R^2 = CO_2Me, R^3 = H
146: R^1 = Me, R^2 = Me, R^3 = Me

Entry	R^1	R^2	R^3	Pg	Yield (%)	*syn*/*anti*	*ee* (%)
1	Me	Me	H	TMS	81	22:1	92
2	Pr	Me	H	TMS	87	31:1	84
3	*i*-Pr	Me	H	TMS	80	7:1	98
4	Ph	Me	H	TMS	77	1:6	99
5	CH_2OBz	Me	H	TMS	86	20:1	90
6	CO_2Me	Me	H	TMS	84	11:1	99
7	Me	H	H	TMS	87	8:1	90
8	Me	Me	H	TMS	80	22:1	92
9	Me	Et	H	TMS	83	16:1	90
10	Me	CO_2Me	H	TIPS	86	6:1	98
11	Me	Me	Me	TMS	73	24:1	90

In 2010, Pansare and co-workers published Mukaiyama–Michael reaction between acrolein (**147**) and compound **148** (**Scheme 16**).[66] They studied the reaction with various popular organocatalysts. Although in the best case they achieved synthetically useful 80% *ee* with the MacMillan catalyst, the yield was poor.



Scheme 16. Organocatalysts studied in the Mukaiyama–Michael reaction with acrolein (**147**) and silyloxyfuran **148**.

Both of these organocatalytic methodologies offered a significant improvement compared to the previously published Lewis acid catalysed Mukaiyama–Michael reactions, owing to the fact that unsaturated aldehydes were used as the electrophilic substrates. As the reaction products were aldehydes, they were more readily useful as building blocks for subsequent reactions.

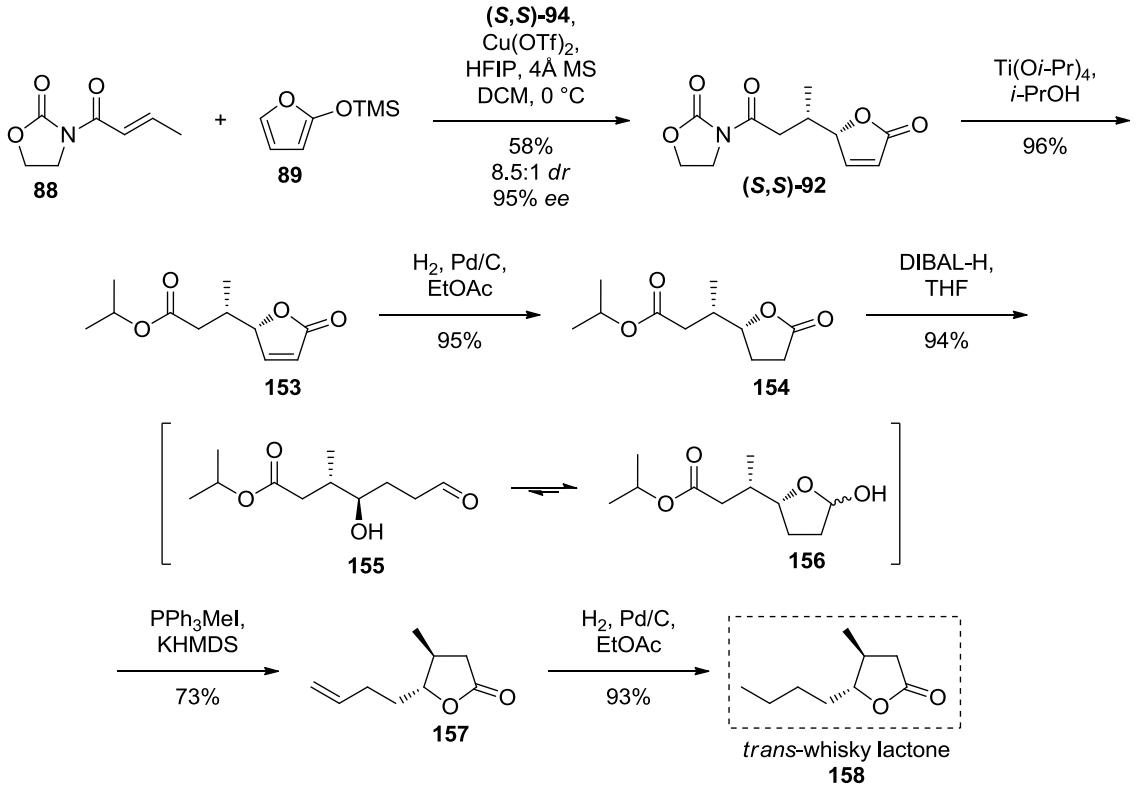
2.2 Applications in Natural Product Synthesis

The asymmetric vinylogous Mukaiyama–Michael reaction methodologies discussed in the preceding section have been utilised in the total synthesis of natural product targets. Some examples of these applications are presented below.

2.2.1 Synthesis of *trans*-Whisky Lactone

Katsuki and co-workers utilised the group's own asymmetric Mukaiyama–Michael method[53] in the synthesis of *trans*-whisky lactone (**158**).[67] *Trans*-whisky lactone was originally isolated together with *cis*-whisky lactone from aged brandy, and the two compounds originate from the oak barrels where the brandy is held. They accumulate in the liquor during the aging process. *Trans*-whisky lactone can be found in various oak barrel aged drinks, such as whisky, brandy and wine.[68]

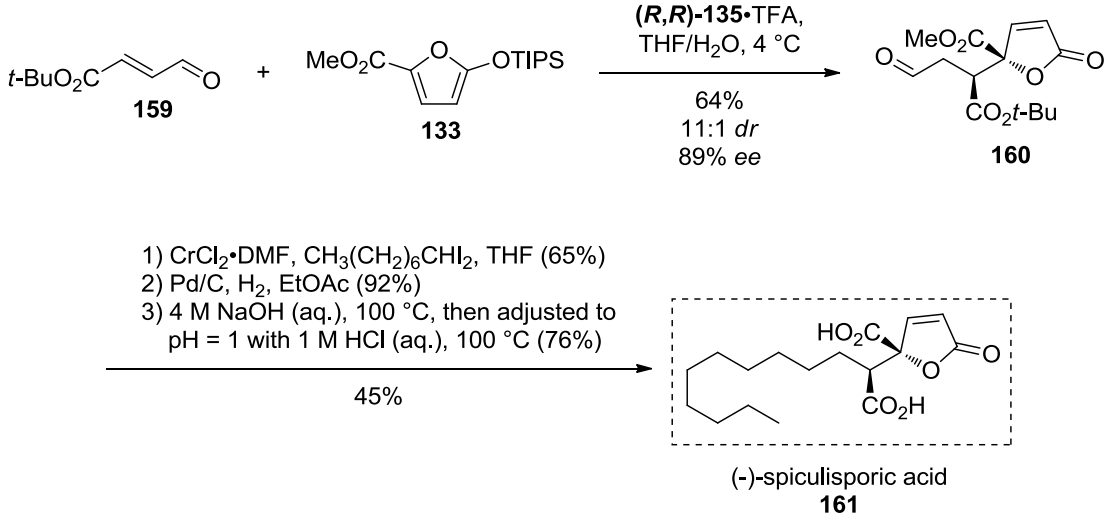
In the Katsuki group's total synthesis, all the stereocentres of the final product were generated in the first reaction step and the synthesis of this small target was accomplished in 6 steps in total.



Scheme 17. Synthesis of *trans*-whisky lactone (**158**) utilising an asymmetric Mukaiyama–Michael reaction as the key step.

2.2.2 Synthesis of (–)-Spiculisporic Acid

In addition to reporting on the new organocatalytic Mukaiyama–Michael methodology, MacMillan and co-workers also reported an application of the chemistry in the total synthesis of a natural product.[63] To demonstrate the practicality of their methodology, they described the synthesis of (–)-spiculisporic acid (**161**) in only four steps beginning from the **159** and **133** (**Scheme 18**).



Scheme 18. Synthetic route to (–)-spiculisporic acid (**161**) *via* an organocatalytic Mukaiyama–Michael reaction.

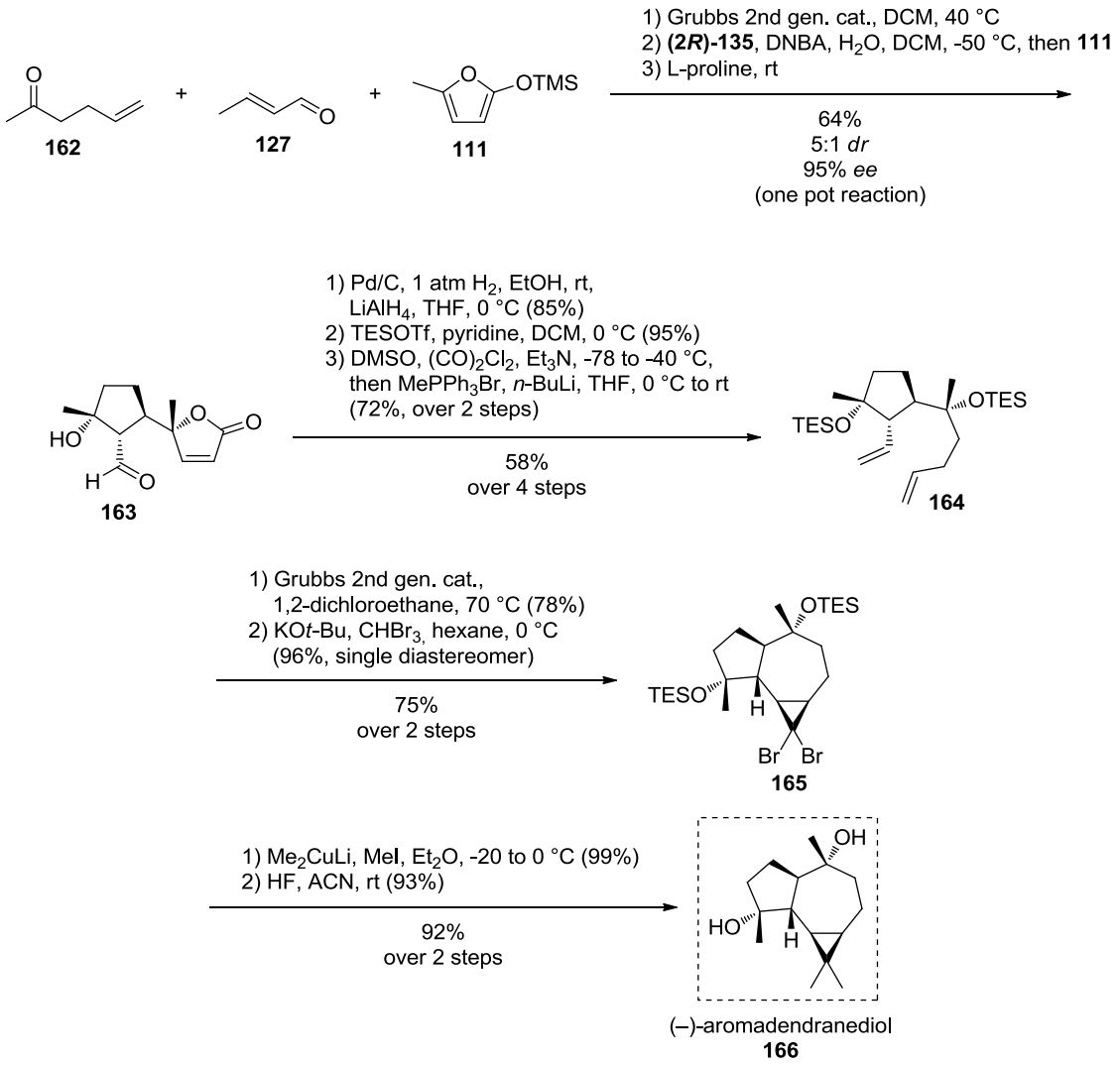
Spiculisporic acid (**161**), a *Penicillium spiculisporum* fermentation adduct, works as a biosurfactant, and it is used to remove metal cations from water, and in fine polymer production.[63,69]

2.2.3 Synthesis of (–)-Aromadendranediol

In 2009, MacMillan and co-workers published the total synthesis of (–)-aromadendranediol (**166**) (**Scheme 19**),[70] a natural product isolated from the marine coral *Sinularia mayi*.[71] The biological activity of the compound has not been extensively studied, but it has some sedative and analgesic activity.[70]

The group applied their own organocatalytic Mukaiyama–Michael methodology in the first step of the reaction route as a component of the triple-

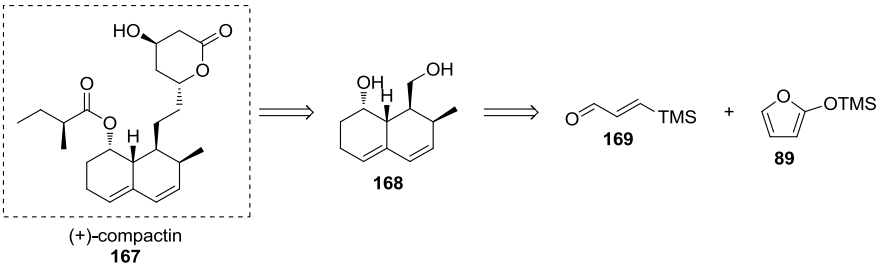
cascade-catalysis sequence. The group was able to form four of the target compound's stereocentres with this impressive technique. The total synthesis of the (–)-aromadendranediol (**166**) was achieved in 9 steps.



Scheme 19. The synthetic route for (–)-aromadendranediol (**166**).

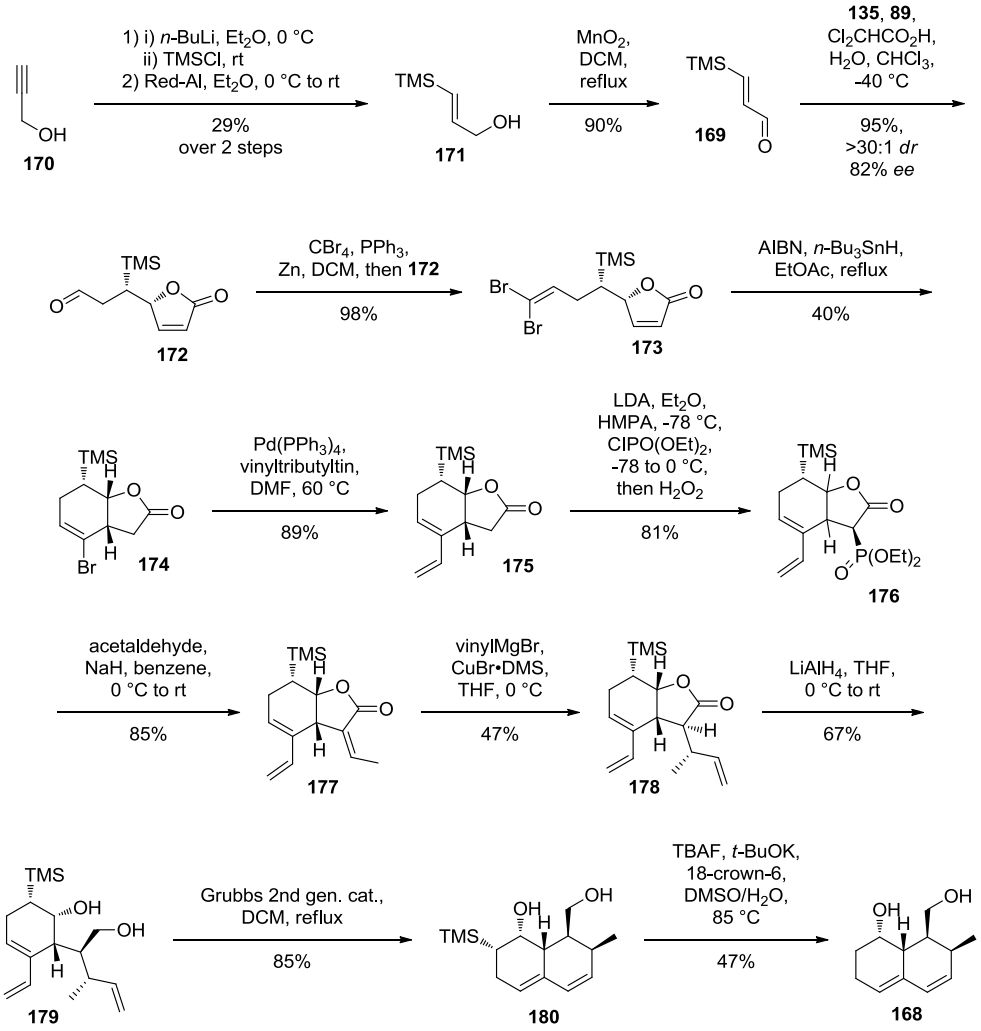
2.2.4 Formal Synthesis of (+)-Compactin

Robichaud and Tremblay reported the synthesis of an important intermediate of (+)-compactin (**167**),[72] where they exploited MacMillan's organocatalytic Mukaiyama–Michael reaction as one of the key steps (**Scheme 20**). The target compound (+)–compactin (**167**) belongs to the class of statins (HMG-CoA reductase inhibitors), which are used as cholesterol-lowering drugs. It was first isolated from *Penicillium citrum* in 1976.[73]



Scheme 20. Retrosynthetic route for (+)-compactin (**167**).

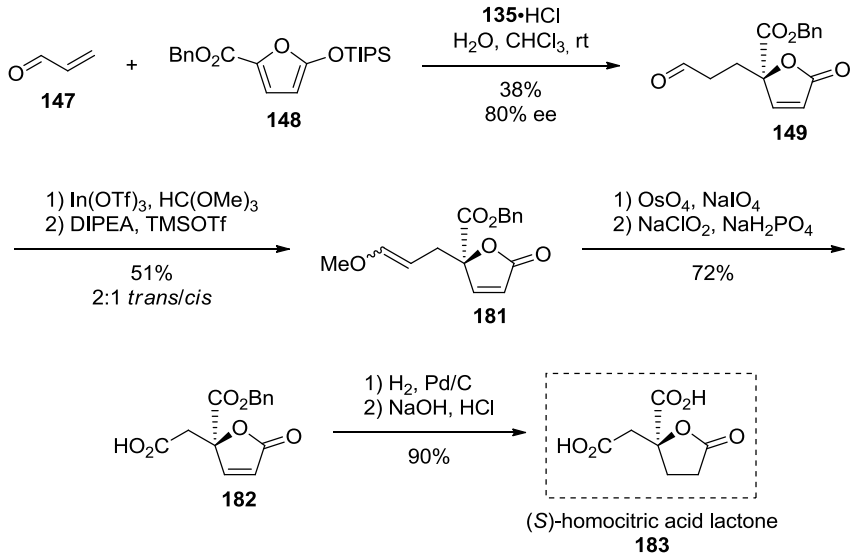
The group used the chiral centres formed in the Mukaiyama–Michael step to guide the formation of all the subsequent chiral centres present in the intermediate **168** (**Scheme 21**).[72] The TMS group was used in the synthesis mainly because the MacMillan methodology worked best with β-substituted acroleins.



Scheme 21. The synthetic route for the intermediate **168** of (+)–compactin (**167**) with enantioselective Mukaiyama–Michael reaction as the key step.

2.2.5 Synthesis of (S)-Homocitric Acid Lactone

Pansare and co-workers reported the synthesis of (*S*)-homocitric acid lactone (**183**) (**Scheme 22**).[66] The group utilised MacMillan's catalyst to form the desired stereocentre in the Mukaiyama–Michael reaction, then spent three steps shortening the side chain by one carbon. Finally oxidation level adjustments and protecting group removal provided the product **183** in a total of 7 steps, starting from the known silyloxyfuran **148**.



Scheme 22. The synthetic route for (*S*)-homocitric acid lactone (**183**).

The vinylogous Mukaiyama–Michael reaction methodologies presented in chapter 2.1 are limited in their scope and generally allow access to butenolides bearing an extra stereogenic centre in the side chain, as the substitution patterns of the starting materials are very limited. The products are commonly obtained in excellent diastereo- and enantiopurity, and the stereocentres generated in the reactions are always situated adjacent to each other. The only exception is the synthesis of (*S*)-homocitric acid lactone (**183**), where acrolein (**147**) was used, but the efficiency of the method still leaves plenty of room for improvement. The presented methods offer an efficient way to produce starting materials for the synthesis of more complex structures, as has been shown in chapter 2.2, but the amount of suitable targets is still limited. Further development of the methodologies is needed to make them more useful and widely applicable. For

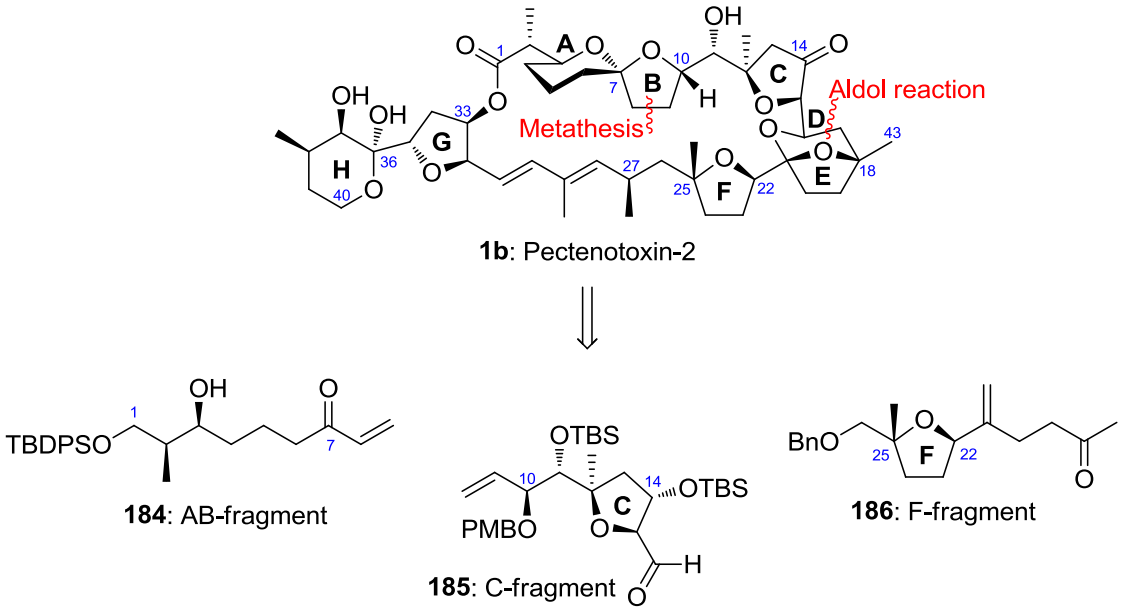
example, the synthesis of (+)-compactin (**167**) could be carried out more efficiently, if acrolein could be used as a starting material instead of β-TMS acrolein **169**.

3 SYNTHESIS OF THE C17-C28 FRAGMENT OF PTX2

3.1 Aims and Background of the Work

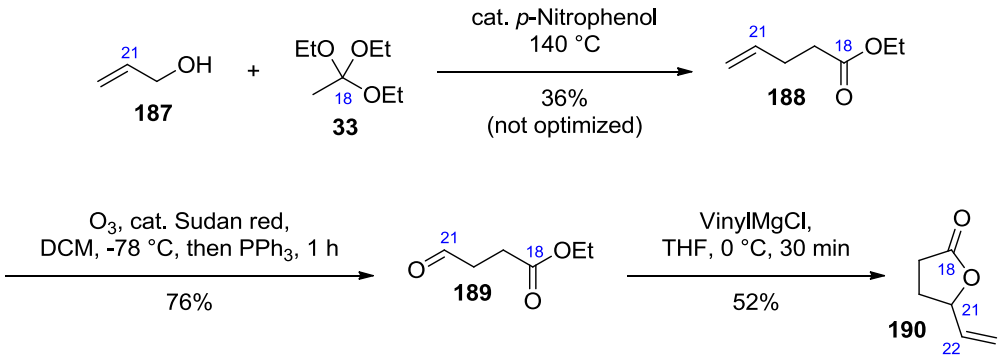
The experimental work for this thesis can be divided in to roughly two parts: 1) the work towards the total synthesis of Pectenotoxin-2, the initial aim of the project, and 2) the work on the expansion of the scope of the Mukaiyama–Michael reaction to include α-substituted acroleins, originated as a "side product" of the main topic. The latter topic is discussed in more detail in chapter four.

My Ph. D. research started in a project aiming towards the total synthesis of PTX2. The PTX2 project was initiated in 2003 by former members of the group, Jatta Aho and Hannes Helmboldt, who successfully synthesised the AB- and CDEF-fragments of the natural product (**Scheme 23**).[74] The coupling of the two fragments was also attempted, but unfortunately it was discovered that a critical vinyl addition step that generated the C10-stereocentre produced the unnatural epimer. In spite of this setback, the assembly of the critical nonanomeric AB spiroketal was nevertheless attempted. Under kinetic conditions, the desired nonanomeric C10-epi-ABCDE ring system could be accessed with moderate selectivity, proving the viability of the kinetic spiroketalisation approach in a complex setting.[75]



Scheme 23. The original PTX2 building blocks, synthesised during 2004–2008 in Pihko group.[74]

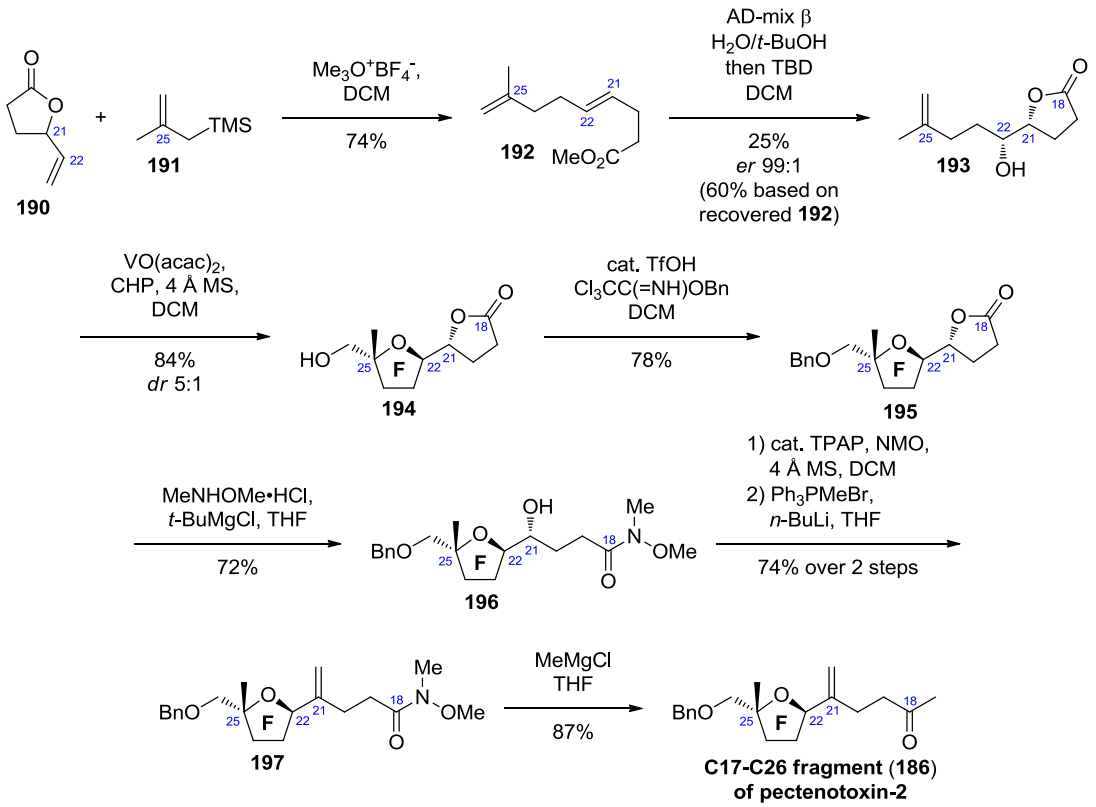
The group's original F-ring fragment (**186**) synthesis, published in 2008, began with the preparation of ethyl pent-4-enoate **188** using the Johnson–Claisen rearrangement reaction (**Scheme 24**).[76] Subsequent ozonolysis of the terminal double bond,[76] followed by a chemoselective Grignard addition to the product aldehyde afforded lactone **190**.[77]



Scheme 24. Preparation of the starting material **190** for the synthesis of the F-ring fragment **186** (C17–C26).[74c, 76–77]

Lactone **190** was converted to diene **192** using methallyltrimethylsilane in the presence of Meerwein's salt (**Scheme 25**).[78] Unfortunately, though highly enantioselective, the attempted Sharpless asymmetric dihydroxylation was not sufficiently regioselective towards the *trans*-double bond in the presence of the

methylene moiety, leading to a very poor yield (25%, 60% based on recovered starting material **192**). The isolated bishomoallylic alcohol **193** was next subjected to epoxidation conditions, and the epoxy alcohol product readily formed the tetrahydrofuran unit in the reaction conditions. The terminal alcohol was then benzyl protected in acidic conditions, and the lactone ring of the product **195** was transformed into the desired sidechain in a sequence of four steps: 1) conversion to the Weinreb amide **196**, 2) Ley oxidation of the secondary hydroxyl at C21 and 3) Wittig methylenation of the resulting ketone, and finally methylation of the Weinreb amide with methylmagnesium chloride. This original F-ring fragment (**186**) synthesis encompassed a total of 11 steps with an overall yield of 0.8%.



Scheme 25. The original synthesis route for the F-ring fragment **186** (C17–C26).[74c]

The original F-ring fragment **186** did not contain the stereogenic centre C27. We were concerned that the C26 position would be unreactive towards the requisite C–C-bond formation due to steric hindrance imposed by the tertiary C25

stereocentre. Additionally, we suspected that it could be challenging to install the methyl group at C27 stereoselectively in the forthcoming steps.

The poorly regioselective dihydroxylation step and the lack of the important stereocentre C27 were the main reasons that led us to attempt designing an improved synthetic route for the extended F-ring fragment **190** (**Figure 8**). The new connecting point at C28 should make it easier to join the F and the GH-fragments in our approach towards the total synthesis of PTX2.

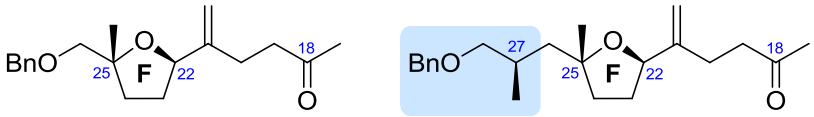
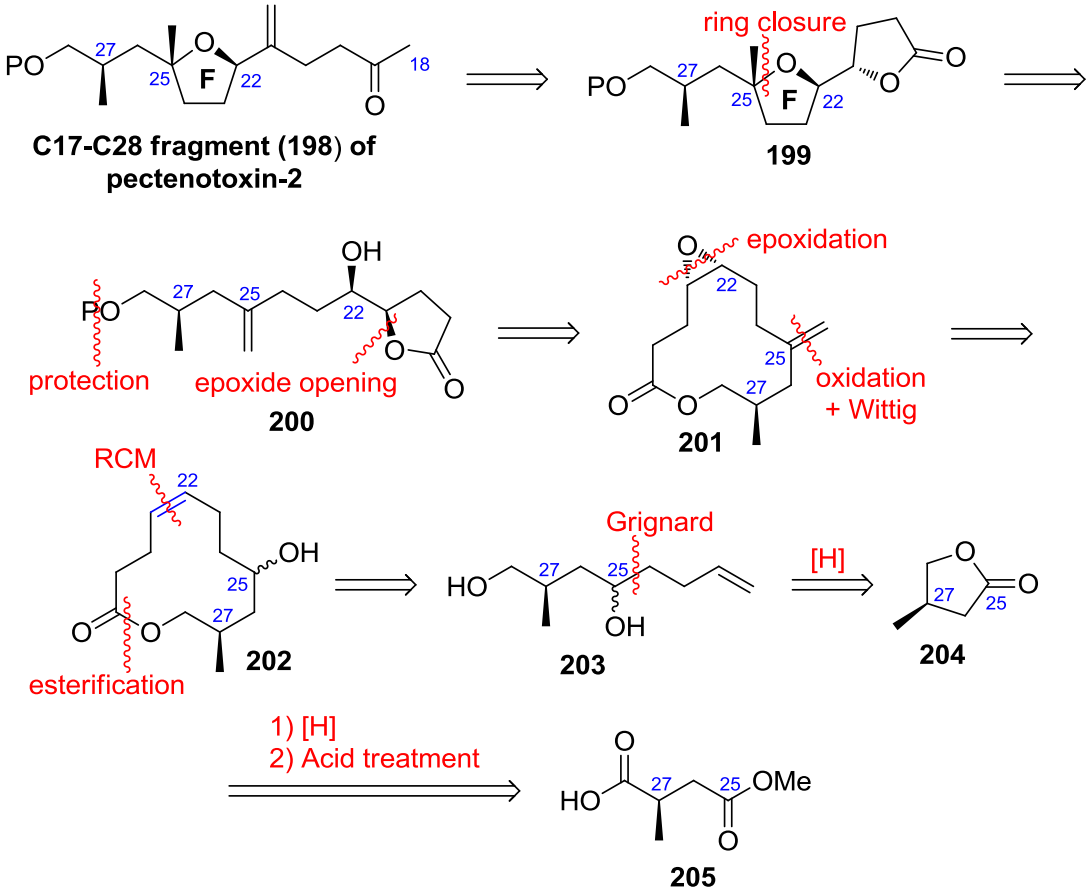


Figure 8. The new version of the F-ring fragment **198** beside the original fragment **186**.

3.2 Macrocycle Approach

3.2.1 Route Design

Our initial approach towards the synthesis of the F-ring fragment **198** (**Scheme 26**) was based on the enantiopure starting material **204**. This material would be transformed in to a long linear ester with two terminal vinyl groups, which would be coupled with ring closing metathesis to form a 12-membered macrocyclic lactone **202**. This macrocycle would then undergo selective epoxidation (see below), followed by oxidation and subsequent Wittig methylenation of the C25 hydroxyl group. The epoxide ring would then be opened to generate a diol intermediate, and the macrolactone would reform into a more energetically favoured 5-membered lactone. The primary hydroxyl group would then be protected to avoid a competing THF ring formation reaction in the next step. The C25 stereocentre could then be generated with either a Lewis acid or platinum catalysed THF-ring formation, or *via* iodolactonisation.[79] The remaining steps would then be carried out as in the synthesis of the original F-fragment. This plan had 16 linear steps in total.



Scheme 26. Retrosynthetic analysis for the F-fragment **198** (C17–C28).

3.2.2 Macrocyclic Stereocontrol in the Epoxidation Reaction

Our plan was to utilise macrocyclic stereocontrol in the epoxidation step: the steric hindrance inside the ring would force the peroxide to attack the double bond from the outer face of the ring to form the epoxide (**Figure 9**). Based on known behaviour of popular alkene metathesis catalysts in RCM,[80] the stereoselectivity of the double bond could be difficult to predict, and the selectivity was likely to be low. However, the desired C22 centre could be generated *via* epoxidation from both the *cis*- and *trans*-stereoisomers: the deciding factor for the stereocentre's formation would be the conformational preference of the macrocycle. Unfortunately, based on our molecular modeling results (**Figure 9**), the energy differences between the minimised structures were likely to be too small to favor any one of the conformers over the others.

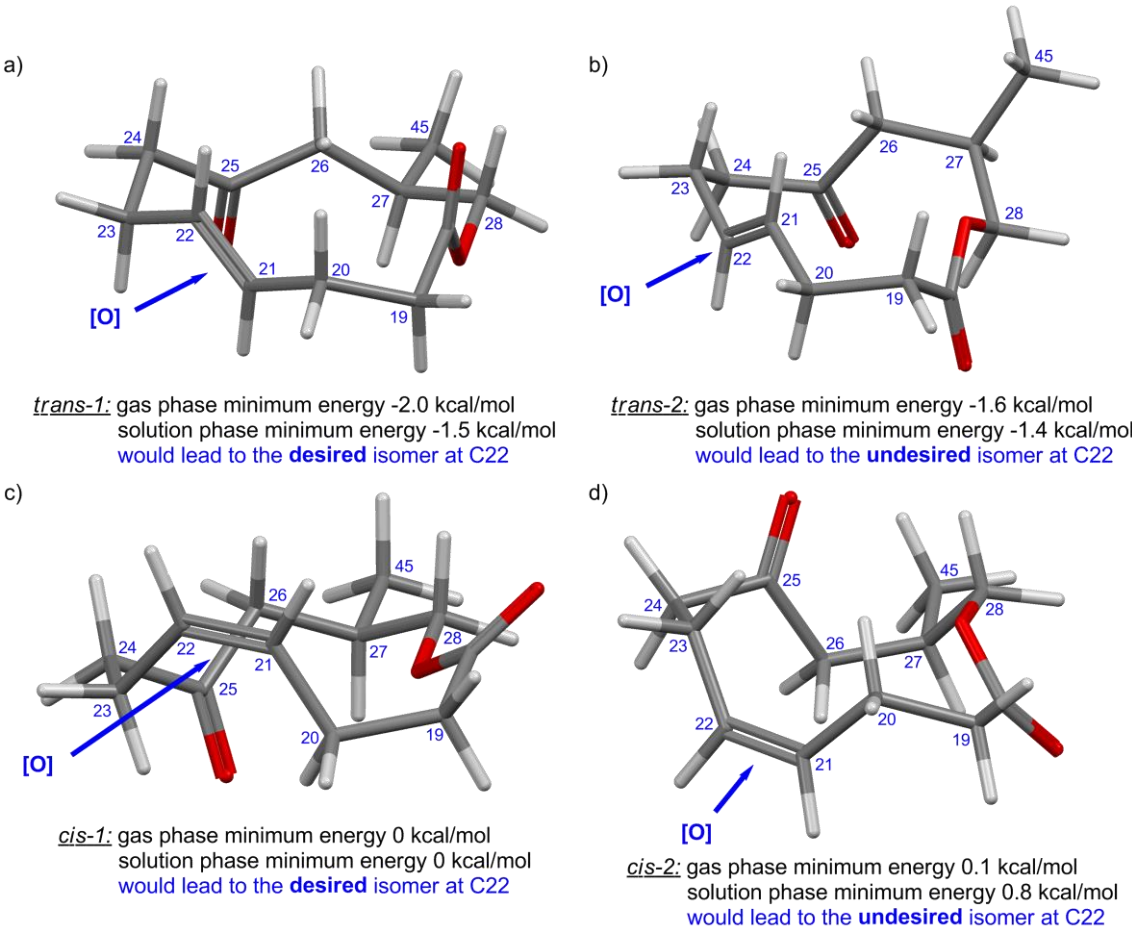
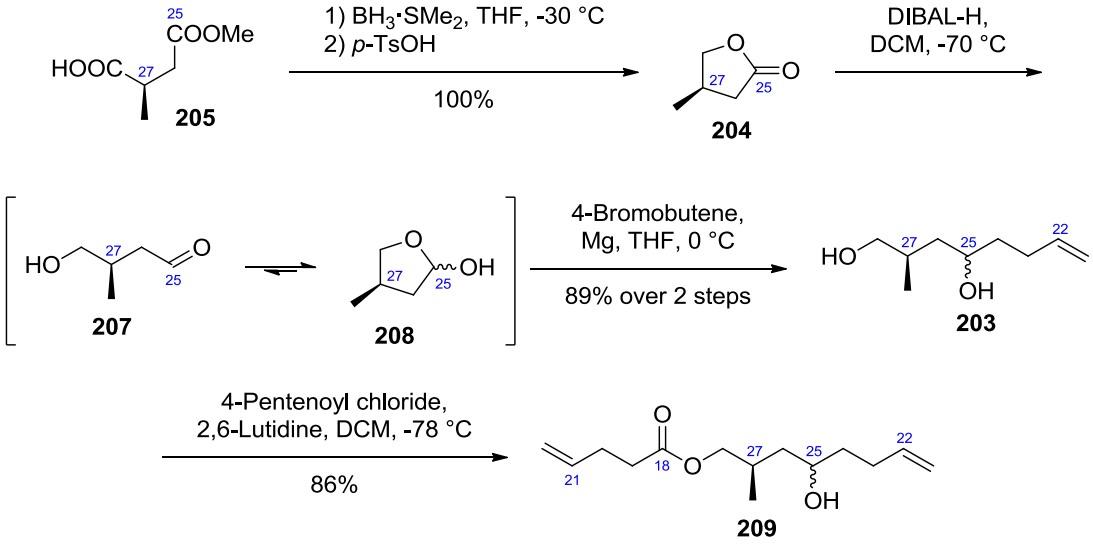


Figure 9. The minimum energy conformations for 12-membered macrocycle (**206**). a) The lowest energy *trans*-conformation, b) the second lowest energy *trans*-conformation, c) the lowest energy *cis*-conformation and d) the second lowest energy *cis*-conformation. The conformations were obtained using a Maestro 9.3.5 suite *via* a Monte Carlo conformational search (MMFFs force field, 2.0Å cutoff for structures) followed by optimisation *via* DFT (B3LYP/6-31G** level of theory, Jaguar suite).

Keeping the Curtin–Hammett principle in mind, it is not safe to assume much about the reactivity of the different conformers simply based on their minimum energies, and a more thorough transition state analysis would be needed. Instead of spending further time on computational modeling, we decided to test experimentally if the macrocyclic stereocontrol would work as we thought. If the macrocyclic stereocontrol didn't work, asymmetric epoxidation could be used as an alternative method to set up the C22 stereocentre.

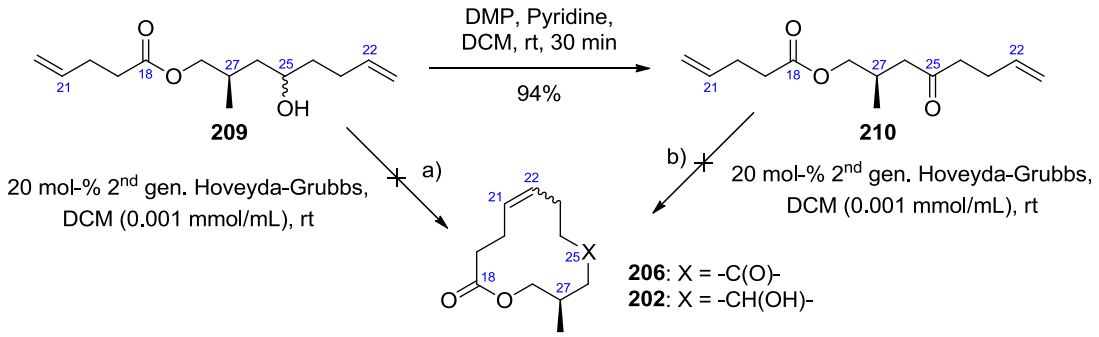
3.2.3 Attempted Synthesis of the Macrocycle

The actual synthesis began with a known reaction sequence,[81] where the 5-membered lactone **204** was synthesised from commercially available starting material **205** by selective reduction of the carboxylic acid moiety by a borane dimethyl sulfide complex, followed by an acid catalysed lactone formation. This equilibrium reaction could be pushed towards the lactone (**204**) by *in vacuo* removal of methanol from the reaction mixture. Direct Grignard addition to the lactone **204** led to the formation of double addition side product, but this side reaction could be avoided by reducing the lactone to the lactol **208** prior to the Grignard addition. The Grignard reaction to the lactol **208** produced an inseparable mixture of the diol diastereomers **203** in high 89% yield over two steps. Selective esterification of the primary hydroxyl group afforded the linear ester **209** in 86% yield (**Scheme 27**).



Scheme 27. Synthesis of the ester **209**.

Ring closing metathesis (**Scheme 28**a) was first tested with the secondary alcohol diastereomers **209** using the 2nd generation Hoveyda–Grubbs catalyst. Unfortunately the result was a mixture of polymerised products, and no RCM product was isolated.



Scheme 28. Ring closing metathesis (RCM) for a) alcohol **209** and b) ketone **210**.

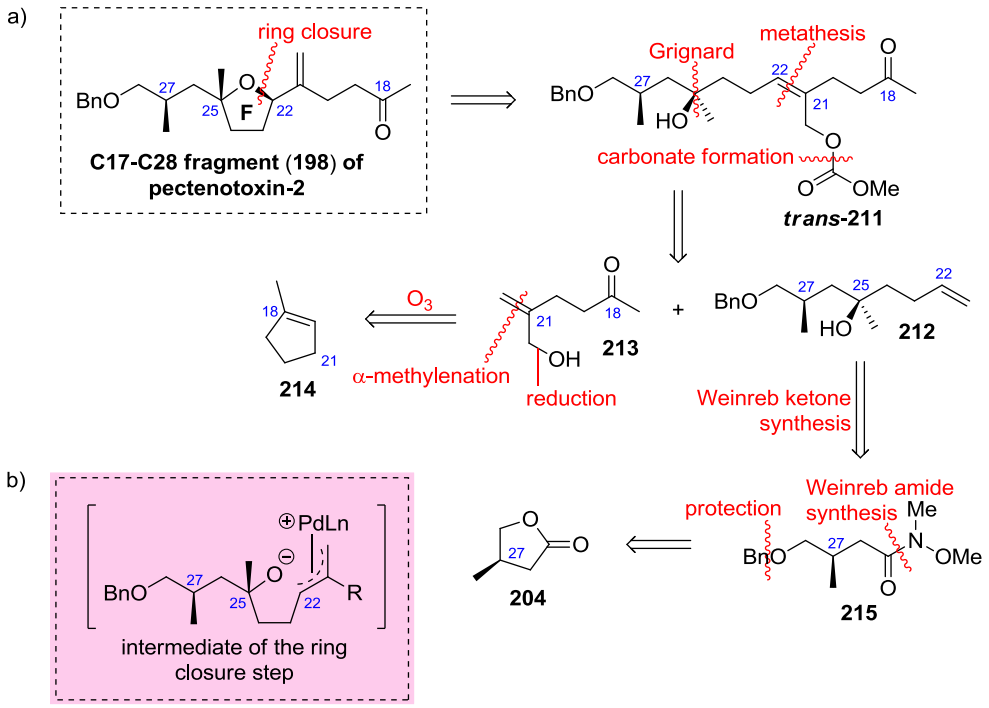
While the metathesis reaction itself should not be sensitive to free hydroxyl groups, having the starting material be a mixture of diastereomers made the product analysis challenging. This problem could be circumvented by performing the hydroxyl oxidation step first. This oxidation was performed in excellent 94% yield using Dess–Martin periodinane, providing the ketone **210** (**Scheme 28**b). However, the RCM once again resulted in an intractable mixture of polymerised products. A partial reason for the difficulties in the RCM could be ring strain, which can complicate the closure of 12-membered macrocycles.[82] Due to these issues faced in the metathesis step, we started planning for another approach.

3.3 Generation of the F-ring *via* a Pd(II)-Catalysed Ring Closure

3.3.1 Route Design

The second strategy (**Scheme 29**) was based on the same starting material and lactone formation step as the previous route. After the lactone formation, the routes diverged. Instead of reduction, the lactone **204** would be opened to form the Weinreb amide and the liberated hydroxyl group would then be benzyl protected. The protected Weinreb amide **215** could then be converted to the tertiary alcohol **212** in two consecutive organometal additions. The stereochemistry at the C22 centre would be set at the second addition step. The terminal olefin of **212** would then be joined with the allylic alcohol **213** *via* cross-

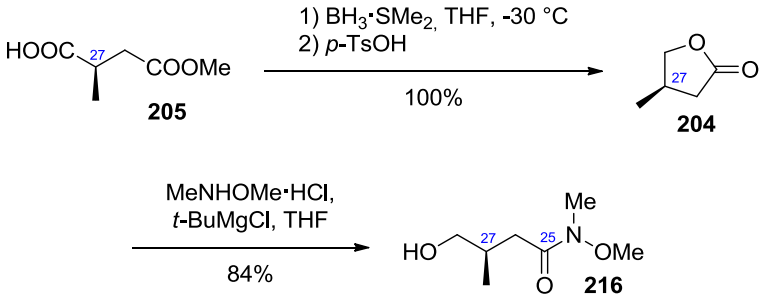
metathesis. The allylic alcohol **213** could be prepared from 1-methylcyclopent-1-ene *via* ozonolysis,[83] subsequent methylenation[84] and a chemoselective reduction.[85] The allylic alcohol would then be activated towards the intramolecular THF-ring closure *via* the formation of the methyl carbonate. Finally, Pd(II)-catalysed ring closure would generate the third stereocentre at C22. Although the Pd(II)-catalysed step could also be controlled with the help of chiral ligands, we anticipated that the C25 stereochemistry would affect the stereochemical outcome of the ring closure and set the C22 stereocentre correctly. This convergent route was very short, encompassing only 9 linear steps.



Scheme 29. a) Retrosynthetic analysis of the F-fragment **198** (C17–C28) b) hypothetical intermediate of the Pd(II)-catalysed THF-ring closure step.

3.3.2 Synthesis of the Substrate for the Ring Closure Experiments

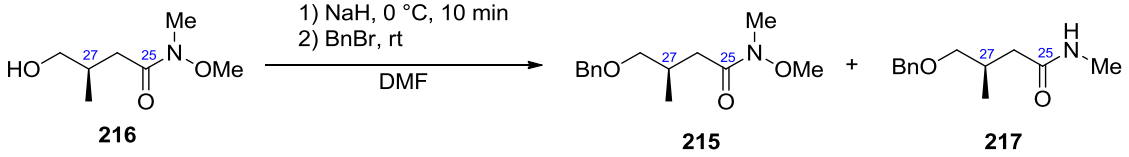
The first two steps of this synthetic route (**Scheme 30**) were identical to the previous route (**Scheme 27**). The lactone product **204** was converted to the Weinreb amide **216** in 84% yield.



Scheme 30. Preparation of the Weinreb amide **216**.

The primary hydroxyl group of the Weinreb amide **216** was benzyl protected at this stage to avoid problems in the forthcoming steps. The benzyl protection was tested under different reaction conditions (**Table 8**). When an excess (2.5 equiv.) of sodium hydride was used, decomposition of the Weinreb amide to form the side product **217** was observed. However, this side reaction was prevented by reducing the amount of NaH used. The optimised reaction afforded the desired product **215** in 85% yield, with no **217** detected.

Table 8. The benzyl protection reaction for **208**.

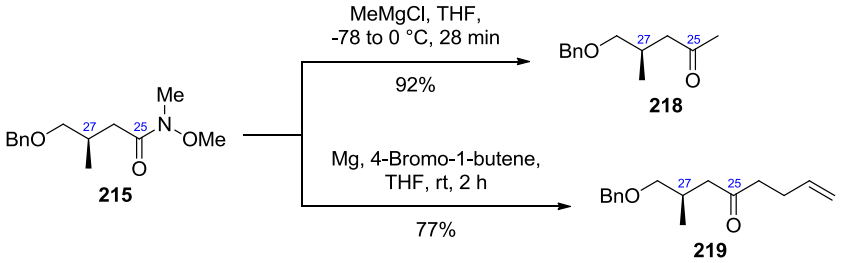


Entry	NaH [equiv]	Time [h]	Products [215/217]	Yield[a] [%]
1	2.5	0.5	1:1	41/42
2	1.1	22	1:0	85/0

[a] Isolated yields.

From the Weinreb amide **215**, two different ketones **218** and **219** (**Scheme 31**) were synthesised. Anticipating that the subsequent addition to generate the tertiary alcohol might not be highly diastereoselective, we decided to screen whether the order of addition of the methyl and 3-butenyl groups would affect the outcome. For the synthesis of the methyl ketone **218**, commercially available MeMgCl solution in THF was used. The reaction afforded the desired ketone in

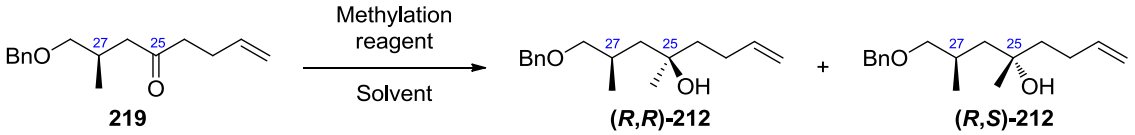
92% yield. The 3-butenyl ketone **219** was synthesised from a freshly prepared Grignard reagent in 77% isolated yield.



Scheme 31. The Weinreb ketone synthesis.

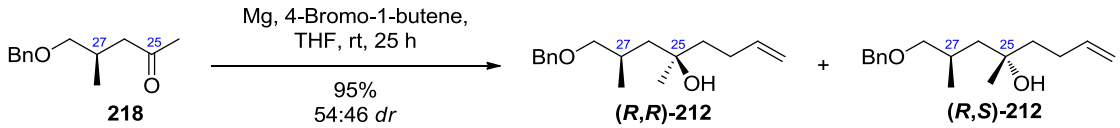
Various different methylation reagents were tested (**Table 9**) in the reaction with the 3-butenyl ketone **219**, but no significant diastereoselectivity was observed. Similarly, practically no selectivity (54:46 *dr*) was observed in the Grignard addition of 4-bromo-1-butene to the methyl ketone **218** (**Scheme 32**). However, this second method afforded a significantly better yield (87% over 2 steps) than the butenylation-methylation sequence (70% yield over 2 steps).

Table 9. Methylation reactions with **219**.



Entry	Methylation reagent	eq.	Solvent	T [°C]	Time [min]	*dr* [(*R*,*R*):(*R*,*S*)][b]	Conversion [%][b]
1	MeTi(O*i*Pr)$_3$[a]	15	Et_2O	–78/0	10/10	-	-
2	MeTi(O*i*Pr)$_3$[a]	15	Et_2O	–78/0	25/10	-	-
3	MeTi(O*i*Pr)$_3$[a]	15	Et_2O	0	10	-	-
4	MeTi(O*i*Pr)$_3$[a]	15	Et_2O	0	1360	-	4
5	MeTi(O*i*Pr)$_3$[a]	64	Et_2O	0	1290	-	5
6	MeTi(O*i*Pr)$_3$[a]	15	Et_2O	rt	1320	42:58	47
7	MeLi	2	Et_2O	–78 to –40	90	56:44	70
8	MeLi	2	Et_2O	0	90	56:44	82
9	MeLi	15	Et_2O	–78 to –40	75	60:40	77
10	MeMgCl	2	Et_2O	–78	15	55:45	8
11	MeMgCl	2	Et_2O	0	15	53:47	100
12	MeMgCl	2	Et_2O	–40	120	55:45	68
13	MeMgCl	2	Et_2O	–78	120	55:45	25
14	MeMgCl/LiBr	5/2	Et_2O	0	300	53:47	100
15	MeMgCl/LiBr	5/2	Toluene	0	300	51:49	100

[a] Reagent was prepared *in situ*. [b] Determined by ^{1}H NMR from the crude reaction mixture.



Scheme 32. Grignard reaction with 4-bromo-1-butene.

In contrast, Brimble and co-workers obtained 68:32 (*R*,*R*):(*R*,*S*) diastereoselectivity from a highly similar Grignard reaction (**Scheme 8**), employing a PMB (*p*-methoxybenzyl) protecting group instead of the benzyl protection used in our synthesis route.[24l] Due to the modest selectivities overall, it is difficult to speculate why the selectivity of the reaction with PMB protection was slightly higher, but it could be that PMB ethers form stronger complexes with Grignard reagents. At any rate, the **(*R*,*R*)-212** and **(*R*,*S*)-212** diastereomers were separable with flash chromatography, and thus the route could be continued with a diastereomerically pure product. The undesired (*R*,*S*)-product was employed in model studies, as detailed below.

3.3.3 Pd(II)-Catalysed Ring Closure Model Studies

The THF ring formation (**Scheme 29**) was studied next, employing a simplified and more readily available model system in the experiments. Our hypothesis for the ring closure was that it should be possible to influence the stereochemistry of the C22 centre with the existing C25 stereocentre during the Pd(II)-catalysed ring closure. We decided to use the undesired (*R*,*S*)-diastereomer (**212**) in the model studies, as the effect of the C27 methyl stereocentre to the ring closure process was estimated to be of little significance. Thus the otherwise unusable (*R*,*S*)-diastereomer **212** could be put to use in the model studies and the correct (*R*,*R*)-diastereomer **212** saved for later studies with the real system.

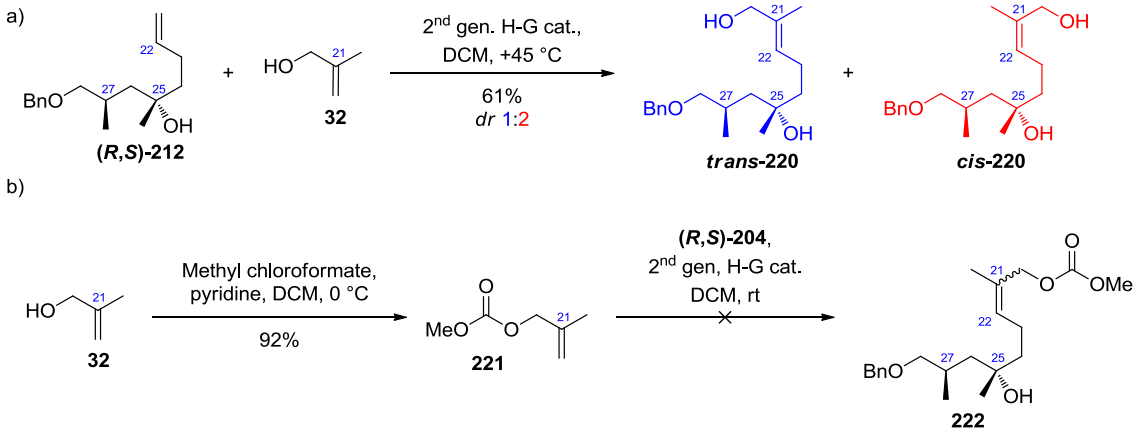
Table 10. Metathesis conditions.

Entry	Catalyst	Amount of cat. [mol-%]	Conditions	Yield[a] [%]
1	Grubbs 2nd gen.	5	rt	23
2	Hoveyda-Grubbs 2nd gen.	5	rt	23
3	Hoveyda-Grubbs 2nd gen.	5	reflux	61

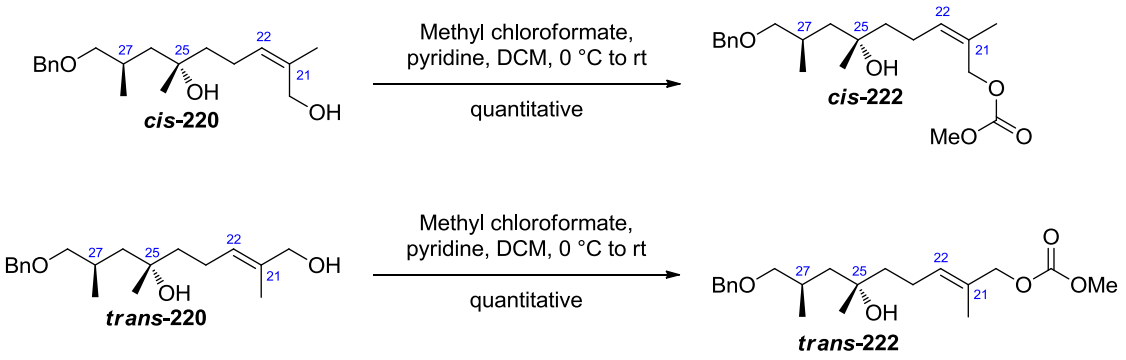
[a] Isolated yield.

To generate the desired allylic electrophile for the Pd(II)-catalysed cyclisation, extension of the carbon chain *via* cross-metathesis was explored. Methallyl alcohol (**32**) and the (*R*,*S*)-diastereomer **212** were subjected to the cross-metathesis reaction with 2nd generation Grubbs and Hoveyda–Grubbs catalysts[86] to form trisubstituted olefins **220** (**Table 10**). This reaction afforded the trisubstituted olefin products (**220**) with unexpectedly the *cis*-product predominating, although the rection was not very stereoselective (2:1 *cis*/*trans*-ratio of 2:1, 61% yield, see **Scheme 33**). However, we expected that the bulkier substrate used for the real system would induce higher stereoselectivity (**Scheme 29**). To improve the convergency of the route, the cross-metathesis

reaction was additionally tested using methallyl methyl carbonate (**221**), but this reaction did not lead to the formation of the desired product. TLC and ^{1}H NMR analysis of the reaction mixture showed only the starting materials, methallyl methyl carbonate and (*R*,*S*)-diastereomer **212**.



Scheme 33. Cross-metathesis reaction with a) methallyl alcohol (**32**) and b) the corresponding carbonate **221**.

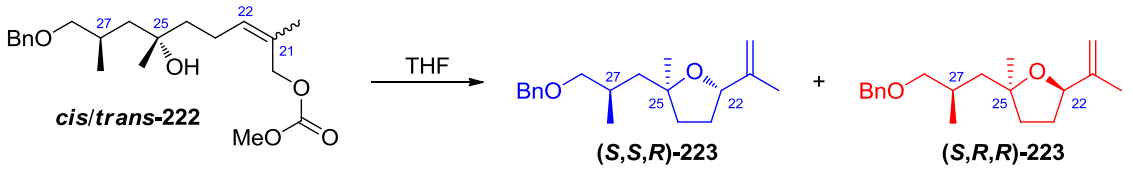


Scheme 34. Carbonate formation reactions.

Both stereoisomers were transformed to the corresponding carbonates (**222**). The carbonates formed selectively at the primary hydroxyl position in quantitative yields (**Scheme 34**). These carbonates were then directly employed in the following Pd(II)-catalysed ring closure experiments. It became apparent that only the *cis*-**222**-isomer reacted to form the THF-ring products **223**. Unfortunately, although a moderate level of diastereoselectivity was achieved, the main product of the ring closure reaction was not the desired diastereomer

(**Table 11**). The configurations of the diastereomers were determined by NOESY-NMR experiment.

Table 11. Pd(II)-catalysed ring closure reactions.



Entry	SM	Ligand	Pd(II) source	Base	Temp. [°C]	*dr*[a] [(S,S,R): (S,R,R)]	Yield[b] [%]
1	***cis*-222**	dppe	$Pd_2(dba)_3 \bullet CHCl_3$	*i*-Pr_2NEt	reflux	35:65	77
2	***trans*-222**	dppe	$Pd_2(dba)_3 \bullet CHCl_3$	*i*-Pr_2NEt	reflux	-	-

[a] Determined form the reaction mixture by NMR. [b] Isolated yield.

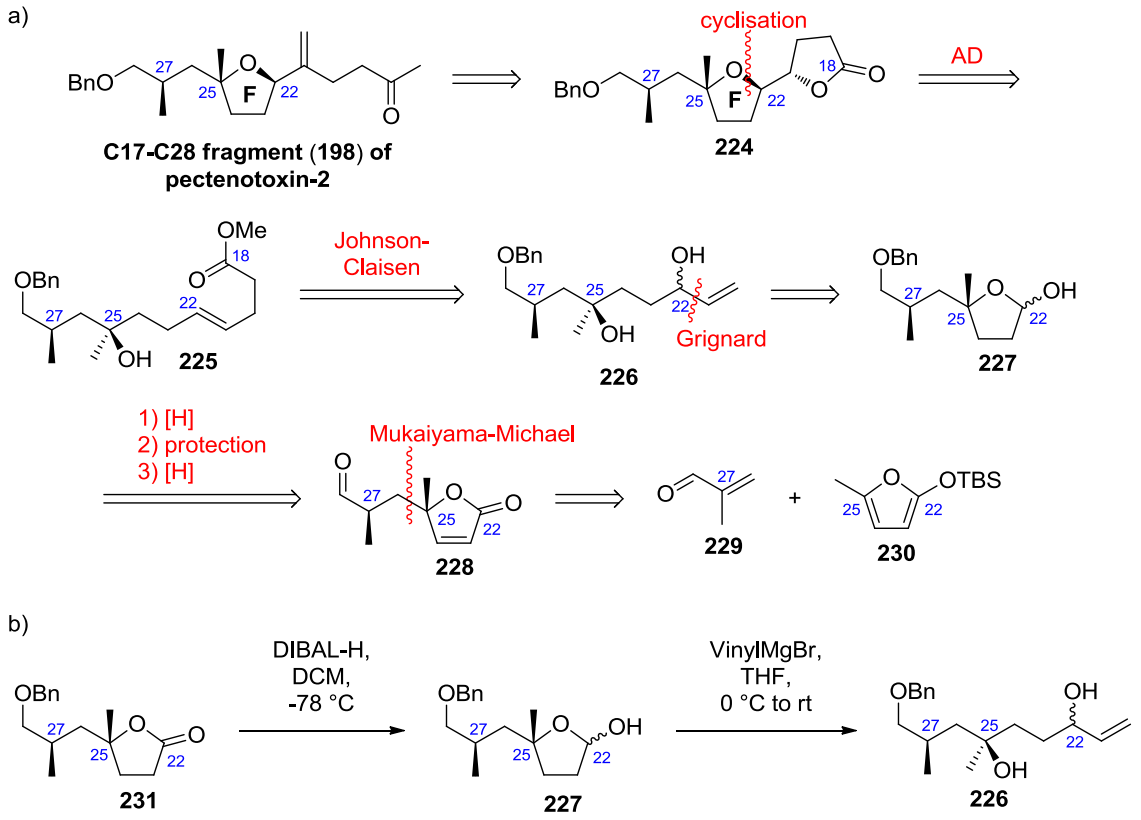
3.3.4 Evaluation of the Route

With these results at hand, some decisions had to be made before optimising the route further. On the positive side, the plan was indeed short – only 9 steps – and highly convergent. However, there were a number of negative points. First, although the chiral starting material **205** was commercially available, it was expensive (45.10 €/g[87] from Sigma–Aldrich or 82.50 €/5 g[88] from TCI Europe). Secondly, we were now facing a situation where we carried this material through not only one, but three poorly stereoselective steps, losing roughly half of the material in each of them. Unless the selectivities could be significantly improved, this route would be too expensive and complicated with several challenging purification/diastereomer separation stages. Due to these considerations, this otherwise short route was abandoned.

3.4 The Mukaiyama–Michael Approach

3.4.1 Route Design

The third plan (**Scheme 35a**) was based on a novel approach, starting from an achiral compound instead of the previously used chiral starting material (**Scheme 26** and **Scheme 29**). Our intention was to set up all of the stereogenic centres with catalytic asymmetric methods, thus potentially lowering the cost of scaling up. We planned to set up the C27 and C25 stereocentres in a single stroke *via* an iminium-catalysed Mukaiyama–Michael reaction with an α-subtituted enal, methacrolein (**229**). If such a reaction could be successfully developed, we could then transform the product *via* sequential aldehyde reduction, hydroxyl protection and double bond reduction to lactone **231**. This lactone **231** could then be further processed employing our previously successful reduction-Grignard addition sequence (**Scheme 26**/**Scheme 27**) to furnish the allylic alcohol **226** (**Scheme 35b**). This alcohol could then be rearranged to the linear *trans*-alkene **225** *via* Johnson–Claisen rearrangement. The advantage of the Johnson–Claisen reaction lies in its ability to control the double bond geometry more precisely than the previously used metathesis reaction.[89] Sharpless asymmetric dihydroxylation of the *trans*-double bond would then set up the final stereocentre at C22. Chemoselective mesylation of the secondary alcohol at C22, followed by base-catalysed cyclisation would afford the F-ring tetrahydrofuran (**224**).[90] Finally, the lactone end of **224** could be transformed to the requisite ketone in a manner similar to the original synthesis of the F-ring fragment **198** (**Scheme 25**).



Scheme 35. a) Retrosynthetic analysis of the F-fragment **198** (C17–C28). b) Reduction and subsequent Grignard reaction.

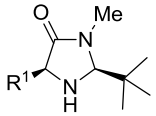
3.4.2 Catalyst Screen

The first challenge of the synthesis route was to find a selective and efficient catalyst for the Mukaiyama–Michael reaction and to optimise the reaction conditions (**Table 12**). Iminium-catalysed enantioselective reactions with α-substituted acroleins, such as methacrolein (**229**), are rare. Prior to this study, to our best knowledge, only reactions that proceeded to give a cyclic product (presumably *via* an enamine-catalysed cyclisation step) had been published.[91] The search for an optimal catalyst proved to be the most difficult and time-consuming part of the planned route.

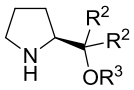
In 2003, the MacMillan group published an organocatalytic procedure for the Mukaiyama–Michael reaction that was restricted to β-substituted enals.[63] With methacrolein (**229**) and 5-(*Me*)-TMS-oxyfuran derived from α-angelica lactone (**111**) as the substrates, the MacMillan 2nd generation catalyst produced only

trace amounts of the Mukaiyama–Michael product **228**. Under the reaction conditions, the TMS-protected α-angelica lactone **111** underwent rapid hydrolysis due to the presence of water in the reaction mixture. Employing the less hydrolysis-prone 5-(*Me*)-TBS-oxyfuran derived from α-angelica lactone **230**, the yields improved to a moderate level (**Table 12**, entry 1). The glycine-derived MacMillan catalyst **232** improved both the reaction rate and conversion (excellent >95% conversion in 1.5 hours), while also giving higher *ee* (**Table 12**, entry 2). Screening the Hayashi–Jørgensen catalyst family (catalysts **151**, **233–237**)[92] revealed that these catalysts afforded good to excellent conversion, but the enantioselectivity of the reactions remained unsatisfactory (**Table 12**, entries 3–8). Finally, we tested catalyst **238**, which had not been previously used as an iminium catalyst, but had been reported by Jørgensen and coworkers to give good selectivities in enamine-catalysed α-chlorination reactions.[93] To our surprise, this *C2*–symmetrical (2*R*,5*R*)-2,5-diphenylpyrrolidine catalyst **238** achieved high conversion with excellent enantioselectivity (**Table 12**, entry 9). Although the diastereoselectivity of the reaction was not high, the product diastereomers **(*S*,*S*)-** and **(*R*,*S*)-228** were separable in flash chromatography.

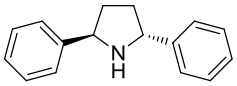
Table 12. Screening of the catalysts for the Mukaiyama–Michael reaction.



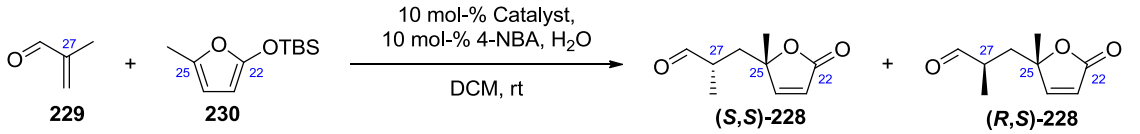
135: R^1=Bn
232: R^1=H



151: R^2=3,5-$(F_3C)_2C_6H_3$, R^3= TMS
233: R^2=Ph, R^3= TMS
234: R^2=Ph, R^3= DPMS
235: R^2=3,5-$(F_3C)_2C_6H_3$, R^3= DPMS
236: R^2=2-naphthyl, R^3= TMS
237: R^2=2-naphthyl, R^3= DPMS



(*R*,*R*)-238

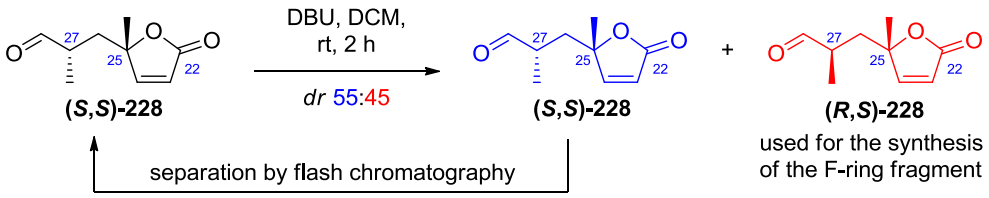


229 **230** **(*S*,*S*)-228** **(*R*,*S*)-228**

Entry	Catalyst	Duration (h)	Conversion (%)[a]	*ee* ((*S*,*S*):(*R*,*S*))	*dr* ((*S*,*S*):(*R*,*S*))
1	**135**	23	33	2.4/1.8	54/45
2	**232**	1.5	>95	37/23	64/36
3	**151**	24	65	20/28	65/35
4	**233**	24	94	54/53	57/43
5	**234**	10	>95	61/63	56/44
6	**235**	24	>95	29/64	59/41
7	**236**	20	>95	59/59	56/44
8	**237**	24	76	30/37	58/42
9	**238**	8	>95	–93/–93	56/44[b]

[a] The conversion of silyloxyfuran **230** was monitored by GC. [b] The ratio of (*R*,*R*):(*S*,*R*).

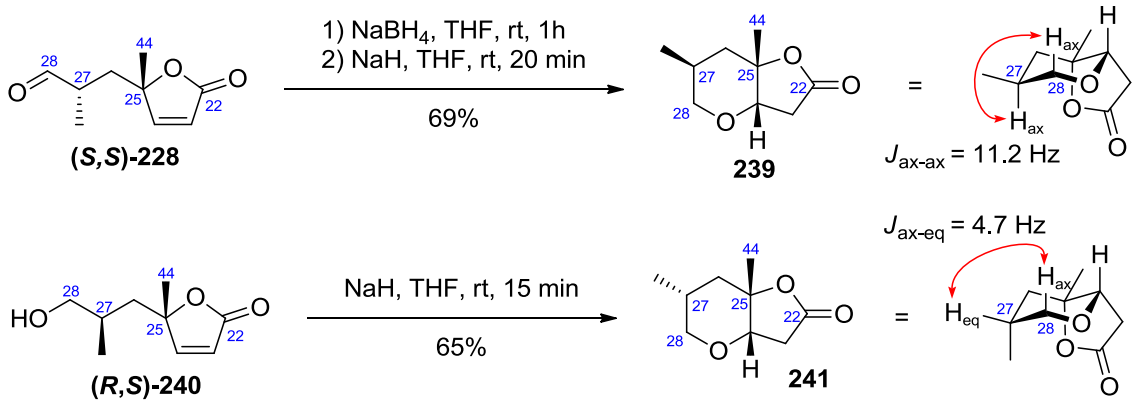
It was observed that the diastereoselectivity of the reactions was largely independent of the enantiopurity of the products, and the *dr* remained consistently at *ca.* 6:4. From this we suspected that the α-centre of the product aldehyde might be rapidly epimerised in the reaction conditions and the *dr* was a thermodynamic equilibrium. Later studies by Dr. Gokarneswar Sahoo with diastereomerically pure compounds **(*S*,*S*)-** and **(*R*,*S*)-228** confirmed this: a brief exposure to DBU epimerised the α-centre and re-formed the expected 6:4 thermodynamic equilibrium. This enabled us to recycle the epi-product (**Scheme 36**).



Scheme 36. Recycling of the product diastereomers *via* epimerisation.

3.4.3 Determination of Relative Stereochemistries of the Mukaiyama–Michael Products

The relative stereochemistries of compounds **(*S*,*S*)-** and **(*R*,*S*)-228** were determined from ring derivatives (**Scheme 37**). The aldehydes were reduced to alcohols and the alcohols were treated with NaH to induce the oxa-Michael reaction to form the 6-membered ring systems **239** and **241**.



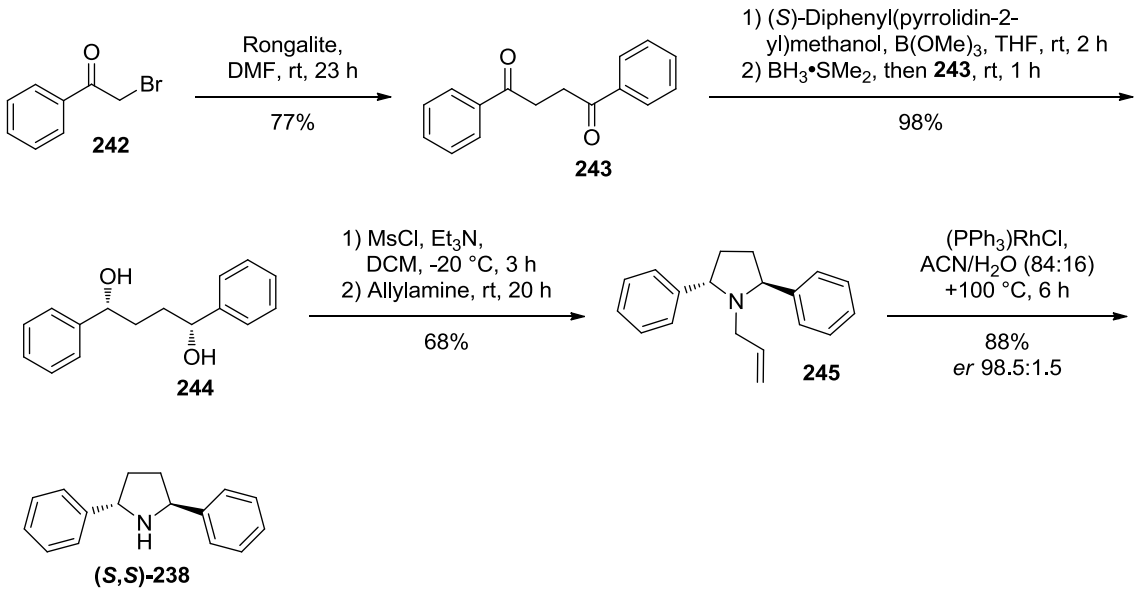
Scheme 37. Confirmation of the relative stereochemistry *via* NMR analysis of the bicyclic derivatives.

(2*R*,5*R*)-2,5-Diphenylpyrrolidine (**238**, used in the screening) afforded opposite enantioselectivity compared to the other screened catalysts (**Table 12**). Comparing our results to the results of MacMillan and coworkers,[63] we predicted that we should achieve the product with the desired absolute stereochemistry by using (2*S*,5*S*)-2,5-diphenylpyrrolidine as the catalyst.

3.4.4 Preparation of the (2*S*,5*S*)-2,5-Diphenylpyrrolidine Catalyst

(2*S*,5*S*)-2,5-Diphenylpyrrolidine (**238**) was commercially available, but prohibitively expensive (477.75 €/100 mg[94] in TCI Europe). For that reason, we

ended up synthesising the catalyst ourselves, following published procedures (**Scheme 38**).[95] The synthesis began with the formation of diketone **243** from 2-bromoacetophenone (**242**) in 77% yield.[95d] Diketone **243** was then reduced to the corresponding diol **244** by chiral Corey–Bakshi–Shibata reduction[96] in excellent 98% yield. No formation of meso-product was observed in NMR. Subsequent mesylation and allylamination generated the allylated pyrrolidine intermediate **245** in 68% yield over 2 steps. The main cause for the low yield for these two steps was the difficult separation of the undesired meso-product (ca. 20% formed during the amination) by flash chromatography. Reductive cleavage with Wilkinson's catalyst provided the desired catalyst **(*S*,*S*)-238** in 88% yield and 98.5:1.5 *er*. The overall yield of the route was 45% over 5 steps. Decagram quantities of catalyst **(*S*,*S*)-238** could be accessed with this protocol.

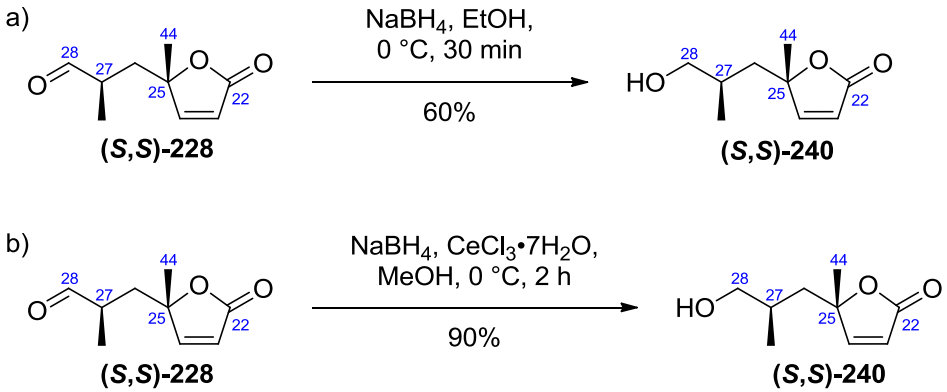


Scheme 38. Preparation of the (2*S*,5*S*)-diphenylpyrrolidine catalyst (**(*S*,*S*)-238**).[95]

3.4.5 Synthesis of the F-ring Containing C17–C28 Fragment

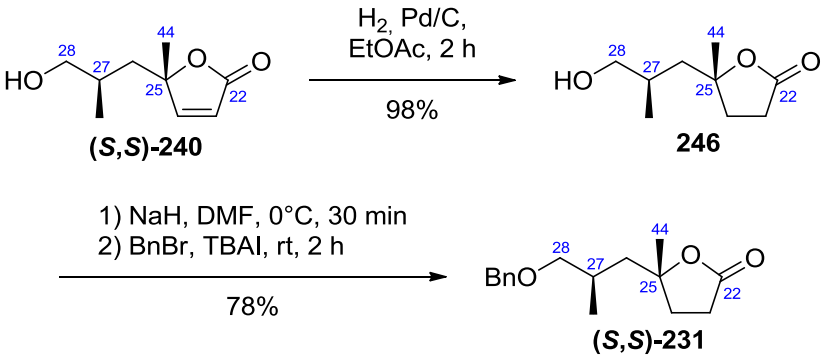
After the preparation of the catalyst **238**, the new methodology was immediately put to use in the synthesis of the F-ring fragment **198**. The aldehyde product **(*S*,*S*)-228** was subjected to the $NaBH_4$ reduction to afford the alcohol **(*S*,*S*)-240**. It was observed that in some cases under the $NaBH_4$

reduction conditions an undesired side reaction occurred where the reduced alkoxide intermediate underwent an oxa-Michael addition to the conjugated double bond to form compound **241**. Fortunately the use of Luche conditions was found by Dr G. Sahoo to prevent the competing Michael addition.[97] The use of Luche conditions did however result in a slower rate of reduction, likely due to the competing reversible acetal formation reaction.



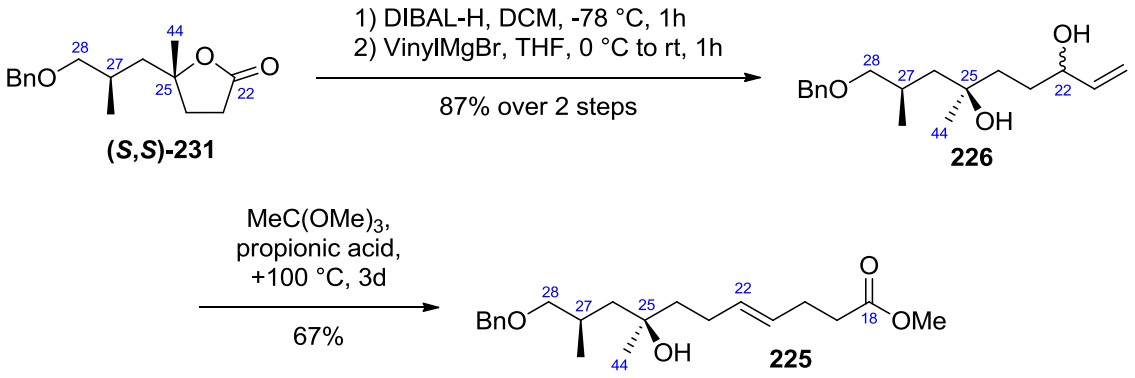
Scheme 39. Aldehyde reductions a) under $NaBH_4$ condition and b) under the Luche[97] conditions.

After reduction of the aldehyde, hydrogenation with $Pd/C/H_2$ readily furnished the saturated lactone **246** in 94% yield (**Scheme 40**). This product was benzyl protected in a satisfactory 78% yield using standard two-step conditions: a brief NaH treatment at 0 °C followed by the addition of BnBr and TBAI. Fortunately, no C-alkylation side reactions to the lactone ring were observed, although lactones are sufficiently basic to be deprotonated with NaH. However, prolonged exposure to aqueous basic conditions during the work-up caused the lactone ring to open. A rapid work-up procedure was sufficient to prevent the ring opening, but acidification treatment of the aqueous layer could also be used to regenerate the lactone **(*S*,*S*)-231** and facilitate the isolation of the product.



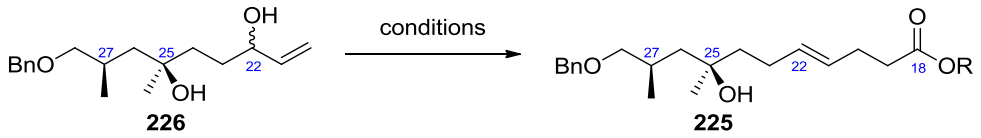
Scheme 40. Reduction and benzyl protection.

Reduction with DIBAL-H, [98] followed by Grignard reaction with vinylmagnesium bromide gave the allylic alcohol **226**, which was subjected to Johnson–Claisen rearrangement conditions. A brief screening of the reaction conditions was conducted (**Table 13**), and the optimised conditions were used to cleanly afford the olefin **225** as essentially pure *E* isomer in satisfactory 67% yield (**Scheme 41**).[89]



Scheme 41. DIBAL-H reduction, Grignard addition and Johnson–Claisen rearrangement.

Table 13. Screening of the Johnson–Claisen rearrangement conditions.

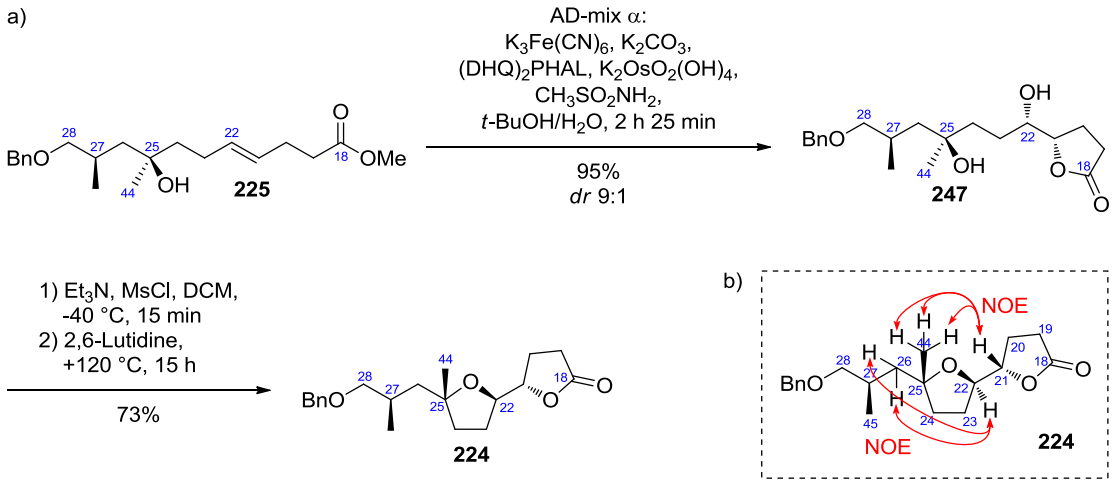


226 **225**

Entry	Acid	$MeC(OR)_3$ [R = Me, Et]	Temperature [°C]	Yield[a] [%]
1	Phenol, 0.09 equiv.	Me, 80 equiv.	+100	58
2	Propionic acid, 0.09 equiv.	Me, 80 equiv.	+100	45
3	Propionic acid, 0.07 equiv.	Me, 7 equiv.	+100	67
4	Propionic acid, 0.07 equiv.	Et, 7 equiv.	+100	54
5	Propionic acid, 0.07 equiv.	Et, 7 equiv.	+138	62

[a] Isolated yield.

Sharpless asymmetric dihydroxylation with AD-mix α ($(DHQ)_2PHAL$ ligand)[99] led to the formation of diol **247** in 9:1 diastereoselectivity in an excellent 95% yield (**Scheme 42**a). The stereochemical outcome of Sharpless AD is reliably predictable, providing the product with the desired stereochemistry at the C22 stereocentre. The free secondary hydroxyl group was then selectively mesylated.[100] Cyclisation of the F-ring with stereoinversion at C22 was readily achieved under the conditions reported by Wu and Sun[90] to yield compound **224** in 73% yield over 2 steps. NMR experiments of lactone **224** showed NOESY cross peaks (**Scheme 42**b) that supported the stereochemical assignment of **224**.

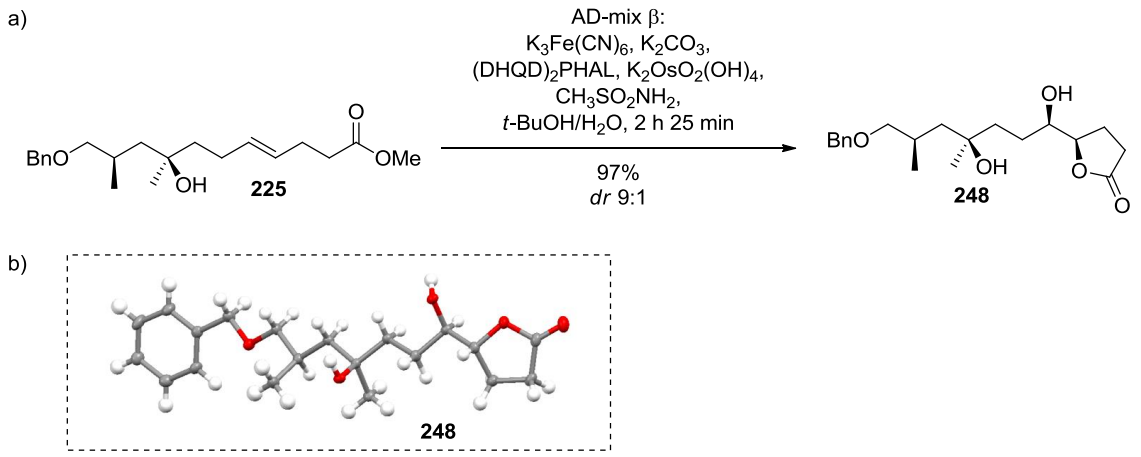


225 **247** **224**

Scheme 42. a) The Sharpless asymmetric dihydroxylation reaction with AD-mix α and subsequent THF-ring closure reaction with the method of Wu and Sun.[90] b) NOESY correlations between different protons.

To obtain further confirmation for the stereochemistry of **224**, we also prepared the alternate diastereomer using AD-mix β ((DHQD)$_2$PHAL ligand) in the reaction with olefin **225** (**Scheme 43**a). To our delight, lactone **248** was crystalline, enabling us to perform single-crystal X-ray analysis. Dr. Arto Valkonen analysed the X-ray structure of compound **248** (**Scheme 43**b), which confirmed the relative stereochemistry and also indirectly the absolute stereochemistry, given the high stereochemical fidelity of the AD reaction with *trans*-1,2-disubstituted olefins.[99] The X-ray structural assignment was in agreement with the NMR-based assignment of lactone **224** (**Scheme 42**), and allowed us to assign the absolute stereochemistry of the Mukaiyama–Michael reaction products. For the purposes of pectenotoxin synthesis, the desired stereochemistry is obtained using (2*S*,5*S*)-2,5-diphenylpyrrolidine as catalyst.

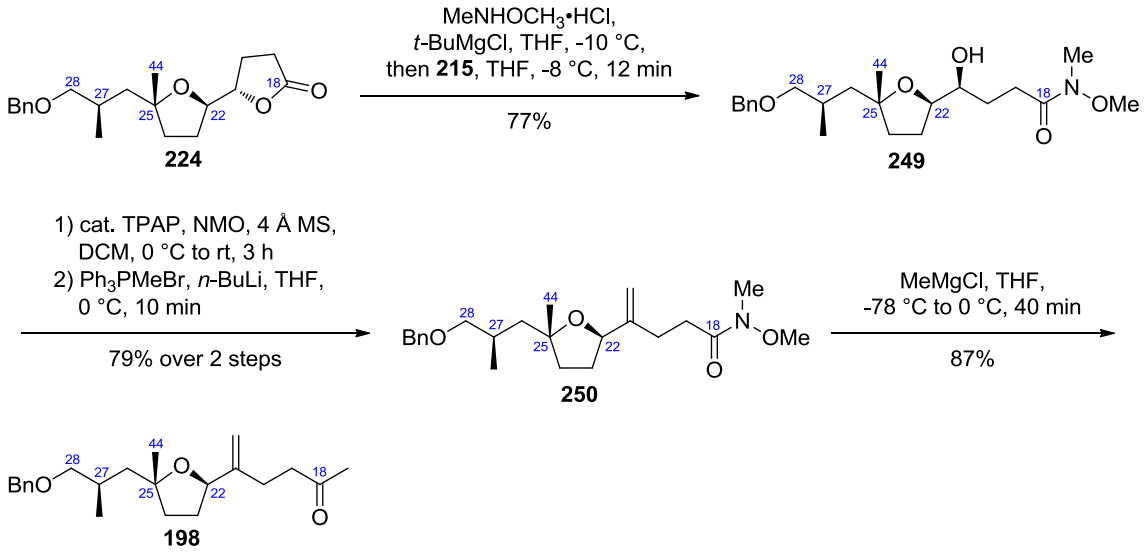
The assignment of absolute stereochemistry to the products in the expanded Mukaiyama–Michael reaction substrate scope (see **Table 18** on page 99) was based on the stereochemical assignment of compound **248**.



Scheme 43. a) The Sharpless asymmetric dihydroxylation reaction with AD-mix β. b) X-Ray structure of compound **240**.

To access the C17–C28 ketone **198**, the final four steps were successfully carried out following to the original F-ring synthesis route (**Scheme 25**): The AD-product lactone was converted to the Weinreb amide **249**. Ley oxidation of the secondary hydroxyl group, Wittig methylenation and finally methylation of the

Weinreb amide **250** afforded ketone **198**, the so-called F-ring fragment (**Scheme 44**).



Scheme 44. The final four steps of the synthesis route to the F-ring fragment **198** (C17–C28).

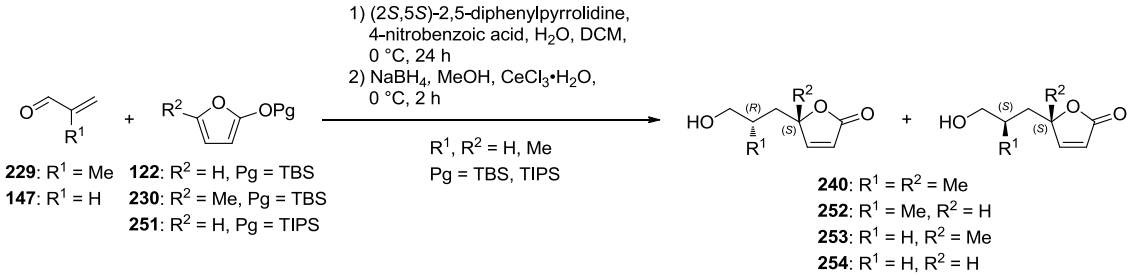
The synthesis of the F-ring fragment **198** was thus successfully completed in 3.3% yield over 15 steps, and the work was published in early 2012. However, there is still room for improvement if the route is to be scaled up to produce useful amounts of the product fragment. The largest obstacle for scale-up is the low diastereoselectivity of the Mukaiyama–Michael reaction and the complications that arise from it (*i.e.* the difficult separation of the product diastereomers, as well as the recycling of the undesired epimer). If a way to push the epimerisation reaction to the desired direction, or an asymmetric reduction combined with epimerisation of the α-stereocentre could be found, the route could be more readily scalable.

3.4.6 Preliminary Scope for Mukaiyama–Michael Substrates

A preliminary exploration of expanding the substrate scope for the Mukaiyama–Michael reaction was performed by Dr. Gokarneswar Sahoo for our joint publication.[97] These results are summarised below (**Table 14**). In this

study, the Mukaiyama–Michael products were directly subjected to Luche reduction conditions and isolated as alcohols.[101]

Table 14. Preliminary expansion of the substrate scope of the Mukaiyama–Michael reaction.

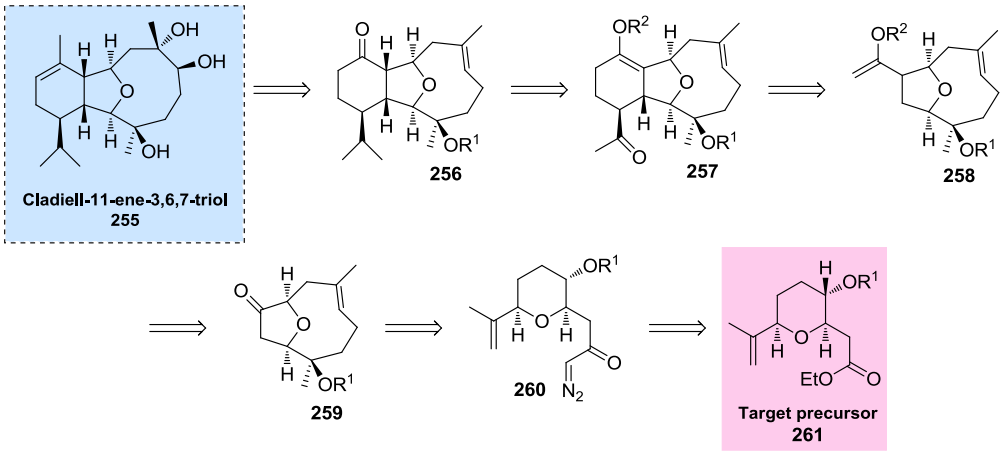


Entry	R^1	R^2	Pg	*er*[a] [%]	*dr*[a] [(*S*,*S*):(*S*,*R*)]	Yield[b] [%]
1	Me	Me	TBS	98:2	55:45	80
2	Me	H	TBS	96.5:3.5	50:50	65
3	H	Me	TBS	97:3	-	65
4	H	H	TBS	95.5:4.5	-	56
5	H	H	TIPS	96:4	-	71

[a] Determined by GC (Supelco Astec CHIRALDEX B-DM column) from the reaction mixture before reduction. In general, the enantiomeric ratio (*er*) was similar (±2 %) for both diastereomers. [b] Isolated yield.

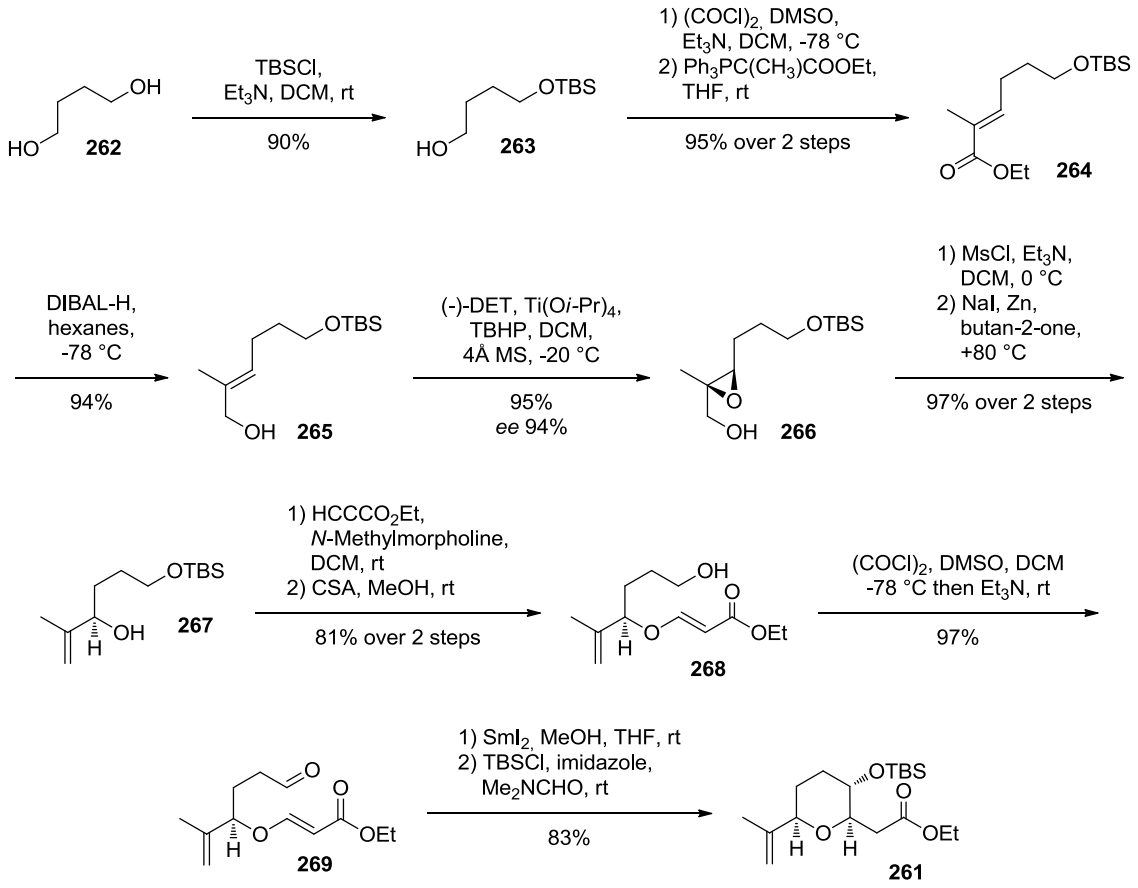
3.5 Another Application for the Mukaiyama–Michael Reaction – the Attempted Synthesis of the Cladiellin Precursor

I also had the opportunity to perform a short scientific collaboration project in the University of Glasgow under the supervision of prof. J. Stephen Clark (08–09/2012). My plan was to apply our then recently discovered Mukaiyama–Michael reaction methodology in the synthesis of a natural product target of the host research group (**Scheme 45**).[102]



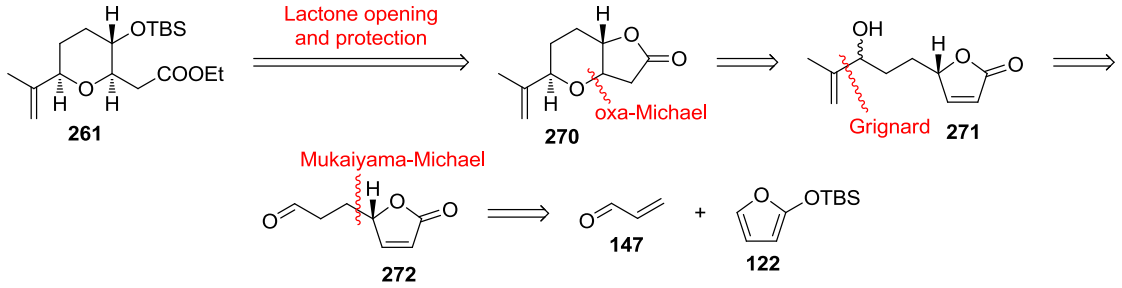
Scheme 45. Retrosynthetic analysis of the Cladiell-11-ene-3,6,7-triol (**255**).

The previous route to **261** in the Clark group (**Scheme 46**) contained a total of 12 linear steps. The route began with selective mono-protection of the starting material **262** with TBSCl. The remaining free hydroxyl group of **263** was oxidised using Swern conditions and the resulting aldehyde was directly subjected to Wittig olefination, delivering the α,β-unsaturated ester **264**. Reduction of the ester functionality provided the allylic alcohol **265**, and the double bond was transformed into an epoxide in high *ee* employing the Sharpless Asymmetric Epoxidation. This product **266** was transformed into a terminal allylic alcohol **267** *via* a three-step process: mesylation, halogen exchange and a zinc-induced elimination. Alkylation of the alcohol, followed by acidic cleavage of the silyl protection provided the primary alcohol **268**. The product alcohol was oxidised *via* Swern oxidation to the corresponding aldehyde **269**, and samarium iodide-induced cyclisation, followed by TBS protection, provided the intermediate **261** in good yield.[103]



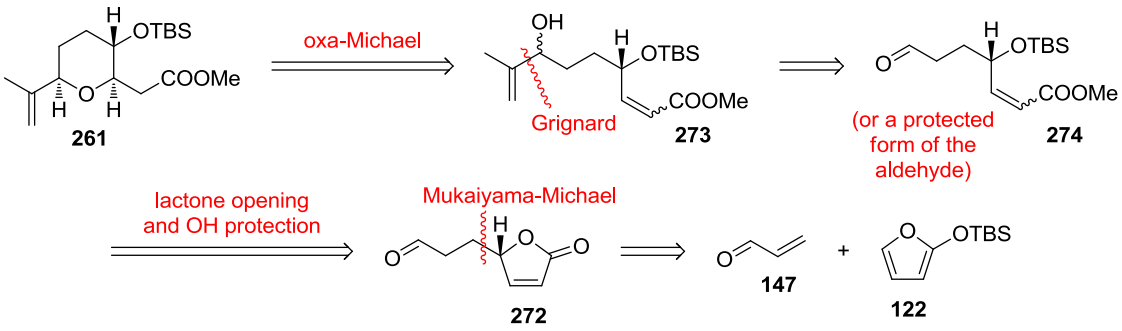
Scheme 46. Clark group's cladiellin precursor (**261**) synthesis.

The planned alternate route for the preparation of precursor **261** (**Scheme 47**) was based on the Mukaiyama–Michael reaction between acrolein (**147**) and silyloxyfuran **122**.[97] The aldehyde product **272** would be exposed to isopropenylmagnesium bromide under cold conditions to achieve a chemoselective addition to the aldehyde and leave the lactone carbonyl intact (**Scheme 47**). The hydroxyl group of compound **271** would then do a base-catalysed oxa-Michael attack to the conjugated double bond of the lactone **271**, furnishing the bicyclic ring system **270**. A similar ring closure reaction had already been successfully performed for the determination of the relative stereochemistries of the methacrolein Mukaiyama–Michael products (**Scheme 37**).[97] The final steps of this route would involve opening of the lactone and silyl protection of the free hydroxyl group.[104]



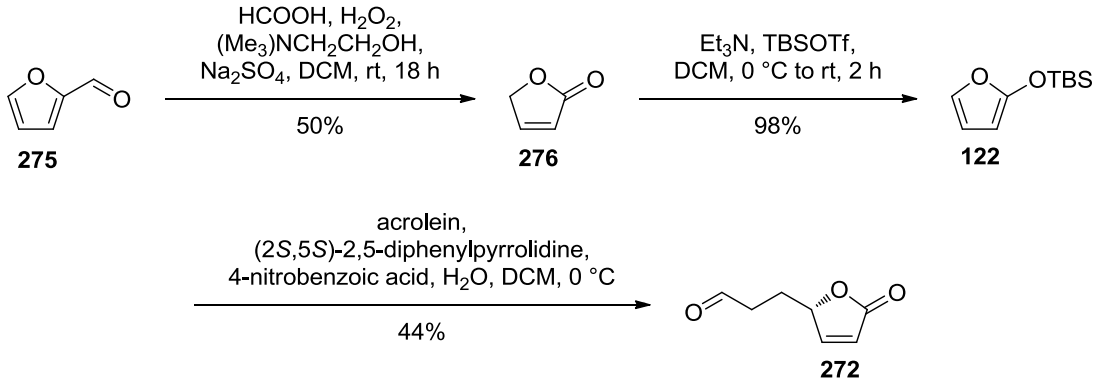
Scheme 47. Retrosynthetic analysis of the improved synthesis of the precursor **261** for the Cladiellin family members.

As a backup plan – should the oxa-Michael ring closure step afford the undesired diastereomer – we anticipated that reversing the sequence of events (performing the oxa-Michael after the lactone opening) could be used to circumvent the problem (**Scheme 48**). Starting from the Mukaiyama–Michael-product **272**, lactone opening and hydroxyl protection would furnish the *cis*-alkene **274**. Chemoselective Grignard addition and finally the oxa-Michael addition to the open chain alkene[105] **273** would afford the cladiellin precursor **261**.



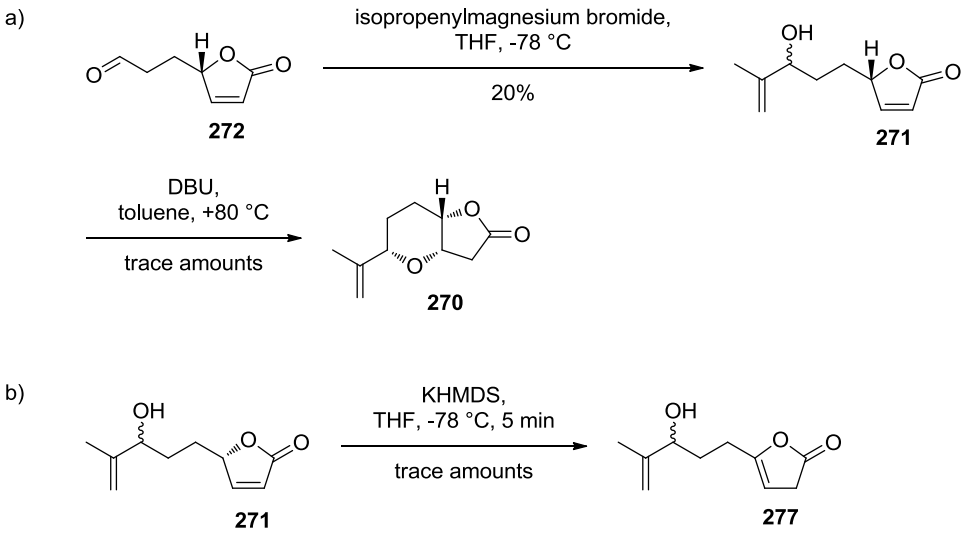
Scheme 48. Alternative route for the synthesis for the cladiellin family precursor **261**.

For the preparation of silyloxyfuran **122**, the procedure of Näsman was used: furfural (**275**) was first oxidised to furanone **276**,[106] which was then enolised in the presence of TBSOTf to afford silyloxyfuran **122**.[107] Unfortunately, scaling up the Mukaiyama–Michael reaction between acrolein (**147**) and silyloxyfuran **122** was anything but straightforward, as the reaction conditions were not fully optimised at the time. The experiments afforded the product **272** at best in 44% isolated yield.



Scheme 49. Preparation of the TBS-protected silyloxyfuran **122** and the Mukaiyama–Michael reaction.

The following Grignard reaction with isopropenylmagnesium bromide was to our disappointment not sufficiently chemoselective, even at low temperatures (**Scheme 50**). The reaction led to an inseparable diastereomeric product mixture (**271**) with a poor isolated yield of 20%. The intramolecular oxa-Michael ring closure reaction with the mixture **271** produced only the unwanted stereoisomer **270**, and further studies with a variety of bases revealed full epimerisation [108] of the lactone stereocentre that was established in the Mukaiyama–Michael reaction. Any route that would utilise these products should take into account the high base sensitivity of the butenolide functionality. For the aforementioned reasons, there seemed to be little potential in applying the route for the preparation of precursor **261**.



Scheme 50. a) Synthesis of the oxa-Michael product **270**. b) Isolated side product **277**.

In summary, although these explorations were not successful in furnishing an alternative route towards the cladiellin precursor based on the Mukaiyama–Michael methodology, these experiments nevertheless prompted us to explore the scope and optimisation of the MM reaction further. These studies are described in the following chapter.

4 EXPANSION OF THE SUBSTRATE SCOPE OF THE ORGANOCATALYTIC MUKAIYAMA–MICHAEL REACTION

In addition to the research aiming towards to total synthesis of the PTX2, we were also interested in expanding the substrate scope of the Mukaiyama–Michael reaction. The fact that the reaction is highly enantioselective was unexpected, and it was deemed important to find out if this was an isolated case for methacrolein (**229**) and 5-(*Me*)-silyloxyfuran, or if the methodology could be applied more widely.

4.1 Optimisation Studies

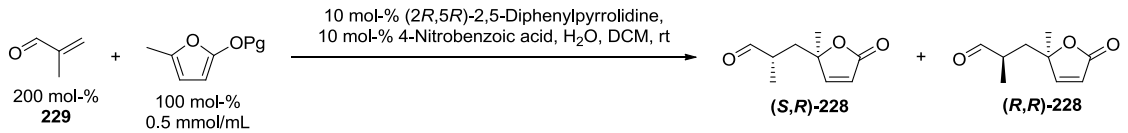
The choice of an analytical method for the reaction tracking was important. In our initial screens, the progress of the Mukaiyama–Michael reaction was monitored by chiral GC, because in the beginning we were mostly interested in optimising the enantioselectivity of the reaction and conversion to the desired product (**Table 12**). The main disadvantage of the GC method is the need to withdraw aliquots from the reaction mixture and thus the number of data points per reaction is limited. In contrast, reaction monitoring with NMR could enable us to detect and track non-volatile intermediates and products. To our disappointment, the Mukaiyama–Michael reactions failed to proceed at all in the NMR tube, as the reactions proceeded only with rapid stirring of the

reaction mixture. This result suggested that the reaction likely occurred (at least partially) at the interface of a biphasic system. With this information at hand, we decided to monitor the reaction by periodically withdrawing samples from vigorously stirred reaction mixtures and diluting them with $CDCl_3$ for NMR analysis.

4.1.1 Effect of the Silyl Protections

During the catalyst screening, it was observed that TMS protection was labile under our aqueous reaction conditions and the silyloxyfuran **111** was rapidly hydrolysed back to the lactone starting material. Additionally, control experiments indicated that TMS-protected silyloxyfurans **111** could undergo Mukaiyama–Michael directly under acid catalysis, leading to a racemic product and thus reduced enantioselectivity. In contrast, TBS and TIPS protected silyloxyfurans (**230** and **278**) were less prone to (though not immune to) these side reactions and therefore these silyloxyfurans were selected for the further studies (**Table 14** and **Table 15**). The reason for mainly using furans bearing the TIPS group was that in some cases they afforded better enantioselectivities and yields for the products (**Table 14**).

Table 15. Effect of the silyl group to the enantioselectivity.



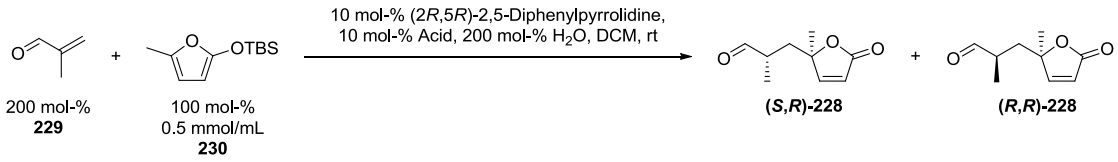
Entry	Pg	Time [h]	*er*[a]	*dr*[b] [(*R*,*R*):(*S*,*R*)]	Yield[a] [%]
1	TMS (**111**)	<3	90:10	55:45	<10
2	TBS (**230**)	8	96.5:3.5	58:42	>95
3	TIPS (**278**)	24[c]	96.5:3.5	58:42	>95

[a] Determined by GC (Supelco Astec CHIRALDEX B-DM column) from the reaction mixture. In general, the enantiomeric ratio (*er*) was similar (±2 %) for both diastereomers. [b] Determined by GC (Supelco Astec CHIRALDEX B-DM column) from the reaction mixture. [c] Stirred for this duration. The reaction was not monitored frequently and likely finished much faster.

4.1.2 Effect of the Acid

In addition to the protecting group optimisations, an acid screening was also undertaken. It was observed that the stronger the acid (*i.e.* lower pKa), the more prominent and faster the side reactions were (**Table 16** and **Table 17**). The lipophilicity of the acid also played a role, as both strongly hydrophilic and lipophilic acids significantly slowed the reaction rate. In our reaction conditions the moderately lipophilic and relatively mild 4-nitrobenzoic acid seemed to be the most optimal. Calculated logP values were used to give a rough estimate of the lipophilicity of the acids (**Table 16** and **Table 17**).

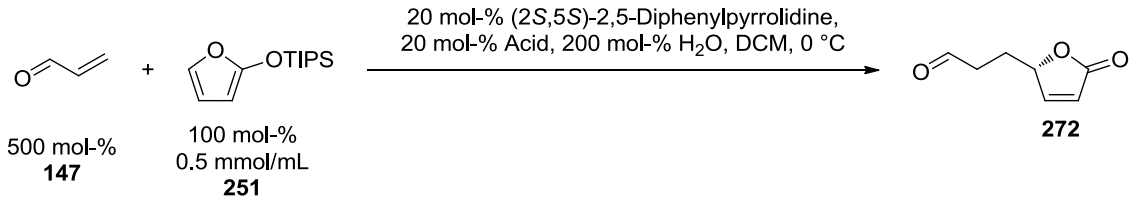
Table 16. Screening of acid co-catalysts for the methacrolein (**229**) reaction.



Entry	Acid	pK_a[a]	logP[a]	Time [h]	Yield[b] [%]	*er*[c]	*dr*[c] [(S,R):(R,R)]
1	TFA	-0.25	1.35	2	63	93.5:6.5	57:43
2	2-NBA	2.17	1.19	5	75	96.5:3.5	56:44
3	3-NBA	2.45	1.68	4	81	95.5:4.5	56:44
4	$ClCH_2COOH$	2.86	0.05	21	>95	93.5:6.5	56:44
5	4-NBA	3.44	1.79	8	>95	96.5:3.5	55:45
6	Formic acid	3.77	-0.54	21	>95	95.5:4.5	57:44

[a] The values are taken from SciFinder® (scifinder.cas.org), and are reportedly generated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2013 ACD/Labs) [b] Determined by GC (Supelco Astec CHIRALDEX B-DM column) from the reaction mixture. [c] Determined by GC (Supelco Astec CHIRALDEX B-DM column). In general, the enantiomeric ratio (er) was similar (±2 %) for both diastereomers.

Table 17. Screening of acid co-catalysts for the acrolein (**147**) reaction.



Entry	Acid	pK_a[a]	logP[a]	Time [h]	Yield [%]	*er*[b]
1	2,4-DNBA	1.43	1.34	2	37[b]	89.5:10.5
2	3,5-DNBA	2.85	1.71	2	40[b]	94:6
3	4-NBA	3.44	1.79	1	70[c]	94.5:5.5
4	3,5-dichlorobenzoic acid	3.46	3.50	4	60[b]	94:6
5	Lactic acid	3.86	–0.85	2	45[b]	89:11

[a] The values are taken from SciFinder® (scifinder.cas.org), and are reportedly generated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2013 ACD/Labs) [b] Determined by GC (Supelco Astec CHIRALDEX B-DM column) from the reaction mixture. [c] Determined by NMR from the reaction mixture.

4.1.3 Optimisation of the Acrolein Reaction

The reaction between acrolein (**147**) and (furan-2-yloxy)triisopropylsilane (**251**) was followed by ^{1}H NMR, varying the amounts of (2*S*,5*S*)-2,5-diphenylpyrrolidine (**238**) catalyst and acrolein (**147**) used (**Figure 10**, **Figure 11** and **Figure 12**). The first two figures only differ in the amount of catalyst used in the reaction. The highest concentration of product in the reaction mixture (0.28 mmol/mL, 55% yield) was nearly identical in both cases.

These experiments revealed that 200 mol-% of acrolein was not sufficient and the depletion of acrolein was limiting the formation of the product. The rate of product formation slowed drastically when the concentration of acrolein diminished, and the highest concentration of product was reached only after 23 hours with 20 mol-% of catalyst, and after 52 hours with 10 mol-% of catalyst. It was also observed that eventually the product began to decompose in the reaction conditions. Using a larger excess of acrolein (1000 mol-% versus the 200 mol-% used previously) dramatically increased both the highest concentration of product as well as the reaction rate (0.33 mmol/mL, 70% yield,

reached only one hour after starting the reaction). In summary, using a large excess of acrolein was crucial to the success of the reaction.

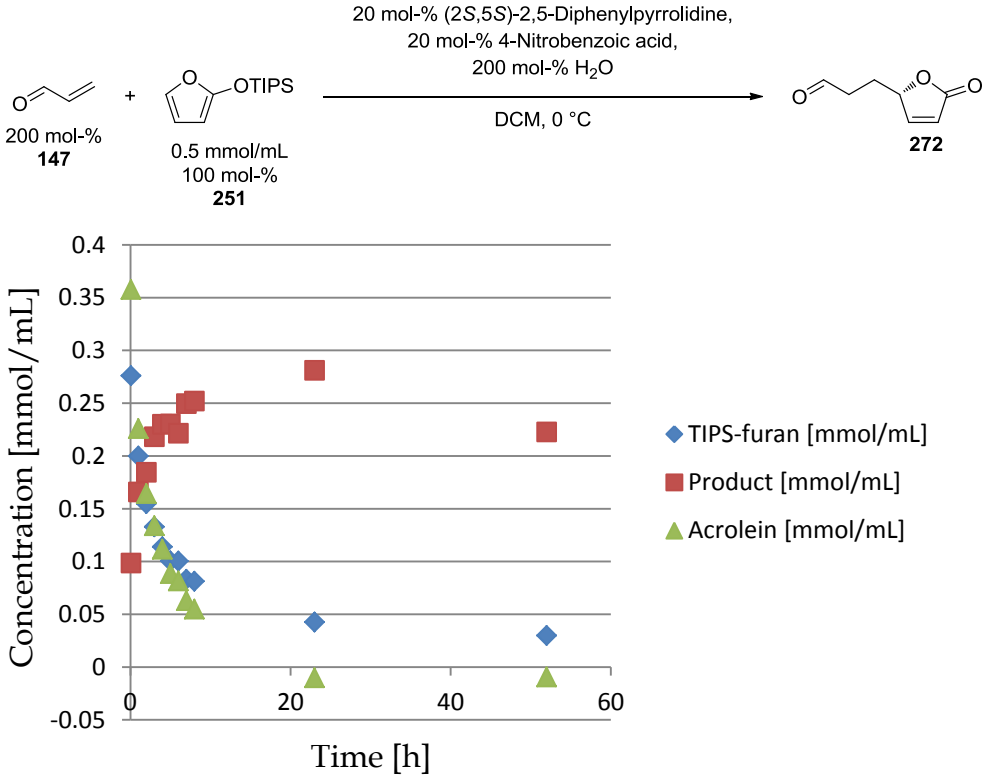


Figure 10. Reaction monitoring for the Mukaiyama–Michael reaction using 200 mol-% of acrolein (**147**) and 20 mol-% of catalyst **238**.

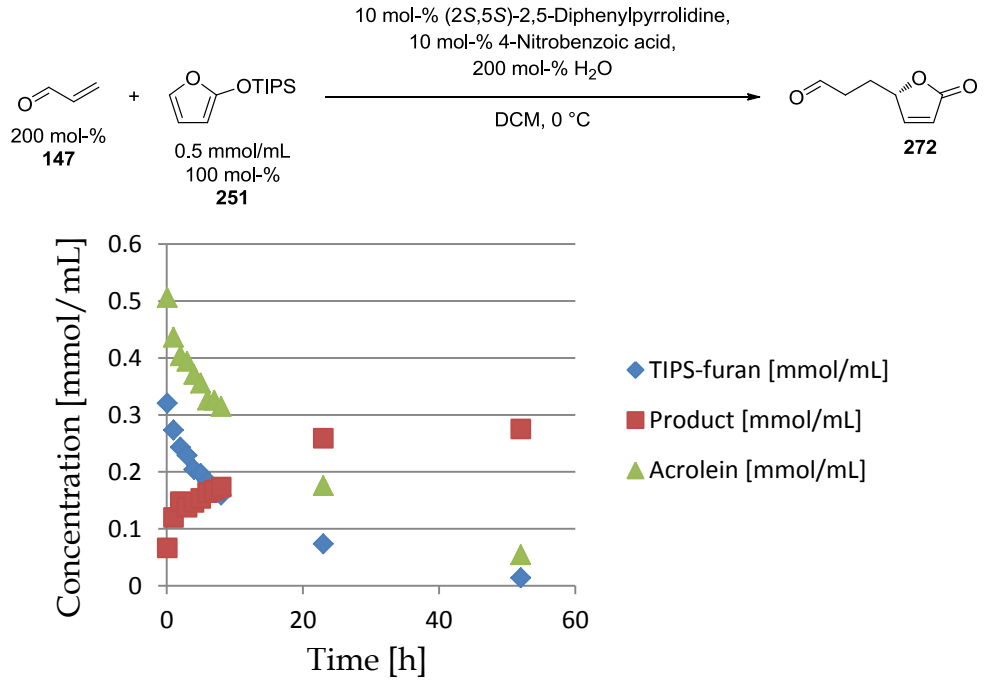


Figure 11. Reaction monitoring for the Mukaiyama–Michael reaction using 200 mol-% of acrolein (**147**) and 10 mol-% of catalyst **238**.

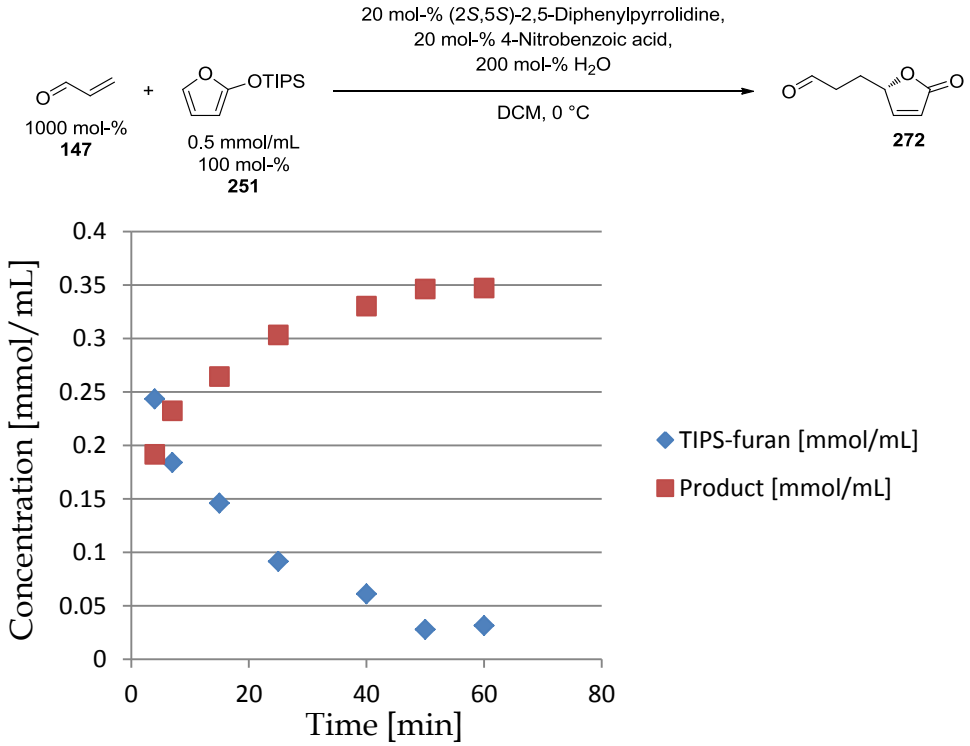


Figure 12. Reaction monitoring for the Mukaiyama–Michael reaction using 1000 mol-% of acrolein (**147**) and 20 mol-% of catalyst **238**.

4.1.4 Observations Regarding the Reaction Rate

The α-substituent of the acroleins also affected the rate of the Mukaiyama–Michael reactions. Acrolein (**147**) itself was readily consumed in side reactions (as detailed before), but this issue was not observed with α-substituted acroleins, and smaller excesses of these reagents could be used.

Differences in reaction rates were also observed between (furan-2-yloxy)triisopropylsilane (**251**) and triisopropyl((5-methylfuran-2-yl)oxy)silane (**278**) (**Figure 13** and **Figure 14**), with **251** being more reactive than **278**. It was also apparent from the data that the product **280** formed from **251** was unstable in the reaction conditions and started to decompose. No such decay occurred with the product **281** formed from **278**. The highest concentration of product **280** (0.33 mmol/mL, 65% yield) was lower than that of product **281** (0.38 mmol/mL, 76% yield). The results are in line with the observations from the other experiments conducted using these furan substrates (see **Table 18** on page 99 and **Table 14** on page 83, where the isolated yields are systematically

slightly lower for products formed from furan **251** compared to those formed from furan **278**).

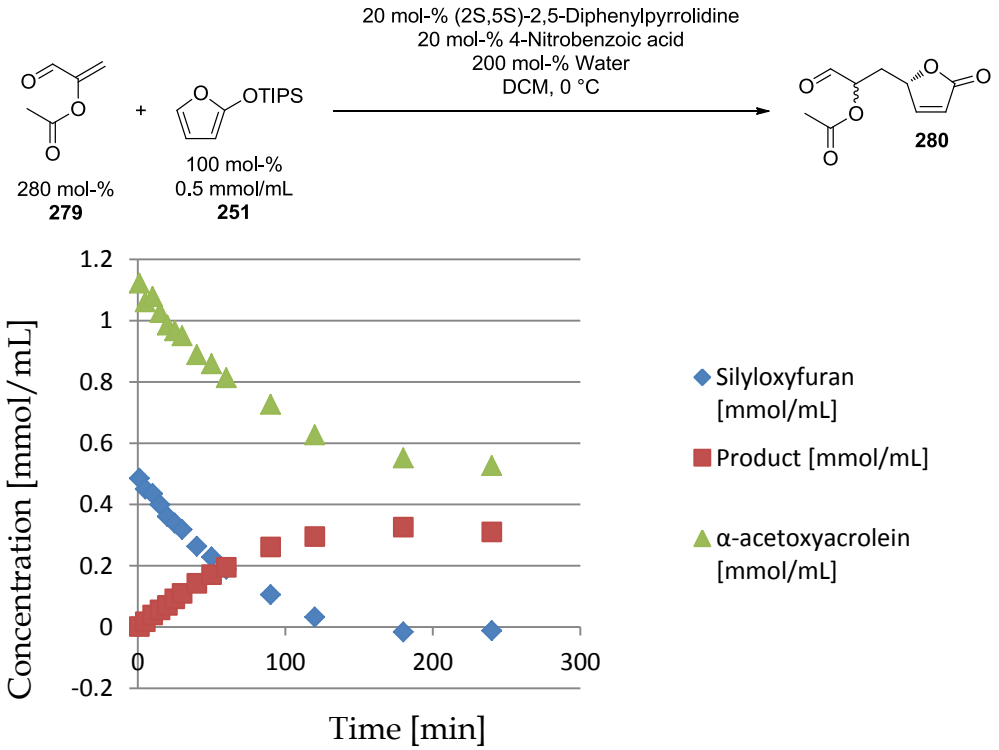


Figure 13. Reaction monitoring for the Mukaiyama–Michael reaction using 280 mol-% of α-acetoxyacrolein (**279**) and 20 mol-% of catalyst **238**.

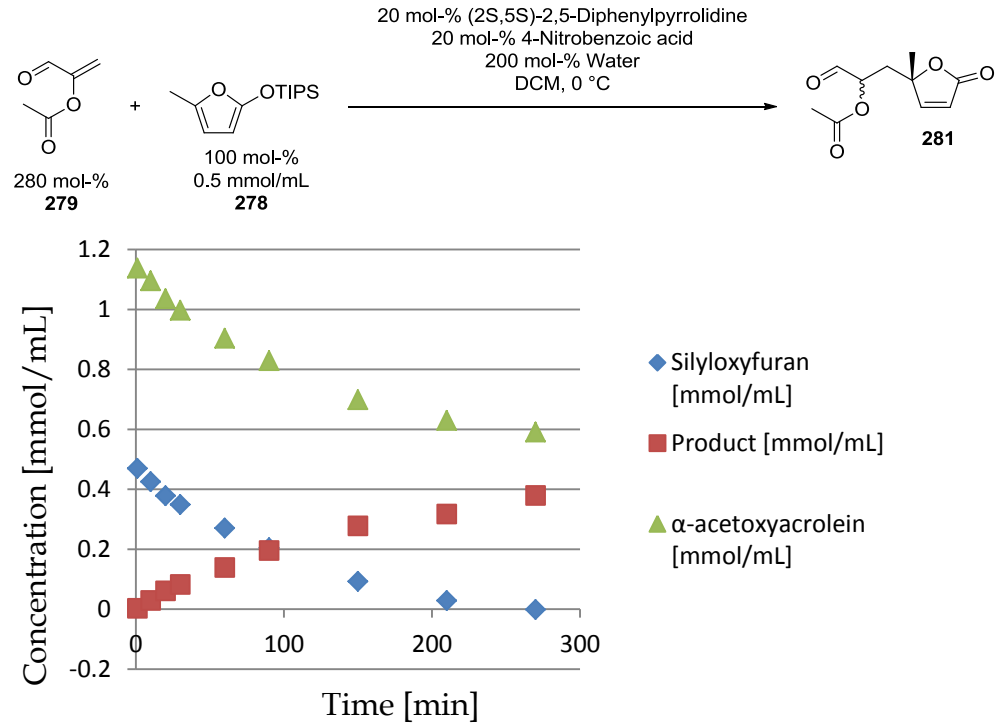


Figure 14. Reaction monitoring for the Mukaiyama–Michael reaction using 280 mol-% of α-acetoxyacrolein (**279**) and 20 mol-% of catalyst **238**.

4.1.5 Water Versus Other Additives

The Mukaiyama–Michael reaction slowed down drastically when bulkier and more lipophilic α-substituted acroleins were employed in the reaction. We decided to study whether the reaction rate could be enhanced by the addition of various additives. Based on earlier experiments, both the acidity (pK_a value) and the lipophilicity (estimated by calculated logD/logP values) of the co-catalyst acid seemed to affect the reaction rate. However, any improvement in the rate beyond a certain point came at the cost of enantioselectivity and yield.

The reaction rate between α-benzylacrolein (**282**) and triisopropyl((5-methylfuran-2-yl)oxy)silane **278** was very low (the reaction took several days to complete). This reaction was screened using different additives. If the rates were limited by the turnover of the catalyst and the rate of hydrolysis of the iminium/enamine intermediates, adding an acid that is soluble in aqueous phase ($KHSO_4$) or a surfactant to increase the rate of transfer between two phases might improve the rates. As such, instead of pure water, we employed saturated $KHSO_4$ solution (**Figure 15**) or a mixture of sodium dodecyl sulfate (SDS) and water (**Figure 16**). The reaction with saturated $KHSO_4$ solution proceeded more rapidly, but unfortunately the amount of hydrolysis product (*i.e.* β-angelica lactone) increased significantly (*ca.* 25% formed). The reaction with SDS-water mixture did not proceed as rapidly as the $KHSO_4$ reaction, but the amount of hydrolysis product formed in the reaction was also significantly lower (*ca.* 6%). In both cases the highest concentration of the product **283** (0.2 mmol/mL, 40% yield) was significantly lower than in the standard reaction, where an isolated yield of 69% was obtained. In summary, these additive experiments did not lead to improved results in this case and water remained the optimal co-solvent.

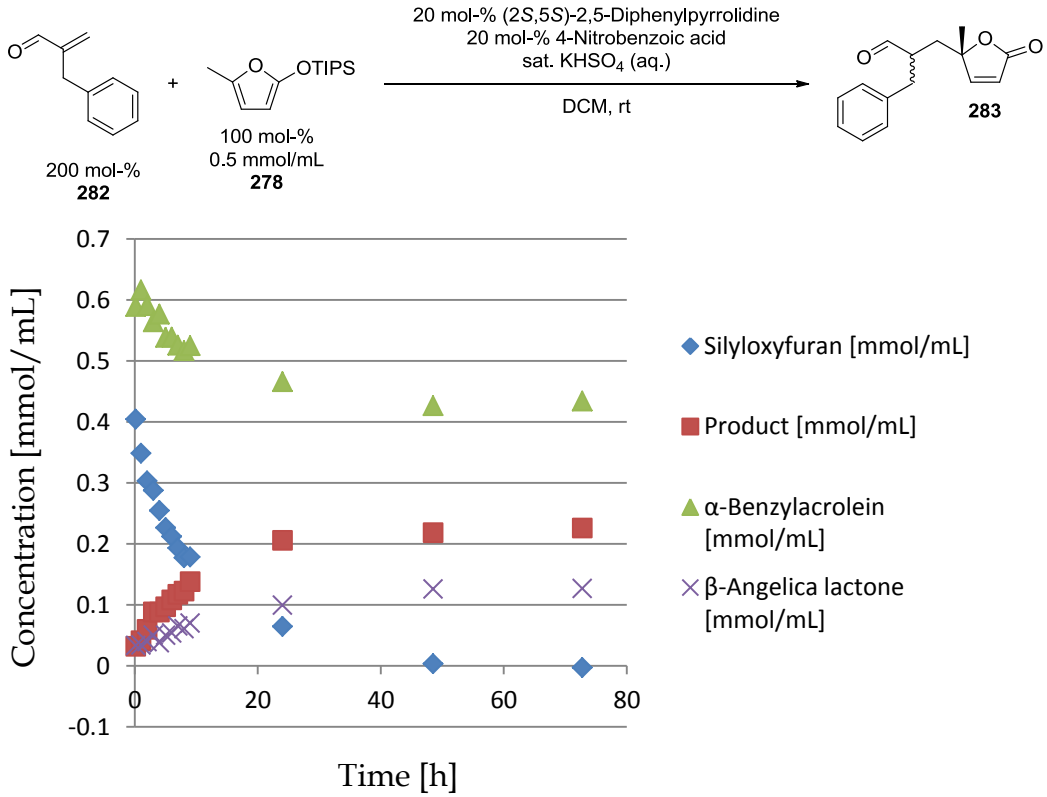


Figure 15. Reaction monitoring for the Mukaiyama–Michael reaction using 200 mol-% of α-benzylacrolein (**282**) and 20 mol-% of catalyst **238**.

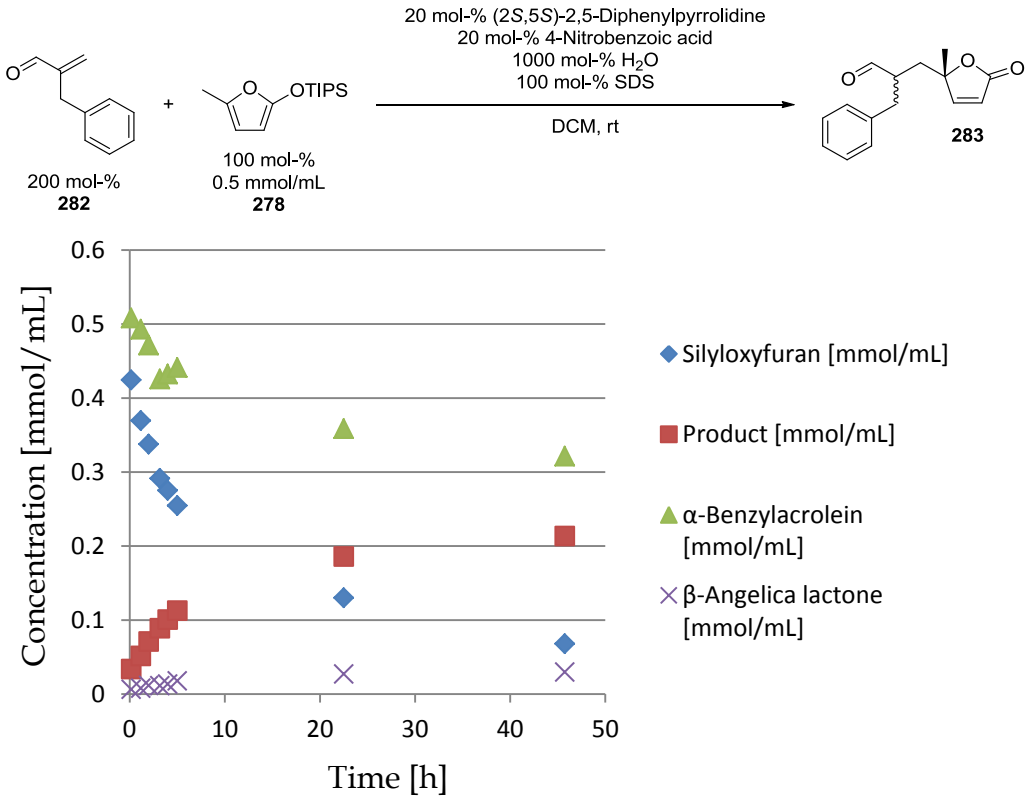
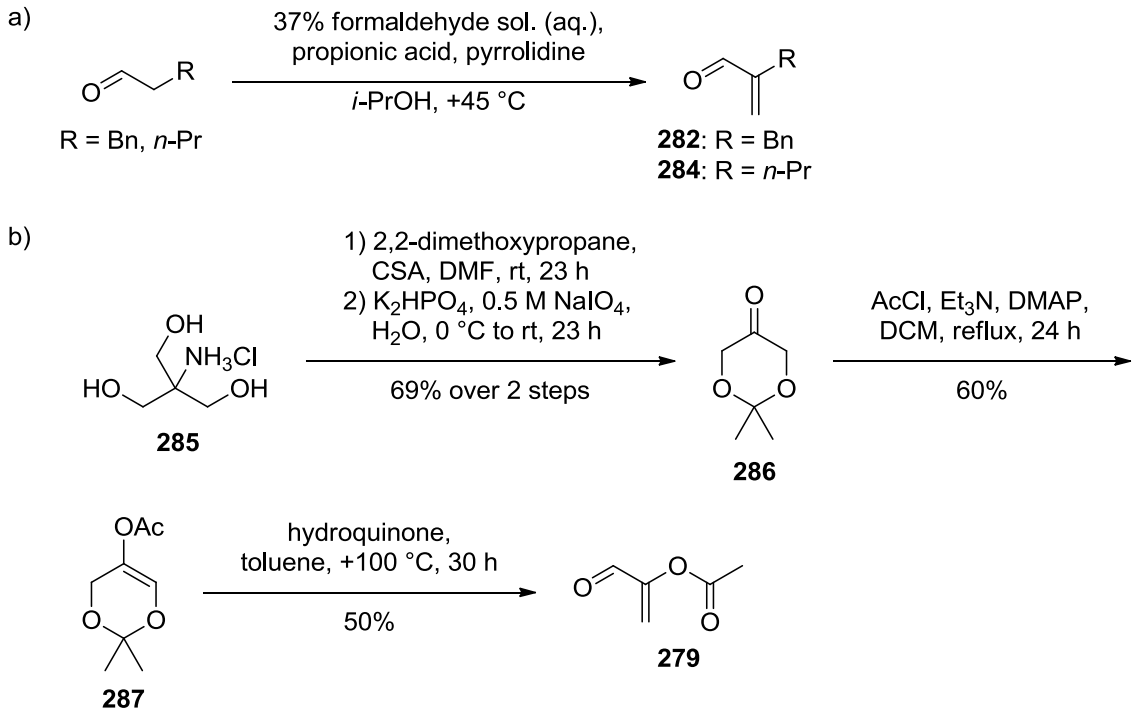


Figure 16. Reaction monitoring for the Mukaiyama–Michael reaction using 200 mol-% of α-benzylacrolein (**282**) and 20 mol-% of catalyst **238**.

4.2 Substrate Scope of α-Substituted Acroleins

Different α-substituted acroleins were studied in the Mukaiyama–Michael reaction. Acrolein (**147**) and methacrolein (**229**) were commercial compounds, but most of the other used α-substituted compounds were prepared by utilising an α-methylenation method previously developed in the group (**Scheme 51**a).[84] An exception to this was α-acetoxyacrolein (**279**), which was prepared following previously reported procedures (**Scheme 51**b).[109]

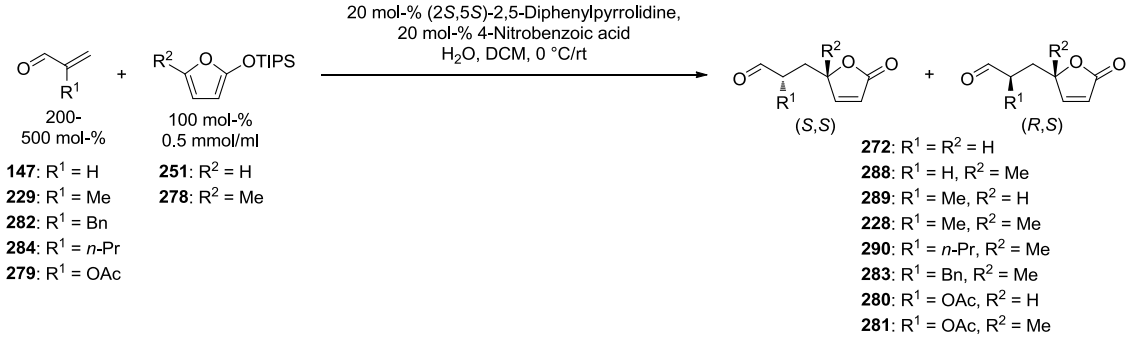


Scheme 51. a) Preparation of the α-methylenated aldehydes using α-methylenation methodology developed in our group.[84] b) Preparation of α-acetoxyacrolein (**279**).[109]

The α-acroleins were subjected to the optimised Mukaiyama–Michael reaction conditions with TIPS-protected silyloxyfurans (**Table 18**). The substrates used originally in the synthesis of the PTX2 F-ring fragment **198**, namely, methacrolein (**229**) and TBS-oxyfuran derived from angelica lactone (**230)**, gave the best results. The reaction furnished the product **228** in 82% isolated yield with excellent enantioselectivity using only 10 mol-% of catalyst **238** (**Table 18**, entry 4). In other entries 20 mol-% of the catalyst **238** was used with TIPS-protected silyloxyfurans, affording 60 to 70% isolated yields with excellent

enantioselectivity. The α-benzyl acrolein (**282**) substrate gave the poorest enantioselectivity (**Table 18**, entry 6), possibly as a result of the slow reaction rate and warmer reaction conditions. Although the enantioselectivities were high, the reactions were not diastereoselective, and the products were obtained in ratios ranging from 1:1 to 2:1 (**Table 18**).

Table 18. The substrate scope for α-substituted acroleins used in the Mukaiyama–Michael reactions with silyloxyfurans.



Entry	R^1	R^2	Temperature [°C]	Stirring Time	Yield[b] [%]	*er*[c]	*dr*[g] [(*S*,*S*):(*S*,*R*)]
1	H	H	0	4 h	56	93.5/6.5	-
2	H	Me	0	3 d	61	93.5/6.5	-
3	Me	H	0	2 d	53	97.5/2.5	50:50
4[a]	Me	Me	0	2 d	82	97/3	55:45
5	*n*-Pr	Me	0	29 h	58	95/5	57:43
6	Bn	Me	rt	5 d	69	85/15[d]	48:52
7	AcO	H	0	4 h	58	96.5/3.5[e]	64:36
8	AcO	Me	0	5 h	71	97/3[f]	50:50

[a] 10 mol-% of catalyst and 10 mol-% acid were used in this reaction, and instead of TIPS-, TBS-protected silyloxyfuran was used. [b] Isolated yield. [c] Determined by GC (Supelco Astec CHIRALDEX B-DM column). In general, the enantiomeric ratio (er) was similar (±2 %) for both diastereomers. [d] Determined by HPLC (Chiralcel IC column) from the alcohol derivative. [e] Determined by HPLC (Chiralcel IC column) from 5,5-Dimethyl-1,3-dioxan-2-yl –derivative. [f] Determined by HPLC (Chiralcel IB column) from 5,5-Dimethyl-1,3-dioxan-2-yl –derivative. [g] Determined by NMR from the crude reaction mixture.

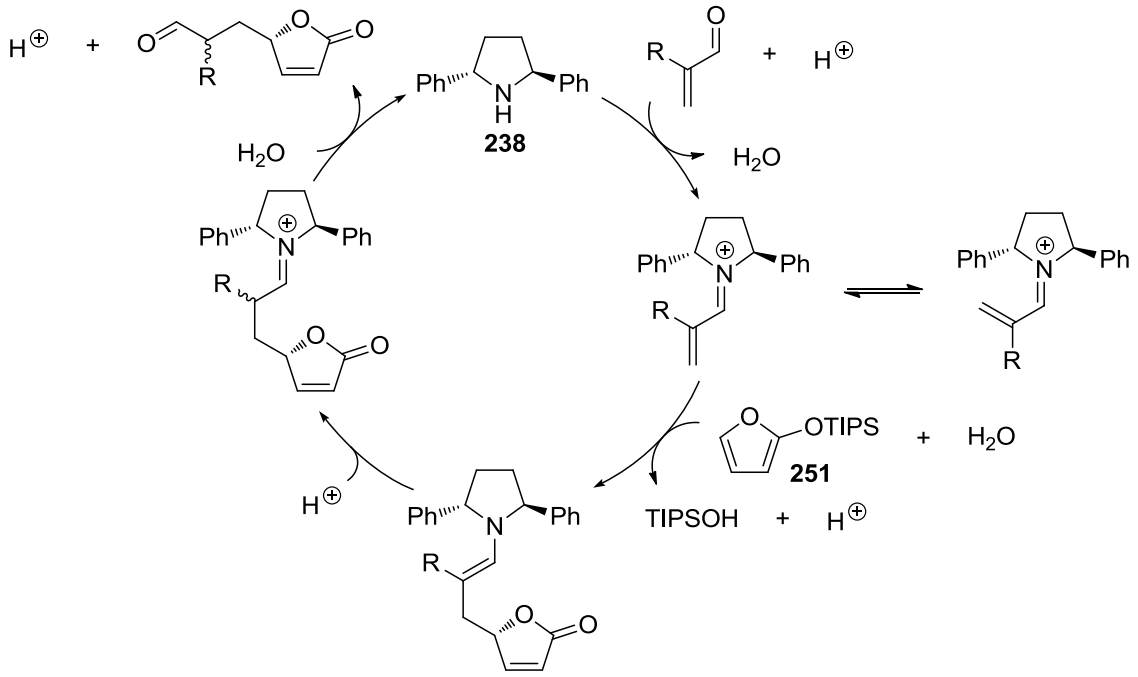
Based on the results detailed above, we concluded that α-substituted acroleins used in the reaction should be small and not too lipophilic. A clearly visible trend among the used substrates was that with the more hydrophilic substrates the reaction is faster (Mukaiyama–Michael reactions with acrolein and

α-oxyacetyl acrolein (**279**) were much faster, whereas the reactions with α-*n*-propyl- (**284**) and α-benzyl acroleins (**282**) were slow). One reason why bulkier and more lipophilic substrates react more slowly in the Mukaiyama–Michael reaction could be simple steric hindrance caused by the heavier side chain. There is some evidence for this from computational studies, where bulkier side chains caused the normally planar conjugated iminium system to bend out of plane, reducing the electrophilicity of the γ-carbon and thus the reactivity of the substrate.

Another explanation is that if the reaction turnover is determined by the hydrolysis of the intermediate enamines or the iminium ions, the lipophilicity of the intermediates could also affect the reaction rate. This theory is supported by the work of Jørgensen and co-workers. Using the same diphenylpyrrolidine catalyst **238** in an α-chlorination reaction, the authors gave evidence for product hydrolysis being the rate determining step. As evidence for this claim it was observed that the reaction proceeded faster when water was used as an additive. [110] However, these studies were not pursued further.

4.3 Rationalisation of the Stereochemistry

The mechanism of the catalytic cycle likely proceeds as depicted below (**Scheme 52**). The cycle begins when the C2-symmetrical secondary amine catalyst forms an iminium intermediate from the aldehyde component. The silyloxyfuran nucleophile then attacks the methylene carbon of the iminium complex to generate the new C–C bond. The resulting enamine intermediate is then protonated. Finally, the iminium is hydrolysed to release the product and the catalytic cycle repeats.



Scheme 52. Proposed catalytic cycle for the iminium catalysed Mukaiyama–Michael reaction of α-substituted acroleins.

However, a thorough understanding of how the new stereocentre is formed in the diphenylpyrrolidine-catalysed reaction in an enantioselective manner is still lacking. The stereogenic carbon centre generated in the C–C formation step is relatively far away from the catalyst and its phenyl groups, but despite that the reaction is highly enantioselective. Simply evoking steric hindrance as the explanation is very likely too simplistic, as can be seen from the iminium structures (**Figure 17**).

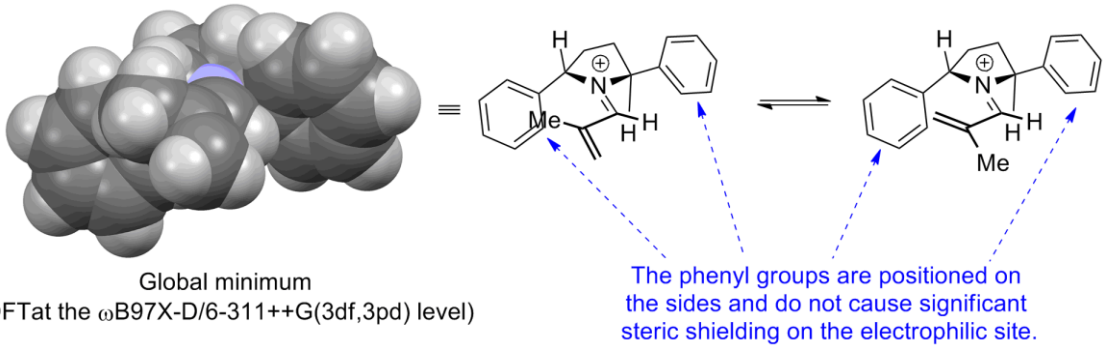


Figure 17. Possible structures of the catalyst-methacrolein iminium intermediates. Pyrrolidine ring of the formed iminium structure can have two different conformations: envelope and half-chair/twisted forms (only the envelope conformation is showed here). Additionally the methacrolein moiety can rotate; either methyl or methylene can point towards the phenyl group of the catalyst.

Dr. Imre Papai and his co-workers have computationally analysed the transition state of the C–C-bond formation step. Their results suggest that attractive dispersion interactions between a phenyl group of the catalyst and the silyl group of the silyloxyfuran have a significant role in the bond formation process (**Figure 18**), and a C–H—π interaction between the C3 proton of the furan ring and the other phenyl group is another major factor behind the enantioselectivity. In the transition state, the pyrrolidine ring of the catalyst can settle in either an envelope or a twisted envelope conformation. The attack of the nucleophilic silyloxyfuran can take place from either of the sides of the catalyst-iminium-complex and still lead to the same product enantiomer, since the deciding factor for the formed stereogenicity is the orientation of the furan moiety. The furan preferably settles into a *si* orientation next to the iminium ion, with the 3H proton pointing towards the phenyl ring of the catalyst, as can be seen from both of the lowest energy transition state models (upper part of the **Figure 18**). The silyl group of the silyloxyfuran can freely rotate as its rotational barrier is very low, and it adapts flexibly to a "pocket" formed between the phenyl groups of the catalyst.

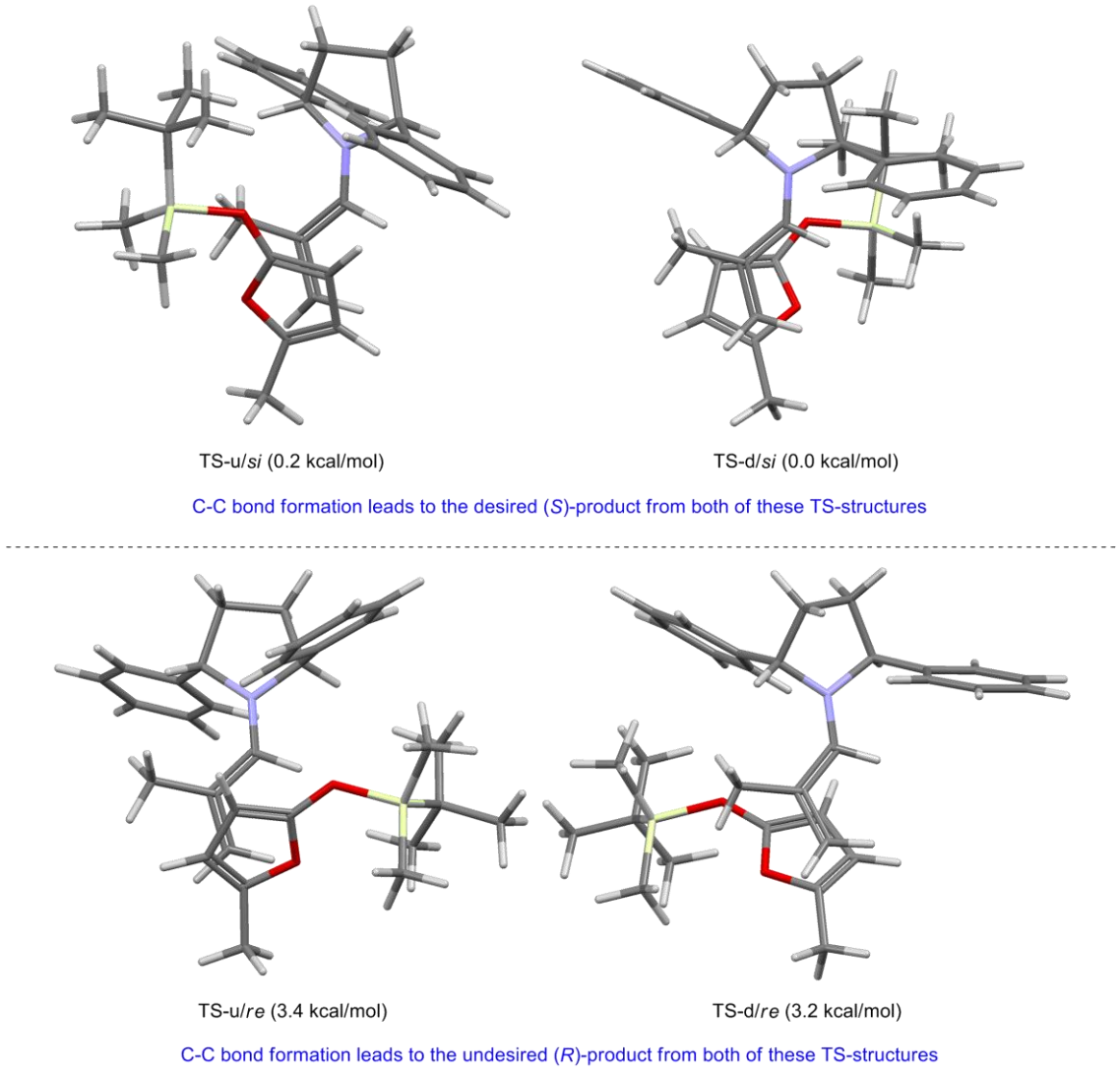


Figure 18. Transition states (TS) of the nucleophile attack. There are attractive interactions between one of the catalyst's phenyl π-systems and the silyl group in all the transition states, and in the two low-energy transition states an additional π–H interaction can be seen between the other phenyl group of the catalyst and the 3H of the furan ring. The labels "u" (up) and "d" (down) indicate the direction of the furan attack, and "*si*" and "*re*" refer to the two faces of the attacking furan molecules. The relative energy differences have been calculated as solvent-phase Gibbs free energies at the B97X-D/6-311G(d,p) level by using the integral equation formalism variant of the polarisable continuum model (IEFPCM). Details of this analysis will be published separately.

4.4 Attempts at Further Expanding the Nucleophile Scope

Other nucleophilic substrates, (**Figure 19**) such as silyl protected amide **292** and silyloxydihydrofuran **291**, were briefly tested in our reaction conditions, but without notable success. The principal difficulty with these substrates was their much higher lability towards hydrolytic cleavage compared to the

silyloxyfurans, resulting in fast degradation of the starting material instead of the desired Mukaiyama–Michael reaction.

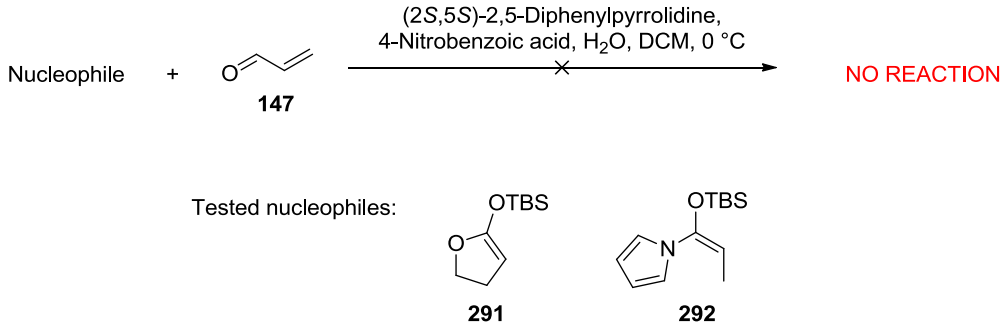
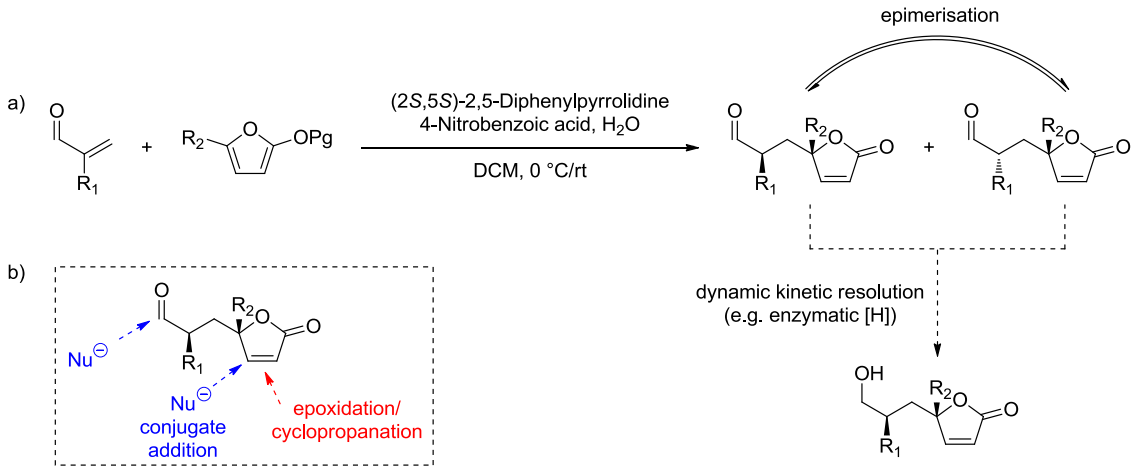


Figure 19. Nucleophiles which were studied in the Mukaiyama–Michael reaction with acrolein (**147**).

4.5 Future of the Reaction

Does this reaction methodology have any future? Is it possible to apply it somewhere? Many questions are still open, but perhaps the largest issue with the methodology is the lack of control over the diastereomeric ratio of the products (**Scheme 53**a). While the epimerisation procedure is an option when the diastereomers are separable, it requires column chromatography and is challenging to scale up. A better alternative, which would also work for inseparable diastereomers, could be a dynamic kinetic resolution method to drive the equilibrium in the desired direction. As the product diastereomers rapidly epimerize under the reaction conditions, achieving the resolution requires that the epimerization is stopped by further derivatization of the aldehyde group. As an example, subjecting the product mixture to e.g. enzymatic reduction conditions could be a viable option for dynamic kinetic resolution.



Scheme 53. a) The organocatalytic Mukaiyama–Michael reaction and the epimerisable product diastereomers, and the possibility for the dynamic kinetic resolution of the products. b) Some possible subsequent reactions for the Mukaiyama–Michael products.

More applications for this method would be required to show its full potential (**Scheme 53**b). This methodology could offer a novel practical approach for synthesising precursors for various natural products. Perhaps the biggest factor limiting the wider use of this method is the poor availability of the catalyst, as the catalyst is very expensive and also laborious to prepare. On the other hand, the catalyst is a bench-stable, crystalline compound and it should not suffer from hydrolytic degradation that sometimes haunts the MacMillan and Jorgensen catalysts.[111] To overcome this barrier, some effort to improve the synthesis of the catalyst might be worthwhile.

More detailed studies of the reaction could reveal new information about the reaction mechanism, which might in turn lead to improvements in yields and diastereoselectivities. The substrate scope of the reaction could likely be expanded further. While the few nucleophiles tested were shown not to work (see chapter 4.4), later experiments in the group using heavily substituted silyl enol thioethers showed some promise.

5 CONCLUSIONS

In this thesis, I have presented a short review on the pectenotoxin family of natural products and highlighted the different synthetical approaches to the pectenotoxin fragments incorporating the F-ring moiety from various research groups. Additionally, I have described our current strategy and the background for the key Mukaiyama–Michael reaction used in my experimental studies. The methodology was applied in the project aiming towards the total synthesis of the pectenotoxin, and the substrate scope of the methodology was expanded to include a variety of α-substituted acroleins.

The C17–C28 fragment of PTX2 was synthesised in 15 steps in 3.3% overall yield, using our own organocatalytic Mukaiyama–Michael reaction, Johnson-Claisen rearrangement, Sharpless asymmetric dihydroxylation and finally the THF-ring closure reaction by the method of Wu and Sun as the key steps. The synthetised C17-C28 fragment contains 3 stereocentres, and it can be conveniently coupled with the C-ring (or even the ABC) fragment to access the whole (AB)CDEF- system in a few extra steps.

The organocatalytic Mukaiyama–Michael reaction was developed as a side product of the total synthesis project. It became an important part of my Ph.D. work, enabling me to include reaction methodology development in my studies. Expansion to the α-substrate scope showed that the reaction could be more

broadly applicable in the future as a potential method for the preparation of natural product precursors.

To address the question of how the C2-symmetrical 2,5-diphenylpyrrolidine catalyst functions in the Mukaiyama–Michael reaction and controls the enantioselective addition of the silyloxyfuran nucleophile, both experimental and molecular modeling approaches have been used. Further studies will be required to obtain a detailed picture of the stereocontrol elements and the rate-controlling steps of the reaction and the participant molecules. Nevertheless, the methodology developed herein is noteworthy in that it allows the control of a remote γ stereocentre with enals that do not possess a β substituent, thus allowing access to scaffolds that are perhaps more natural product-like than with the original MacMillan methodology.

6 EXPERIMENTAL SECTION

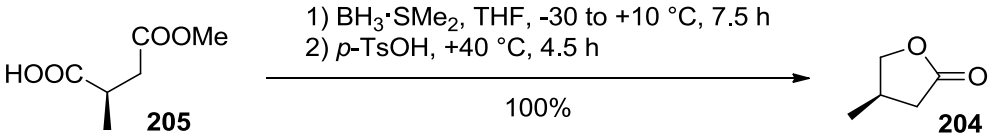
6.1 General Experimental

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. When needed, nonaqueous reagents were transferred under argon *via* syringe or cannula and dried prior to use. THF, Et_2O, DCM (CH_2Cl_2), ACN and toluene were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system). MeOH was distilled from magnesium oxide, DMF and Et_3N were distilled over CaH, and allylamine and MsCl were fractionally distilled prior to their use. TBSOTf and TIPSOTf were prepared according to Corey's procedure.[112] Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analysed by UV light or by staining upon heating with anisaldehyde solution [anisaldehyde (2.8 mL), H_2SO_4 (2 mL), acetic acid (1.2 mL), EtOH (100 mL)], vanillin solution [vanillin (6 g), H_2SO_4 (5 mL), acetic acid (3 mL), EtOH (250 mL)] or $KMnO_4$ solution [$KMnO_4$ (1 g), K_2CO_3 (6.7 g), NaOH solution (1M aq., 1.7 mL), water (100 mL)]. For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted. Additionally, CombiFlash purification system was used for some purifications.

The ^{1}H, ^{13}C, COSY, NOE and NOESY NMR spectra were recorded in $CDCl_3$, CD_3CN or CD_3OD on NMR spectrometers operating at 500 (^{1}H 500.13 MHz; ^{13}C 125.76 MHz), 400 (^{1}H 400.13 MHz; ^{13}C 100.62 MHz) or 250 (^{1}H 250.13 MHz; ^{13}C 62.90 MHz). For ^{1}H NMR, the chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.26), CHD_2CN (δ 1.94) or CHD_2OD (δ 3.31) and for the ^{13}C NMR spectra, $CDCl_3$ (δ 77.16), CD_3CN (δ 118.26) or CD_3OD (δ 49.00). The enantiomeric excess (*ee*), enantiomeric ratios (*er*) and diastereomeric ratios (*dr*) of the products were determined either by GC in comparison to the corresponding racemic samples using a SUPELCO Astec CHIRALDEX B-DM Column (ø 0.25 mm × 30 m), by HPLC using UV detection monitored at appropriate wavelength (254 or 214 nm) using CHIRALPAK IB (ø 0.46 cm × 25 cm) or CHIRALPAK IC column (ø 0.46 cm × 25 cm) columns with precolumns at ambient temperature, or by NMR analysis. Melting points (mp) were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor27 FT-IR spectrometer. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter. High resolution mass spectrometric data were measured using MicroMass LCT Premier Spectrometer.

6.2 Macrocycle Approach

6.2.1 (*R*)-4-Methyldihydrofuran-2(3*H*)-one (204)



To a solution of **205** (18.9 g, 16.4 mL, 129 mmol, 10 mol-%) in THF (100 mL) at –30 °C was slowly added BH_3•SMe_2 (10.9 g, 13.6 mL, 143 mmol, 110 mmol-%). The reaction mixture was allowed to warm while it was monitored by NMR. After 6 hours of first addition another batch of BH_3•SMe_2 (16.1 g, 201.1 mL, 210 mmol, 160 mol-%) was added and stirring was continued at +10 °C for 1.5 hours. The reaction was quenched by addition of MeOH (80 mL) and the

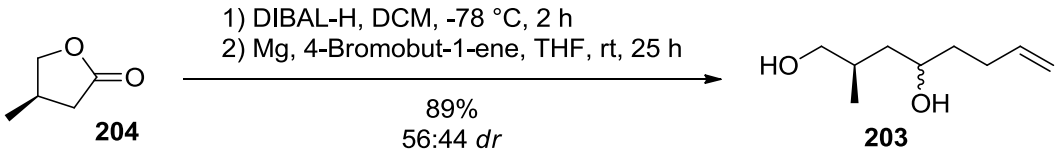
mixture was concentrated under reduced pressure. The MeOH addition–concentration cycle was repeated twice to afford the crude alcohol as a clear oil. This crude material was used in the next step without further purification. The spectroscopic data match those reported in the literature.[81]

R_f (EtOAc/hexanes 2:1) = 0.41; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.57 (ddd, 1H, *J* = 10.8, 5.2, 0.8 Hz), 3.45 (ddd, 1H, *J* = 10.8, 6.6, 0.7 Hz), 2.45 (dd, 1H, *J* = 15.0, 6.4 Hz), 2.26–2.04 (m, 1H), 2.23 (dd, 1H, *J* = 15.0, 6.8 Hz), 1.69 (br. s, 1H), 0.96 (d, 3H, *J* = 6.6 Hz).

A mixture of the crude alcohol (17.1 g, 129 mmol, 100 mol-%) and *p*-TsOH•H_2O (39.6 mg, 0.21 mmol, 0.2 mol-%) was mixed in a rotary evaporator (bath +40 °C) under reduced pressure for 4.5 hours to distill off the forming MeOH, and then fractionally distilled *in vacuo* (94–99 °C/11 torr) to afford the lactone product **204** as a clear oil (13.0 g, 130 mmol, 100%). The spectroscopic data match those reported in the literature.[81]

R_f (EtOAc/hexanes 1:2) = 0.43; $[\alpha]_D$ = +24.2 (*c* 2.0, $CHCl_3$) (lit. $[\alpha]_D$ = -24.8 (*c* 4.35, MeOH)) for (*S*)-enantiomer); IR (film, cm^{-1}): 2969, 2934, 2910, 2880, 1769, 1170, 1016, 995; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.39 (dd, 1H, *J* = 8.9, 7.2 Hz), 3.85 (dd, 1H, *J* = 8.9, 6.5 Hz), 2.69–2.58 (m, 1H), 2.61 (dd, 1H, *J* = 16.5, 8.2 Hz), 2.12 (dd, 1H, *J* = 16.5, 9.6 Hz), 1.14 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3, 74.8, 36.2, 30.5, 18.0; HRMS (ESI$^+$): m/z calcd for [$C_5H_8O_2Na$] 123.0416, found 123.0418, Δ = 1.2 ppm.

6.2.2 (2*R*,4*R*)-2-Methyloct-7-ene-1,4-diol and (2*R*,4*S*)-2-methyloct-7-ene-1,4-diol (203)



To a stirred solution of **204** (481 mg, 0.5 mL, 4.8 mmol, 100 mol-%) in DCM (10 mL) at –78 °C was slowly added DIBAL-H solution (1M in DCM, 7.2 mL,

7.2 mmol, 150 mol-%). The reaction mixture was stirred at –78 °C for 2 hours. The reaction was then quenched by addition of Rochelle's salt solution (sat. aq., 20 mL) and the mixture was allowed to warm to rt. The layers were separated and the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude **208** as a clear oil. This crude material was used in the next step without further purification.

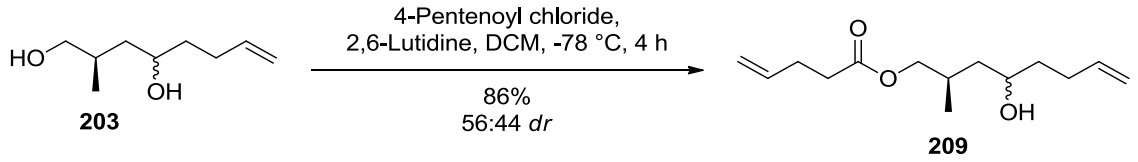
R_f (EtOAc/hexanes 2:1) = 0.51; ^{1}H NMR (250 MHz, $CDCl_3$, major): δ 5.51 (app. br. d, 1H, *J* = 5.0 Hz), 4.15 (t, 1H, *J* = 7.7 Hz), 3.37 (t, 1H, *J* = 7.7 Hz), 2.86 (br. s, 1H), 2.65–2.45 (m, 1H), 2.03 (ddd, 1H, *J* = 12.9, 7.2, 0.6 Hz), 1.57 (ddd, 1H, *J* = 12.9, 9.0, 5.0 Hz), 1.04 (d, 3H, *J* = 6.7); ^{1}H NMR (250 MHz, $CDCl_3$, minor): δ 5.51 (app. br. d, 1H, *J* = 5.0 Hz), 3.94 (t, 1H, *J* = 8.0), 3.56 (t, 1H, *J* = 8.0), 2.99 (br. s, 1H), 2.42–2.18 (m, 1H), 1.85–1.64 (m, 1H), 1.55–1.35 (m, 1H), 1.10 (d, 3H, *J* = 6.4).

To a stirred suspension of Mg powder (350 mg, 14.4 mmol, 300 mol-%) in THF (10 mL) at rt was added 4-bromo-1-butene (1.94 g, 1.46 mL, 14.4 mmol, 300 mol-%). Heat was evolved and the formation of the Grignard reagent was evident from the darkening of the reaction mixture. After stirring for 45 minutes, the crude lactol **208** (490 mg, 4.8 mmol, 100 mol-%) in THF (4 mL) was added and stirring was continued at rt for 24 hours. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 40 mL) and diluted with EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the product **203** as a mixture of diastereomers as a clear oil (673 mg, 4.25 mmol, 89%, 56:44 *dr*).

R_f (EtOAc/hexanes 1:2) = 0.36; IR (film, cm^{-1}): 3317, 3078, 2928, 2873, 1641, 1452, 1378, 1038, 996, 911; ^{1}H NMR (500 MHz, $CDCl_3$, one diastereomer): δ 5.83 (ddt, 1H, *J* = 17.1, 10.2, 6.7 Hz), 5.03 (ddt, 1H, *J* = 17.1, 1.9, 1.6 Hz), 4.96 (ddt, 1H, *J* = 10.2, 1.9, 1.0 Hz), 3.78 (tt, 1H, *J* = 7.0, 5.2 Hz), 3.53 (dd, 1H, *J* = 10.6, 4.6 Hz),

3.46 (dd, 1H, *J* = 10.6, 6.9 Hz), 3.15 (br. s, 1H), 3.12 (br. s, 1H), 2.23–2.06 (m, 2H), 1.96–1.86 (m, 1H), 1.61–1.47 (m, 4H), 0.92 (d, 3H *J* = 7.0 Hz); ^{1}H NMR (500 MHz, $CDCl_3$, other diastereomer): δ 5.83 (ddt, 1H, *J* = 17.1, 10.2, 6.7 Hz), 5.03 (ddt, 1H, *J* = 17.1, 1.9, 1.6 Hz), 4.96 (ddt, 1H, *J* = 10.2, 1.9, 1.0 Hz), 3.69 (dddd, 1H, *J* = 9.4, 7.1, 4.9, 2.6 Hz), 3.55 (dd, 1H, *J* = 10.6, 4.5 Hz), 3.35 (dd, 1H, *J* = 10.6, 7.9 Hz), 3.15 (br. s, 1H), 3.12 (br. s, 1H), 2.23–2.06 (m, 2H), 1.96–1.76 (m, 1H), 1.61–1.47 (m, 3H), 1.47–1.37 (m, 3H), 0.89 (d, 3H *J* = 6.9 Hz); ; ^{13}C NMR (125 MHz, $CDCl_3$, one diastereomer): δ 138.7, 114.9, 70.6, 68.87, 43.2, 37.7, 34.6, 30.2, 18.1; ^{13}C NMR (125 MHz, $CDCl_3$, other diastereomer): δ 138.6, 114.9, 68.91, 68.0, 42.1, 36.7, 32.3, 30.3, 17.6; HRMS (ESI$^+$): m/z calcd for [$C_9H_{18}O_2Na$] 181.1204, found 181.1200, Δ = 2.2 ppm.

6.2.3 (2*R*,4*R*)-4-Hydroxy-2-methyloct-7-en-1-yl pent-4-enoate ((*R*,*R*)-209) and (2*R*,4*S*)-4-hydroxy-2-methyloct-7-en-1-yl pent-4-enoate ((*R*,*S*)-209)

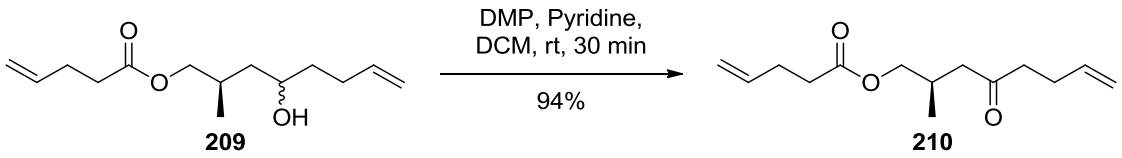


To a stirred solution of **203** (673 mg, 4.3 mmol, 100 mol-%) in DCM (20 mL) at –78 °C was added 2,6-lutidine (911 mg, 0.99 mL, 8.5 mmol, 200 mol-%) and 4-pentenoyl chloride (555 mg, 0.52 mL, 4.7 mmol, 110 mol-%). The reaction mixture was stirred at –78 °C for 4 hours. The reaction was then quenched by addition of water (20 mL) and the mixture was allowed to warm to rt. The layers were separated and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:3) to afford the product **209** as a mixture of diastereomers as a slightly yellow oil (878 mg, 3.7 mmol, 86%, 56:44 *dr*).

R_f (EtOAc/hexanes 1:2) = 0.62; IR (film, cm^{-1}): 3439, 3079, 2961, 2931, 1734, 1641, 1264, 1174, 992, 912; ^{1}H NMR (500 MHz, $CDCl_3$, both diastereomers): δ 5.89–5.77 (m, 2H), 5.06 (ddt, 1H, *J* = 17.1, 1.58, 1.56 Hz), 5.05 (ddt, 1H, *J* = 17.1, 1.65,

1.57 Hz), 5.00 (ddt, 1H, *J* = 10.2, 2.8, 1.1 Hz), 4.97 (ddt, 1H, *J* = 10.2, 3.2, 1.3 Hz), 4.03 (dd, ½ × 1H, *J* = 10.8, 5.5 Hz), 3.97 (dd, ½ × 1H, *J* = 10.7, 6.1 Hz), 3.93 (dd, ½ × 1H, *J* = 10.7, 6.4 Hz), 3.91 (dd, ½ × 1H, *J* = 10.8, 6.4 Hz), 3.77–3.69 (m, 1H), 2.45–2.34 (m, 4H), 2.26–2.09 (m, 2H), 2.09–1.88 (m, 1H), 1.60–1.52 (m, 3H), 1.52–1.49 (m, ½ × 1H), 1.47 (ddd, ½ × 1H, *J* = 14.3, 7.5, 4.5 Hz), 1.37 (ddd, ½ × 1H, *J* = 14.3, 8.5, 5.8 Hz), 1.25 (ddd, ½ × 1H, *J* = 14.0, 9.3, 3.2 Hz), 0.98 (d, ½ × 3H, *J* = 6.8 Hz), 0.96 (d, ½ × 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, one diastereomer): δ 173.29, 138.6, 136.8, 115.7, 115.0, 69.3, 69.0, 41.6, 37.0, 33.76, 30.1, 29.67, 29.02, 18.1; ^{13}C NMR (125 MHz, $CDCl_3$, other diastereomer): δ 173.27, 138.5, 136.9, 115.6, 115.0, 69.8, 69.2, 41.4, 37.5, 33.75, 30.2, 29.74, 29.03, 16.8; HRMS (ESI$^+$): m/z calcd for [$C_{14}H_{24}O_3Na$] 263.1623, found 263.1625, Δ = 0.8 ppm.

6.2.4 (*R*)-2-Methyl-4-oxooct-7-en-1-yl pent-4-enoate (210)



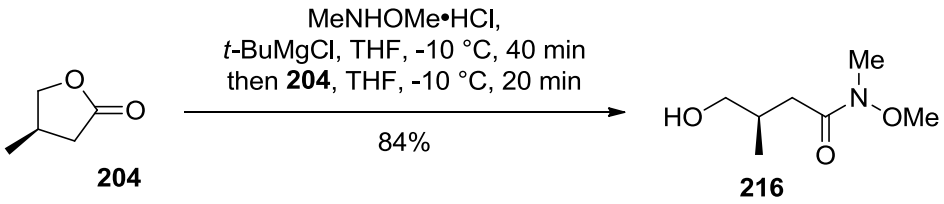
To a stirred solution of Dess-Martin periodinane (929 mg, 2.19 mmol, 170 mol-%) and pyridine (100 mg, 0.10 mL, 1.26 mmol, 100 mol-%) in DCM (40 mL) at rt was added the ester **209** (304 mg, 1.26 mmol, 100 mol-%) in DCM (5 mL) *via* cannula. Wet DCM (10 mL) was added to the reaction mixture *via* dropping funnel over 10 minutes, at which point the reaction mixture turned from clear to opaque white. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexanes 1:4) to afford the product **210** as a clear oil (283 mg, 1.19 mmol, 94%).

R_f (EtOAc/hexanes 1:2) = 0.83; $[\alpha]_D$ = +2.1 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 3079, 2964, 2923, 1733, 1713, 1642, 1415, 1374, 1245, 1168, 994, 912; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85–5.72 (m, 2H), 5.07–4.93 (m, 4H), 3.95 (dd, 1H, *J* = 10.8, 5.7 Hz), 3.87 (dd, 1H, *J* = 10.8, 6.4 Hz), 2.52–2.44 (m, 3H), 2.44–2.21 (m, 8H), 0.92 (d, 3H,

J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.7, 173.0, 137.1, 136.7, 115.6, 115.4, 68.5, 46.6, 42.4, 33.6, 28.9, 28.8, 27.8, 17.0; HRMS (ESI$^+$): m/z calcd for [$C_{14}H_{22}O_3Na$] 261.1467, found 261.1474, Δ = 2.7 ppm.

6.3 Generation of the F-ring *via* a Pd(II)-Catalysed Ring Closure

6.3.1 (*R*)-4-Hydroxy-*N*-methoxy-*N*,3-dimethylbutanamide (216)

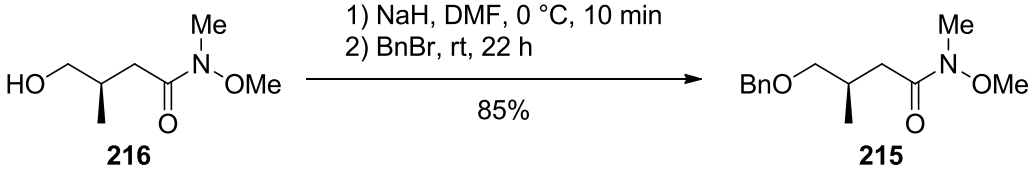


To a suspension of *N*,*O*-dimethyl hydroxylamine hydrochloride (7.1 g, 73 mmol, 280 mol-%) in THF (340 mL) at –10 °C was slowly (over 30 min) added *t*-BuMgCl solution (2M in Et_2O, 67.5 mL, 135 mmol, 520 mol-%). The reaction mixture was then stirred at –10 °C for 10 minutes and lactone **204** (2.6 g, 2.5 mL, 26 mmol, 100 mol-%) was added. The stirring was continued at –10 °C for 20 minutes. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 200 mL) and diluted with EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (7 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH/DCM 0:1 to 1:19) to afford the product **216** as a clear oil (3.5 g, 22 mmol, 84%).

R_f (EtOAc/hexanes 2:1) = 0.11; $[\alpha]_D$ = +1.3 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 3426, 2960, 2937, 2874, 1640, 1462, 1419, 1387, 1180, 1044, 1003, 951; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.66 (s, 3H), 3.39 (dt, 1H, *J* = 10.6, 5.6 Hz), 3.34 (ddd, 1H, *J* = 10.6, 6.3, 5.6 Hz), 3.11 (s, 3H), 2.85 (t, 1H, *J* = 5.6 Hz), 2.48 (dd, 1H, *J* = 15.6, 6.2 Hz), 2.26 (dd, 1H, *J* = 15.6, 7.4 Hz), 2.11–1.99 (m, 1H), 0.91 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8, 67.8, 61.9, 36.5, 33.6, 32.7, 17.4;

HRMS (ESI$^+$): m/z calcd for [$C_7H_{15}O_3NNa$] 184.0944, found 184.0946, Δ = 1.0 ppm.

6.3.2 (*R*)-4-(Benzyloxy)-*N*-methoxy-*N*,3-dimethylbutanamide (215)



216 **215**

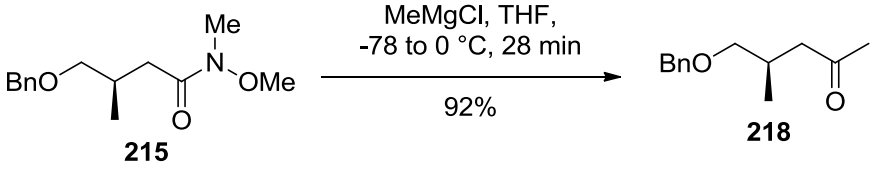
To a stirred solution of Weinreb amide **216** (3.24 g, 20 mmol, 100 mol-%) in DMF (40 mL) at 0 °C was added NaH (55-65% dispersion in mineral oil, 0.94 g, 24 mmol, 120 mol-%).[i] The reaction mixture was stirred at 0 °C for 10 minutes (strong gas evolution was observed immediately after the addition, which then quickly subsided). To the mixture was then added Benzyl bromide (3.80 g, 2.6 mL, 22 mmol, 110 mol-%), the ice bath was removed and the reaction mixture was stirred at rt for 22 hours. The reaction was quenched by addition of brine (aq., 200 mL) and diluted with EtOAc (150 mL). The layers were separated and the organic layer was washed with brine (5 × 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:1) to afford the product **215** as a slightly yellow oil (4.28 g, 17 mmol, 85%).

R_f (EtOAc/hexanes 2:1) = 0.61; $[\alpha]_D$ = +11.5 (*c* 2.55, $CHCl_3$); IR (film, cm^{-1}): 2961, 2935, 2858, 1660, 1454, 1414, 1384, 1098, 1004, 738, 699; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.31 (m, 4H), 7.30–7.25 (m, 1H), 4.50 (dd^{AB}, 2H, $|J_{AB}|$ = 12.1 Hz, $\Delta\nu$ = 6.9 Hz), 3.66 (s, 3H), 3.39 (ddd^{ABX}, 2H, $|J_{AB}|$ = 9.3 Hz, $|J_{AX}|$ = 5.7 Hz, $|J_{BX}|$ = 6.5 Hz, $\Delta\nu_{AB+}$ = 14.0 Hz, $\Delta\nu_{AB-}$ = 13.2 Hz), 3.17 (s, 3H), 2.61 (dd, 1H,

[i] When 250 mol-% of NaH was used, formation of the side product **209** ((*R*)-4-(benzyloxy)-*N*,3-dimethylbutanamide) was observed (**Table 8** on page 65). R_f (EtOAc/hexanes)= 0.19; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.24 (m, 5H), 5.64 (br. s, 1H), 4.49 (s, 2H), 3.40 (dd, 1H, *J* = 9.2, 5.0 Hz), 3.31 (dd, 1H, *J* = 9.2, 6.2 Hz), 2.72 (d, 3H, *J* = 4.8 Hz), 2.39–2.19 (m, 2H), 2.12–1.18 (m, 1H), 0.99 (d, 3H, *J* = 6.7 Hz); LRMS (ESI$^-$): m/z calcd for [$C_{13}H_{18}NO_2$] 220.1 found 220.1.

J = 15.4, 5.8 Hz), 2.46–2.36 (m, 1H), 2.28 (dd, 1H, *J* = 15.4, 7.8 Hz), 1.01 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 138.8, 128.4, 127.6, 127.5, 75.2, 73.0, 61.2, 35.9, 32.3, 30.4, 17.4; HRMS (ESI$^+$): m/z calcd for [$C_{14}H_{21}O_3NNa$] 274.1413, found 274.1415, Δ = 0.5 ppm.

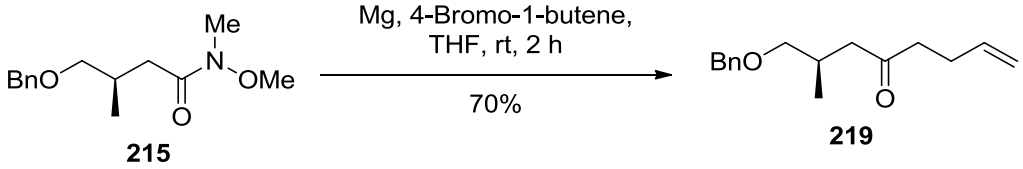
6.3.3 (*R*)-5-(Benzyloxy)-4-methylpentan-2-one (218)



To a stirred suspension of benzyl protected Weinreb amide **215** (4.08 g, 16 mmol, 100 mol-%) in THF (40 mL) at –78 °C was slowly added MeMgCl solution (3M in THF, 27 mL, 81 mmol, 500 mol-%). After 8 minutes of stirring at –78 °C the reaction was allowed to warm to 0 °C while stirring for 20 minutes. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 200 mL) and diluted with EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:4) to afford the desired product **218** as a clear oil (3.08 g, 15 mmol, 92%).

R_f (EtOAc/hexanes 1:2) = 0.74; $[\alpha]_D$ = +3.8 (*c* 1.85, $CHCl_3$); IR (film, cm^{-1}): 2959, 2931, 2857, 1712, 1454, 1361, 1171, 1095, 1028, 737, 698; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 4.48 (s, 2H), 3.36 (dd, 1H, *J* = 9.2, 5.4 Hz), 3.25 (dd, 1H, *J* = 9.2, 7.0 Hz), 3.36 (dd, 1H, *J* = 15.9, 5.6 Hz), 2.42–2.30 (m, 1H), 2.25 (dd, 1H, *J* = 15.9, 7.6 Hz), 2.12 (s, 3H), 0.94 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.6, 138.5, 128.4, 127.6, 127.5, 75.0, 73.0, 48.0, 30.4, 29.9, 17.1; HRMS (ESI$^+$): m/z calcd for [$C_{13}H_{18}O_2Na$] 229.1204, found 229.1200, Δ = 1.7 ppm.

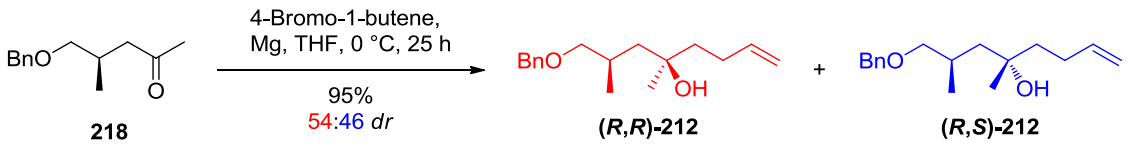
6.3.4 (*R*)-1-(Benzyloxy)-2-methyloct-7-en-4-one (219)



To a stirred suspension of Mg powder (656 mg, 27 mmol, 600 mol-%) in THF (100 mL) at rt was added 4-bromo-1-butene (3.65 g, 2.7 mL, 27 mmol, 600 mol-%). Heat was evolved and the formation of the Grignard reagent was evident from the darkening of the reaction mixture. After stirring for 1 hour, (*R*)-5-(Benzyloxy)-4-methylpentan-2-one (**215**) (1.11 g, 4.4 mmol, 100 mol-%) in THF (25 mL) was added and stirring was continued at rt for 1 hour. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 80 mL) and diluted with DCM (100 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:4) to afford the product **219** as a clear oil (756 mg, 3.1 mmol, 70%).

R_f (Et_2O/hexanes 1:2) = 0.34; ^1H NMR (250 MHz, $CDCl_3$): δ 7.39–7.23 (m, 5H), 5.89 (ddt, 1H, *J* = 17.0, 10.3, 6.5 Hz), 5.06–4.92 (m, 2H), 4.47 (s, 2H), 3.36 (dd, 1H, *J* = 9.2, 5.3 Hz), 3.25 (dd, 1H, *J* = 9.2, 6.8 Hz), 2.59 (dd, 1H, *J* = 15.7, 5.5 Hz), 2.53–2.16 (m, 6H), 0.94 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 209.9, 138.6, 137.4, 128.5, 127.70, 127.66, 115.2, 75.1, 73.1, 47.2, 42.4, 30.0, 27.9, 17.3.

6.3.5 (2*R*,4*R*)-1-(Benzyloxy)-2,4-dimethyloct-7-en-4-ol ((*R*,*R*)-212) and (2*R*,4*S*)-1-(benzyloxy)-2,4-dimethyloct-7-en-4-ol ((*R*,*S*)-212)



To a stirred suspension of Mg powder (350 mg, 14.4 mmol, 300 mol-%) in THF (10 mL) at rt was added 4-bromo-1-butene (1.94 g, 1.46 mL, 14.4 mmol,

300 mol-%). Heat was evolved and the formation of the Grignard reagent was evident from the darkening of the reaction mixture. After 40 minutes, **218** (990 mg, 1 mL, 4.8 mmol, 100 mol-%) was added and stirring was continued at rt for 24 hours. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 40 mL) and diluted with EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Et_2O/hexanes 1:2) to afford the product **212** as a mixture of diastereomers as a clear oil (1.19 g, 4.5 mmol, 95%, 56:44 *dr*).

(2*R*,4*R*)-1-(Benzyloxy)-2,4-dimethyloct-7-en-4-ol ((*R*,*R*)-212): R_f (Et_2O/hexanes 1:2) = 0.34; $[\alpha]_D$ = +16.6 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 3445, 2958, 2926, 2854, 1455, 1373, 1090, 1077, 909, 736, 698; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5H), 5.84 (ddt, 1H, *J* = 17.0, 10.2, 6.6 Hz), 5.02 (ddt, 1H, *J* = 17.0, 1.8, 1.6 Hz), 4.94 (ddt, 1H, *J* = 10.2, 2.0, 1.2 Hz), 4.53 (dd^{AB}, 2H, $|J_{AB}|$ = 12.0 Hz, Δν = 6.4 Hz), 3.43 (s, 1H), 3.40 (dd, 1H, *J* = 8.9, 4.4 Hz), 3.27 (t, 1H, *J* = 8.9 Hz), 2.18–2.00 (m, 3H), 1.63 (ddd, 1H, *J* = 13.5, 11.4, 5.2 Hz), 1.58 (dd, 1H, *J* = 14.7, 7.5 Hz), 1.56 (ddd, 1H, *J* = 13.5, 11.4, 5.4 Hz), 1.51 (dd, 1H, *J* = 14.7, 4.1 Hz), 1.17 (s, 3H), 0.94 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.3, 137.8, 128.6, 127.9, 127.8, 114.2, 77.3, 73.4, 71.8, 48.4, 40.8, 29.4, 28.9, 28.1, 19.7; HRMS (ESI^+): m/z calcd for $[C_{17}H_{26}O_2Na]$ 285.1831, found 285.1828, Δ = 1.1 ppm.

(2*R*,4*S*)-1-(Benzyloxy)-2,4-dimethyloct-7-en-4-ol ((*R*,*S*)-212): R_f (Et_2O/hexanes 1:2) = 0.28; $[\alpha]_D$ = +12.7 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 3435, 2966, 2927, 2856, 1454, 1373, 1091, 1076, 909, 736, 698; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5H), 5.85 (ddt, 1H, *J* = 17.1, 10.3, 6.6 Hz), 5.02 (ddt, 1H, *J* = 17.1, 1.8, 1.7 Hz), 4.93 (ddt, 1H, *J* = 10.3, 2.1, 1.2 Hz), 4.53 (dd^{AB}, 2H, $|J_{AB}|$ = 12.0 Hz, Δν = 9.3 Hz), 3.50 (s, 1H), 3.42 (dd, 1H, *J* = 8.9, 4.4 Hz), 3.25 (t, 1H, *J* = 8.9 Hz), 2.18–2.05 (m, 3H), 1.59 (dd, 1H, *J* = 14.5, 7.7 Hz), 1.56–1.51 (m, 2H), 1.43 (dd, 1H, *J* = 14.5, 3.6 Hz), 1.18 (s, 3H), 0.94 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 137.9,

128.6, 127.89, 127.85, 114.1, 77.3, 73.4, 71.5, 48.1, 43.3, 29.4, 28.5, 26.6, 19.9; HRMS (ESI^+): m/z calcd for [$C_{17}H_{26}O_2Na$] 285.1831, found 285.1823, Δ = 2.8 ppm.

6.4 Methylation Reactions

The methylation reactions were performed (**Table 9**) using either commercially available MeLi solution (1.6 M in Et_2O) or MeMgBr solution (3M in THF), or by using freshly prepared MeTi(O*i*-Pr)$_3$ (0.5 M in Et_2O. Detailed preparation presented below).

Reactions with MeTi(O*i*-Pr)$_3$ (Table 9, entries 1–6): To a stirred solution of ketone **219** (25 mg, 0.1 mmol, 100 mol-%) in Et_2O (3.5 mL) at the given temperature was added MeTi(O*i*-Pr)$_3$ solution (0.5 M in Et_2O, amounts used reported in **Table 9**). Stirring was continued at the given temperature for the duration specified in the table. The reaction was quenched by addition of HCl solution (2M aq., 2 mL) and diluted with Et_2O (2 mL). The mixture was stirred at rt until both layers were clear. The layers were separated, and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. ^1H NMR was measured from the crude product.

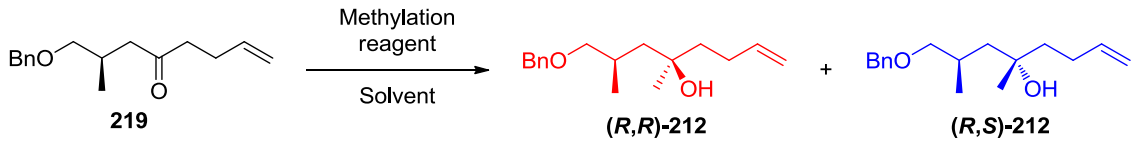
Reactions with MeLi (Table 9, entries 7–9): To a stirred solution of ketone **219** (25 mg, 0.1 mmol, 100 mol-%) in Et_2O (1 mL) at the given temperature was added MeLi solution (1.6 M in Et_2O, amounts used reported in **Table 9**). Stirring was continued at the given temperature for the duration specified in the table. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 2 mL) and diluted with Et_2O (2 mL). The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. ^1H NMR was measured from the crude product.

Reactions with MeMgCl (Table 9, entries 10–13): To a stirred solution of ketone **219** (25 mg, 0.1 mmol, 100 mol-%) in Et_2O (1 mL) at the given temperature was added MeMgCl solution (3 M in THF, amounts used are

reported in the **Table 9**). Stirring was continued at the given temperature for the duration specified in the table. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 2 mL) and diluted with Et_2O (2 mL). The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. ^1H NMR was measured from the crude material.

Reactions with LiBr and MeMgCl (Table 9, entries 14–15): To a flask containing solid LiBr (17 mg, 0.2 mmol, 200 mol-%) was added *via* cannula a solution of ketone **219** (25 mg, 0.1 mmol, 100 mol-%) in Et_2O or toluene (1 mL). This suspension was stirred at 0 °C for 10 minutes. To this mixture was added MeMgCl solution (3 M in THF, amounts used are reported in the **Table 9**) and stirring was continued at 0 °C for 5 hours. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 2 mL) and diluted with Et_2O (2 mL). The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. ^1H NMR was measured from the crude product.

Table 9. Methylation reactions **with 219**.



Entry	Methylation reagent	Eqv	Solvent	T [°C]	Time [min]	*dr* [(*R*,*R*):(*R*,*S*)][b]	Conversion [%][b]
1	MeTi(O*i*-Pr)$_3$[a]	15	Et_2O	–78/0	10/10	-	-
2	MeTi(O*i*-Pr)$_3$[a]	15	Et_2O	–78/0	25/10	-	-
3	MeTi(O*i*-Pr)$_3$[a]	15	Et_2O	0	10	-	-
4	MeTi(O*i*-Pr)$_3$[a]	15	Et_2O	0	1360	-	4
5	MeTi(O*i*-Pr)$_3$[a]	64	Et_2O	0	1290	-	5
6	MeTi(O*i*-Pr)$_3$[a]	15	Et_2O	rt	1320	42:58	47
7	MeLi	2	Et_2O	–78 to –40	90	56:44	70
8	MeLi	2	Et_2O	0	90	56:44	82
9	MeLi	15	Et_2O	–78 to –40	75	60:40	77
10	MeMgCl	2	Et_2O	–78	15	55:45	8
11	MeMgCl	2	Et_2O	0	15	53:47	100
12	MeMgCl	2	Et_2O	–40	120	55:45	68
13	MeMgCl	2	Et_2O	–78	120	55:45	25
14	MeMgCl/LiBr	5/2	Et_2O	0	300	53:44	100
15	MeMgCl/LiBr	5/2	Toluene	0	300	51:49	100

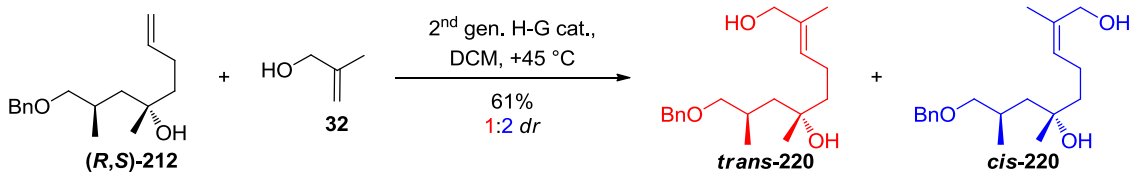
[a] Reagent were prepared *in situ*. [b] Determined by 1H NMR from the crude reaction mixture.

6.4.1 Preparation of the Triisopropoxymethyltitanium Stock Solution (0.5 M in Et_2O)[113]

To neat titanium(IV) isopropoxide (2.56 g, 2.7 mL, 9 mmol, 300 mol-%) at 0 °C was added dropwise titanium(IV) tetrachloride (0.57 g, 0.33 mL, 3 mmol, 100 mol-%). The ice bath was removed and the reaction mixture was stirred at rt for 10 minutes, during which a thick white suspension formed. Et_2O (13.5 mL) was added to dissolve the suspension and the stirring was continued at rt for 30 minutes, after which a pale yellow solution remained. The reaction mixture was chilled to 0 °C and MeLi solution (1.6 M in Et_2O, 7.5 mL, 12 mmol, 400 mol-%) was added, turning the solution orange. The stirring was continued at 0 °C for 1 hour, and the orange colour changed to bright yellow. This solution was used directly in the methylation reactions.

6.5 Model Studies for the Pd(II)-Catalysed Ring Closure

6.5.1 (6*S*,8*R*,*E*)-9-(Benzyloxy)-2,6,8-trimethylnon-2-ene-1,6-diol (*trans*-212) and (6*S*,8*R*,*Z*)-9-(benzyloxy)-2,6,8-trimethylnon-2-ene-1,6-diol (*cis*-212)



To a stirred solution of **(*R*,*S*)-212** (307 mg, 1.17 mmol, 100 mol-%) in DCM (flushed with Ar gas, 5 mL) at rt was added 2-methylprop-2-ene-1-ol (421 mg, 5.84 mmol, 500 mol-%) and 2nd generation Hoveyda–Grubbs catalyst (39.9 mg, 0.06 mmol, 5 mmol-%). The reaction mixture was refluxed (bath +45 °C) for 23 hours and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:2) to afford the product **220** as a mixture of diastereomers as a clear oil (215 mg, 0.70 mmol, 60%, 67:33 *dr*).

(6*S*,8*R*,*Z*)-9-(benzyloxy)-2,6,8-trimethylnon-2-ene-1,6-diol (*cis*-220):

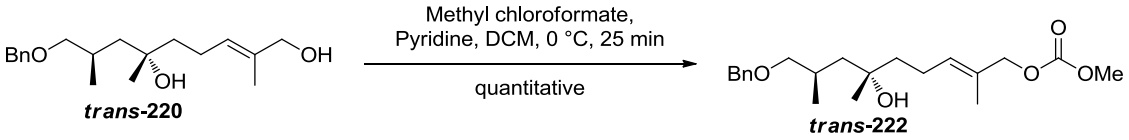
R_f (Et_2O) = 0.59; $[\alpha]_D$ = +5.7 (*c* 2.0, $CHCl_3$); IR (film, cm^{-1}): 3369, 2963, 2921, 2858, 1454, 1374, 1074, 1028, 1012, 737, 698; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.25 (m, 5H), 5.39 (ttq, 1H, *J* = 7.1, 1.3, 1.3 Hz), 4.51 (dd^{AB}, 2H, $|J_{AB}|$ = 11.9 Hz, Δν = 8.3 Hz), 3.96 (s, 2H), 3.53 (br. s, 1H), 3.39 (dd, 1H, *J* = 8.9, 4.4 Hz), 3.26 (t, 1H, *J* = 8.9 Hz), 2.14–1.96 (m, 3H), 1.83 (br. s, 1H), 1.63 (s, 3H), 1.62–1.45 (m, 2H), 1.57 (app. dd, 1H, *J* = 14.6, 7.5 Hz), 1.50 (app. dd, 1H, *J* = 14.6, 4.3 Hz), 1.16 (s, 3H), 0.93 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 134.7, 128.5, 127.83, 127.78, 126.3, 77.3, 73.4, 71.8, 68.9, 48.4, 41.2, 29.4, 28.0, 22.8, 19.7, 13.7; HRMS (ESI^+): m/z calcd for [$C_{19}H_{30}O_3Na$] 329.2093, found 329.2100, Δ = 2.1 ppm.

(6*S*,8*R*,*E*)-9-(benzyloxy)-2,6,8-trimethylnon-2-ene-1,6-diol (*trans*-220):

R_f (Et_2O) = 0.38; $[\alpha]_D$ = +10.7 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 3375, 2959, 2921, 2856,

1454, 1374, 1090, 1074, 1028, 1013, 737, 698; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5H), 5.48 (ttq, 1H, *J* = 7.5, 1.3, 1.3 Hz), 4.53 (dd^{AB}, 2H, $|J_{AB}|$ = 12.0, 8.7 Hz), 4.00 (s, 2H), 3.57 (br. s, 1H), 3.40 (dd, 1H, *J* = 8.9, 4.4 Hz), 3.27 (t, 1H, *J* = 8.9 Hz), 2.31 (dd, 1H, *J* = 14.3, 7.4 Hz), 2.21 (dd, 1H, *J* = 14.3, 7.5 Hz), 2.14–2.00 (m, 1H), 1.66 (s, 3H), 1.57 (dd, 1H, *J* = 14.6, 7.3 Hz), 1.52 (dd, 1H, *J* = 14.6, 4.3 Hz), 1.23 (br. s, 1H), 1.20–1.16 (m, 1H), 1.15 (s, 3H), 0.94 (d, 3H, *J* = 7.0 Hz), 0.94–0.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 137.2, 128.6, 127.9, 125.6, 121.8, 77.3, 73.5, 72.5, 69.1, 48.2, 39.7, 30.5, 29.6, 28.2, 19.7, 14.1; HRMS (ESI^+): m/z calcd for [$C_{19}H_{30}O_3Na$] 329.2093, found 329.2086, Δ = 2.1 ppm.

6.5.2 (6*S*,8*R*,*E*)-9-(Benzyloxy)-6-hydroxy-2,6,8-trimethylnon-2-en-1-yl methyl carbonate (*trans*-222)

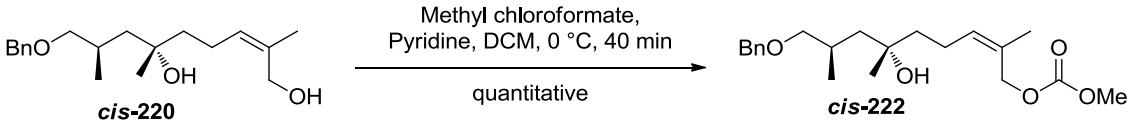


To a stirred solution of ***trans*-220** (24.9 mg, 0.08 mmol, 100 mol-%) in DCM (1 mL) at 0 °C was added pyridine (19.3 mg, 0.02 mL, 0.24 mmol, 300 mol-%) and methyl chloroformate (8.4 mg, 0.01 mL, 0.09 mmol, 110 mol-%). The reaction mixture was stirred at 0 °C for 25 minutes. The reaction was then quenched by addition of water (5 mL) and diluted with EtOAc (10 mL). The layers were separated and the organic layer was washed with NH_4Cl solution (sat. aq., 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product (quantitative) as a yellow oil. This crude material (***trans*-222**) was used in the next step without further purification.

R_f (EtOAc/hexanes 1:2) = 0.48; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H), 5.54 (ttq, 1H, *J* = 7.6, 1.3, 1.3 Hz), 4.54 (s, 2H), 4.53 (s, 2H), 3.77 (s, 3H), 3.66 (br. s, 1H), 3.41 (dd, 1H, *J* = 8.9, 4.4 Hz), 3.25 (t, 1H, *J* = 8.9 Hz), 2.37–2.17 (m, 2H), 2.15–1.96 (m, 1H), 1.67 (s, 3H), 1.58–1.49 (m, 2H), 1.20–1.14 (m, 1H), 1.14 (s, 3H), 0.92

(d, 1H, *J* = 6.9 Hz), 0.93–0.80 (m, 1H); HRMS (ESI⁺): m/z calcd for [$C_{21}H_{32}O_5Na$] 387.2147, found 387.2162, Δ = 3.9 ppm.

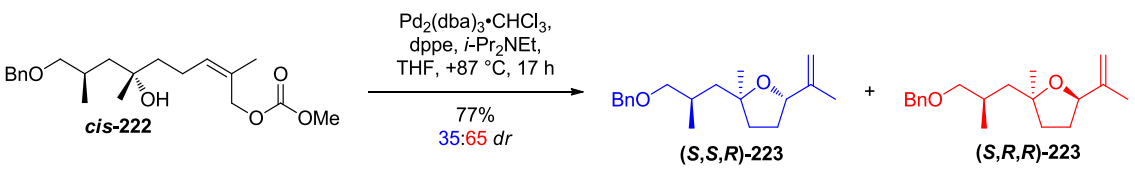
6.5.3 (6*S*,8*R*,*Z*)-9-(Benzyloxy)-6-hydroxy-2,6,8-trimethylnon-2-en-1-yl methyl carbonate (*cis*-222)



To a stirred solution of ***cis*-220** (80.5 mg, 0.26 mmol, 100 mol-%) in DCM (3 mL) at 0 °C was added pyridine (62.3 mg, 0.06 mL, 0.79 mmol, 300 mol-%) and methyl chloroformate (27.3 mg, 0.02 mL, 0.29 mmol, 110 mol-%). The reaction mixture was stirred at 0 °C for 40 minutes. The reaction was then quenched by addition of water (5 mL) and diluted with EtOAc (10 mL). The layers were separated and the organic layer was washed with NH_4Cl solution (sat. aq., 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product (quantitative yield) as a yellow oil. This crude material (***cis*-222**) was used in the next step without further purification.

R_f (EtOAc/hexanes 1:2) = 0.54; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.22 (m, 5H), 5.49 (ttq, 1H, *J* = 6.9, 1.2, 1.2 Hz), 4.51 (s, 2H), 4.50 (s, 2H), 3.77 (s, 3H), 3.52 (br. s, 1H), 3.39 (dd, 1H, *J* = 8.9, 4.4 Hz), 3.25 (t, 1H, *J* = 8.9 Hz), 2.20–1.95 (m, 3H), 1.64 (s, 3H), 1.60–1.40 (m, 4H), 1.15 (s, 3H), 0.92 (d, 3H, *J* = 6.9 Hz); HRMS (ESI⁺): m/z calcd for [$C_{21}H_{32}O_5Na$] 387.2147, found 387.2147, Δ = 0.0 ppm.

6.5.4 (2*S*,5*S*)-2-((*R*)-3-(Benzyloxy)-2-methylpropyl)-2-methyl-5-(prop-1-en-2-yl)tetrahydrofuran ((*S*,*S*,*R*)-223) and (2*S*,5*R*)-2-((*R*)-3-(benzyloxy)-2-methylpropyl)-2-methyl-5-(prop-1-en-2-yl)tetrahydrofuran ((*S*,*R*,*R*)-223)



1,2-Bis(diphenylphosphino)ethane (7.4 mg, 19 µmol, 46 mol-%) and $Pd_2(dba)_3 \bullet CHCl_3$ (4.3 mg, 4 µmol, 10 mol-%) were dissolved in THF (0.5 mL). A colour change from red to yellow was observed over several minutes. ***cis*-222** (14.6 mg, 40 µmol, 100 mol-%) in THF (1.5 mL) was added *via* cannula. *i*-Pr_2NEt (20.7 mg, 27 µL, 160 µmol, 400 mol-%) was then added to the reaction mixture and the mixture was heated (bath +87 °C) and stirred for 17 hours. The reaction mixture was allowed to cool to rt, and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:19) to afford the product **223** as a mixture of diastereomers as a clear oil (8.9 mg, 31 µmol, 77 %, 35:65 *dr*).

(2*S*,5*S*)-2-((*R*)-3-(Benzyloxy)-2-methylpropyl)-2-methyl-5-(prop-1-en-2-yl)tetrahydrofuran ((*S*,*S*,*R*)-223): R_f (EtOAc/hexanes 1:5) = 0.68; $[\alpha]_D$ = –6 (*c* 0.1, $CHCl_3$); IR (film, cm^{-1}): 2966, 2927, 2854, 1454, 1373, 1097, 1075, 1028, 898, 771, 751, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 5.00–4.97 (m, 1H), 4.78–4.75 (m, 1H), 4.51 (s, 2H), 4.33–4.26 (m, 1H), 3.34 (dd, 1H, *J* = 9.0, 6.1 Hz), 3.23 (dd, 1H, *J* = 9.0, 6.9 Hz), 2.06–1.99 (m, 1H), 1.99–1.90 (m, 1H), 1.87–1.67 (m, 3H), 1.70 (s, 3H), 1.64 (dd, 1H, *J* = 14.1, 4.4 Hz), 1.37 (dd, 1H, *J* = 14.1, 7.2 Hz), 1.24 (s, 3H), 1.03 (d, 3H, *J* = 6.7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 139.0, 128.5, 127.6, 127.5, 110.2, 83.7, 82.1, 77.4, 73.0, 44.5, 38.2, 31.2, 30.4, 27.1, 19.2, 18.1; HRMS (ESI^+): m/z calcd for $[C_{19}H_{28}O_2Na]$ 311.1987, found 311.1986, Δ = 0.3 ppm.

(2*S*,5*R*)-2-((*R*)-3-(Benzyloxy)-2-methylpropyl)-2-methyl-5-(prop-1-en-2-yl)tetrahydrofuran ((*S*,*R*,*R*)-223): R_f (EtOAc/hexanes 1:5) = 0.65; $[\alpha]_D$ = +12 (*c* 0.1, $CHCl_3$); IR (film, cm^{-1}): 2965, 2927, 2854, 1454, 1373, 1216, 1100, 1077, 1028, 897, 773, 750, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 5.01–4.99 (m, 1H), 4.78–4.76 (m, 1H), 4.50 (s, 2H), 4.48–4.33 (m, 1H), 3.36 (dd, 1H, *J* = 9.0, 6.0 Hz), 3.24 (dd, 1H, *J* = 9.0, 6.9 Hz), 2.10–2.00 (m, 1H), 2.00–1.92 (m, 1H), 1.84–1.77 (m, 1H), 1.74–1.68 (m, 3H), 1.71 (s, 3H), 1.39 (dd, 1H, *J* = 14.1, 7.0 Hz), 1.23 (s, 3H), 1.05 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.2, 139.0,

128.4, 127.6, 127.5, 110.1, 83.6, 81.4, 77.4, 73.0, 45.6, 38.0, 31.2, 30.4, 26.1, 13.4, 18.4; HRMS (ESI$^+$): m/z calcd for [$C_{19}H_{28}O_2Na$] 311.1987, found 311.1982, Δ = 1.6 ppm.

6.6 Determination of the Structures of *cis*-220, *trans*-220, (*S*,*S*,*R*)-223 and (*S*,*R*,*R*)-223

6.6.1 *Cis*- and *trans*-Trisubstituted Olefin Products *cis*-220 and *trans*-220

Fortunately, the *cis*- and *trans*-trisubstituted olefin products ***cis*-220** and ***trans*-220** were separable by flash chromatography. A tentative assignment of the stereochemistry of the double bond in the allylic alcohols is based on NMR studies of the isomers (**Figure 21**, **Figure 22** and **Figure 23**). The NOESY spectrum (**Figure 21**) contained the correlation between 20H–23H, which is evident for the *trans* compound. The weak 23H–C**H$_2$**OH NOE correlation was found from the other compound (**Figure 23**).

Further evidence for the double bond geometry was obtained by comparison of the chemical shifts of the metathesis products with literature values of similar compounds. Rapoport and coworkers listed chemical shifts of similar *cis* and *trans* trisubstituted olefins (**Figure 20**), and a comparison of the chemical shifts of their vinylic protons to ours revealed a similar downfield shift in both olefin groups. These results supported our interpretations.[114]

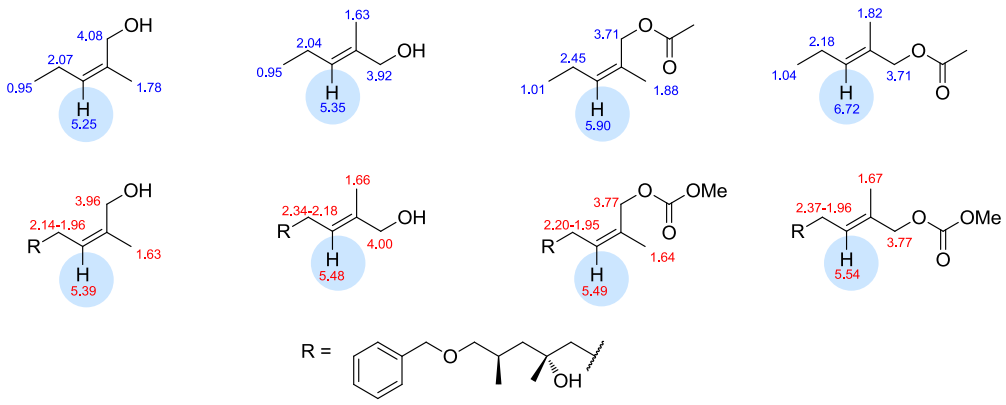


Figure 20. Chemical shifts of trisubstituted olefins prepared by Rapoport (in blue) and our compounds (in red). Chemical shifts are reported in ppm.

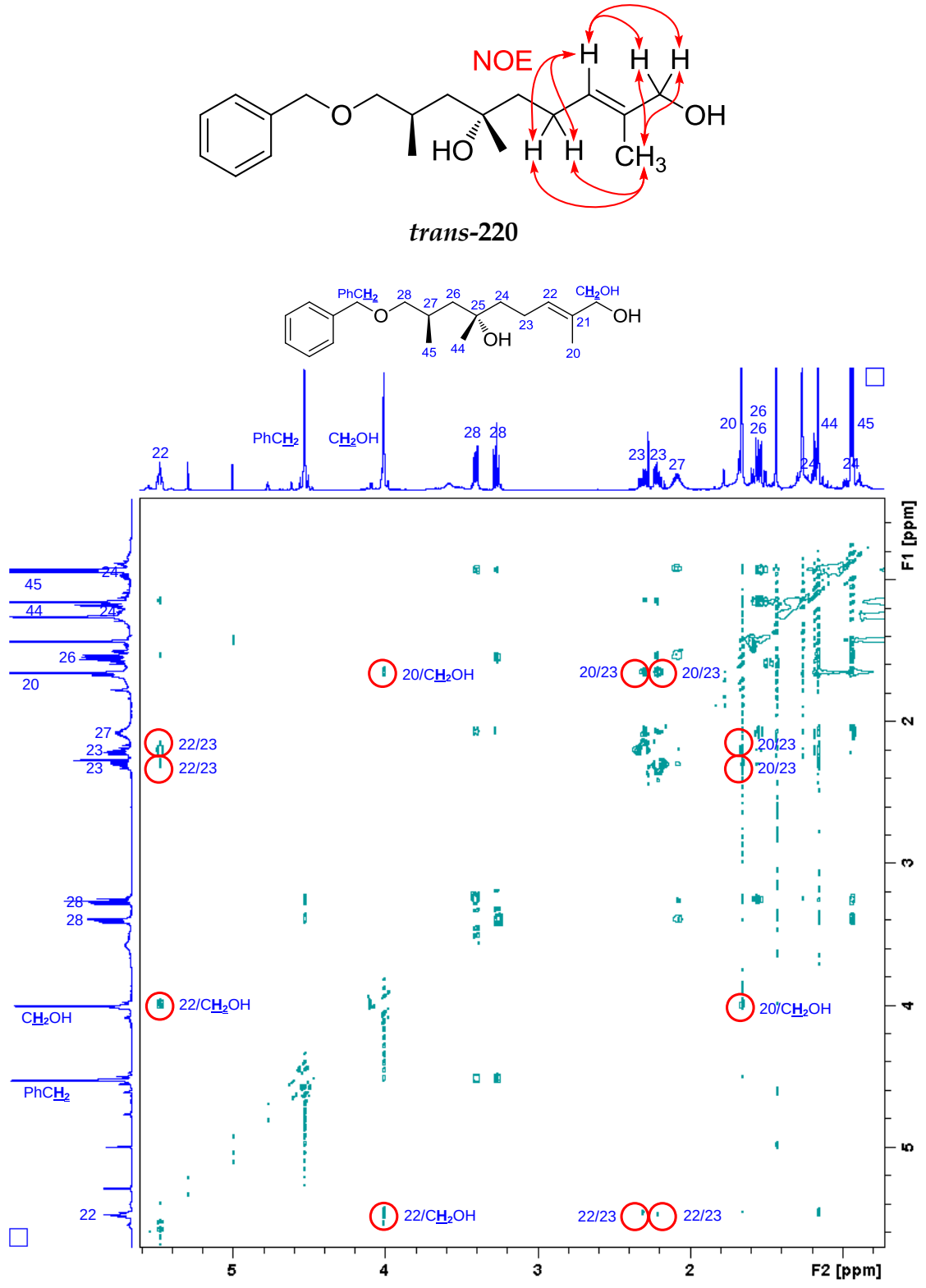


Figure 21. NOESY experiment of the *trans*-olefin compound ***trans*-220**.

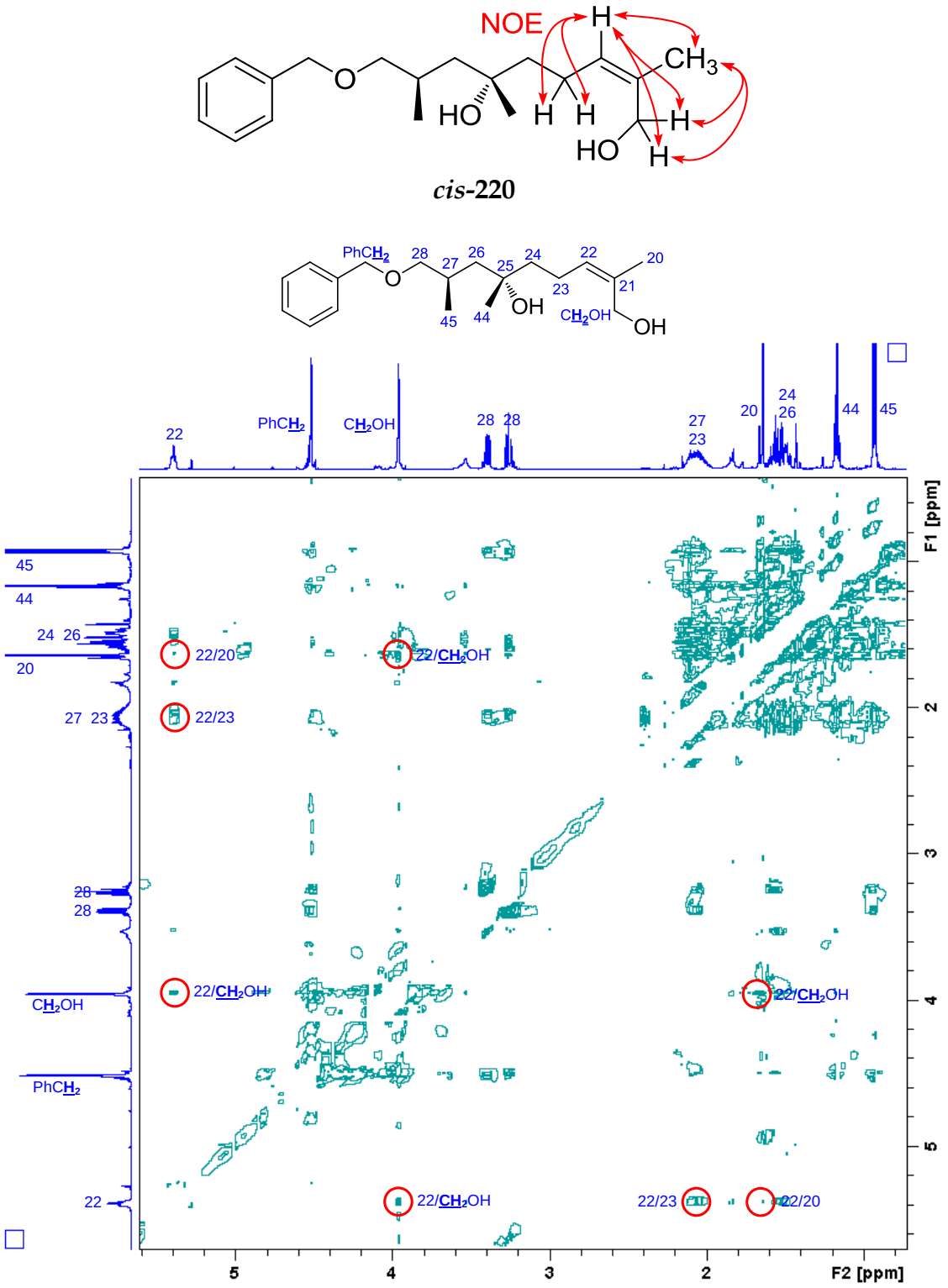


Figure 22. NOESY experiment of the *cis*-olefin compound ***cis*-220**.

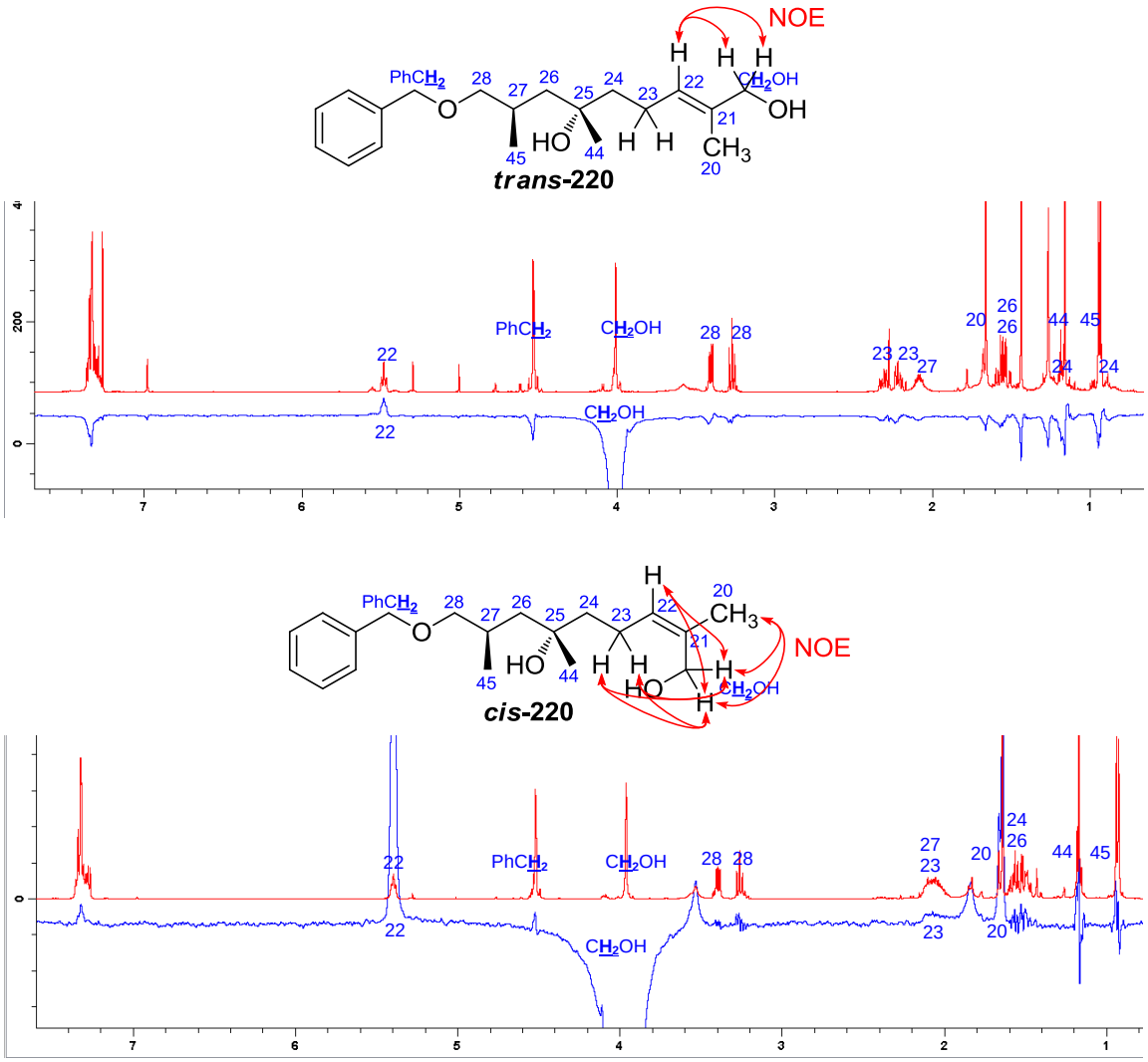


Figure 23. 1H DPGFSE-NOE experiments with irradiation of C**H**$_2$OH at 4.00 ppm (for ***trans*-220**) and 3.96 ppm (for ***cis*-220**).

6.6.2 Determination of the Conformation of the (2*S*,5*S*)-2-((*R*)-3-(Benzyloxy)-2-methylpropyl)-2-methyl-5-(prop-1-en-2-yl)tetrahydrofuran ((*S*,*S*,*R*)-223) and (2*S*,5*R*)-2-((*R*)-3-(Benzyloxy)-2-methylpropyl)-2-methyl-5-(prop-1-en-2-yl)tetrahydrofuran ((*S*,*R*,*R*)-223)

NOESY experiments were performed for both the diastereomers **(*S*,*S*,*R*)-223** and **(*S*,*R*,*R*)-223**. The structures of the diastereomers can be identified unambiguously from the correlations visible in the spectra (**Figure 24** and **Figure 25**). In the spectrum of compound **(*S*,*R*,*R*)-223** was observed a correlation between 22H–26H, which indicated the formation of the desired THF-ring system (*S*,*S*). In the spectrum of compound **(*S*,*S*,*R*)-223** was observed

a clear correlation between 22H–44H, which indicated the formation of an undesired THF-ring system (*S*,*R*).

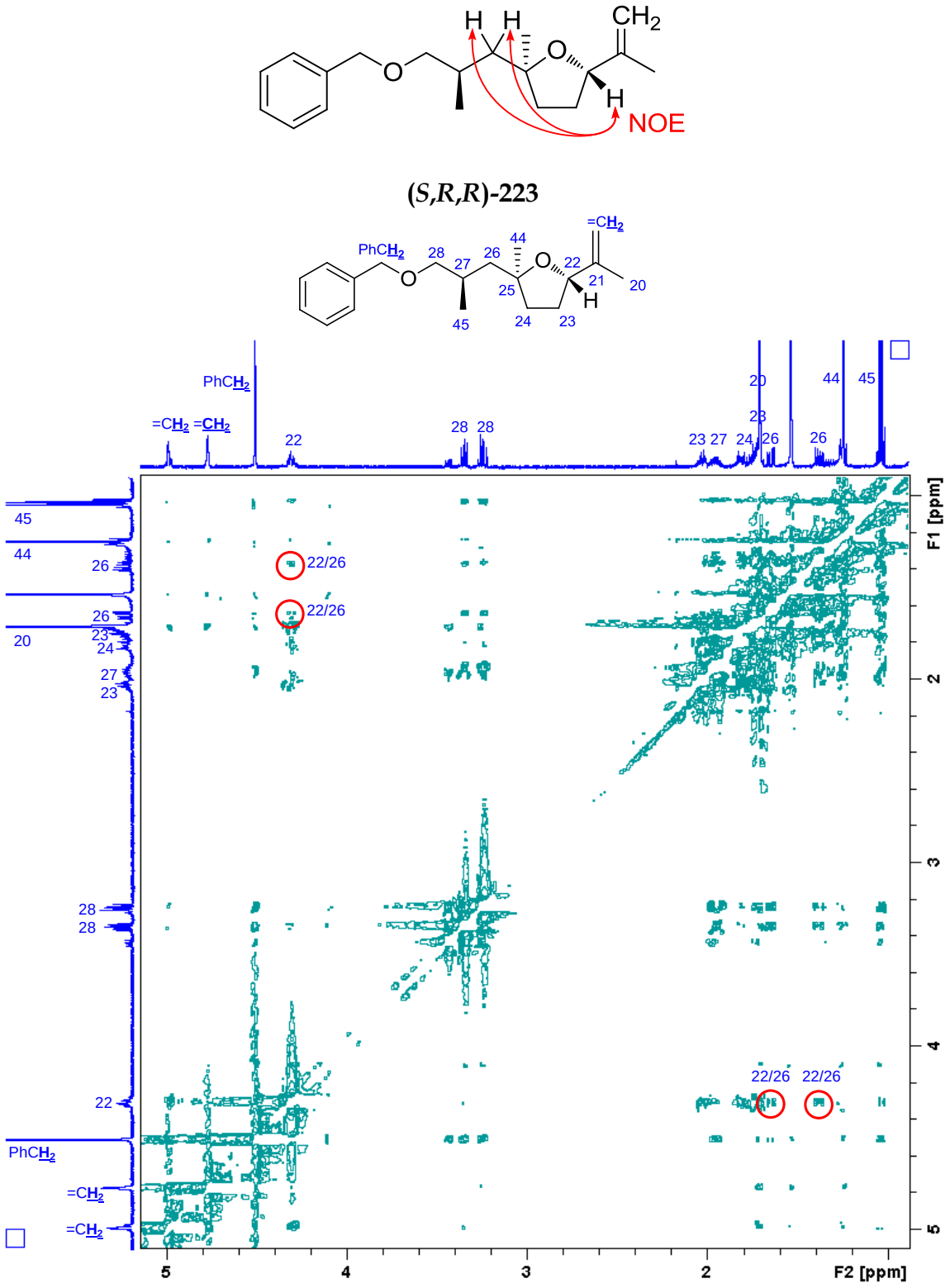
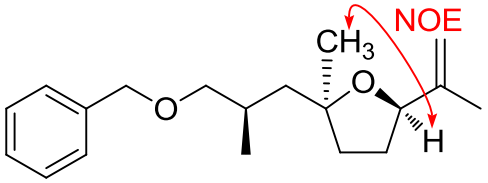
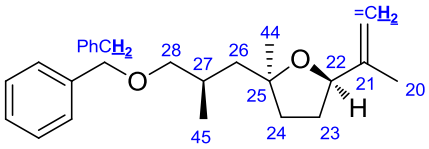


Figure 24. NOESY spectrum of compound **(S,R,R)-223**, showing the correlation between 26H–22H and the lack of correlation between 22H–44H.



(*S*,*S*,*R*)-223



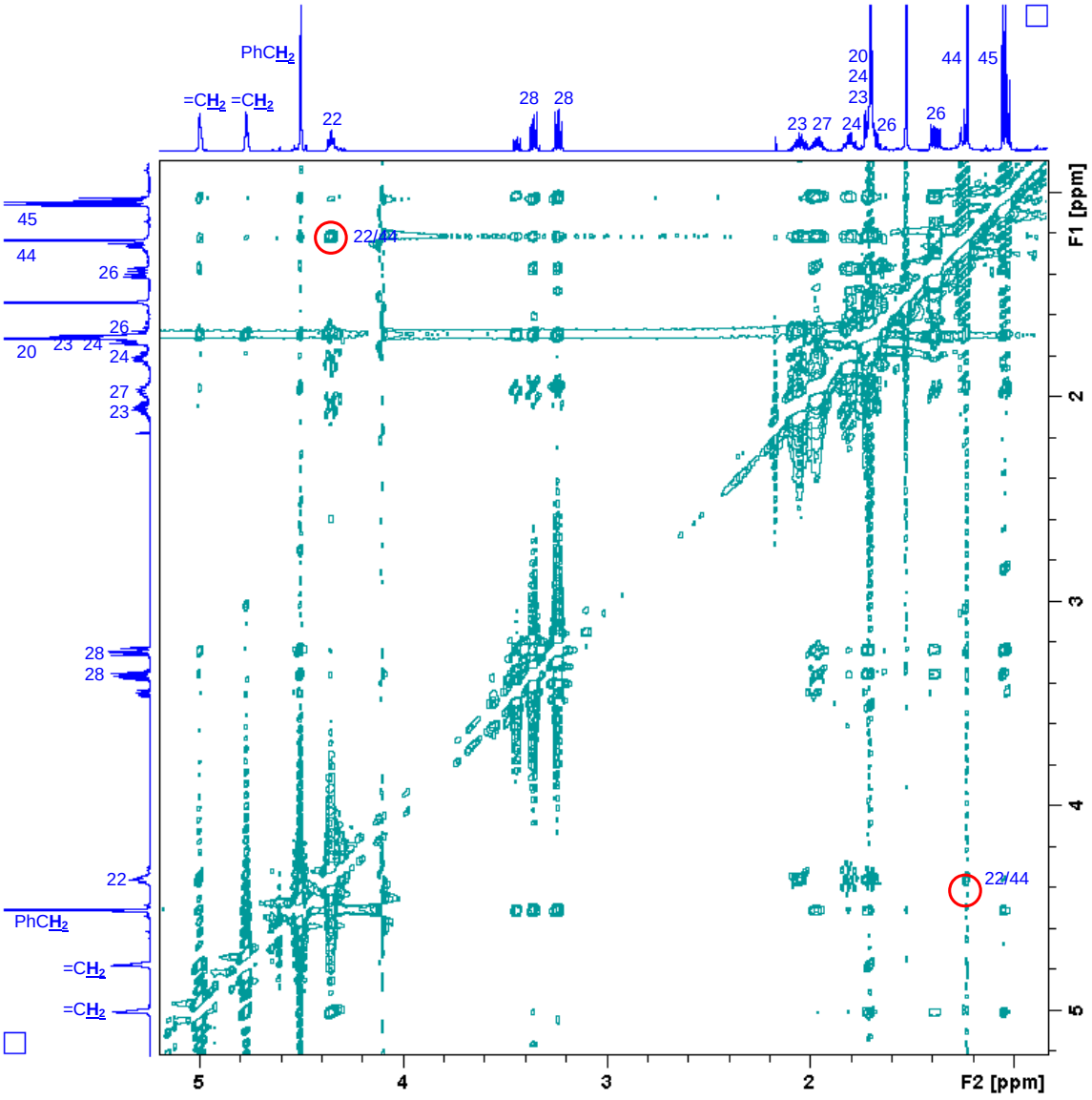
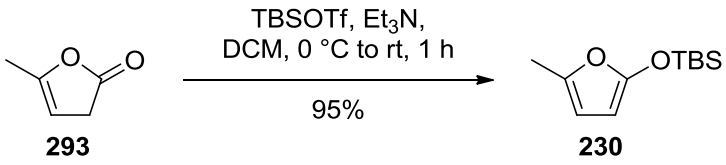


Figure 25. NOESY spectrum of the compound **(*S*,*S*,*R*)-223**, showing the correlation between 22H–44H and the lack of correlation between 26H–22H.

6.7 The Mukaiyama–Michael Approach – Synthesis of the C17-C28 Fragment of Pectenotoxin-2

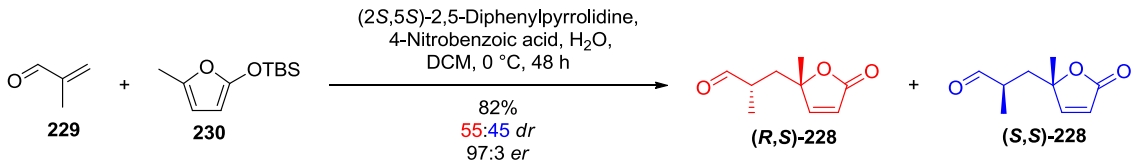
6.7.1 *tert*-Butyldimethyl((5-methylfuran-2-yl)oxy)silane (230)



To a solution of α-angelica lactone (**293**) (5.9 g, 5.4 mL, 60 mmol, 100 mol-%) and Et_3N (12.1 g, 16.7 mL, 120 mmol, 200 mol-%) in DCM (60 mL) at 0 °C was added TBSOTf (19.0 g, 16.5 mL, 72 mmol, 120 mol-%). The ice bath was removed and stirring was continued at rt for 1 hour. The reaction was quenched by the addition of water (80 mL). The layers were separated and the aqueous layer was extracted with DCM (60 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes) to afford the product **230** as a clear slightly yellow oil (12.2 g, 57 mmol, 95%). The spectroscopic data match those reported in the literature.[115]

R_f (EtOAc/hexanes 1:5) = 0.88; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.75 (dq, 1H, J = 3.0, 1.1 Hz), 4.95 (d, 1H, J = 3.0 Hz), 2.16 (d, 3H, J = 1.1 Hz), 0.97 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 155.3, 141.4, 106.2, 83.7, 25.6, 18.2, 13.6, –4.8.

6.7.2 (*S*)-2-Methyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal ((*S*,*S*)-228) and (*R*)-2-Methyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal ((*R*,*S*)-228)

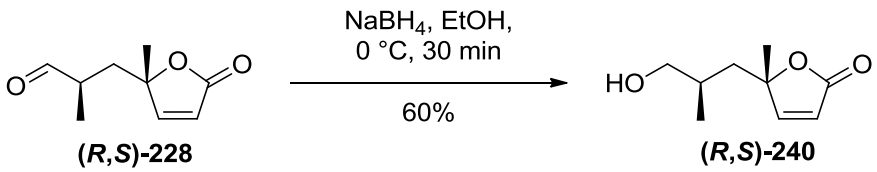


To a mixture of (2*S*,5*S*)-2,5-diphenylpyrrolidine (**238**) (125 mg, 0.56 mmol, 10 mol-%), 4-nitrobenzoic acid (96.8 mg, 0.58 mmol, 10 mol-%) and water (202 mg, 0.20 mL, 11.2 mmol, 200 mol-%) in DCM (11.2 mL) at 0 °C was added methacrolein (**229**) (785 mg, 0.92 mL, 11.2 mmol, 200 mol-%) and *tert*-butyldimethyl((5-methylfuran-2-yl)oxy)silane (**230**) (1.19 g, 1.3 mL, 5.6 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 48 hours. The mixture was then concentrated under reduced pressure and the residue was purified by flash chromatography (Et_2O) to afford the product **228** as a mixture of diastereomers as a slightly yellow oil (770 mg, 4.6 mmol, 82%, 55:45 *dr*, 97:3 *er* (for both diastereomers)).

(*S*)-2-Methyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal ((*S*,*S*)-228): R_f (Et_2O) = 0.62; $[\alpha]_D$ = –19.7 (*c* 1.07, DCM); IR (film, cm^{-1}): 2980, 2935, 1745, 1719, 1456, 1193, 1115, 954, 920, 820, 703; ^1H NMR (250 MHz, CD_3CN): δ 9.47 (d, 1H, *J* = 1.7 Hz), 7.47 (d, 1H, *J* = 5.7 Hz), 5.97 (d, 1H, *J* = 5.7 Hz), 2.37–2.23 (m, 2H), 1.80 (dd, 1H, *J* = 13.9, 3.5 Hz), 1.45 (s, 3H), 1.06 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (62.9 MHz, CD_3CN): δ 204.9, 173.1, 162.1, 121.1, 89.2, 42.6, 38.7, 24.9, 15.5; HRMS (ESI^+): m/z calcd for [$C_9H_{12}O_3Na$] 191.0684, found 191.0680, Δ = 3.1 ppm.

(*R*)-2-Methyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal ((*R*,*S*)-228): R_f (Et_2O) = 0.51; $[\alpha]_D$ = +51.3 (*c* 1.13, DCM); IR (film, cm^{-1}): 2980, 2936, 1748, 1722, 1457, 1192, 1115, 954, 922, 822, 750; ^1H NMR (250 MHz, CD_3CN): δ 9.44 (d, 1H, *J* = 2.6 Hz), 7.53 (d, 1H, *J* = 5.7 Hz), 6.01 (d, 1H, *J* = 5.7 Hz), 2.44 (dd, 1H, *J* = 14.8, 7.6 Hz), 2.30–2.16 (m, 1H), 1.69 (dd, 1H, *J* = 14.8, 4.7 Hz), 1.43 (s, 3H), 1.04 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (62.9 MHz, CD_3CN): δ 205.1, 173.4, 162.5, 121.8, 89.5, 43.2, 39.6, 25.3, 15.8; HRMS (ESI^+): m/z calcd for [$C_9H_{12}O_3Na$] 191.0684, found 191.0690, Δ = 2.3 ppm.

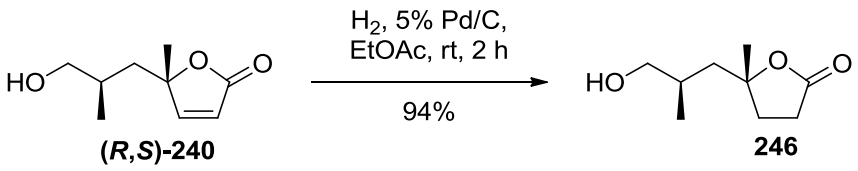
6.7.3 (*S*)-5-((*R*)-3-Hydroxy-2-methylpropyl)-5-methylfuran-2(5*H*)-one ((*R*,*S*)-240)



To a stirred solution of **(*R*,*S*)-228** (141 mg, 0.84 mmol, 100 mol-%) in EtOH (1 mL) at 0 °C was added $NaBH_4$ (46.8 mg, 1.24 mmol, 150 mol-%). The reaction mixture was stirred at 0 °C for 30 minutes. The reaction was quenched by addition of HCl solution (2M aq., 5 mL) and diluted with DCM (10 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH/DCM 1:49) to afford the product **240** as a clear oil (84.9 mg, 0.50 mmol, 60%).

R_f (MeOH/DCM 1:49) = 0.09; $[\alpha]_D$ = +32.1 (*c* 1.06, $CHCl_3$); IR (film, cm^{-1}): 3417, 1737, 1458, 1380. 1246, 1126, 1076, 1040, 994, 956, 823; ^1H NMR (250 MHz, $CDCl_3$): δ 7.39 (d, 1H, *J* = 5.6 Hz), 6.01 (d, 1H, *J* = 5.6 Hz), 3.48–3.35 (m, 2H), 2.08 (dd, 1H, *J* = 14.4, 3.9 Hz), 1.77 (br. s, 1H), 1.68–1.56 (m, 1H), 1.47 (s, 3H), 1.46 (dd, 1H, *J* = 14.5, 7.6 Hz), 0.94 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 172.6, 160.9, 120.3, 88.9, 68.0, 41.3, 31.4, 24.5, 18.2; HRMS (ESI^+): m/z calcd for [$C_9H_{14}O_3Na$+] 193.0841; found 193.0842, Δ = 0.6 ppm.

6.7.4 (*R*)-5-((*R*)-3-Hydroxy-2-methylpropyl)-5-methyldihydrofuran-2(3*H*)-one (246)

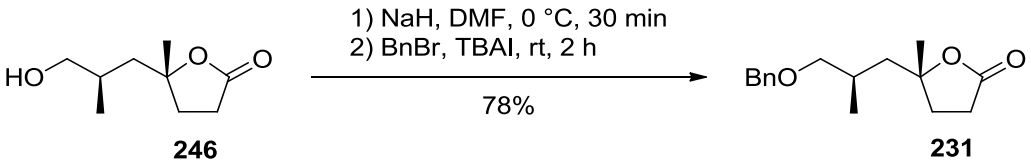


To a stirred solution of **(*R*,*S*)-240** (113 mg, 0.67 mmol, 100 mol-%) in EtOAc (3 mL) at rt was added 5% Palladium on charcoal (283 mg, 0.13 mmol,

20 mol-%). The reaction mixture was first flushed with Argon/vacuum cycles, and then with H_2/vacuum cycles (the gas/vacuum cycles were repeated three times). The reaction mixture was stirred under 1 bar H_2 atmosphere at rt for 2 hours. The H_2 atmosphere was then replaced by Argon and the reaction mixture was filtered through a short celite layer (ø 2 × 4 cm). The filtrate was concentrated under reduced pressure to afford the product **246** as a clear oil (108 mg, 0.62 mmol, 94%).

R_f (EtOAc/hexanes 2:1) = 0.22; $[\alpha]_D$ = +12.1 (*c* 1.01, $CHCl_3$); IR (film, cm^{-1}): 3432, 1764, 1460, 1384, 1198, 1162, 1137, 1043, 960, 938; ^1H NMR (250 MHz, $CDCl_3$): δ 3.48–3.35 (m, 2H), 2.70–2.47 (m, 2H), 2.17–1.94 (m, 2H), 1.90–1.78 (m, 3H), 1.52-1.43 (m, 1H), 1.40 (s, 3H), 1.00 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 177.0, 87.1, 67.8, 43.6, 33.7, 31.7, 28.6, 25.2, 17.9; HRMS (ESI^+): m/z calcd for [$C_9H_{16}O_3Na$+] 195.0997; found 195.0990, Δ = –3.8 ppm.

6.7.5 (*R*)-5-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5-methyldihydrofuran-2(3*H*)-one (231)



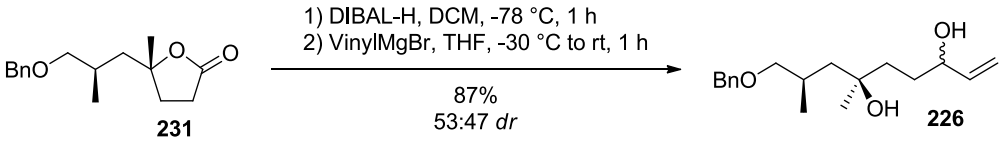
246 **231**

To a solution of **246** (51.8 mg, 0.30 mmol, 100 mol-%) in DMF (1.5 mL) at 0 °C was added NaH (55-65% dispersion in mineral oil, 24.0 mg, 0.60 mmol, 200 mol-%) in one portion and the resulting suspension was stirred at 0 °C for 30 min. Benzyl bromide (122 mg, 0.08 mL, 0.33 mmol, 110 mol-%) and tetrabutylammonium iodide (15.4 mg, 0.09 mmol, 30 mol-%) were added and the ice bath was removed. After 2 h of stirring at rt, the reaction mixture was quenched by addition of water (10 mL). EtOAc (10 mL) was added and the layers were separated. The organic layer was washed with water (10 mL). The combined aqueous layers were acidified by addition of HCl solution (3M aq., ~5 mL, the acidity was measured with pH-indicator paper) and extracted with EtOAc (10 mL). The combined organic extracts were dried over Na_2SO_4, filtered

and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/hexanes 1:2) afforded the desired product **231** as a clear pale yellow oil (61.8 mg, 0.24 mmol, 78%).

R_f (EtOAc/hexanes 1:2) = 0.42; $[\alpha]_D$ = +12.0 (*c* 0.1, $CHCl_3$); IR (film, cm^{-1}): 2971, 2931, 2857, 1766, 1101, 961, 739, 699; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.24 (m, 5H), 4.50 (s, 2H), 3.31 (dd, 1H, *J* = 9.0, 5.7 Hz), 3.25 (dd, 1H, *J* = 9.0, 7.0 Hz), 2.58 (ddd, 1H, *J* = 17.9, 9.3, 8.3 Hz), 2.55 (ddd, 1H, *J* = 17.9, 9.3, 6.2 Hz), 2.09 (ddd, 1H, *J* = 12.8, 9.3, 8.3 Hz), 2.01–1.91 (obs. m, 1H), 1.98 (ddd, 1H, *J* = 12.8, 8.3, 6.2 Hz), 1.89 (dd, 1H, *J* = 14.4, 4.0 Hz), 1.49 (dd, 1H, *J* = 14.4, 7.8 Hz), 1.40 (s, 3H), 1.03 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7, 138.5, 128.4, 127.55, 127.53, 87.0, 76.0, 73.1, 44.4., 34.2, 30.0, 28.8, 25.4, 18.6; HRMS (ESI^+): m/z calcd for $[C_{16}H_{22}O_3Na]$ 285.1467, found 285.1473, Δ = 2.2 ppm.

6.7.6 (6*R*,8*R*)-9-(Benzyloxy)-6,8-dimethylnon-1-ene-3,6-diol (226)



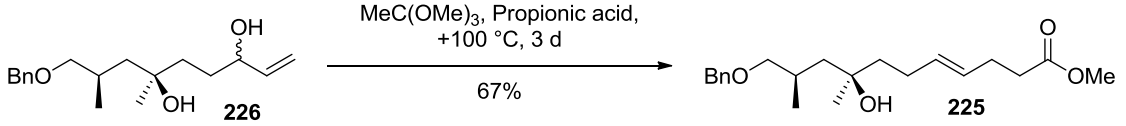
To a stirred solution of lactone **231** (0.439 g, 1.67 mmol, 100 mol-%) in DCM (15 mL) at –78 °C was added DIBAL-H solution (1M in DCM, 2.5 mL, 2.49 mmol, 150 mol-%) dropwise. After stirring for 1 hour at –78 °C, the reaction was quenched by the addition of Rochelle salt solution (sat. aq., 60 mL). The cold mixture was allowed to warm to rt and stirring was continued until both phases were clear. The mixture was diluted by DCM (15 mL) and the layers were separated. The aqueous layer was extracted with DCM (2 × 40 mL). The combined organic extracts were then washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude lactol **227** intermediate as a clear oil. This crude material was used in the next step without further purification.

R_f (EtOAc/hexanes 1:2) = 0.44.

To a stirred solution of the crude lactol (0.442 g, 1.67 mmol, 100%) in THF (10 mL) at –30 °C was added vinylmagnesium bromide solution (1M in THF, 16.6 mL, 16.6 mmol, 1000 mol-%). The reaction mixture was allowed to warm to rt while stirring for one hour. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 40 mL) and diluted with EtOAc (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc/hexanes 1:2) afforded the product **226** as a mixture of diastereomers as a slightly yellow oil (0.424 g, 1.45 mmol, 87 %, 53:47 *dr*).

R_f (EtOAc/hexanes 1:2) = 0.16; IR (film, cm^{-1}): 3367, 2926, 2859, 1073, 992, 917, 735, 697; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H), 5.85 (ddd, ½H, *J* = 17.1, 10.6, 6.2 Hz), 5.84 (ddd, ½H, *J* = 17.1, 10.6, 6.2 Hz), 5.21 (dt, ½H, *J* = 10.6, 1.5 Hz), 5.20 (dt, ½H, *J* = 10.6, 1.5 Hz), 5.08 (obs. dt, ½H, *J* = 17.1, 1.5 Hz), 5.07 (obs. dt, ½H, *J* = 17.1, 1.5 Hz), 4.52 (s, 2H), 4.10 (app. tq, ½H, *J* = 6.2, 1.5 Hz), 4.03 (app. tq, ½H, *J* = 6.2, 1.5 Hz), 3.41 (dd, ½H, *J* = 9.0, 1.8 Hz), 3.40 (dd, ½H, *J* = 9.0, 1.8 Hz), 3.25 (dd, ½H, *J* = 9.0, 2.5 Hz), 3.24 (dd, ½H, *J* = 9.0, 2.5 Hz), 2.13–2.02 (m, 1H), 1.73–1.45 (m, 6H), 1.17 (s, 1½H), 1.16 (s, 1½H), 0.92 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.31, 141.25, 137.6, 137.5, 128.45, 128.44, 127.79, 127.76, 114.3, 114.2, 77.1, 77.0, 73.5, 73.30, 73.28, 73.1, 71.51, 71.48, 48.8, 48.7, 37.4, 36.7, 32.0, 31.6, 29.21, 29.19, 27.98, 27.96, 19.54, 19.52; HRMS (ESI^+): m/z calcd for [$C_{18}H_{28}O_3Na$] 315.1936, found 315.1936, Δ = 1.6 ppm.

6.7.7 (8*R*,10*R*,*E*)-Methyl 11-(benzyloxy)-8-hydroxy-8,10-dimethylundec-4-enoate (225)

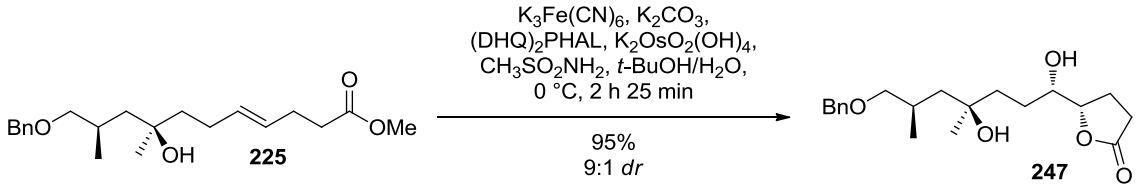


To a solution of alcohol **226** (21.9 mg, 0.075 mmol, 100 mol-%) in trimethyl orthoacetate (1 mL) was added propionic acid (0.4 mg, 0.4 μL, 0.005 mmol,

7 mol-%). The reaction mixture was stirred at +100 °C for 3 days. The mixture was allowed to cool and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:5) to afford the olefin **225** as a clear oil (17.6 mg, 0.051 mmol, 67%).

R_f (EtOAc/hexanes 1:5) = 0.16; $[\alpha]_D$ = –0.8 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 3443, 2927, 2854, 1738, 1454, 1438, 1168, 1092, 738, 699; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.25 (m, 5H), 5.51–5.37 (m, 2H), 4.52 (dd^{AB}, 2H, $|J_{AB}|$ = 12.1 Hz, Δν = 6.9 Hz), 3.66 (s, 3H), 3.39 (dd, 1H, *J* = 8.9, 4.5 Hz), 3.37 (br. s, 1H), 3.26 (t, 1H, *J* = 8.9 Hz), 2.39–2.33 (m, 2H), 2.33–2.26 (m, 2H), 2.09–1.92 (m, 3H), 1.60–1.46 (m, 4H), 1.14 (s, 3H), 0.93 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 137.7, 131.9, 128.4, 127.8, 127.72, 127.70, 77.1, 73.3, 71.7, 51.4, 48.2, 41.2, 34.1, 29.2, 27.94, 27.86, 27.5, 19.6; HRMS (ESI^+): m/z calcd for $[C_{21}H_{32}O_4Na]$ 371.2204, found 371.2198, Δ = 1.6 ppm.

6.7.8 (*S*)-5-((1*S*,4*R*,6*R*)-7-(Benzyloxy)-1,4-dihydroxy-4,6-dimethylheptyl)-dihydrofuran-2(3*H*)-one (247)



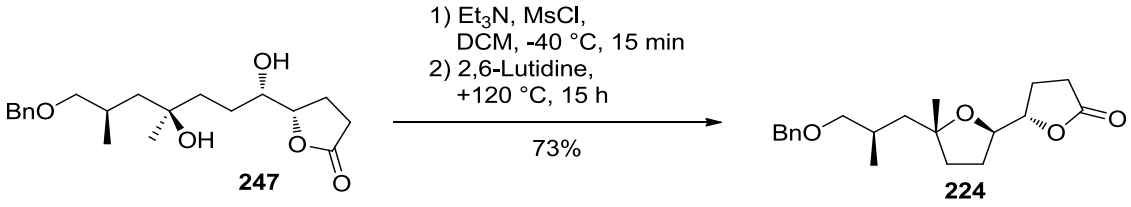
To a dry mixture of potassium hexacyanoferrate(III) (670 mg, 2.025 mmol, 300 mol-%), potassium carbonate (280 mg, 2.025 mmol, 300 mol-%), potassium osmate dihydrate (5.0 mg, 0.014 mmol, 2 mol-%), methanesulfonamide (64 mg, 0.675 mmol, 100 mol-%) and $(DHQ)_2PHAL$ (52 mg, 0.068 mmol, 10 mol-%)[ii] were added water (4.3 mL) and *tert*-butanol (2.4 mL) and the resulting slurry was stirred at rt until all solids dissolved.[iii] The clear biphasic solution was then cooled to 0 °C. Olefin **225** (235 mg, 0.675 mmol, 100 mol-%) in a small amount of

[ii] It is also possible to use the commercially available AD-mix α.
[iii] The use of an ultrasonic bath speeds up the process.

tert-butanol (1 mL+1 mL for rinsing the container) was added and the mixture was stirred for 2 h 25 minutes at 0 °C. Sodium sulfite (1.5 g, excess) was then added in one portion to the mixture and the ice bath was removed. After stirring at rt for 1 hour, the layers were separated. The aqueous layer was diluted with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford the desired product **247** as a clear oil (224 mg, 0.64 mmol, 95%, 9:1 *dr*).

R_f (EtOAc/hexanes 1:5) = 0.38; $[\alpha]_D$ = +13.9 (*c* 2.0, $CHCl_3$); IR (film, cm^{-1}): 3416, 2957, 2928, 2870, 1765, 1496, 1190, 1076, 741, 699; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.27 (m, 5H), 4.52 (s, 2H), 4.36 (ddd, 1H, *J* = 7.3, 7.3, 4.8 Hz), 3.78 (br. s, 1H), 3.55–3.49 (m, 1H), 3.43 (dd, 1H, *J* = 9.0, 4.1 Hz), 3.25 (app. t, 1H, *J* = 9.0 Hz), 2.59 (ddd, 1H, *J* = 17.9, 10.0, 5.0 Hz), 2.58 (br. s, 1H), 2.49 (ddd, 1H, *J* = 17.9, 10.0, 8.7 Hz), 2.20 (dddd, 1H, *J* = 12.8, 10.0, 7.3, 5.0 Hz), 2.13–2.03 (m, 1H), 2.04 (dddd, 1H, *J* = 12.8, 10.0, 8.7, 7.3 Hz), 1.70–1.50 (m, 7H), 1.16 (s, 3H), 0.93 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1, 137.5, 128.5, 127.86, 127.83, 83.3, 77.1, 74.1, 73.4, 71.4, 49.0, 37.0, 29.2, 28.6, 28.1, 27.5, 24.2, 19.5; HRMS (ESI^+): m/z calcd for $[C_{20}H_{30}O_5Na]$ 373.1995, found 373.1991, Δ = 1.2 ppm.

6.7.9 (2*S*,2'*R*,5'*R*)-5'-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5'-methylhexahydro-[2,2'-bifuran]-5(2*H*)-one (224)



To a stirred solution of diol **247** (224 mg, 0.64 mmol, 100 mol-%) and Et_3N (647 mg, 0.89 mL, 6.39 mmol, 1000 mol-%) in DCM (13 mL) at –40 °C was added methanesulfonyl chloride (220 mg, 0.15 mL, 1.92 mmol, 300 mol-%). After

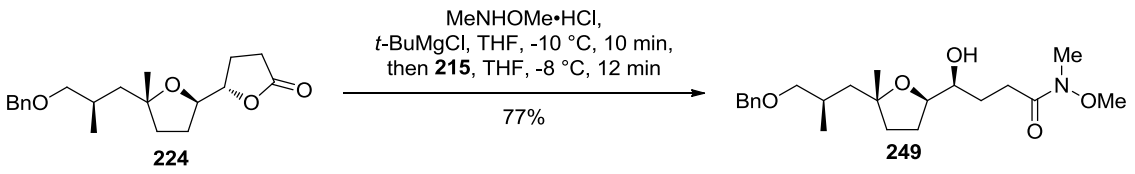
15 minutes of stirring at –40 °C, the reaction was quenched by addition of MeOH (1.5 mL). The cold mixture was allowed to warm to rt and water (20 mL) was added. The layers were separated and the aqueous layer was extracted with DCM (2 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude mesyl intermediate as a clear oil. This material was used directly in the next reaction without further purification.

R_f (EtOAc) = 0.58; HRMS (ESI$^+$): m/z calcd for [$C_{21}H_{32}O_7SNa$] 451.1766, found 451.1776, Δ = 2.2 ppm.

A solution of the crude mesyl intermediate (274 mg, 0.64 mmol, 100 mol-%) in 2,6-lutidine (6 mL, excess) was stirred at +120 °C for 15 hours and then allowed to cool to rt. The mixture was diluted with water (20 mL) and DCM (20 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH/DCM 1:99) to afford the product **224** as a clear oil (157 mg, 0.47 mmol, 73% over 2 steps).

R_f (MeOH/DCM 1:99) = 0.21; $[\alpha]_D$ = +19.1 (*c* 2.0, $CHCl_3$); IR (film, cm^{-1}): 2965, 2929, 2870, 1775, 1454, 1176, 1095, 1075, 738, 699; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.31 (m, 4H), 7.30–7.25 (m, 1H), 4.50 (s, 2H), 4.38 (ddd, 1H, *J* = 7.3, 5.8, 5.8 Hz), 3.96 (ddd, 1H, *J* = 7.3, 6.3, 5.8 Hz), 3.29 (dd, 1H, *J* = 9.1, 6.4 Hz), 3.23 (dd, 1H, *J* = 9.1, 6.5 Hz), 2.55 (ddd, 1H, *J* = 17.7, 9.8, 6.3 Hz), 2.46 (ddd, 1H, *J* = 17.7, 9.8, 7.3 Hz), 2.27 (dddd, 1H, *J* = 13.0, 9.8, 7.4, 6.3 Hz), 2.12–2.00 (m, 1H), 2.07 (dddd, 1H, *J* = 13.0, 9.8, 7.3, 5.8 Hz), 1.97–1.86 (m, 1H), 1.85–1.69 (m, 3H), 1.64 (dd, 1H, *J* = 14.2, 4.1 Hz), 1.33 (dd, 1H, *J* = 14.2, 7.6 Hz), 1.22 (s, 3H), 1.00 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 138.8, 128.3, 127.5, 127.4, 84.2, 82.1, 79.5, 76.6, 72.9, 44.0, 37.8, 30.3, 28.2, 28.1, 26.7, 23.9, 18.7; HRMS (ESI$^+$): m/z calcd for [$C_{20}H_{28}O_4Na$] 355.1885, found 355.1891, Δ = 1.5 ppm.

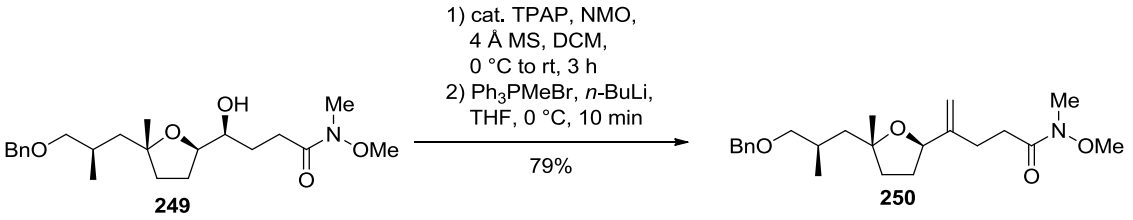
6.7.10 (*S*)-4-((2*R*,5*R*)-5-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5-methyl-tetrahydrofuran-2-yl)-4-hydroxy-*N*-methoxy-*N*-methylbutanamide (249)



To a suspension of *N*,*O*-dimethyl hydroxylamine hydrochloride (129 mg, 1.32 mmol, 280 mol-%) in THF (1.6 mL) at –10 °C was slowly added *t*-BuMgCl solution (2M in Et_2O, 1.23 mL, 2.46 mmol, 520 mol-%). The resulting mixture was stirred for 10 minutes and a solution of lactone **224** (157 mg, 0.47 mmol, 100 mol-%) in THF (1 mL+1 mL for rinsing the container) was added *via* cannula. After 12 minutes of stirring at –8 °C, the reaction was quenched by addition of NH_4Cl solution (sat. aq., 20 mL). The mixture was diluted with water (10 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford the product **249** as a clear oil (143 mg, 0.36 mmol, 77%).

R_f (EtOAc) = 0.43; $[\alpha]_D$ = +10.6 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 3436, 2964, 2929, 2870, 1661, 1454, 1377, 1095, 1074, 736, 699; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.30 (m, 4H), 7.29–7.23 (m, 1H), 4.49 (s, 2H), 3.81 (ddd, 1H, *J* = 8.3, 6.3, 4.5 Hz), 3.68 (s, 3H), 3.62 (dddd, 1H, *J* = 9.3, 4.5, 2.3, 2.3 Hz), 3.30 (dd, 1H, *J* = 9.0, 6.2 Hz), 3.22 (dd, 1H, *J* = 9.0, 6.8 Hz), 3.17 (s, 3H), 2.79 (d, 1H, *J* = 2.3 Hz), 2.69–2.54 (m, 2H), 1.97–1.73 (m, 5H), 1.71–1.61 (m, 2H), 1.62 (dd, 1H, *J* = 14.1, 4.1 Hz), 1.33 (dd, 1H, *J* = 14.1, 7.4 Hz), 1.20 (s, 3H), 1.00 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8, 138.7, 128.2, 127.41, 127.3, 83.3, 81.7, 76.6, 72.8, 72.0, 61.1, 44.1, 38.1, 32.2, 30.2, 28.7, 27.3, 26.7, 25.6, 18.9; HRMS (ESI^+): m/z calcd for $[C_{22}H_{35}O_5NNa]$ 416.2413, found 416.2405, Δ = –1.9 ppm.

6.7.11 4-((2*R*,5*R*)-5-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5-methyltetrahydrofuran-2-yl)-*N*-methoxy-*N*-methylpent-4-enamide (250)



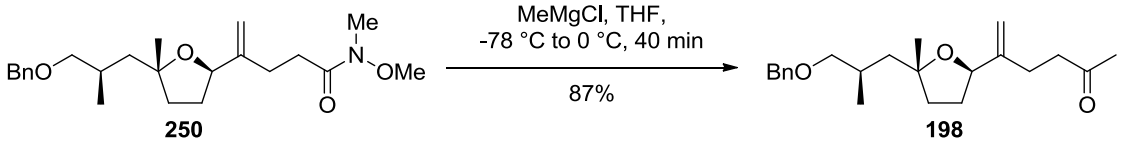
To a solution of alcohol **249** (142 mg, 0.36 mmol, 100 mol-%) in DCM (7.2 mL) were added 4-methylmorpholine *N*-oxide (423 mg, 3.61 mmol, 1000 mol-%) and 4 Å molecular sieves (360 mg, 50 mg/mL of solvent). The slurry was cooled to 0 °C and a catalytic amount of tetrapropylammonium perruthenate (11.7 mg, 0.03 mmol, 9 mol-%) was added. The ice bath was removed and the reaction mixture was stirred at rt for 3 hours. The mixture was then filtered through a silica pad (⌀ 2 cm × 3.5 cm), which was rinsed with EtOAc (2 × 20 mL). The filtrate was concentrated under reduced pressure to afford the crude ketone intermediate as a yellow oil. This crude material was used directly in next reaction without further purification.

R_f (EtOAc/hexanes 1:1) = 0.4; HRMS (ESI$^+$): m/z calcd for [$C_{22}H_{33}O_5NNa$] 414.2256, found 414.2261, Δ = 1.2 ppm.

To a suspension of methyltriphenylphosphonium bromide (193 mg, 0.54 mmol, 150 mol-%) in THF (3.6 mL) at 0 °C was added *n*-BuLi solution (2.5M in hexanes, 0.18 mL, 0.45 mmol, 125 mol-%). The mixture was stirred for 10 minutes and the crude ketone (141 mg, 0.36 mmol, 100 mol-%) in THF (1 mL+1 mL for rinsing the container) was added *via* cannula. After 20 minutes of stirring at 0 °C, the reaction was quenched by addition of NH_4Cl solution (sat. aq., 15 mL) and diluted with EtOAc (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:4) to afford the product **250** as a clear oil (111 mg, 0.28 mmol, 79%).

R_f (EtOAc/hexanes 1:1) = 0.55; $[\alpha]_D$ = +16.4 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 2965, 2931, 2869, 1667, 1454, 1417, 1377, 1100, 740, 698; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.29 (m, 4H), 7.28–7.22 (m, 1H), 5.09 (s, 1H), 4.78 (s, 1H), 4.49 (s, 2H), 4.35 (dd, 1H, *J* = 7.3, 6.8 Hz), 3.66 (s, 3H), 3.32 (dd, 1H, *J* = 9.1, 6.2 Hz), 3.23 (dd, 1H, *J* = 9.1, 6.8 Hz), 3.16 (s, 3H), 2.64 (ddd, 1H, *J* = 16.0, 9.6, 6.3 Hz), 2.59 (ddd, 1H, *J* = 16.0, 9.3, 6.5 Hz), 2.38 (ddd, 1H, *J* = 15.7, 9.3, 6.3 Hz), 2.30 (ddd, 1H, *J* = 15.7, 9.6, 6.5 Hz), 2.11–2.01 (m, 1H), 1.99–1.88 (m, 1H), 1.84–1.67 (m, 3H), 1.64 (dd, 1H, *J* = 14.1, 4.3 Hz), 1.36 (dd, 1H, *J* = 14.1, 7.4 Hz), 1.24 (s, 3H), 1.02 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 149.7, 138.7, 128.2, 127.33, 127.25, 108.5, 83.4, 81.4, 76.5, 72.8, 61.1, 44.3, 38.0, 32.1, 31.5, 30.5, 30.2, 26.7, 26.3, 18.9; HRMS (ESI^+): m/z calcd for $[C_{23}H_{35}O_4NNa]$ 412.2464, found 412.2470, Δ = 1.6 ppm.

6.7.12 5-((2*R*,5*R*)-5-((*R*)-3-(Benzyloxy)-2-methylpropyl)-5-methyl-tetrahydrofuran-2-yl)hex-5-en-2-one (198)

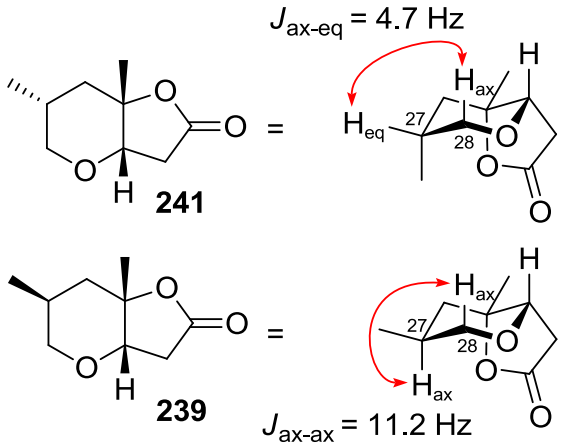


To a solution of amide **250** (52.7 mg, 0.13 mmol, 100 mol-%) in THF (1.3 mL) at –78 °C was slowly added MeMgCl solution (3M in THF, 0.22 mL, 0.66 mmol, 500 mol-%). After 10 minutes the –78 °C bath was replaced by an ice bath and the reaction mixture was stirred at 0 °C for another 30 minutes. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 15 ml). The resulting mixture was diluted with EtOAc (20 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:5) to afford the product **198** as a clear oil (39.6 mg, 0.11 mmol, 87%).

R_f (EtOAc/hexanes 1:2) = 0.70; $[\alpha]_D$ = +22.7 (*c* 2.3, $CHCl_3$); IR (film, cm^{-1}): 2965, 2927, 2853, 1717, 1454, 1360, 1095, 1042, 737, 698; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.30 (m, 4H), 7.30–7.29 (m, 1H), 5.10–5.04 (m, 1H), 4.75–4.71 (m, 1H), 4.50 (s, 2H), 4.33 (app. t, 1H, *J* = 7.0 Hz), 3.33 (dd, 1H, *J* = 9.0, 6.2 Hz), 3.24 (dd, 1H, *J* = 9.0, 6.8 Hz), 2.66 (ddd^{AB}, 1H, *J* = 17.2, 9.3, 6.2 Hz), 2.60 (ddd^{AB}, 1H, *J* = 17.2, 9.0, 6.3 Hz), 2.38–2.29 (m, 1H), 2.29–2.21 (m, 1H), 2.15 (s, 3H), 2.08–2.00 (m, 1H), 1.99–1.89 (m, 1H), 1.85–1.68 (m, 3H), 1.65 (dd, 1H, *J* = 14.0, 4.5 Hz), 1.37 (dd, 1H, *J* = 14.0, 7.4 Hz), 1.24 (s, 3H), 1.03 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.3, 149.3, 138.7, 128.2, 127.4, 127.3, 108.7, 83.4, 81.4, 76.6, 72.8, 44.3, 42.1, 38.0, 31.5, 30.2, 29.8, 26.7, 25.5, 18.9; HRMS (ESI^+): m/z calcd for $[C_{22}H_{32}O_3Na]$ 367.2249, found 367.2248, Δ = –0.3 ppm.

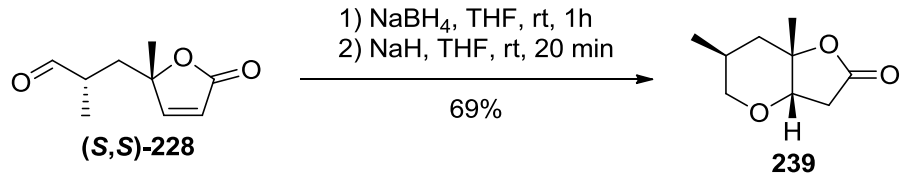
6.8 Determination of the Relative Stereochemistries of the Methacrolein Products

Relative stereochemistries were determined by ^1H-NMR from compounds **239** and **241** (Scheme 54). The characteristic coupling constants between the two vicinal protons in the six membered rings confirmed the relative stereochemistry. The axial–axial coupling was significantly larger (11.1 Hz) than the axial-equatorial coupling (4.7 Hz).



Scheme 54. Conformational drawings of **241** and **239**.

6.8.1 (3a*S*,6*S*,7a*S*)-6,7a-Dimethylhexahydro-2*H*-furo[3,2-b]pyran-2-one (239)



To a stirred solution of **(*S*,*S*)-228** (23.0 mg, 0.14 mmol, 100 mol-%) in THF (2 mL) at rt was added $NaBH_4$ (10.3 mg, 0.27 mmol, 200 mol-%) and the reaction mixture was stirred for 1 hour. The reaction was quenched by addition of water (5 mL) and diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude alcohol as a clear oil. This crude material was used in the next step without further purification.

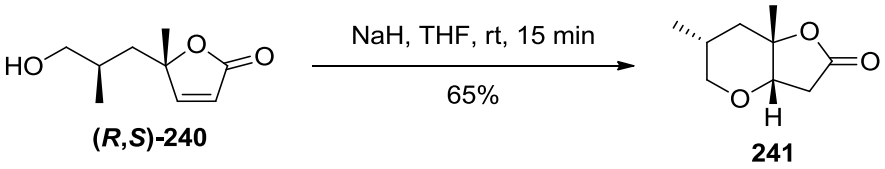
R_f (EtOAc/hexanes 1:1) = 0.14

To a stirred solution of the crude alcohol (23.3 mg, 0.14 mmol, 100 mol-%) in THF (2 mL) at rt was added NaH (55-65% dispersion in mineral oil, 11.0 mg, 0.27 mmol, 200 mol-%) in one portion and the mixture was stirred at rt for 20 minutes. The reaction was quenched by addition of water (5 mL) and diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:1) to afford the product **239** as white crystals (16.1 mg, 0.09 mmol, 69%).

R_f (Et_2O) = 0.69; mp 49–53 °C; $[\alpha]_D$ = –46.1 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 2956, 2931, 1771, 1144, 1095, 929; ^1H NMR (500 MHz, $CDCl_3$): δ 3.90 (d, 1H, *J* = 4.2 Hz), 3.75 (ddd, 1H, *J* = 11.2, 3.9, 2.8 Hz), 2.93 (app. t, 1H, *J* = 11.2 Hz), 2.85 (dd, 1H, *J* = 17.5, 4.2 Hz), 2.46 (dd, 1H, *J* = 17.5, 0.7 Hz), 2.26 (app. dt, 1H, *J* = 14.8, 3.0 Hz), 2.01–1.90 (m, 1H), 1.29 (s, 3H), 1.21 (dd, 1H, *J* = 14.8, 12.2 Hz), 0.82 (d, 3H,

J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 82.9, 76.7, 71.7, 40.6, 38.0, 25.9, 25.5, 16.4; HRMS (ESI$^+$): m/z calcd for [$C_9H_{14}O_3Na$] 193.0841, found 193.0838, Δ = –1.1 ppm.

6.8.2 (3a*S*,6*R*,7a*S*)-6,7a-Dimethylhexahydro-2*H*-furo[3,2-b]pyran-2-one (241)



(*R*,*S*)-240 **241**

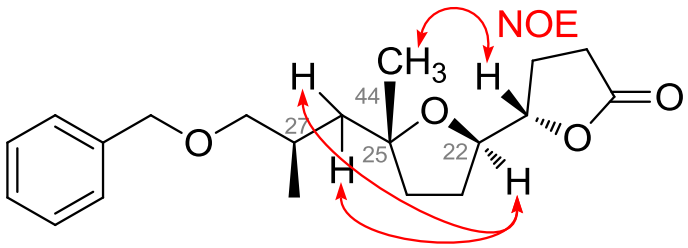
To a stirred solution of **(*R*,*S*)-240** (79.7 mg, 0.47 mmol, 100 mol-%) in THF (10 mL) at rt was added NaH (55-65% dispersion in mineral oil, 37.4 mg, 0.94 mmol, 200 mol-%) in one portion and the mixture was stirred at rt for 15 minutes. The reaction was quenched by addition of HCl solution (1M aq., 10 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Et_2O) to afford the product **241** as a white solid (51.8 mg, 0.30 mmol, 65%).

R_f (Et_2O) = 0.67; mp 55–57 °C; $[\alpha]_D$ = +16.0 (*c* 0.1 $CHCl_3$); IR (film, cm^{-1}): 2926, 1772, 1136, 1081, 932; ^{1}H NMR (500 MHz, $CDCl_3$): 3.94 (dd, 1H, *J* = 5.5, 2.2 Hz), 3.61 (dd, 1H, *J* = 11.3, 4.1 Hz), 3.50 (ddd, 1H, *J* = 11.3, 4.7, 1.2 Hz), 2.80 (dd, 1H, *J* = 17.7, 5.5 Hz), 2.57 (dd, 1H, *J* = 17.7, 2.2 Hz), 1.94–1.87 (m, 1H), 1.87–1.78 (m, 2H), 1.33 (s, 3H), 1.07 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8, 83.1, 76.9, 69.7, 37.8, 36.0, 26.8, 25.2, 17.8; HRMS (ESI$^+$): m/z calcd for [$C_9H_{14}O_3Na$] 193.0841, found 193.0844, Δ = 1.6 ppm.

6.9 Determination of the Absolute Stereochemistry of the C17-C28 Fragment (198)

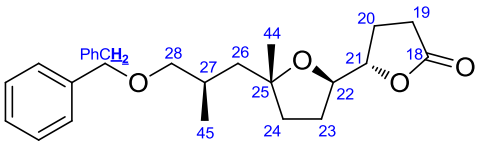
Determination of the absolute stereochemistry of compound **224** was based on the known relative stereochemistries of centres C25 and C27 of molecules **(*R*,*S*)-228** and **(*S*,*S*)-228**, and the reliably stereospecific Sharpless asymmetric dihydroxylation reaction. As the reaction "ignores" existing stereocentres and the selectivity is determined mainly by the employed ligand and the size of the substituents around the double bond, the absolute configuration of the stereocentres C21 and C22 formed in the reaction could be assigned unambiguously.

NOE experiments for compound **224** gave evidence for the desired stereochemistry between the newly generated stereocentres and the ones installed earlier (**Figure 26**). Conclusive evidence for the relative stereochemistry was obtained from the crystal structure of compound **248** (**Figure 27**). Compound **248** was made from **225** using the AD-mix β and therefore had the opposite stereochemistry at centres C21 and C22 compared to compound **247**/**224**, which was made using the AD-mix α. The reason for using compound **248** for the x-ray studies was that compound **224**/**247** was not crystalline.

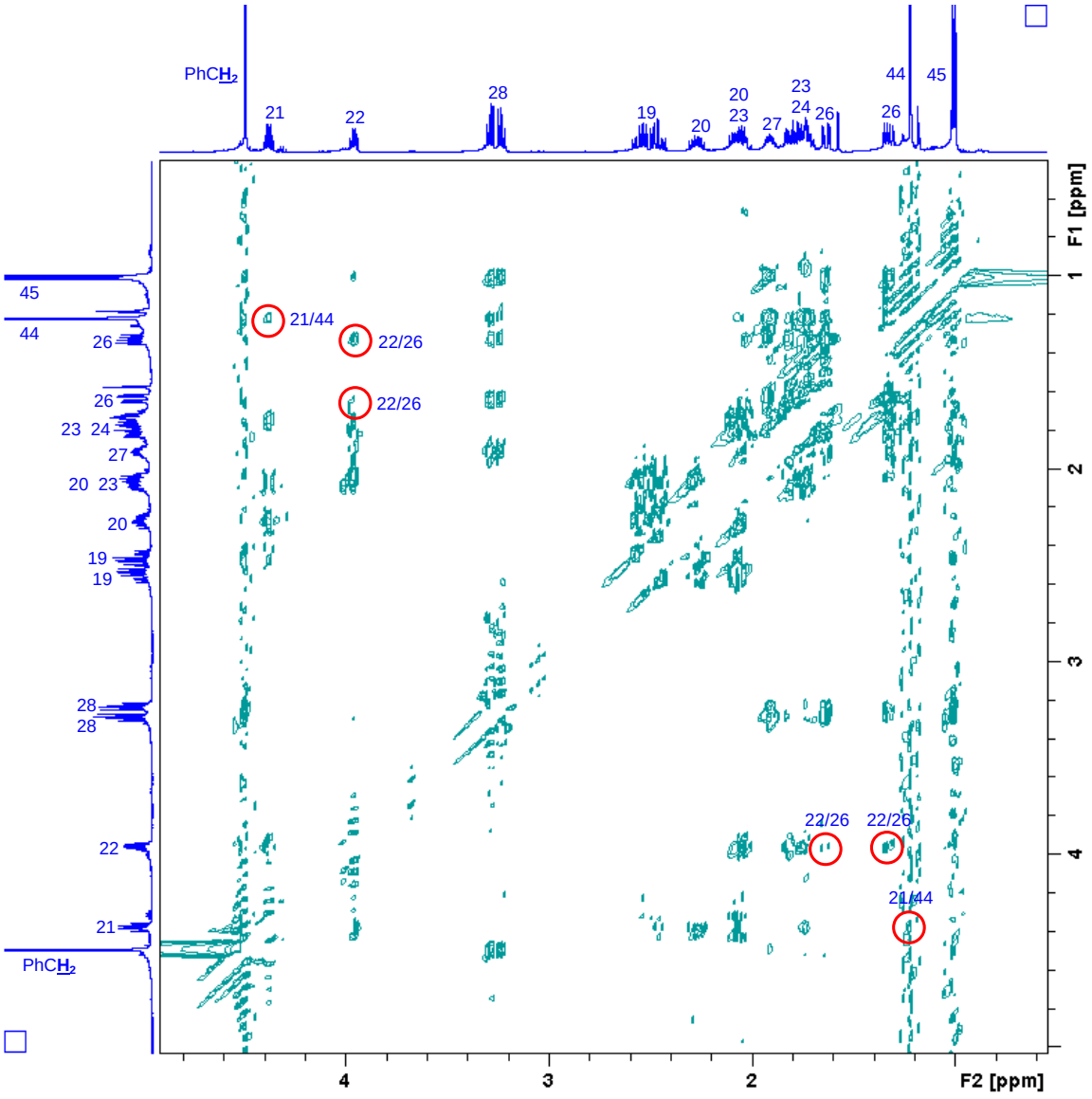

NOE
H
CH3
H
44
O
O
27
25
22
O
H
H

224

a)


PhCH2
28
27
26
44
20
19
21
18
O
O
O
25
22
45
24
23

224


PhCH2
21
22
28
19
20
20
23
27
23
24
26
44
45
26
21/44
22/26
22/26
22/26
22/26
21/44
F1 [ppm]
F2 [ppm]
1
2
3
4

b)

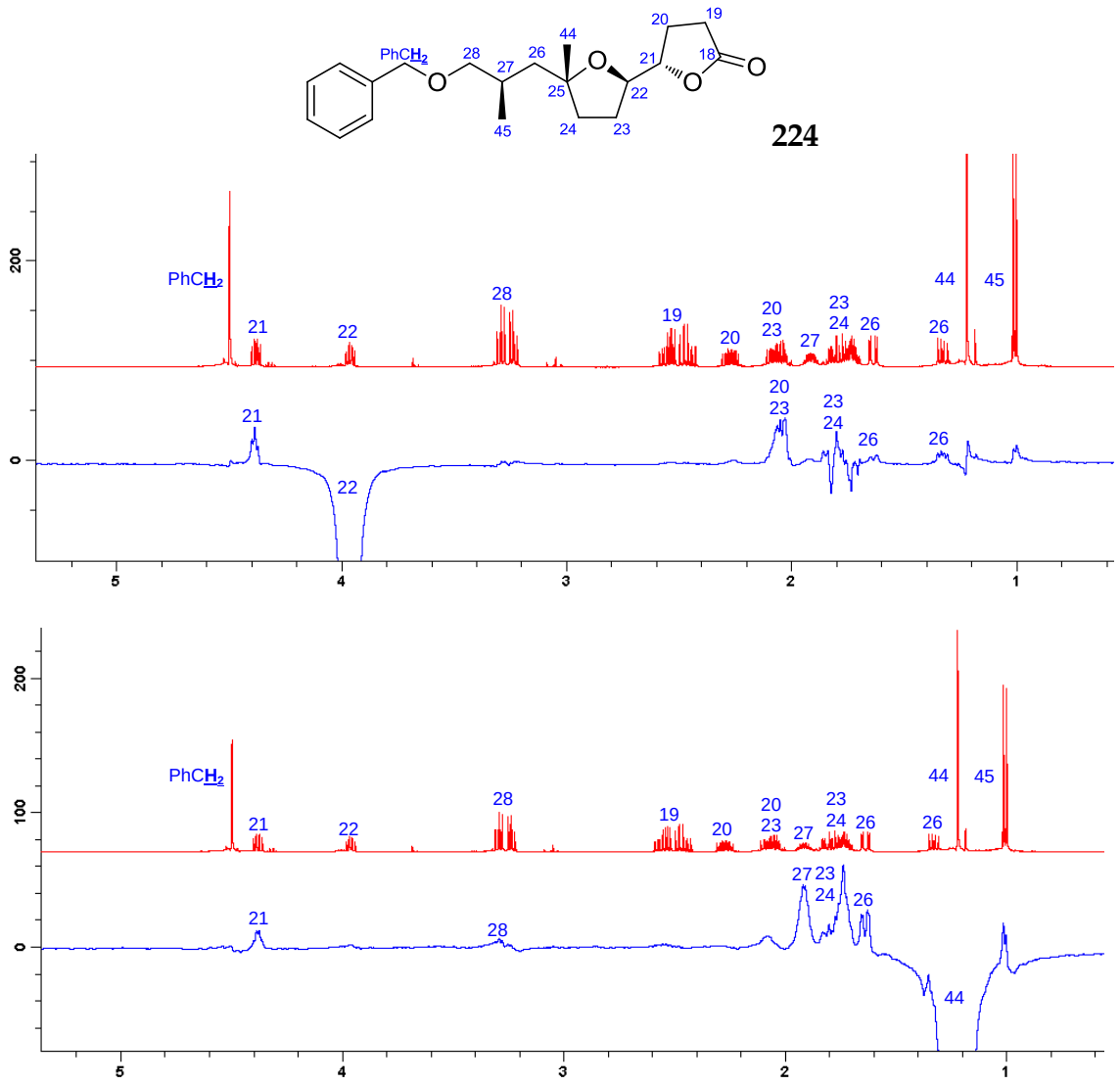
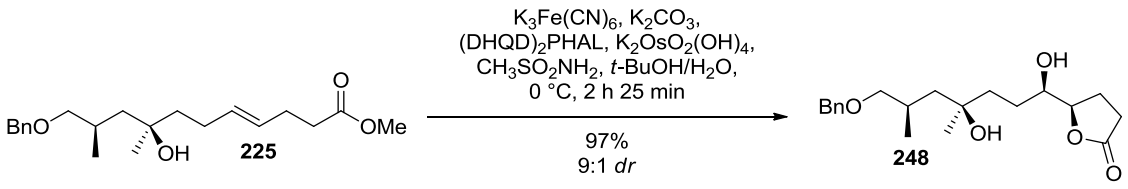


Figure 26. a) NOESY spectrum of compound **224**. b) 1H DPGFSE-NOE experiments with irradiation at 1.21 and 3.95 ppm. The key NOE-cross peaks of **224**.

6.9.1 (*R*)-5-((1*R*,4*R*,6*R*)-7-(Benzyloxy)-1,4-dihydroxy-4,6-dimethylheptyl)-dihydrofuran-2(3*H*)-one (248)



To a dry mixture of potassium hexacyanoferrate(III) (94.5 mg, 0.284 mmol, 300 mol-%), potassium carbonate (39.3 mg, 0.28 mmol, 300 mol-%), potassium osmate dihydrate (0.7 mg, 2.0 µmol, 2 mol-%), methanesulfonamide (9.0 mg,

0.095 mmol, 100 mol-%) and $(DHQD)_2PHAL$ (7.4 mg, 0.009, 10 mol-%)[iv] were added water (3.2 mL) and *tert*-butanol (1.8 mL) and the resulting slurry was stirred until all solids dissolved.[iii] The clear biphasic solution was then cooled to 0 °C. Olefin **225** (33.0 mg, 0.095 mmol, 100 mol-%) in a small amount of *tert*-butanol (1 mL+1 mL for rinsing the container) was added and the mixture was stirred for 2 h 25 minutes at 0 °C. Sodium sulfite (1.5 g, excess) was then added in one portion and the mixture was allowed to warm to rt. After stirring for 1 hour at rt, the layers were separated. The aqueous layer was diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford the product **248** as a white crystalline solid (32.1 mg, 0.092 mmol, 97%, 9:1 *dr*).

R_f (EtOAc) = 0.38; mp 93–96 °C; $[\alpha]_D$ = –11.3 (*c* 2.2, $CHCl_3$); IR (film, cm^{-1}): 3406, 2956, 2928, 2870, 1761, 1190, 1089, 1074, 740, 699; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.27 (m, 5H), 4.52 (s, 2H), 4.39 (ddd, 1H, *J* = 7.6, 6.6, 3.6 Hz), 4.14 (br. s, 1H), 3.71 (br. s, 1H), 3.46 (ddd, 1H, *J* = 8.8, 6.9, 3.6 Hz), 3.43 (dd, 1H, *J* = 9.0, 4.1 Hz), 3.23 (app. t, 1H, *J* = 9.0 Hz), 2.61 (ddd, 1H, *J* = 17.8, 9.9, 5.9 Hz), 2.45 (ddd, 1H, *J* = 17.8, 9.9, 8.0 Hz), 2.17 (dddd, 1H, *J* = 12.8, 9.9, 7.6, 5.9 Hz), 2.26–2.04 (obs. m, 1H), 2.12 (dddd, 1H, *J* = 12.8, 9.9, 8.0, 6.6 Hz), 1.81–1.69 (m, 2H), 1.66–1.48 (m, 4H), 1.17 (s, 3H), 0.92 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7, 137.5, 128.6, 128.05, 127.98, 83.1, 77.2, 74.1, 73.6, 71.6, 49.6, 37.7, 29.3, 28.7, 28.0, 27.9, 24.1, 19.6; HRMS (ESI^+): m/z calcd for $[C_{20}H_{30}O_5Na]$ 373.1991, found 373.1986, Δ = –1.2 ppm.

[iv] It is also possible to use the commercially available AD-mix β.

6.9.2 Crystal Data of 248[v]

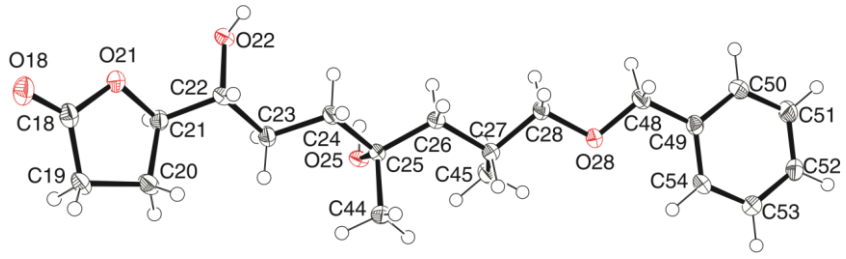


Figure 27. The crystal structure of **240**. Atom colours: C grey, H white, O red.

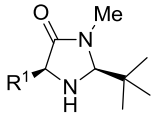
Colorless plates, T = 123.0(2) K, λ = 1.54184 Å, crystal size = 0.21 × 0.11 × 0.05 mm, FW = 350.44, $C_{20}H_{30}O_5$, orthorhombic, space group $P2_12_12_1$, a = 6.03188(17), b = 12.4097(4), c = 25.1549(6) Å, V = 1882.94(9) Å^3, Z = 4, D_c = 1.236 g/cm^3, $F(000)$ = 760, μ = 0.709 mm-1 , θ range = 3.97 − 69.98°, 5719 reflections, 3500 unique reflections and 3169 with $I_o > 2\sigma(I_o)$, R_{int} = 0.0395, 234 parameters, 2 restraints, GoF = 1.049, R = 0.0373 [$I_o > 2\sigma(I_o)$], wR = 0.0914 (all reflections), absolute structure parameter = –0.02(17), largest diffraction peak / hole = 0.164 / –0.214 e./Å^3.

6.10 Screening of Catalysts for the Mukaiyama–Michael Reaction

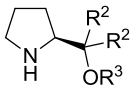
General procedure: To a stirred suspension of the catalyst (0.05 mmol, 10 mol-%), 4-nitrobenzoic acid (8.4 mg, 0.05 mmol, 10 mol-%), tetradecane (as an internal standard, 22.8 mg, 30 µL, 0.115 mmol, 23 mol-%) and water (18 mg, 18 µL, 1 mmol, 200 mol-%) in DCM (1 mL) at rt were added methacrolein (**229**) (70.1 mg, 80 µL, 1 mmol, 200 mol-%) and silyloxyfuran **230** (106 mg, 120 µL, 0.5 mmol, 100 mol-%). The mixture was stirred at rt and the reaction progression was monitored by GC, using a SUPELCO Astec CHIRALDEX B-DM column.

[v] The crystal structure was measured and the data was analysed by Dr. Arto Valkonen.

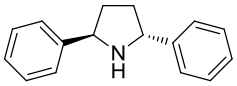
Table 19. Screening of the catalysts for the Mukaiyama–Michael reaction.



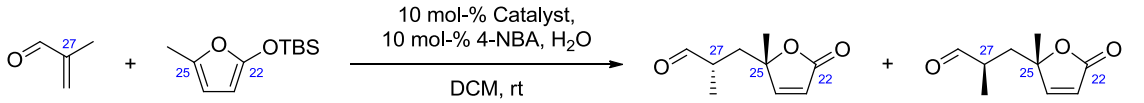
135: R^1=Bn
232: R^1=H



151: R^2=3,5-$(F_3C)_2C_6H_3$, R^3= TMS
233: R^2=Ph, R^3= TMS
234: R^2=Ph, R^3= DPMS
235: R^2=3,5-$(F_3C)_2C_6H_3$, R^3= DPMS
236: R^2=2-naphthyl, R^3= TMS
237: R^2=2-naphthyl, R^3= DPMS



(*R*,*R*)-238



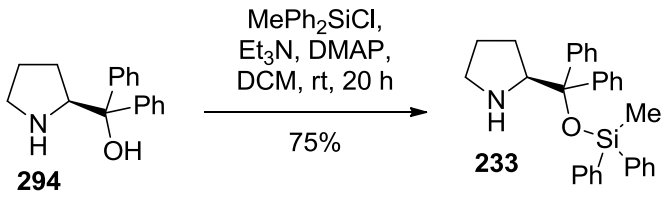
229 + **230** → **(*S*,*S*)-228** + **(*R*,*S*)-228**

Entry	Catalyst	Duration (h)	Conversion (%)[a]	*ee* ((*S*,*S*):(*R*,*S*))	*dr* ((*S*,*S*):(*R*,*S*))
1	**135**	23	33	2.4/1.8	54/45
2	**232**	1.5	>95	37/23	64/36
3	**151**	24	65	20/28	65/35
4	**233**	24	94	54/53	57/43
5	**234**	10	>95	61/63	56/44
6	**235**	24	>95	29/64	59/41
7	**236**	20	>95	59/59	56/44
8	**237**	24	76	30/37	58/42
9	**238**	8	>95	–93/–93	56/44[b]

[a]The conversion of silyloxyfuran **230** was monitored by GC. [b] The ratio of (*R*,*R*):(*S*,*R*).

6.11 Preparation of the Hayashi/Jørgensen-Type Catalysts

6.11.1 (*S*)-2-(((Methyldiphenylsilyl)oxy)diphenylmethyl)pyrrolidine (233)



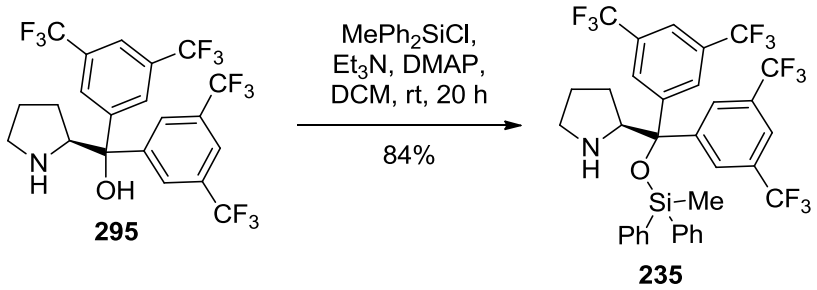
294 → **233**

To a stirred solution of **294** (500 mg, 1.97 mmol, 100 mol-%) and Et_3N (399 mg, 0.55 mL, 3.94 mmol, 200 mol-%) in DCM (5 mL) at rt was added methyldiphenylsilyl chloride (550 mg, 0.50 mL, 2.36 mmol, 120 mol-%) and 4-

(dimethylamino)pyridine (48.1 mg, 0.39 mmol, 20 mol-%). The mixture was stirred at rt for 20 hours. The reaction was quenched by addition of water (25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:2 to 1:1) to afford the product **233** as a white solid (661 mg, 1.47 mmol, 75%). Spectral data match those reported previously in the literature.[116]

R_f(EtOAc/hexanes 1:1) = 0.27; mp 86–87 °C (lit. mp 88 – 90 °C)[116]; $[\alpha]_D$ = −44.3 (*c* 1.0, $CHCl_3$) (lit. $[\alpha]_D$ = 48.2 (*c* 1.02, $CHCl_3$))[116]; IR (film, cm^1): 3066, 2960, 2872, 1428, 1113, 1071, 699; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57–7.49 (m, 6H), 7.41–7.29 (m, 8 H), 7.29–7.19(m, 6H), 4.04 (dd, 1H, *J* = 8.4, 6.9 Hz), 2.76 (ddd, 1H, *J* = 9.6, 7.9, 6.5 Hz), 2.58 (ddd, 1H, *J* = 9.6, 7.6, 5.1 Hz), 1.90 (br. s, 1H), 1.68–1.60 (m, 1H), 1.46–1.36 (m, 2H), 1.08–0.98 (m, 1H), 0.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.4, 145.5, 139.3, 139.1, 134.3, 134.2, 128.98, 128.95, 128.4, 127.62, 127.60, 127.47 127.46, 127.0 126.7, 83.9, 65.2, 46.7, 27.2, 24.2,–1.0; HRMS (ESI$^+$): m/z calcd for [$C_{30}H_{32}ONSi$] 450.2253, found 450.2260, Δ = 1.5 ppm.

6.11.2 (*S*)-2-(Bis(3,5-bis(trifluoromethyl)phenyl)((methyldiphenylsilyl)oxy)-methyl)pyrrolidine (235)

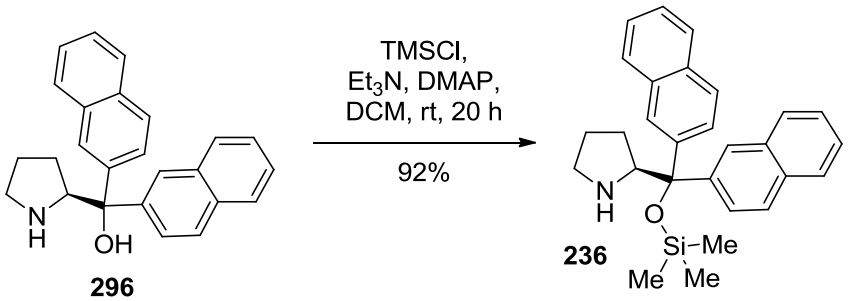


To a stirred solution of (*S*)-(–)-α,α-bis[3,5-(trifluoromethyl)phenyl]-2-pyrrolidine methanol (**295**) (1.00 g, 1.9 mmol, 100 mol-%) and Et_3N (385 mg, 0.53 mL, 3.8 mmol, 200 mol-%) in DCM (20 mL) at rt were added methyldiphenylsilyl chloride (535 mg, 0.48 mL, 2.3 mmol, 120 mol-%) and

4-(dimethylamino)pyridine (61.2 mg, 0.5 mmol, 26 mol-%). The mixture was stirred at rt for 20 hours. The reaction was quenched by addition of water (30 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes to EtOAc/hexanes 1:5) to afford the product **235** as a thick yellow oil (1.16 g, 1.6 mmol, 84%).

R_f(EtOAc/hexanes 1:5) = 0.63; $[\alpha]_D$ = −8.1 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 3072, 2968, 2876, 1373, 1277, 1173, 1132; ^1H NMR (500 MHz, $CDCl_3$): δ 8.12 (br. s, 2H), 7.87 (br. s, 1H), 7.77 (br. s, 1H), 7.66 (br. s, 1H), 7.59–7.55 (m, 1H), 7.47–7.55 (m, 10H), 4.23 (dd, 1H, *J* = 8.0, 6.5 Hz), 2.85 (app. dt, 1H, *J* = 10.0, 7.0 Hz), 2.47 (ddd, 1H, *J* = 10.0, 6.7, 5.9 Hz), 1.83–1.75 (m, 1H), 1.69 (br. s, 1H), 1.61–1.62 (m, 1H), 1.51–1.42 (m, 1H), 0.97–0.87 (m, 1H), 0.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.0, 145.8, 136.6, 136.1, 134.0 133.9, 131.4 (q, $^2J_{C,F}$ = 33.4 Hz), 130.7 (q, $^2J_{C,F}$ = 33.3 Hz), 130.0, 129.9, 128.9 (q, $^3J_{C,F}$ = 2.8 Hz), 128.5 (q, $^3J_{C,F}$ = 2.6 Hz), 127.90, 127.87, 123.3 (q, $^1J_{C,F}$ = 272.7 Hz), 123.1 (q, $^1J_{C,F}$ = 272.9 Hz), 121.8 (sept., $^3J_{C,F}$ = 3.7 Hz), 121.5 (sept., $^3J_{C,F}$ = 3.6 Hz), 83.3, 63.9, 47.1, 27.8, 25.2, –1.0; HRMS (ESI+): m/z calcd for [$C_{34}H_{28}ONF_{12}Si$] 722.1749, found 722.1749, Δ = 0.1 ppm.

6.11.3 (*S*)-2-(Di(naphthalen-2-yl)((trimethylsilyl)oxy)methyl)pyrrolidine (236)

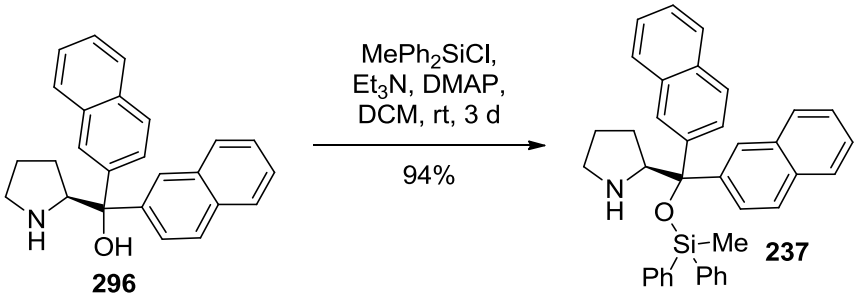


To a stirred solution of **296** (217 mg, 0.61 mmol, 100 mol-%) and Et_3N (124 mg, 0.17 mL, 1.22 mmol, 200 mol-%) in DCM (5 mL) at rt were added trimethylsilyl chloride (80.4 mg, 0.09 mL, 0.74 mmol, 120 mol-%) and

4-(dimethylamino)pyridine (14.9 mg, 0.12 mmol, 20 mol-%). The mixture was stirred at rt for 20 hours. The mixture was then concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexanes 1:5) to afford the product **236** as a thick yellow oil (240 mg, 0.56 mmol, 92%). Spectral data match those reported previously in the literature.[117]

R_f(EtOAc/hexanes 1:2) = 0.08; $[\alpha]_D$ = −59.5 (*c* 1.0, $CHCl_3$) (lit. $[\alpha]_D$ = -62.6 (*c* 0.9, DCM))[117]; IR (film, cm^{-1}): 3057, 2954, 2873, 1249, 840, 794, 749, 478; ^1H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, 1H, *J* = 1.4 Hz), 8.06 (d, 1H, *J* = 1.5 Hz), 7.93–7.75 (m, 4H), 7.72 (d, 1H, *J* = 4.4 Hz), 7.69 (d, 1H, *J* = 4.4 Hz), 7.54–7.42 (m, 5H), 7.34 (dd, 1H, *J* = 8.7, 1.8 Hz), 4.32 (app. t, 1H, *J* = 7.4 Hz), 3.01–2.90 (m, 1H), 2.90–2.79 (m, 1H), 2.09 (br. s, 1H), 1.85–1.57 (m, 3H), 1.56–1.35 (m, 1H), –0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2, 143.2, 133.0, 132.9, 132.64, 132.57, 128.6, 127.61, 127.56, 127.4, 127.3, 126.7, 126.6, 126.04, 125.99, 125.8, 83.7, 65.5, 47.4, 27.8, 25.3, 2.5; HRMS (ESI^+): m/z calcd for $[C_{28}H_{32}ONSi]$ 426.2253, found 426.2255, Δ = 0.4 ppm.

6.11.4 (*S*)-2-(((Methyldiphenylsilyl)oxy)di(naphthalen-2-yl)methyl)pyrrolidine (237)



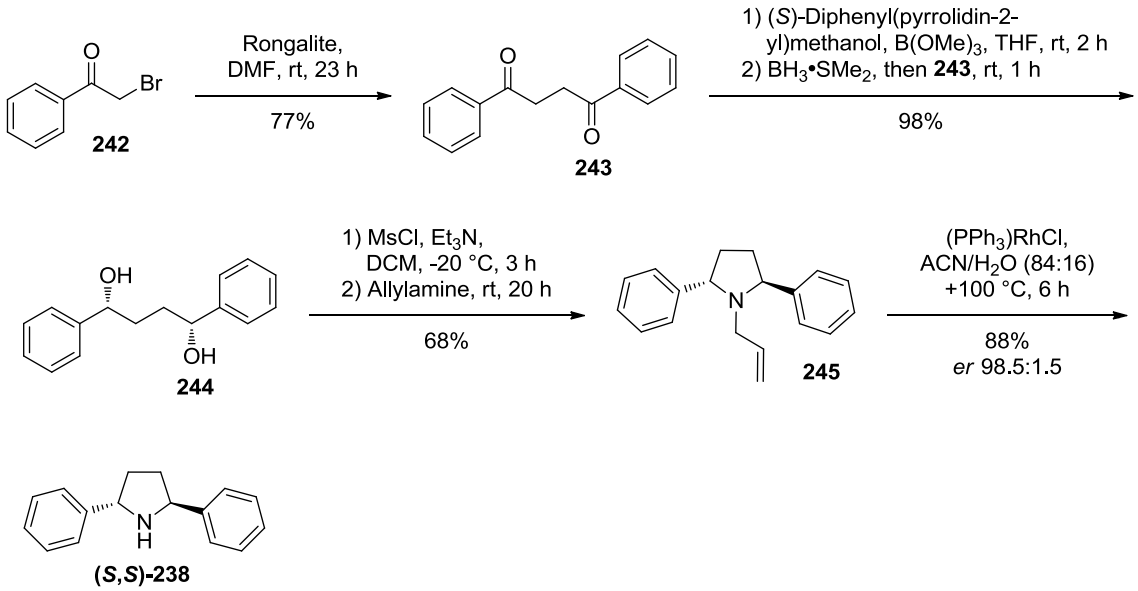
To a stirred solution of **296** (177 mg, 0.5 mmol, 100 mol-%) and Et_3N (101 mg, 0.14 mL, 1.0 mmol, 200 mol-%) in DCM (5 mL) at rt were added methyldiphenylsilyl chloride (140 mg, 0.13 mL, 0.6 mmol, 120 mol-%) and 4-(dimethylamino)pyridine (12.2 mg, 0.1 mmol, 20 mol-%). The mixture was stirred at rt for 3 days. The mixture was then concentrated under reduced

pressure and the residue was purified by flash chromatography (EtOAc/hexanes 0:1 to 1:5 to 1:0) to afford the product **237** as a white solid (258 mg, 0.47 mmol, 94%).

R_f(EtOAc/hexanes 1:2) = 0.17; mp 77–78 °C; $[\alpha]_D$ = −68.7 (*c* 1.0, $CHCl_3$); IR (film, cm^1): 3054, 2961, 2872, 1428, 1116, 793, 742, 700, 478; ^1H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, 1H, *J* = 1.4 Hz), 7.99 (d, 1H, *J* = 1.3 Hz), 7.81–7.72 (m, 4H), 7.66 (d, 1H, *J* = 8.7 Hz), 7.62 (d, 1H, *J* = 8.7 Hz), 7.55 (dd, 1H, *J* = 8.7, 1.8 Hz), 7.54–7.50 (m, 4H), 7.49–7.43 (m, 4H), 7.34 (dd, 1H, *J* = 8.6, 1.8 Hz), 7.33–7.28 (m, 2H), 7.27–7.22 (m, 4H), 4.25 (app. t, 1H, *J* = 7.6 Hz), 2.84–2.77 (m, 1H), 2.62–2.56 (m, 1H), 1.80–1.65 (m, 2H), 1.53–1.34 (m, 2H), 1.12–1.03 (m, 1H), 0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.6, 142.8, 139.0, 138.8, 134.4, 134.2, 132.8, 132.7, 132.6, 132.5, 129.11, 129.06, 128.49, 128.47, 127.6, 127.47, 127.46, 127.45, 127.42, 127.29, 127.27, 126.7, 126.4, 126.1, 126.0, 125.9, 125.8, 84.4, 65.2, 46.9, 27.6, 24.5, –0.8; HRMS (ESI^+): m/z calcd for [$C_{38}H_{36}ONSi$] 550.2566, found 550.2574, Δ = 1.5 ppm.

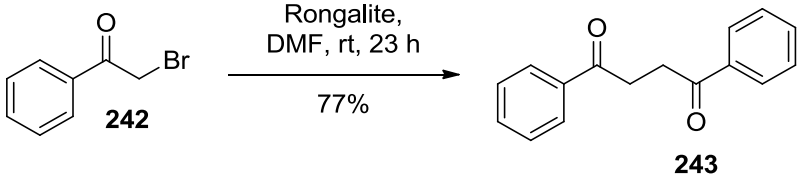
6.12 Synthesis of the (2*S*,5*S*)-2,5-Diphenylpyrrolidine Catalyst ((*S*,*S*)-238)

The synthesis of catalyst **(*S*,*S*)-238** is based on previously reported procedures.[95]



Scheme 38. Preparation of the (2S,5S)-diphenylpyrrolidine catalyst **((*S*,*S*)-238**).

6.12.1 1,4-Diphenylbutane-1,4-dione (243)

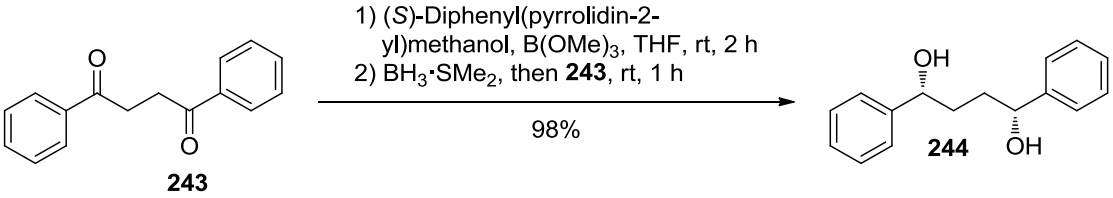


To a dry mixture of 2-bromo-1-phenylethanone (**242**) (20.2 g, 101 mmol, 100 mol-%) and sodium hydroxymethanesulfinate dihydrate (15.6 g, 101 mmol, 100 mol-%) was added freshly distilled DMF (150 mL) and the mixture was stirred at rt for 23 hours. Water (400 mL) was added and the mixture was filtered through a sintered funnel (porosity 4). The solid remnant was dissolved in DCM (200 mL) and the resulting solution was washed with NaOH solution (1M aq., 150 mL) and brine (150 mL), dried over Na_2SO_4, filtered and

concentrated under reduced pressure to afford the product **243** as a white crystalline solid (9.3 g, 39 mmol, 77%). The spectroscopic data match those reported in the literature.[95d]

R_f(EtOAc/hexanes 1:1) = 0.82; mp 144–147 °C (lit. mp 143–144 °C) [95d]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08–8.01 (m, 4H), 7.62–7.44 (m, 6H), 3.47 (s, 4H).

6.12.2 (1*R*,4*R*)-1,4-Diphenylbutane-1,4-diol (244)

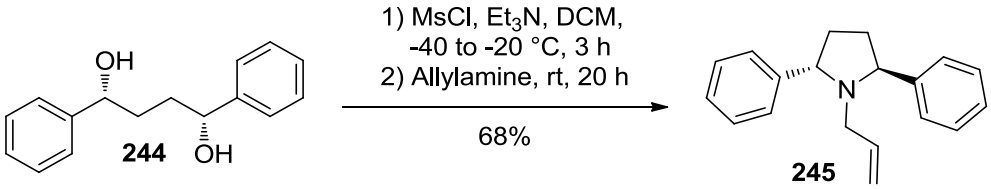


To a solution of (*S*)-diphenyl(pyrrolidine-2-yl)methanol (**294**) (4.8 g, 19 mmol, 20 mol-%) in THF (100 mL) at rt was added $B(OMe)_3$ (2.5 g, 2.7 mL, 24 mmol, 25 mol-%) and the resulting mixture was stirred at rt for 2 hours. Borane dimethyl sulfide complex (14.5 g, 18 mL, 190 mmol, 200 mol-%) was added and then a solution of **243** (22.7 g, 95 mmol, 100 mol-%) in THF (500 mL) was added *via* cannula over 40 min. Stirring was then continued for 1 hour and the reaction was quenched by addition of HCl solution (2M aq., 120 mL). The solvents were evaporated under reduced pressure and the residue was diluted with EtOAc (100 mL) and water (50 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:2 to 1:1) to afford the product **244** as a colourless viscous oil, which solidified after keeping under high vacuum overnight (22.6 g, 93 mmol, 98%). The spectroscopic data match those reported in the literature.[95]

R_f (EtOAc/hexanes 1:2) = 0.22; mp 77–78 °C; $[\alpha]_D$ = +57.7 (*c* 1.0, $CHCl_3$) (lit. $[\alpha]_D$ = +58 (*c* 1.02, $CHCl_3$))[95b]; ^{1}H NMR (250 MHz, CD_3OD): δ 7.30–7.19 (m, 10H),

4.60 (t, 2H, *J* = 6.1 Hz), 1.93–1.76 (m, 2H), 1.74–1.59 (m, 2H); ^{13}C NMR (62.9 MHz, CD_3OD): δ 146.4, 129.2, 128.2, 127.0, 75.0, 36.4.

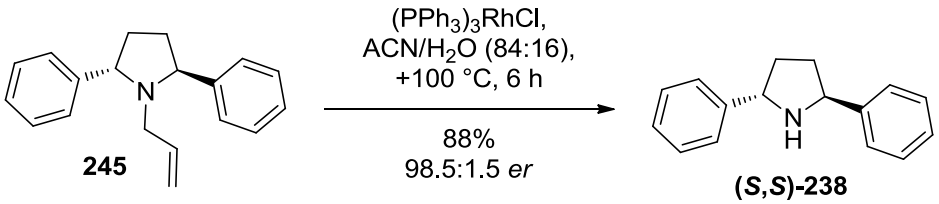
6.12.3 (2*S*,5*S*)-1-Allyl-2,5-diphenylpyrrolidine (245)



To a stirred solution of **244** (22.6 g, 93 mmol, 100 mol-%) in DCM (250 mL) at –40 °C were added Et_3N (28.3 g, 39 mL, 280 mmol, 300-mol%) and MsCl (26.7 g, 18 mL, 233 mmol, 250 mol-%) and the reaction mixture was slowly allowed to warm (from –40 to –20 °C) while stirring for 3 hours. Allylamine (153 g, 201 mL, 2670 mmol, 2900 mol-%) was added *via* cannula and the reaction mixture was allowed to slowly warm to rt while stirring for 20 hours. The reaction was quenched by addition of water (500 mL). The layers were separated and the organic layer was washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was adsorbed to silica gel (100 g) and purified by CombiFlash system (automatic gradient method, EtOAc/hexanes 0:1 to 2:3) to afford the product **245** as a clear oil (16.8 g, 64 mmol, 68%). The spectroscopic data match those reported in the literature.[95]

R_f (10% EtOAc-hexanes) = 0.65; $[\alpha]_D$ = –115.9 (*c* 1.03, $CHCl_3$) (lit. $[\alpha]_D$ = -115 (*c* 0.56, $CHCl_3$))[95b]; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.34–7.21 (m, 10H), 5.65 (dddd, 1H, *J* = 17.9, 10.7, 7.3, 4.6 Hz), 4.96–4.86 (m, 2H), 4.39–4.30 (m, 2H), 2.99 (ddt, 1H, *J* = 14.7, 4.5, 1.9 Hz), 2.73 (dd, 1H, *J* = 14.7, 7.3 Hz), 2.61–2.43 (m, 2H), 2.00–1.84 (m, 2H).

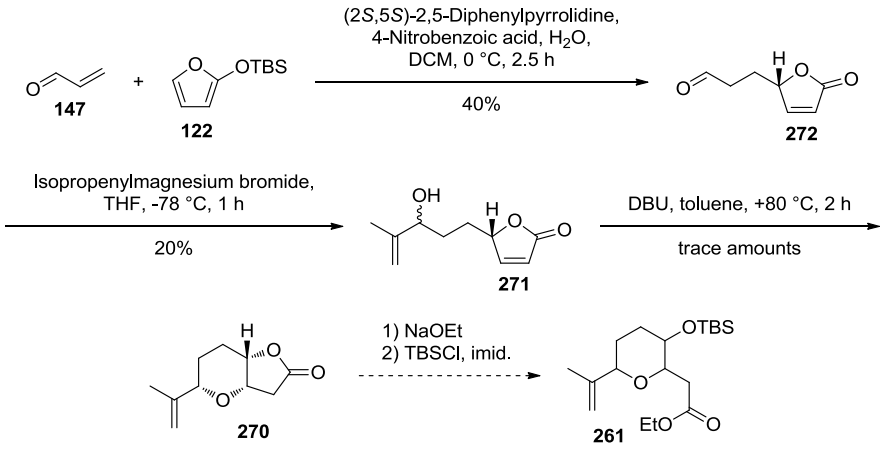
6.12.4 (2*S*,5*S*)-2,5-Diphenylpyrrolidine ((*S*,*S*)-238)



A stirred solution of **245** (16.8 g, 64 mmol, 100 mol-%) in a solvent mixture of ACN/H_2O (84:16, 567 mL) at rt was flushed with Argon for 30 minutes. $(PPh_3)_3RhCl$ (Wilkinson's catalyst, 2.9 g, 3.2 mmol, 5 mol-%) was added and the reaction mixture was heated (bath +100 °C) and stirred for 6 hours. The reaction mixture was then allowed to cool to rt and concentrated under reduced pressure. The residue was diluted with water (200 mL) and DCM (200 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was adsorbed to silica gel (40 g) and purified by CombiFlash system (automatic gradient method, EtOAc/hexanes 0:1 to 1:1) to afford the product **(*S*,*S*)-238** as white crystals (10.4 g, 46 mmol, 73%, 98.5:1.5 *er*). The enantiomeric ratio was determined by HPLC (CHIRALPAK IB column, hexane/2-propanol/diethyl amine 99.5:0.5:0.1, 0.5 ml/min flow rate); $\tau_{(R)\text{-isomer, minor}}$ = 20.3 min; $\tau_{(S)\text{-isomer,major}}$ = 22.0 min. The spectroscopic data match those reported in the literature.[95]

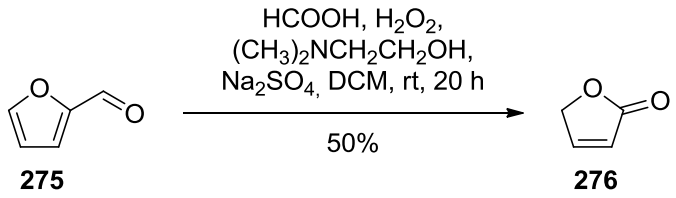
R_f (10% EtOAc-hexanes) = 0.31; mp 47–48 °C (lit. mp 43 °C)[95b]; $[\alpha]_D$ = –103.5 (*c* 0.99, $CHCl_3$) (lit. $[\alpha]_D$ = –108.2 (*c* 0.45, $CHCl_3$))[95b]; ^1H NMR (250 MHz, $CDCl_3$): δ 7.43–7.38 (m, 4H), 7.37–7.30 (m, 4H), 7.27–7.20 (m, 2H), 4.60–4.49 (m, 2H), 2.48–2.31 (m, 2H), 1.99–1.82 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 145.9, 128.4, 126.8, 126.3, 62.2, 35.5; HRMS (ESI^+): m/z calcd for $[C_{16}H_{18}N]$ 224.1439, found 224.1439, Δ = 0.0 ppm

6.13 Synthesis of the Cladiellin Precursor



Scheme 55. Route for the synthesis of the cladiellin precursor.

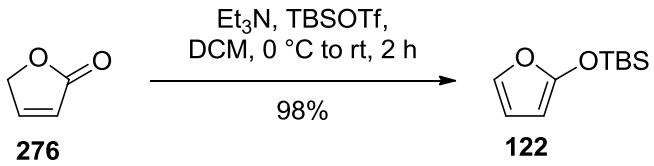
6.13.1 Furan-2(5*H*)-one (276)



To a solution of **275** (30 g, 26 mL, 308 mmol, 100 mol-%) in DCM (100 mL) at rt was added Na_2SO_4 (15 g, 50 wt-%), *N*,*N*-dimethylethanolamine (9.3 g, 11 mL, 105 mmol, 34 mol-%) and formic acid (28 g, 23 mL, 615 mmol, 200 mol-%). To the resulting reaction mixture was then added H_2O_2 solution (30% aq., 65 g, 57 mL, 573 mmol, 190 mol-%) over 2 hours, and the stirring was then continued at rt for 18 hours. The layers were separated and the aqueous layer was extracted with DCM (50 mL). The combined organic extracts were washed with $Na_2S_2O_5$ solution (sat. aq., 3×50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by distillation under reduced pressure (80–84 °C/5 torr) to afford the product **276** as a yellow oil (13 g, 155 mmol, 50%). Spectral data match those reported previously in the literature.[106]

R*f*(Et_2O) = 0.34; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (dt, 1H, *J* = 5.8, 1.7 Hz), 6.09 (dt, 1H, *J* = 5.8, 2.2 Hz), 4.86 (dd, 2H, *J* = 2.2, 1.7 Hz).

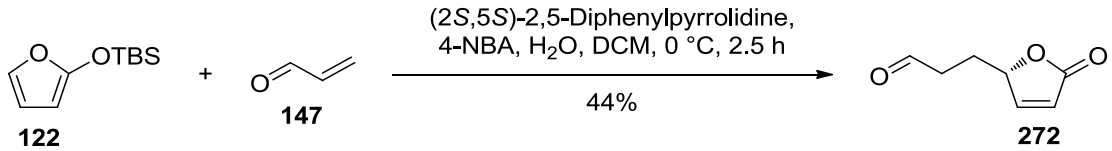
6.13.2 *tert*-Butyl(furan-2-yloxy)dimethylsilane (122)



To a solution of **276** (2.4 g, 2 mL, 29 mmol, 100 mol-%) in DCM (25 mL) was added Et_3N (5.9 g, 8 mL, 58 mmol, 200 mol-%). The mixture was cooled to 0 °C, and *tert*-butyldimethylsilyl triflate (9.2 g, 8 mL, 35 mmol, 120 mol-%) was added slowly to the cold mixture. The ice bath was removed and stirring was continued at rt for 2 hours. The reaction was then quenched by addition of water (50 mL), and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether 40–60 °C) to afford the product **122** as a clear oil (5.7 g, 29 mmol, 98%). Spectral data match those reported previously in the literature.[107]

R*f*(Et_2O) = 0.95; ^1H NMR (400 MHz, $CDCl_3$): δ 6.81 (dd, 1H, *J* = 2.2, 1.1 Hz), 6.20 (dd, 1H, *J* = 3.2, 1.1 Hz), 5.10 (dd, 1H, *J* = 3.2, 1.1 Hz), 0.97 (s, 9H), 0.24 (s, 6H).

6.13.3 (*S*)-3-(5-Oxo-2,5-dihydrofuran-2-yl)propanal (272)

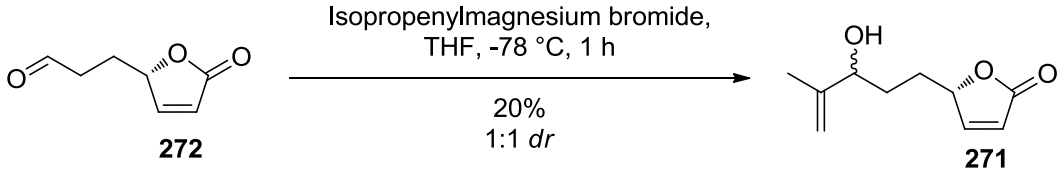


To a stirred solution of (2*S*,5*S*)-2,5-diphenylpyrrolidine (119 mg, 0.53 mmol, 10 mol-%), 4-nitrobenzoic acid (89.2 mg, 0.53 mmol, 10 mol-%) and water (191 mg, 0.19 mL, 10.6 mmol, 200 mol-%) in DCM (6 mL) at 0 °C were added acrolein (**147**) (897 mg, 1.1 mL, 15.9 mmol, 300 mol-%) and **122** (1.06 g, 1.1 mL, 5.3 mmol, 100 mol-%). The mixture was stirred at 0 °C for 2.5 hours, then

concentrated under reduced pressure and purified by flash chromatography (Et_2O) to afford the product **272**[vi] as a yellow oil (324 mg, 2.3 mmol, 44%).

R*f*(Et_2O) = 0.11; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.44 (dd, 1H, *J* = 5.7, 2.0 Hz), 6.13 (dd, 1H, *J* = 5.7, 2.0 Hz), 5.12 (ddt, 1H, *J* = 8.1, 4.1, 2.0 Hz), 2.72 (dt, 1H, *J* = 19.0, 7.1 Hz), 2.64 (dt, 1H, *J* = 19.0, 7.1 Hz), 2.25 (dtd, 1H, *J* = 14.5, 7.1, 4.1 Hz), 1.85 (ddt, 1H, *J* = 14.5, 8.1, 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 172.7, 155.9, 121.9, 81.9, 38.7, 25.2.

6.13.4 (5*S*)-5-(3-Hydroxy-4-methylpent-4-en-1-yl)furan-2(5*H*)-one (271)



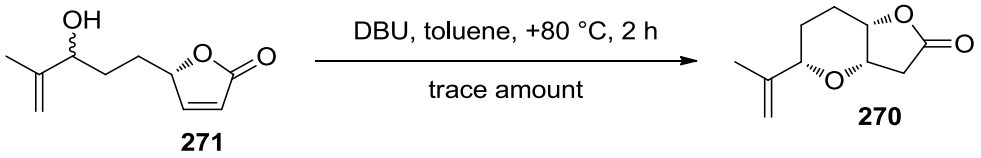
To a solution of **272** (100 mg, 0.71 mmol, 100 mol-%) in THF (1 mL) at –78 °C was added isopropenylmagnesium bromide solution (0.5M in THF, 1.7 mL, 0.86 mmol, 120 mol-%). The mixture was allowed to slowly warm for 1 hour while stirring. The reaction was quenched by addition of NH_4Cl solution (sat. aq., 20 mL) and allowed to warm to rt. The crude mixture was then diluted with EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to afford the product **271** as a clear oil (28.5 mg, 0.16 mmol, 20%, 1:1 *dr*).

R*f*(EtOAc) = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, 1H, *J* = 5.7, 1.3 Hz), 6.12 (dd, 1H, *J* = 5.7, 2.0 Hz), 5.16–5.10 (m, ½H), 5.10–5.05 (m, ½H), 4.96 (s, 1H), 4.89–4.85 (m, 1H), 4.16–4.06 (m, 1H), 2.02–1.74 (m, 2H), 1.73 (s, ½×3H), 1.72 (s,

[vi] The *er* of the product from this reaction batch was not determined. The amount of the catalyst used affects the resulting *er*, *i.e.* a low catalyst loading will lead to lower *er*. With 20 mol-% catalyst loading 93.5:6.5 *er* can be achieved.

½×3H), 1.71–1.60 (m, 2H), 1.60–1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, one diastereomer): δ 173.2; 156.3, 147.2, 121.9, 111.43, 83.1, 75.1, 29.9, 29.2, 17.95; ^{13}C NMR (100 MHz, $CDCl_3$, other diastereomer): δ 173.2; 156.3, 147.2, 121.8, 111.41, 83.5, 75.3, 30.4, 29.6, 17.93.

6.13.5 (3*aS*,5*S*,7*aS*)-5-(Prop-1-en-2-yl)hexahydro-2*H*-furo[3,2-*b*]pyran-2-one *epi*-2 (270)

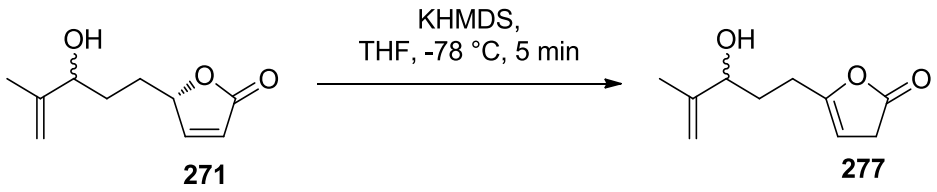


271 **270**

To a solution of **271** (52.4 mg, 0.29 mmol, 100 mol-%) in toluene (2.9 mL) was added 1,8-Diazabicyclo[5.4.0]undec-7-ene (438 mg, 0.43 mL, 2.9 mmol, 1000 mol-%). The reaction mixture was heated to +80 °C and stirred for 2 hours. The mixture was then allowed to cool, and HCl solution (1M aq., 20mL) and EtOAc (20 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Et_2O/petroleum ether 40-60 °C 1:1) to afford the product **270** as a clear oil (a trace amount).

R*f*(Et_2O) = 0.53; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.98–4.95 (m, 1H), 4.87–4.84 (m, 1H), 4.36–4.29 (m, 1H), 3.76 (br. d, 1H, *J* = 10.9 Hz), 2.71 (dd, 1H, *J* = 17.3, 4.1 Hz), 2.61 (d, 1H, *J* = 17.3 Hz), 2.43–2.35 (m, 1H), 1.88 (dddd, *J* = 15.1, 13.2, 5.2, 3.6 Hz), 1.73 (s, 3H), 1.70 (dddd, 1H, *J* = 13.4, 13.2, 11.0, 4.0 Hz), 1.58 (dddd, 1H, *J* = 13.4, 4.9, 2.4, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 145.0, 111.6, 78.8, 76.2, 73.6, 39.2, 25.5, 23.7, 18.6.

6.13.6 5-(3-Hydroxy-4-methylpent-4-en-1-yl)furan-2(3*H*)-one (268)



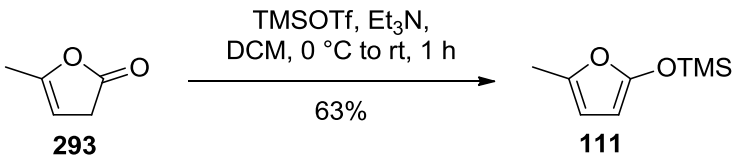
271 **277**

A solution of **271** (42.7 mg, 0.23 mmol, 100 mol-%) in THF (2.3 mL) was cooled to –78 °C. Potassium bis(trimethylsilyl)amide solution (1M in THF, 0.28 mmol, 0.28 mL, 120 mol-%) was added and stirring was continued for 5 minutes. The reaction was quenched by addition of $NaHCO_3$ solution (sat. aq., 50 mL) and diluted with DCM (20 mL) and allowed to warm to rt. The layers were separated and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Et_2O/petroleum ether 40-60 °C 1:1) to afford the product **277** as a clear oil (a trace amount).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15 (tt, 1H, *J* = 2.3, 1.3 Hz), 4.99–4.96 (m, 1H), 4.90–4.87 (m, 1H), 4.11 (t, 1H, *J* = 6.1 Hz), 3.18 (dt, 2H, *J* = 2.3, 2.3 Hz), 2.48–2.29 (m, 2H), 1.90–1.75 (m, 2H), 1.74 (s, 3H), 1.55 (br. s, 1H).

6.14 Preparation of the Silyl Protected Lactones

6.14.1 Trimethyl((5-methylfuran-2-yl)oxy)silane (111)



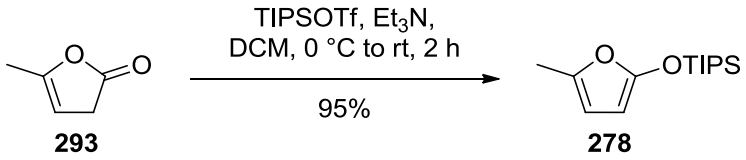
293 **111**

To a stirred solution of α-angelica lactone (**293)** (13.1 g, 12 mL, 134 mmol, 100 mol-%) in DCM (134 mL) at 0 °C was added Et_3N (19.0 g, 26 mL, 188 mmol, 140 mol-%) and TMSOTf (32.7 g, 25 mL, 147 mmol, 110 mol-%). The ice bath

was removed and stirring was continued at rt for 1 hour. The reaction mixture was concentrated under reduced pressure and the upper layer from the resulting biphasic system was isolated and distilled (+54 °C/10 torr) to afford the product **111** as a slightly yellow oil (14.4 g, 84.3 mmol, 63 %). The spectroscopic data match those reported in the literature.[70]

^{1}H NMR (250 MHz, $CDCl_3$): δ 5.75 (dq, 1H, *J* = 2.9, 1.1 Hz), 4.96 (d, 1H, *J* = 2.9 Hz), 2.16 (d, 3H, *J* = 1.1 Hz), 0.29 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 155.1, 141.7, 106.2, 83.6, 13.6, –0.1.

6.14.2 Triisopropyl((5-methylfuran-2-yl)oxy)silane (278)

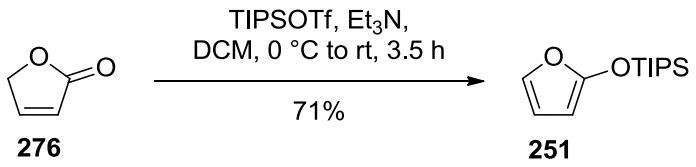


293 **278**

To a stirred solution of α-angelica lactone (**293**) (6.6 g, 6.0 mL, 66.8 mmol, 100 mol-%) in DCM (50 mL) at 0 °C was added Et_3N (13.5 g, 18.6 mL, 134 mmol, 200 mol-%) and TIPSOTf (24.6 g, 21.5 mL, 80.1 mmol, 120 mol-%). The ice bath was removed and stirring was continued at rt for 2 hours. The reaction was quenched by addition of water (100 mL). The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes) to afford the product **278** as a clear oil (16.2 g, 63.7 mmol, 95 %). The spectroscopic data match those reported in the literature.[118]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (dq, 1H, *J* = 2.9, 1.1 Hz), 4.97 (d, 1H, *J* = 2.9 Hz), 2.16 (d, 3H, *J* = 1.1 Hz), 1.32–1.18 (m, 3H), 1.10 (d, 18H, *J* = 7.2 Hz); ^{13}C NMR (63 MHz, $CDCl_3$): δ 155.3, 140.9, 106.0, 83.5, 17.6, 13.5, 12.2.

6.14.3 (Furan-2-yloxy)triisopropylsilane (251)



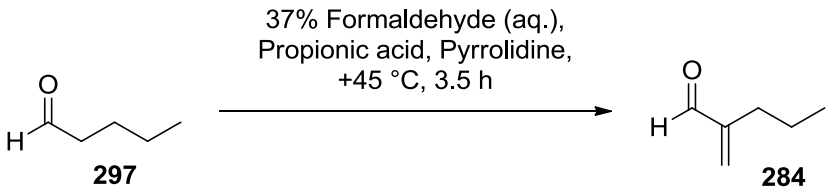
276 **251**

To a stirred solution of **276** (4.0 g, 3.4 mL, 48 mmol, 100 mol-%) in DCM (50 mL) at 0 °C was added Et_3N (9.6 g, 13 mL, 95 mmol, 200 mol-%) and TIPSOTf (17.5 g, 15 mL, 57 mmol, 120 mol-%). The ice bath was removed and stirring was continued at rt for 3.5 hours. The reaction was quenched by addition of water (100 mL). The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes) to afford the product **251** as a clear oil (8.2 g, 34 mmol, 71%). The spectroscopic data match those reported in the literature.[119]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (dd, 1H, *J* = 2.2, 1.0 Hz), 6.20 (dd, 1H, *J* = 3.1, 2.2 Hz), 5.12 (dd, 1H, *J* = 3.1, 1.0 Hz), 1.37–1.17 (m, 3H), 1.10 (d, 18H, *J* = 6.8 Hz).

6.15 Preparation of the α-Substituted Acroleins

6.15.1 α-Propylacrolein (284)



297 **284**

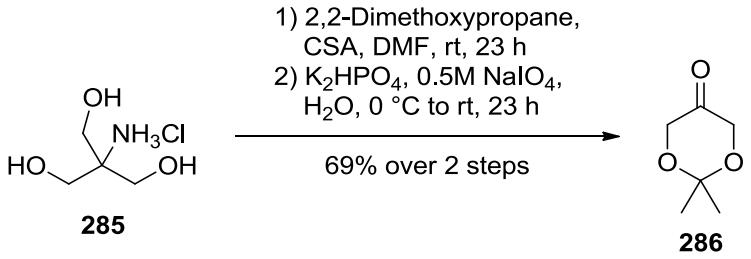
To a stirred solution of valeraldehyde (**297**) (14.8 g, 12 mL, 172 mmol, 100 mol-%) and formaldehyde solution (37% aq., 14.0 g, 12.8 mL, 172 mmol, 100 mol-%) in *i*-PrOH (7.5 mL) at rt were added propionic acid (1.27 g, 1.3 mL, 17.2 mmol, 10 mol-%) and pyrrolidine (1.22 g, 1.4 mL, 17.2 mmol, 10 mol-%). The reaction

mixture was heated to (bath +45 °C) and stirred for 3.5 hours. The reaction was quenched by addition of $NaHCO_3$ solution (sat. aq., 50 mL) and diluted with DCM (50 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by fractional distillation (32 °C/10 torr) to afford the product **284** as a slightly yellow oil (2.2 g, 23 mmol, 13%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 6.25–6.23 (m, 1H), 6.00–5.98 (m, 1H), 2.22 (t, 2H, *J* = 7.5 Hz), 1.48 (sext., 2H, *J* = 7.5 Hz), 0.92 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 150.2, 134.0, 29.8, 21.0, 13.7.

6.16 Preparation of 3-Oxoprop-1-en-2-yl Acetate

6.16.1 2,2-Dimethyl-1,3-dioxan-5-one (286)



285 **286**

To a stirred solution of 2-amino-2-hydroxymethyl-1,3-propandiol hydrochloride (**285**) (21.5 g, 127 mmol, 100 mol-%) and 2,2-dimethoxypropane (15.9 g, 19 mL, 152 mmol, 120 mol-%) in DMF (140 mL) was added (1*S*)-(+)-10-camphorsulfonic acid (1.49 g, 6.35 mmol, 5 mol-%). The reaction mixture was stirred at rt for 23 hours. Et_3N (1.2 mL) was added and the reaction mixture was concentrated under reduced pressure. EtOAc (325 mL) and Et_3N (18 mL) were added and the reaction mixture was stirred at rt for 2 hours. The resulting white suspension was filtered and the filtrate was concentrated under reduced pressure to afford the crude product. This material was used directly in

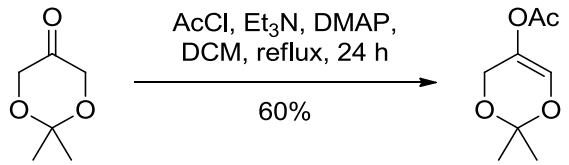
the next reaction without further purification. The spectroscopic data match those reported in the literature. [109a,b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (d, 2H, *J* = 11.5 Hz), 3.43 (d, 2H, *J* = 11.5 Hz), 3.36 (s, 2H), 1.35 (s, 3H), 1.27 (s, 3H).

To a stirred (a mechanical stirrer was used) suspension of the crude material (20.5 g, 127 mmol, 100 mol-%) and K_2HPO_4 (22.1 g, 127 mmol, 100 mol-%) in water (190 mL) at 0 °C was slowly (over 4.5 hours) added $NaIO_4$ solution (0.5M aq., 390 mL). The temperature of the reaction mixture was kept below +2 °C during the addition. The ice bath was removed and stirring was continued at rt for 23 hours. The mixture was then extracted with DCM (24 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the product **286** as a slightly yellow oil (11.4g, 87 mmol, 69% over 2 steps). The spectroscopic data match those reported in the literature. [109a,b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (s, 4H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.0, 100.1, 66.8, 23.5.

6.16.2 2,2-Dimethyl-4*H*-1,3-dioxin-5-yl acetate (287)



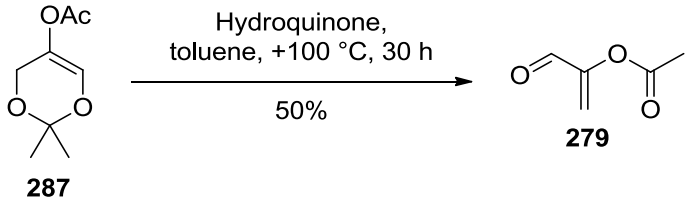
286 **287**

To a stirred solution of **286** (11.4 g, 9.5 mL, 87.3 mmol, 100 mol-%) in DCM (150 mL) at 0 °C were added Et_3N (17.7 g, 24.3 mL, 175 mmol, 200 mol-%), DMAP (2.13 g, 17.5 mmol, 20 mol-%) and acetyl chloride (8.91 g, 8.0 mL, 114 mmol, 130 mol-%). The ice bath was replaced by an oil bath and the reaction mixture was refluxed (bath +60 °C) for 12 hours. Et_3N (8.71 g, 12 mL, 86.1 mmol, 100 mol-%) and acetyl chloride (6.63 g, 6.0 mL, 84.5 mmol, 100 mol-%) were

added, and refluxing was continued for an additional 12 hours. The reaction mixture was then quenched by addition of water (200 mL), allowed to cool to rt and diluted with Et_2O (300 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 150 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Et_2O/pentane 1:1) to afford the product **287** as a yellow oil (9.04 g, 52.5 mmol, 60%). The spectroscopic data match those reported in the literature. [109a,b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (t, 1H, *J* = 1.5 Hz), 4.24 (d, 2H, *J* = 1.5 Hz), 2.13 (s, 3H), s, 6H).

6.16.3 3-Oxoprop-1-en-2-yl acetate (279)

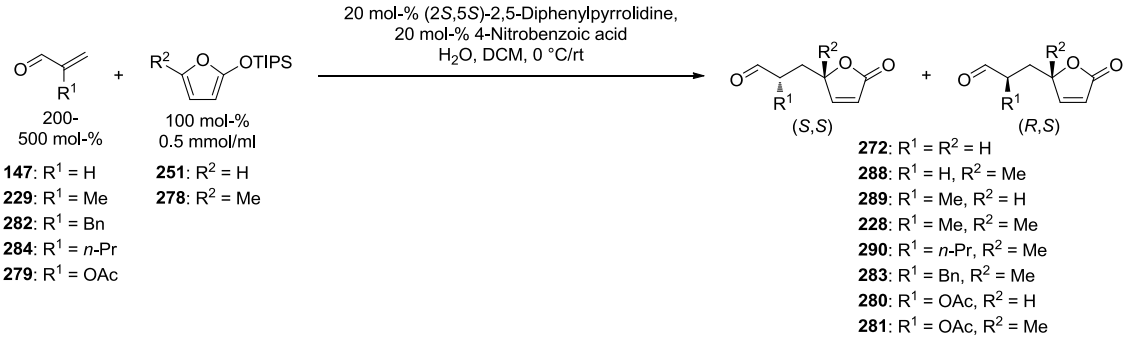


To a stirred solution of **287** (9.0 g, 8 mL, 52.5 mmol, 100 mol-%) in toluene (100 mL) at rt was added hydroquinone (2.3 g, 21 mmol, 40 mol-%). The reaction mixture was stirred at +100 °C for 30 hours. The reaction mixture was then allowed to cool and concentrated under reduced pressure. The residue was purified by flash chromatography (Et_2O/pentane 1:5 to 1:1) to afford the product **279** as a yellow oil (3.0 g, 26.2 mmol, 50%). The spectroscopic data match those reported in the literature. [109c]

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 6.03 (d, 1H, *J* = 2.3 Hz), 5.90 (d, 1H, *J* = 2.3 Hz), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.3, 168.1, 152.7, 121.5, 20.3.

6.17 The Mukaiyama–Michael Reaction with a Variety of α-Substituted Acroleins

Table 20. The substrate scope for α-substituted acroleins used in the Mukaiyama–Michael reactions with silyloxyfurans.

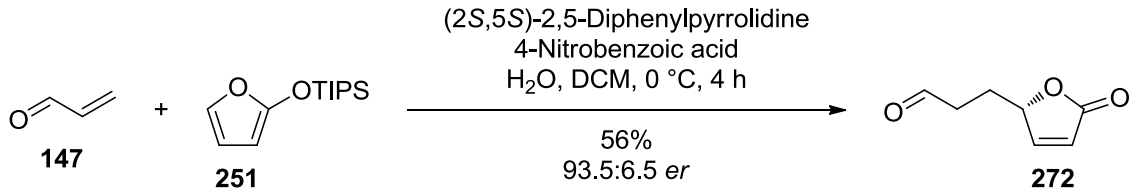


Entry	R¹	R²	Temperature [°C]	Stirring Time	Yield[b] [%]	*er*[c]	*dr*[g] [(*S*,*S*):(*S*,*R*)]
1	H	H	0	4 h	56	93.5/6.5	-
2	H	Me	0	3 d	61	93.5/6.5	-
3	Me	H	0	2 d	53	97.5/2.5	50:50
4[a]	Me	Me	0	2 d	82	97/3	55:45
5	*n*-Pr	Me	0	29 h	58	95/5	57:43
6	Bn	Me	rt	5 d	69	85/15[d]	48:52
7	AcO	H	0	4 h	58	96.5/3.5[e]	64:36
8	AcO	Me	0	5 h	71	97/3[f]	50:50

[a] 10 mol-% of catalyst and 10 mol-% acid were used in this reaction. [b] Isolated yield. [c] Determined by GC (Supelco Astec CHIRALDEX B-DM column). In general, the enantiomeric ratio (*er*) was similar (±2 %) for both diastereomers. [d] Determined by HPLC (Chiralcel IC column) from alcohol derivative. [e] Determined by HPLC (Chiralcel IC column) from 5,5-Dimethyl-1,3-dioxan-2-yl –derivative. [f] Determined by HPLC (Chiralcel IB column) from 5,5-Dimethyl-1,3-dioxan-2-yl –derivative. [g] Determined by NMR from the crude reaction mixture.

General procedure: To a stirred solution of (2*S*,5*S*)-2,5-diphenylpyrrolidine (20 mol-%), 4-nitrobenzoic acid (20 mol-%) and water (200 mol-%) in DCM were added α-substituted acrolein (200-500 mol-%) and silyloxyfuran (0.5 mmol/mL, 100 mol-%). The mixture was stirred at either 0 °C or rt. After completion of the reaction (determined by TLC or NMR), the mixture was either filtered through a layer of silica and concentrated, or the mixture was poured directly into the flash column and purified by flash chromatography to afford the desired products.

6.17.1 (*S*)-3-(5-Oxo-2,5-dihydrofuran-2-yl)propanal (272)



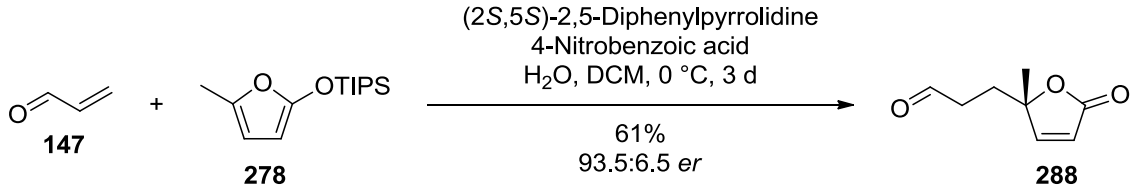
The reaction was carried out according to the general procedure using **147**(561 mg, 0.67 mL, 10 mmol, 1000 mol-%) and **251** (481 mg, 0.52 mL, 2 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 4 hours. The cold reaction mixture was filtered through a silica layer (ø 2 cm × 2 cm), which was washed with Et_2O (15 mL) and DCM (15 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Et_2O) to afford the product **272** as a yellow oil (156 mg, 1.1 mmol, 56%, 93.5:6.5 *er*). The enantiomeric ratio was determined by GC (SUPELCO Astec CHIRALDEX B-DM column, 150 °C isothermic); $\tau_{(R)\text{-isomer, minor}}$ = 5.2 min; $\tau_{(S)\text{-isomer,major}}$ = 5.9 min.

R_f (EtOAc) = 0.54; $[\alpha]_D$ = +60.0 (*c* 1.1, $CHCl_3$) ; IR (film, cm^{-1}): 2927, 2850, 1746, 1720, 1163, 1095, 817; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (t, 1H, *J* = 0.7 Hz), 7.43 (dd, 1H, *J* = 5.7, 1.8 Hz), 6.10 (dd, 1H, *J* = 5.7, 2.0 Hz), 5.10 (dddd, 1H, *J* = 8.0, 4.1, 2.0, 1.8 Hz), 2.68 (dddd, 1H, *J* = 18.9, 7.3, 7.3, 0.7 Hz), 2.61 (dddd, 1H , *J* = 18.9, 7.0, 6.4, 0.7 Hz), 2.22 (dddd, 1H, *J* = 14.7, 7.3, 7.0, 4.1 Hz), 1.83 (dddd, 1H, *J* = 14.7, 8.0, 7.3, 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 172.7, 155.9, 122.0, 81.9, 38.8, 25.2; HRMS (ESI^+): m/z calcd for $[C_7H_8O_3Na]$ 163.0371, found 163.0363, Δ = 4.9 ppm.

Preparation of the racemic product: To a stirred solution of trifluoroacetic acid (45.6 mg, 0.03 mL, 0.4 mmol, 20 mol-%) and water (72.1 mg, 0.07 mL, 4 mmol, 200 mol-%) in DCM (4 mL) at 0 °C were added **147** (561 mg, 0.67 mL, 10 mmol, 500 mol-%) and **251** (481 mg, 0.52 mL, 2 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 6.5 hours and then poured directly in the flash column and purified by flash chromatography (Et_2O) to afford the product **272**

as a yellow oil (84.7 mg, 0.60 mmol, 30%). The spectroscopic data match those of the enantiopure compound.

6.17.2 (*S*)-3-(2-Methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (288)



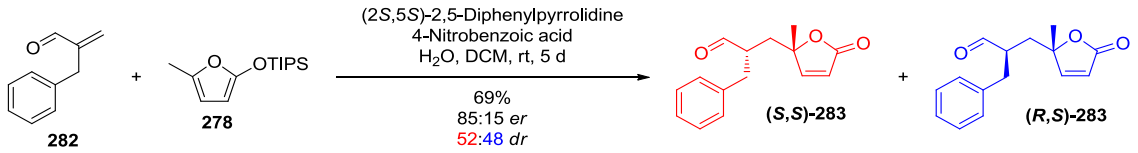
The reaction was carried out according to the general procedure using **147** (399 mg, 0.47 mL, 7.1 mmol, 200 mol-%) and **278** (904 mg, 1.0 mL, 3.6 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 3 days and then poured directly in the flash column and purified by flash chromatography (Et_2O) to afford the product **288** as a yellow oil (333 mg, 2.2 mmol, 61%, 93.5:6.5 *er*). The enantiomeric ratio was determined by GC (SUPELCO Astec CHIRALDEX B-DM column, 150 °C isothermic); $\tau_{(R)\text{-isomer, minor}}$ = 4.6 min; $\tau_{(S)\text{-isomer, major}}$ = 4.8 min.

R_f (Et_2O) = 0.35; $[\alpha]_D$ = +38.9 (*c* 1.0, $CHCl_3$) ; IR (film, cm^{-1}): 3058, 2982, 2935, 2840, 2733, 1752, 1722, 1185, 1116, 953, 822; ^1H NMR (250 MHz, $CDCl_3$): δ 9.70 (t, 1H, *J* = 0.9 Hz), 7.31 (d, 1H, *J* = 5.6 Hz), 5.99 (d, 1H, *J* = 5.6 Hz), 2.50 (dddd, 1H, *J* = 18.5, 8.0, 6.5, 0.9 Hz),2.37 (dddd, 1H, *J* = 18.5, 7.5, 6.7, 0.9 Hz), 2.14 (ddd, 1H, *J* = 14.5, 7.5, 6.5 Hz), 2.06 (ddd, 1H, *J* = 14.5, 8.0, 6.7), 1.47 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 200.4, 172.1, 160.0, 121.0, 87.8, 38.0, 29.7, 24.3; HRMS (ESI^+): m/z calcd for $[C_8H_{10}O_3Na]$ 177.0528, found 177.0522, Δ = 3.4 ppm.

Preparation of the racemic product: To a stirred solution of trifluoroacetic acid (45.6 mg, 0.03 mL, 0.4 mmol, 20 mol-%) and water (72.1 mg, 0.07 mL, 4 mmol, 200 mol-%) in DCM (4 mL) at 0 °C were added **147** (561 mg, 0.67 mL, 10 mmol, 500 mol-%) and **278** (509 mg, 0.56 mL, 2 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 6.5 hours and then filtered through a silica layer (ø 2 cm × 2 cm), which was washed with Et_2O (15 mL) and DCM (15 mL). The

filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Et_2O) to afford the product **288** as a yellow oil (106 mg, 0.69 mmol, 34%). The spectroscopic data match those of the enantiopure compound.

6.17.3 (*S*)-2-Benzyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal ((*S*,*S*)-283) and (*R*)-2-benzyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal ((R,S)-283)



The reaction was carried out according to the general procedure using **282** (565 mg, 0.57 mL, 3.44 mmol, 200 mol-%) and **278** (438 mg, 0.48 mL, 1.72 mmol, 100 mol-%). The reaction mixture was stirred at rt for 5 days and then poured directly in the flash column and purified by flash chromatography (Et_2O/Pentane 1:1) to afford the product **283** as a mixture of diastereomers as a slightly yellow oil (290 mg, 1.19 mmol, 69%, 85:15 *er*, 52:48 *dr*). The enantiomeric ratio was determined by HPLC (CHIRALPAK IC column, 10% *i*-PrOH/hexane, flow rate 1.0 mL/min, 214 nm) of the corresponding alcohols (prepared by Luche reduction[97]); $\tau_{\text{"(S,S)-isomer", minor}}$ = 42.7 min; $\tau_{\text{(S,S)-isomer,major}}$ = 70.4 min; $\tau_{\text{"(R,S)-isomer", major}}$ = 46.6 min; $\tau_{\text{"(R,S)-isomer", minor}}$ = 59.0 min.

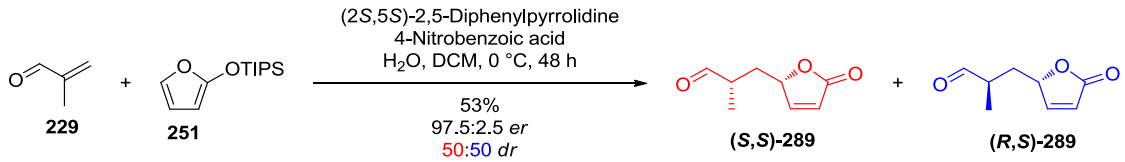
(*S*)-2-Benzyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal ((*S*,*S*)-283): R_f (Et_2O/hexanes 2:1) = 0.24; $[\alpha]_D$ = –34.2 (*c* 1.6, $CHCl_3$) ; IR (film, cm^{-1}): 3029, 2982, 2933, 2850, 2726, 1748, 1723, 1198, 1114, 952, 819, 702; ^1H NMR (400 MHz, $CDCl_3$): δ 9.62 (dd, 1H, *J* = 1.2, 0.8 Hz), 7.33–7.27 (m, 2H), 7.26–7.20 (m, 1H), 7.23 (d, 1H, *J* = 5.6 Hz), 7.15–7.11 (m, 2H), 5.94 (d, 1H, *J* = 5.6 Hz), 2.95 (dd, 1H, *J* = 14.0, 7.3 Hz), 2.77 (dd, 1H, *J* = 14.0, 7.3 Hz), 2.62 (app. dtdd, 1H, *J* = 9.2, 7.3, 2.3, 1.2 Hz), 7.28 (dd, 1H, *J* = 14.7, 9.2 Hz), 1.87 (dd, 1H, *J* = 14.7, 2.3 Hz), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.4, 172.3, 160.7, 137.2, 129.1, 128.9, 127.1,

120.5, 88.0, 47.8, 36.4, 35.5, 25.1; HRMS (ESI$^+$): m/z calcd for [$C_{15}H_{16}O_3Na$] 267.0997, found 267.1002, Δ = 1.9 ppm.

(*R*)-2-Benzyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal ((R,S)-283): R_f (Et_2O/hexanes 2:1) = 0.17; $[\alpha]_D$ = +69.4 (*c* 0.6, $CHCl_3$) ; IR (film, cm^{-1}): 3030, 2982, 2930, 2851, 1754, 1724, 1455, 1114, 951, 819, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (d, 1H, *J* = 2.3 Hz), 7.33–7.20 (m, 3H), 7.15–7.09 (m, 2H), 7.05 (d, 1H, *J* = 5.6 Hz), 6.00 (d, 1H, *J* = 5.6 Hz), 2.96 (dd, 1H, *J* = 13.8, 6.5 Hz), 2.67 (dd, 1H, *J* = 13.8, 8.3 Hz), 2.57 (tddd, 1H, *J* = 8.3, 6.5, 3.1, 2.3 Hz), 2.42 (dd, 1H, *J* = 14.8, 8.3 Hz), 1.68 (dd, 1H, *J* = 14.8, 3.1 Hz), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 171.7, 159.6, 137.4, 129.1, 128.8, 126.9, 121.3, 87.8, 48.6, 36.0, 35.9, 24.6; HRMS (ESI$^+$): m/z calcd for [$C_{15}H_{16}O_3Na$] 267.0997, found 267.1003, Δ = 2.2 ppm.

Preparation of the racemic product: To a stirred solution of pyrrolidine (28.4 mg, 0.03 mL, 0.4 mmol, 20 mol-%), 4-nitrobenzoic acid (66.8 mg, 0.4 mmol, 20 mol-%) and $KHSO_4$ solution (sat. aq., 0.18 mL) in DCM (4 mL) were added **282** (657 mg, 0.66 mL, 4 mmol, 200 mol-%) and **278** (509 mg, 0.56 mL, 2 mmol, 100 mol-%). The reaction mixture was stirred at rt for 26.5 hours and then filtered through a silica layer (ø 2 cm × 2 cm), which was washed with Et_2O (20 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Et_2O/hexanes 1:1) to afford the product **283** as a mixture of diastereomers as a slightly yellow oil (101 mg, 0.4 mmol, 21%, 52:48 *dr*). The spectroscopic data match those of the enantiopure compound.

6.17.4 (*R*)-1-Oxo-3-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)propan-2-yl acetate ((*S*,*S*)-289) and (*S*)-1-oxo-3-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)propan-2-yl acetate ((*R*,*S*)-289)



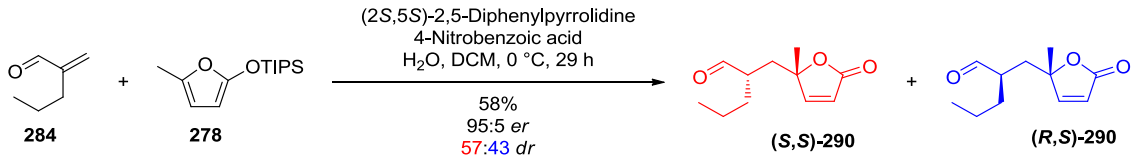
The reaction was carried out according to the general procedure using **229**(280 mg, 0.33 mL, 4 mmol, 200 mol-%) and **251** (481 mg, 0.52 mL, 2 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 48 hours and then filtered through a silica layer (ø 2 cm × 4 cm), which was washed with Et_2O (30 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Et_2O) to afford the product **289** as a mixture of diastereomers as a clear oil (161 mg, 1.1 mmol, 53%, 97.5:2.5 *er*, 50:50 *dr*). The enantiomeric ratio was determined by GC (SUPELCO Astec CHIRALDEX B-DM column, 120 °C isothermic); τ_{minor} = 18.9 min; τ_{minor} = 20.5 min; τ_{major} = 20.8 min; τ_{major} = 22.7 min.

R_f (Et_2O) = 0.39; IR (film, cm^{-1}): 3092, 2969, 2937, 2867, 2832, 2723, 1745, 1721, 1163, 1105, 1023, 910, 814; ^1H NMR (400 MHz, $CDCl_3$, other half): δ 9.68 (app. t, 1H, *J* = 0.8 Hz), 7.45 (dd, 1H, *J* = 5.8, 1.8 Hz), 6.12 (dd, 1H, *J* = 1.8, 1.2 Hz), 5.17–5.12 (m, 1H), 2.68–2.58 (m, 1H), 2.07 (ddd, 1H, *J* = 14.6, 8.8, 5.9 Hz), 1.80 (ddd, 1H, *J* = 14.6, 7.3, 4.1 Hz), 1.24 (d, 3H, *J* = 7.4 Hz); ^1H NMR (400 MHz, $CDCl_3$, other half): δ 9.64 (d, 1H, *J* = 0.9 Hz), 7.46 (dd, 1H, *J* = 5.8, 1.8 Hz), 6.10 (dd, 1H, *J* = 1.8, 1.2 Hz), 5.15–5.10 (m, 1H), 2.81–2.71 (m, 1H), 2.27 (ddd, 1H, *J* = 14.5, 8.8, 3.5 Hz), 1.44 (dddd, 1H, *J* = 14.5, 9.9, 4.3, 0.7 Hz), 1.22 (d, 1H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, other half): δ 203.3, 172.74, 156.2, 121.8, 80.9, 43.1, 34.1, 14.6; ^{13}C NMR (100 MHz, $CDCl_3$, other half): δ 203.1, 172.67, 156.2, 121.9, 81.6, 42.6, 33.2, 13.6; HRMS (ESI^+): m/z calcd for [$C_8H_{10}O_3Na$] 177.0528, found 177.0524, Δ = 2.3 ppm.

Preparation of the racemic product: To a stirred solution of (2*S*,5*S*)-2,5-diphenylpyrrolidine (42.0 mg, 0.2 mmol, 10 mol-%), (2*R*,5*R*)-2,5-diphenylpyrrolidine (44.8 mg, 0.2 mmol, 10 mol-%), 4-nitrobenzoic acid (69.6 mg, 0.4 mmol, 20 mol-%) and water (72.1 mg, 0.07 mL, 4 mmol, 200 mol-%) in DCM (4 mL) were added **229** (280 mg, 0.33 mL, 4 mmol, 200 mol-%) and **251** (481 mg, 0.52 mL, 2 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 24 hours and then filtered through a silica layer (ø 2 cm × 4 cm), which was

washed with Et_2O (30 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Et_2O) to afford the product **289** as a mixture of diastereomers as a clear oil (203 mg, 1.3 mmol, 66%, 50:50 *dr*). The spectroscopic data match those of the enantiopure compound.

6.17.5 (*S*)-2-(((*S*)-2-Methyl-5-oxo-2,5-dihydrofuran-2-yl)methyl)pentanal ((*S*,*S*)-290) and (*R*)-2-(((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)methyl)pentanal ((*R*,*S*)-290)



The reaction was carried out according to the general procedure using **284** (98.1 mg, 0.12 mL, 1 mmol, 200 mol-%) and **278** (127 mg, 0.14 mL, 0.5 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 29 hours and then filtered through a silica layer (ø 2 cm × 4 cm), which was washed with Et_2O (30 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Et_2O/Pentane 1:1) to afford the product **290** as a mixture of diastereomers as a clear oil (56.6 mg, 0.29 mmol, 58%, 95:5 *er*, 57:43 *dr*). The enantiomeric ratio was determined by GC (SUPELCO Astec CHIRALDEX B-DM column, 150 °C isothermic); $\tau_{\text{"(S,S)-isomer", minor}}$ = 6.0 min; $\tau_{(S,S)\text{-isomer, major}}$ = 6.2 min; $\tau_{\text{"(R,S)-isomer", minor}}$ = 7.6 min; $\tau_{(R,S)\text{-isomer, major}}$ = 8.1 min.

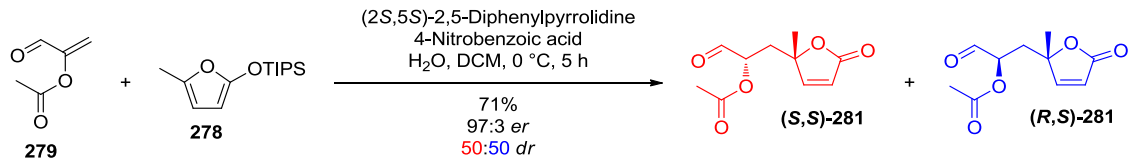
(*S*)-2-(((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)methyl)pentanal ((*S*,*S*)-290): R_f (Et_2O/Pentane 2:1) = 0.41; $[\alpha]_D$ = –53.5 (*c* 2.8, $CHCl_3$) ; IR (film, cm^{-1}): 3085, 2960, 2933, 2874, 2719, 1752, 1722, 1191, 1115, 952, 820; ^1H NMR (400 MHz, $CDCl_3$): δ 9.52 (dd, 1H, *J* = 1.0, 0.8 Hz), 7.25 (d, 1H, *J* = 5.6 Hz), 5.92 (d, 1H, *J* = 5.6 Hz), 2.33 (dd, 1H, *J* = 14.5, 9.3 Hz), 2.24–2.15 (m, 1H), 1.83 (dd, 1H, 14.5, 1.8 Hz), 1.65–1.55 (m, 1H), 1.48 (s, 3H), 1.45–1.34 (m, 1H), 1.33 (app. sext, 2H, *J* = 7.3 Hz), 0.90 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.5, 172.2,

160.5, 120.4, 88.0, 46.2, 35.4, 31.9, 25.1, 19.8, 14.0; HRMS (ESI⁺): m/z calcd for [$C_{11}H_{16}O_3Na$] 219.0997, found 219.0998, Δ = 0.5 ppm.

(*R*)-2-(((*S*)-2-Methyl-5-oxo-2,5-dihydrofuran-2-yl)methyl)pentanal ((*R*,*S*)-290): R_f (Et_2O/Pentane 2:1) = 0.30; $[\alpha]_D$ = +49.4 (*c* 0.98, $CHCl_3$) ; IR (film, cm^{-1}): 3085, 2960, 2933, 2874, 2718, 1755, 1722, 1456, 1190, 1113, 952, 820; ^1H NMR (400 MHz, $CDCl_3$): δ 9.55 (d, 1H, *J* = 2.7 Hz), 7.33 (d, 1H, *J* = 5.6 Hz), 6.04 (d, 1H, *J* = 5.6 Hz), 2.41 (dd, 1H, *J* = 14.4, 8.7 Hz), 2.38–2.29 (m, 1H), 1.67 (dd, 1H, *J* = 14.4, 3.0 Hz), 1.64–1.55 (m, 1H), 1.44 (s, 3H), 1.44–1.36 (m, 1H), 1.36–1.23 (m, 2H), 0.90 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.0, 171.8, 159.8, 121.2, 87.9, 47.2, 36.8, 32.1, 24.3, 19.8, 14.0; HRMS (ESI⁺): m/z calcd for [$C_{11}H_{16}O_3Na$] 219.0997, found 219.0998, Δ = 0.5 ppm.

Preparation of the racemic product: To a stirred solution of pyrrolidine (14.2 mg, 0.02 mL, 0.2 mmol, 20 mol-%), 4-nitrobenzoic acid (37.9 mg, 0.2 mmol, 20 mol-%) and water (36.0 mg, 0.04 mL, 2 mmol, 200 mol-%) in DCM (2 mL) were added **284** (196 mg, 0.23 mL, 2 mmol, 200 mol-%) and **278** (254 mg, 0.28 mL, 1 mmol, 100 mol-%). The reaction mixture was stirred at rt for 55 hours and then filtered through a silica layer (ø 2 cm × 2 cm), which was washed with Et_2O (30 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Et_2O/Pentane 1:1) to afford the product **290** as a mixture of diastereomers as a clear oil (103 mg, 0.5 mmol, 52%, 56:44 *dr*). The spectroscopic data match those of the enantiopure compound.

6.17.6 (*S*)-1-((*S*)-2-Methyl-5-oxo-2,5-dihydrofuran-2-yl)-3-oxopropan-2-yl acetate ((*S*,*S*)-281) and (*R*)-1-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-3-oxopropan-2-yl acetate ((*R*,*S*)-281)



The reaction was carried out according to the general procedure using **279** (228 mg, 0.21 mL, 2 mmol, 200 mol-%) and **278** (254 mg, 0.28 mL, 1 mmol,

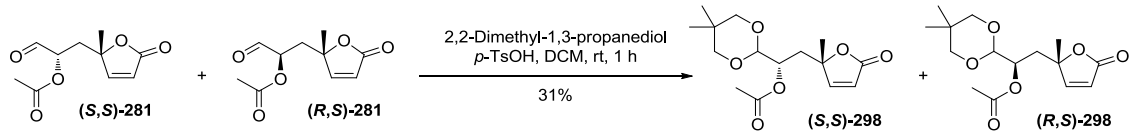
100 mol-%). The reaction mixture was stirred at 0 °C for 5 hours and then poured directly to the flash column and purified by flash chromatography (Et_2O) to afford the product **281** as a mixture of diastereomers as a reddish oil (151 mg, 0.71 mmol, 71%, 97:3 *er*, 51:49 *dr*). The enantiomeric ratio was determined by HPLC (CHIRALPAK IC column, 98% *i*-PrOH/hexane, flow rate 1.0 ml/min, 214 nm) of the corresponding (*S*)-1-(5,5-dimethyl-1,3-dioxan-2-yl)-2-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl acetate and (*R*)-1-(5,5-dimethyl-1,3-dioxan-2-yl)-2-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl acetate; τ_{major} = 26.6 min; τ_{major} = 34.1 min; τ_{minor} = 39.7 min; τ_{minor} = 59.3 min.

R_f (Et_2O) = 0.13; IR (film, cm^{-1}): 3467, 2982, 2937, 2842, 1742, 1373, 1229, 1123, 956, 825; ^1H NMR (400 MHz, $CDCl_3$, other half): δ 9.46 (s, 1H), 7.36 (d, 1H, *J* = 5.6 Hz), 5.99 (d, 1H, *J* = 5.6 Hz), 4.98 (dd, 1H, *J* = 9.0, 2.9 Hz), 2.52 (dd, 1H, *J* = 15.4, 2.9 Hz), 2.13 (dd, 1H, *J* = 15.4, 9.0 Hz), 2.12 (s, 3H), 1.51 (s, 3H); ^1H NMR (400 MHz, $CDCl_3$, other half): δ 9.45 (s, 1H), 7.39 (d, 1H, *J* = 5.6 Hz), 6.05 (d, 1H, *J* = 5.6 Hz), 4.94 (dd, 1H, *J* = 8.0, 4.2 Hz), 2.35 (dd, 1H, *J* = 15.4, 4.2 Hz), 2.28 (dd, 1H, *J* = 15.4, 8.0 Hz), 2.15 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, other half): δ 197.1, 171.7, 170.3, 159.6, 121.5, 86.2, 74.1, 36.6, 25.1, 20.6; ^{13}C NMR (100 MHz, $CDCl_3$, other half): δ 197.1, 171.6, 169.9, 159.2, 120.5, 86.7, 75.1, 36.5, 24.7, 20.6; HRMS (ESI^+): m/z calcd for [$C_{10}H_{12}O_5Na$] 235.0582, found 235.0584, Δ = 0.9 ppm.

Preparation of the racemic product: To a stirred solution of (2*S*,5*S*)-2,5-diphenylpyrrolidine (26.5 mg, 0.1 mmol, 10 mol-%), (2*R*,5*R*)-2,5-diphenylpyrrolidine (23.7 mg, 0.1 mmol, 10 mol-%), 4-nitrobenzoic acid (35.2 mg, 0.2 mmol, 20 mol-%) and water (36.0 mg, 0.04 mL, 2 mmol, 200 mol-%) in DCM (2 mL) at 0 °C were added **279** (228 mg, 0.21 mL, 2 mmol, 200 mol-%) and **278** (254 mg, 0.28 mL, 1 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 7 hours and then filtered through a silica layer (ø 2 cm × 4 cm), which was washed with Et_2O (30 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (Et_2O)

to afford the product **281** as a reddish oil (55.5 mg, 0.3 mmol, 26%, 50:50 *dr*). The spectroscopic data match those of the enantiopure compound.

6.17.7 (*S*)-1-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl acetate ((*S*,*S*)-298) and (*R*)-1-(5,5-dimethyl-1,3-dioxan-2-yl)-2-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl acetate ((*R*,*S*)-298)



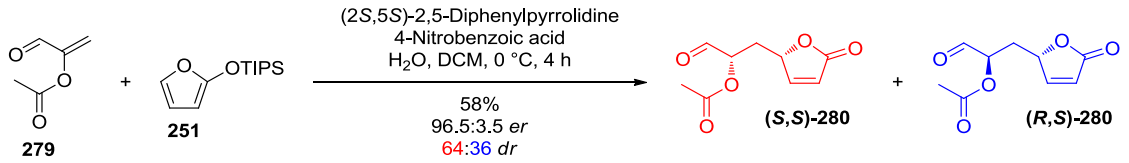
To a stirred solution of **(*S*,*S*)-281** and **(*R*,*S*)-281** (182 mg, 0.86 mmol, 100 mol-%, 50:50 *dr*) in DCM (2 mL) were added 2,2-dimethyl-1,3-propanediol (107 mg, 1.0 mmol, 120 mol-%) and *p*-TsOH (53.5 mg, 0.28 mmol, 30 mol-%). The reaction mixture was stirred at rt for 1 hour and then poured directly in the flash column and purified by flash chromatography (Et_2O/Pentane 2:1) to afford the product **298** as a mixture of diastereomers as a clear oil (69.0 mg, 0.23 mmol, 27%, 83:17 *dr*[vii]).

$R_{f(\text{one diastereomer})}$ (Et_2O) = 0.67; $R_{f(\text{other diastereomer})}$ (Et_2O) = 0.55; IR (film, cm^{-1}): 2957, 2853, 1738, 1373, 1232, 1112, 1096, 1029, 951, 909, 818, 731; ^1H NMR (400 MHz, $CDCl_3$, one diastereomer): δ 7.32 (d, 1H, *J* = 5.7 Hz), 6.01 (d, 1H, *J* = 5.7 Hz), 4.90 (ddd, 1H, *J* = 6.8, 5.5, 3.1 Hz), 4.46 (d, 1H, *J* = 3.1 Hz), 3.60 (dd, 1H, *J* = 11.4, 2.7 Hz), 3.58 (dd, 1H, *J* = 11.3, 2.7 Hz), 3.39 (d, 1H, *J* = 11.3 Hz), 3.37 (d, 1H, *J* = 11.4 Hz), 2.56 (d, 1H, *J* = 6.8 Hz), 2.25 (d, 1H, *J* = 5.5 Hz), 2.08 (s, 3H), 1.47 (s, 3H), 1.13 (s, 3H), 0.70 (s, 3H); ^1H NMR (400 MHz, $CDCl_3$, other diastereomer): δ 7.35 (d, 1H, *J* = 5.6 Hz), 5.92 (d, 1H, *J* = 5.6 Hz), 4.93–4.88 (m, 1H), 4.45 (d, 1H, *J* = 2.9 Hz), 3.63–3.55 (m, 2H), 3.41–3.35 (m, 2H), 2.34 (dd, 1H, *J* = 15.4, 1.9 Hz), 2.16 (dd, 1H, *J* = 15.4, 10.2 Hz), 2.03 (s, 3H), 1.47 (s, 3H), 1.13 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, one diastereomer): δ 172.0, 170.4, 159.6, 121.3, 99.7, 87.6, 77.2, 77.0, 70.0, 36.2, 30.4, 24.5, 23.04, 21.7, 21.2; ^{13}C NMR (100 MHz, $CDCl_3$,

[vii] The diastereomeric ratio was enhanced during purification.

other diastereomer): δ 172.0, 170.0, 159.8, 119.9, 99.8, 86.8, 77.4, 77.2, 68.9, 36.8, 30.4, 25.0, 23.01, 21.7, 21.2; HRMS (ESI+): m/z calcd for [$C_{15}H_{22}O_6Na$] 321.1314, found 321.1317, Δ = 0.9 ppm.

6.17.8 (*S*)-1-oxo-3-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)propan-2-yl acetate ((*S*,*S*)-280) and (*R*)-1-Oxo-3-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)propan-2-yl acetate ((*R*,*S*)-280)

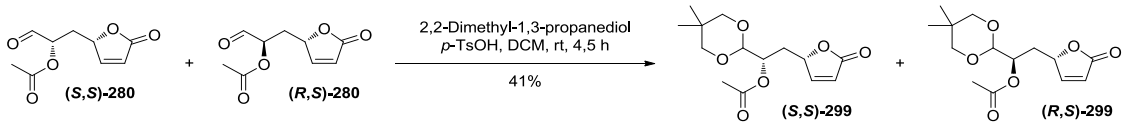


The reaction was carried out according to the general procedure using **279** (228 mg, 0.21 mL, 2 mmol, 200 mol-%) and **251** (240 mg, 0.26 mL, 1 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 4 hours and then poured directly to the flash column and purified by flash chromatography (Et_2O) to afford the product **280** as a mixture of diastereomers as reddish oil (116 mg, 0.58 mmol, 58%, 96.5:3.5 *er*, 64:36 *dr*). The enantiomeric ratio was determined by HPLC (CHIRALPAK IC column, 50% *i*-PrOH/hexane, flow rate 1.0 ml/min, 214 nm) of the corresponding (*S*)-1-(5,5-dimethyl-1,3-dioxan-2-yl)-2-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)ethyl acetate and (*R*)-1-(5,5-dimethyl-1,3-dioxan-2-yl)-2-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)ethyl acetate; τ_{major} = 15.2 min; τ_{minor} = 20.5 min; τ_{minor} = 23.1 min; τ_{major} = 37.6 min.

R_f (Et_2O) = 0.09; IR (film, cm^{-1}): 3469, 3101, 2926, 2850, 1736, 1373, 1231, 1164, 1100; ^1H NMR (400 MHz, $CDCl_3$, major): δ 9.57 (s, 1H), 7.48 (dd, 1H, *J* = 5.7, 1.5 Hz), 6.15 (dd, 1H, *J* = 5.7, 2.0 Hz), 5.25–5.15 (m, 2H), 2.42 (ddd, 1H, *J* = 15.0, 4.9 Hz), 2.20 (s, 3H), 2.20–2.08 (m, 1H); ^1H NMR (400 MHz, $CDCl_3$, minor): δ 9.55 (s, 1H), 7.47 (dd, 1H, *J* = 5.7, 1.6 Hz), 6.18 (dd, 1H, *J* = 5.7, 2.0 Hz), 5.25–5.15 (m, 2H), 2.21 (s, 3H), 2.27–2.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, major): δ 197.2, 171.9, 170.0, 155.0, 122.1, 79.1, 74.4, 32.7, 20.6; ^{13}C NMR (100 MHz, $CDCl_3$, minor): δ196.8, 172.0, 170.1, 155.0, 122.5, 78.9, 75.0, 32.2, 20.5; HRMS (ESI+): m/z calcd for [$C_7H_{10}O_5Na$] 221.0426, found 221.0424, Δ = 0.9 ppm.

Preparation of the racemic product: To a stirred solution of (2*S*,5*S*)-2,5-diphenylpyrrolidine (26.7 mg, 0.1 mmol, 10 mol-%), (2*R*,5*R*)-2,5-diphenylpyrrolidine (25.0 mg, 0.1 mmol, 10 mol-%), 4-nitrobenzoic acid (33.7 mg, 0.2 mmol, 20 mol-%) and water (36.0 mg, 0.04 mL, 2 mmol, 200 mol-%) in DCM (2 mL) at 0 °C were added **279** (228 mg, 0.21 mL, 2 mmol, 200 mol-%) and **251** (240 mg, 0.26 mL, 1 mmol, 100 mol-%). The reaction mixture was stirred at 0 °C for 3.5 hours and then poured directly in the flash column and purified by flash chromatography (Et_2O) to afford the product **280** as a reddish oil (113 mg, 0.57 mmol, 57%, 61:39 *dr*). The spectroscopic data match those of the enantiopure compound.

6.17.9 (*S*)-1-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)ethyl acetate ((*S*,*S*)-299) and (*R*)-1-(5,5-dimethyl-1,3-dioxan-2-yl)-2-((*S*)-5-oxo-2,5-dihydrofuran-2-yl)ethyl acetate ((*R*,*S*)-299)



To a stirred solution of **(*S*,*S*)-280** and **(*R*,*S*)-280** (115 mg, 0.58 mmol, 100 mol-%, 64:36 *dr*) in DCM (2 mL) were added 2,2-dimethyl-1,3-propanediol (91.1 mg, 0.87 mmol, 150 mol-%) and *p*-TsOH (19.5 mg, 0.10 mmol, 20 mol-%). The reaction mixture was stirred at rt for 4.5 hours and then poured directly in the flash column and purified by flash chromatography (Et_2O/Pentane 2:1) to afford the product **299** as a mixture of diastereomers as a clear oil (58.3 mg, 0.21 mmol, 35%, 61:39 *dr*[viii]).

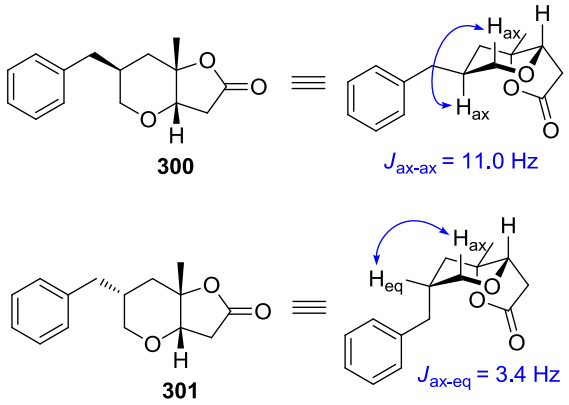
R_f (Et_2O) = 0.54; IR (film, cm^{-1}): 2958, 2855, 1741, 1372, 1231, 1154, 1104, 1020, 987, 911, 816, 731; ^1H NMR (400 MHz, $CDCl_3$, one diastereomer): δ 7.54 (dd, 1H, *J* = 5.7, 1.5 Hz) 6.08 (dd, 1H, *J* = 5.7, 2.0 Hz), 5.17–5.11 (m, 1H), 5.10–5.03 (m, 1H), 4.53 (d, 1H, *J* = 3.4 Hz), 3.66–3.58 (m, 2H), 3.45–3.39 (m, 2H), 2.27–2.04 (m, 2H),

[viii] The diastereomeric ratio was enhanced during purification.

2.10 (s, 3H), 1.144 (s, 3H), 0.713 (s, 3H); ^{1}H NMR (400 MHz, $CDCl_3$, other diastereomer): δ 7.46 (dd, 1H, *J* = 5.7, 1.5 Hz), 6.11 (dd, 1H, *J* = 5.7, 2.0 Hz), 5.17–5.11 (m, 1H), 5.10–5.03 (m, 1H), 4.60 (d, 1H, *J* = 2.9 Hz), 3.66–3.58 (m, 2H), 3.45–3.39 (m, 2H), 2.27–2.04 (m, 2H), 2.11 (s, 3H), 1.136 (s, 3H), 0.710 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, one diastereomer): δ 172.73, 170.4, 156.07, 121.6, 99.9, 80.7, 77.21, 77.11, 70.0, 32.5, 30.45, 23.0, 21.8, 21.2; ^{13}C NMR (100 MHz, $CDCl_3$, other diastereomer): δ 172.70, 170.2, 156.09, 122.0, 99.5, 80.1, 77.19, 77.07, 70.4, 32.0, 30.47, 23.0, 21.8, 21.1; HRMS (ESI^{+}): m/z calcd for [$C_{14}H_{20}O_6Na$] 307.1158, found 307.1155, Δ = 1.0 ppm.

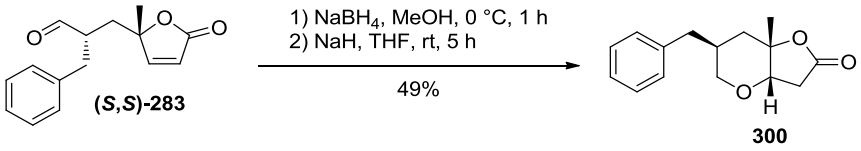
6.18 Determination of the Relative Stereochemistry of the (*R*)-2-Benzyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (300) and (*S*)-2-Benzyl-3-((*S*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (301)

The relative stereochemistries were determined from ^{1}H NMR of compounds **300** and **301** (**Scheme 56**). The characteristic coupling constants between the two vicinal protons in the six membered rings confirmed the relative stereochemistry. The axial–axial coupling was significantly larger (11.0 Hz) than the axial–equatorial coupling (3.4 Hz). These results are in line with our earlier observations (**Scheme 54**).



Scheme 56. Conformational drawings of (3a*S*,6*S*,7a*S*)-6-benzyl-7a-methylhexahydro-2*H*-furo[3,2-b]pyran-2-one (**300**) and (3a*S*,6*R*,7a*S*)-6-benzyl-7a-methylhexahydro-2*H*-furo[3,2-b]pyran-2-one (**301**).

6.18.1 (3a*S*,6*S*,7a*S*)-6-Benzyl-7a-methylhexahydro-2*H*-furo[3,2-b]pyran-2-one (300)



To a stirred solution of **(*S*,*S*)-283** (30.5 mg, 0.12 mmol, 100 mol-%) in MeOH (1 mL) at 0 °C was added $NaBH_4$ (12.8 mg, 0.34 mmol, 271 mol-%). The reaction mixture was stirred at 0 °C for 1 hour. The reaction was quenched by addition of HCl solution (2M aq., 5 mL) and crude mixture was diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude alcohol as a clear oil. This crude material was used in the next step without further purification.

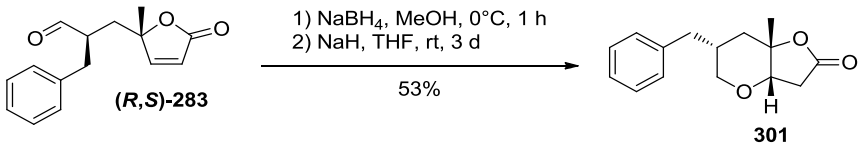
R_f (EtOAc) = 0.51.

To a stirred solution of the crude alcohol (30.8 mg, 0.12 mmol, 100 mol-%) in THF (1 mL) at rt was added NaH (55–65% dispersion in mineral oil, 20.6 mg, 0.48 mmol, 400 mol-%). The reaction mixture was stirred at rt for 5 hours. The reaction was quenched by addition of HCl solution (2M aq., 2 mL) and the

crude mixture was diluted with DCM (5 mL). The layers were separated and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:1) to afford the product **300** as a clear oil (15.0 mg, 0.06 mmol, 49%).

R_f (EtOAc) = 0.79; IR (film, cm^{-1}): 3027, 2973, 2920, 2850, 1772, 1277, 1108, 928, 754, 702; ^1H NMR (500 MHz, $CDCl_3$, major): δ 7.31–7.26 (m, 2H), 7.23–7.18 (m, 1H), 7.14–7.09 (m, 2H), 3.91 (d, 1H, *J* = 4.2 Hz), 3.79 (ddd, 1H, *J* = 11.1, 3.7, 2.7 Hz), 3.04 (t, 1H, *J* = 11.1 Hz), 2.84 (dd, 1H, *J* = 17.4, 4.2 Hz), 2.49 (dd, 1H, *J* = 13.6, 7.3 Hz), 2.44 (dd, 1H, *J* = 17.4, 0.8 Hz), 2.42 (dd, 1H, *J* = 13.6, 7.5 Hz), 2.23 (app. dt, 1H, *J* = 13.9, 3.4 Hz), 2.23–2.14 (m, 1H), 1.28 (s, 3H), 1.27 (t, 1H, *J* = 13.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, minor): δ 175.0, 140.2, 129.3, 128.4, 126.3, 82.8, 77.5, 67.8, 37.8, 36.7, 34.9, 34.1, 25.5; HRMS (ESI^+): m/z calcd for $[C_{15}H_{18}O_3Na]$ 269.1154, found 269.1153, Δ = 0.4 ppm.

6.18.2 (3a*S*,6*R*,7a*S*)-6-Benzyl-7a-methylhexahydro-2*H*-furo[3,2-b]pyran-2-one (301)



To a stirred solution of **(*R*,*S*)-283** (27.7 mg, 0.11 mmol, 100 mol-%) in MeOH (1 mL) at 0 °C was added $NaBH_4$ (13.6 mg, 0.36 mmol, 320 mol-%). The reaction mixture was stirred at 0 °C for 1 hour. The reaction was quenched by addition of HCl solution (2M aq., 5 mL) and the crude mixture was diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude alcohol as a clear oil. This crude material was used in the next step without further purification.

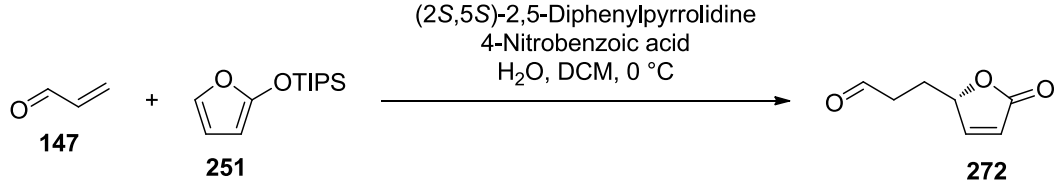
R_f (EtOAc) = 0.59.

To a stirred solution of the crude alcohol (27.9 mg, 0.11 mmol, 100 mol-%) in THF (1 mL) at rt was added NaH (55–65% dispersion in mineral oil, 22.4 mg, 0.54 mmol, 490 mol-%). The reaction mixture was stirred at rt for 3 days. The reaction was quenched by addition of HCl solution (2M aq., 5 mL) and the crude mixture was diluted with DCM (5 mL). The layers were separated and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 1:1) to afford the product **301** as a clear oil (14.9 mg, 0.06 mmol, 53%).

R_f (EtOAc) = 0.79; IR (film, cm^{-1}): 3026, 2972, 2918, 2852, 1775, 1454, 1278, 1146, 1111, 1067, 936, 744, 702; ^1H NMR (500 MHz, $CDCl_3$, major): δ 7.31–7.26 (m, 2H), 7.23–7.17 (m, 3H), 3.97 (dd, 1H, *J* = 5.0, 1.2 Hz), 3.79 (ddd, 1H, *J* = 11.4, 3.7, 2.7 Hz), 3.53 (dd, 1H, *J* = 11.4, 3.4 Hz), 2.86 (dd, 1H, *J* = 17.7, 5.0 Hz), 2.78 (t, 2H, *J* = 7.4 Hz), 2.58 (ddd, 1H, *J* = 17.7, 1.2, 0.7 Hz), 2.07 (ddd, 1H, *J* = 14.9, 1.8 Hz), 1.95–1.87 (m, 1H), 1.77 (dd, 1H, *J* = 14.9, 5.6 Hz), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, minor): δ 175.5, 138.6, 129.0, 128.6, 126.5, 83.0, 77.1, 70.4, 38.7, 38.4, 38.1, 32.6, 25.6; HRMS (ESI^+): m/z calcd for $[C_{15}H_{18}O_3Na]$ 269.1154, found 269.1155, Δ = 0.4 ppm.

6.19 Procedures for Reactions Followed by NMR

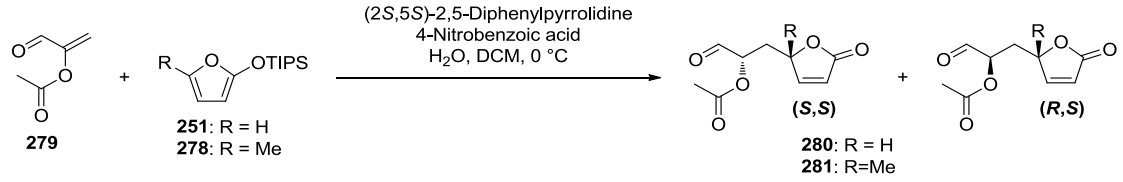
6.19.1 General Procedure for NMR-Monitored Acrolein Reactions



To a stirred solution of (2*S*,5*S*)-2,5-diphenylpyrrolidine (11.2 mg, 0.05 mmol, 10 mol-% or 22.3 mg, 0.1 mmol, 20 mol-%), 4-nitrobenzoic acid (8.4 mg,

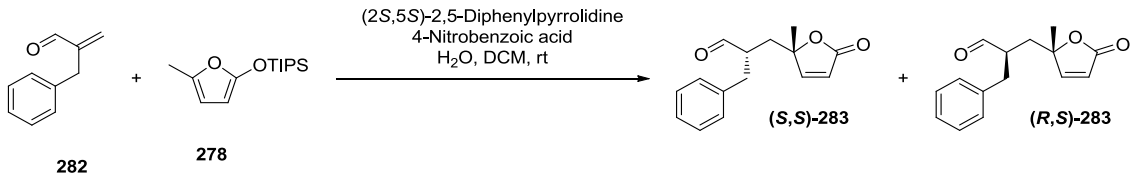
0.05 mmol, 10 mol-% or 16.7 mg, 0.1 mmol, 20 mol-%), dibenzyl ether (as an internal standard, 22.8 mg, 22 µL, 0.115 mmol, 23 mol-%) and water (18.0 mg, 0.02 mL, 1.0 mmol, 200 mol-%) in DCM (1 mL) were added **147** (56.1 mg, 0.07 mL, 1.0 mmol, 200 mol-% or 280 mg, 0.33 mL, 5.0 mmol, 1000 mol-%) and **251** (120 mg, 0.13 mL, 0.5 mmol, 0.5 mmol/mL, 100 mol-%). The mixture was stirred at 0 °C. The reaction was monitored by ^{1}H NMR. Samples were taken at set time points. The NMR-samples were prepared by diluting 50 µL of reaction mixture with 0.6 mL of $CDCl_3$.

6.19.2 General Procedure for NMR-Monitored α-Acetoxyacrolein Reactions



To a stirred solution of (2*S*,5*S*)-2,5-diphenylpyrrolidine (22.3 mg, 0.1 mmol, 20 mol-%), 4-nitrobenzoic acid (16.7 mg, 0.1 mmol, 20 mol-%), dibenzyl ether (as an internal standard, 25.0 mg, 24 µL, 0.126 mmol, 25 mol-%) and water (18.0 mg, 0.02 mL, 1.0 mmol, 200 mol-%) in DCM (1 mL) were added **279** (160 mg, 0.15 mL, 1.4 mmol, 280 mol-%) and silyloxyfuran (0.5 mmol, 0.5 mmol/mL, 100 mol-%). The mixture was stirred at 0 °C. The reaction was monitored by ^{1}H NMR. Samples were taken at set time points. The NMR-samples were prepared by diluting 50 µL of reaction mixture to 0.6 mL of $CDCl_3$.

6.19.3 General Procedure for NMR-Monitored α-Benzylacrolein Reactions



To a stirred solution of (2*S*,5*S*)-2,5-diphenylpyrrolidine (22.3 mg, 0.1 mmol, 20 mol-%), 4-nitrobenzoic acid (16.7 mg, 0.1 mmol, 20 mol-%), dibenzyl ether (as an internal standard, 22.8 mg, 22 µL, 0.115 mmol, 23 mol-%) and additives

(either $KHSO_4$ solution (sat. aq., 50 µL), or SDS (141 mg, 0.5 mmol, 100 mol-%) and water (90 mg, 0.09 mL, 5 mmol, 1000 mol-%)) in DCM (1 mL) were added **282** (146 mg, 0.15 mL, 1.0 mmol, 200 mol-%) and **278** (128 mg, 0.14 mL, 0.5 mmol, 0.5 mmol/mL, 100 mol-%). The mixture was stirred at rt. The reaction was monitored by ^1H NMR. Samples were taken at set time points. The NMR samples were prepared by diluting a 50 µL aliquot of reaction mixture with 0.6 mL of $CDCl_3$.

6.20 Preparation of Nucleophiles for Additional Mukaiyama–Michael Reaction Experiments

Two additional silyl-protected compounds were prepared to determine if they might be applicable for the Mukaiyama–Michael reaction (**Figure 28**).

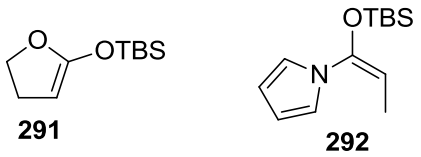
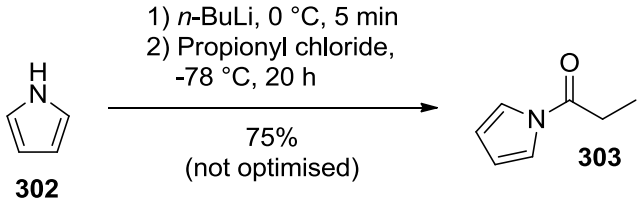


Figure 28. Nucleophiles used in the Mukaiyama–Michael reaction.

6.20.1 1-(1*H*-Pyrrol-1-yl)propan-1-one (303)

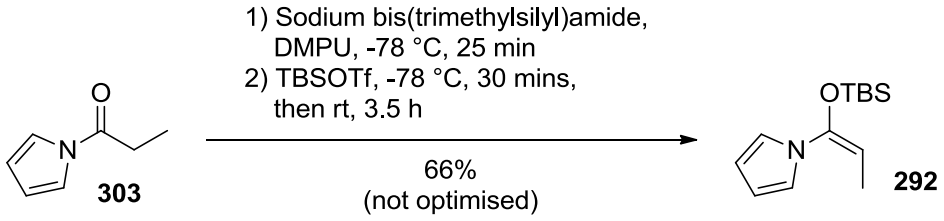


To a stirred solution of **302** (4.8 g, 5 mL, 72 mmol, 110 mol-%) in Et_2O (60 mL) at 0 °C was added *n*-BuLi solution (2.5 M in hexanes, 26 mL, 66 mmol, 100 mol-%). The reaction mixture was first stirred at 0 °C for 5 mins and then chilled to –78 °C. Propionyl chloride (6.1 g, 5.7 mL, 66 mmol, 100 mol-%) was added and the stirred reaction was allowed to slowly warm to rt over 20 hours. The reaction mixture was then poured into a separatory funnel containing Et_2O (200 mL) and H_2O (100 mL). The layers were separated and the organic layer

was washed with cold water (2 × 100 mL) and brine (2 × 100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by fractional distillation (+83 °C/1 mbar) to afford the product **303** as a clear oil (6.7 g, 54 mmol, 83%). The spectroscopic data match those reported in the literature.[120]

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (t, 2H, *J* = 2.3 Hz), 6.28 (t, 2H, *J* = 2.3 Hz), 2.85 (q, 2H, *J* = 7.4 Hz), 1.29 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (67 MHz, $CDCl_3$): δ 171.3, 118.9, 112.9, 27.9, 8.6.

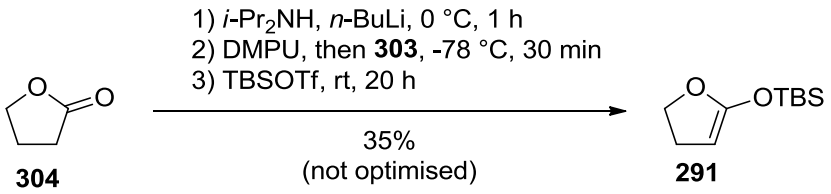
6.20.2 (*E*)-1-(1-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-1*H*-pyrrole (292)



Sodium bis(trimethylsilyl)amide solution (1.0 M in THF, 4.86 g, 26.5 mL, 26.5 mmol, 110 mol-%) was diluted with THF (60 mL) and chilled to –78 °C. 1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one (4.33 g, 4.1 mL, 33.8 mmol, 140 mol-%) and **303** (2.97 g, 3.0 mL, 24.1 mmol, 100 mol-%) were added to the solution and stirring was continued at –78 °C for 25 mins. TBSOTf (8.93 g, 7.8 mL, 33.8 mmol, 140 mol-%) was added and stirring was continued for 30 mins at –78 °C, then at rt for 3.5 hours. The reaction mixture was then poured into a separatory funnel containing pH 7 phosphate buffer solution (aq., 300 mL) and hexanes (200 mL). The layers were separated and the organic layer was washed with brine (2 × 100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by fractional distillation (+57–93 °C/0.25 mbar) to afford the product **292** as a clear oil (3.78 g, 15.9 mmol, 66%). The double bond geometry was assigned by comparison with a TMS-derivative.[120]

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.81 (t, 2H, *J* = 2.2 Hz), 6.14 (t, 2H, *J* = 2.2 Hz), 4.68 (q, 1H, *J* = 6.8 Hz), 1.67 (d, 3H, *J* = 6.8 Hz), 0.98 (s, 9H), –0.01 (s, 6H).

6.20.3 *tert*-Butyl((4,5-dihydrofuran-2-yl)oxy)dimethylsilane (291)



To a stirred solution of *i*-Pr_2NH (1.86 g, 2.5 mL, 14.4 mmol, 110 mol-%) in THF (10 mL) at 0 °C was added *n*-BuLi solution (2.5 M in hexanes, 0.92 g, 5.8 mL, 14.4 mmol, 110 mol-%) and stirring was continued at 0 °C for 1 hour, and then the reaction mixture was chilled to –78 °C. 1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one (2.02 g, 1.9 mL, 15.7 mmol, 120 mol-%) and γ-butyrolactone (**304**) (1.3 g, 1.0 mL, 13.1 mmol, 100 mol-%) were added and stirring was continued at –78 °C for 30 mins. TBSOTf (3.81 g, 3.3 mL, 14.4 mmol, 110 mol-%) was added and the cold bath was removed. The reaction mixture was allowed to warm to rt and stirring was continued for 20 hours. The reaction mixture was then diluted with hexanes (30 mL) and cold water (20 mL). The layers were separated and the organic layer was washed with cold water (2 × 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by fractional distillation (+50–100 °C/0.05 mbar) to afford the product **291** as a clear oil (0.91 g, 4.56 mmol, 35%). The spectroscopic data match those reported in the literature.[121]

^{1}H NMR (250 MHz, $CDCl_3$): δ 4.28 (dd, 2H, *J* = 9.2, 8.5 Hz), 3.69 (t, 1H, *J* = 2.2 Hz), 2.62 (ddd, 2H, *J* = 9.2, 8.5, 2.2 Hz), 0.94 (s, 9H), 0.20 (s, 6H).

REFERENCES

1. Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019–1025.
2. For a review of PTXs, see: a) Draisci, R.; Lucentini, L.; Mascioni, A. *Seafood and Freshwater Toxins: Pharmacology, Physiology and detection*, ed. Botana, L. M., Marcel Dekker, Inc.: New York, USA, **2000**, 289–324. b) Suzuki, T.; Vilariño, N.; Espiña, B.; Munday, R. *Seafood and Freshwater Toxins: Pharmacology, Physiology and detection 2nd edition*, ed. Botana, L. M., CRC Press Taylor & Francis Group: Florida, USA, **2008**, 343–380. c) Burgess, V.; Shaw, G. *Environ. Int.* **2001**, *27*, 275–283. d) Miles, C. O. *Phycotoxins: Chemistry and Biochemistry*, ed. Botana, L. M., Blackwell Publishing: Iowa, USA, **2007**, 159–186.
3. Suzuki, T.; Beuzenberg, V.; Mackenzie, L.; Quilliam, M. A. *J. Chromatogr. A* **2003**, *992*, 141–150.
4. Murata, M.; Sano, M.; Iwashita, T.; Naoki, H.; Yasumoto, T. *Agric. Biol. Chem.* **1986**, *50*, 2693–2695.
5. Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475–2480.
6. Synthesis of PTX4: a) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4569–4573. b) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4573–4576.
7. a) Lee, J.–S.; Murata, M.; Yasumoto, T. *Bioactive molecules: Mycotoxins and Phycotoxins '88*, ed. Natori, S.; Hashimoto, K.; Ueno, Y., Elsevier Science Publisher B. V.: Amsterdam, The Netherlands, **1988**, 327–334. b) Yasumoto, T.; Murata, M.; Lee, J.–S.; Torigoe, K. *Bioactive molecules: Mycotoxins and Phycotoxins '88*, ed. Natori, S.; Hashimoto, K.; Ueno, Y., Elsevier Science Publisher B. V.: Amsterdam, The Netherlands, **1988**, 375–382.
8. Sasaki, K.; Satake, M.; Yasumoto, T. *Biosci. Biotech. Biochem.* **1997**, *61*, 1783–1785.

9. a) MacKenzie, L.; Holland, P.; McNabb, P.; Beuzenberg, V.; Selwood, A.; Suzuki, T. *Toxicon*, **2002**, *40*, 1321–1330. b) Suzuki, T.; Walter, J. A.; LeBlanc, P.; MacKinnon, S.; Miles, C. O.; Wilkins, A. L.; Munday, R.; Beuzenberg, V.; MacKenzie, A. L.; Jensen, D. J.; Cooney, J. M.; Quilliam, M. A. *Chem. Res. Toxicol.* **2006**, *19*, 310–318.
10. Miles, C. O.; Wilkins, A. L.; Samdal, I. A.; Sandvik, M.; Petersen, D.; Quilliam, M. A.; Naustvoll, L. J.; Rundberget, T.; Torgersen, T.; Hovgaard, P.; Jensen, D. J.; Cooney, J. M. *Chem. Res. Toxicol.* **2004**, *17*, 1423–1433.
11. Miles, C. O.; Wilkins, A. L.; Hawkes, A. D.; Jensen, D. J.; Selwood, A. I.; Beuzenberg, V.; MacKenzie, A. L.; Cooney, J. M.; Holland, P. T. *Toxicon* **2006**, *48*, 152–159.
12. a) Nagai, Y.; Kusumi, T. *Tetrahedron Lett.* **1995**, *36*, 1853–1856. b) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202–4205.
13. Daiguji, M.; Satake, M.; James, K. J.; Bishop, A.; MacKenzie, L.; Naoki, H.; Yasumoto, T. *Chem. Lett.* **1998**, *7*, 653–654.
14. Miles, C. O.; Wilkins, A. L.; Munday, R.; Dines, M. H.; Hawkes, A. D.; Briggs, L. R.; Sandvik, M.; Jensen, D. J.; Cooney, J. M.; Holland, P. T.; Quillam, M. A.; MacKenzie, A. L.; Beuzenberg, V.; Towers, N. R. *Toxicon* **2004**, *43*, 1–9.
15. a) Wilkins, A. L.; Rehmann, N.; Torgersen, T.; Rundberget, T.; Keogh, M.; Petersen, D.; Hess, P.; Rise, F.; Miles, C. O. *J. Agric. Food Chem.* **2006**, *54*, 5672–5678. b) Torgersen, T.; Lindegarth, S.; Ungfors, A.; Sandvik, M. *Toxicon* **2008**, *52*, 407–417.
16. Espiña, B.; Louzao, M. C.; Ares, I. R.; Cagide, E.; Vieytes, M. R.; Vega, F. V.; Rubiolo, J. A.; Miles, C. O.; Suzuki, T.; Yasumoto, T.; Botana, L. M. *Brit. J. Pharmacol.* **2008**, *155*, 934–944.
17. Espiña, B.; Rubiolo, J. A. *FEBS Journal* **2008**, *275*, 6082–6088.
18. Toxicology investigations of PTX2sa: Burgess, V. A. *PhD Thesis*, Griffith University, **2003**.
19. Jung, J. H.; Sim, C. J.; Lee, C.–O. *J. Nat. Prod.* **1995**, *58*, 1722–1726.

20. Spector, I.; Braet, F.; Shochet, N. R.; Bubb, M. R. *Microsc. Res. Tech.* **1999**, *47*, 18–37.

21. Allingham, J. S.; Miles, C. O.; Rayment, I. *J. Mol. Biol.* **2007**, *371*, 959–970.

22. Ares, I. R.; Louzao, M. C.; Espiña, B.; Vieytes, M. R.; Miles, C. O.; Yasumoto, T.; Botana, L. M. *Cell. Physiol. Biochem.* **2007**, *19, 283–292.*

23. For a review of the synthetic studies towards PTX: Halim, R.; Brimble, M. A. *Org. Biomol. Chem.* **2006**, *4*, 4048–4058.

24. For recent papers concerning the synthesis of fragments of PTX (excluding Pihko's publications): *ABCDEF-fragment:* a) O'Connor, P. D.; Knight, C. K.; Friedrich, D.; Peng, X.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 1747–1754. b) Kubo, O.; Canterbury, D. P.; Micalizio, G. C. *Org. Lett.* **2012**, *14*, 5748–5751. *AB-fragment:* c) Vellucci, D.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 711–714. d) Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869–872. *ABC-fragment:* e) Joyasawal, S.; Lotesta, S. D.; Akhmedov, N. G.; Williams, L. J. *Org. Lett.* **2010**, *12*, 988–991. f) Vassilikogiannakis, G.; Alexopoulou, I.; Tofi, M.; Montagnon, T. *Chem. Commun.* **2011**, *47*, 259–261. g) Donohoe, T. J.; Lipiński, R. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2491–2494. *C-fragment:* h) Fujiwara, K.; Suzuki, Y.; Koseki, N.; Murata, S.–I.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2011**, *52*, 5589–5592. *DE-fragment:* i) Kouridaki, A.; Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Org. Lett.* **2012**, *14*, 2374–2377. *CDE-fragment:* j) Kouridaki, A.; Montagnon, T.; Kalaitzakis, D.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2013**, *11*, 537–541. *CDEF-fragment:* k) Fujiwara, K.; Aki, Y.–I.; Yamamoto, F.; Kawamura, M.; Kobayashi, M.; Okano, A.; Awakura, D.; Shiga, S.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2007**, *48*, 4523–4527. l) Carley, S.; Brimble, M. A. *Org. Lett.* **2009**, *11*, 563–566. m) Canterbury, D. P.; Micalizio, G. C. *Org. Lett.* **2011**, *13*, 2384–2387. *F-fragment:* n) Kolakowski, R. V.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 4761–4764. *GH-fragment:* o) Heapy, A. M.; Wagner, T. W.; Brimble, M. A. *Synlett* **2007**, 2359–2362. p) Heapy, A. M.; Brimble, M. A. *Tetrahedron* **2010**, *66*, 5424–5431.

25. Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949–1952.
26. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
27. Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413–9417.
28. Masse, C. E.; Panek, J. S. *Chem. Rev.***1995**, *95*, 1293–1316.
29. Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568.
30. Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Am. Chem. Soc.* **2001**, *119*, 11224–11235.
31. a) Gage, J. R.; Evans, D. A. *Org. Syn. Coll. Vol. 8*, **1993**, 528. b) Gage, J. R.; Evans, D. A. *Org. Syn. Coll. Vol. 8*, **1993**, 339.
32. Evans, D. A.; Fitch, D. M. *J. Org. Chem.* **1997**, *62*, 454–455.
33. Chen, A.; Nelson, A.; Tanikkul, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 1251–1254.
34. a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Soc. Chem.* **1976**, *98*, 5399–5400. b) Pine, S. H.; Zahler, R.; Evans, D. A. Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270–3272.
35. Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
36. Bondar, D.; Liu, J.; Müller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813–1816.
37. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.–T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.
38. a) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263–4265. b) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.
39. a) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836. b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829–834.
40. Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.

41. a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938. b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776–6777.
42. Mancuso, A. J.; Huang, S.–L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
43. Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.
44. Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180–7184.
45. Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223–1224.
46. a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011–1014. b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.
47. Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179–563.
48. For a review of vinylogous aldol and related reactions (including Mukaiyama–Michael reaction): Casiraghi, G.; Battstini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076–3154.
49. Over 13000 hits were found from a Beilstein database search, performed 08.07.2013.
50. a) Pansare, S. V.; Paul, E. K. *Chem. Eur. J.* **2011**, *17*, 8770–8779. b) Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540–1543. c) Claraz, A.; Oudeyer, S.; Levacher, V. *Adv. Synth. Catal.* **2013**, *355*, 841–846.
51. Recently, Deng and co-workers proposed that silyloxyfurans could be desilylated and used in aldol reactions with a chiral ammonium salt, see: Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558–9560.
52. Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.
53. a) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568–570. b) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, 17015–17028.
54. For a more about reactions catalysed by BOX-Cu(II) complexes: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335.
55. Yang, H.; Kim, S. *Synlett* **2008**, 555–560.

56. Jusseau, X.; Retailleau, P.; Chabaud, L.; Guillou, C. *J. Org. Chem.* **2013**, *78*, 2289–2300.

57. a) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, 10203–10212. b) Desimoni, G.; Faita, G.; Guala, M.; Laurenti, A.; Mella, M. *Chem. Eur. J.* **2005**, *11*, 3816–3824.

58. Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500–508.

59. a) Suga, H.; Kakehi, A.; Ito, S.; Sugimoto, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 327–334. b) Suga, H.; Kakehi, A.; Mashashi, M. *Bull. Chem. Soc. Jpn.* **2004**, *77, 561–568.*

60. Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun.* **2004**, 1414–1415.

61. a) General method for a reparation of the chiral ligands: Huang, J.; Liu, X.; Wen, Y.; Qin, B.; Feng, X. *J. Org. Chem.* **2007**, *72*, 204–208. For a more about reactions catalysed by chiral *N*-oxides: b) Chelucci, G.; Murineddu, G.; Pinna, G. *Tetrahedron: Asym.* **2004**, *15*, 1373–1389. c) Malkov, A.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29–36.

62. Zhang, Q.; Xiao, X.; Lin, L.; Liu, X.; Feng, X. *Org. Biomol. Chem.* **2011**, *9*, 5748–5754.

63. Brown, S. P.; Goodwinm N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194.

64. Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470.

65. Iminium-catalysed Friedel-Crafts methodologies: a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371. b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894–7895. c) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173. d) Brown, S. P. *Ph.D. Thesis.* California Institute of Technology, **2005**.

66. Pansare, S. V.; Adsool, S. V.; Dyapa, R. *Tetrahedron: Asym.* **2010**, *21*, 771–773.

67. Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asym.* **1998**, *9*, 1165–1170.

68. Otsuka, K.–I.; Zenibayashi, Y.; Itoh, M.; Totsuka, A. *Agr. Biol. Chem.* **1974**, *38*, 485–490.

69. Goodwin, N. C. *Ph.D. Thesis.* California Institute of Technology, **2007**.

70. Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4349–4353.

71. Beechan, C. M.; Djerassi, C.; Eggert, H. *Tetrahedron* **1978**, *34*, 2503–2508.

72. Robichaud, J.; Tramblay, F. *Org. Lett.* **2006**, *8*, 597–600.

73. Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346–1348.

74. a) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849–3852. b) Aho, J. E.; Salomäki, E.; Rissanen, K.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4179–4182. c) Helmboldt, H.; Aho, J. E.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4183–4185.

75. Aho, J. E.; Piisola, A.; Krishnan, K. S.; Pihko, P. M. *Eur. J. Org. Chem.* **2011**, 1682–1694.

76. Winter, M.; Naf, F.; Furrer, A.; Pickenhagen, W.; Giersch, W.; Meister, A.; Willhalm, B.; Thommen, W.; Ohloff, G. *Helvetica Chimica Acta* **1979**, *62*, 135–139.

77. a) Fischer, M.; Hoffmann, W.; Langguth, E.; Siegel, H. *Eur. Pat. Appl.* **1995**, 4179–4961. (EP 632023; A1 – 19950104) b) Silvesteri, M. A.; He, C.; Khoram, A.; Lepore, S. D. *Tetrahedron Lett.* **2006**, *47*, 1625–1626.

78. a) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954–4961. b) Kawashima, M.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4051–4055.

79. a) Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N; Rosini, G. *Org. Lett.* **2002**, *4*, 4451–4453. b) Qian, H.; Han, X.; Windenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536–9537. c) Koshino, H.; Togiya, S.; Terada, S.-I.; Yoshihara, T.; Sakamura, S.; Shimanuki, T.; Sato, T.; Tajimi, A. *Agric. Biol. Chem.* **1989**, *53*, 789-796.

80. a) Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345–351. b) Matsuya, Y.; Takayanagi, S.–I.; Nemoto, H. *Chem. Eur. J.* **2008**, *14*, 5275–5281. c) Banwell,

M. G.; Loong, D. T. J. *Org. Biomol. Chem.* **2004**, *2*, 2050–2060. d) Urbach, A.; Dive, G.; Marchand–Brynaert, J. *Eur. J. Org. Chem.* **2009**, 1757–1770.

81. Ostermeier, M.; Brunner, B.; Korff, C.; Helmchen, C. *Eur. J. Org. Chem.* **2003**, 3453–3459.
82. Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117–3125.
83. Hsu, J.–L.; Fang, J.–M. *J. Org. Chem.* **2001**, *66*, 8573–8584.
84. a) Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538–2541. b) Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, 4205–4216. c) Benohoud, M.; Erkkilä, A.; Pihko, P. M. *Org. Synth.* **2010**, *87*, 201–208.
85. a) Abd, A.; Agulló, C.; Arnó, M.; Cantín, A.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *J. Chme. Soc., Perkin Trans. 1* **1997**, 1837–1843. b) Arnarp, J.; Chu, W. L. A.; Enzell, C. R.; Hewitt, G. M.; Kurtney, J. P.; Li, K.; Milanova, R. K.; Nakata, H.; Nasiri, A.; Tsuda, T. *Acta Chemica Scandinavica*, **1993**, *47*, 793–798.
86. a) Schrodi, Y.; Pederson, R. L. *Aldrichchimica Acta* **2007**, *40*, 45–52. b) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.
87. Price information from Sigma–Aldrich web page on 25.7.2013.
88. Price information from TCI Europe web page on 25.7.2013.
89. a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.–t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *95*, 741–743. b) Frank, S. A.; Roush, W. R. *J. Org. Chem.* **2002**, *67*, 4316–4324.
90. Wu, Y.; Sun, Y.–P. *Org. Lett.* **2006**, *8*, 2831–2834.
91. Examples of iminium–catalysed reactions with α-substituted acroleins where the products are cyclised during the reaction: <u>*Epoxidations:*</u> a) Erkkilä, A.; Pihko, P. M.; Clarke, M.–R. *Adv. Synth. Catal.* **2007**, *349*, 802–806. b) Lifchits, O.; Reisinger, C. M..; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227–10229. <u>*Cyclopropanations:*</u> c) Terrasson, V.; van der Lee, A.; de Figueiredo, R. M.; Campagne, J. M. *Chem.–Eur. J.* **2010**, *16*, 7875–7880. <u>*Cycloadditions:*</u> d) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504–10505. e) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.*

2006, *8*, 2229–2232. f) Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457–2465. g) Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893–2896. h) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930–8931. i) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, *15*, 1956–1958. Aziridinations: j) Deiana, L.; Dziedzic, P.; Zhao, G.–L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem.–Eur. J.* **2011**, *17*, 7904–7917.

92. a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4210. b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. c) Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta* **2009**, *92*, 1225.
93. Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* 2004, *126*, 4790–4791.
94. Price information from TCI Europe web page on 25.7.2013.
95. a) Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J. *Tetrahedron: Asym.* **1995**, *6*, 409–418. b) Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Tetrahedron: Asym.* **2000**, *11*, 2455–2462. c) Sato, M.; Gunji, Y.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, *9*, 1434–1438. d) Jarvis, W. F.; Hoey, M. D.; Finocchio, A. L.; Dittmer, D. C. *J. Org. Chem.* **1988**, *53*, 5750–5756.
96. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
97. Kemppainen, E. K.; Sahoo, G.; Valkonen, A.; Pihko, P. M. *Org. Lett.* **2012**, *14*, 1086–1089.
98. a) Bernat, V.; André–Barrès, C.; Baltas, M.; Saffon, N.; Vial, H. *Tetrahedron*, **2008**, *64*, 9216–9224. b) Tóth, F.; Oláh, J.; Kalaus, G.; Greiner, I.; Szöllösy, Á.; Gömöry, Á.; Hazai, L.; S´zantay, C. *Tetrahedron* **2008**, *64*, 7949–7955.
99. Sharpless, B. K.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.–S.; Kwong, H.–L.; Morikawa, K.; Wang, Z.–M.; Xu, D.; Zhang, X.–L. *J. Org. Chem.* **1992**, *57*, 2768–2771.
100. Hashimoto, M.; Hariqaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56* 2299–2311.

101. Luche, J. L.; RodriguesHahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601–602.

102. Clark, J. S.; Berger, R.; Hayes, S. T.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9867–9870.

103. Berger, R. *PhD Thesis* University of Glasgow, **2011**.

104. a) Hande, S. M.; Uenishi, J. *Tetraherdron Lett.* **2009**, *50*, 189–192. b) Nagasawa, T.; Nukada, T.; Kuwahara, S. *Tetrahedron* **2011**, *67*, 2882–2888.

105. Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Pala´zon, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570–4583.

106. Näsman, J. H. *Org. Syn. Coll. Vol. 8*, **1993**, 396.

107. Curti, C.; Battistini, L.; Zanardi, F.; Rassu, G.; Zambrano, V.; Pinna, L.; Casiraghi, G. *J. Org. Chem.* **2010**, *75*, 8681–8684.

108. Lee, H.; Kim, K. W.; Park, J.; Kim, H.; Kim, S.; Kim, D.; Hu, X.; Yang, W.; Hong, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 4200–4203.

109. a) Enders, D.; Voith, M.; Ince, S. J. *Synthesis* **2002** 1775–1779. b) Forbes, D. C.; Ene, D. G.; Doyle, M. P. *Syntheis* **1997**, 879–882. c) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504–10505.

110. Halland, N.; Lie, M. A.; Kjærsgaard, A.; Marigo, M.; Schiøtt, Jørgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 7083–7090.

111. a) Puglisi, A.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Eur. J. Org. Chem.* **2004**, 567–573. b) Haindl, M. H.; Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *RSC Adv.* **2012**, *2*, 5941–5943.

112. Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455–3458.

113. Seebach, D.; Imwinkelried, R. *Org. Synth.* **1989**, *67*, 180–183.

114. Chan, K. C.; Jewell, R. A.; Nutting, W. H.; Rapoport, H. *J. Org. Chem.* **1968**, *33*, 3382–3385.

115. Takahashi, A.; Yanai, H.; Taguchi, T. *Chem. Commun.*, **2008**, *44*, 2385-2387.

116. Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta,* **2009**, *92*, 1225–1259.

117. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797.
118. Martin, S. F.; Bur, S. K. *Tetrahedron*, **1999**, *55*, 8905–8914.
119. Boukouvalas, J.; Loach, R. P. *J. Org. Chem.* **2008**, *73*, 8109–8112.
120. Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595–598.
121. Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027–3037.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF JYVÄSKYLÄ
RESEARCH REPORT SERIES

1. Vuolle, Mikko: Electron paramagnetic resonance and molecular orbital study of radical ions generated from (2.2)metacyclophane, pyrene and its hydrogenated compounds by alkali metal reduction and by thallium(III)trifluoroacetate oxidation. (99 pp.) 1976
2. Pasanen, Kaija: Electron paramagnetic resonance study of cation radical generated from various chlorinated biphenyls. (66 pp.) 1977
3. Carbon-13 Workshop, September 6-8, 1977. (91 pp.) 1977
4. Laihia, Katri: On the structure determination of norbornane polyols by NMR spectroscopy. (111 pp.) 1979
5. Nyrönen, Timo: On the EPR, ENDOR and visible absorption spectra of some nitrogen containing heterocyclic compounds in liquid ammonia. (76 pp.) 1978
6. Talvitie, Antti: Structure determination of some sesquiterpenoids by shift reagent NMR. (54 pp.) 1979
7. Häkli, Harri: Structure analysis and molecular dynamics of cyclic compounds by shift reagent NMR. (48 pp.) 1979
8. Pitkänen, Ilkka: Thermodynamics of complexation of 1,2,4-triazole with divalent manganese, cobalt, nickel, copper, zinc, cadmium and lead ions in aqueous sodium perchlorate solutions. (89 pp.) 1980
9. Asunta, Tuula: Preparation and characterization of new organometallic compounds synthesized by using metal vapours. (91 pp.) 1980
10. Sattar, Mohammad Abdus: Analyses of MCPA and its metabolites in soil. (57 pp.) 1980
11. Bibliography 1980. (31 pp.) 1981
12. Knuuttila, Pekka: X-Ray structural studies on some divalent 3d metal compounds of picolinic and isonicotinic acid N-oxides. (77 pp.) 1981
13. Bibliography 1981. (33 pp.) 1982
14. 6th National NMR Symposium, September 9-10, 1982, Abstracts. (49 pp.) 1982
15. Bibliography 1982. (38 pp.) 1983
16. Knuuttila, Hilkka: X-Ray structural studies on some Cu(II), Co(II) and Ni(II) complexes with nicotinic and isonicotinic acid N-oxides. (54 pp.) 1983
17. Symposium on inorganic and analytical chemistry May 18, 1984, Program and Abstracts. (100 pp.) 1984
18. Knuutinen, Juha: On the synthesis, structure verification and gas chromatographic determination of chlorinated catechols and guaiacols occuring in spent bleach liquors of kraft pulp mill. (30 pp.) 1984
19. Bibliography 1983. (47 pp.) 1984
20. Pitkänen, Maija: Addition of BrCl, B_2 and Cl_2 to methyl esters of propenoic and 2-butenoic acid derivatives and ^{13}C NMR studies on methyl esters of saturated aliphatic mono- and dichlorocarboxylic acids. (56 pp.) 1985
21. Bibliography 1984. (39 pp.) 1985
22. Salo, Esa: EPR, ENDOR and TRIPLE spectroscopy of some nitrogen heteroaromatics in liquid ammonia. (111 pp.) 1985
23. Humppi, Tarmo: Synthesis, identification and analysis of dimeric impurities of chlorophenols. (39 pp.) 1985
24. Aho, Martti: The ion exchange and adsorption properties of sphagnum peat under acid conditions. (90 pp.) 1985
25. Bibliography 1985 (61 pp.) 1986
26. Bibliography 1986. (23 pp.) 1987
27. Bibliography 1987. (26 pp.) 1988
28. Paasivirta, Jaakko (Ed.): Structures of organic environmental chemicals. (67 pp.) 1988
29. Paasivirta, Jaakko (Ed.): Chemistry and ecology of organo-element compounds. (93 pp.) 1989
30. Sinkkonen, Seija: Determination of crude oil alkylated dibenzothiophenes in environment. (35 pp.) 1989
31. Kolehmainen, Erkki (Ed.): XII National NMR Symposium Program and Abstracts. (75 pp.) 1989
32. Kuokkanen, Tauno: Chlorocymenes and Chlorocymenenes: Persistent chlorocompounds in spent bleach liquors of kraft pulp mills. (40 pp.) 1989
33. Mäkelä, Reijo: ESR, ENDOR and TRIPLE resonance study on substituted 9,10-anthraquinone radicals in solution. (35 pp.) 1990
34. Veijanen, Anja: An integrated sensory and analytical method for identification of off-flavour compounds. (70 pp.) 1990
35. Kasa, Seppo: EPR, ENDOR and TRIPLE resonance and molecular orbital studies on a substitution reaction of anthracene induced by thallium(III) in two fluorinated carboxylic acids. (114 pp.) 1990
36. Herve, Sirpa: Mussel incubation method for monitoring organochlorine compounds in freshwater recipients of pulp and paper industry. (145 pp.) 1991
37. Pohjola, Pekka: The electron paramagnetic resonance method for characterization of Finnish peat types and iron (III) complexes in the process of peat decomposition. (77 pp.) 1991

38. Paasivirta, Jaakko (Ed.): Organochlorines from pulp mills and other sources. Research methodology studies 1988-91. (120 pp.) 1992
39. Veijanen, Anja (Ed.): VI National Symposium on Mass Spectrometry, May 13-15, 1992, Abstracts. (55 pp.) 1992
40. Rissanen, Kari (Ed.): The 7. National Symposium on Inorganic and Analytical Chemistry, May 22, 1992, Abstracts and Program. (153 pp.) 1992
41. Paasivirta, Jaakko (Ed.): CEOEC'92, Second Finnish-Russian Seminar: Chemistry and Ecology of Organo-Element Compounds. (93 pp.) 1992
42. Koistinen, Jaana: Persistent polychloroaromatic compounds in the environment: structure-specific analyses. (50 pp.) 1993
43. Virkki, Liisa: Structural characterization of chlorolignins by spectroscopic and liquid chromatographic methods and a comparison with humic substances. (62 pp.) 1993
44. Helenius, Vesa: Electronic and vibrational excitations in some biologically relevant molecules. (30 pp.) 1993
45. Leppä-aho, Jaakko: Thermal behaviour, infrared spectra and x-ray structures of some new rare earth chromates(VI). (64 pp.) 1994
46. Kotila, Sirpa: Synthesis, structure and thermal behavior of solid copper(II) complexes of 2-amino-2- hydroxymethyl-1,3-propanediol. (111 pp.) 1994
47. Mikkonen, Anneli: Retention of molybdenum(VI), vanadium(V) and tungsten(VI) by kaolin and three Finnish mineral soils. (90 pp.) 1995
48. Suontamo, Reijo: Molecular orbital studies of small molecules containing sulfur and selenium. (42 pp.) 1995
49. Hämäläinen, Jouni: Effect of fuel composition on the conversion of fuel-N to nitrogen oxides in the combustion of small single particles. (50 pp.) 1995
50. Nevalainen, Tapio: Polychlorinated diphenyl ethers: synthesis, NMR spectroscopy, structural properties, and estimated toxicity. (76 pp.) 1995
51. Aittola, Jussi-Pekka: Organochloro compounds in the stack emission. (35 pp.) 1995
52. Harju, Timo: Ultrafast polar molecular photophysics of (dibenzylmethine)borondifluoride and 4-aminophthalimide in solution. (61 pp.) 1995
53. Maatela, Paula: Determination of organically bound chlorine in industrial and environmental samples. (83 pp.) 1995
54. Paasivirta, Jaakko (Ed.): CEOEC'95, Third Finnish-Russian Seminar: Chemistry and Ecology of Organo-Element Compounds. (109 pp.) 1995
55. Huuskonen, Juhani: Synthesis and structural studies of some supramolecular compounds. (54 pp.) 1995
56. Palm, Helena: Fate of chlorophenols and their derivatives in sawmill soil and pulp mill recipient environments. (52 pp.) 1995
57. Rantio, Tiina: Chlorohydrocarbons in pulp mill effluents and their fate in the environment. (89 pp.) 1997
58. Ratilainen, Jari: Covalent and non-covalent interactions in molecular recognition. (37 pp.) 1997
59. Kolehmainen, Erkki (Ed.): XIX National NMR Symposium, June 4-6, 1997, Abstracts. (89 pp.) 1997
60. Matilainen, Rose: Development of methods for fertilizer analysis by inductively coupled plasma atomic emission spectrometry. (41 pp.) 1997
61. Koistinen, Jari (Ed.): Spring Meeting on the Division of Synthetic Chemistry, May 15-16, 1997, Program and Abstracts. (36 pp.) 1997
62. Lappalainen, Kari: Monomeric and cyclic bile acid derivatives: syntheses, NMR spectroscopy and molecular recognition properties. (50 pp.) 1997
63. Laitinen, Eira: Molecular dynamics of cyanine dyes and phthalimides in solution: picosecond laser studies. (62 pp.) 1997
64. Eloranta, Jussi: Experimental and theoretical studies on some quinone and quinol radicals. (40 pp.) 1997
65. Oksanen, Jari: Spectroscopic characterization of some monomeric and aggregated chlorophylls. (43 pp.) 1998
66. Häkkänen, Heikki: Development of a method based on laser-induced plasma spectrometry for rapid spatial analysis of material distributions in paper coatings. (60 pp.) 1998
67. Virtapohja, Janne: Fate of chelating agents used in the pulp and paper industries. (58 pp.) 1998
68. Airola, Karri: X-ray structural studies of supramolecular and organic compounds. (39 pp.) 1998
69. Hyötyläinen, Juha: Transport of lignin–type compounds in the receiving waters of pulp mills. (40 pp.) 1999
70. Ristolainen, Matti: Analysis of the organic material dissolved during totally chlorine-free bleaching. (40 pp.) 1999
71. Eklin, Tero: Development of analytical procedures with industrial samples for atomic emission and atomic absorption spectrometry. (43 pp.) 1999

72. Välisaari, Jouni: Hygiene properties of resol-type phenolic resin laminates. (129 pp.) 1999
73. Hu, Jiwei: Persistent polyhalogenated diphenyl ethers: model compounds syntheses, characterization and molecular orbital studies. (59 pp.) 1999
74. Malkavaara, Petteri: Chemometric adaptations in wood processing chemistry. (56 pp.) 2000
75. Kujala Elena, Laihia Katri, Nieminen Kari (Eds.): NBC 2000, Symposium on Nuclear, Biological and Chemical Threats in the 21st Century. (299 pp.) 2000
76. Rantalainen, Anna-Lea: Semipermeable membrane devices in monitoring persistent organic pollutants in the environment. (58 pp.) 2000
77. Lahtinen, Manu: *In situ* X-ray powder diffraction studies of Pt/C, CuCl/C and Cu_2O/C catalysts at elevated temperatures in various reaction conditions. (92 pp.) 2000
78. Tamminen, Jari: Syntheses, empirical and theoretical characterization, and metal cation complexation of bile acid-based monomers and open/closed dimers. (54 pp.) 2000
79. Vatanen, Virpi: Experimental studies by EPR and theoretical studies by DFT calculations of α-amino-9,10-anthraquinone radical anions and cations in solution. (37 pp.) 2000
80. Kotilainen, Risto: Chemical changes in wood during heating at 150-260 °C. (57 pp.) 2000
81. Nissinen, Maija: X-ray structural studies on weak, non-covalent interactions in supramolecular compounds. (69 pp.) 2001
82. Wegelius, Elina: X-ray structural studies on self-assembled hydrogen-bonded networks and metallosupramolecular complexes. (84 pp.) 2001
83. Paasivirta, Jaakko (Ed.): CEOEC'2001, Fifth Finnish-Russian Seminar: Chemistry and Ecology of Organo-Element Compounds. (163 pp.) 2001
84. Kiljunen, Toni: Theoretical studies on spectroscopy and atomic dynamics in rare gas solids. (56 pp.) 2001
85. Du, Jin: Derivatives of dextran: synthesis and applications in oncology. (48 pp.) 2001
86. Koivisto, Jari: Structural analysis of selected polychlorinated persistent organic pollutants (POPs) and related compounds. (88 pp.) 2001
87. Feng, Zhinan: Alkaline pulping of non-wood feedstocks and characterization of black liquors. (54 pp.) 2001
88. Halonen, Markku: Lahon havupuun käyttö sulfaattiprosessin raaka-aineena sekä havupuun lahontorjunta. (90 pp.) 2002
89. Falábu, Dezsö: Synthesis, conformational analysis and complexation studies of resorcarene derivatives. (212 pp.) 2001
90. Lehtovuori, Pekka: EMR spectroscopic studies on radicals of ubiquinones Q-*n*, vitamin K_3 and vitamine E in liquid solution. (40 pp.) 2002
91. Perkkalainen, Paula: Polymorphism of sugar alcohols and effect of grinding on thermal behavior on binary sugar alcohol mixtures. (53 pp.) 2002
92. Ihalainen, Janne: Spectroscopic studies on light-harvesting complexes of green plants and purple bacteria. (42 pp.) 2002
93. Kunttu, Henrik, Kiljunen, Toni (Eds.): 4th International Conference on Low Temperature Chemistry. (159 pp.) 2002
94. Väisänen, Ari: Development of methods for toxic element analysis in samples with environmental concern by ICP-AES and ETAAS. (54 pp.) 2002
95. Luostarinen, Minna: Synthesis and characterisation of novel resorcarene derivatives. (200 pp.) 2002
96. Louhelainen, Jarmo: Changes in the chemical composition and physical properties of wood and nonwood black liquors during heating. (68 pp.) 2003
97. Lahtinen, Tanja: Concave hydrocarbon cyclophane B-prismands. (65 pp.) 2003
98. Laihia, Katri (Ed.): NBC 2003, Symposium on Nuclear, Biological and Chemical Threats – A Crisis Management Challenge. (245 pp.) 2003
99. Oasmaa, Anja: Fuel oil quality properties of wood-based pyrolysis liquids. (32 pp.) 2003
100. Virtanen, Elina: Syntheses, structural characterisation, and cation/anion recognition properties of nano-sized bile acid-based host molecules and their precursors. (123 pp.) 2003
101. Nättinen, Kalle: Synthesis and X-ray structural studies of organic and metallo-organic supramolecular systems. (79 pp.) 2003
102. Lampiselkä, Jarkko: Demonstraatio lukion kemian opetuksessa. (285 pp.) 2003
103. Kallioinen, Jani: Photoinduced dynamics of $Ru(dcbpy)_2(NCS)_2$ – in solution and on nanocrystalline titanium dioxide thin films. (47 pp.) 2004
104. Valkonen, Arto (Ed.): VII Synthetic Chemistry Meeting and XXVI Finnish NMR Symposium. (103 pp.) 2004
105. Vaskonen, Kari: Spectroscopic studies on atoms and small molecules isolated in low temperature rare gas matrices. (65 pp.) 2004
106. Lehtovuori, Viivi: Ultrafast light induced dissociation of $Ru(dcbpy)(CO)_2I_2$ in solution. (49 pp.) 2004
107. Saarenketo, Pauli: Structural studies of metal complexing schiff bases , Schiff base derived

N-glycosides and cyclophane π-prismands. (95 pp.) 2004

108. Paasivirta, Jaakko (Ed.): CEOEC'2004, Sixth Finnish-Russian Seminar: Chemistry and Ecology of Organo-Element Compounds. (147 pp.) 2004
109. Suontamo, Tuula: Development of a test method for evaluating the cleaning efficiency of hard-surface cleaning agents. (96 pp.) 2004
110. Güneş, Minna: Studies of thiocyanates of silver for nonlinear optics. (48 pp.) 2004
111. Ropponen, Jarmo: Aliphatic polyester dendrimers and dendrons. (81 pp.) 2004
112. Vu, Mân Thi Hong: Alkaline pulping and the subsequent elemental chlorine-free bleaching of bamboo (*Bambusa procera*). (69 pp.) 2004
113. Mansikkamäki, Heidi: Self-assembly of resorcinarenes. (77 pp.) 2006
114. Tuononen, Heikki M.: EPR spectroscopic and quantum chemical studies of some inorganic main group radicals. (79 pp.) 2005
115. Kaski, Saara: Development of methods and applications of laser-induced plasma spectroscopy in vacuum ultraviolet. (44 pp.) 2005
116. Mäkinen, Riika-Mari: Synthesis, crystal structure and thermal decomposition of certain metal thiocyanates and organic thiocyanates. (119 pp.) 2006
117. Ahokas, Jussi: Spectroscopic studies of atoms and small molecules isolated in rare gas solids: photodissociation and thermal reactions. (53 pp.) 2006
118. Busi, Sara: Synthesis, characterization and thermal properties of new quaternary ammonium compounds: new materials for electrolytes, ionic liquids and complexation studies. (102 pp.) 2006
119. Mäntykoski, Keijo: PCBs in processes, products and environment of paper mills using wastepaper as their raw material. (73 pp.) 2006
120. Laamanen, Pirkko-Leena: Simultaneous determination of industrially and environmentally relevant aminopolycarboxylic and hydroxycarboxylic acids by capillary zone electrophoresis. (54 pp.) 2007
121. Salmela, Maria: Description of oxygen-alkali delignification of kraft pulp using analysis of dissolved material. (71 pp.) 2007
122. Lehtovaara, Lauri: Theoretical studies of atomic scale impurities in superfluid ^{4}He. (87 pp.) 2007
123. Rautiainen, J. Mikko: Quantum chemical calculations of structures, bonding, and spectroscopic properties of some sulphur and selenium iodine cations. (71 pp.) 2007
124. Nummelin, Sami: Synthesis, characterization, structural and retrostructural analysis of self-assembling pore forming dendrimers. (286 pp.) 2008
125. Sopo, Harri: Uranyl(VI) ion complexes of some organic aminobisphenolate ligands: syntheses, structures and extraction studies. (57 pp.) 2008
126. Valkonen, Arto: Structural characteristics and properties of substituted cholanoates and *N*-substituted cholanamides. (80 pp.) 2008
127. Lähde, Anna: Production and surface modification of pharmaceutical nano- and microparticles with the aerosol flow reactor. (43 pp.) 2008
128. Beyeh, Ngong Kodiah: Resorcinarenes and their derivatives: synthesis, characterization and complexation in gas phase and in solution. (75 pp.) 2008
129. Välisaari, Jouni, Lundell, Jan (Eds.): Kemian opetuksen päivät 2008: uusia oppimisympäristöjä ja ongelmalähtöistä opetusta. (118 pp.) 2008
130. Myllyperkiö, Pasi: Ultrafast electron transfer from potential organic and metal containing solar cell sensitizers. (69 pp.) 2009
131. Käkölä, Jaana: Fast chromatographic methods for determining aliphatic carboxylic acids in black liquors. (82 pp.) 2009
132. Koivukorpi, Juha: Bile acid-arene conjugates: from photoswitchability to cancer cell detection. (67 pp.) 2009
133. Tuuttila, Tero: Functional dendritic polyester compounds: synthesis and characterization of small bifunctional dendrimers and dyes. (74 pp.) 2009
134. Salorinne, Kirsi: Tetramethoxy resorcinarene based cation and anion receptors: synthesis, characterization and binding properties. (79 pp.) 2009
135. Rautiainen, Riikka: The use of first-thinning Scots pine (*Pinus sylvestris*) as fiber raw material for the kraft pulp and paper industry. (73 pp.) 2010
136. Ilander, Laura: Uranyl salophens: synthesis and use as ditopic receptors. (199 pp.) 2010
137. Kiviniemi, Tiina: Vibrational dynamics of iodine molecule and its complexes in solid krypton - Towards coherent control of bimolecular reactions? (73 pp.) 2010
138. Ikonen, Satu: Synthesis, characterization and structural properties of various covalent and non-covalent bile acid derivatives of N/O-heterocycles and their precursors. (105 pp.) 2010
139. Siitonen, Anni: Spectroscopic studies of semiconducting single-walled carbon nanotubes. (56 pp.) 2010
140. Raatikainen, Kari: Synthesis and structural studies of piperazine cyclophanes –

Supramolecular systems through Halogen and Hydrogen bonding and metal ion coordination. (69 pp.) 2010

141. Leivo, Kimmo: Gelation and gel properties of two- and three-component Pyrene based low molecular weight organogelators. (116 pp.) 2011
142. Martiskainen, Jari: Electronic energy transfer in light-harvesting complexes isolated from *Spinacia oleracea* and from three photosynthetic green bacteria *Chloroflexus aurantiacus*, *Chlorobium tepidum*, and *Prosthecochloris aestuarii*.(55 pp.) 2011
143. Wichmann, Oula: Syntheses, characterization and structural properties of [O,N,O,X´] aminobisphenolate metal complexes. (101 pp.) 2011
144. Ilander, Aki: Development of ultrasound-assisted digestion methods for the determination of toxic element concentrations in ash samples by ICP-OES. (58 pp.) 2011
145. The Combined XII Spring Meeting of the Division of Synthetic Chemistry and XXXIII Finnish NMR Symposium. Book of Abstracts. (90 pp.) 2011
146. Valto, Piia: Development of fast analysis methods for extractives in papermaking process waters. (73 pp.) 2011
147. Andersin, Jenni: Catalytic activity of palladium-based nanostructures in the conversion of simple olefinic hydro- and chlorohydrocarbons from first principles. (78 pp.) 2011
148. Aumanen, Jukka: Photophysical properties of dansylated poly(propylene amine) dendrimers. (55 pp.) 2011
149. Kärnä, Minna: Ether-functionalized quaternary ammonium ionic liquids – synthesis, characterization and physicochemical properties. (76 pp.) 2011
150. Jurček, Ondřej: Steroid conjugates for applications in pharmacology and biology. (57 pp.) 2011
151. Nauha, Elisa: Crystalline forms of selected Agrochemical actives: design and synthesis of cocrystals. (77 pp.) 2012
152. Ahkola, Heidi: Passive sampling in monitoring of nonylphenol ethoxylates and nonylphenol in aquatic environments. (92 pp.) 2012
153. Helttunen, Kaisa: Exploring the self-assembly of resorcinarenes: from molecular level interactions to mesoscopic structures. (78 pp.) 2012
154. Linnanto, Juha: Light excitation transfer in photosynthesis revealed by quantum chemical calculations and exiton theory. (179 pp.) 2012
155. Roiko-Jokela, Veikko: Digital imaging and infrared measurements of soil adhesion and cleanability of semihard and hard surfaces. (122 pp.) 2012
156. Noponen, Virpi: Amides of bile acids and biologically important small molecules: properties and applications. (85 pp.) 2012
157. Hulkko, Eero: Spectroscopic signatures as a probe of structure and dynamics in condensed-phase systems – studies of iodine and gold ranging from isolated molecules to nanoclusters. (69 pp.) 2012
158. Lappi, Hanna: Production of Hydrocarbon-rich biofuels from extractives-derived materials. (95 pp.) 2012
159. Nykänen, Lauri: Computational studies of Carbon chemistry on transition metal surfaces. (76 pp.) 2012
160. Ahonen, Kari: Solid state studies of pharmaceutically important molecules and their derivatives. (65 pp.) 2012
161. Pakkanen, Hannu: Characterization of organic material dissolved during alkaline pulping of wood and non-wood feedstocks (76 pp.) 2012
162. Moilanen, Jani: Theoretical and experimental studies of some main group compounds: from closed shell interactions to singlet diradicals and stable radicals. (80 pp.) 2012
163. Himanen, Jatta: Stereoselective synthesis of Oligosaccharides by *De Novo* Saccharide welding. (133 pp.) 2012
164. Bunzen, Hana: Steroidal derivatives of nitrogen containing compounds as potential gelators.(76 pp.) 2013
165. Seppälä, Petri: Structural diversity of copper(II) amino alcohol complexes. Syntheses, structural and magnetic properties of bidentate amino alcohol copper(II) complexes. (67 pp.) 2013
166. Lindgren, Johan: Computational investigations on rotational and vibrational spectroscopies of some diatomics in solid environment. (77 pp.) 2013
167. Giri, Chandan: Sub-component self-assembly of linear and non-linear diamines and diacylhydrazines, formulpyridine and transition metal cations. (145 pp.) 2013
168. Riisiö, Antti: Synthesis, Characterization and Properties of Cu(II)-, Mo(VI)- and U(VI) Complexes With Diaminotetraphenolate Ligands. (51 pp.) 2013
169. Kiljunen, Toni (Ed.): Chemistry and Physics at Low Temperatures. Book of Abstracts. (103 pp.) 2013
170. Hänninen, Mikko: Experimental and Computational Studies of Transition Metal Complexes with Polydentate Amino- and Aminophenolate Ligands: Synthesis, Structure, Reactivity and Magnetic Properties. (66 pp.) 2013