Studies Toward the Synthesis of the Dihydropyran Fragment of Neosorangicin A

Dissertation

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Abstract

Neosorangicin A **2** is a novel type of macrocyclic natural product which was first discovered in 2017, and the total synthesis of which is of great interest to the community. Therefore, the main objective of this thesis was to develop the synthesis of the C(1) – C(12) dihydropyran fragment of neosorangicin A.

The retrosynthetic analysis of the dihydropyran fragment **155** envisioned two main strategies for incorporating the side chain. The first was with the use of an alkyne as a precursor and the second was adopting a ketone. Starting from D-galactose **237**, alkynes **175**, **178** and **179** were synthesized on a multigram scale. In order to furnish the dihydropyran fragment **155**, alkynes **175**, **178** and **179** took part in a zirconocene-catalyzed methylalumination reaction. Unfortunately, under the explored conditions none of the alkynes successfully yielded the desired products. Therefore, homopropargylic alcohol **186** was synthesized, using alkyne **175** and epoxide **157**. Alcohol **186** then took part in a hydroalumination, hydrosulfuration and hydrostannylation reactions. None of these approaches, however, yielded the desired product **188**.

The second approach towards the dihydropyran fragment **155** necessitated the synthesis of ketones **205**, **206**, **207** and **208**. Starting from D-galactose **237**, ketones **205**, **206**, **207** and **208** were synthesized on a multigram scale. We then first investigated the Julia-Kocienski olefination for the synthesis of the trisubstituted olefins **211**, **212**, **213** and **214**. For this purpose, sulfones **209** and **210** were synthesized on a multigram scale starting from *cis*-2-butene **278** and acetaldehyde **279**. Many attempts were made in order to couple ketones **205**, **206**, **207** and **208** with sulfone **209**, but none of them resulted in the successful synthesis of the corresponding trisubstituted olefins **211**, **212**, **213** and **214**. However, while using ketones **205**, **206**, **207** and **208** and sulfone **210** we were able to isolate the desired olefins **211**, **212**, **213** and **214**, although we were only able to mainly isolate the *Z*-isomers. Inversion of the reaction partners in the Julia-Kocienski olefination was not possible under the explored conditions, since the Mitsunobu thioetherification of alcohols **215**, **216** and **217** was unsuccessful. Next a Takai olefination of ketones **205**, **206**, **207** and **208** was explored. Surprisingly, ketones **205**, **206** and **207** yielded the corresponding *Z*-vinyl iodides **Z-227**, **Z-228** and **Z-229**. However, towards the end of the thesis, ketone **208** when subjected to the Takai olefination furnished the *E*-vinyl iodide **E-230**.

Zussamenfassung

Neosorangicin A **2** ist ein neuartiger makrozyklischer Naturstoff, der erstmals im Jahr 2017 entdeckt wurde und dessen Totalsynthese von großem Interesse für die Community ist. Daher war das Hauptziel dieser Arbeit, die Synthese des C(1) – C(12) Dihydropyranfragmentes des Moleküls von Neosorangicin A zu entwickeln.

Die retrosynthetische Analyse des Dihydropyranfragmentes **155** sah zwei Hauptstrategien für die Einbindung der Seitenkette vor. Die erste war die Verwendung eines Alkins als Zwischenprodukt und die zweite der Einsatz eines Ketons. Ausgehend von D-Galaktose **237** wurden die Alkine **175**, **178** und **179** im Multigramm-Maßstab synthetisiert. Um das Dihydropyranfragment **155** zu erhalten, nahmen die Alkine **175**, **178** und **179** an einer Zirconocen-katalysierten Methylaluminierungsreaktion teil. Leider lieferte unter den untersuchten Bedingungen keines der Alkine erfolgreich die gewünschten Produkte. Daher wurde Homoropargylalkohol **186** unter Verwendung des Alkins **175** und des Epoxids **157** synthetisiert. Der Alkohol **186** nahm dann an einer Hydroaluminierungs-, Hydrosulfurierungs- und Hydrostannylierungsreaktion teil. Keiner dieser Ansätze lieferte jedoch das Produkt **188**.

Der zweite Ansatz zum Dihydropyranfragment **155** erforderte die Synthese der Ketone **205**, **206**, **207** und **208**. Ausgehend von D-Galaktose **237** wurden die Ketone **205**, **206**, **207** und **208** im Multigramm-Maßstab synthetisiert. Anschließend untersuchten wir zunächst die Julia-Kocienski-Olefinierung zur Synthese der trisubstituierten Olefine **211**, **212**, **213** und **214**. Dazu wurden die Sulfone **209** und **210** im Multigramm-Maßstab ausgehend von *cis*-2-Buten **278** und Acetaldehyd **279** synthetisiert. Es wurden viele Versuche unternommen, um die Ketone **205**, **206**, **207** und **208** mit dem Sulfon **209** zu koppeln, aber keiner davon führte zu einer erfolgreichen Synthese der entsprechenden trisubstituierten Olefine **211**, **212**, **213** und **214**. Bei der Verwendung der Ketone **205**, **206**, **207** und **208** und des Sulfons **210** konnten wir jedoch die gewünschten Olefine **211**, **212**, **213** und **214** isolieren. Leider isolierten wir hauptsächlich die *Z*-Isomere. Die Inversion der Reaktionspartner bei der Julia-Kocienski-Olefinierung war unter den untersuchten Bedingungen nicht möglich, da die Mitsunobu-Thioetherifizierung der Alkohole **215**, **216** und **217** nicht erfolgreich war. Als nächstes wurde eine Takai-Olefinierung der Ketone **205**, **206**, **207** und **208** untersucht. Überraschenderweise ergaben die Ketone **205**, **206** und **207** die entsprechenden *Z*-Vinyliodide *Z*-**227**, *Z*-**228** und *Z*-**229**. Gegen Ende der Arbeit lieferte jedoch das Keton **208** bei der Takai-Olefinierung das *E*-Vinyliodid *E*-**230**.

Table of Contents

List of abbreviations

Å	angstrom
Ac	acetyl
Act	activator
aq	aqueous
AQN	anthraquinone
ATR	attenuated total reflection
Bn	benzyl
bp	boiling point
BT	benzothiazole-2-yl
Bu	butyl
c	concentration
ca.	*circa* (approximately)
calcd.	calculated
cat.	catalytic
CBS	Corey-Bakshi-Shibata reagent
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DCE	1,1-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	*N*,*N*-4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N*-dimethyl propylene urea

DMSO	dimethylsulfoxide
DPP	diphenylpyrazinopyridazine
dr	diastereomeric ratio
E^+	electrophile (denotes any electrophile in general)
EDTA	ethylenediaminetetraacetic acid
e.g.	*exempli gratia* (for example)
epi	epimer
ESI	electrospray ionization
Et	ethyl
et al.	*et alia* (and others)
FT-IR	Fourier transform infrared
G1	Grubbs first generation catalyst
G2	Grubbs second generation catalyst
gem	geminal
h	hours (length of reaction time)
HCAI	health care-associated infections
HG2	Hoveyda-Grubbs second generation catalyst
HMPA	hexamethylphosphoric acid triamide (hexamethylphosphoramide)
HRMS	high resolution mass spectrometry
i	iso
i.e.	*id est* (that is)
IC_{50}	half-inhibitory concentration
Icr	isocaranyl
Ipc	isopinocamphenyl
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar (concentration of solutions)
mCPBA	meta chloroperbenzoic acid
Me	methyl
MIC	minimum inhibitory concentration

MOM	methoxymethyl
Mp	melting point
MPLC	medium pressure liquid chromatography
MPM	methoxy(phenylthio)methyl
MS	molecular sieves
Ms	mesyl (methanesulfonyl)
n	normal (*e.g.* unbranched alkyl chain)
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
ox.	oxidation
p	para
PG	protecting group
Ph	phenyl
PHAL	phthalazine
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PT	1-phenyl-1*H*-tetrazole-5-yl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
PYDZ	pyridazine
PYR	pyridine-2-yl
Red-Al®	sodium bis(2-methoxyethoxy) aluminum hydride
RNA	ribonucleic acid
RP	reversed-phase
RT	room temperature
s	secondary
sat.	saturated
t, *tert*	tertiary

|	
TBABr	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TBT	1-*tert*-butyl-1*H*-tetrazole-5-yl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
TOF	time-of-flight
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*p*-toluenesulfonyl
UV	ultraviolet
WHO	World Health Organization

1. Background

1.1. Introduction

Infectious diseases have been a major problem since ancient times. Bacterial infections rival wars in the total number of deaths they cause, and recent problems like antibiotic resistance are expected to only make things worse, with some experts[1] forecasting up to 10 million annual deaths from "superbugs" by 2050. As access to healthcare improves all around the world, health care-associated infections (HCAI), or "nosocomial" infections are increasingly finding themselves under the spotlight. In the summary "The Burden of Health Care-Associated Infection Worldwide" published by the World Health Organization (WHO), HCAI is defined as: "An infection occurring in a patient during the process of care in a health-care facility which was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and also occupational infections among staff."[2]

The gathering of reliable data on HCAI is a hard process, making it difficult to determine the exact number of patients suffering from nosocomial infections. According to a systematic review conducted by WHO[2] for the period 1995 – 2008, HCAI prevalence in developed countries was found to vary between 5.1% (Norway) and 11.6% (Canada). In the USA, 1.7 million patients suffer from hospital diseases, while in Europe the number is around 2.5 times higher (4,131,000 patients). The sources of information in the developing countries are more limited since only 23 out of 147 developing countries are reported to have a functioning national surveillance system. The data reveals that the spread of hospital infections in these countries vary in the range of 5.7% (Latvia) – 19.1% (Albania) but is above 10% in most cases.

30-35% of the nosocomial infections are caused by the so called ESKAPE pathogens – *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter spp.*[2]. ESKAPE is an acronym derived from the first letters of the most common pathogens that are resistant to more than three (or even all) clinical antibiotics – a cause for great concern in the clinical and scientific communities. Since the effectiveness of the existing antibiotics is decreasing and bacteria develop resistance faster than new antibiotics are released to the market, there is a great necessity for the discovery and development of new antibiotics. However, the synthesis of new antibiotics remains one of the great challenges of modern organic chemistry.

1.2. Neosorangicins: A prospective solution

Myxobacteria are a prolific source of biologically active natural products. They are soil-dwelling bacteria with a unique social life. Myxobacteria form swarms and move by gliding on solid surfaces when the environmental conditions are appropriate. However, when the nutrients are scarce the bacteria cooperate with each other and agglomerate in specific fruiting bodies. The myxobacteria can be divided in two groups depending on their nutritional behavior. The first group are the so-called predators who lyse whole living cells of other microorganisms using lytic enzymes, and the second group are the cellulose-decomposers which are represented by the *Sorangium* and *Byssovorax* genera[3]. In 1985 Höfle *et al.*[4] isolated sorangicin A **1** (Figure 1) from the So ce12 strain of myxobacterium *Soranginium cellulosum*. In 2017 Müller *et al.*[5] isolated neosorangicin A **2** (Figure 1) from another strain (So ce439) of the myxobacterium *Soranginium cellulosum*. This novel type of macrocyclic natural product is a prospective solution to the problem of antibiotic resistance. Neosorangicins are early-stage drug candidates currently in the preclinical phase. They show antibacterial activity towards both Gram-positive and Gram-negative pathogens, including *Enterococcus spp.*, *Staphylococcus aureus* (MRSA/VISA), *Streptococcus pneumoniae*, *Acinetobacter sp.*, *Pseudomonas aeruginosa*, *Escherichia coli*. Neosorangicin A is currently of great interest due to the fact that it has weak or no cross-resistance to rifampicin, a commonly prescribed antibiotic, especially against Gram-negative bacteria. In addition, neosorangicin A has a higher and broader spectrum of activity towards both Gram-positive and Gram-negative bacteria when compared to sorangicin A.

Sorangicin A **1**
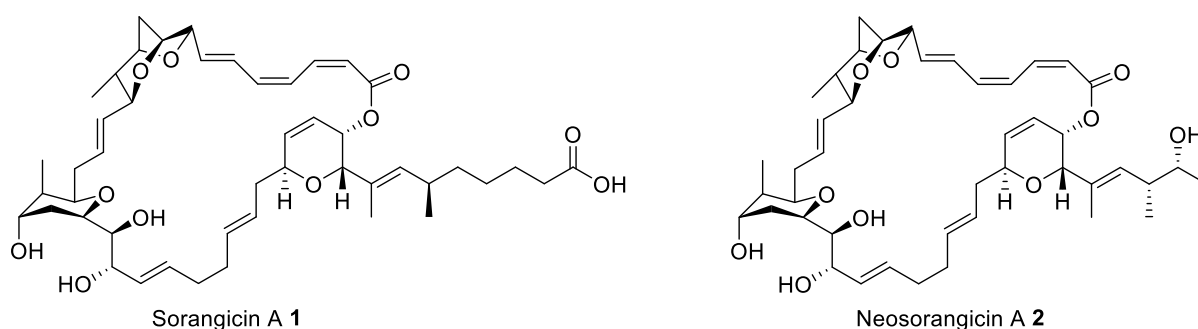
Neosorangicin A **2**

Figure 1: *Chemical structures of sorangicin A **1** and neosorangicin A **2***

Neosorangicin A was found to be chemically and biologically similar to sorangicin A. However, it is the first derivative of this type known to be active against Gram-negative bacteria. Neosorangicin A has a 10-fold better activity on *Staphylococcus aureus* Newman *in vitro* compared to sorangicin A. Neosorangicin A also shows efficient intracellular activity

against *Staphylococcus aureus* Newman in human macrophages. It causes a 3-Log reduction of the total bacterial load in human macrophages while not expressing any apparent toxicity towards them. The minimum inhibitory concentration (MIC) values on *S. aureus* Newman are found to be 0.01, 0.13, 0.01 µg/ml for neosorangicin A, sorangicin A and rifampicin respectively. The MIC values of neosorangicin A, sorangicin A and rifampicin (as a reference antibiotic) on a panel of selected Gram-positive and Gram-negative bacteria are represented in Table 1.

Table 1: *MIC values for neosorangicin A (neosor A), sorangicin A (sor A), and rifampicin (rif) on various bacteria*[5]

Bacteria species	neosor A	sor A	rif
Enterococcus faecalis DSM-20478	0.5	2	6.4
Enterococcus faecium DSM-20477	8	16	> 6.4
Staphylococcus aureus ATCC29213	0.01	0.03	0.01
Staphylococcus aureus DSM-346	0.25	1	0.006
Staphylococcus aureus Newman	0.01	0.13	0.01
Staphylococcus aureus Newman (rif resistant)	> 64	> 64	> 6.4
Streptococcus pneumoniae DSM-11865 (PRSP)	0.5	32	0.1
Acinetobacter baumannii DSM-30008	8	8	1.6
Escherichia coli DSM-1116	8	16	6.4
Escherichia coli DSM-1116 + 3 µg/ml PMBN	0.25	0.25	0.4
Escherichia coli DSM-26863 (tolC3)	2	8	6.4
Escherichia coli (TolC-deficient)	1	8	6.4
Klebsiella pneumoniae DSM-30104	8	16	6.4
Pseudomonas aeruginosa PA-14	33	67	-
Pseudomonas aeruginosa DSM-1128	8	32	> 6.4

As shown in Table 1, the MIC values of neosorangicin A against pathogens like *Enterococcus spp.*, *S. aureus*, *S. pneumoniae*, *A. baumannii*, *E. coli* and *P. aeruginosa* are in the mid ng/ml and low µg/ml area, indicating excellent inhibitory activity against Gram-positive as well as Gram-negative bacteria. On average, neosorangicin A is more active than sorangicin A by a factor of 2-10. However, both neosorangicin A and sorangicin A are not active towards rifampicin-resistant *S. aureus* Newman – suggesting that those compounds have overlying binding sites on the RNA polymerase. For *Escherichia coli* pathogens, the activity of both neosorangicin A and sorangicin A increases when sub-inhibitory concentrations of polymyxin B nonapeptide (PMBN) are added. Furthermore, for efflux-deficient *E. coli* mutants the MIC of neosorangicin A decreases. The *in vitro* tests on *S. aureus* RNA polymerase determined the half-inhibitory concentrations (IC$_{50}$) for neosorangicin A, sorangicin A and rifampicin, as

0.06 ± 0.01 µM, 0.21 ± 0.12 µM, and 0.03 ± 0.02 µM respectively. These results confirm that neosorangicin A demonstrates higher activity than sorangicin A.

1.3. Fermentation process of neosorangicin A

Soranginium cellulosum strain So ce439 was stored at –80 °C and it was reactivated in 20 ml of liquid medium containing 0.5% soy peptone, 0.2% yeast extract, 0.1% $MgSO_4 \cdot 7H_2O$, 0.1% $CaCl_2 \cdot 2H_2O$, 10% glucose $\cdot 7H_2O$ and 8 mg/l Na-Fe-EDTA. The culture was used for fermentation of the So ce439 strain in the same liquid medium as above but including also 2% amberlite XAD-16 resin. After completion of the fermentation process the XAD resin (1.71 kg) was sieved out and recovered. The XAD adsorber resin was first extracted with methanol/H_2O (3/7) and then again with pure methanol. The extracts were combined and evaporated to an aqueous mixture, which was diluted with water and extracted three times with ethyl acetate. The organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to yield 5.3 g of crude extract. This crude extract was redissolved in methanol containing 1% H_2O and extracted three times with heptane. After evaporation of the combined organic layers under reduced pressure, 3.91 g of enriched crude extract were obtained. The enriched crude extract was taken in methanol and filtered through a Strata-column (10 g, 55 µm, 70 Å) two times. After evaporation of the methanol, 3.45 g of crude extract were isolated. Finally, the crude extract was purified by RP-MPLC and 247 mg of pure neosorangicin A were obtained. The biotechnological production of neosorangicin A gives rather low yields, making the development of a multi-gram scale synthetic route of great practical and research interest[5].

1.4. Structural similarities between neosorangicin A and sorangicin A

Neosorangicin A and sorangicin A can be considered as analogues based on their chemical similarities. Both compounds comprise of a characteristic bicyclic ether, a trisubstituted dihydropyran with a carbon side chain (carboxylic in the case of sorangicin A, and alcoholic in the case of neosorangicin A) and a tetrasubstituted tetrahydropyran moiety, which are incorporated in a 31-membered lactone. In addition, the macrocyclic lactone is highly unsaturated including a very sensitive (*E,Z,Z*)-trienoate linkage which in sorangicin A is theorized to be the cause for the instability of the natural product towards certain reagents. Based on the structural similarity, the synthesis of neosorangicin A can therefore be accomplished in a way that is analogous to that of sorangicin A.

1.5. Current progress towards the synthesis of sorangicin A

1.5.1. Total synthesis of Smith *et al.*

The first and so far the only successful total synthesis of sorangicin A **1** was achieved by the group of Amos B. Smith III in 2009[6,7]. The retrosynthesis of Smith *et al.* is shown in Scheme **1**, where the molecule of sorangicin A **1** was split into four key building blocks: dioxabicyclooctane fragment **3**, tetrahydropyran **4**, dihydropyran fragment **6** and the *Z,Z*-diene **5**. They first used a Julia-Kocienski olefination for the coupling of the dioxabicyclooctane fragment **3** with the tetrahydropyran **4**, which upon a second Julia-Kocienski olefination was linked to the dihydropyran fragment **6**. For incorporation of the (*E,Z,Z*)-trienoate system they used a Stille coupling between **3** and the *Z,Z*-diene **5**. The last step was the macrolactonization and the ring closure under suitable conditions.
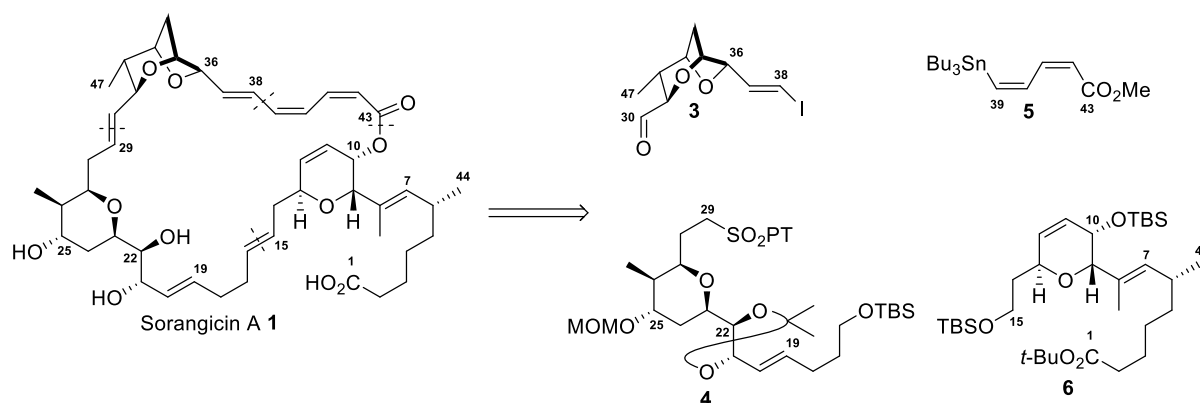
Scheme 1: *Retrosynthetic approach of Smith et al.[6,7] towards sorangicin A **1***

The first Julia-Kocienski olefination turned out to be very challenging with respect to yields and stereoselectivity. Several combinations between bases and solvents were tested, the results of which are summarized in Table 2.

Table 2: *Julia-Kocienski olefination between the dioxabicyclooctane fragment 3 and the tetrahydropyran fragment 4*

Base	Solvents	Yield	*E/Z* ratio	Recovered sulfone	Recovered aldehyde
LiHMDS	DMF/HMPA (3:1)	24%	*E*-only	63%	36%
NaHMDS	DME/HMPA (3:1)	40%	3.6:1	39%	23%
KHMDS	DME	54%	2.0:1	0%	0%
LDA	DMF/HMPA (3:1)	11%	*E*-only	38%	42%
t-BuLi	DMF/HMPA (3:1)	39%	*E*-only	39%	13%

Using Jacobsen conditions (LiHMDS as a base and DMF/HMPA as a solvent mixture) the yield of the *E*-olefin **7** was low (24%) but the stereoselectivity was excellent, with only the

desired *E*-isomer observed in the product (Scheme 2). The replacement of the Li-ion with a Na-ion in the base resulted in a higher yield (40%) but lower *E/Z* stereoselectivity (3.6:1). Surprisingly, when the standard *E*-selective conditions (KHMDS in DME) were used the observed *E/Z* stereoselectivity was the poorest (2.0:1), but provided the highest yield (54%). The most suitable conditions with regards to both yield and stereoselectivity turned out to be the use of *t*-BuLi as a base and a mixture of DMF/HMPA as a solvent. This resulted in the formation of the steoreochemically pure *E*-olefin **7** in 39% yield.
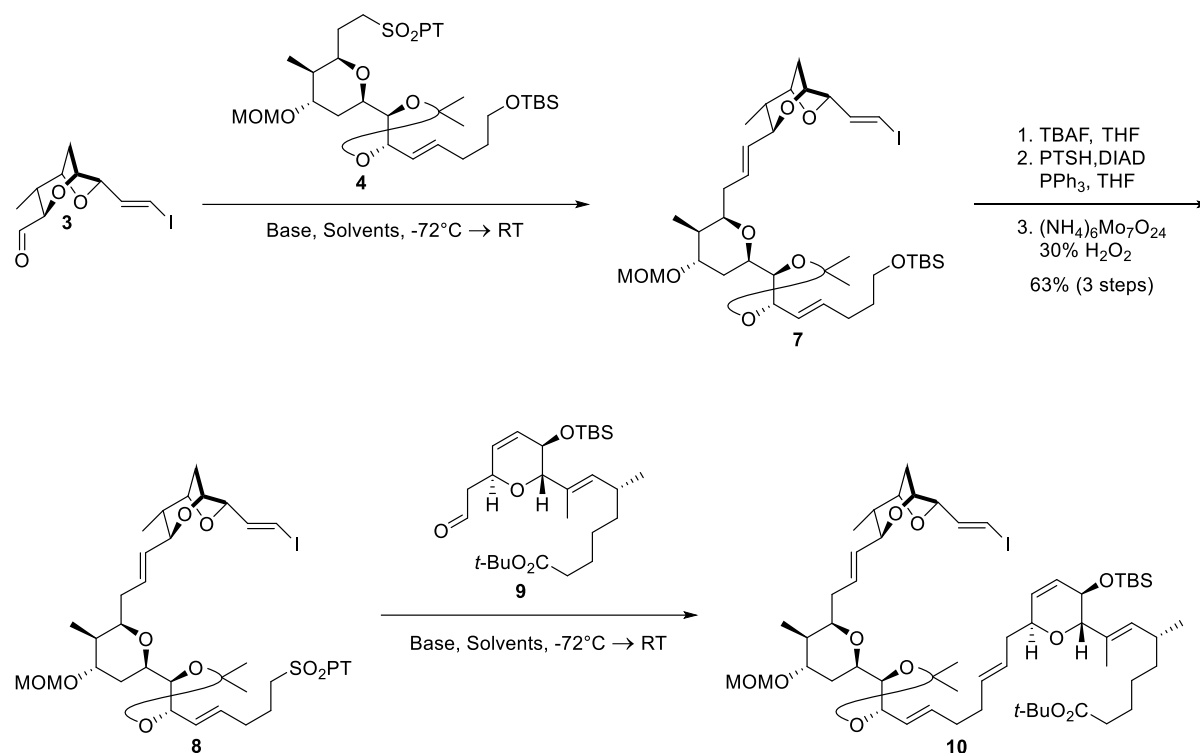
Scheme 2: *Formation of C(29) – C(30) and C(15) – C(16) trans olefins using Julia-Kocienski olefination*

The second Julia-Kocienski olefination between sulfone **8** and aldehyde **9** was also troublesome. The use of LiHMDS as a base and a solvent mixture of DMF/HMPA (3:1) resulted in 30% yield and no *E/Z* stereoselectivity. Comparably low yield (28%) was also observed when KHMDS in DME was used, but in this case only the desired *E*-isomer **10** was isolated (Scheme 2). Those results necessitated the inversion of the coupling partners. Sulfone **14** was obtained from (−)-10-*epi*-**6** as shown in Scheme 3. Compound **6** was first globally desilylated and then the primary alcohol was chemoselectively silylated to yield alcohol **11**. Ley oxidation of compound **11**, followed by Luche reduction generated alcohol **12**, which had inverted stereochemistry at the C(10) center. Silylation of compound **12** and a selective deprotection of the primary alcohol furnished compound **13**. Mitsunobu thioetherification of

alcohol **13** and subsequent oxidation of the formed thioether afforded sulfone **14** (46% over eight steps).
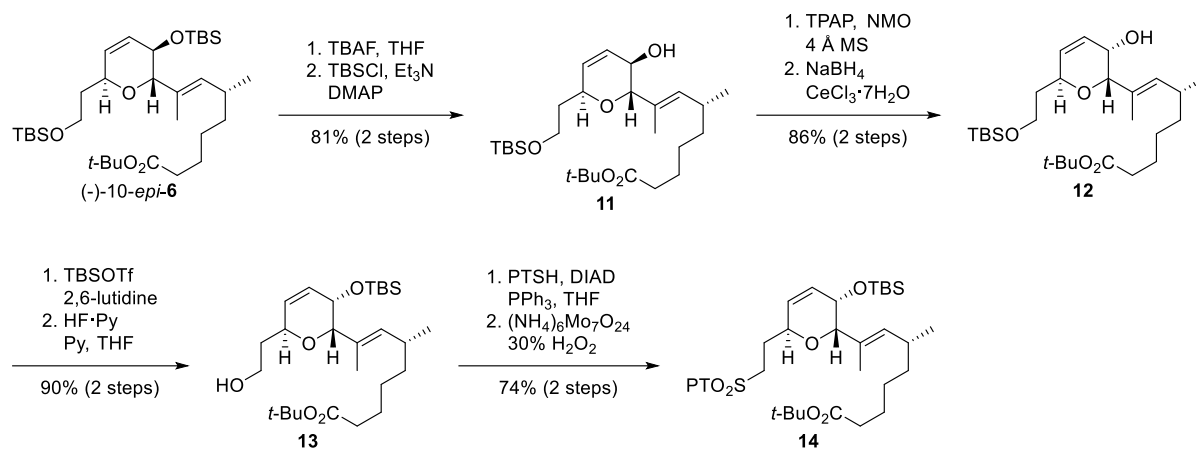
Scheme 3: *Synthesis of sulfone* **14**

Aldehyde **15** was prepared from compound **7** via a two-step sequence of desilylation and Dess-Martin oxidation. Sulfone **14** and aldehyde **15** were then coupled using KHMDS in DME. Under these conditions and after desilylation *E*-olefin **16** was isolated in 86% yield with the desired stereochemistry at C(10) (Scheme 4).
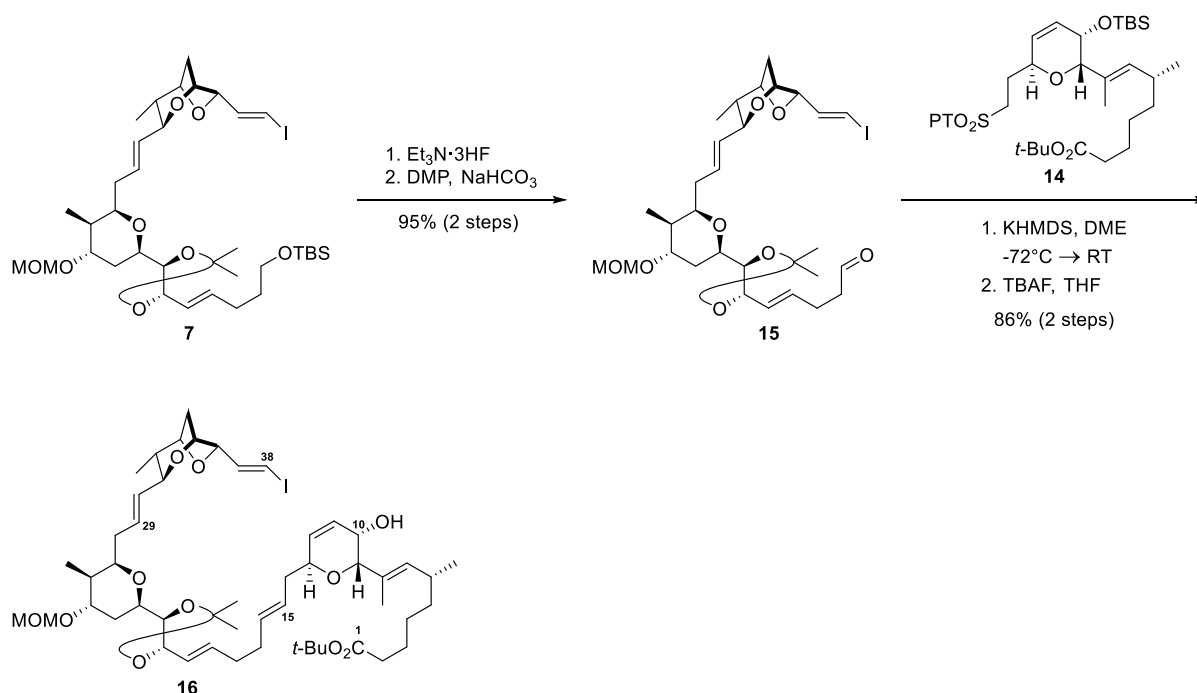

Scheme 4: *Julia-Kocienski olefination between aldehyde* **15** *and sulfone* **14**

For the introduction of the sensitive (*E,Z,Z*)-trienoate moiety, the stable stannyl dienoate **5** and compound **16** took part in a Stille coupling reaction. The desired product **17** was isolated in

88% yield, although a large excess of $Ph_2PO_2NBu_4$ (12 eq.) was necessary in order to avoid an *E/Z* isomerization. Geometrical isomerization was also not observed in the following hydrolysis of **17** to the trienoacid **18** with LiOH in THF (Scheme 5).
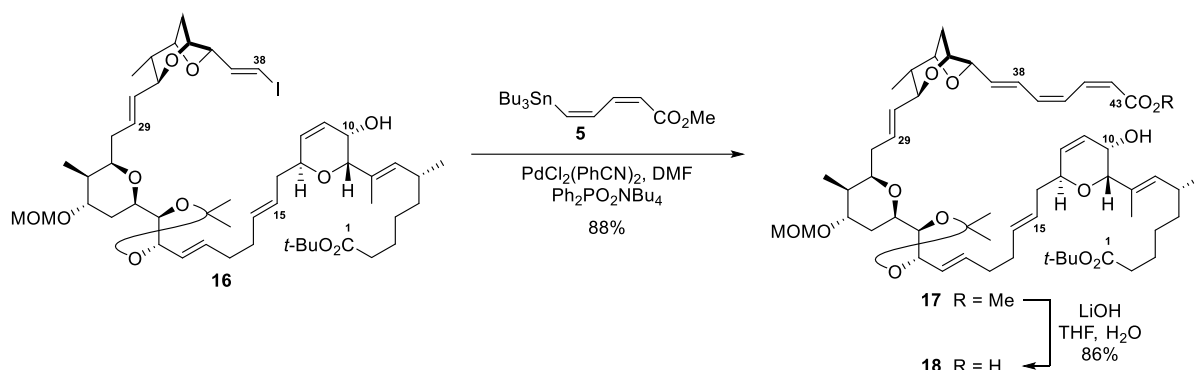
Scheme 5: *Introduction of the (E,Z,Z)- trienoate moiety to obtain compound 18*

The macrocyclization step was also very critical since the possibility of significant isomerization was high. Two mild conditions were used to obtain the necessary (*E,Z,Z*)-configured macrolactone **20**: the Yonemitsu modification of the Yamaguchi conditions and the Evans-modified Mukaiyama protocol. Although those conditions resulted in solving the challenging step of macrolactonization, compound **20** was contaminated with small amounts of unwanted geometric isomers which were difficult to separate. To circumvent this problem, the modified Mukaiyama reagent **19**, which has a non-nucleophilic counterion (*i.e.*, tetrafluoroborate) was adopted (Scheme 6). The use of **19** resulted in minimum isomerization (ca. < 4%) and the macrolide **20** was furnished in high yield (85%).
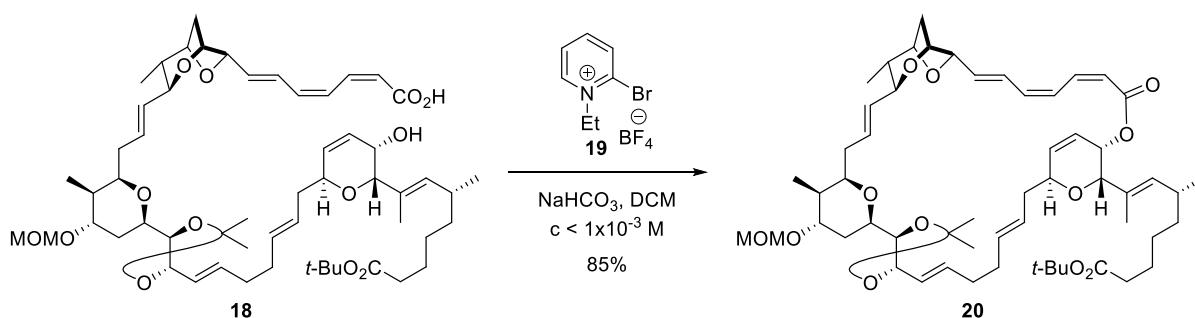
Scheme 6: *Macrocyclization of compound 18*

In the next step the MOM protecting group was removed with TBSOTf and the *tert*-butyl ester was converted into the corresponding ester without destroying and/or isomerizing the highly sensitive (*E,Z,Z*)-trienoate linkage. Sorangicin A **1** could then be obtained by treating the crude product with 4N HCl in THF with 70% yield for the last two steps (Scheme 7).
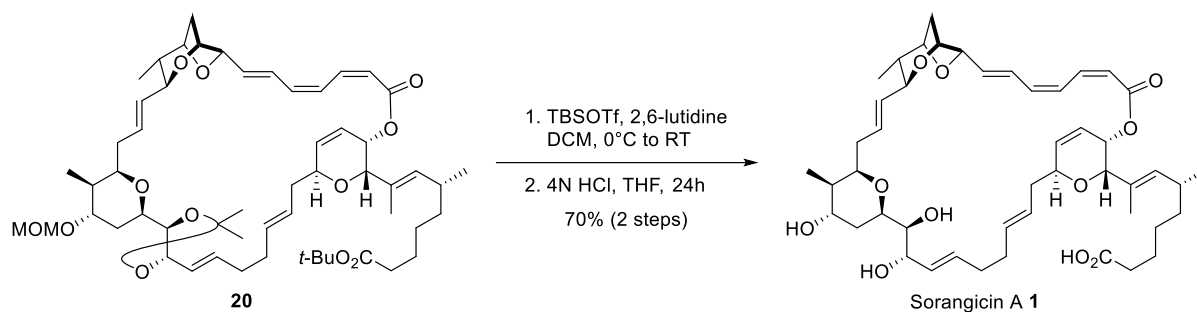
Scheme 7: *Final deprotection steps from the total synthesis of sorangicin A* **1**

1.5.2. Formal synthesis of Crimmins *et al.*

The synthetic approach of Crimmins *et al.*[8] towards the synthesis of sorangicin A **1** is shown in Scheme 8. They fragmented the molecule to the following three key building blocks: dioxabicyclooctane **21**, tetrahydropyran **22** and dihydropyran **23** or **24**. Comparing to the previously described approach by Smith *et al.*[6,7], it can be seen that Crimmins *et al.* disconnected the fragments in the same manner, but planned to use cross metathesis for the formation of the C(29) – C(30) and C(15) – C(16) trans olefins.
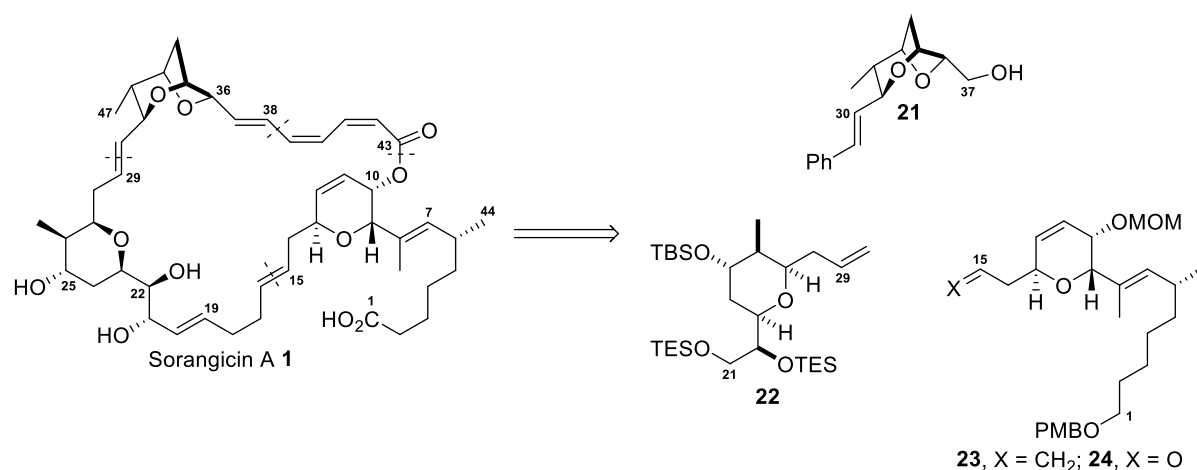
Scheme 8: *Retrosynthetic approach of Crimmins et al.[8] towards sorangicin A* **1**

The first cross metathesis was to form the C(29) – C(30) double bond. Before this can be accomplished compound **21** was subjected to acylation, ozonolysis and methylenation, a three-step process which afforded compound **25** in 85% overall yield (Scheme 9).
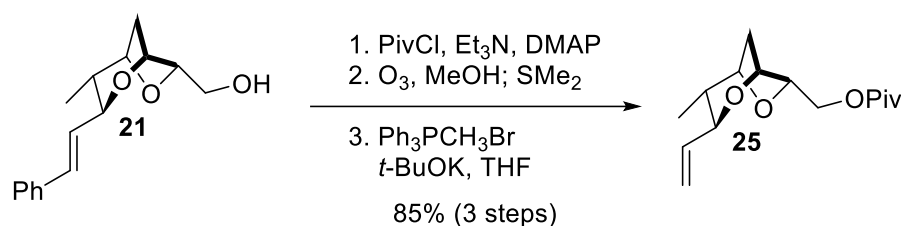
Scheme 9: *Synthesis of compound 25*

Compound **22** was also modified prior to the cross-metathesis step. Compound **22** was first converted to the corresponding aldehyde using modified Swern conditions, which allowed the selective deprotection and oxidation of the primary TES-ether. Vinyl iodide **26** was converted *in situ* to the vinyl zinc species which was added to the previously obtained aldehyde in a stereo controlled manner using Felkin-Anh addition (8:1 dr). The obtained 1,2-diol was finally protected as an acetonide in further two steps. The yield of the four-step sequence to convert compound **22** into compound **27** was 66% (Scheme 10).
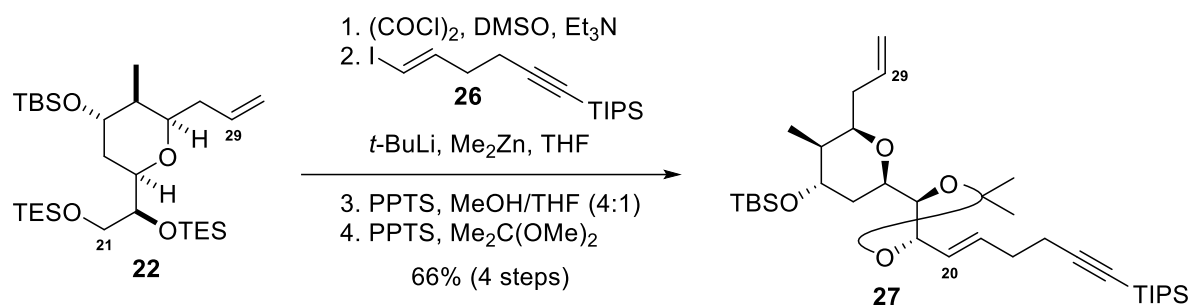
Scheme 10: *Synthesis of compound 27*

The cross-metathesis between the dioxabicyclooctane **25** and tetrahydropyran **27** was accomplished by the use of Grubbs second generation (G2) catalyst and afforded compound **28** in 40% yield. Compound **28** was subjected to TIPS-deprotection and Lindlar reduction as well as a replacement of the Piv protecting group with a PMB protecting group generating compound **29**. In further two steps the TBS-ether in compound **29** was exchanged for a MOM-ether to obtain compound **30**. The six-step sequence of converting compound **28** to compound **30** was accomplished in 55% overall yield (Scheme 11).
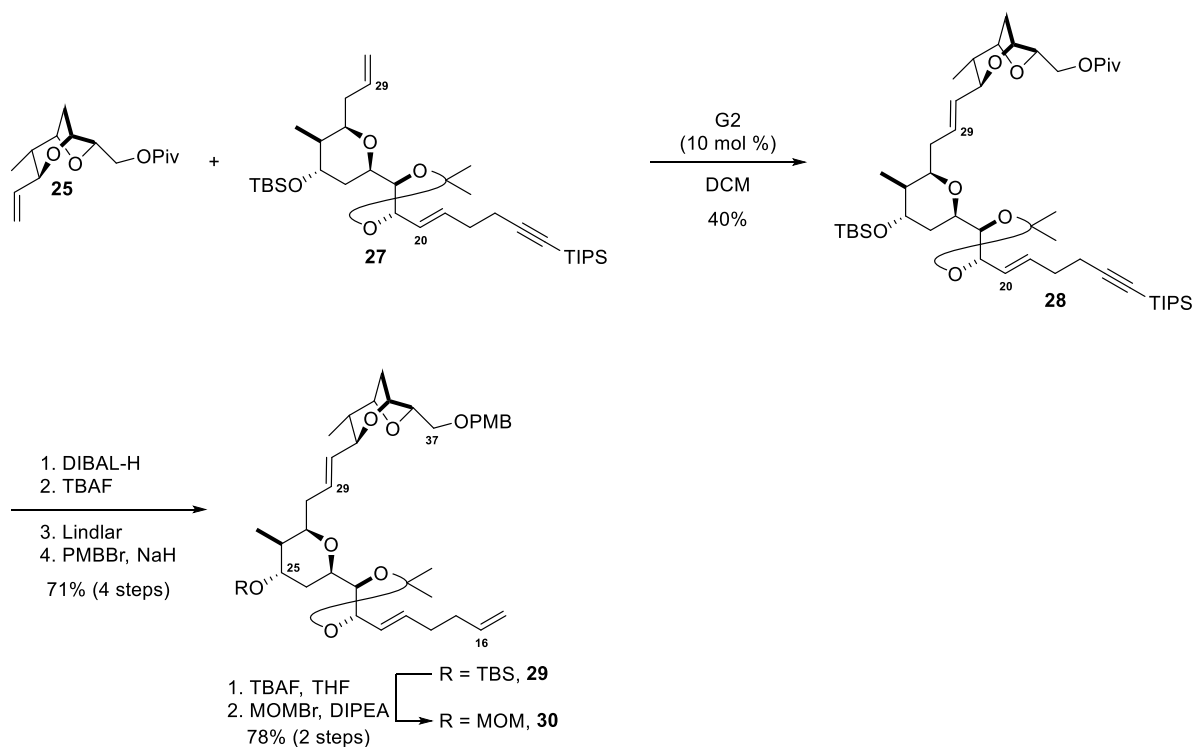
Scheme 11: *Cross-metathesis between dioxabicyclooctane fragment 25 and tetrahydropyran fragment 27*

The second cross-metathesis was between compound **30** and dihydropyran **31**. In this reaction Hoveyda-Grubbs second generation (HG2) catalyst was used. The desired product **32** was obtained in a low yield (16%). This was expected to be due to the formation of homodimer of the dihydropyran fragment **31** as well as of compound **30**. Regardless of the low yield of the metathesis reaction compound **32** was transformed to compound **33** in three steps with a 31% overall yield (Scheme 12).
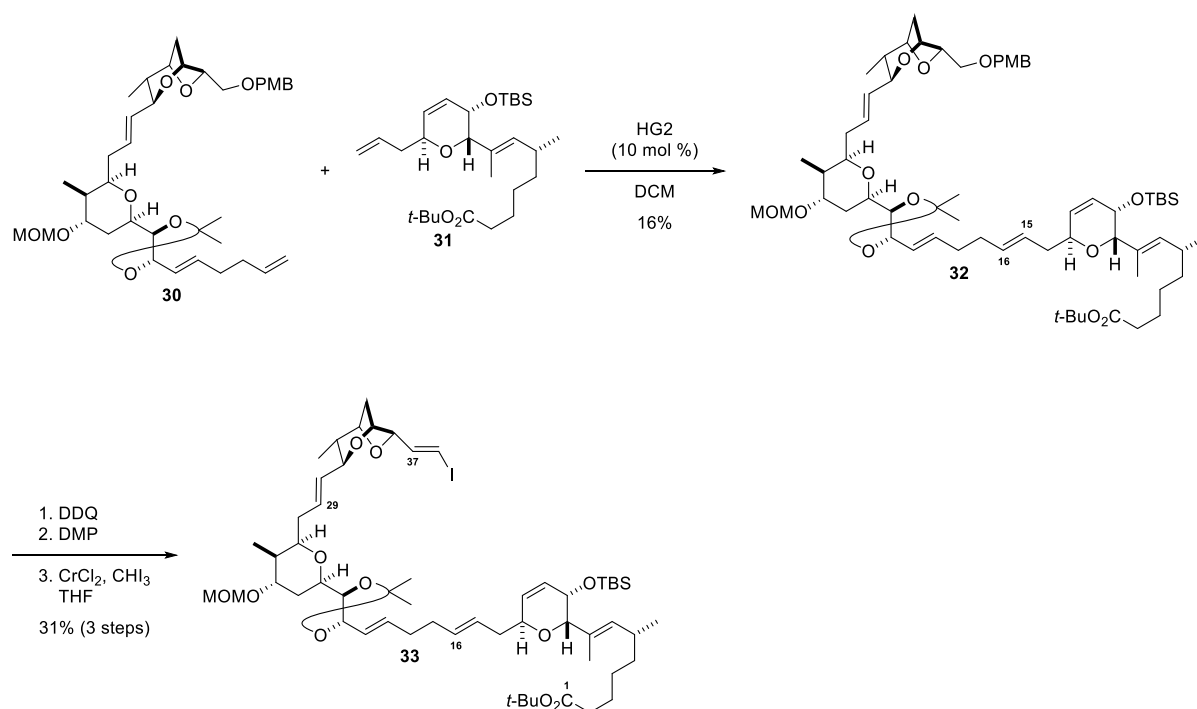
Scheme 12: *Second cross-metathesis between compound 30 and dihydropyran fragment 31*

Due to the low yield from the second cross-metathesis reaction, Crimmins *et al.* decided to use Julia-Kocienski olefination instead for the C(15) – C(16) bond formation. To be able to perform this task some modifications of the previously used strategy for connecting the dioxabicyclooctane fragment and the tetrahydropyran fragment were necessary. First, compound **21** was converted into compound **34** in 82% yield via a three-step reaction sequence, consisting of PMB-protection, Johnson-Lemieux oxidation and Wittig olefination. Compound **34** and compound **22** were subjected to cross metathesis, using Grubbs second generation (G2) catalyst (Scheme 13). These conditions have yielded compound **35** in 77% as a single *E*-isomer.
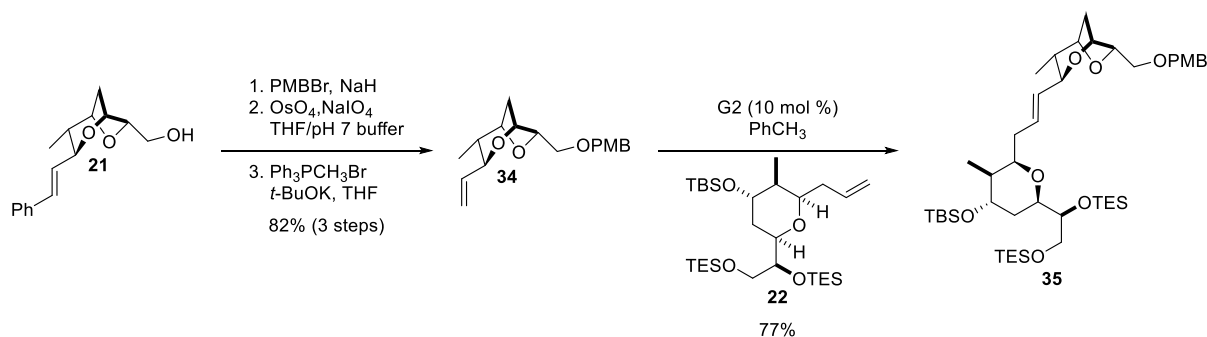
Scheme 13: *Cross-metathesis between dioxabicyclooctane fragment 34 and tetrahydropyran fragment 22*

Compound **35** took part in a modified Swern oxidation which afforded the selective deprotection of the alcohol at C(21) and its subsequent oxidation to the corresponding aldehyde. The so formed aldehyde reacted in the next step with the vinyl zinc species formed from the vinyl iodide **36** to provide compound **37** in 61% overall yield. Manipulation of the protecting groups in **37** resulted in the formation of compound **38** in 45% yield over four steps (Scheme 14).
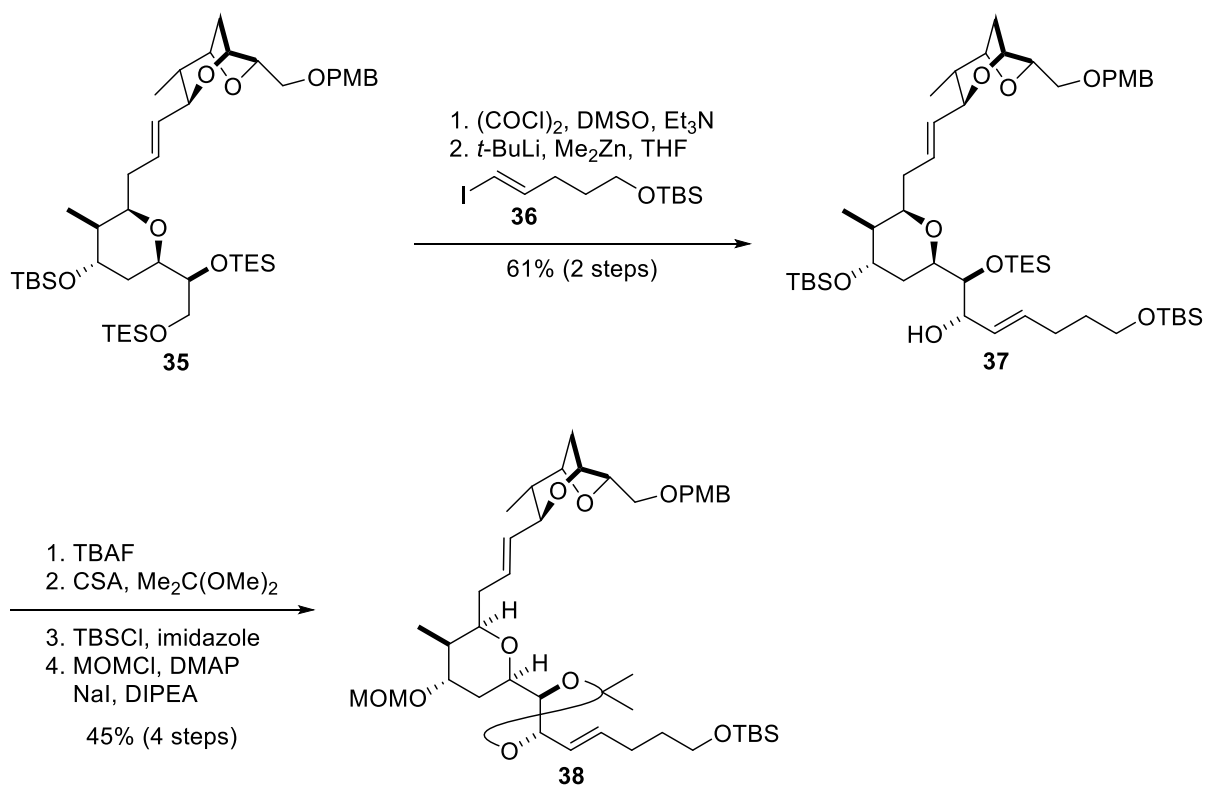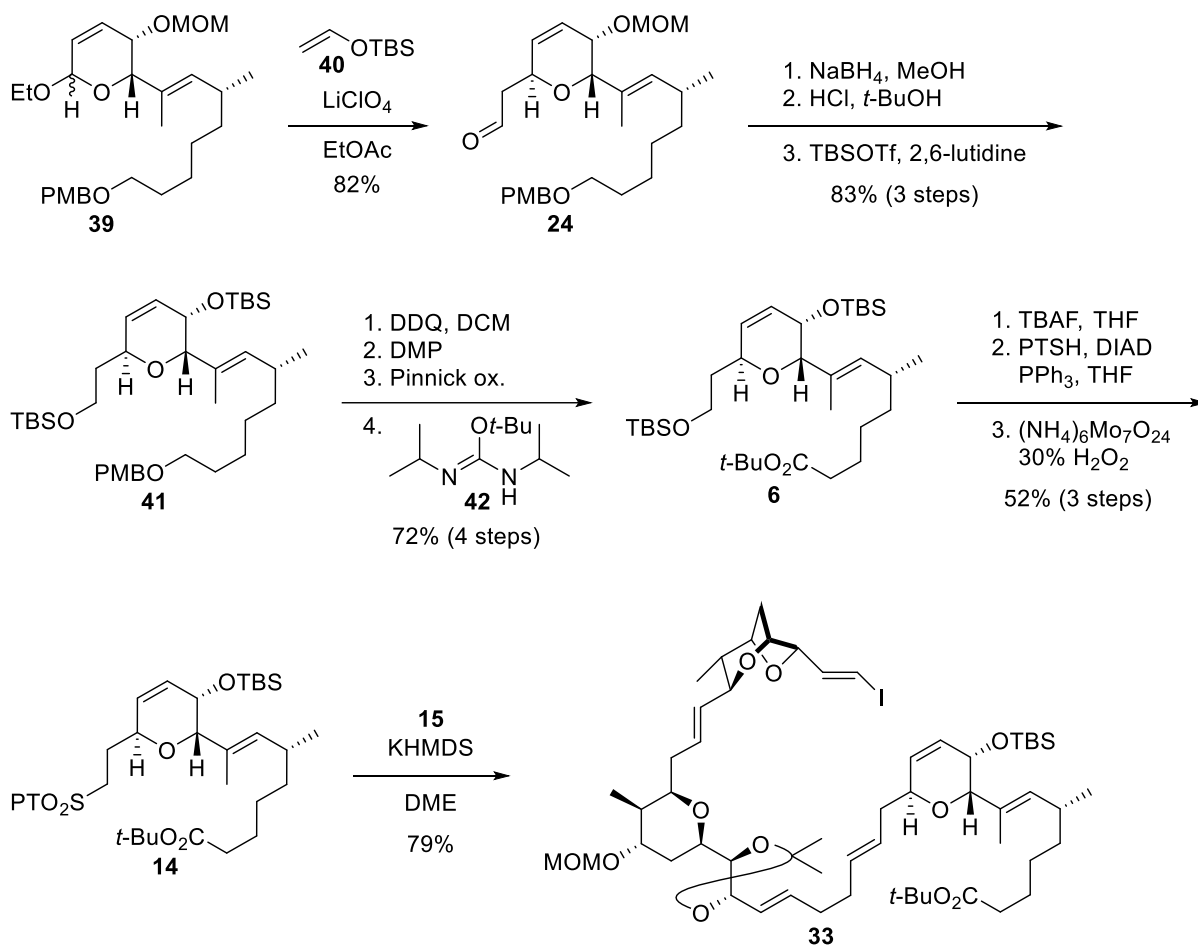

Scheme 14: *Synthesis of compound 38*

The next step was to utilize the vinyl iodide moiety. This was accomplished by oxidative cleavage of the PMB protecting group in compound **38**, followed by a Dess-Martin oxidation of the primary alcohol and finally a Takai olefination. The *E/Z* stereoselectivity in the Takai reaction was 4:1 and after a purification by column chromatography the desired *E*-vinyl iodide **7** was obtained in 28% yield over three steps. The final aldehyde **15** necessary for the Julia-Kocienski olefination was obtained in 68% yield over two steps (Scheme 15) from compound **7** by deprotecting the TBS-group via TBAF and oxidation of the primary alcohol using Dess-Martin periodinane (DMP).
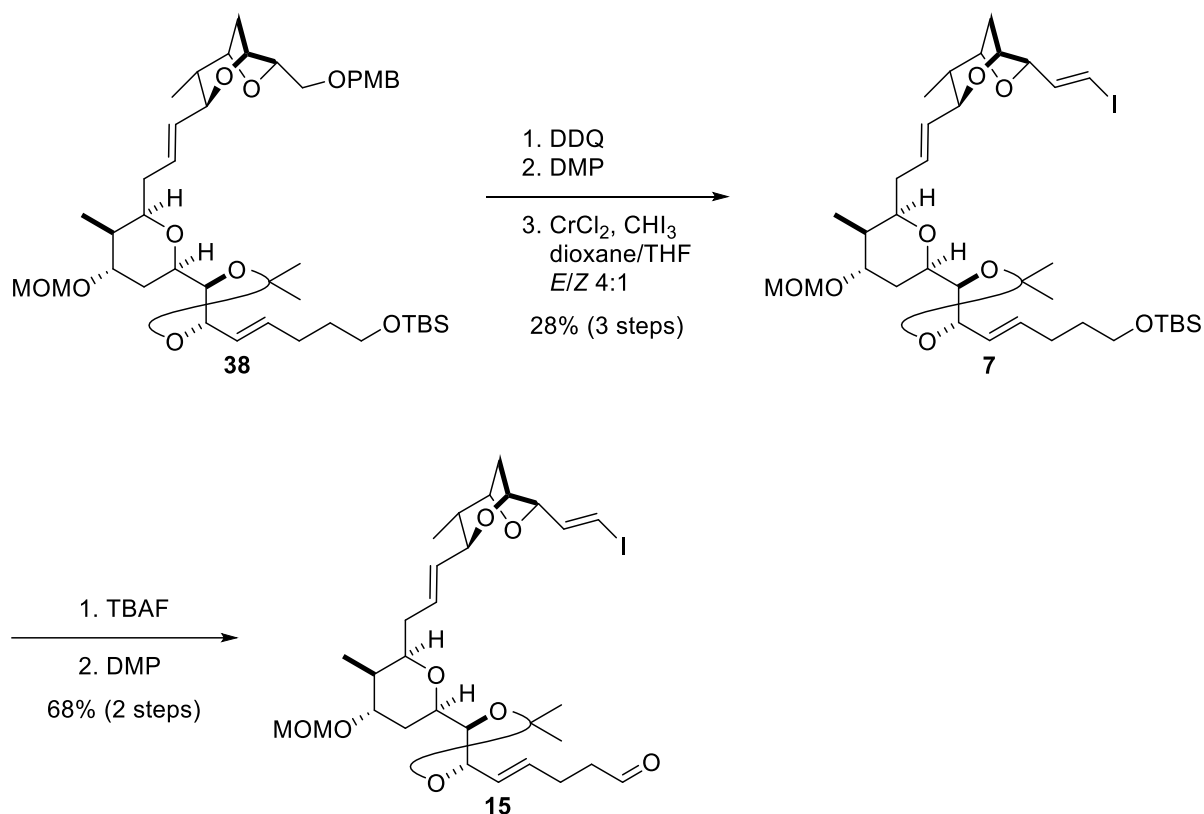
Scheme 15: *Synthesis of aldehyde 15*

Modification of the synthetic route towards the dihydropyran moiety was also necessary. To afford the necessary sulfone **14**, compound **39** was added to acetaldehyde silyl ether **40** using Lewis acid. This generated aldehyde **24** as a single diastereomer in 82% yield. Aldehyde **24** was subjected successively to a reduction with NaBH₄, MOM-deprotection and TBS-protection to afford the bis-TBS ether **41** (83% yield over three steps). In four steps and with 72% yield over four reactions the PMB-ether was converted to *tert*-butyl ester **6**. Ester **6** took part in a three-step sequence in order to furnish sulfone **14**, which was identical to that obtained by Smith *et al.*[6,7], in 52% overall yield. The final step was Julia-Kocienski olefination between aldehyde **15** and sulfone **14**, using the already described protocol by Smith *et al*. Using this method, the C(1) – C(38) fragment **33** was obtained in 79% yield (Scheme 16).

Scheme 16: *Synthesis of the dihydropyran moiety **14** and Julia-Kocienski olefination between compound **14** and compound **15***

1.5.3. Synthesis of the dihydropyran moiety

1.5.3.1. Synthesis of Smith et al.

The synthetic approach of Smith *et al.*[6,7] towards the dihydropyran fragment of sorangicin A **1** started with the formation of enone **46** and vinyl bromide **50**. Enone **46** was obtained via a hetero Diels-Alder reaction between aldehyde **43** and the Danishefsky diene **44** (Scheme 17). The reaction was promoted by chromium(III) complex **45** and afforded enone **46** in 98% yield.
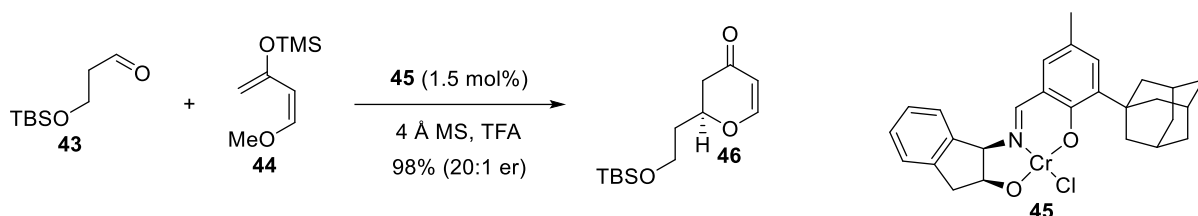
Scheme 17: *Synthesis of enone **46***

The synthesis of the vinyl bromide **50** adopted as a first step a Myers alkylation between amide **47** and alkyl iodide **48** and compound **49** was obtained in 99% yield (>20:1 dr). The amide **49**

was then subjected successively to reduction, Corey-Fuchs homologation and hydrozirconation/bromination and the vinyl bromide **50** was formed in 65% yield over four steps (Scheme 18).
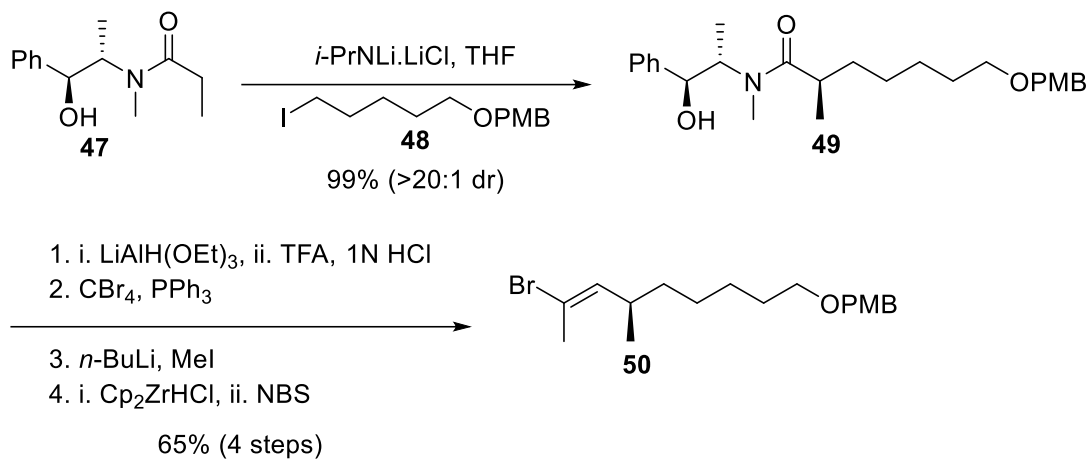

Scheme 18: Synthesis of the vinyl bromide 50

The cuprate, derived from the vinyl bromide **50**, reacted with enone **46** in the presence of TESCl to furnish the enol ether **51** in 77% yield. Oxidation of **51** according to the Rubottom protocol and conversion of the TES-ether to a TBS-ether yielded compound **52** (51% over three steps). Next the enolate of compound **52** was formed using LDA/HMPA, which was followed by enol triflate formation using Comin's reagent. Finally, a palladium-catalyzed reduction afforded diene **41** in 77% yield over two steps. Compound (−)-10-*epi*-**6** was formed from diene **41** by cleavage of the PMB-ether using DDQ, followed by a two-step oxidation (first Dess-Martin then Pinnick oxidation) and a *tert*-butyl ester formation (69% over four steps). Selective removal of the primary TBS protecting group in (−)-10-*epi*-**6** followed by a Dess-Martin oxidation led to the formation of aldehyde **9** in 70% yield over two steps (Scheme 19).
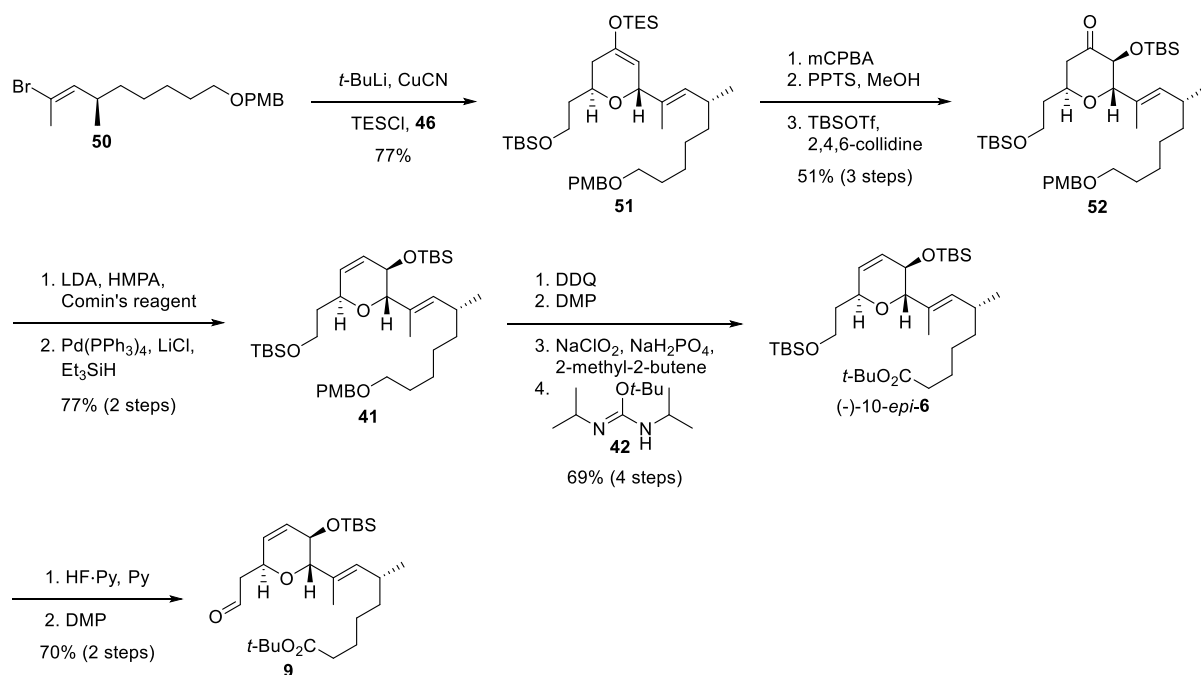
Scheme 19: *Synthesis of aldehyde 9*

1.5.3.2.   Synthesis of Crimmins et al.

Crimmins *et al.*[8] reported in 2011 as a part of their formal synthesis an approach towards the synthesis of the C(1) – C(15) fragment of sorangicin A **1**. Aldehyde **53** was adopted as a starting material. It was subjected to Wittig olefination, reduction and oxidation reactions to give finally the trisubstituted olefin **55** in 92% overall yield. Aldehyde **55** was exposed to a Brown alkoxy-allylation to obtain as a product the *syn*-1,2-diol **57** (96% yield). The diol **57** reacted with acrolein diethyl acetal to afford an intermediate diene, which was subjected to a ring-closing metathesis with Grubbs second generation (G2) catalyst and resulted in the formation of the mixed acetal **39** in 72% yield over two steps (1:1 dr). The mixed acetal **39** took part in a Hosomi-Sakurai reaction with allylTMS in the presence of BF$_3$·OEt$_2$ to obtain the allylated product **23** as a single diastereomer in 92% yield. To furnish the dihydropyran fragment **58**, compound **23** was subjected subsequently to an oxidative cleavage of the PMB-ether, Dess-Martin oxidation, Pinnick oxidation and an ester formation. Ester **58** was obtained in 57% overall yield. Cleavage of the MOM-ether in compound **58** and subsequent TBS-protection led to the formation of compound **31** in 93% yield over two steps (Scheme 20).
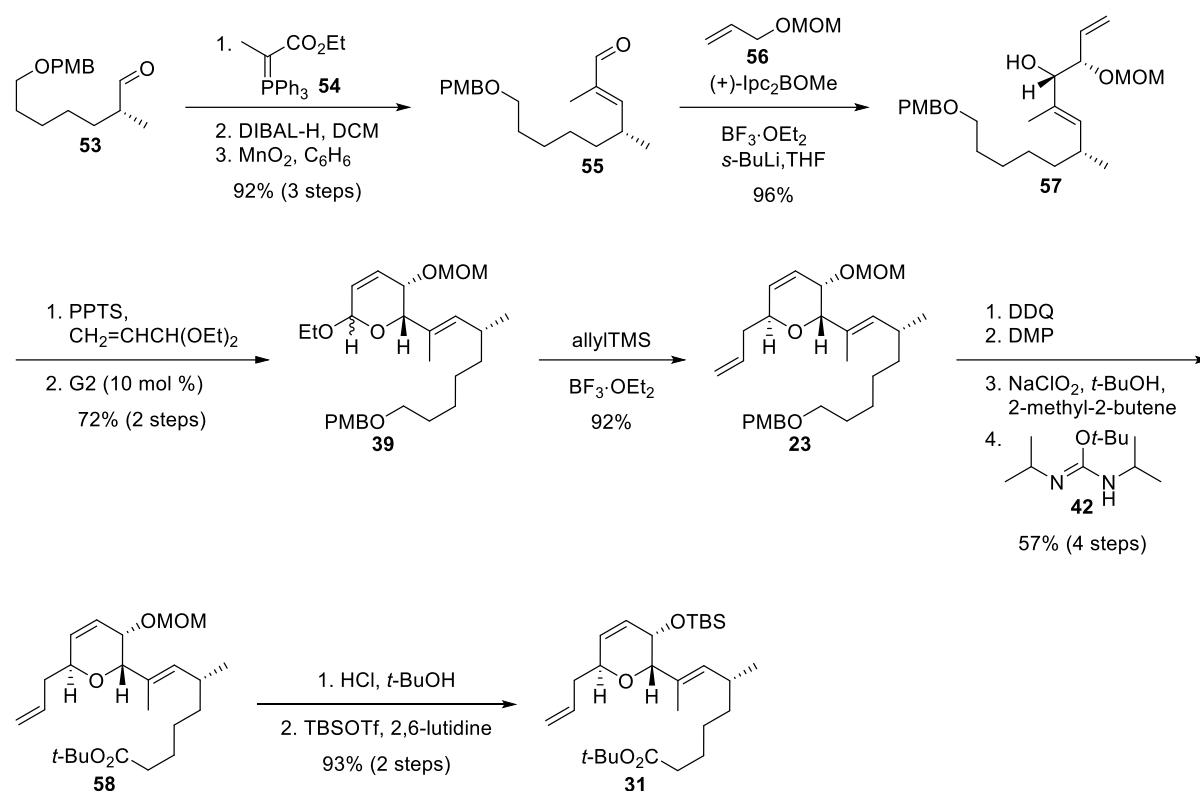
Scheme 20: *Synthesis of dihydropyran fragment 31*

1.5.3.3. Synthesis of Lee et al.

Lee *et al.*[9] proposed two synthetic approaches towards the dihydropyran fragment of sorangicin A **1**. The first approach used alcohol **59** as a starting material. It was converted to a glycolic acid and subsequently to a pivalic anhydride. The so formed anhydride then reacted with (*R*)-3-lithio-4-benzyl-2-oxazolidinone (prepared *in situ* from (*R*)-4-benzyl-2-oxazolidinone **60** and *n*-BuLi) to produce *N*-glycolyloxazolidinone **61** (80% over three steps). Compound **61** reacted with acrolein to furnish the hydroxy compound **62** (73% yield, 93:7 dr) which underwent a TBS-protection and reductive cleavage of the chiral auxiliary in order to form compound **63** (80% yield over two steps). The desired dihydropyran fragment **64** was finally furnished in 86% yield using an olefinic ring-closing metathesis in the presence of Grubbs first generation (G1) catalyst (Scheme 21).
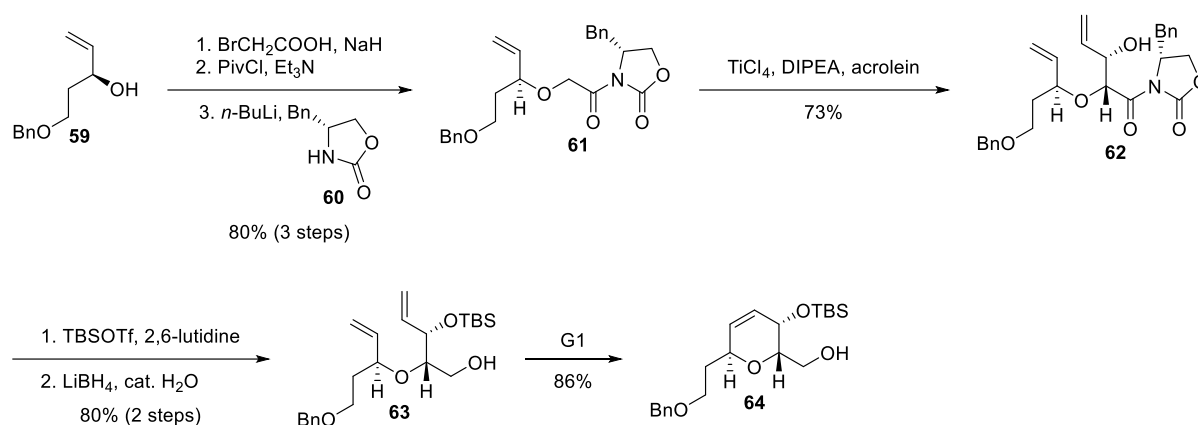
Scheme 21: *Synthesis of compound **64**, starting from compound **59***

The second approach towards the dihydropyran fragment started from the chiral oxazolidinone **65** which participated in an aldol addition with acrolein to obtain the *syn*-aldol alcohol in 84% yield (92:8 dr). This was then protected as a TBS-ether to afford compound **66** in 91% yield. Reductive removal of the chiral auxiliary, followed by a TBS-protection and an oxidative removal of the MPM protecting group yielded alkenyl alcohol **67** in 77% over three steps. In the next step, diene **69** was formed in 67% yield (98:2 dr) by a reaction between the allylic carbonate **68** which was treated with trimethylphosphite-modified Wilkinson catalyst and the copper(I) alkoxide derived from alcohol **67**. Finally, desilylation of the primary alcohol gave alcohol **63**, which was followed by an olefinic ring-closing metathesis in the presence of Grubbs first generation (G1) catalyst to furnished the desired dihydropyran **64** in 65% yield over two steps (Scheme 22).
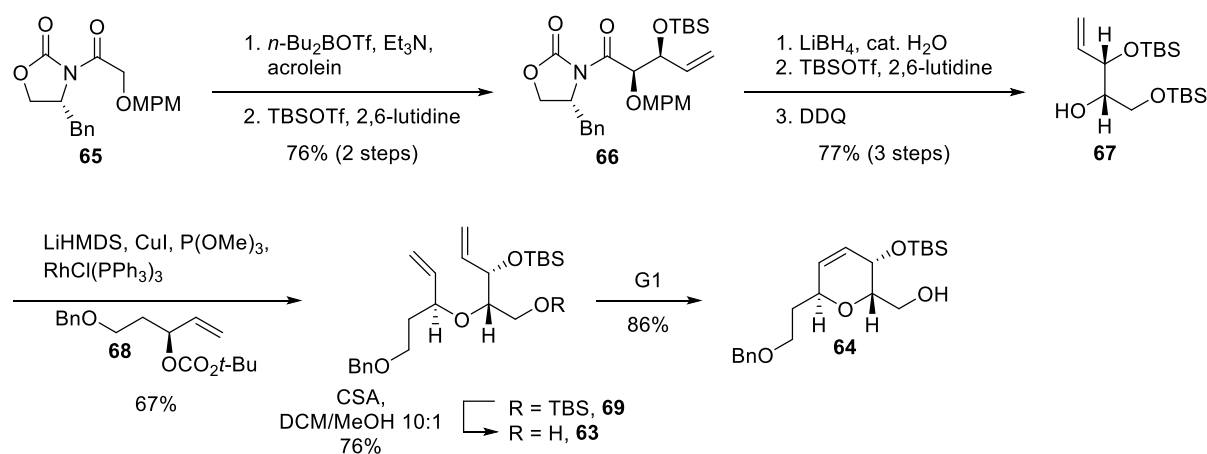
Scheme 22: *Synthesis of compound **64**, starting from compound **65***

1.5.3.4.   Synthesis of Srihari et al.

In 2013, Srihari *et al.*[10] published a stereoselective approach towards the C(1) – C(16) segment of sorangicin A **1**. They started from geraniol **70** which was converted in three steps to aldehyde

71, which in turn was subjected to a Wittig olefination with ylide **54** to give ester **72** (64% yield over four steps). Ester **72** was converted to the Weinreb amide **74**, using *N,O*-dimethylhydroxylamine **73**, and then to the α,β-unsaturated ketone **75** in 88% yield over two steps. Aldehyde **76** was obtained through chemoselective epoxidation of compound **75** followed by an oxidative cleavage with NaIO$_4$ (88% over two steps). Upon treatment of aldehyde **76** with ylide **77**, compound **78** was furnished in 90% yield (Scheme 23).
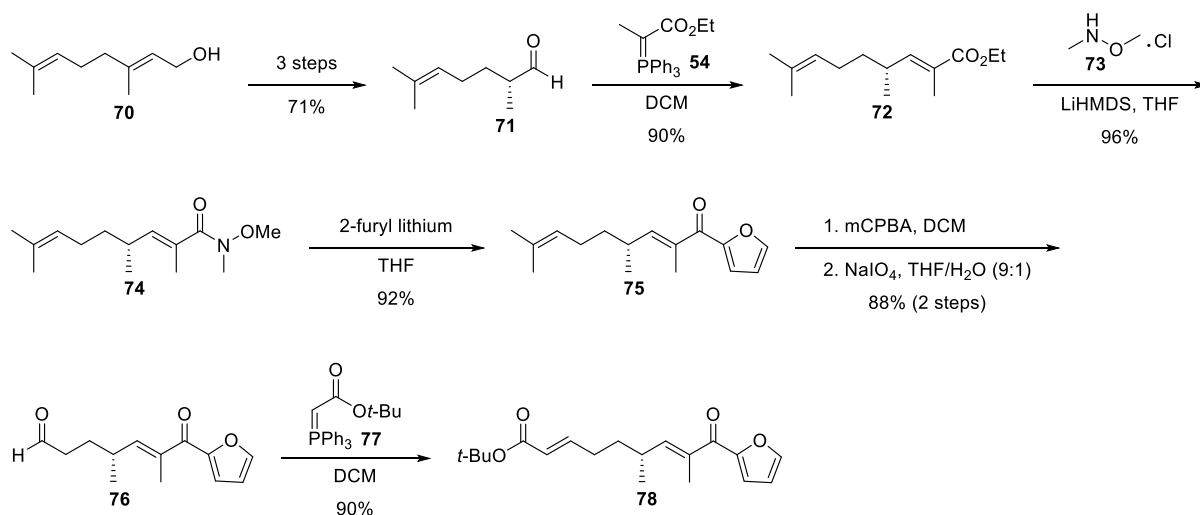
Scheme 23: Synthesis of ketone 78

Using Noyori's asymmetric transfer hydrogenation protocol (Scheme 24), ketone **78** was stereoselectively reduced with the use of ruthenium catalyst **80** to alcohols **81** and **82** in 95% yield as an inseparable diastereomeric mixture (5:1 dr). In contrast, while using (*R*)-Me-CBS catalyst **79** for the stereoselective reduction of ketone **78**, alcohols **81** and **82** were obtained in lower yield (90%) and lower diastereoselectivity (4:1 dr).

a) **79**, BH$_3$·SMe$_2$, THF, 90% (4:1 dr)
b) **80**, *t*-BuOK, *i*-PrOH, 95%, (5:1 dr)
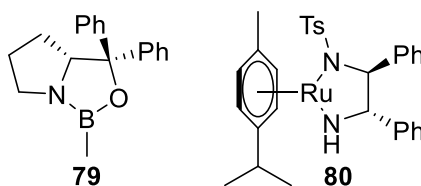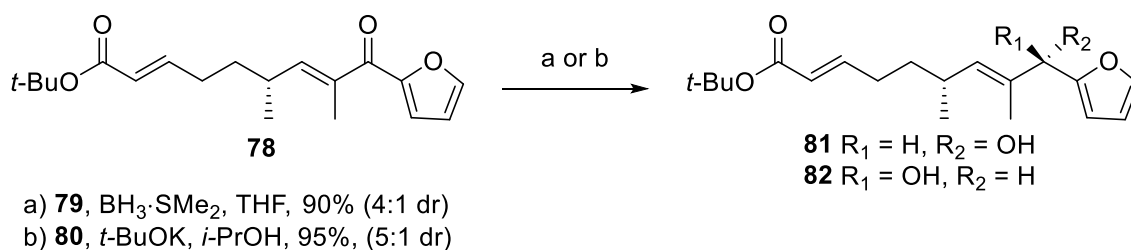
Scheme 24: Synthesis of alcohol 81 and alcohol 82

Alcohols **81** and **82** were stereoselectively reduced to the furfuryl alcohols **83** and **84**. The pyranone lactol was then formed by subjecting compounds **83** and **84** to an Achmatowicz oxidative rearrangement. The two diastereomers **85** and **86** of the pyranone lactol were separated easily at this stage via column chromatography. The alcohol group in **85** was then acetylated with a yield of 95%. The obtained acetate **87** was allylated at room temperature and under solvent-free conditions with allylTMS in the presence of BF$_3$·OEt$_2$ to yield compound **88** (88% yield). Allylation of compound **87** in DCM and lower temperatures (–78 °C to 0 °C) resulted in lower yields and major formation of byproducts. Stereo- and chemoselective reduction of compound **88** under Luche's conditions afforded the desired dihydropyran moiety **89** in 94% yield (Scheme 25).
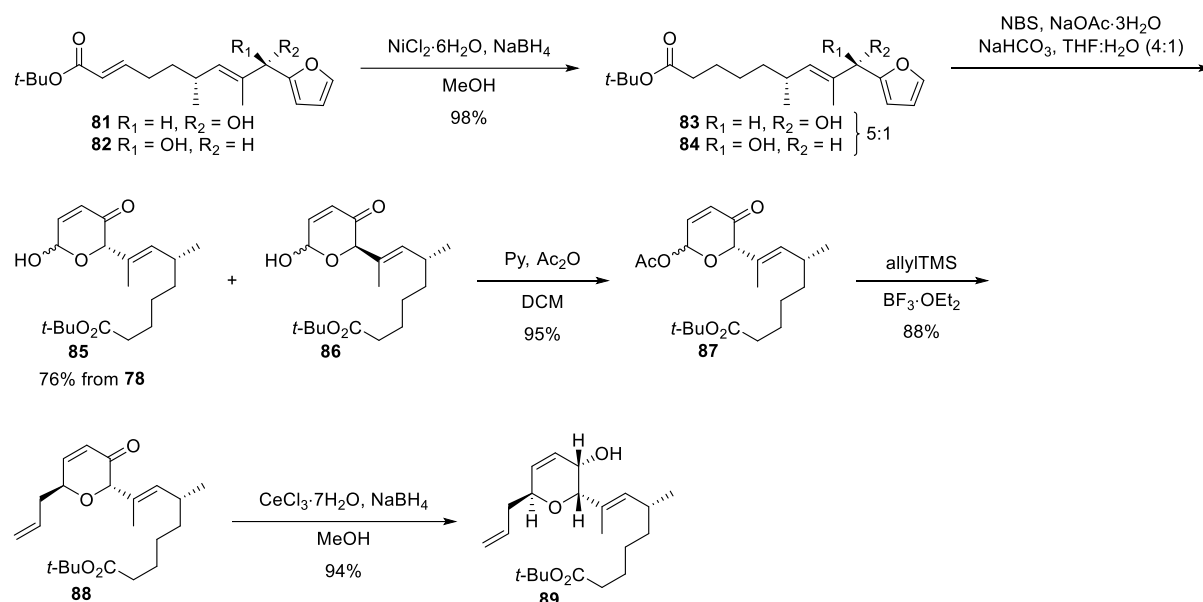
Scheme 25: Synthesis of dihydropyran fragment 89

1.5.3.5.   Synthesis of Raghavan et al.

Raghavan *et al.*[11] reported in 2016 the employment of gold(I)-catalyzed cyclisation of an allenic alcohol to furnish the C(1) – C(15) fragment of sorangicin A **1**. For their synthetic approach, Raghavan *et al.* used as a starting material sulfide **90** which was protected as a benzyl ether **91**. The benzyl ether **91** was converted to α-chloro sulfide **92** which reacted with the alkynylzinc reagent **94**, prepared from compound **93**, to give the propargylic sulfide **95** in 65% overall yield (4.5:5.5 dr). Sulfide **95** underwent reduction and hydrogenation to form alcohol **96** in 86% yield. Swern oxidation of **96** yielded aldehyde **97** in 90%. Compound **97** reacted with the Bestmann reagent **98** in an Ohira-Bestmann modification of the Seyferth-Gilbert homologation to furnished alkyne **99** (84% yield). Methylation of compound **99** afforded

alkyne **100** which in turn reacted with Schwartz reagent and upon quenching with iodine gave iodoalkene **101** (76% over two steps) (Scheme 26).
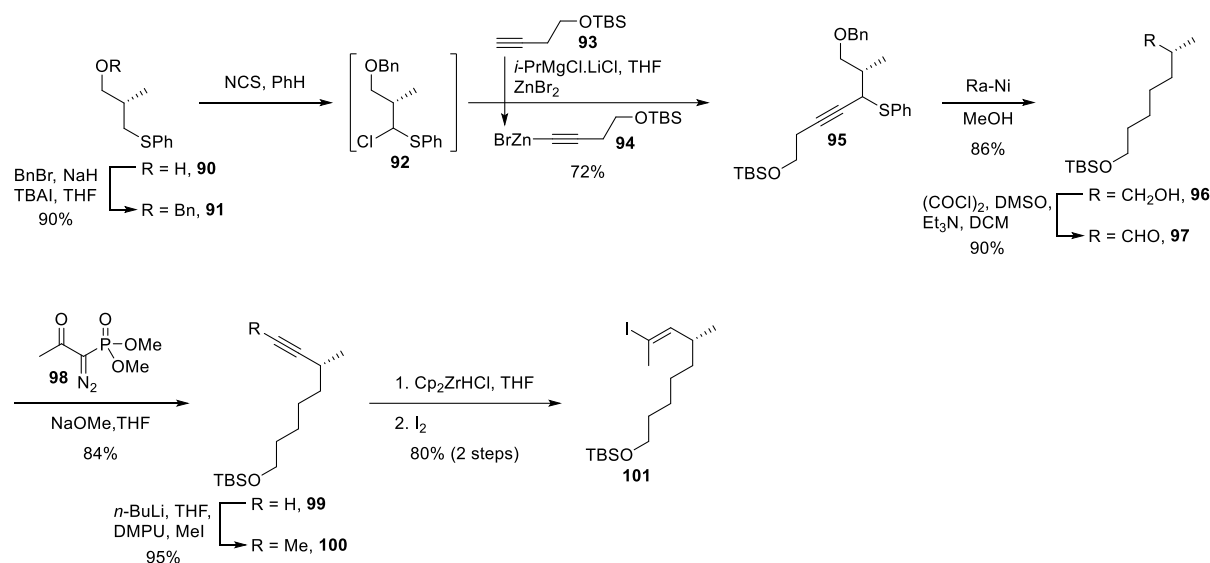
**Scheme 26:** *Synthesis of iodoalkene 101*

Aldehyde **112** was synthesized starting from D-tartaric acid **102** which was converted into chloroacetonide **103** in four steps. Upon treatment with LiNH$_2$ the chloroacetonide **103** was transformed into an alkynol, which was protected as a MOM-ether **104** (81% yield over two steps). The MOM-ether **104** reacted with the Weinreb amide **105** to give ketone **106**, which after a stereoselective Noyori reduction using catalyst **107**, yielded alcohol **108** in 71% over two steps. Using Myers-Movassaghi protocol, alcohol **108** was converted to allene **111** in 83% yield. Allene **111** was then subjected to a PMB-deprotection followed by a Dess-Martin oxidation to obtain aldehyde **112** in 83% yield over two steps (Scheme 27).
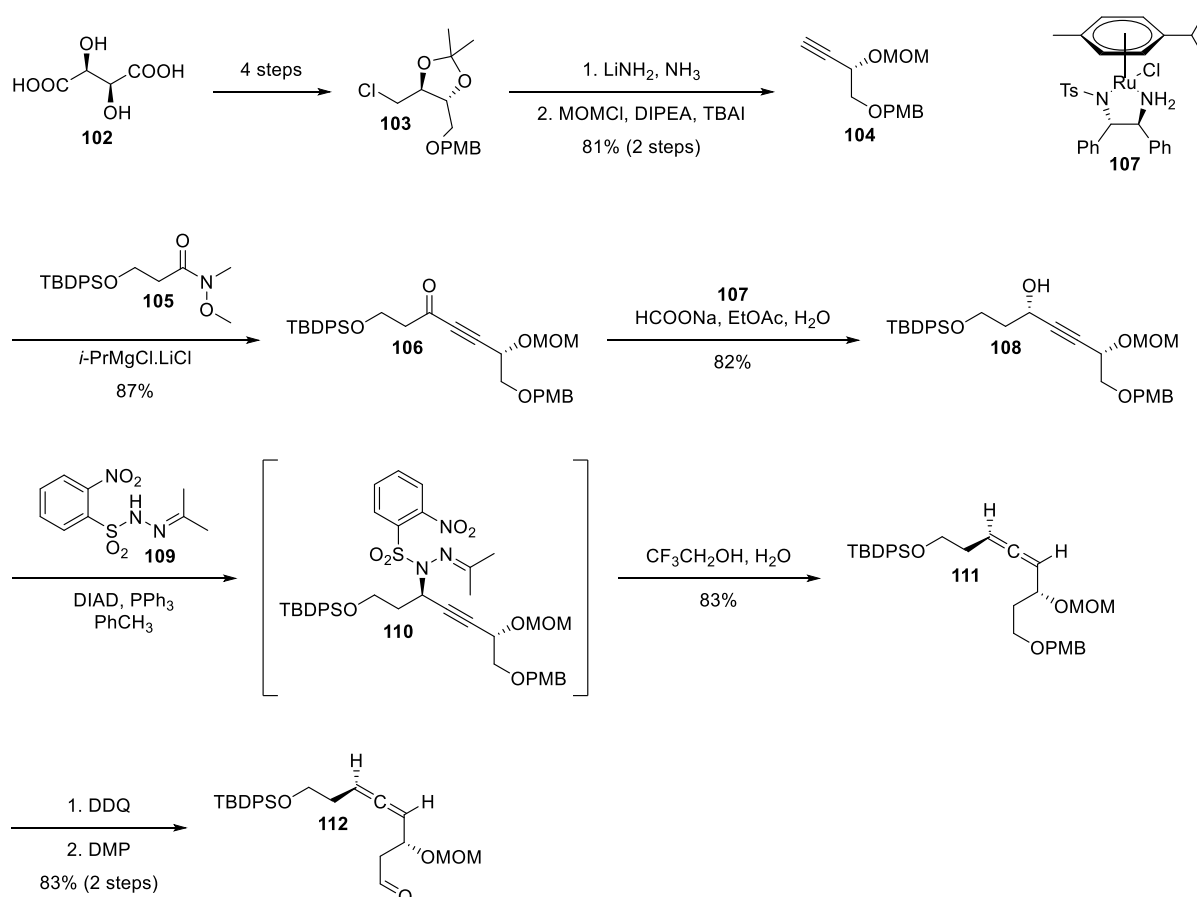
Scheme 27: *Synthesis of aldehyde 112*

The reaction between the alkenyllithium derived from iodoalkene **101** and aldehyde **112** was highly sensitive to the reaction conditions with respect to yield and diastereoselectivity. The best results were obtained when an equimolar mixture of ZnCl$_2$ and aldehyde **112** was added at −78 °C to the alkenyllithium, followed by immediate warming to 0 °C and quenching after 10 min. These conditions gave alcohol **114** in 60% yield (7:3 dr). The undesired alcohol **113** was converted to the desired compound **114** via oxidation with DMP and subsequent Noyori hydrogenation (75% yield over two steps, 9:1 dr). The final transformation of the allenic alcohol **114** to dihydropyran **115** was accomplished using AuCl(PPh$_3$)$_2$ in the presence of AgSbF$_6$ in 62 % yield (Scheme 28).
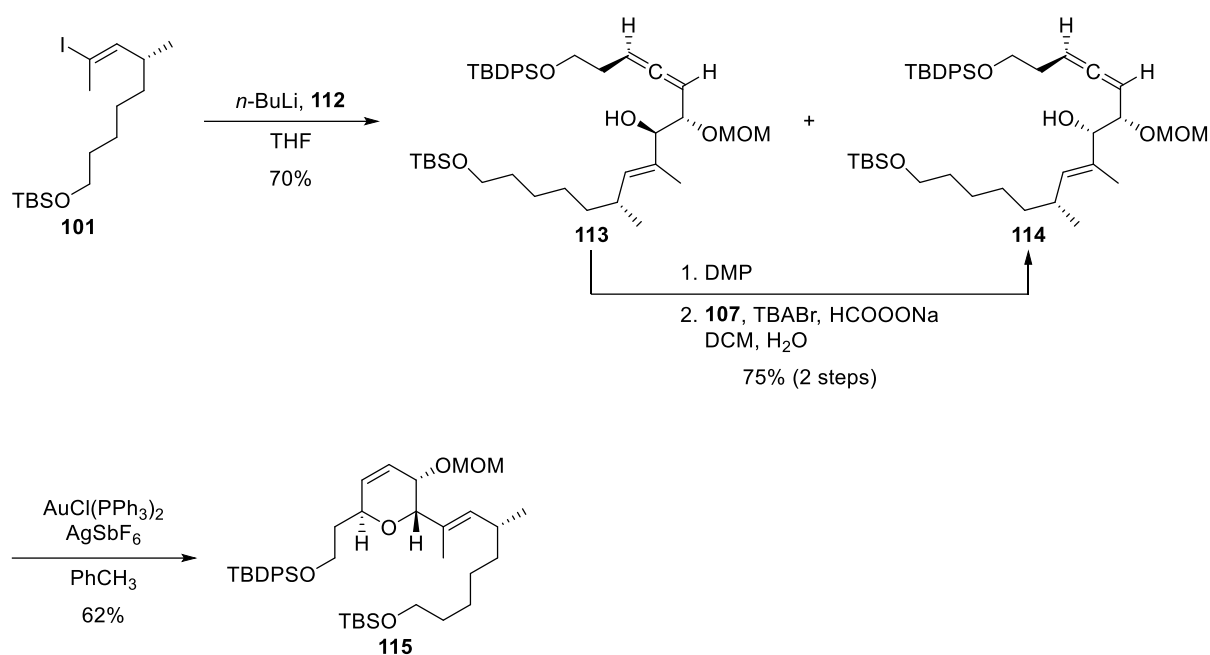
Scheme 28: *Synthesis of dihydropyran fragment 115*

1.6. Synthesis of Schinzer *et al.* – current progress

The retrosynthetic analysis of Schinzer *et al.*[12,13] towards the sorangicin A **1** is shown in Scheme 29. They split the molecule into four key fragments: dioxabicyclooctane fragment **116**, tetrahydropyran fragment **117**, dihydropyran fragment **118** and side chain fragment **119**.
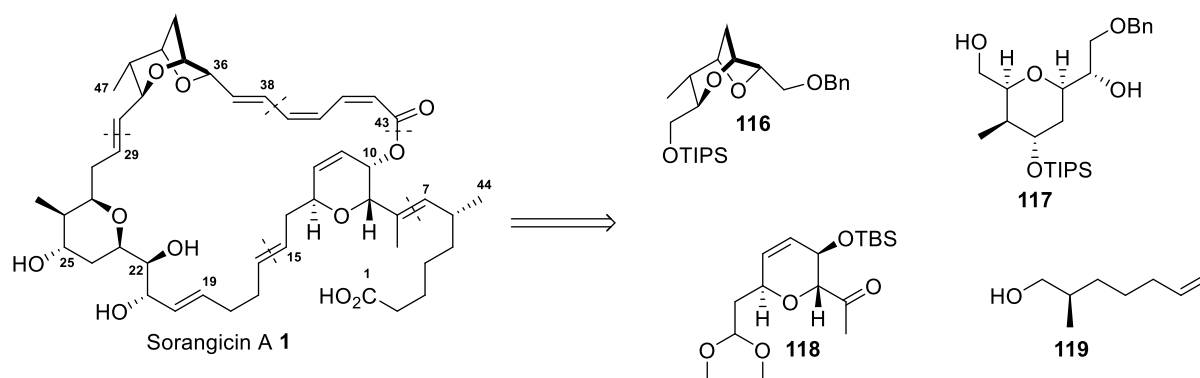

Scheme 29: *Retrosynthetic approach of Schinzer et al.[12,13] towards sorangicin A 1*

1.6.1. Synthesis of the tetrahydropyran fragment 117

Schinzer *et al.*[12] used 1,3-propanediol **120** as a starting material for the synthesis of the tetrahydropyran fragment **117**. Selective protection of one of the alcohol groups in diol **120** as a TBS-ether, followed by Swern oxidation afforded aldehyde **121** in 79% yield over two steps. Aldehyde **121** took part in an asymmetric crotylboration using (Z)-but-2-ene to yield the corresponding alcohol, which was then protected as a TIPS-ether **122** (60% over two steps). The terminal alkene moiety was dihydroxylated using OsO_4 and both diastereomers **123** and

124 were isolated in 2:1 ratio (Scheme 30). Comparable diastereoselectivity was achieved while using AD-mix-*α* or AD-mix-*β*.
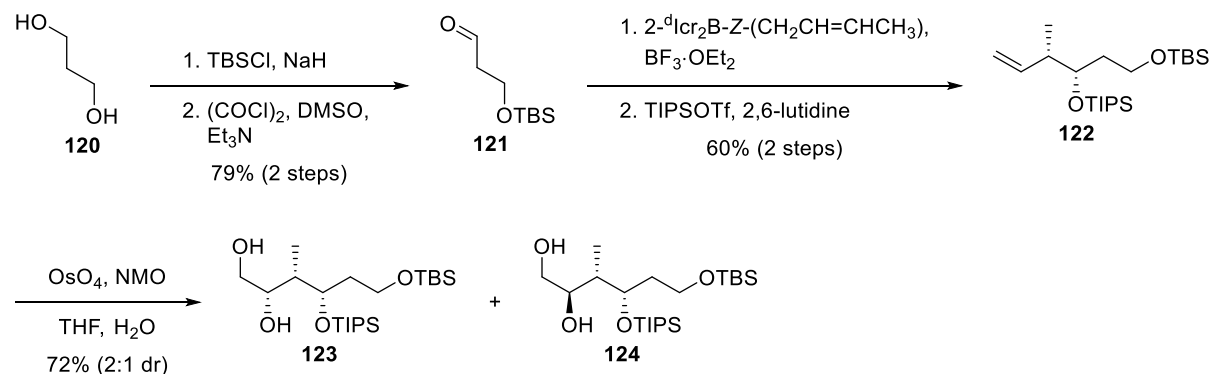
Scheme 30: Synthesis of diols 123 and 124

Diol **123** was protected as an acetonide using PTSA, acetone, and copper(II) sulfate, and simultaneously a selective deprotection of the primary alcohol took place. This was followed by Ley's oxidation and yielded aldehyde **125** in 62% over two steps. Aldehyde **125** then took place in a Z-selective Horner-Wadsworth-Emmons reaction with the Still-Gennari reagent to afford the corresponding ester as a single diastereomer. The ester was then reduced with DIBAL-H to alcohol **126** in 90% yield over two steps. Selective Sharpless epoxidation of alcohol **126** followed by a protection of the primary alcohol as a Bn-ether gave compound **127** in 45% yield over two steps. Finally, the tetrahydropyran fragment **117** was obtained from compound **127** via a ring-closing-epoxide-opening sequence in 82% yield (Scheme 31).
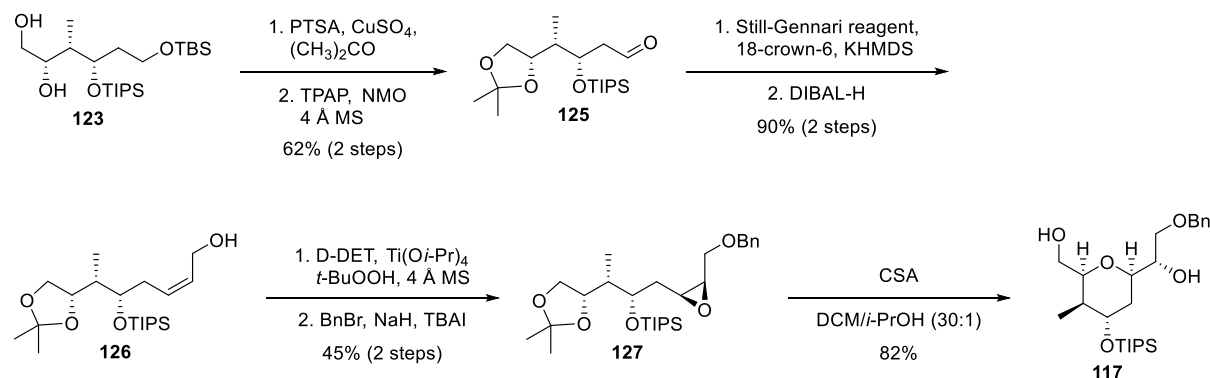

Scheme 31: Synthesis of tetrahydropyran fragment 117

### 1.6.2. Synthesis of the dioxabicyclooctane fragment **116**

Schinzer *et al.*[12,13] proposed two synthetic approaches towards the dioxabicyclooctane fragment **116** of sorangicin A **1**. The first approach towards the dioxabicyclooctane fragment **116** was according to Scheme 32. Alcohol **128** was obtained using the same procedure as the

tetrahydropyran fragment (see Chapter 1.6.1), but starting from diol **124**. The primary alcohol in compound **128** was protected as a TIPS-ether, the secondary alcohol as a PMB-ether, and finally TBAF-deprotection of the TIPS-ethers furnished the corresponding diol. The primary alcohol in this diol was protected as a TIPS-ether and the secondary alcohol **129** was obtained in 49% yield over four steps. The mesylation of alcohol **129** resulted in the formation of the dioxabicyclooctane fragment **116** (28% yield) and the mesylate **130** (59% yield). Mesylate **130** was then subjected to deprotection of the PMB-ether, followed by a cyclisation to obtain the desired dioxabicyclooctane fragment **116** in 45% yield over two steps.
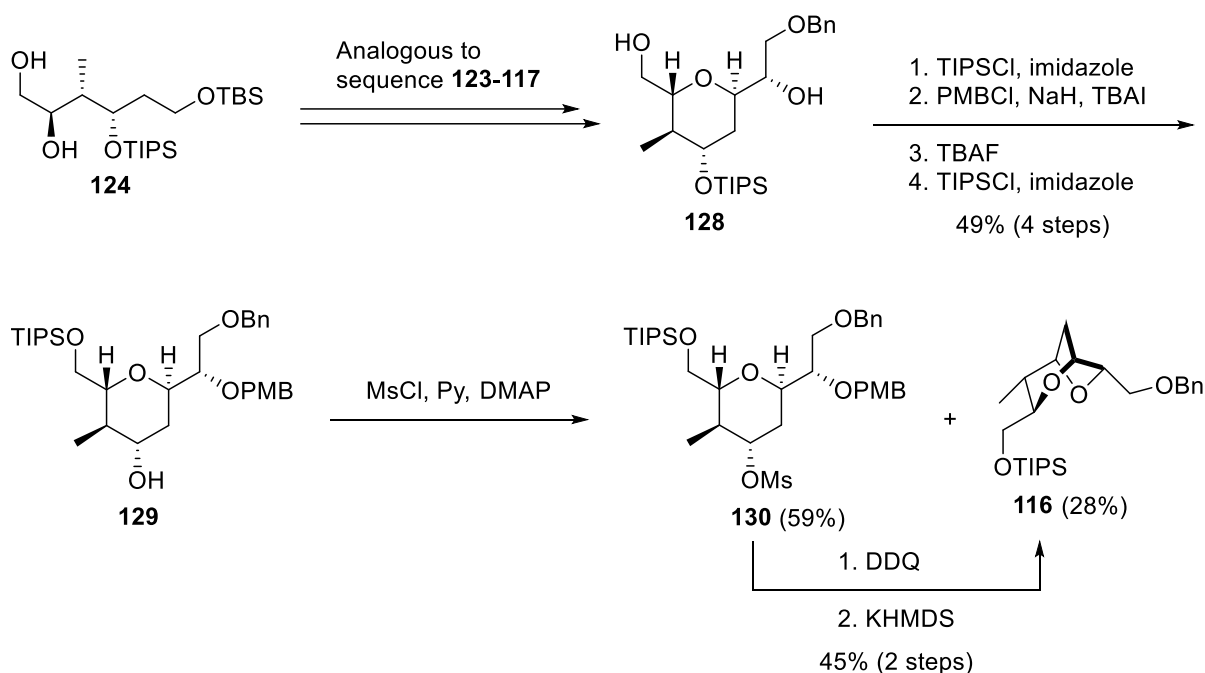

Scheme 32: Synthesis of dioxabicyclooctane fragment 116

The second approach to the dioxabicyclooctane fragment started from (*S*)-4-benzyl-1,3-oxazolidin-2-thion **131**. Thion **131** was subjected to acylation with propionylchloride, which resulted in the formation of the corresponding ketone. The ketone then took part in an Evans anti-aldol reaction with aldehyde **132**, followed by a removal of the TMS protecting group, which furnished alcohol **133** in 90% yield over 3 steps. Alcohol **133** was then acetylated in order to obtain compound **134** (99% yield). Compound **134** was subjected to a cyclisation under a cleavage of the auxiliary using NaHMDS, forming the keto lactone which was then methylated to afford compound **135** in 65% yield over two steps. Reduction of compound **135** with DIBAL-H yielded dihydropyranone **136** in 70% (Scheme 33).
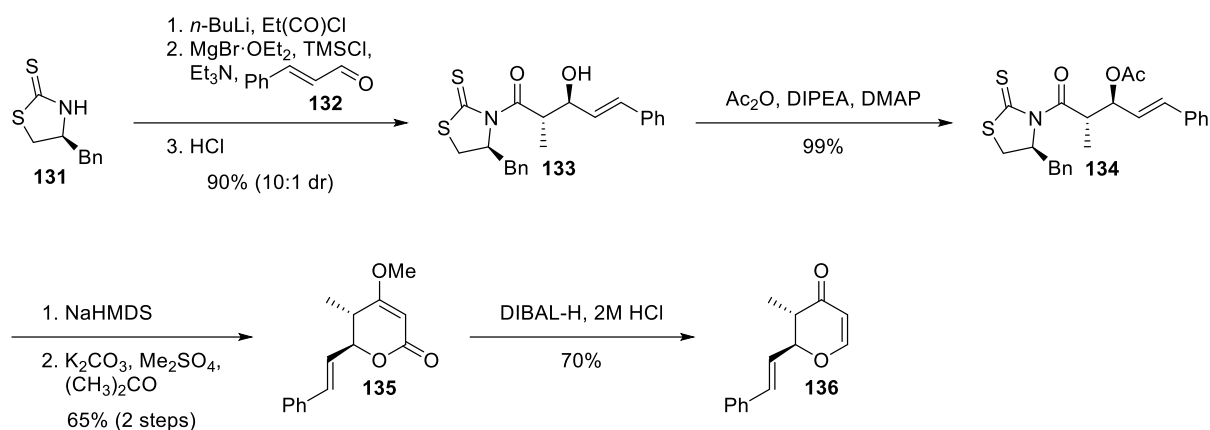
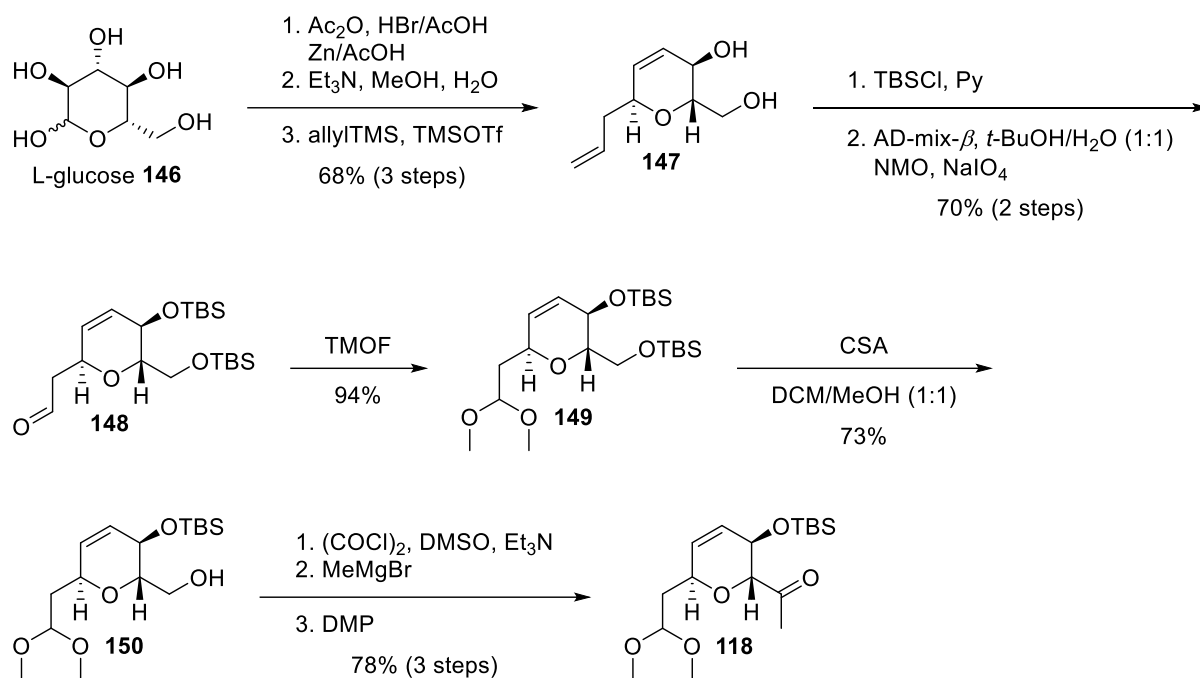**Scheme 33:** *Synthesis of dihydropyranone 136*

Compound **137** was added to dihydropyranone **136**, using scandium triflate as a catalyst to obtain compound **138** (72%, 6:1 dr). Stereoselective reduction of the carbonyl group with lithium triethylborohydride yielded the axial alcohol, and a reduction of the ester carbonyl group with DIBAL-H generated diol **139** in 82% yield. Diol **139** was subjected to a TBS-deprotection and protection as an acetonide in a one-pot reaction. The acetonide was acetylated and then hydrolyzed to diol **140** in another one-pot reaction (70% over two steps). The primary alcohol of diol **140** was protected as a TIPS-ether and the secondary as a triflate, giving compound **141** in 76% yield over two steps. Compound **141** reacted with TBAF in THF, which allowed the deprotection of the TIPS-ether and initiated the formation of epoxide **142**. Addition of K_2CO_3 and methanol caused deacetylation and epoxide opening, followed by a cyclisation to obtain the desired dioxabicyclooctane fragment **144** (62% yield). Parikh-Doering oxidation of the primary alcohol in compound **144** followed by a Colvin rearrangement furnished alkyne **145** (62% over two steps), which was necessary for the later elaboration of the *E,Z,Z*-triene moiety (Scheme 34).
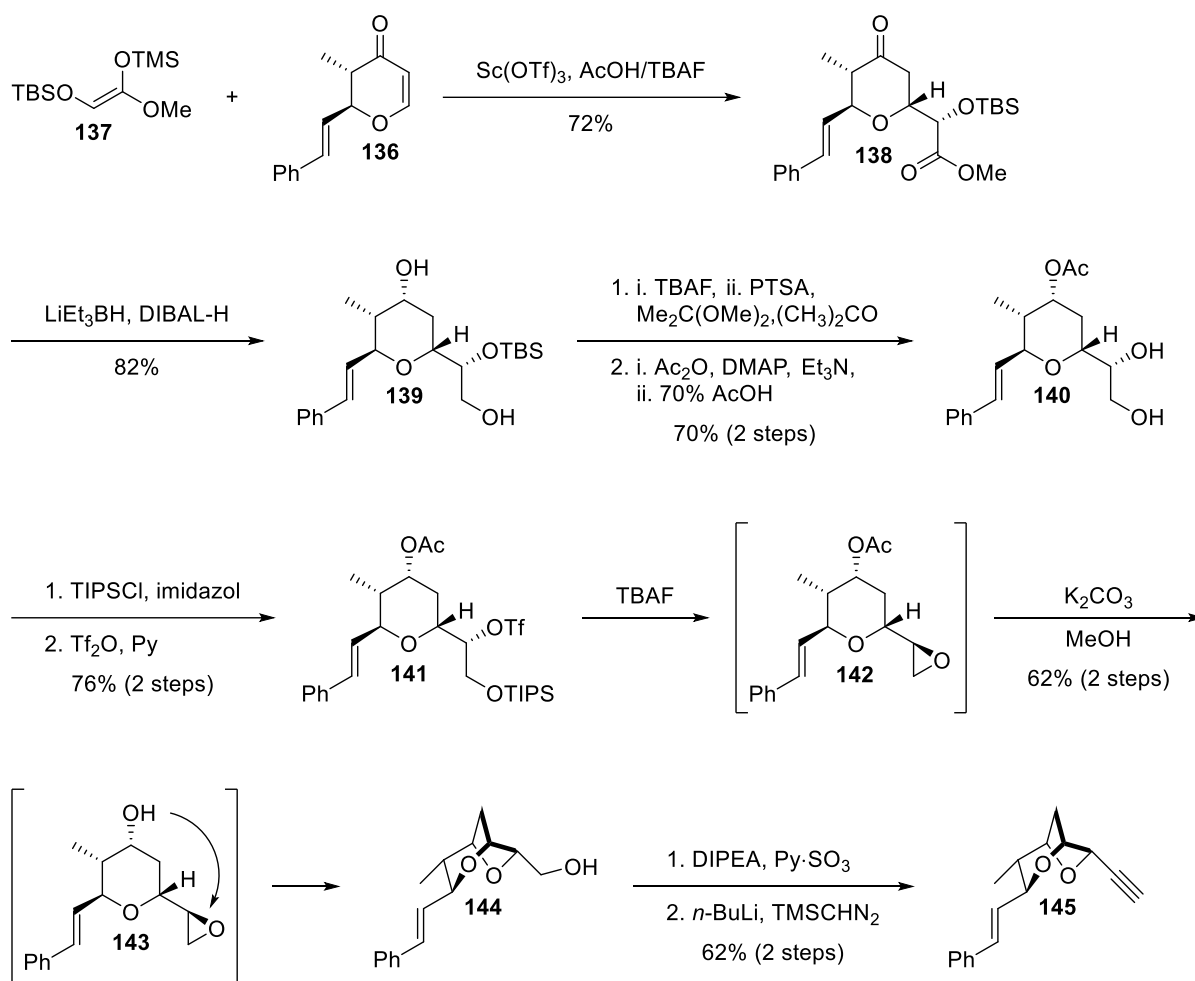
Scheme 34: *Synthesis of alkyne **145***

1.6.3. Synthesis of the dihydropyran fragment **118**

The synthesis of Schinzer *et al.*[12] of the dihydropyran fragment **118** adopted L-glucose **146** as a starting material. In a one-pot reaction the L-glucose was converted to tri-*O*-acetyl-L-glucal, which was subsequently deprotected with $Et_3N/MeOH/H_2O$ to obtain the corresponding triol. The so formed triol then took part in a carbon Ferrier rearrangement to yield diol **147** (68% over three steps). TBS-protection of both hydroxyl groups in compound **147**, followed by a Sharpless asymmetric dihydroxylation and oxidative cleavage of the vicinal diol afforded aldehyde **148** in 70% yield over two steps. Substituting OsO_4/NMO in place of AD-mix-*β* during the dihydroxylation step decreased the yield of aldehyde **148** to 54% over two steps. Aldehyde **148** was then protected as an acetal **149** with a yield of 94%. Compound **149** underwent a selective deprotection of the primary alcohol generating compound **150**. Swern oxidation of alcohol **150**, followed by a Grignard addition with MeMgBr and an oxidation with DMP resulted in the formation of the desired dihydropyran fragment **118** with a yield of 57% over four steps (Scheme 35).

Scheme 35: *Synthesis of dihydropyran fragment 118*

1.6.4. Synthesis of the carboxylic acid containing side chain 119

The construction of the side chain by Schinzer *et al.*[12] was achieved starting from 6-heptanoic acid chloride **152**. This was coupled with the Seebach auxiliary **151** and then alkylated using MeI to obtain compound **154** in a 66% yield over two steps. The Seebach auxiliary was cleaved via reduction with LAH to furnish the side chain **119** in 95% yield (Scheme 36).
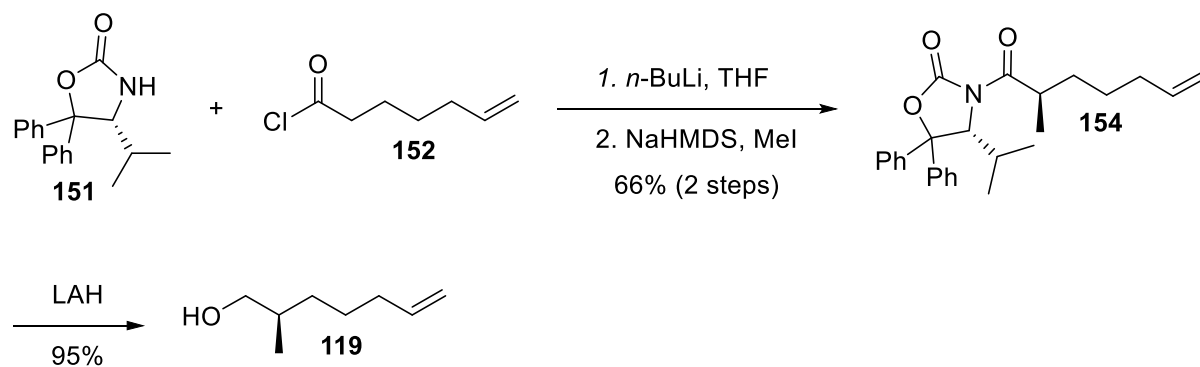

Scheme 36: *Synthesis of the side chain 119*

2. Objectives of the thesis

Neosorangicin A **2** is a novel type of antibiotic and our group focused on its total synthesis. As already discussed before, the bicyclooctane fragment as well as the tetrahydropyran fragment of neosorangicin A **2** are identical to the ones in sorangicin A **1** (see Figure 1 in Chapter 1.2). In Chapter 1.6.1 and Chapter 1.6.2 we also saw that reliable synthetic approaches for these two key fragments have already been broadly studied and developed by previous members of the group. However, due to the structural differences between neosorangicin A **2** and sorangicin A **1**, the synthesis of the dihydropyran and the side chain fragments (as described in Chapter 1.6.3 and Chapter 1.6.4) cannot be directly used for the total synthesis of neosorangicin A **2**. Therefore, the main objective of this thesis is the synthesis of the dihydropyran fragment of neosorangicin A **2**. The synthesis of this fragment is quite challenging since it contains four stereogenic centers and an *E*-trisubstituted double bond in an *α*-position to the dihydropyran ring. The main focus of the current work is to develop a short synthetic pathway towards the dihydropyran fragment, with respect to maximal length of a single linear sequence. Moreover, this pathway should be high yielding and reproducible. Last, but not the least the established synthetic route towards the dihydropyran fragment of neosorangicin A should be scaled-up to a multigram scale.

3. Theoretical part

The retrosynthetic approach towards neosorangicin A **2** was similar to that of sorangicin A **1**, due to the structural similarities between the two molecules. The molecule of neosorangicin A **2** was split into three key building blocks: dioxabicyclooctane fragment **116**, tetrahydropyran **117**, and dihydropyran fragment **154** (Scheme 37). The following chapters describe the efforts toward the synthesis of the C(1) – C(12) dihydropyran fragment **154**, since this fragment forms the main objective of this thesis.
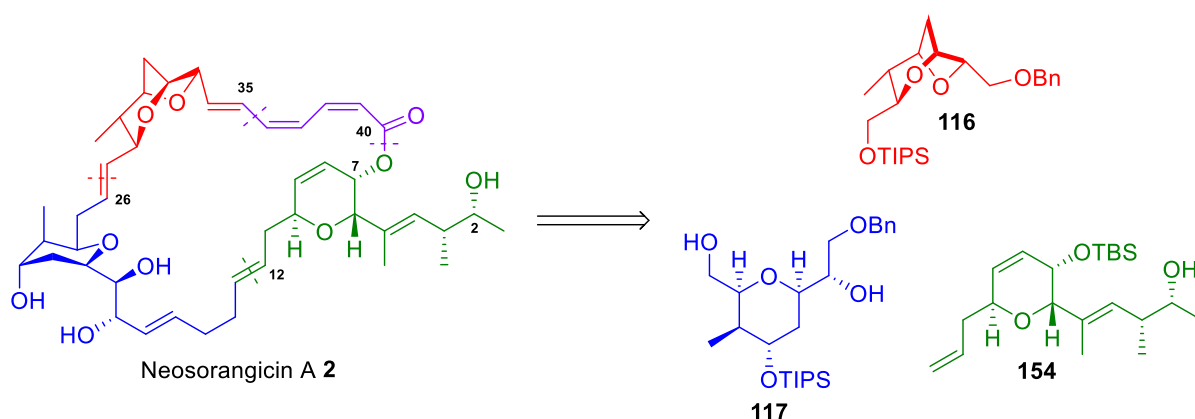
Scheme 37: *Retrosynthetic approach towards neosorangicin A by Schinzer et al.*

Since this thesis explored the synthesis of the dihydropyran fragment **154** using multiple synthetic strategies, in interests of readability, the following chapters are organized in reverse order of the synthetic steps. We will therefore begin with connecting the C(1) – C(5) side chain of the dihydropyran fragment **154**, and work backwards to describe the various strategies we followed in synthesizing the necessary precursors from commercially available compounds. Although the stereochemical configuration of the dihydropyran ring of neosorangicin A can be derived from L-galactose, we used D-galactose as a starting point in our synthesis for two reasons. Most importantly, D-galactose is ca. 3000 times less[1] expensive to source commercially, making synthetic strategies that incorporate the conversion of D-galactose to L-galactose more attractive. However, this conversion is time consuming and also limits the amount of starting material available in the early steps of the synthesis. Once a reliable and reproducible synthetic route has been demonstrated to work using D-galactose, we expect that it can be applied to its enantiomer L-galactose with no changes required apart from the additional step of its conversion. However, since our synthesis builds on D-galactose, it is

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[1] Prices from https://www.carbosynth.com/ as of 01.07.2021 (63 EUR per kilogram vs 190 EUR per gram)

necessary to preserve homochiral relationships within the molecule because interaction effects may affect the outcomes of various synthetic strategies.

3.1. Incorporation of the side chain

Based on the biological experiments carried by Müller *et al.* with isolated neosorangicin A **2**[5], the side chain of the molecule is responsible for the biological activity. In contrast to sorangicin A **1** the side chain of neosorangicin A **2** is shorter and doesn't contain a carboxylic acid. Although relatively short, the side chain is synthetically challenging since it contains two stereo centers and a trisubstituted *E*-double bond in an *α*-position to the dihydropyran ring. Considering all of the characteristic features of the side chain, we envisioned two prospective coupling strategies for incorporating the side chain and obtaining the dihydropyran moiety with the desired stereochemistry as shown in general formula **155** (Scheme 38). The first is via a carbometallation reaction using alkyne **156** and epoxide **157** and the second uses a Julia-Kocienski olefination between methyl ketone **158** and sulfone **159**.
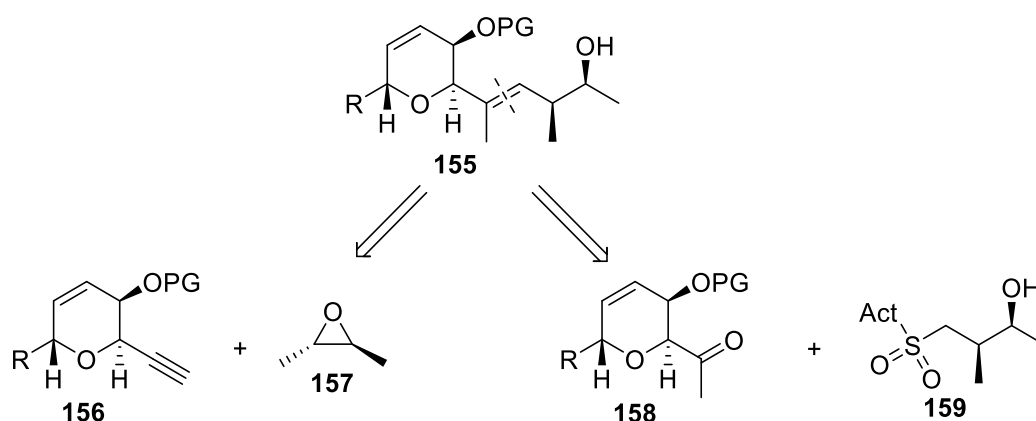

Scheme 38: *Retrosynthesis of the dihydropyran fragment 155*

3.1.1. Attempt to introduce the side chain via carboalumination

One possibility to obtain the necessary trisubstituted *E*-double bond and at the same time obtain the necessary stereochemistry at C(2) and C(3) is via a carbometallation of an alkyne with general formula **156** and opening of epoxide **157** through a nucleophilic addition (Scheme 38). One advantage of this method is the fact that it allows for control over the geometry at the double bond by choosing a suitable metal, which gives rise to the *syn*-product in the carbometallation step. The stereochemistry at C(2) and C(3) is determined by the stereochemistry of the epoxide used for the nucleophilic attack. Another advantage of the

carbometallation method is the fact that it has the minimum length for the longest linear sequence.

The general mechanism of carbometallation is shown in Scheme 39. The carbon-metal σ-bond in **160** reacts with the carbon-carbon π-bond of the alkyne triple bond in **161**. This leads to the formation of a new carbon-carbon σ-bond and a carbon-metal σ-bond[14,15]. The carbon-metal bond can then react further with a variety of electrophiles generating products **164** and/or **165**. Highly geometrically pure products can be obtained as a result of the carbometallation of alkynes. The *syn-* or *anti*-addition can be influenced by the choice of a suitable metal, since some metals (*e.g.* aluminium, titanium, copper, *etc.*) give preferentially the *syn*-product **162**, while others (*e.g.* lithium, magnesium, zinc, *etc.*) yield the *anti*-addition product **163**.
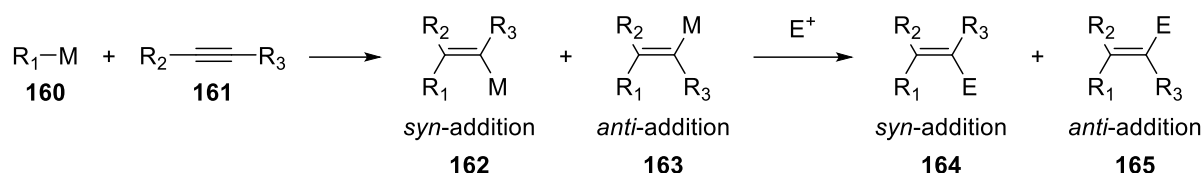
Scheme 39: General mechanism of the carbometallation of alkynes

For our purposes two conditions should be met: first, the carbometallation should afford the *syn*-product and second, a methyl group should be added in an α-position to the dihydropyran ring. Since zirconocene dichloride catalyzed carboalumination[16,17] fulfilled both these conditions, it was the method of choice for the carbometallation of an alkyne with a general formula **156**. The aluminium reagent necessary for the addition of the methyl group was trimethyl aluminium which should yield the *syn*-alkenylalane. The mechanism of the Zr-catalyzed carboalumination of alkynes was described in detail by Negishi et al.[14,15,17,18] (Scheme 40).
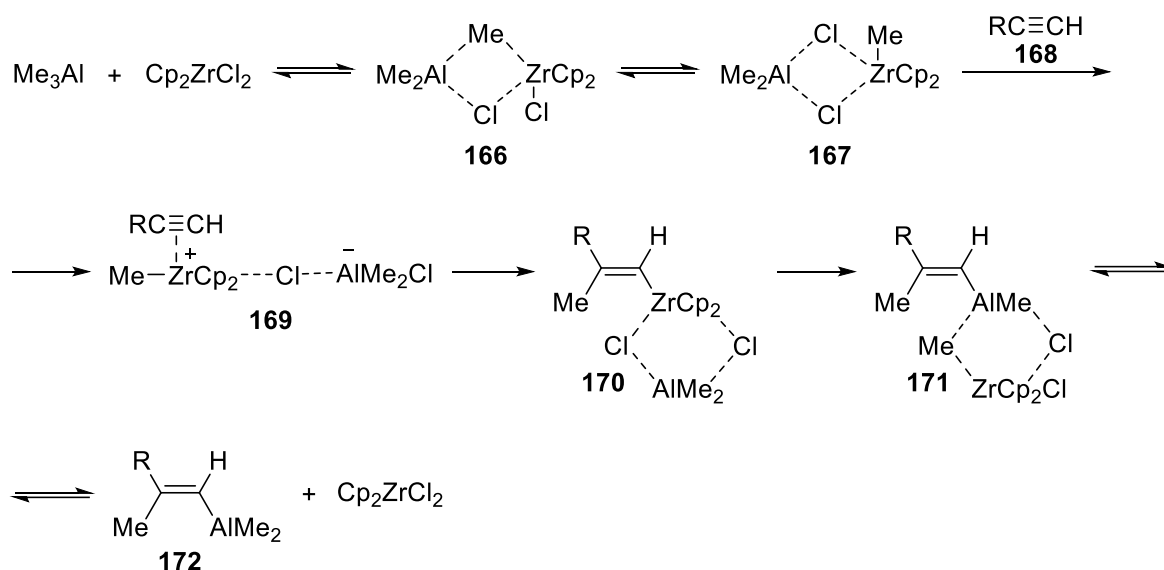
Scheme 40: *Mechanism of zirconocene-catalyzed carboalumination of alkynes*

First, the active catalytic species **167** is formed by transmetallation of a methyl group from aluminium to zirconium. The aluminium then abstracts a chloride from the zirconium species, forming a cationic zirconium species, which is associated with an anionic aluminum complex. The zirconium cation coordinates then to alkyne **168** forming intermediate **169** and a migratory insertion of a methyl group generates intermediate **170**. Next, the vinyl zirconium species **170** undergoes a reversible but stereoretentive transmetallation with an organoaluminium to provide the alkenylalane **172**, and to regenerate the zirconocene dichloride catalyst[14,15,17,18] (Scheme 40). Alkenylalane **172** is not nucleophilic enough to deliver organic groups to electrophilic substrates. However, upon activation by a nucleophile like *n*-BuLi (Scheme 41), the resulting aluminate **173** is highly nucleophilic. It adds to electrophiles such as **157** with retention of configuration at the migration carbon, generating products such as **174**[19]. Thus, stereospecific methylalumination followed by nucleophilic attack provides a method for the stereospecific synthesis of trisubstituted olefins from alkynes.
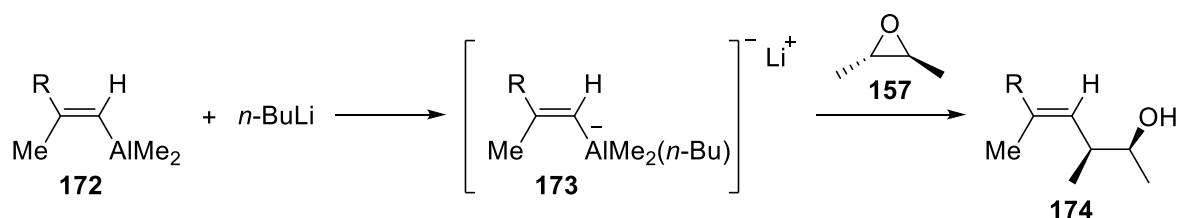

Scheme 41: *General mechanism for epoxide opening via nucleophilic substitution*

Our initial approach was using alkyne **175,** obtained from D-galactose **237** (see Chapter 3.2.1) in nine steps with an overall yield of 28%, and the commercially available epoxide **157**. The

terminal alkyne **175** was subjected to a one-pot reaction of methylalumination with trimethyl aluminium and catalytic amount of zirconocene dichloride. This was followed by a nucleophilic activation with *n*-BuLi of the formed alkenylalane, and finally a nucleophilic addition to epoxide **157**[19] (Scheme 42).

Several conditions have been tried with respect to the formation of the active catalytic species and are summarized in Table 3. Unfortunately, none of our efforts resulted in the formation of the expected product **176**. In all cases we were able to isolate only the starting materials. It is worth noting that neither catalytic[19,20] nor stochiometric[21,22] amounts of zirconocene dichloride resulted in any improvement. Raising the temperature from 0 °C to room temperature[15,20,21] as well as the addition of water[19,20,23] to accelerate the reaction rate also did not result in any positive outcome.
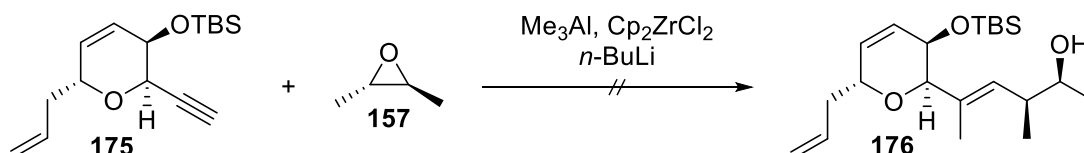
Scheme 42: *Attempted one-pot synthesis of compound 176*

Table 3: *Reaction conditions for the attempted one-pot synthesis of alkyne 175*

| Entry	Educt	Conditions	Product (yield)
1		Me₃Al (4 eq) Cp₂ZrCl₂ (0.07 eq) H₂O (1.3 eq) DCM 2 h, –41 °C	(0%)
2	**175**	Me₃Al (2 eq) Cp₂ZrCl₂ (0.5 eq) H₂O (1.5 eq) DCE 30 min, 0 °C; ON, RT	**176** (0%)
3	**175**	Me₃Al (2 eq) Cp₂ZrCl₂ (1 eq) DCM 48 h, RT	**176** (0%)

Since all our efforts to produce **176** with the one-pot method failed to give the desired results, we tried to better understand each of the individual steps comprising the one-pot reaction to identify the cause for failure. To this purpose, we decided first to trap the vinylalane as iodide **177** (Scheme 43), and in a second step, to open and add epoxide **157** to the vinyl iodide **177**.

This strategy also proved to be unsuccessful and resulted only in the reisolation of the educt **175**. Neither an increase of temperature[24] nor an increase in the amount of zirconocene dichloride[15,25] resulted in the formation of the desired vinyl iodide **177**. These results led us to the conclusion that the formation of the alkenylalane was obstructed by either steric or electronic factors, resulting in the unsuccessful reactions observed.
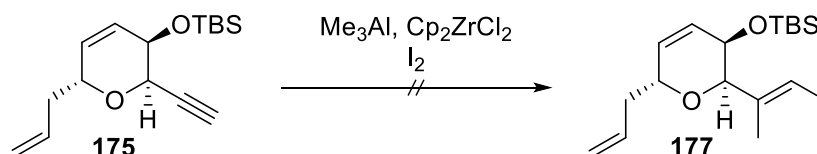

Scheme 43: *Attempted synthesis of vinyl iodide **177***

Analyzing the previously obtained results we identified two regions of alkyne **175** that might be responsible for the previously described synthetic obstacles: the first was the protecting group (blue region) and the second was the allylic side chain (yellow region). To test these hypotheses, we synthesized two further alkynes (**178** and **179**) in which only one of the two regions has been modified in order to identify the cause for failure of the carboalumination synthetic strategy (Scheme 44).
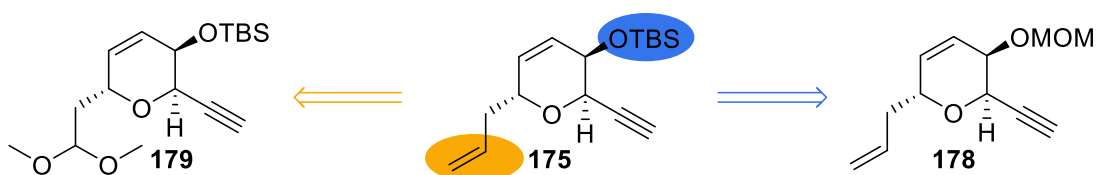

Scheme 44: *Investigating the two suspected causes of failure of the carboalumination step*

First, we investigated the influence of the protecting group on the carboalumination reaction. For that purpose, we obtained alkyne **178** in ten steps in 25% overall yield, starting from D-galactose (see Chapter 3.2.2). Alkyne **178** was subjected to a zirconocene-catalyzed carboalumination. Unfortunately, none of the changes in the reaction conditions (temperature[20,21], stochiometric ratios of the reactants[15,21], solvents[20,24], or the addition of water[19,23]) resulted in the formation of the trisubstituted olefin **180** or the vinyl iodide **181** (Scheme 45). Most importantly, as in the case of the TBS-protected alkyne **175**, we were able to recover only the starting material **178**, which indicated that the alkenylalane formation was not taking place. These results refute the hypothesis that the protecting group is responsible for the failure of the reaction.
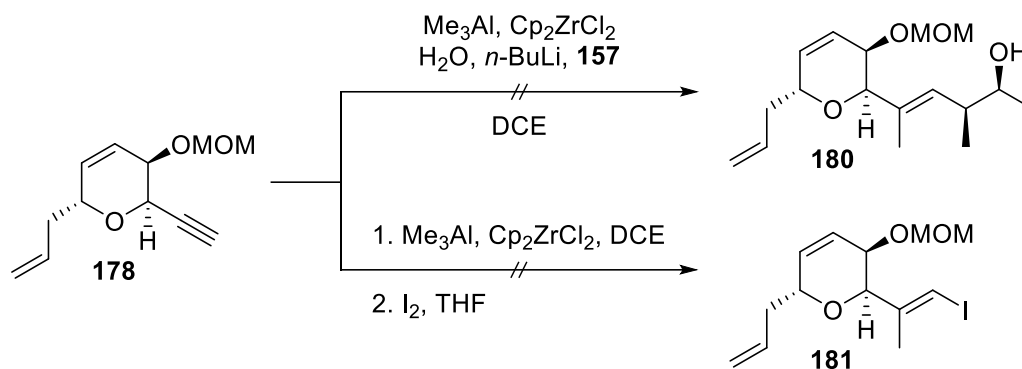
Scheme 45: *Attempts for carboalumination of alkyne 178*

In order to investigate the influence of the allylic side chain on the carboalumination reaction we synthesized alkyne **179** in twelve steps and with 15% overall yield, using D-galactose as a starting material (see Chapter 3.2.3). In this case the carboalumination[17] proceeded with a full conversion of the starting material. However, the isolated product didn't correspond either to compound **182** or to compound **183** (Scheme 46).
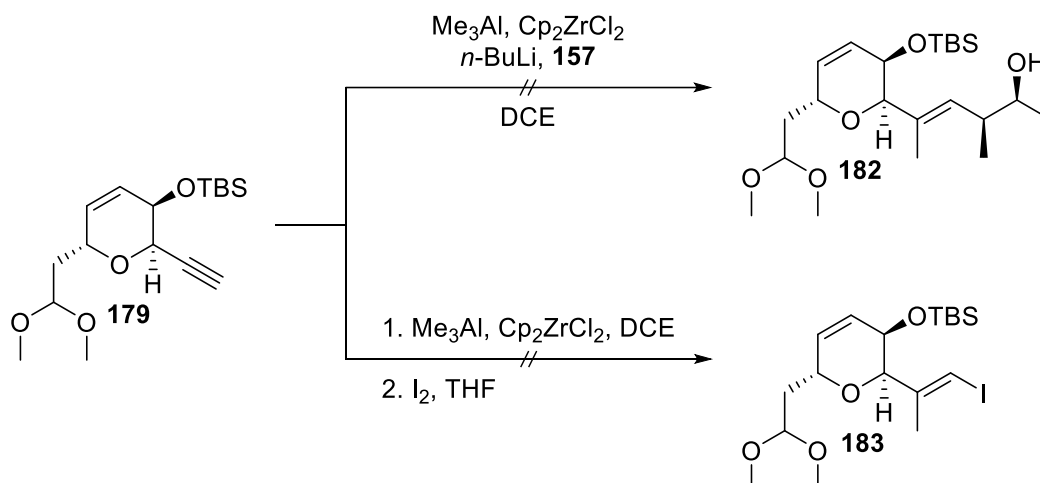
Scheme 46: *Attempts for carboalumination of alkyne 179*

As a summary we can conclude that alkynes of general formula **156**, where PG = TBS, MOM and R = allyl, $CH_2CH(OCH_3)_2$, proved to be unsuitable for the desired carbometallation reaction under the examined conditions.

3.1.2. Attempt to introduce the side chain via hydrometallation

Another approach for obtaining compound **155** is with the use of a homopropargylic alcohol **185**, which can be obtained by opening epoxide **157** and adding it to alkyne of general formula **184** (Scheme 47). A methyl group can be then added to the triple bond of alcohol **185** in order to obtain the trisubstituted *E*-olefin **155**.
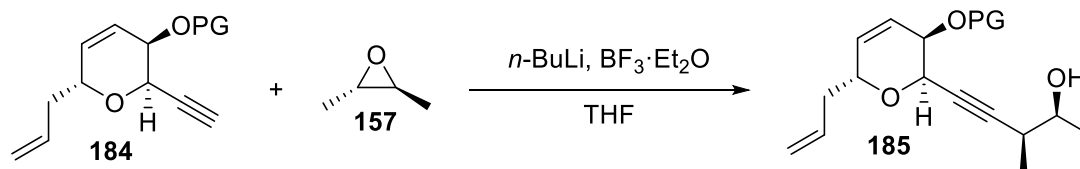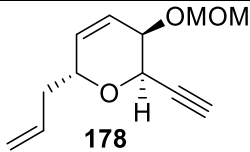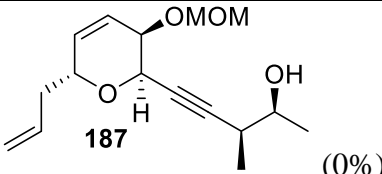

***Scheme 47:*** *Synthesis of homopropargylic alcohols with general formula **185***

Using alkyne **175** and the commercially available epoxide **157** in the presence of *n*-BuLi and BF$_3$·Et$_2$O[26–28], homopropargylic alcohol **186** was obtained with a yield of 71% (Table 4, entries 1 – 5). The use of analogous conditions for alkyne **178** and epoxide **157** didn't result in the formation of the expected homopropargylic alcohol **187** even after optimization of the reaction conditions (Table 4, entries 6 and 7).

Table 4: *Optimization of the reaction conditions for the synthesis of homopropargylic alcohols*

Entry	Substrate	Conditions	Product (yield)
1		**157** (1 eq) *n*-BuLi (1 eq) BF$_3$·Et$_2$O (1 eq) 2 h, −78 °C	(50%)
2	**175**	**157** (1 eq) *n*-BuLi (1.4 eq) BF$_3$·Et$_2$O (1 eq) 2 h, −78 °C	**186** (54%)
3	**175**	**157** (1.1 eq) *n*-BuLi (2 eq) BF$_3$·Et$_2$O (1.1 eq) 2 h, −78 °C	**186** (57%)
4	**175**	**157** (1.5 eq) *n*-BuLi (2 eq) BF$_3$·Et$_2$O (1.4 eq) 3 h, −78 °C	**186** (64%)
5	**175**	**157** (1.4 eq) *n*-BuLi (3 eq) BF$_3$·Et$_2$O (3 eq) 2 h, −78 °C	**186** (71%)

Entry	Substrate	Conditions	Product (yield)
6	**178**	**157** (1 eq) *n*-BuLi (2 eq) BF₃·Et₂O (1.4 eq) 3 h, −78 °C	**187** (0%)
7	**178**	**157** (1.5 eq) *n*-BuLi (3 eq) BF₃·Et₂O (3 eq) 3 h, −78 °C	**187** (0%)

Next, a hydrometallation of homopropargylic alcohol **186** should afford a compound with a general formula **188** (Scheme 48). The leaving group should be introduced in an α-position of the dihydropyran ring and should be replaced with a methyl group in a following step.


LG = -I, -SBu, -SnBu₃
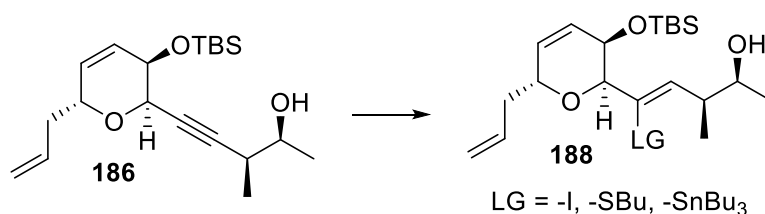
Scheme 48: *General scheme for the introduction of a leaving group (LG) in an α-position of the dihydropyran ring*

Several approaches, including hydroalumination, hydrosulfuration, hydrostannylation, *etc*. are described in the literature[29–35] for the introduction of different leaving groups. In our case two main factors should be considered: first, we have a homopropargylic alcohol and second, we have a dihydropyran ring in an α-position to the triple bond. These two limiting factors together with the necessary *E*-geometry of the final trisubstituted double bond narrowed down the synthetic approaches we could choose from for accomplishing this challenging task.

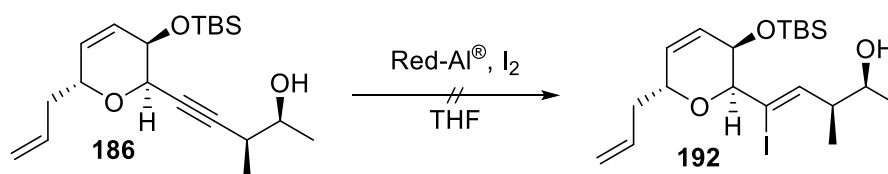### 3.1.2.1. *Hydroalumination of 186 via Red-Al*[®]

The first method we explored was the hydroalumination approach. The anti-hydroalumination of homopropargylic alcohols with high stereoselectivity can be observed while using sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al[®]) as a reducing agent. Generally, the high stereoselectivity of the reaction can be explained by the formation of an intermediate alkenyl aluminate **190** which is formed after the trans addition of aluminium-hydrogen to the triple bond of homopropargylic alcohol **189** (Scheme 49)[29].
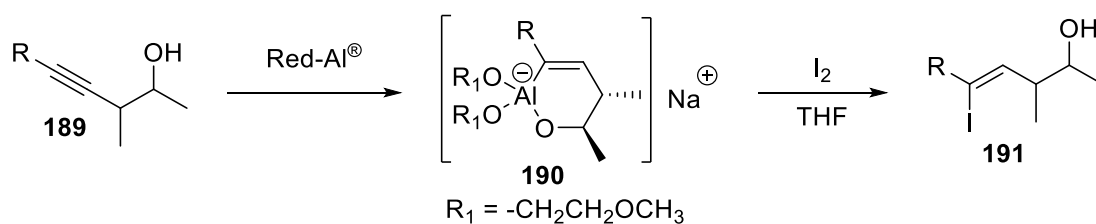
Scheme 49: *Mechanism of the hydroalumination with Red-Al® of homopropargylic alcohols*

The reaction of homopropargylic alcohol **186** with Red-Al® in refluxing THF[29] and afterwards treatment with iodine at −78 °C didn't result in the formation of the desired product **192** (Scheme 50). Thus, several variations of the reaction conditions were explored and are summarized in Table 5. Unfortunately, all the attempted reactions resulted only in the recovery of the educt **186**. As a conclusion we can say that the hydroalumination of the homopropargylic alcohol **186** induced by the coordinatively saturated nucleophilic reagent Red-Al® appeared to be ineffective.


Scheme 50: *Attempt to synthesize 192 via hydroalumination with Red-Al®*

Table 5: *Reaction conditions for the attempted hydroalumination of homopropargylic alcohol 186 via Red-Al®*

| Entry	Educt	Conditions	Product (yield)
1		Red-Al® (3 eq) I₂ (2.4 eq) 30 min, RT	(0%)
2	**186**	Red-Al® (1.2 eq) I₂ (2.4 eq) 1.5 h, RT	**192** (0%)
3	**186**	Red-Al® (3 eq) I₂ (2.4 eq) 1.5 h, RT	**192** (0%)
4	**186**	Red-Al® (3 eq) I₂ (2.4 eq) 1.5 h, reflux	**192** (0%)
5	**186**	Red-Al® (4 eq) I₂ (6 eq) 30 min, RT	**192** (0%)

3.1.2.2.   *Hydroalumination of 186 via Me₃Al and DIBAL-H or DIBAL-H only*

Another possibility for the anti-hydroalumination of the homopropargylic alcohol **189** is its sequential treatment with Me₃Al and DIBAL-H[30] or the use of DIBAL-H both as metalating and hydroaluminating agent[30]. In contrast to the hydroalumination with Red-Al®, the hydroalumination with Me₃Al and DIBAL-H or DIBAL-H only is non-stereoselective in its initial addition step to generate intermediate **193**. The observed *E/Z* ratios are obtained after an additional chelation-controlled isomerization step, furnishing intermediate **194** (Scheme 51).
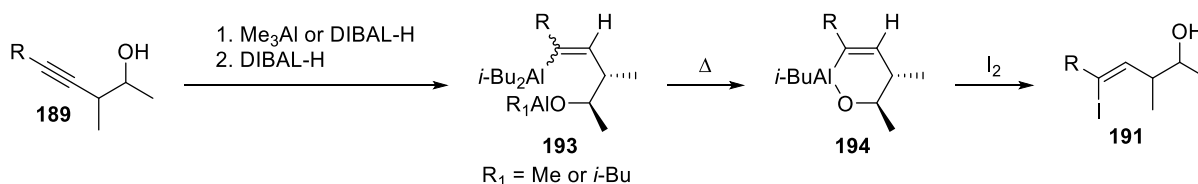
Scheme 51: *Mechanism of the hydroalumination via DIBAL-H of homopropargylic alcohols*

Unfortunately, when applied towards our homopropargylic alcohol **186** (Scheme 52), neither of these hydroalumination conditions (Me₃Al and DIBAL-H[30] or DIBAL-H only[30]) resulted in the formation of the expected product **192**. These results suggested that a probable cause for failure might be either the steric hindrance of the triple bond or the electronic effects of the dihydropyran ring and/or the homopropargylic alcohol group.
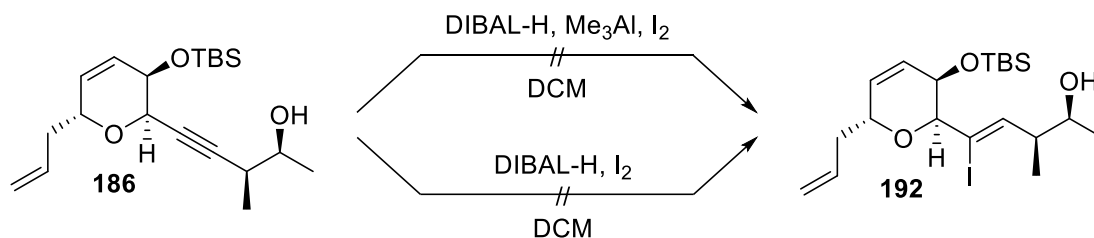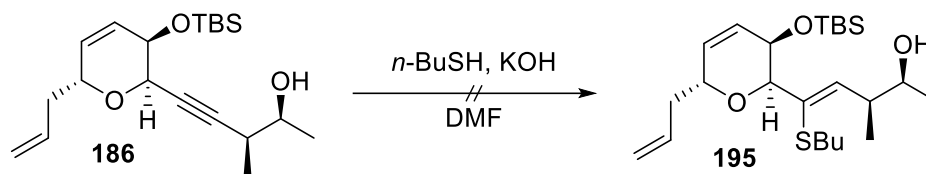

Scheme 52: *Attempt to synthesize 192 via hydroalumination with DIBAL-H*

3.1.2.3.   *Hydrosulfuration of 186 via n-BuSH*

Another possibility for the addition of a leaving group at the triple bond of the homopropargylic alcohol **186** would be a hydrosulfuration. Successful addition of BuS-group to propargylic alcohols has already been described[31,32], but the addition of the BuS-group occurs in an *α*-position to the secondary alcohol. We decided to examine if an addition will occur in the case of homopropargylic alcohol **186**, and if yes, will the addition occur at a *β*- or a *γ*-position to the secondary alcohol group. We carried out the hydrosulfuration of alcohol **186** with the use of *n*-BuSH and KOH in DMF (Scheme 53). Unfortunately, even after stirring the reaction

for 3 days at 50 °C, we didn't observe the formation of compound **195** and we were able to recover only the educt **186**.

Scheme 53: *Attempt to synthesize 195 via hydrosulfuration*

3.1.2.4. Hydrostannylation of 186 via n-Bu₃SnH

Hydrostannylation is another possible way for the addition of a leaving group (SnBu₃-group) at the triple bond of the homopropargylic alcohol **186**. The reaction was done using *n*-Bu₃SnH and PdCl₂(Ph₃P)₂ as a catalyst[33–35]. It is worth noting that the tributyltin hydride should be added dropwise in order to minimize the homocoupling reaction. The homopropargylic alcohol **186** reacted under these conditions to yield a new compound, which was detected by TLC. The newly formed compound was purified, but the observed yield of 17% was not satisfactory. Analysis via NMR-spectroscopy showed that addition did in fact take place, but not as expected. The SnBu₃-group added to the double bond from the allylic side chain instead of the homopropargylic triple bond and as a result instead of compound **196** we isolated compound **197** (Scheme 54). These results led us to the conclusion that the allylic side chain participates in a competing side reaction, hence we were not able to obtain the desired product **196**.
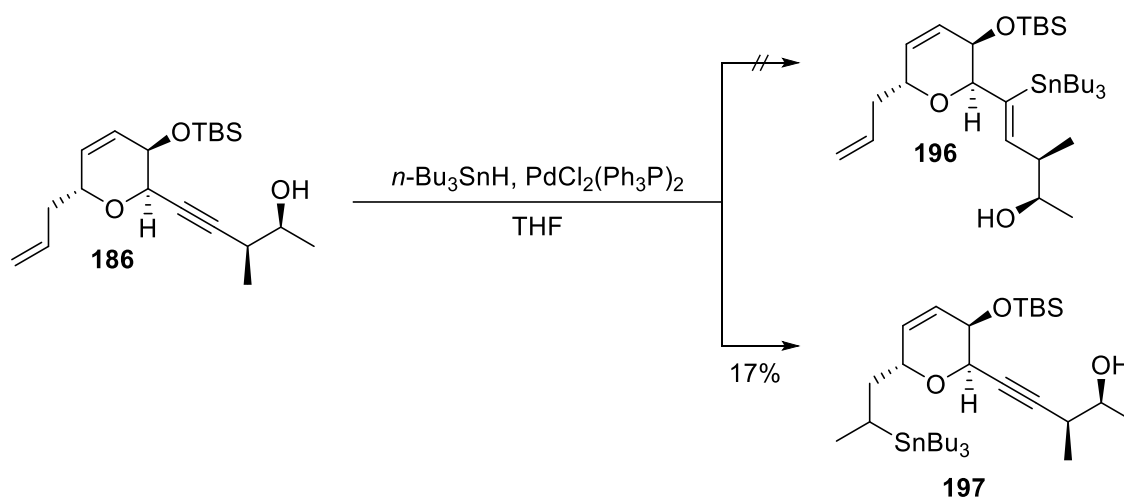

Scheme 54: *Attempt to synthesize 196 via hydrostannylation*

3.1.3. Julia-Kocienski olefination

At this point several other strategies appeared to be a sensible choice for furnishing the necessary trisubstituted *E*-double bond. Amongst them reactions like Wittig, Horner-Wadsworth-Emmons and Julia-Kocienski olefinations were the most promising. Literature search[36] and previous efforts from our group[37] narrowed down the choice to the Julia-Kocienski olefination. The exact mechanistic pathway is not yet known, but Scheme 55 describes a general mechanism with benzothiazole-2-yl (BT) sulfones as an example. Besides BT, pyridine-2-yl (PYR), 1-phenyl-1*H*-tetrazole-5-yl (PT), 1-*tert*-butyl-1*H*-tetrazole-5-yl (TBT) are widely used as activating groups (Figure 2). The *α*-metalated benzothiazolyl sulfone nucleophile **198** adds to the carbonyl electrophile **199** to form the diastereomeric pair of *syn*- and *anti*-*β*-alkoxy sulfone intermediates **200**. *Syn*-**200** and *anti*-**200** can undergo a spontaneous Smiles rearrangement forming spirocyclic intermediates *trans*-**201** and *cis*-**201**, respectively. *Trans*- and *cis*-**201** in turn open to generate *syn*- and *anti*-*β*-aryloxy sulfinates **202**, respectively. Elimination of sulfur dioxide and a lithium aryloxide **204** from the *syn*-**202** leads to the formation of *Z*-alkene **203**, whereas *anti*-**202** yields the *E*-alkene **203**[38–40] (Scheme 55).
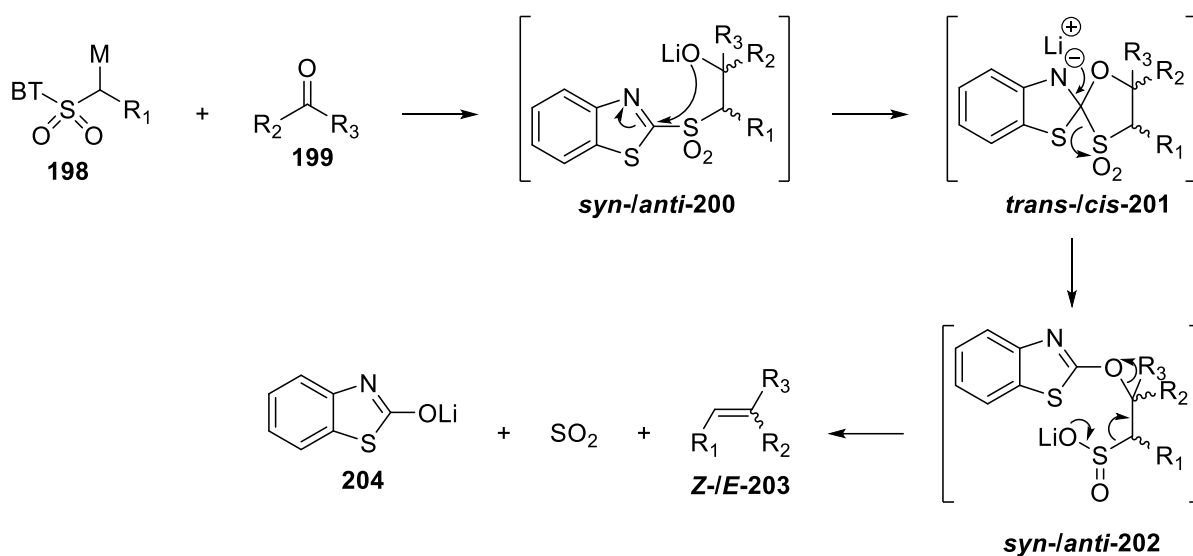
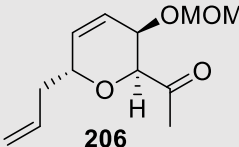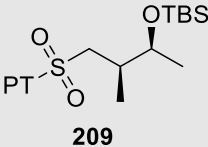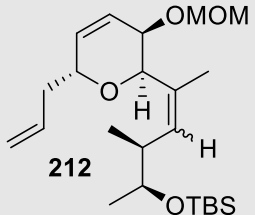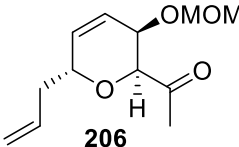**Scheme 55:** *Mechanism of the Julia-Kocienski olefination*
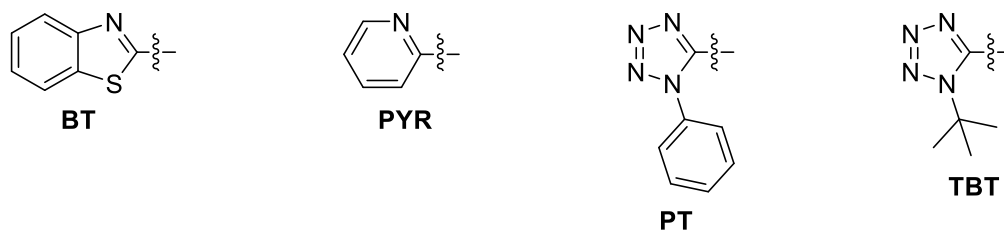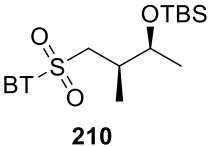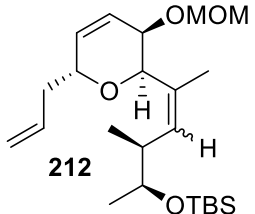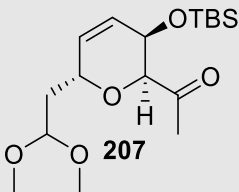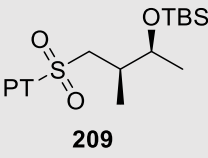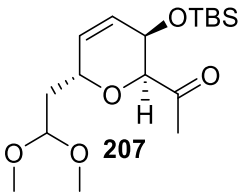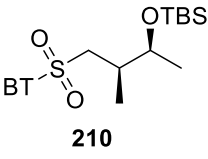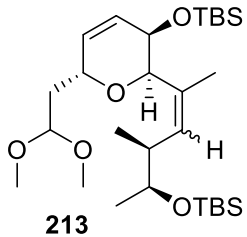
Figure 2: Activating groups commonly used in the Julia-Kocienski olefination (benzothiazole- -2-yl (BT), pyridine-2-yl (PYR), 1-phenyl-1H-tetrazole-5-yl (PT), 1-tert-butyl-1H-tetrazole-5-yl (TBT))
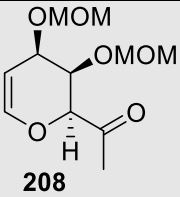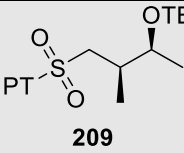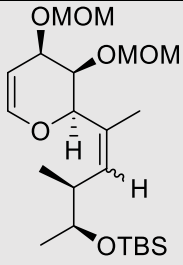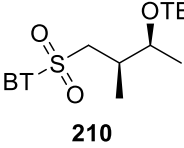
The *E/Z*-ratio in this type of olefination is mainly influenced by two factors: the sulfone activating group and the cation of the base used. Our efforts were aimed at obtaining the necessary *E*-configuration, which is favored by phenyltetrazolyl and benzylthiazolyl activating groups as well as the presence of a Li-cation in the base[38–41]. All reagents and reaction conditions explored for the Julia-Kocienski olefination are summarized in Table 6.

Table 6: Reagent screening for the Julia–Kocienski olefination

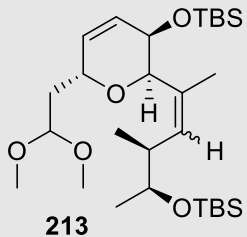| Entry	Educt	Sulfone	Conditions	Product (yield)
1	205	209 (1 eq)	LiHMDS (1.4 eq)[1] THF 3 h, −78 °C	211 (0%)
2	205	209 (1 eq)	LDA (1 eq)[1] CeCl₃ (30 eq) THF 3 h, 0 °C	211 (0%)
3	205	209 (1 eq)	NaHMDS (1.4 eq)[2] THF 3 h, −78 °C	211 (0%)
4	205	210 (1 eq)	LiHMDS (1.4 eq)[1] THF 4 h, −78 °C	211 (18%, Z-only; E/Z = 1:17)

Entry	Educt	Sulfone	Conditions	Product (yield)
5	**205**	**210** (1 eq)	LiHMDS (1.4 eq)[1] CeCl$_3$ (0.4 eq) DCM 1 h, –42 °C	**211** (8%, E/Z = 1:16)
6	**205**	**210** (1 eq)	NaHMDS (1.4 eq)[1] THF 3 h, –78 °C	**211** (0%)
7	**206**	**209** (1 eq)	LiHMDS (1.4 eq)[1] THF 3 h, –78 °C	**212** (0%)
8	**206**	**209** (1 eq)	LiHMDS (1.4 eq)[1] DMF/HMPA (4:1 v/v) 30 min, –42 °C	**212** (0%)
9	**206**	**209** (1.2 eq)	LiHMDS (1.4 eq)[1] CeCl$_3$ (0.4 eq) DCM 1 h, –42 °C	**212** (0%)
10	**206**	**209** (1 eq)	KHMDS (1.2 eq)[1] THF 2 h, –78 °C	**212** (0%)
11	**206**	**209** (1 eq)	KHMDS (1.2 eq)[1] 18-crown-6 (2 eq) THF 1 h, –78 °C	**212** (0%)
12	**206**	**210** (1.2 eq)	LiHMDS (1.4 eq)[1] THF 3 h, –78 °C	**212** (46%, E/Z = 1:14)
13	**206** (1.4 eq)	**210** (1 eq)	LiHMDS (1.4 eq)[2] THF 4 h, –78 °C	**212** (53%, Z-only; E/Z = 1:14)
14	**206**	**210** (1 eq)	LiHMDS (1.4 eq)[1] CeCl$_3$ (0.4 eq) DCM 1 h, –42 °C	**212** (34%, Z-only; E/Z = 1:12)

Entry	Educt	Sulfone	Conditions	Product (yield)
15	206	210 (1 eq)	KHMDS (1.4 eq)[1] THF 3 h, −78 °C	212 (0%)
16	206	210 (1 eq)	NaHMDS (1.4 eq)[1] THF 3 h, −78 °C	212 (0%)
17	207	209 (1.2 eq)	LiHMDS (1.4 eq)[1] THF 4 h, −78 °C	213 (0%)
18	207	209 (1.2 eq)	LiHMDS (1.4 eq)[1] DMF/HMPA (4:1 v/v) 1 h, −42 °C	213 (0%)
19	207	209 (1.2 eq)	LiHMDS (1.4 eq)[1] CeCl₃ (0.4 eq) THF 1 h, −42 °C	213 (0%)
20	207 (2.2 eq)	209 (1 eq)	LDA (1 eq)[1] CeCl₃ (1.02 eq) THF 1 h, −78 °C	213 (0%)
21	207	209 (1 eq)	NaHMDS (1.4 eq)[1] THF 4 h, −78 °C	213 (0%)
22	207	210 (1 eq)	LiHMDS (1.4 eq)[1] THF 4 h, −78 °C	213 (38%, Z-only; E/Z = 1:20)
23	207	210 (1 eq)	LiHMDS (1.4 eq)[1] CeCl₃ (0.4 eq) DCM 1 h, −42 °C	213 (5%, Z-only; E/Z = 1:20)
24	207	210 (1 eq)	NaHMDS (1.4 eq)[1] THF 3 h, −78 °C	213 (0%)

Entry	Educt	Sulfone	Conditions	Product (yield)
25	**208**	**209** (1 eq)	LiHMDS (1 eq)[1] THF 4 h, −78 °C	**214** (0%)
26	**208** (1.4 eq)	**210** (1 eq)	LiHMDS (1 eq)[1] THF 4 h, −78 °C	**214** (6%, Z-only; E/Z = 1:23)
27	**208**	**210** (1 eq)	LiHMDS (1 eq)[2] THF 4 h, −78 °C	**214** (25%, Z-only; E/Z = 1:25)

[1] Premetallation conditions (base added to the sulfone and then the ketone was added)
[2] 'Barbier' conditions (base added to a mixture of the sulfone and the ketone)

Using ketone **205** (obtained from D-galactose **237** in ten steps with an overall yield of 28% – see Chapter 3.2.1) and phenyltetrazolyl sulfone **209** (obtained from *cis*-2-butene **278** and acetaldehyde **279** in four steps with an overall yield of 49% – see Chapter 3.2.5) we tried Julia-Kocienski olefination with a variety of bases (LiHMDS[42–44], NaHMDS[42,45], LDA[36,46]) as well as with the addition of additives such as anhydrous $CeCl_3$[36,44,46] for the precomplexation of ketone **205** (Table 6, entries 1 – 3). Unfortunately, no formation of the desired product **211** was observed by TLC in any of the cases. Entries 1 and 2 resulted in the reisolation of the starting materials, whereas a detectable decomposition of sulfone **209** was observed in the case of entry 3 (Table 6). Although Julia-Kocienski olefination is well known to be compatible with a great variety of functional groups[36,43,45–48], we decided to study the steric effects of the protecting group at the secondary alcohol as well as the effect of the allylic side chain on the Julia-Kocienski olefination.

The steric effects of the protecting group on the Julia-Kocienski reaction was studied by replacing the bulky TBS-group with the smaller MOM-group. The obtained MOM-protected ketone **206** (obtained from D-galactose **237** in eleven steps with an overall yield of 36% – see Chapter 3.2.2) then took part in a Julia-Kocienski olefination reaction with the phenyltetrazolyl sulfone **209** (Table 6, entries 7 – 11). Entries 7 – 9 incorporate LiHMDS as a base for the

formation of the metalated sulfone nucleophile. Entry 7 uses THF[36,42,44] as a solvent, entry 8 – the more polar DMF and HMPA[43] as a cosolvent and entry 9 uses THF as a solvent and anhydrous CeCl$_3$[44] for the precomplexation of ketone **206**. Formation of the desired product **212** was observed in none of the cases, and it was only possible to recover the educts **206** and **209**. We then tried conditions that promote the dissociation of the metal cation from the sulfone anion – KHMDS in THF[41,42,47] and KHMDS in THF in the presence of 18-crown-6[43] (Table 6, entries 10 and 11). Those conditions also didn't yield the desired product **212** and led only to the reisolation of the educts **206** and **209**.

To study the effect of the allylic group we used two different strategies. The first was to convert the double bond to an aldehyde and then protect the carbonyl group in the form of a dimethyl acetal in order to obtain ketone **207** (synthesized from D-galactose **237** in thirteen steps with an overall yield of 14% – see Chapter 3.2.3). The results from the Julia-Kocienski olefination between ketone **207** and the phenyltetrazolyl sulfone **209** are summarized in Table 6 (entries 17 – 21). The use of LiHMDS in THF[36,42,44], LiHMDS in the polar DMF with HMPA[43] as a cosolvent, or LiHMDS in THF in the presence of an activator (anhydrous CeCl$_3$[44]) didn't produce the expected product **213**. Using LDA and CeCl$_3$[36,44,46] for the precomplexation of ketone **207** or changing the counter-cation in the base to Na-cation[41,43] also didn't yield product **213**. Under all of the examined reaction conditions we observed no change in either the sulfone **209** or the ketone **207** and we were able to recover them at the end of the reaction.

The second strategy that we adopted for studying the effect of the allylic group was using ketone **208** (obtained from D-galactose **237** in ten steps with an overall yield of 10% – see Chapter 3.2.4). This allows us to perform first the Julia-Kocienski olefination and then at a later stage to incorporate the allylic side chain via Ferrier rearrangement. Ketone **208** was reacted with phenyltetrazolyl sulfone **209** (Table 6, entry 25) in the presence of LiHMDS[36,42,44] as a base, but formation of the desired product **214** was not observed. No change in either the sulfone **209** or the ketone **208** was detected by TLC and we were able to recover both starting materials at the end of the reaction.

Analyzing the obtained results so far, we decided as a next step to investigate the influence of the aromatic activator of the sulfone on the Julia-Kocienski olefination, thus we synthesized benzylthiazolyl sulfone **210** (obtained from *cis*-2-butene **278** and acetaldehyde **279** in four steps with an overall yield of 43% – see Chapter 3.2.5). Each of the previously discussed ketones **205**, **206**, **207** and **208** was reacted with benzylthiazolyl sulfone **210** under three

different conditions (Table 6, entries 4 – 6, 12 – 16, 22 – 24 and 26 – 27). The conditions we chose for conducting these olefinations are: first, LiHMDS in THF[36,42,44] since the Li+ counter-cation is mostly preferred when *E*-olefins are the target products; second, LiHMDS with addition of anhydrous CeCl3[44] for precomplexation of the ketone; and third, NaHMDS or KHMDS in THF[41–43,47] since the Na+ or the K+ counter-cation will promote the dissociation of the metal cation from the sulfone anion.

Ketones **205**, **206**, **207** and **208** reacted with benzylthiazolyl sulfone **210** using LiHMDS as a base in THF[36,42,44] and yielded the respective products **Z-211** (18% yield), **Z-212** (46% yield), **Z-213** (38% yield) and **Z-214** (6% yield). In all four cases the reaction was very stereo specific (*E*/*Z* ratios between 1:12 to 1:25, see Table 6) and mainly one isomer was observed. After detailed analysis of the obtained NMR-results and more specifically the ones obtained from the NOESY NMRs (see Chapter 7), we established that the major observed isomer in every case was the *Z*-trisubstituted olefin. In all of the cases a coupling signal between the protons of the methyl group and the olefinic proton was observed, which confirmed the *Z*-geometry of the double bond. Applying the 'Barbier' protocol[39,40] and using LiHMDS as a base resulted in better yield, but a comparable *E*/*Z* ratio and compound **Z-212** was obtained in 53% yield whereas compound **Z-214** was furnished with a yield of 25%. When LiHMDS with addition of anhydrous CeCl3[44] was used for the Julia-Kocienski olefination we observed lower yields compared to the ones with LiHMDS alone (**Z-211**, 8% yield; **Z-212**, 34% yield; **Z-213**, 5% yield), but the relative *E*/*Z* ratio was preserved with the *Z*-isomer being favored (see Table 6). The lower yields are presumably due to the self-condensation of the benzylthiazolyl sulfone, most probably due to the high net electrophilicity of the benzylthiazolyl activator. The use of NaHMDS or KHMDS in THF[41–43,47] for the olefination between ketones **205**, **206** and **207** and sulfone **210** didn't result in the formation of the expected products **211**, **212** and **213** respectively and fast self-condensation of the benzothiazolyl sulfone was detected by TLC.

At that point a logical solution appeared to be the inversion of the coupling partners for the Julia-Kocienski olefination – the DHP-fragment as a sulfone part, and the side chain as the carbonyl component. However, that was not possible since we were not able to synthesize the phenyltetrazolyl sulfones **219**, **220** and **221** from the corresponding secondary alcohols **215**, **216** and **217** via a Mitsunobu thioetherification followed by an oxidation of the thioether (Table 7).

Table 7: *Attempted synthesis of sulfones **219**, **220** and **221***

Entry	Educt	Conditions	Product (yield)
1	**215** (OTBS, OH)	PTSH (1.2 eq) Ph$_3$P (1.2 eq) DEAD (1.2 eq) Mo$_7$O$_{24}$(NH$_4$)$_6$·4H$_2$O (0.2 eq) 30% aq. H$_2$O$_2$	**219** (0%)
2	**216** (OMOM, OH)	PTSH (1.2 eq) Ph$_3$P (1.2 eq) DEAD (1.2 eq) Mo$_7$O$_{24}$(NH$_4$)$_6$·4H$_2$O (0.2 eq) 30% aq. H$_2$O$_2$	**220** (0%)
3	**217** (OMOM, OMOM, OH)	PTSH (1.2 eq) Ph$_3$P (1.2 eq) DEAD (1.2 eq) Mo$_7$O$_{24}$(NH$_4$)$_6$·4H$_2$O (0.2 eq) 30% aq. H$_2$O$_2$	**221** (0%)

3.1.4. Takai olefination

Another strategy to furnish the *E*-trisubstituted double bond is with the use of a ketone, which can be converted to *E*-alkenyl iodide via Takai olefination. The desired *E*-olefin can then be obtained via a cuprate addition to epoxide **157**.

The exact mechanism of the Takai olefination is not fully known. However, the proposed mechanism of the Takai olefination is depicted in Scheme 56. The haloform **222**/chromium(II) chloride (CHX$_3$/CrCl$_2$) system is first converted to the *gem*-dichromium intermediate **224**, which is nucleophilic and attacks the carbonyl group in compound **199** to form the β-oxychromium species **225**. The corresponding alkenes ***E*-226** and ***Z*-226** are then formed from **225** by an elimination[38,49].
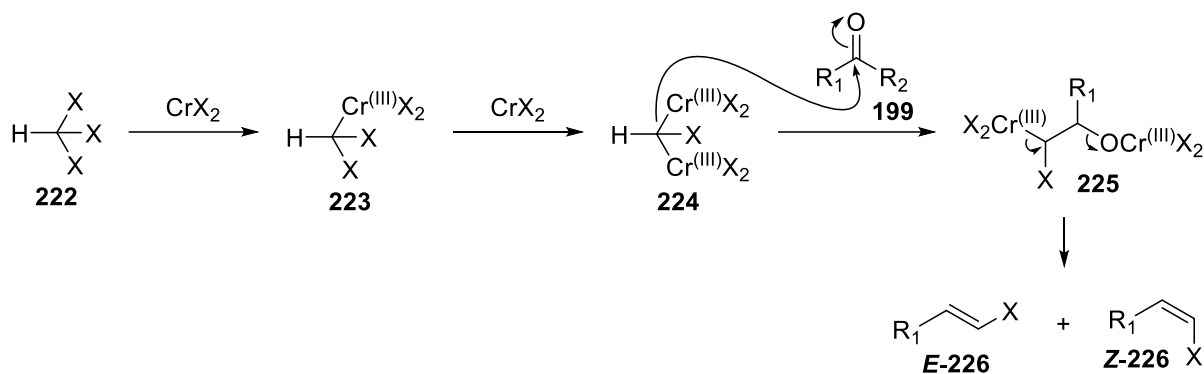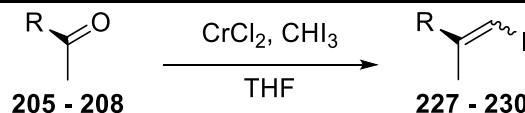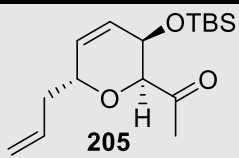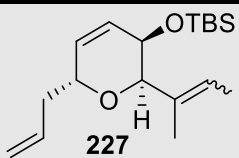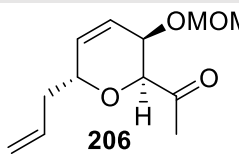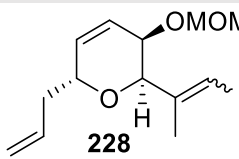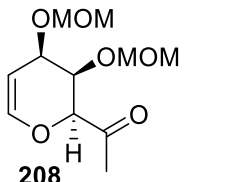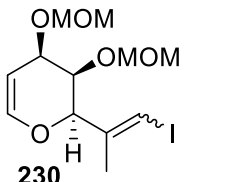
Scheme 56: *Mechanism of the Takai olefination*

Ketones **205**, **206**, **207**, and **208** (see chapters 3.2.1 through 3.2.4 for their synthesis) took place in a Takai olefination, using $CrCl_2$ and CHI_3[50–52] (Table 8). Surprisingly, however, the Takai olefination of ketones **205**, **206**, and **207** yielded *Z*-vinyl iodides **Z-227** (76% yield), **Z-228** (51% yield) and **Z-229** (62% yield) respectively as the major isomers (*E/Z* ratios varying between 1:10 to 1:13, see Table 8). The major isolated isomer was the *E*-vinyl iodide **E-230** (47% yield) only in the case of ketone **208**. These results were verified by the NOESY NMRs (see Chapter 7). Coupling signal between the methyl group and the olefinic proton was observed in vinyl iodides **227**, **228** and **229**, which confirmed the *Z*-geometry of the double bond. In the case of iodide **230** a lack of a coupling signal between the methyl group and the olefinic proton in the NOESY NMR confirmed the *E*-configuration of the vinyl iodide **E-230**. It is noteworthy that the Takai olefination was highly stereospecific towards either the *Z*- or the *E*-isomer.

Analyzing the previously described results it has been established that the change of the protecting group from TBS- to MOM-group as well as the transformation of the double bond to a dimethylacetal did not have an effect on the diastereoselectivity of the Tak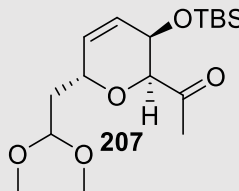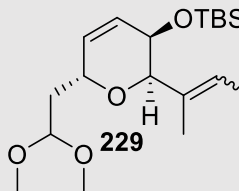ai olefination. Only when the allylic side chain was not present was the *E/Z* diastereomeric ratio in favor of the *E*-isomer. These observations led us to the conclusion that not the steric effect of the protecting group, but the presence of an allylic side chain is the reason why the Takai olefination unexpectedly yielded the *Z*-isomer.

Table 8: *Takai olefination of ketones 205, 206, 207 and 208*

Entry	Educt	Conditions	Product (yield)
1	**205**	CrCl$_2$ (11 eq) CHI$_3$ (3 eq)	**227** (76%, Z-only; E/Z = 1:13)
2	**206**	CrCl$_2$ (8.5 eq) CHI$_3$ (2.3 eq)	**228** (51%, Z-only; E/Z = 1:10)
3	**207**	CrCl$_2$ (11 eq) CHI$_3$ (3 eq)	**229** (62%, Z-only; E/Z = 1/12)
4	**208**	CrCl$_2$ (11 eq) CHI$_3$ (3 eq)	**230** (47%, E-only; E/Z = 9:1)

The exploratory work for the incorporation of the neosorangicin A side chain turned out to be a far greater synthetic challenge than initially expected. It has been demonstrated in this chapter that neither carboalumination nor hydrometallation approaches succeeded in the synthesis of compound **155**. The Julia-Kocienski olefination using phenyltetrazolyl sulfone **209** and a variety of ketones also failed to produce the desired results. However, the Julia-Kocienski olefination with the use of benzylthiazolyl sulfone **210** and ketones **205**, **206**, **207**, and **208** yielded the corresponding Z-trisubstituted olefins with great stereospecificity. The Takai olefination of ketones **205**, **206**, and **207** resulted in the formation of the corresponding Z-vinyl iodides with high E/Z diastereomeric ratios. Towards the end of this thesis Takai olefination of ketone **208**, yielded E-vinyl iodide **230**. It is expected that iodide **230** can be transformed to the target molecule via a cuprate addition to epoxide **157**, TBS-protection of the free alcohol group, bis MOM-deprotection and a Ferrier carboalumination. However, considering the previous

obstacles, this transformation is expected to be a challenging effort both in terms of synthesis and optimization.

3.2. Syntheses of the precursors

In order to carry out the experiments described in Chapter 3.1, it was necessary to synthesize the nine precursors used, since they were not commercially available. Chapters 3.2.1 through 3.2.5 describe the established gram scale synthesis of each of these precursors as well as the explored optimizations.

3.2.1. Synthesis of alkyne **175** and ketone **205**

The retrosynthesis of alkyne **175** and ketone **205** is shown in Scheme 57. The necessary alkyne **175** can be obtained from aldehyde **231** via a Colvin rearrangement. Ketone **205** can also be obtained from aldehyde **231** via a two-step sequence of a Grignard reaction and a Dess-Martin oxidation. Aldehyde **231** can be afforded via a Swern oxidation of primary alcohol **232**, which in turn can be obtained from compound **233** via a selective TBS-deprotection of the primary alcohol. Compound **233** is easily accessible from allylglycal **235** in a two-step sequence of cleavage of the acetyl protecting groups to yield diol **234** and a subsequent bis TBS-protection. Allylglycal **235** can be obtained from D-galactal **236** via a Ferrier rearrangement. D-galactal **236** in turn can be synthesized from D-galactose **237** in a three-step sequence of pentaacetylation, hydrobromination and zinc reduction.
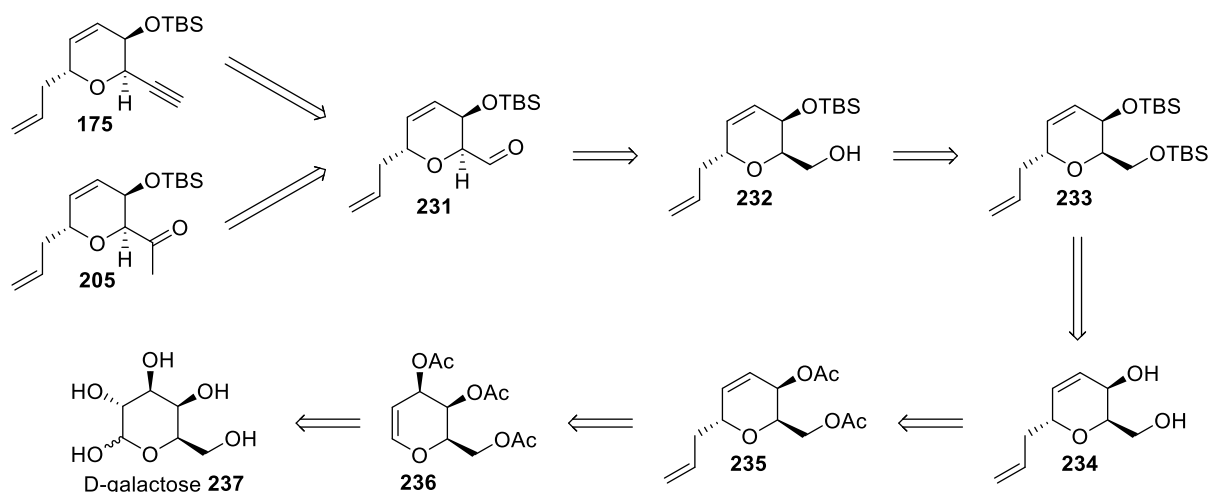
***Scheme 57:*** *Retrosynthesis of alkyne 175 and ketone 205*

D-galactose was adopted as the starting material since it is cost and time effective. The enantiomer L-galactose is more expensive and converting the D-galactose to L-galactose is a tedious process. These were the two main factors taken in consideration when we chose to

carry out the preliminary exploratory work with the D-galactose. After establishing reliable and reproducible procedures, the synthesis could be repeated starting from L-galactose.

D-galactal **236** was first synthesized via a one-pot reaction from D-galactose **237**[53–55] in 30% yield according to Scheme 58.
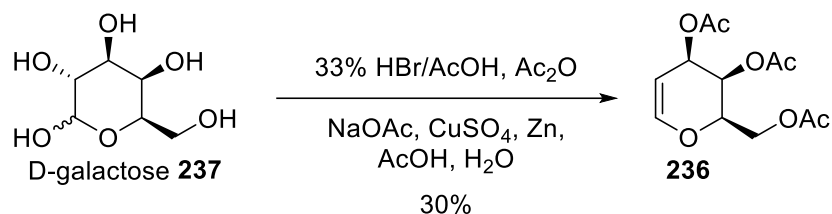
Scheme 58: *One-pot synthesis of D-galactal **236***

Starting from D-galactose **237**, another approach towards D-galactal **236** included a three-step sequence of pentaacetylation, hydrobromination and zinc reduction (Scheme 59).
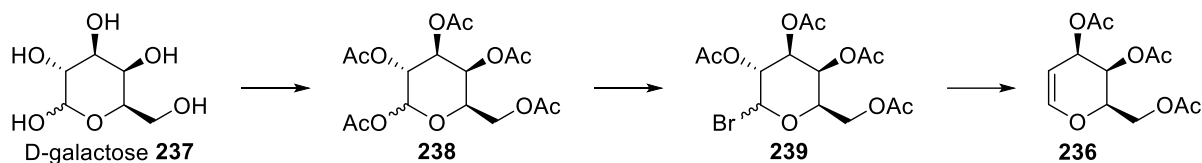
Scheme 59: *General scheme for the three-step synthesis of D-galactal **236***

First, using acetic anhydride and DMAP in pyridine[56–58] peracetylated galactose **238** was obtained. The following hydrobromination step was done either with PBr₃[59–61] in DCM or with 33% HBr/AcOH in DCM[57,58,62] and yielded compound **239**. Finally, D-galactal **236** was obtained via a reduction with zinc dust in a 2:1 mixture of acetone and saturated NaH_2PO_4 solution[63–65]. We found that using 33% HBr/AcOH for the hydrobromination resulted in slightly better yields on a gram scale (66% versus 61%) over the three steps (Scheme 60).
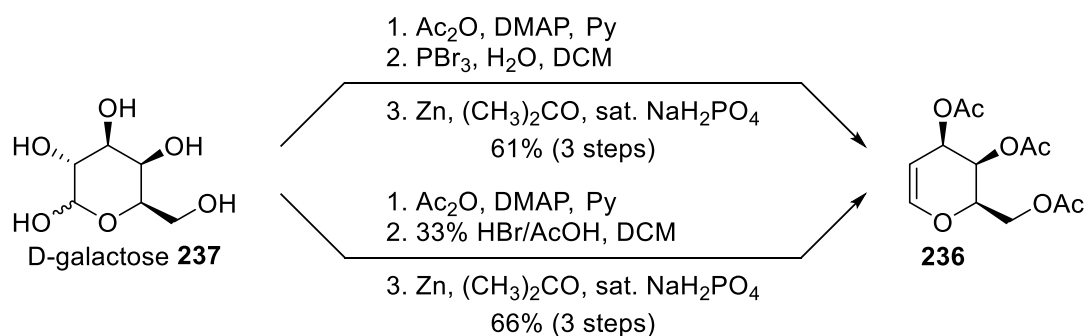
Scheme 60: *Three-step synthesis of D-Galactal **236***

D-galactal **236** then participated in a classical carbon Ferrier rearrangement in order to obtain allylglycal **235**. The reaction was initiated by a Lewis acid (TMSOTf)[66–68], which allowed the

formation of the resonance-stable oxocarbenium ion **240**[69], which was then subjected to a nucleophilic attack with the use of allyltrimethylsilane. This resulted in the final nucleophilic substituted product **235**, which was obtained with a yield of 95% (Scheme 61).
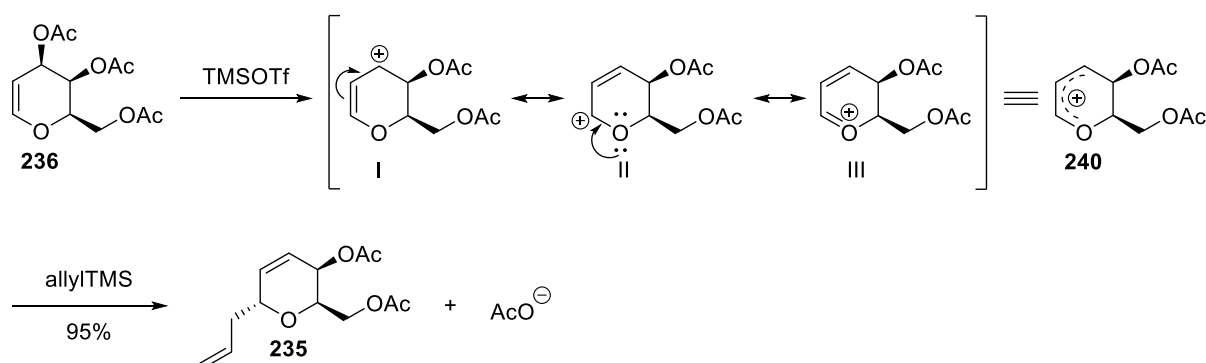
Scheme 61: Mechanism of the carbon Ferrier rearrangement for the synthesis of 235
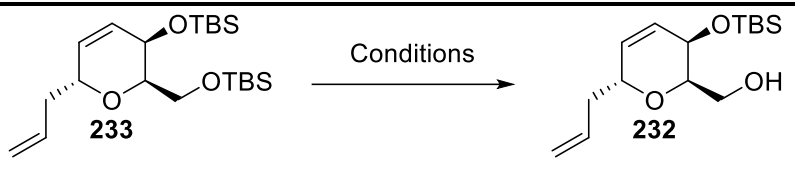
Allylglycal **235** was subjected to a manipulation of the protecting groups. First, a cleavage of the acetyl protecting groups using K_2CO_3 in MeOH[70,71] yielded diol **234** in a nearly quantitative yield (98%). Subsequent protection of both alcohol groups in diol **234** as TBS-ethers using TBSCl and imidazole in DCM[72–74] afforded compound **233** with a yield of 95% (Scheme 62).
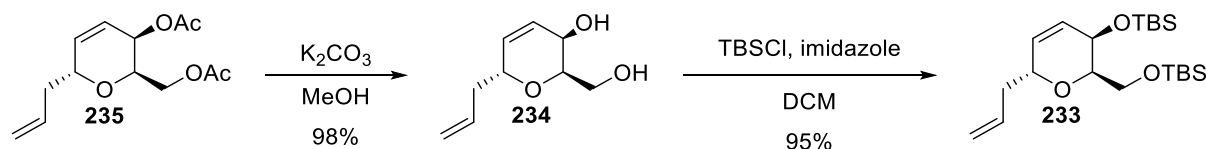
Scheme 62: Acetyl deprotection of 235 and TBS-protection of diol 234

The primary alcohol in compound **233** was selectively deprotected using mild deprotecting conditions such as $AcOH/H_2O/THF$ in 3:1:1 ratio[75–77], which yielded alcohol **232** in 35% (Table 9, entry 1 – 2). Since the yield was not that high, three further methods for the selective deprotection of the primary alcohol in compound **233** were explored. First, a mixture of $HCOOH/H_2O/MeCN$ in 2:1:7 ratio[78] was used and compound **232** was obtained with a yield of 52% (Table 9, entry 3 – 4). The deprotection of the TBS-ether with PPTS in MeOH[79,80] afforded alcohol **232** in 55% yield (Table 9, entry 5 – 7). The best yield, however, was observed with CSA as a deprotecting agent in a 1:1 mixture of DCM/MeOH[12,81]. Optimization of the reaction conditions (amount of CSA and reaction time) finally furnished the primary alcohol **232** in 70% yield (Table 9, entry 8 – 12).

Table 9: *Reagent screening and optimization of the reaction conditions for the selective deprotection of the primary alcohol in compound **233***

Entry	Conditions	Yield
1	AcOH/H$_2$O/THF (3:1:1) 2 h, 0 °C; 10 h, RT	33%
2	AcOH/H$_2$O/THF (3:1:1) 30 min, 0 °C; 2 h, RT	35%
3	HCOOH/H$_2$O/MeCN (2:1:7) 1.5 h, RT	44%
4	HCOOH/H$_2$O/MeCN (2:1:7) 20 min, RT	52%
5	PPTS (1.3 eq), MeOH 30 min, RT	33%
6	PPTS (1.3 eq), MeOH 1.5 h, RT	46%
7	PPTS (1.3 eq), MeOH 2.5 h, RT	55%
8	CSA (0.1 eq), DCM/MeOH = 1:1 30 min, 0 °C	70%
9	CSA (0.3 eq), DCM/MeOH = 1:1 10 min, 0 °C	68%
10	CSA (0.3 eq), DCM/MeOH = 1:1 30 min, 0 °C	69%
11	CSA (0.5 eq), DCM/MeOH = 1:1 15 min, 0 °C	59%
12	CSA (0.9 eq), DCM/MeOH = 1:1 45 min, 0 °C	50%

Alcohol **232** was then oxidized to aldehyde **231** using Dess-Martin oxidation[82,83]. The isolated yields of the product were moderate – 59%. However, Swern oxidation[84–86] afforded aldehyde **231** in an excellent yield – 88% (Scheme 63).
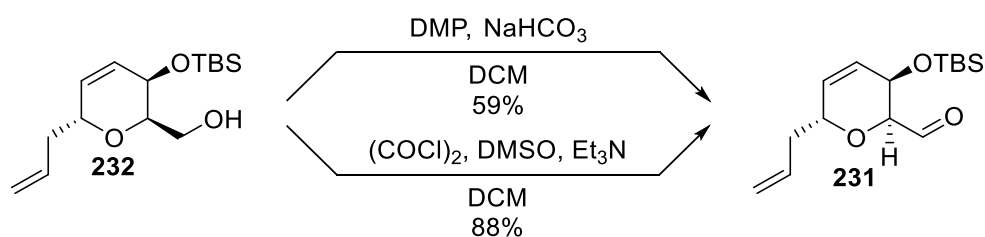
Scheme 63: *Synthesis of **231** via Swern oxidation*

Alkyne **175** can then be synthesized from aldehyde **231** via the so-called Colvin rearrangement[43,87,88]. In this reaction TMSC(Li)N$_2$, prepared *in situ* from TMSCHN$_2$ and *n*-BuLi, attacks the carbonyl carbon atom in compound **231** and forms the *α*-diazoalkoxide **241**. Elimination of TMSOLi and expulsion of N$_2$ from alkoxide **241** (in either order) affords the intermediate alkylidene carbene intermediate **242**. The carbene **242** then undergoes 1,2-rearrangement[89,90] to form the corresponding alkyne **175** (Scheme 64). Aldehyde **231** was successfully transformed via the Colvin rearrangement to the homologous alkyne **175** with a yield of 77%.
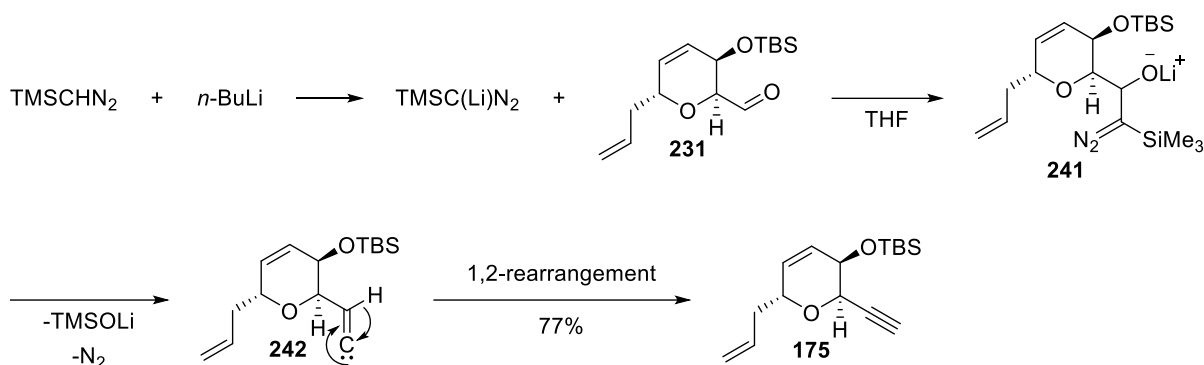
Scheme 64: *Mechanism of the Colvin rearrangement for the synthesis of alkyne 175*

Carbaldehyde **231** can also be transformed to ketone **205** in a two-step sequence of Grignard reaction for the introduction of the necessary methyl group and consequent oxidation of alcohol **215**. The Grignard reaction between the carbaldehyde **231** and MeMgBr[36,91] easily afforded alcohol **215** in an excellent yield (92%, 5:1 dr). The alcohol **215** was then oxidized, using a Dess-Martin oxidation[92–94]. This gave ketone **205** with a yield of 85% (Scheme 65).
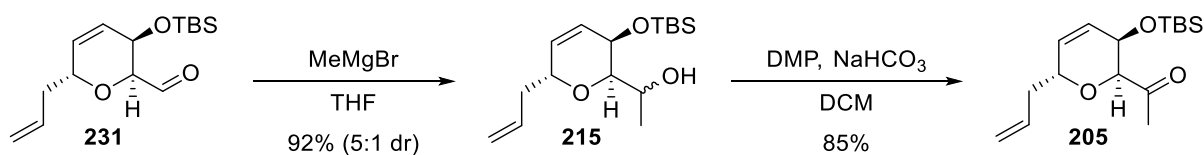
Scheme 65: *Synthesis of ketone 205*

3.2.2.   Synthesis of alkyne **178** and ketone **206**

The retrosynthetic approach towards alkyne **178** and ketone **206** is shown in Scheme 66. Alkyne **178** can be obtained from aldehyde **243** via a Colvin rearrangement or an Ohira-Bestmann modification of the Seyferth-Gilbert homologation. Ketone **206** can also be obtained from aldehyde **243** via a Grignard reaction, followed by a Dess-Martin oxidation. Aldehyde **243** can be afforded via a Swern oxidation of the primary alcohol **244**. Alcohol **244**

can be obtained either from compound **245** or compound **246** via a TBS- or a TIPS-deprotection respectively. Compound **245** is easily accessible from diol **234** in a two-step sequence. First, a selective mono TBS-protection of the primary alcohol group can yield compound **247**, which can then be protected as a MOM-ether. On the other hand, a selective mono TIPS-protection of the primary alcohol group in diol **234** can yield compound **248**. The secondary alcohol **248** can then be protected as a MOM-ether to form compound **246**.
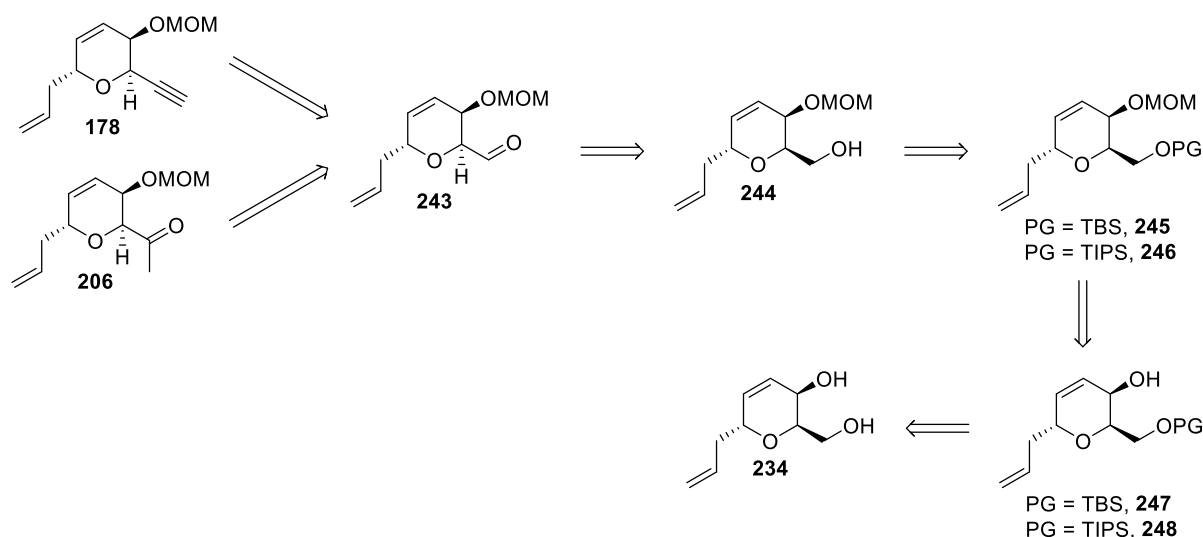
Scheme 66: *Retrosynthesis of alkyne **178** and ketone **206***

Diol **234** was subjected to a selective protection of the primary alcohol as a TBS-ether, using TBSCl and imidazole[70,95,96]. This furnished the secondary alcohol **247** with a yield of 80%. The consequent protection of the secondary alcohol **247** as a MOM-ether, using MOMCl and DIPEA[97,98] gave compound **245** with a yield of 97%. The following TBS-deprotection of compound **245** with TBAF[99–101] resulted in the isolation of the primary alcohol **244** in 96% yield (Scheme 67).
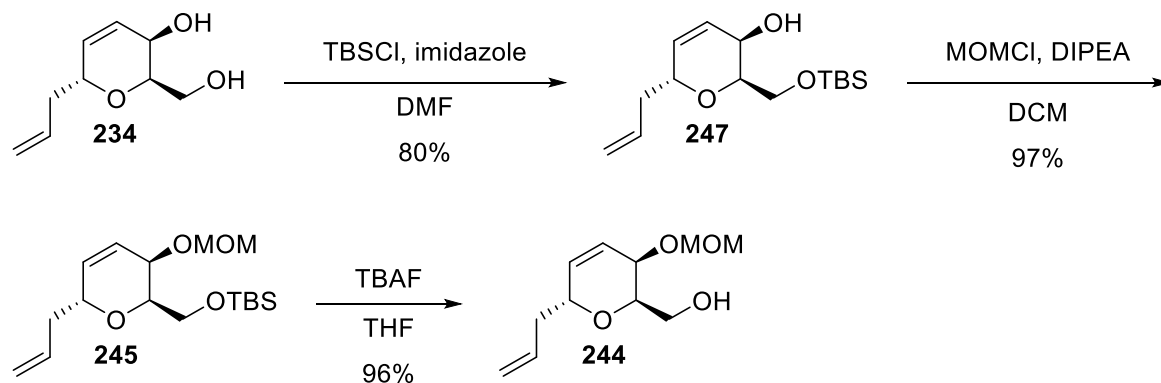
Scheme 67: *Synthesis of alcohol **244** via compounds **247** and **245***

The obtained results with the TBS-protection of the primary alcohol were satisfactory, although the mono TBS-protection was not always a smooth reaction. In most of the cases a mixture of the mono TBS-protected product, the bis TBS-protected side product and the starting material was observed. Thus, a second approach for the protection of the primary alcohol in diol **234** was investigated. The primary alcohol in compound **234** was protected as TIPS-ether, using TIPSCl and imidazole[102–104]. This resulted in the formation of alcohol **248** with a very high yield (89%) as well as with a greater selectivity. The crude mixture was containing just the mono TIPS-protected product and a small amount of unreacted starting material. The following MOM-protection of the secondary alcohol **248** using MOMCl, DIPEA and a catalytic amount of DMAP[105,106] furnished compound **246** in 96% yield. Finally, the TIPS-group was cleaved by the use of TBAF[103,107,108] to obtain the primary alcohol **244** in 94% yield (Scheme 68).
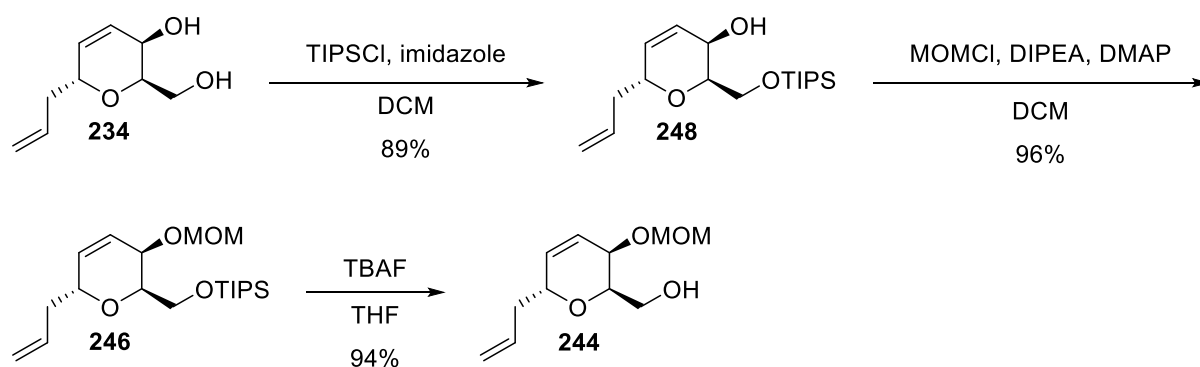
Scheme 68: *Synthesis of alcohol **244** via compounds **248** and **246***

In conclusion the TIPS-protection of the primary alcohol appeared to be better since the overall yield over 3 steps was a bit higher (80% overall yield versus 75% overall yield, while using TBS-group), it was more selective, but most importantly it was more reproducible.

Primary alcohol **244** was then oxidized using Swern oxidation[38,109] to yield aldehyde **243** in 87% yield. This was followed by a Colvin rearrangement[43,87,88] in order to obtain alkyne **178** (Scheme 69). Unfortunately, using this method the isolated yields for compound **178** were rather low (27% yield).
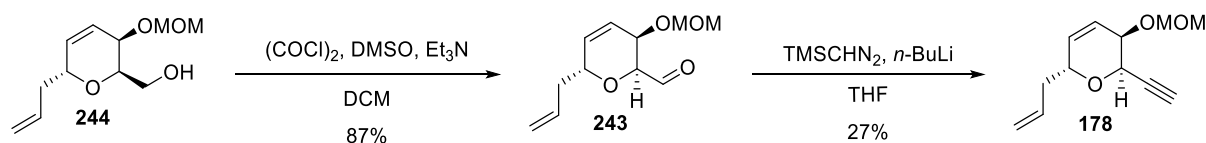
Scheme 69: *Synthesis of alkyne **178** via Colvin rearrangement*

Another possibility to synthesize alkyne **178** from aldehyde **243** is the Ohira-Bestmann modification of the Seyferth-Gilbert homologation[89], the mechanism for which is shown in Scheme 70. The reaction is usually carried out with potassium carbonate in methanol. This generates small amounts of alkoxide, which attacks the carbonyl group in the dimethyl (1-diazo-2-oxopropyl)phosphonate (Bestmann reagent) **98** and forms intermediate **249**. Expulsion of methyl acetate leads to the formation of the dimethyl (diazomethyl)phosphonate anion **250**. Anion **250** then attacks the carbonyl group of an aldehyde (or aryl ketone) **199** forming adduct **251**. Alkoxide **251** closes to give an oxaphosphetane **252**, which upon cycloelimination furnishes a stable phosphate anion and a thermally unstable diazoalkene **253**. Diazoalkene **253**, upon expulsion of N_2 forms alkylidene carbene **254**. The carbene **254** then undergoes a 1,2-alkyl shift to generate the corresponding alkyne **255**[38,110,111].
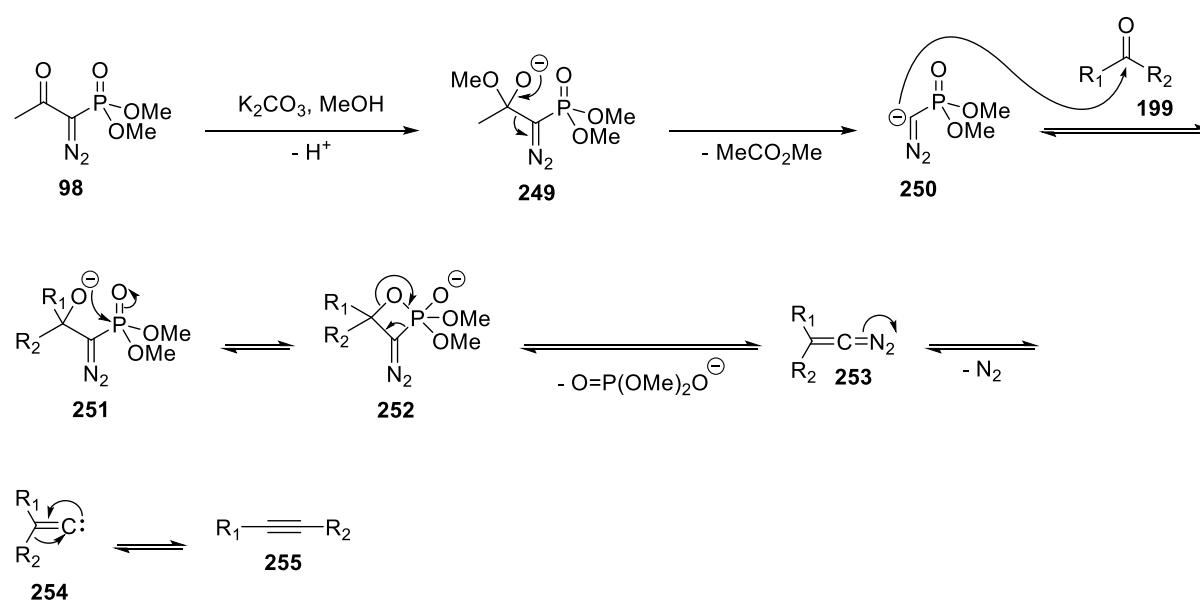
Scheme 70: Mechanism of the Ohira-Bestmann reaction

Aldehyde **243** took part in an Ohira-Bestmann variation[112–114] of the Seyferth-Gilbert homologation and alkyne **178** was furnished in 59% yield (Scheme 71).
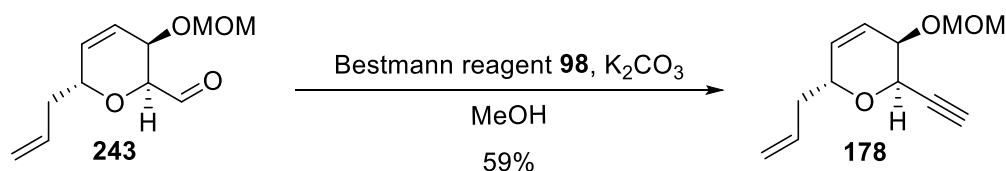
Scheme 71: Synthesis of alkyne 178 via Ohira-Bestmann reaction

Ketone **206** was synthesized according to Scheme 72. The previously obtained carbaldehyde **243** took place in a Grignard reaction with MeMgBr[36,91] to give the secondary alcohol **216**

(95%, 4:1 dr). Finally, alcohol **216** underwent a Dess-Martin oxidation[92–94] to give the necessary ketone **206** with a yield of 87%.
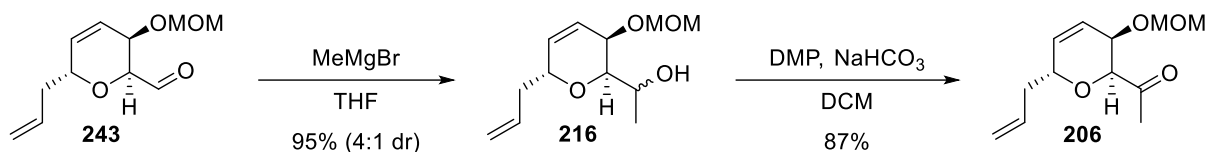
Scheme 72: Synthesis of ketone 206

3.2.3. Synthesis of alkyne **179** and ketone **207**

The retrosynthetic approach towards alkyne **179** and ketone **207** is shown in Scheme 73. Alkyne **179** can be obtained from aldehyde **256** either via Colvin rearrangement or via Ohira-Bestmann modification of the Seyferth-Gilbert homologation. Ketone **207** can be synthesized from aldehyde **256** via Grignard reaction followed by Dess-Martin oxidation. Aldehyde **256** can be furnished from the primary alcohol **257**, using a Swern oxidation. Selective deprotection of the primary TBS-ether in compound **258** will yield alcohol **257**. Compound **258** can be afforded from aldehyde **259** via an acetalization. Aldehyde **259** is easily formed from the previously obtained compound **233** using dihydroxylation to generate diol **260**, followed by an oxidative cleavage of the diol.
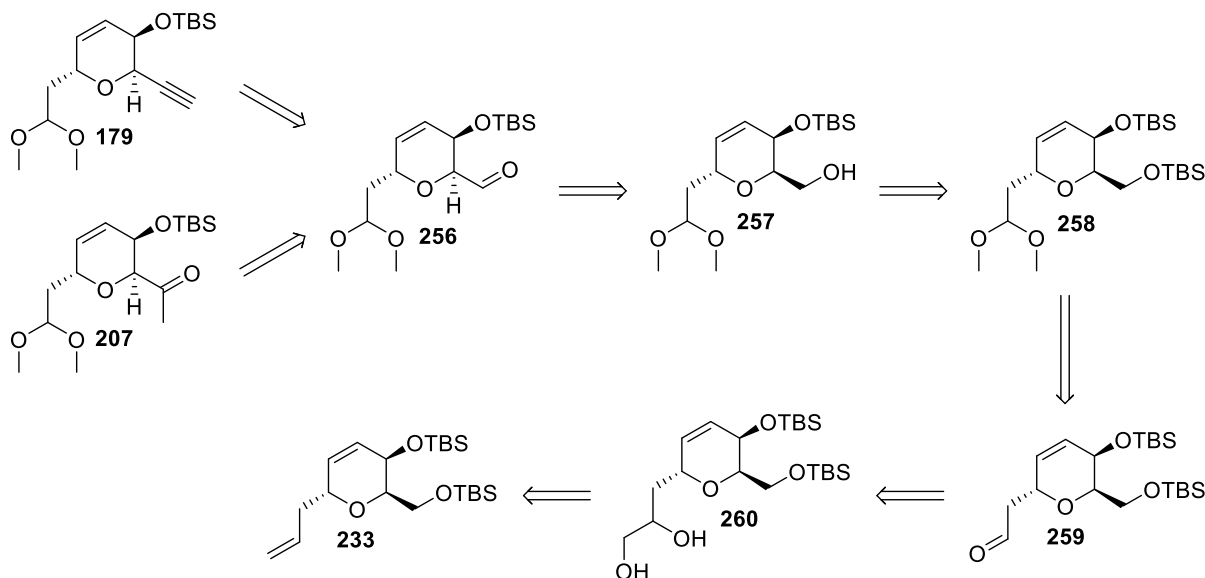
Scheme 73: Retrosynthesis of alkyne 179 and ketone 207
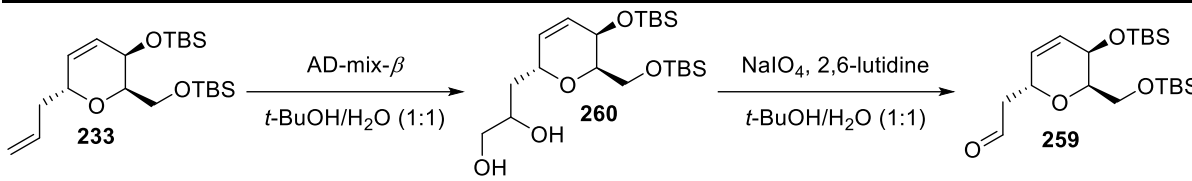
Previously obtained compound **233** was subjected to a Sharpless asymmetric dihydroxylation and consequent oxidative cleavage of the formed 1,2-diol **260**[115,116]. We decided to use Sharpless asymmetric dihydroxylation of compound **233**, since previous attempts using OsO$_4$/NMO by other members of our group[12,37] gave lower yields. The mechanism of the Sharpless dihydroxylation starts with the formation of a complex **262** between the *in situ*

generated OsO₄ and the (DHQD)₂PHAL **261** ligand. Other ligands such as (DHQ)₂PHAL, (DHQD)₂PYDZ, (DHQD)₂AQN, (DHQD)₂DPP *etc.* can be also used instead of the (DHQD)₂PHAL[117]. The active catalyst possesses a U-shaped binding pocket for the OsO₄ complex as seen in **264**. In this way the OsO₄ is held in a chiral environment, which sterically hinders the approach of only one side of the olefin **263**. A [3+2]-cycloaddition yields the osmylate ester **265**. Upon basic hydrolysis of intermediate **265**, diol **267**, reduced osmate **266**, and the ligand **261** are formed. Osmate **266** is then oxidized to OsO₄ with potassium ferricyanide **268**[118] (Scheme 74).
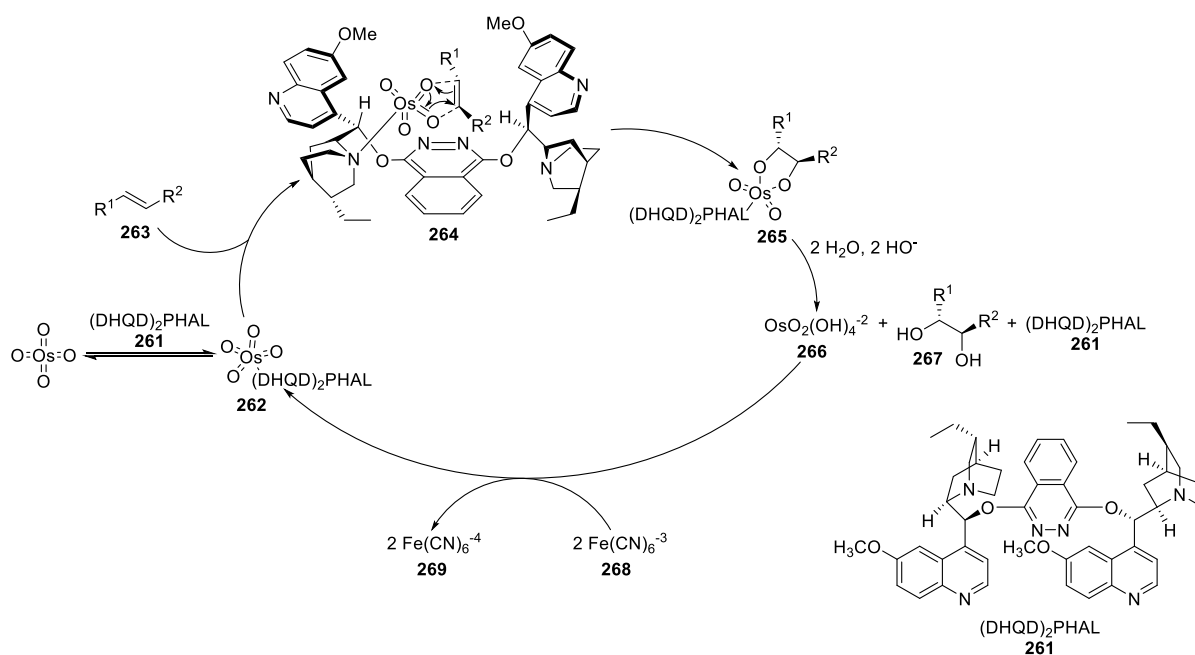
Scheme 74: *Mechanism of the Sharpless dihydroxylation with (DHQD)₂PHAL **261** as a ligand*

The Sharpless asymmetric dihydroxylation of compound **233** was performed with the commercially available AD-mix-*β*, containing K₃Fe(CN)₆, K₂CO₃, K₂OsO₂(OH)₄ and (DHQD)₂PHAL, in 1:1 mixture of *t*-BuOH/H₂O[12,119,120]. The subsequent oxidative cleavage of diol **260** was carried out with NaIO₄ as an oxidant and 2,6-lutidine as a base in a solvent mixture of *t*-BuOH/H₂O (1:1)[121]. The reaction conditions explored and their overall yields are given in Table 10. Using the conditions described in Table 10, entry 6 aldehyde **259** was obtained in two steps from compound **233** with an overall yield of 80%.

Table 10: *Optimization of the reaction conditions for the synthesis of compound **259***

Entry	Conditions for dihydroxylation	Conditions for cleavage of the diol	Overall yield
1	AD-mix-β (2 eq) t-BuOH/H$_2$O = 1:1 48 h, 0 °C	NaIO$_4$ (4 eq) 2,6-lutidine (2 eq) t-BuOH/H$_2$O = 1:1 3 h, RT	35%
2	AD-mix-β (3 eq) t-BuOH/H$_2$O = 1:1 48 h, RT	NaIO$_4$ (4 eq) 2,6-lutidine (2 eq) t-BuOH/H$_2$O = 1:1 3 h, RT	55%
3	AD-mix-β (2 eq) t-BuOH/H$_2$O = 1:1 48 h, RT	NaIO$_4$ (4 eq) 2,6-lutidine (2 eq) t-BuOH/H$_2$O = 1:1 3 h, RT	62%
4	AD-mix-β (1.4 eq) t-BuOH/H$_2$O = 1:1 24 h, RT	NaIO$_4$ (4 eq) 2,6-lutidine (2 eq) t-BuOH/H$_2$O = 1:1 3 h, RT	69%
5	AD-mix-β (2 eq) t-BuOH/H$_2$O = 1:1 12 h, RT	NaIO$_4$ (4 eq) 2,6-lutidine (2 eq) t-BuOH/H$_2$O = 1:1 3 h, RT	72%
6	AD-mix-β (2 eq) t-BuOH/H$_2$O = 1:1 24 h, RT	NaIO$_4$ (4 eq) 2,6-lutidine (2 eq) t-BuOH/H$_2$O = 1:1 3 h, RT	80%

Aldehyde **259** was then further protected as an acetal (Scheme 75). The acetalization of aldehyde **259**, using TMOF and catalytic amount of PTSA[12,122,123], generated compound **258** with a yield of 98%. The selective deprotection of the primary alcohol in acetal **258** was accomplished using CSA[12] as a deprotecting agent. Several conditions have been explored and summarized in Table 11, where entry 2 gave the best results for obtaining the necessary alcohol **257** (68% yield).
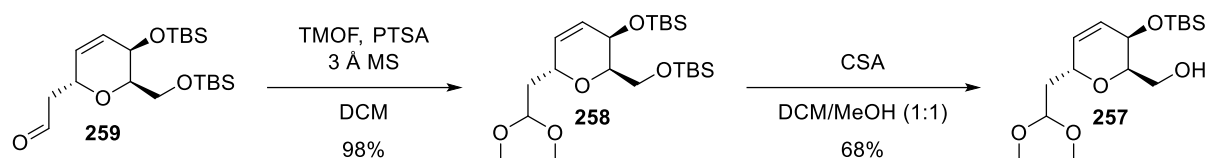
Scheme 75: *Synthesis of compound 257*

Table 11: *Reagent optimization for the synthesis of compound 257*

Entry	Deprotecting agent	Reaction time	Temperature	Yield
1	CSA (0.1 eq)	30 min	0 °C	55%
2	CSA (0.6 eq)	30 min	0 °C	68%
3	CSA (0.9 eq)	20 min	0 °C	59%

Alcohol **257** can be also obtained in one step from aldehyde **259** via a simultaneous acetalization and deprotection of the primary alcohol. This was achieved by the use of iodine and methanol[124] and the necessary alcohol **257** was furnished in 47% yield (Scheme 76). This method is convenient with respect to number of reactions and purification steps, but the isolated yields were lower than the previously described two-step approach (47% vs. 66% in 2 steps).
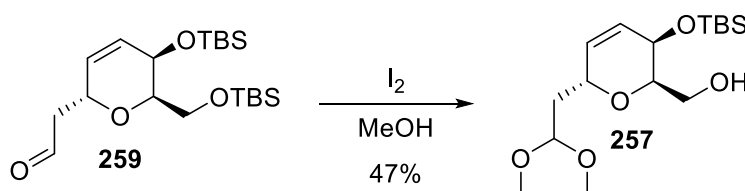
Scheme 76: *Synthesis of alcohol 257 in one step from aldehyde 259*

Swern oxidation[12,82,109] of alcohol **257** yielded aldehyde **256** in 68% yield. Aldehyde **256** was then subjected to a Colvin rearrangement[87–89] and alkyne **179** was isolated with a yield of 58%. However, better results (72% yield) were obtained while using the Ohira-Bestmann protocol[112–114] of the Seyferth-Gilbert homologation (Scheme 77).
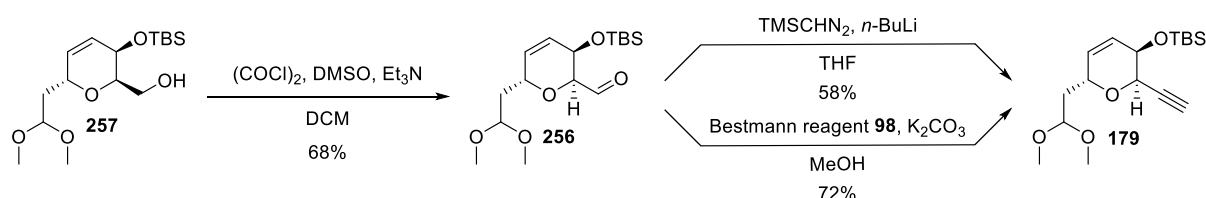
Scheme 77: *Synthesis of alkyne 179*

Previously obtained aldehyde **256** can be easily converted to ketone **207** (64% yield over 2 steps) using Grignard reaction with MeMgBr[12,36,91] to obtain the secondary alcohol **269**, which was then subjected to a Dess-Martin oxidation[12,92,93] (Scheme 78).
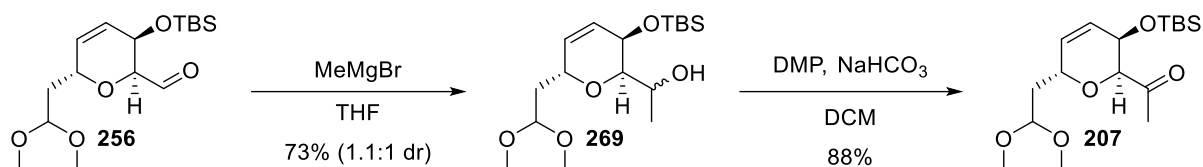
Scheme 78: *Synthesis of ketone 207*

3.2.4. Synthesis of ketone 208

The retrosynthetic approach towards ketone **208** is shown in Scheme 79. Ketone **208** can be synthesized from alcohol **217** via a Dess-Martin oxidation, which is in turn synthesized from aldehyde **270** via a Grignard reaction. Aldehyde **270** can be furnished from the primary alcohol **271**, using a Dess-Martin oxidation. Deprotection of the primary TBS-ether in compound **272** can yield alcohol **271**. Compound **272** can be afforded from triol **274** via a selective TBS-protection of the primary alcohol to yield diol **273**, followed by a bis MOM-protection. Triol **274** is easily accessible from the previously obtained D-galactal **236** through cleavage of the three acetyl groups.
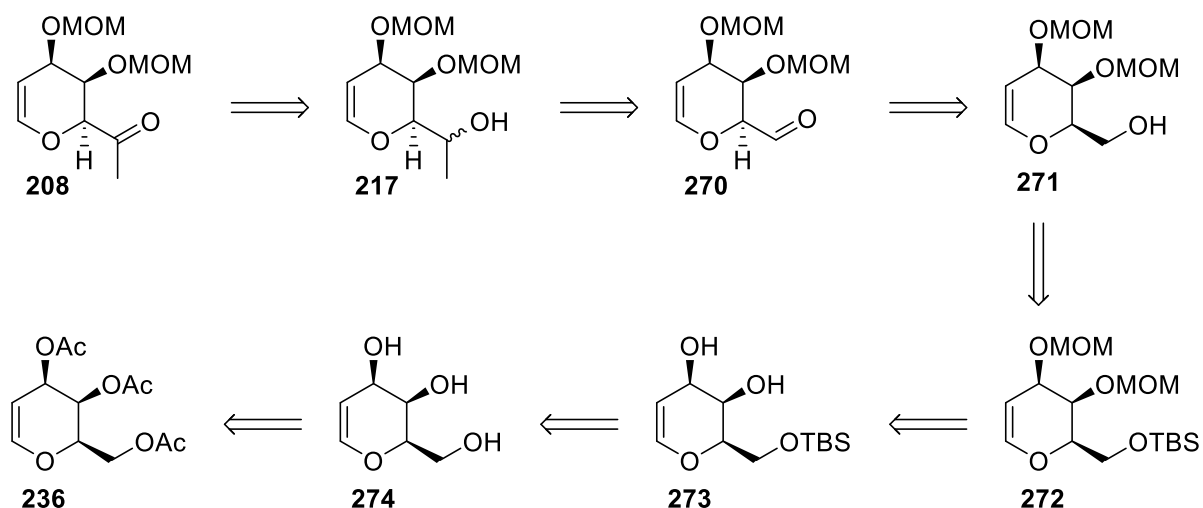
Scheme 79: *Retrosynthesis of ketone 208*

Previously obtained D-galactal **236** was deacetylated, using K_2CO_3 in methanol[125,126], yielding triol **274** in a nearly quantitative yield (99% yield). The TBS-protection of the primary alcohol in triol **274** was performed with TBSCl and imidazole in DMF[127–129] and furnished diol **273** in 49% yield. Better results were obtained while using TBSCl and triethylamine in 10:1 mixture of acetonitrile/DMF[130]. These conditions afforded diol **273** with a yield of 70% (Scheme 80).
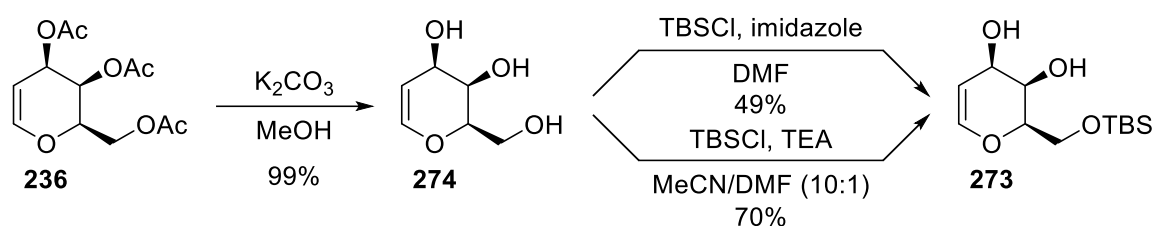
Scheme 80: *Synthesis of diol 273*

The bis MOM-protection of diol **273** was done using MOMCl, DIPEA and a catalytic amount of DMAP[131–133]. The reaction was smooth, but the isolation of the product **272** was troublesome. Quenching the reaction with either a saturated NaHCO$_3$ solution or water caused a decomposition of product **272**. The decomposition during the work-up process was registered by TLC, and it was also observed that the decomposition was more severe at larger scales. On 200 mg scale and quenching with a saturated NaHCO$_3$ solution, compound **272** was isolated in 56% yield, while on a 2.2 g scale the target product **272** was obtained in just 15% yield. The solution to this problem was to concentrate the reaction mixture upon completion of the reaction and then directly purify it by a column chromatography on silica gel. This method furnished compound **272** with a yield of 98%. The following TBS-deprotection of compound **272** with TBAF in THF[129,132,134] yielded alcohol **271** with a yield of 86% (Scheme 81).
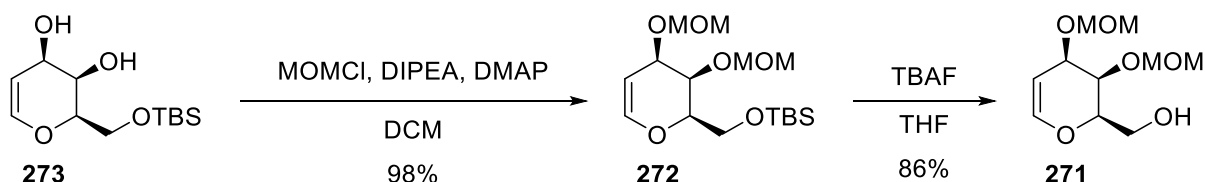
Scheme 81: *Synthesis of alcohol 271*

Alcohol **271** was oxidized with Dess-Martin periodinane[135–137] to obtain aldehyde **270** (68%), which was converted to the alcohol **217** via a Grignard reaction[138,139] (56%, 1.5:1 dr). The ketone **208** was finally generated from alcohol **217** via a Dess-Martin oxidation[140,141] with a yield of 66% (Scheme 82).
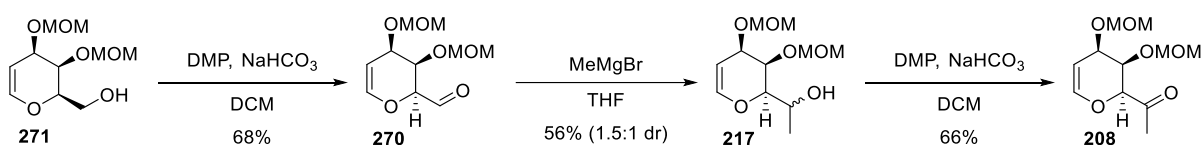
Scheme 82: *Synthesis of ketone 208*

3.2.5. Synthesis of the side chain

The retrosynthesis of sulfones **209** and **210** is shown in Scheme 83. Sulfone **209** as well as **210** can be synthesized from alcohol **275** via a Mitsunobu thioetherification followed by an

oxidation of the corresponding thioether. Reductive ozonolysis of olefin **276** can yield alcohol **275** in one step. Olefin **276** can in turn be obtained from alcohol **277** via a TBS-protection of the secondary alcohol. Alcohol **277** can be easily synthesized from the commercially available *cis*-2-butene **278** and acetaldehyde **279** via crotylboration of the carbonyl compound.
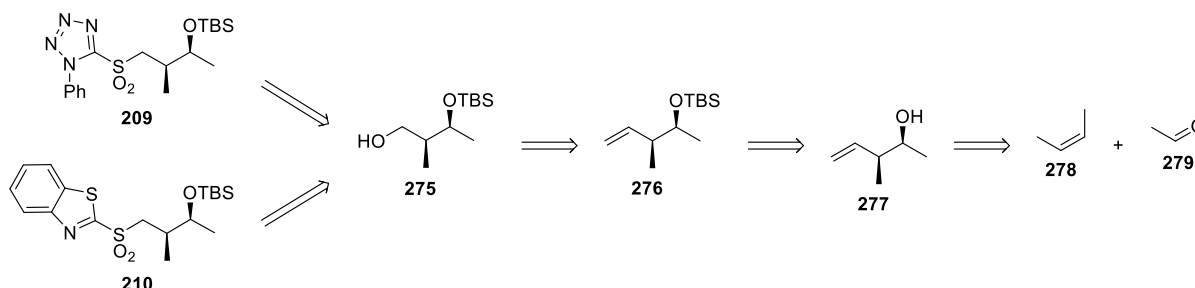
Scheme 83: *Retrosynthetic approach towards sulfones 209 and 210*

The synthesis of the side chain started from the commercially available *cis*-2-butene **278** and acetaldehyde **279**. First, *cis*-2-butene **278** reacts with a Schlosser's base to generate the stable crotylpotassium anion **280**, which is then trapped with methoxydiisopinocamphenylborane to give the dialkylborane intermediate **281**. Intermediate **281** is highly Lewis acidic, hence the addition of boron trifluoride etherate (BF$_3$·Et$_2$O) is necessary in order to cleave the methoxide anion from the ate complex and generate the crotyldialkylborane **282**. Borane **282** is too sensitive to be isolated and in order to avoid isomerization it is immediately treated with the carbonyl compound (acetaldehyde **279**) and a chair-like transition state **283** is reached. Upon alkaline hydrogen peroxide workup, the secondary alcohol **277** is furnished[142–146] (Scheme 84).
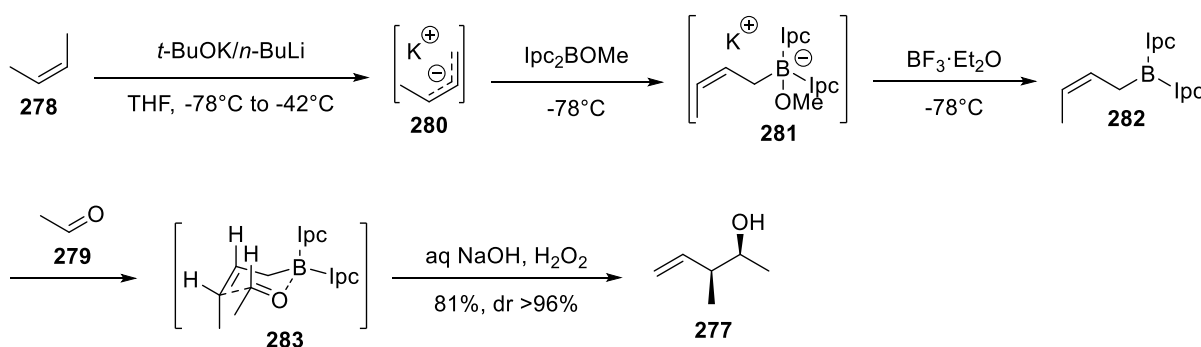
Scheme 84: *Mechanism of the crotylboration of aldehyde 279*

Alcohol **277** was purified by vacuum distillation and immediately protected as a TBS-ether, since it was a very volatile liquid. The TBS-protection of the secondary OH-group of alcohol **277** under standard conditions (TBSCl and imidazole[147,148]) yielded alkene **276** (70% over

two steps). Reductive ozonolysis[149–152] of olefin **276** afforded the primary alcohol **275** in 78% yield (Scheme 85).
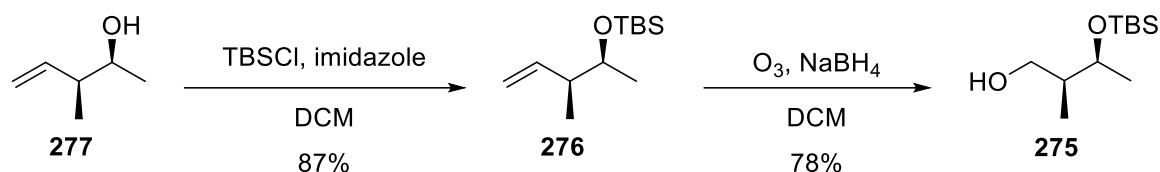
Scheme 85: *Synthesis of alcohol 275*

Alcohol **275** was then converted to a phenyltetrazolyl sulfone **209** or a benzylthiazolyl sulfone **210** via a one-pot reaction of a Mitsunobu thioetherification, followed by a chemoselective oxidation of the corresponding thioethers **284** and **285**[153–155]. The Mitsunobu reaction was performed using the redox couple of triphenylphosphine and diethylazodicarboxylate (DEAD)[43,48] and the chemoselective oxidation of thioethers **284** and **285** was carried out with aqueous H_2O_2 and a catalytic amount of $(NH_4)_6Mo_7O_{24}\cdot4H_2O$[42–44]. These conditions furnished the phenyltetrazolyl sulfone **209** with a yield of 89% and the benzylthiazolyl sulfone **210** with a yield of 78% (Scheme 86).
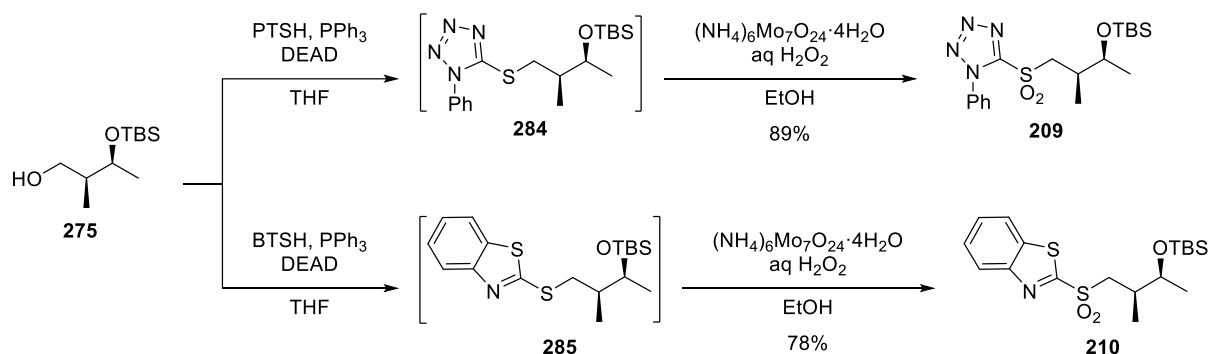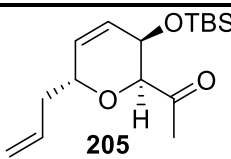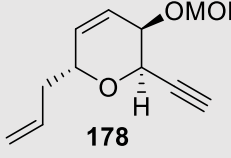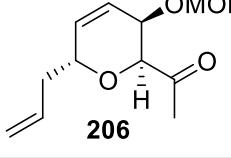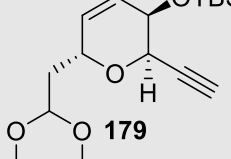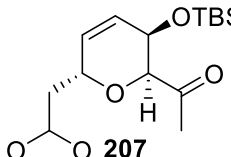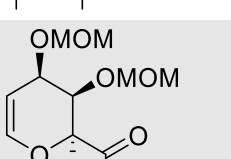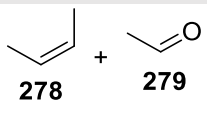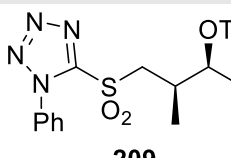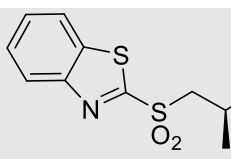
Scheme 86: *Synthesis of phenyltetrazolyl sulfone 209 and benzylthiazolyl sulfone 210*

This chapter explored the synthesis of nine precursors required for the synthesis of the C(1) – C(12) dihydropyran fragment, and also the optimization of the synthetic routes. The number of steps and the overall yield for each of these precursors are summarized in Table 12.

Table 12: *Synthesis and yield of the precursors*

Entry	Educt(s)	Product	Number of steps	Overall yield
1	D-galactose **237**	**175**	9	28%

Entry	Educt(s)	Product	Number of steps	Overall yield
2	D-galactose **237**	**205**	10	28%
3	D-galactose **237**	**178**	10	25%
4	D-galactose **237**	**206**	11	36%
5	D-galactose **237**	**179**	12	15%
6	D-galactose **237**	**207**	13	14%
7	D-galactose **237**	**208**	10	10%
8	**278** + **279**	**209**	4	49%
9	*cis*-2-butene **278**, acetaldehyde **279**	**210**	4	43%

The precursors were then used to introduce the side chain using four main synthetic strategies. Incorporating the side chain via carboalumination and hydrometallation were found to be unsuccessful. In the case of hydrostannylation, we found out that a reaction occurred, but unexpectedly, the double bond from the allylic side chain was found to participate in the reaction. The Julia-Kocienski olefination using the phenyltetrazolyl sulfone was unsuccessful,

and the benzylthiazolyl sulfone was found to preferentially yield the undesired *Z*-isomer. The Takai olefination yielded the undesired *Z*-isomer in most cases, but using ketone **208** successfully resulted in the isolation of the *E*-isomer in 47% yield and high stereoselectivity.

Reflecting on the results of the multiple synthetic strategies we have attempted in the generation of compound **155**, we expect that the main cause for deviation from the literature is the presence of the allylic side chain and not the size of the protecting group. This is because exchanging the bulky TBS-group for a MOM-group had no effect, while the absence of the allylic side chain resulted in the formation of the compound with the desired stereochemistry when subjected to the Takai olefination.

Reflecting on the results from the Takai olefination, we expect that compound **230** can be used to synthesize compound **155** in four steps. However, given the fact that many of our synthetic strategies failed despite being well-supported in the literature leads us to believe that the proposed four-step synthesis is likely to be challenging both in execution and in optimization.

4. Summary and outlook

4.1. Summary

The main objective of this thesis was the synthesis of the C(1) – C(12) dihydropyran fragment of neosorangicin A. This is to be used as a starting material for the further investigations on the coupling with the other substructures of neosorangicin A. Therefore, a synthetic strategy that is high yielding and reproducible on a multigram scale needed to be developed.

The early retrosynthetic analysis of dihydropyran fragment **155** envisioned two main strategies for incorporating the side chain. The first was with the use of an alkyne as an intermediate compound and the second was adopting a ketone. Starting from D-galactose **237**, alkynes **175** (28%, nine steps), **178** (25%, ten steps) and **179** (15%, twelve steps) were synthesized on a multigram scale. In order to furnish the dihydropyran fragment **155**, alkynes **175**, **178** and **179** took part in a zirconocene-catalyzed methylalumination reaction. Unfortunately, under the explored conditions none of the alkynes successfully yielded the desired products. This necessitated a slight deviation in the synthetic strategy, and the synthesis of homopropargylic alcohols **186** and **187** was attempted. The opening of the commercially available epoxide **157** and its addition to alkyne **178** in order to obtain the propargylic alcohol **187** was unsuccessful. However, while using alkyne **175** we were able to successfully generate homopropargylic alcohol **186** with a yield of 71%. Homopropargylic alcohol **186** took part in hydroalumination (via Red**-**Al®, via Me₃Al and DIBAL-H or via DIBAL-H only), hydrosulfuration (via *n*-BuSH) and hydrostannylation (via *n*-Bu₃SnH) reactions. However, none of these approaches yielded the desired product **188**.

Due to the unsuccessful attempts to synthesize the dihydropyran fragment **155** using an alkyne as an intermediate, we then tried to use a ketone as a precursor for obtaining the target molecule **155** instead. Starting from D-galactose **237**, ketones **205** (28%, ten steps), **206** (36%, eleven steps), **207** (14%, thirteen steps) and **208** (10%, ten steps) were synthesized on a multigram scale.

First, we investigated the Julia-Kocienski olefination for the synthesis of the trisubstituted olefins **211**, **212**, **213** and **214**. For this purpose, sulfones **209** (49%, four steps) and **210** (43%, four steps) were synthesized on a multigram scale starting from *cis*-2-butene **278** and acetaldehyde **279**. Many attempts were made in order to couple ketones **205**, **206**, **207** and **208** with sulfone **209** but none of them resulted in the successful synthesis of the corresponding trisubstituted olefins **211**, **212**, **213** and **214**. However, while using ketones **205**, **206**, **207** and

208 and sulfone **210** we were able to isolate the desired dihydropyran fragment **155** in each case. Unfortunately, after a detailed analysis of the obtained analytical data it turned out that we were able to isolate mainly the Z-isomers. However, the achieved stereoselectivity, although opposite of what we were aiming for, was excellent with *E/Z* ratios ranging from 1:12 to 1:25. Olefin **Z-211** was obtained in 18% yield, **Z-212** – in 53% yield, **Z-213** – in 38% yield and **Z-214** – in 25% yield. The inversion of the reaction partners was not possible under the explored conditions, since the Mitsunobu thioetherification of alcohols **215**, **216** and **217** was unsuccessful.

Next, a Takai olefination of ketones **205**, **206**, **207** and **208** was explored. Ketones **205**, **206** and **207** surprisingly yielded the corresponding Z-vinyl iodides **Z-227**, **Z-228** and **Z-229**, which was confirmed by the analytical data collected. Although the yields were moderate, the stereoselectivity was excellent. Vinyl iodide **Z-227** was isolated in 76% yield (*E/Z* = 1:13), **Z-228** – in 51% yield (*E/Z* = 1:10) and **Z-229** – in 62% yield (*E/Z* = 1:12). Surprisingly towards the end of the thesis, ketone **208**, when subjected to the Takai olefination, furnished the *E*-vinyl iodide **E-230** in 47% yield (*E/Z* = 9:1).

4.2. Outlook

Towards the end of this thesis *E*-vinyl iodide **E-230** was synthesized. This result is a good starting point for further investigations as a cuprate addition of epoxide **157** to the vinyl iodide **E-230** can afford the corresponding trisubstituted olefin. This olefin after a protection of the free alcohol group, followed by a deprotection of the MOM-ethers can be subjected to a Ferrier rearrangement to generate the necessary dihydropyran fragment **155**.

Another possibility that one can try for the coupling of the ketones **205**, **206**, **207** and **208** is the Wittig olefination. The main limitation of the traditional Wittig olefination is that the reaction proceeds mainly via the erythro betaine intermediate, which leads to the Z-alkene. However, the Schlosser modification of the Wittig olefination overcomes this problem by using phenyllithium at low temperatures. This allows the conversion of the erythro betaine to the threo betaine and results in the formation of the *E*-alkene. The necessary phosphonium ylide for the Schlosser modification can be obtained from the already synthesized alcohol **275**. First, a halogenation of **275** can yield the corresponding alkyl halide, which can react with triphenylphosphine and *n*-BuLi in order to furnish the necessary phosphonium ylide.

Another approach to the dihydropyran fragment **155** can be the reaction between ketones **205**, **206**, **207** and **208** with the Li-compound of the side chain. This can form a diastereomeric

mixture of the corresponding alcohols, which after a selective elimination (*i.e.* with Burgess reagent) can lead to the formation of the trisubstituted *E*-double bond. The necessary Li-compound for this transformation can easily be obtained from alcohol **275**. Tosylation of the free alcohol group in **275**, followed by a nucleophilic substitution with NaI and acetone can yield the corresponding iodide. This iodide when reacted with *t*-BuLi can generate *in situ* the necessary Li-compound of the side chain.

5. Experimental part

5.1. Materials and methods

All reactions involving air- and moisture-sensitive compounds were carried out under nitrogen atmosphere in a flame dried glassware. Generally, all reactions were carried out only in dry, absolute **solvents**. Tetrahydrofuran (THF) and diethyl ether were dried with sodium/benzophenone and dichloromethane (DCM) was dried with calcium hydride under nitrogen and were freshly distilled before use. All other reaction solvents were purchased either in a dry form over molecular sieves or, if possible, in a reagent grade quality and were used without any further purification.

The commercially available **fine chemicals** were used without further purification. Liquid reagents and solutions were added through a septum or in a nitrogen counter-current, using commercially available plastic injection syringes. Solid reagents, when possible, were dissolved in the corresponding solvent and added through a septum, otherwise they were directly added in a nitrogen counter-current. Air-sensitive solids were measured and filled under argon atmosphere in a LABmaster 130 glove box from M. Braun GmbH.

The **preparative column chromatography** was performed using Macherey-Nagel Silica Gel 60 M (0.040 – 0.063 mm). If applicable, the column chromatography was accelerated with a slight excess pressure, approx. 0.2 – 0.4 bar. The specified solvent mixtures are given in volume ratios.

POLYGRAM SIL G/UV$_{254}$ prefabricated TLC plates with fluorescent indicator from the company Macherey-Nagel have been used for the analytical **thin layer chromatography (TLC)**. The separated substances were detected by irradiation with UV light with a wavelength of 254 nm or staining with vanillin or potassium permanganate reagent and subsequent warming with a heat gun.

Vanillin reagent: 8.6 g vanillin were dissolved in 200 ml ethanol and 2.5 ml concentrated sulfuric acid was added slowly.

Potassium permanganate reagent: 3 g potassium permanganate and 20 g potassium carbonate were dissolved in 300 ml water and 5 ml 5% sodium hydroxide solution was added.

The **nomenclature** was done according to the IUPAC rules using the software ChemBioDraw Ultra 13.0. The **end-of-line hyphenation** of the chemical names follows the recommendations of IUPAC from 2020[156].

The **^{1}H-** and **^{13}C-NMR spectra** were measured either on Brucker AVIII 400 MHz or on Brucker AV Neo 600 MHz spectrometer. The used solvent is reported for each spectrum and the chemical shifts (δ) are reported in [ppm] from tetramethylsilane, referenced to the solvent resonance resulting from incomplete deuteration (CDCl$_3$: ^{1}H-NMR = 7.26 ppm, ^{13}C-NMR = 77.16 ppm; CD$_3$OD: ^{1}H-NMR = 3.31, ^{13}C-NMR = 49.00; (CD$_3$)$_2$CO: ^{1}H-NMR = 2.05, ^{13}C-NMR = 29.84, 206.26).The signal multiplicity is abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, dt = doublet of triplet, br = broad signal.

The **high-resolution mass spectra (HRMS)** were measured either on Waters Xevo G2 TOF spectrometer, using electrospray ionization (ESI) technique or on Finnigan MAT 95 spectrometer, using electron ionization (EI).

The **IR-spectra** were measured on Vertex 70V FT-IR spectrometer, using attenuated total reflection (ATR) technique. The position of the absorption bands is given in wavenumbers ($\tilde{\nu}$) [cm^{-1}]. The relative intensity of the bands is abbreviated as follows: w = weak, m = medium, s = strong, br = broad signal.

The **melting points (Mp)** were measured on a BÜCHI B-540 melting point apparatus.

The **specific optical rotations** were measured on an Anton Paar MCP150 polarimeter at 589 nm and at a concentration (c) in [g/100 ml].

5.2. Experimental procedures

Synthesis of (2R,3R,4R)-2-(acetoxymethyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate 236
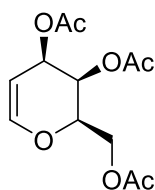
Method A: HBr in glacial acetic acid (33% w/w, 0.07 mol) was added dropwise at 0 °C to a suspension of D-galactose **237** (10 g, 0.06 mol) in acetic anhydride (37 ml). After the addition, the reaction mixture was slowly warmed to room temperature and stirred for another 2 h. Additional HBr in glacial acetic acid (33% w/w, 0.26 mol) was added dropwise and the reaction mixture was stirred overnight at room temperature, after which it was cooled to 0 °C and anhydrous NaOAc (20.03 g, 0.24 mol) was added. In another flask, CuSO$_4$·5H$_2$O (1.66 g, 6.66 mmol) and zinc dust (124.86 g, 1.91 mol) were suspended in a buffer of NaOAc·3H$_2$O

(94.42 g, 0.69 mol), water (100 ml), and acetic acid (150 ml), and the above solution was added to it while stirring vigorously. After stirring overnight at room temperature, the reaction mixture was filtered through Celite. The residue was washed with ethyl acetate. The filtrate was washed with water, saturated $NaHCO_3$ solution and water, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography on silica gel (pentane/diethyl ether 2:1) yielded galactal **236** as a pale-yellow oil (4.54 g, 30%). The analytical data for compound **236** is given below.

Method B: To a suspension of D-galactose **237** (25 g, 0.14 mol) in pyridine (140 ml, 1.73 mol) were added acetic anhydride (98 ml, 1.04 mol) and catalytic amount of DMAP (848 mg, 6.94 mmol). After stirring overnight at room temperature, the reaction mixture was quenched with methanol and diluted with ethyl acetate. After separation of the phases, the organic layer was washed with water, 1 M HCl solution, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude pentaacetylgalactose **238** (57.03 g) was used in the next reaction without further purification. The analytical data for compound **238** is given below.

PBr_3 (34.67 ml, 0.37 mol) was added dropwise at 0 °C to a solution of pentaacetylgalactose **238** (57.03 g, 0.15 mol) in a mixture of DCM (200 ml) and water (14 ml). After the addition, the mixture was slowly warmed to room temperature. After stirring for 1.5 h, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant crude product **239** (50.54 g) was directly used for the next step without any further purification. The analytical data for compound **239** is given below.

Compound **239** (50.54 g, 0.12 mol) was dissolved in acetone (200 ml) and saturated NaH_2PO_4 solution (100 ml). Zinc dust (100.48 g, 1.54 mol) was added to the above solution and the reaction mixture was stirred for 5 h at room temperature. Upon completion of the reaction followed by TLC, the resulting mixture was filtered and the remaining zinc was washed with ethyl acetate. The filtrate was washed with water, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel (pentane/diethyl ether 2:1) yielded galactal **236** as a pale-yellow oil (22.89 g, 61% over three steps). The analytical data for compound **236** is given below.

Method C: To a suspension of D-galactose **237** (50 g, 0.28 mol) in pyridine (279 ml, 3.47 mol) were added acetic anhydride (196 ml, 2.08 mol) and catalytic amount of DMAP (1.70 g,

13.88 mmol). After stirring overnight at room temperature, the reaction mixture was quenched with methanol and diluted with ethyl acetate. After separation of the phases, the organic layer was washed with water, 1 M HCl solution, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude pentaacetylgalactose **238** (107.74 g) was used in the next reaction without further purification. The analytical data for compound **238** is given below.

HBr in glacial acetic acid (33% w/w, 2.07 mol) was added at room temperature to pentaacetylgalactose **238** (107.74 g, 0.28 mol). The reaction was stirred for 1 h and diluted with DCM. The organic phase was washed with water, saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resultant crude product **239** (106.24 g) was directly used for the next step without any further purification. The analytical data for compound **239** is given below.

Compound **239** (106.24 g, 0.26 mol) was dissolved in acetone (300 ml) and saturated NaH_2PO_4 solution (150 ml). Zinc dust (211.22 g, 3.23 mol) was added to the above solution and the reaction mixture was stirred for 5 h at room temperature. Upon completion of the reaction followed by TLC, the resulting mixture was filtered and the remaining zinc was washed with ethyl acetate. The filtrate was washed with water, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel (pentane/diethyl ether 2:1) yielded galactal **236** as a pale-yellow oil (49.72 g, 66% over three steps). The analytical data for compound **236** is given below.

Analytical data for compound **238**:

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 6.38 – 6.35 (m, 1H), 5.50 – 5.48 (m, 1H), 5.33 – 5.31 (m, 2H), 4.36 – 4.31 (m, 1H), 4.13 – 4.04 (m, 2H), 2.16 (s, 3H), 2.15 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H)

^{13}C-NMR (CDCl$_3$, 100 MHz): δ = 170.5, 170.3, 170.3, 170.0, 169.1, 89.8, 68.9, 67.5, 67.5, 66.5, 61.4, 21.0, 20.8, 20.8, 20.7, 20.7

The analytical data agree with those in the literature[157].

Analytical data for compound **239**:

¹H-NMR (CDCl₃, 600 MHz): δ = 6.69 (d, *J* = 4.0 Hz, 1H), 5.51 (dd, *J* = 3.3, 1.1 Hz, 1H), 5.40 (dd, *J* = 10.7, 3.3 Hz, 1H), 5.04 (dd, *J* = 10.7, 4.0 Hz, 1H), 4.50 – 4.46 (m, 1H), 4.18 (dd, *J* = 11.5, 6.4 Hz, 1H), 4.11 (dd, *J* = 11.5, 6.8 Hz, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 170.5, 170.2, 170.1, 169.9, 88.2, 71.2, 68.1, 67.9, 67.1, 61.0, 20.9, 20.8, 20.7, 20.7

The analytical data agree with those in the literature[158].

Analytical data for compound **236**:

¹H-NMR (CDCl₃, 600 MHz): δ = 6.43 (dd, *J* = 6.3, 1.7 Hz, 1H), 5.54 – 5.50 (m, 1H), 5.42 – 5.38 (m, 1H), 4.70 (ddd, *J* = 6.3, 2.7, 1.5 Hz, 1H), 4.32 – 4.27 (m, 1H), 4.24 (dd, *J* = 11.6, 7.4 Hz, 1H), 4.19 (dd, *J* = 11.6, 5.3 Hz, 1H), 2.10 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 170.6, 170.3, 170.2, 145.5, 98.9, 72.9, 64.0, 63.8, 62.0, 20.9, 20.8, 20.7

IR (ATR): ṽ = 2967 (w), 1737 (s), 1651 (m), 1435 (w), 1370 (m), 1213 (s), 1147 (m), 1079 (m), 1062 (m), 1030 (s), 986 (m), 965 (m), 922 (m), 895 (m), 863 (w), 836 (w), 812 (w), 745 (w), 716 (w), 686 (w), 669 (w), 642 (w), 624 (w), 604 (w), 566 (w), 544 (w), 495 (w), 477 (w), 455 (w), 409 (w)

HRMS (ESI) (m/z) [C₁₂H₁₆O₇Na]⁺ = [M+Na]⁺: calcd. 295.0794, found 295.0784

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -15° (c = 1.1 in CHCl₃)

The analytical data agree with those in the literature[159].

Synthesis of [(2*R*,3*R*,6*R*)-3-acetoxy-6-allyl-3,6-dihydro-2*H*-pyran-2-yl]methyl acetate 235
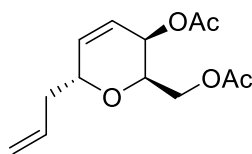
A solution of galactal **236** (16.82 g, 0.06 mol) in acetonitrile (150 ml) was cooled to 0 °C, and allyltrimethylsilane (14.71 ml, 0.09 mol) and trimethylsilyltriflate (13.45 ml, 0.07 mol) were

added to it. Saturated NaHCO$_3$ solution was added after 45 min, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO$_4$ and the solvent was removed *in vacuo*. Purification of the residue by column chromatography on silica gel (pentane/diethyl ether 3:1) gave compound **235** as a colourless oil (14.88 g, 95%).

Note: In order to fully characterize the product, the crude mixture was purified as described above. However, this purification step can be omitted, since the purity of the crude compound was high enough to be directly used in the following reaction.

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 6.04 (dd, *J* = 10.3, 3.0 Hz, 1H), 5.97 (ddd, *J* = 10.3, 5.1, 2.1 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.15 – 5.08 (m, 2H), 5.06 (dd, *J* = 5.1, 2.6 Hz, 1H), 4.37 – 4.32 (m, 1H), 4.22 – 4.15 (m, 2H), 4.14 – 4.10 (m, 1H), 2.46 – 2.39 (m, 1H), 2.31 – 2.25 (m, 1H), 2.07 (s, 3H), 2.05 (s, 3H)

^{13}C-NMR (CDCl$_3$, 150 MHz): δ = 170.9, 170.7, 134.9, 134.0, 122.1, 117.8, 72.4, 68.1, 64.0, 63.1, 36.9, 21.0, 20.9

IR (ATR): ṽ = 3656 (w), 3078 (w), 3043 (w), 2980 (w), 2890 (w), 1733 (s), 1642 (w), 1436 (w), 1370 (m), 1223 (s), 1189 (m), 1150 (w), 1079 (m), 1046 (m), 1026 (m), 982 (w), 955 (m), 912 (m), 863 (w), 834 (w), 799 (w), 750 (m), 645 (w), 605 (w), 560 (w), 519 (w), 509 (w), 481 (w), 453 (w), 429 (w)

HRMS (ESI) (m/z) [C$_{13}$H$_{18}$O$_5$Na]$^+$ = [M+Na]$^+$: calcd. 277.1052, found 277.1044

$[\alpha]_D^{20}$ = -241° (c = 1.2 in CHCl$_3$)

The analytical data agree with those in the literature[160].

Synthesis of (2*R*,3*R*,6*R*)-6-allyl-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-ol 234
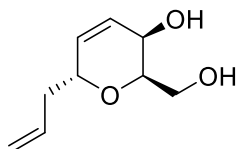
Acetate **235** (14.41 g, 0.06 mol) was dissolved in methanol (200 ml) and K$_2$CO$_3$ (1.57 g, 11.33 mmol) was added to the solution. The reaction mixture was stirred for 2 h at room temperature. It was quenched with freshly prepared saturated NH$_4$Cl solution and diluted with ethyl acetate. After separation of the phases, the aqueous layer was extracted multiple times

with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification of the crude material by column chromatography on silica gel (*n*-hexane/ethyl acetate 1:1) gave diol **234** as white crystals (9.49 g, 98%).

Note: In order to fully characterize the product, the crude mixture was purified as described above. However, this purification step can be omitted, since the purity of the crude compound was high enough to be directly used in the following reaction.

¹H-NMR (CDCl₃, 600 MHz): δ = 6.01 (ddd, *J* = 10.2, 5.5, 2.0 Hz, 1H), 5.92 (dd, *J* = 10.2, 3.2 Hz, 1H), 5.82 (ddt, *J* = 17.1,10.1, 7.0 Hz, 1H), 5.13 – 5.07 (m, 2H), 4.31 – 4.26 (m, 1H), 3.89 (dd, *J* = 5.5, 1.9 Hz, 1H), 3.85 – 3.75 (m, 3H), 2.68 (s br, 2H), 2.46 – 2.38 (m, 1H), 2.30 – 2.23 (m, 1H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 134.4, 132.9, 126.3, 117.7, 72.8, 71.9, 62.8, 62.8, 36.8

IR (ATR): ṽ = 3360 (w br), 3262 (w br), 3069 (w), 3030 (w), 2968 (w), 2933 (w), 2914 (w), 2873 (w), 1995 (w), 1835 (w), 1724 (w), 1704 (w), 1637 (w), 1435 (w), 1408 (w), 1385 (w), 1360 (w), 1347 (w), 1329 (w), 1297 (w), 1257 (w), 1227 (w), 1186 (w), 1140 (w), 1115 (w), 1102 (w), 1061 (m), 1020 (m), 1004 (w), 982 (w), 963 (w), 929 (w), 914 (m), 864 (m), 801 (w), 740 (m), 695 (w), 660 (w), 618 (w), 565 (w), 515 (w), 490 (w), 467 (w), 413 (w)

HRMS (ESI) (m/z) [C₉H₁₄O₃Na]⁺ = [M+Na]⁺: calcd. 193.0841, found 193.0834

Mp = 51 – 53 °C

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -286° (c = 1.2 in CHCl₃)

The analytical data agree with those in the literature[67].

Synthesis of {[(2*R*,3*R*,6*R*)-6-allyl-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-3,6-dihydro--2*H*-pyran-3-yl]oxy}(*tert*-butyl)dimethylsilane 233
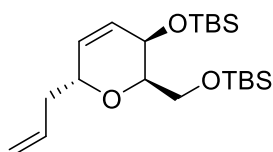
Imidazole (10.12 g, 0.15 mol) and TBSCl (21.01 g, 0.14 mol) were added to a solution of diol **234** (7.91 g, 0.05 mol) in DCM (75 ml). The reaction mixture was stirred overnight at room

temperature. Upon completion of the reaction (indicated by TLC), water was added, the layers were separated, and the aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude material by column chromatography on silica gel (pentane/diethyl ether 50:1) afforded compound **233** as a colourless oil (17.68 g, 95%).

1H-NMR (CDCl₃, 600 MHz): δ = 5.90 – 5.79 (m, 3H), 5.13 – 5.05 (m, 2H), 4.25 (dd, *J* = 7.9, 5.9 Hz, 1H), 4.10 (dt, *J* = 3.1, 1.6 Hz, 1H), 3.82 – 3.70 (m, 3H), 2.43 – 2.36 (m, 1H), 2.27 – 2.21 (m, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H)

13C-NMR (CDCl₃, 150 MHz): δ = 134.8, 131.7, 127.2, 117.2, 74.1, 71.3, 63.4, 61.8, 37.8, 26.1, 26.0, 18.5, 18.4, -4.1, -4.5, -5.1, -5.2

IR (ATR): ṽ = 3079 (w), 3035 (w), 2955 (w), 2929 (w), 2886 (w), 2857 (w), 1644 (w), 1541 (w), 1472 (w), 1436 (w), 1389 (w), 1361 (w), 1347 (w), 1327 (w), 1252 (m), 1189 (w), 1144 (w), 1094 (m), 1062 (m), 1017 (w), 1005 (w), 938 (w), 914 (w), 874 (m), 832 (s), 773 (s), 728 (w), 677 (w), 666 (w), 639 (w), 603 (w), 573 (w), 516 (w), 484 (w), 457 (w), 419 (w)

HRMS (ESI) (m/z) $[C_{21}H_{43}O_3Si]^+ = [M+H]^+$: calcd. 399.2751, found 399.2747

$[\alpha]_D^{20}$ = -133° (c = 1.0 in CHCl₃)

Synthesis of [(2R,3R,6R)-6-allyl-3-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2H-pyran--2-yl]methanol 232
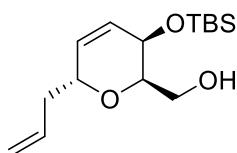
Method A: Water (1 ml) and acetic acid (3 ml) were added to a solution of compound **233** (200 mg, 0.50 mmol) in THF (1 ml) at 0 °C. The reaction was stirred for 30 min at 0 °C and was allowed to slowly warm to room temperature. After 2 h, the volatiles were removed *in vacuo* and the excess water was removed by azeotropic distillation with toluene. The crude residue was purified by column chromatography on silica gel (pentane/diethyl ether 3:1) to yield alcohol **232** as a colourless oil (50 mg, 35%).

Method B: Water (1 ml) and formic acid (2 ml) were added to a solution of compound **233** (280 mg, 0.70 mmol) in acetonitrile (7 ml). After 20 min the reaction was quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography on silica gel (pentane/diethyl ether 3:1) yielded alcohol **232** as a colourless oil (103 mg, 52%).

Method C: Compound **233** (200 mg, 0.50 mmol) was dissolved in methanol (5 ml) and PPTS (164 mg, 0.65 mmol) was added to this solution at ambient temperature. After 2.5 h the reaction was quenched by the addition of water and diluted with diethyl ether. The layers were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 3:1) to obtain alcohol **232** as a colourless oil (78 mg, 55%).

Method D: CSA (1.03 g, 4.43 mmol) was added to a solution of compound **233** (17.68 g, 0.04 mol) in a 1:1 mixture of DCM (100 ml) and methanol (100 ml) at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was quenched with triethylamine (247 ml, 1.77 mol) and was allowed to slowly warm to room temperature. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (pentane/diethyl ether 3:1) to give primary alcohol **232** as a colourless oil (8.84 g, 70%).

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 5.87 – 5.78 (m, 3H), 5.15 – 5.07 (m, 2H), 4.29 – 4.25 (m, 1H), 4.20 – 4.16 (m, 1H), 3.90 (dt, J = 7.8, 3.9 Hz, 1H), 3.80 (ddd, J = 55.1, 11.4, 5.9 Hz, 2H), 2.41 – 2.35 (m, 1H), 2.29 – 2.24 (m, 1H), 1.99 (s br, 1H), 0.89 (s, 9H), 0.09 (s, 6H)

^{13}C-NMR (CDCl$_3$, 150 MHz): δ = 134.5, 131.5, 126.9, 117.6, 73.2, 70.9, 64.5, 62.3, 37.9, 25.9, 18.3, -4.1, -4.6

IR (ATR): ṽ = 3441 (w br), 3077 (w), 3036 (w), 2954 (w), 2929 (w), 2887 (w), 2857 (w), 1642 (w), 1469 (w), 1436 (w), 1409 (w), 1390 (w), 1361 (w), 1348 (w), 1324 (w), 1253 (w), 1188 (w), 1073 (m), 1004 (w), 919 (m), 878 (m), 834 (m), 799 (w), 774 (m), 728 (w), 678 (w), 649 (w), 606 (w), 570 (w), 518 (w), 456 (w), 418 (w)

HRMS (ESI) (m/z) $[C_{15}H_{28}O_3SiNa]^+$ = $[M+Na]^+$: calcd. 307.1705, found 307.1696

$[\alpha]_D^{20}$ = -128° (c = 1.1 in CHCl$_3$)

Synthesis of (2*S*,3*R*,6*R*)-6-allyl-3-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-2-carbaldehyde 231
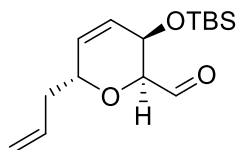
Method A: NaHCO$_3$ (390 mg, 4.64 mmol) and DMP (984 mg, 2.32 mmol) were added to a solution of alcohol **232** (330 mg, 1.16 mmol) in DCM (8 ml) at ambient temperature. After 3 h the reaction was quenched with a saturated solution of Na$_2$S$_2$O$_3$. The layers were separated and the aqueous phase was extracted with DCM. The combined organic extracts were washed with water and brine, dried over MgSO$_4$ and concentrated under reduced pressure. Column chromatography on silica gel (pentane/diethyl ether 15:1) afforded aldehyde **231** as a pale-yellow oil (191 mg, 59%).

Method B: Oxalyl chloride (4.80 ml, 0.06 mol) was dissolved in DCM (100 ml) and the solution was cooled to −78 °C. DMSO (5.96 ml, 0.08 mol) dissolved in DCM (40 ml) was added to this solution dropwise. After stirring the reaction mixture for 45 min at −78 °C, a solution of alcohol **232** (7.96 g, 0.03 mol) in DCM (100 ml) was added dropwise and the stirring was continued for 1 h at −78 °C. Finally, triethylamine (27.30 ml, 0.20 mol) was added dropwise and after 20 min the reaction mixture was slowly warmed to room temperature. It was quenched with 5% KHSO$_4$ solution and the aqueous layer was extracted with DCM. The combined organic layers were dried over MgSO$_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 15:1) to give aldehyde **231** as a pale-yellow oil (6.92 g, 88%).

Note: In order to fully characterize the product, the crude mixture was purified as described above. However, it is better to omit this purification step, since the compound has been observed to decompose during both purification and storage.

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 9.75 (s, 1H), 5.87 – 5.77 (m, 3H), 5.13 – 5.07 (m, 2H), 4.52 – 4.48 (m, 1H), 4.47 – 4.44 (m, 1H), 4.19 (d, *J* = 4.5 Hz, 1H), 2.39 – 2.32 (m, 1H), 2.31 – 2.25 (m, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H)

^{13}C-NMR (CDCl$_3$, 150 MHz): δ = 202.0, 133.9, 131.0, 127.0, 117.8, 78.2, 71.6, 64.4, 38.4, 25.8, 18.2, -4.3, -4.7

IR (ATR): ṽ = 3078 (w), 3039 (w), 2954 (w), 2930 (w), 2887 (w), 2857 (w), 1737 (w), 1642 (w), 1471 (w), 1436 (w), 1410 (w), 1389 (w), 1362 (w), 1346 (w), 1321 (w), 1254 (w), 1190 (w), 1099 (m), 1079 (m), 1029 (w), 990 (m), 937 (w), 916 (w), 863 (m), 836 (s), 812 (w), 776 (s), 726 (w), 677 (w), 606 (w), 554 (w), 481 (w), 451 (w), 426 (w)

HRMS (ESI) (m/z) $[C_{15}H_{26}O_3SiNH_4]^+ = [M+NH_4]^+$: calcd. 300.1995, found 300.1987

$[\alpha]_D^{20}$ = -115° (c = 0.9 in CHCl$_3$)

Synthesis of {[(2R,3R,6R)-6-allyl-2-ethynyl-3,6-dihydro-2H-pyran-3-yl]oxy}(*tert*--butyl)dimethylsilane 175
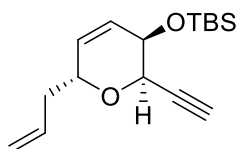
Trimethylsilyldiazomethane (2.0 M in hexane) (3.16 ml, 6.32 mmol) was dissolved in THF (20 ml) and the solution was cooled to −78 °C. At this temperature a 2.5 M solution of *n*-BuLi in hexane (2.53 ml, 6.32 mmol) was added dropwise. After stirring for 30 min at −78 °C, a solution of aldehyde **231** (1.19 g, 4.21 mmol) in THF (20 ml) was added. After stirring for 1 h, the mixture was slowly warmed to room temperature and stirred for an additional 3 h. Finally, the reaction was quenched with freshly prepared saturated NH$_4$Cl solution and the aqueous layer was extracted with ethyl acetate. The combined organic phases were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. After purification by column chromatography on silica gel (pentane/diethyl ether 100:1) alkyne **175** was obtained as a colourless oil (906 mg, 77%).

¹H-NMR (CDCl$_3$, 400 MHz): δ = 5.82 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.75 – 5.71 (m, 1H), 5.69 – 5.64 (m, 1H), 5.16 – 5.07 (m, 2H), 4.75 (ddd, *J* = 6.0, 2.3, 0.9 Hz, 1H), 4.49 – 4.39 (m, 2H), 2.37 (d, *J* = 2.3 Hz, 1H), 2.34 – 2.28 (m, 2H), 0.91 (s, 9H), 0.11 (s, 3H) , 0.10 (s, 3H)

**¹³C-NMR** (CDCl$_3$, 100 MHz): δ = 134.1, 129.6, 128.6, 117.6, 79.4, 74.7, 69.7, 67.8, 64.9, 39.3, 25.9, 18.3, -4.5, -4.6

IR (ATR): ṽ = 3732 (w), 3311 (w), 3078 (w), 3040 (w), 2956 (w), 2929 (w), 2889 (w), 2857 (w), 1643 (w), 1470 (w), 1433 (w), 1389 (w), 1359 (w), 1348 (w), 1320 (w), 1254 (m), 1188 (w), 1110 (m), 1074 (m), 1006 (w), 995 (w), 975 (w), 956 (w), 940 (w), 914 (w), 888 (w), 866 (m), 836 (m), 801 (w), 774 (m), 679 (m), 656 (m), 627 (m), 571 (w), 520 (w), 442 (w), 420 (w)

HRMS (ESI) (m/z) $[C_{16}H_{27}O_2Si]^+$ = $[M+H]^+$: calcd. 279.1780, found 279.1780

$[\alpha]_D^{20}$ = -51° (c = 0.9 in CHCl$_3$)

Synthesis of (2*S*,3*S*)-5-[(2*R*,3*R*,6*R*)-6-allyl-3-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro--2*H*-pyran-2-yl]-3-methylpent-4-yn-2-ol 186
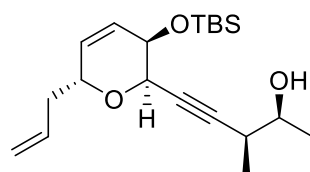
A 2.5 M solution of *n*-BuLi in hexane (1.98 ml, 4.96 mmol) was added dropwise to a solution of alkyne **175** (460 mg, 1.65 mmol) in THF (30 ml) at −78 °C. After stirring the reaction mixture for 20 min, BF$_3$·Et$_2$O (0.62 ml, 4.96 mmol) was added dropwise. After 15 min, epoxide **157** (0.21 ml, 2.31 mmol) was added to the above solution and the stirring was continued for another 3 h at −78 °C. A saturated solution of NH$_4$Cl solution was added upon completion of the reaction (indicated by TLC). The mixture was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (pentane/diethyl ether 9:1) to give homopropargylic alcohol **186** as a colourless oil (411 mg, 71%).

¹H-NMR (CDCl$_3$, 400 MHz): δ = 5.81 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.72 – 5.67 (m, 1H), 5.64 – 5.59 (m, 1H), 5.15 – 5.07 (m, 2H), 4.76 – 4.71 (m, 1H), 4.44 – 4.37 (m, 2H), 3.60 – 3.51 (m, 1H), 2.49 – 2.40 (m, 1H), 2.30 (dd, *J* = 6.9, 6.2 Hz, 2H), 2.05 (s br, 1H), 1.21 (dd, *J* = 6.1, 4.9 Hz, 3H), 1.17 (dd, *J* = 7.0, 3.0 Hz, 3H), 0.91 (s, 3H), 0.90 (s, 6H), 0.09 (s, 6H)

¹³C-NMR (CDCl$_3$, 100 MHz): δ = 134.2, 129.4, 128.8, 117.6, 87.9, 78.8, 71.2, 69.6, 67.9, 65.4, 39.3, 35.3, 25.9, 21.2, 18.3, 17.5, -4.5, -4.6

IR (ATR): ṽ = 3485 (w br), 3078 (w), 3038 (w), 2956 (w), 2930 (w), 2886 (w), 2857 (w), 1643 (w), 1464 (w), 1389 (w), 1348 (w), 1319 (w), 1254 (w), 1179 (w), 1164 (w), 1107 (m), 1068 (m), 1004 (w), 993 (w), 962 (w), 938 (w), 914 (w), 896 (w), 865 (m), 835 (m), 775 (m), 745 (w), 729 (w), 693 (w), 678 (w), 660 (w), 617 (w), 591 (w), 568 (w), 553 (w), 538 (w), 509 (w), 478 (w)

HRMS (ESI) (m/z) $[C_{20}H_{34}O_3SiNa]^+$ = $[M+Na]^+$: calcd. 373.2175, found 373.2168

$[\alpha]_D^{20}$ = -53° (c = 1.1 in CHCl$_3$)

Synthesis of (2*S*,3*S*)-5-((2*R*,3*R*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)-6-(2-(tributyl-stannyl)propyl)-3,6-dihydro-2*H*-pyran-2-yl)-3-methylpent-4-yn-2-ol 197
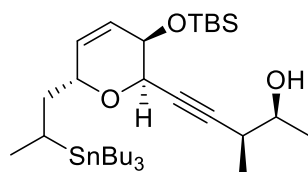
Bis(triphenylphosphine)palladium(II) chloride (4 mg, 0.01 mmol) was added to a solution of alcohol **186** in THF (5 ml). To this solution, *n*-Bu$_3$SnH (0.09 ml, 0.34 mmol) was added dropwise over 10 min. After stirring for 2 h at room temperature, the mixture was extracted with ethyl acetate. The combined organic layers were washed with freshly prepared saturated NH$_4$Cl solution, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane/diethyl ether 9:1) to give compound **197** as a colourless oil (32 mg, 17%).

¹H-NMR (CDCl$_3$, 400 MHz): δ = 5.69 – 5.64 (m, 1H), 5.61 – 5.56 (m, 1H), 4.73 – 4.69 (m, 1H), 4.42 – 4.38 (m, 1H), 4.36 – 4.30 (m, 1H), 3.59 – 3.52 (m, 1H), 2.48 – 2.41 (m, 1H), 1.67 – 1.49 (m, 5H), 1.49 – 1.43 (m, 6H), 1.43 – 1.33 (m, 1H), 1.32 – 1.25 (m, 7H), 1.21 (t, *J* = 6.3 Hz, 3H), 1.18 (dd, *J* = 6.8, 5.5 Hz, 3H), 0.92 – 0.87 (m, 18H), 0.81 (t, *J* = 8.1 Hz, 6H), 0.10 (s, 6H)

¹³C-NMR (CDCl$_3$, 100 MHz): δ = 129.2, 127.0, 86.5, 77.9, 70.0, 68.6, 66.6, 64.4, 38.5, 34.2, 28.2, 26.4, 24.8, 21.5, 20.0, 17.1, 16.4, 12.7, 7.8, 7.7, -5.7, -5.8

HRMS (ESI) (m/z) $[C_{32}H_{62}O_3SiSnNa]^+$ = $[M+Na]^+$: calcd. 657.3414, found 657.3408

Synthesis of 1-[(2*R*,3*R*,6*R*)-6-allyl-3-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-2-yl]ethan-1-ol 215
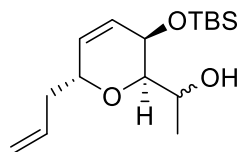
A 3.0 M solution of methylmagnesium bromide in diethyl ether (8.64 ml, 25.92 mmol) was added dropwise to a stirred solution of aldehyde **231** (2.44 g, 8.64 mmol) in THF (50 ml) at −78 °C. The solution was stirred at −78 °C for 1 h and it was slowly warmed to room temperature. The reaction mixture was quenched with 5% KHSO$_4$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (pentane/diethyl ether 10:1) to afford alcohol **215** as a colourless oil and as a mixture of diastereomers (2.36 g, 92%, 5:1 dr).

The analytical data for the major isomer is as follows:

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 5.93 – 5.77 (m, 3H), 5.16 – 5.05 (m, 2H), 4.37 (dd, *J* = 9.1, 5.2 Hz, 1H), 4.06 – 3.97 (m, 2H), 3.34 (dd, *J* = 6.5, 2.3 Hz, 1H), 2.80 (s br, 1H), 2.46 – 2.36 (m, 1H), 2.27 – 2.19 (m, 1H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H)

^{13}C-NMR (CDCl$_3$, 150 MHz): δ = 134.8, 132.8, 126.1, 117.6, 75.9, 72.5, 67.5, 63.9, 36.8, 26.0, 18.2, 18.0, -3.3, -4.4

IR (ATR): ṽ = 3496 (w br), 3077 (w), 3036 (w), 2988 (w), 2955 (w), 2929 (w), 2885 (w), 2857 (w), 1642 (w), 1470 (w), 1465 (w), 1436 (w), 1404 (w), 1391 (w), 1360 (w), 1342 (w), 1319 (w), 1253 (w), 1190 (w), 1167 (w), 1112 (m), 1068 (m), 1045 (m), 1005 (w), 989 (w), 961 (w), 939 (m), 911 (m), 888 (w), 864 (w), 834 (m), 809 (w), 774 (m), 730 (w), 684 (w), 648 (w), 607 (w), 573 (w), 532 (w), 522 (w), 500 (w), 487 (w), 454 (w)

HRMS (ESI) (m/z) [C$_{16}$H$_{31}$O$_3$Si]$^+$ = [M+H]$^+$: calcd. 299.2042, found 299.2043

$[\alpha]_D^{20}$ = -182° (c = 1.0 in CHCl$_3$, 5:1 dr)

Synthesis of 1-[(2*S*,3*R*,6*R*)-6-allyl-3-[(*tert*-butyldimethylsilyl)oxy]-3,6-dihydro-2*H*-pyran-
-2-yl]ethan-1-one 205
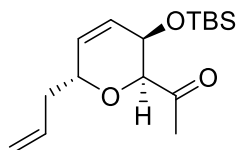
Alcohol **215** (1.28 g, 4.29 mmol) was dissolved in DCM (40 ml) at room temperature. NaHCO$_3$ (1.44 g, 17.15 mmol) and DMP (3.64 g, 8.58 mmol) were added to this solution and the mixture was stirred for 4 h. After completion of the reaction (indicated by TLC), saturated Na$_2$S$_2$O$_3$ solution was added and the stirring was continued for additional 10 min. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with saturated NaHCO$_3$ solution and brine, dried over MgSO$_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (pentane/diethyl ether 50:1) afforded ketone **205** as a colourless oil (1.08 mg, 85%).

¹H-NMR (CDCl$_3$, 400 MHz): δ = 5.94 – 5.89 (m, 2H), 5.83 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.14 – 5.05 (m, 2H), 4.48 – 4.43 (m, 1H), 4.27 – 4.24 (m, 1H), 4.10 (d, *J* = 2.7 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.30 – 2.20 (m, 1H), 2.25 (s, 3H), 0.84 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H)

¹³C-NMR (CDCl$_3$, 100 MHz): δ = 209.6, 134.4, 132.3, 125.8, 117.6, 78.2, 72.8, 64.0, 36.9, 28.2, 25.9, 18.2, -4.0, -4.7

IR (ATR): ṽ = 3078 (w), 3038 (w), 3005 (w), 2955 (w), 2930 (w), 2894 (w), 2858 (w), 1719 (w), 1642 (w), 1471 (w), 1415 (w), 1354 (w), 1317 (w), 1254 (w), 1229 (w), 1188 (w), 1109 (m), 1069 (m), 1027 (w), 997 (w), 963 (w), 937 (w), 900 (m), 835 (m), 803 (w), 776 (m), 749 (w), 726 (w), 684 (w), 648 (w), 617 (w), 600 (w), 564 (w), 546 (w), 510 (w), 495 (w), 466 (w), 442 (w)

HRMS (ESI) (m/z) [C$_{16}$H$_{28}$O$_3$SiNa]$^+$ = [M+Na]$^+$: calcd. 319.1705, found 319.1704

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -193° (c = 1.2 in CHCl$_3$)

Synthesis of {[(2*R*,3*R*,6*R*)-6-allyl-2-[(*Z*)-1-iodoprop-1-en-2-yl]-3,6-dihydro-2*H*-pyran--3-yl]oxy}(*tert*-butyl)dimethylsilane 227
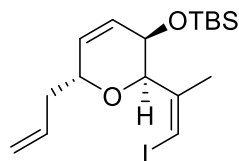
A solution of ketone **205** (150 mg, 0.51 mmol) and iodoform (598 mg, 1.52 mmol) in THF (4 ml) was added to a solution of chromium(II) chloride (684 mg, 5.57 mmol) in THF (3 ml). The mixture was stirred overnight at room temperature. After completion of the reaction (indicated by TLC) the reaction mixture was quenched with water and stirred for another 10 min. The mixture was extracted with diethyl ether, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture ($E/Z = 1:13$, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 50:1) to yield *Z*-vinyl iodide **227** as a colourless oil (162 mg, 76%).

^{1}H-NMR ((CD_3)$_2$CO, 600MHz): δ = 6.34 – 6.33 (m, 1H), 5.98 – 5.92 (m, 2H), 5.86 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.10 – 5.00 (m, 2H), 4.33 (d, J = 1.8 Hz, 1H), 4.30 – 4.26 (m, 1H), 4.20 – 4.18 (m, 1H), 2.43 – 2.37 (m, 1H), 2.30 – 2.24 (m, 1H), 1.86 (s, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H)

^{13}C-NMR ((CD_3)$_2$CO, 150 MHz): δ = 145.7, 135.9, 132.7, 127.3, 117.2, 78.8, 76.3, 73.6, 64.8, 37.5, 26.3, 22.5, 18.6, -3.7, -4.3

IR (ATR): ṽ = 3077 (w), 3035 (w), 2953 (w), 2928 (w), 2886 (w), 2856 (w), 1641 (w), 1625 (w), 1573 (w), 1554 (w), 1469 (w), 1435 (w), 1413 (w), 1390 (w), 1359 (w), 1324 (w), 1283 (w), 1252 (w), 1190 (w), 1109 (m), 1068 (m), 1031 (w), 1005 (w), 960 (w), 915 (m), 891 (w), 868 (w), 834 (m), 809 (w), 772 (m), 750 (w), 730 (w), 675 (w), 645 (w), 612 (w), 588 (w), 567 (w), 520 (w), 505 (w), 470 (w), 446 (w), 419 (w)

HRMS (ESI) (m/z) [$C_{17}H_{30}IO_2Si$]$^+$ = [M+H]$^+$: calcd. 421.1060, found 421.1056

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -186° (c = 1.1 in CHCl$_3$)

Synthesis of {[(2*R*,3*R*,6*R*)-6-allyl-2-[(4*S*,5*S*,*Z*)-5-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-hex-2-en-2-yl]-3,6-dihydro-2*H*-pyran-3-yl]oxy}(*tert*-butyl)dimethylsilane 211
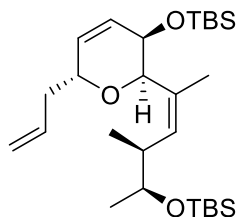
Method A: LiHMDS (1 M in THF) (0.17 ml, 0.17 mmol) was slowly added at –42 °C to a solution of sulfone **210** (50 mg, 0.12 mmol) in DCM (2 ml). After 30 min cerium(III) chloride (12 mg, 0.05 mmol) was added and subsequently a solution of ketone **205** (37 mg, 0.12 mmol) in DCM (3 ml) was added dropwise. The reaction mixture was stirred for 1 h before it was allowed to slowly warm to room temperature. The reaction was quenched with a freshly prepared saturated NH$_4$Cl solution and the mixture was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture (*E*/*Z* = 1:16, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 100:1) to yield compound **211** as a colourless oil (5 mg, 8%).

Method B: LiHMDS (1 M in THF) (0.35 ml, 0.35 mmol) was slowly added at –78 °C to a solution of sulfone **210** (100 mg, 0.25 mmol) in THF (6 ml). After 1 h a solution of ketone **205** (74 mg, 0.25 mmol) in THF (8 ml) was added dropwise. The reaction mixture was stirred for 4 h before it was allowed to slowly warm to room temperature. After this, water was added and the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture (*E*/*Z* = 1:17, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 100:1) to yield compound **211** as a colourless oil (21 mg, 18%).

^{1}H-NMR ((CD$_3$)$_2$CO, 600 MHz): δ = 5.97 – 5.82 (m, 3H), 5.17 (d, *J* = 10.1 Hz, 1H), 5.10 – 5.00 (m, 2H), 4.61 (d, *J* = 2.6 Hz, 1H), 4.28 – 4.23 (m, 1H), 4.07 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.69 – 3.64 (m, 1H), 2.46 – 2.34 (m, 2H), 2.32 – 2.25 (m, 1H), 1.84 (s, 3H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 9H)

^{13}C-NMR ((CD$_3$)$_2$CO, 150 MHz): δ = 136.20, 134.91, 132.46, 131.70, 128.13, 116.99, 73.29, 73.06, 71.55, 67.19, 40.91, 37.71, 26.31, 26.30, 23.11, 21.70, 18.70, 18.69, 17.02, -3.81, -3.96, -4.35, -4.53

IR (ATR): ṽ = 3078 (w), 3034 (w), 2956 (w), 2929 (w), 2883 (w), 2857 (w), 1738 (w), 1642 (w), 1470 (w), 1463 (w), 1408 (w), 1389 (w), 1371 (w), 1322 (w), 1293 (w), 1252 (m), 1212 (w), 1188 (w), 1158 (w), 1095 (m), 1058 (m), 1025 (m), 1006 (w), 983 (w), 960 (w), 933 (m), 916 (m), 867 (w), 834 (m), 806 (m), 772 (m), 746 (m), 685 (w), 664 (w), 619 (w), 611 (w), 595 (w), 568 (w), 510 (w), 481 (w), 457 (w), 438 (w)

HRMS (ESI) (m/z) $[C_{27}H_{52}O_3Si_2NH_4]^+ = [M+NH_4]^+$: calcd. 498.3799, found 498.3791

$[\alpha]_D^{20}$ = -115° (c = 0.7 in CHCl₃)

Synthesis of (2R,3R,6R)-6-allyl-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-3,6-dihydro--2H-pyran-3-ol 247
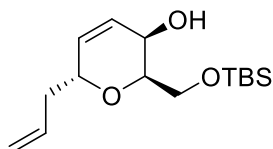
TBSCl (4.82 g, 31.99 mmol) was added to a solution of Diol **234** (4.95 g, 29.08 mmol) and imidazole (2.97 g, 43.62 mmol) in DMF (50 ml) at 0 °C. After 30 minutes, the solution was slowly warmed to room temperature, and stirred for an additional 2 h. The reaction was quenched with saturated NaHCO₃ solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the crude mixture by column chromatography on silica gel (pentane/diethyl ether 3:1) afforded compound **247** as a colourless oil (6.65 g, 80%).

¹H-NMR (CDCl₃, 400 MHz): δ = 6.05 (ddd, *J* = 10.2, 5.5, 2.0 Hz, 1H), 5.91 (dd, *J* = 10.2, 3.1 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.14 – 5.06 (m, 2H), 4.29 – 4.24 (m, 1H), 3.94 (dd, *J* = 5.5, 1.9 Hz, 1H), 3.85 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.80 (dt, *J* = 5.7, 1.9 Hz, 1H), 3.77 (dd, *J* = 9.1, 5.7 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.29 – 2.22 (m, 1H), 1.95 (s br, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 134.6, 132.9, 126.7, 117.5, 73.0, 72.0, 63.0, 62.4, 37.1, 26.0, 18.4, -5.2, -5.3

IR (ATR): ṽ = 3444 (w br), 3078 (w), 3035 (w), 2953 (w), 2929 (w), 2885 (w), 2856 (w), 1642 (w), 1469 (w), 1434 (w), 1405 (w), 1391 (w), 1362 (w), 1329 (w), 1253 (w), 1186 (w), 1144 (w), 1089 (m), 1047 (m), 996 (w), 978 (w), 963 (w), 939 (w), 914 (w), 865 (m), 833 (s), 815 (m), 775 (m), 743 (m), 689 (w), 665 (w), 598 (w), 572 (w), 515 (w), 492 (w), 458 (w), 419 (w)

HRMS (ESI) (m/z) $[C_{15}H_{29}O_3Si]^+ = [M+H]^+$: calcd. 285.1886, found 285.1877

$[\alpha]_D^{20}$ = -157° (c = 1.2 in CHCl_3)

The analytical data agree with those in the literature[95].

Synthesis of {[(2R,3R,6R)-6-allyl-3-(methoxymethoxy)-3,6-dihydro-2H-pyran-2-yl]methoxy}(tert-butyl)dimethylsilane 245
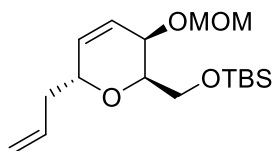
DIPEA (10.18 ml, 58.44 mmol) and MOMCl (3.99 ml, 52.60 mmol) were added to a solution of compound **247** (6.65 g, 23.38 mmol) in DCM (80 ml) at 0 °C. The reaction mixture was stirred for 40 min before it was slowly warmed to room temperature and stirred overnight. After completion of the reaction (indicated by TLC), the reaction was quenched with water. After separation of the phases, the aqueous phase was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (pentane/diethyl ether 20:1) yielded compound **245** as a colourless oil (7.44 g, 97%).

¹H-NMR (CDCl_3, 600 MHz): δ = 6.03 (ddd, J = 10.3, 5.3, 2.1 Hz, 1H), 5.94 (dd, J = 10.3, 3.0 Hz, 1H), 5.85 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.12 – 5.05 (m, 2H), 4.71 (dd, J = 8.8, 6.7 Hz, 2H), 4.32 – 4.27 (m, 1H), 3.89 (dd, J = 5.3, 2.1 Hz, 1H), 3.83 – 3.68 (m, 3H), 3.37 (s, 3H), 2.45 – 2.39 (m, 1H), 2.29 – 2.23 (m, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H)

**¹³C-NMR** (CDCl_3, 150 MHz): δ = 134.7, 133.3, 124.9, 117.3, 96.3, 72.6, 72.0, 67.1, 62.0, 55.6, 37.3, 26.0, 18.4, -5.2, -5.3

IR (ATR): ṽ = 3077 (w), 3038 (w), 2952 (w), 2929 (w), 2885 (w), 2857 (w), 2823 (w), 2775 (w), 1641 (w), 1471 (w), 1464 (w), 1439 (w), 1399 (w), 1389 (w), 1361 (w), 1327 (w), 1298 (w), 1253 (w), 1213 (w), 1188 (w), 1149 (w), 1098 (m), 1086 (m), 1037 (m), 1005 (w), 997 (w), 936 (w), 915 (w), 834 (m), 815 (w), 775 (m), 740 (w), 710 (w), 680 (w), 665 (w), 594 (w), 516 (w), 492 (w), 465 (w), 442 (w), 418 (w)

HRMS (ESI) (m/z) $[C_{17}H_{32}O_4SiNa]^+ = [M+Na]^+$: calcd. 351.1968, found 351.1959

$[\alpha]_D^{20}$ = -161° (c = 1.0 in CHCl₃)

Synthesis of (2R,3R,6R)-6-allyl-2-{[(triisopropylsilyl)oxy]methyl}-3,6-dihydro-2H-pyran--3-ol 248
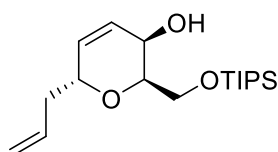
TIPSCl (10.03 ml, 46.88 mmol) was added dropwise to a solution of Diol **234** (5.32 g, 31.26 mmol) and imidazole (4.26 g, 62.51 mmol) in DCM (175 ml) at 0 °C. After stirring for 15 min, the solution was slowly warmed to room temperature and stirred for another 4 h. The reaction was quenched with a saturated solution of NaHCO₃ and extracted with DCM. The combined organic layers were washed with 1 M HCl solution and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to obtain alcohol **248** as a colourless oil (9.10 g, 89%).

¹H-NMR (CDCl₃, 600 MHz): δ = 6.06 (ddd, *J* = 10.2, 5.4, 2.0 Hz, 1H), 5.92 (dd, *J* = 10.2, 3.1 Hz, 1H), 5.86 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.13 – 5.06 (m, 2H), 4.29 – 4.25 (m, 1H), 3.99 (dd, *J* = 5.4, 1.6 Hz, 1H), 3.96 – 3.82 (m, 3H), 2.47 – 2.41 (m, 1H), 2.30 – 2.24 (m, 1H), 1.98 (s br, 1H), 1.15 – 1.06 (m, 21H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 134.6, 132.8, 126.6, 117.4, 73.0, 72.0, 63.2, 62.4, 37.2, 18.1, 12.0

IR (ATR): ṽ = 3443 (w br), 3078 (w), 3035 (w), 2941 (w), 2866 (w), 1642 (w), 1463 (w), 1435 (w), 1385 (w), 1367 (w), 1328 (w), 1251 (w), 1185 (w), 1093 (m), 1072 (m), 1047 (m), 995 (w), 980 (w), 915 (w), 881 (m), 816 (w), 779 (w), 744 (w), 680 (m), 657 (m), 573 (w), 524 (w), 494 (w), 457 (w), 444 (w), 419 (w)

HRMS (ESI) (m/z) $[C_{18}H_{34}O_3SiNa]^+ = [M+Na]^+$: calcd. 349.2175, found 349.2168

$[\alpha]_D^{20} = -135°$ (c = 1.1 in CHCl$_3$)

Synthesis of {[(2R,3R,6R)-6-allyl-3-(methoxymethoxy)-3,6-dihydro-2H-pyran-2-yl]meth-oxy}triisopropylsilane 246
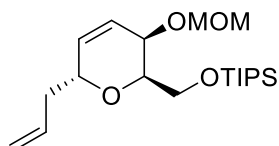
DMAP (232 mg, 1.90 mmol), DIPEA (5.78 ml, 47.39 mmol) and MOMCl (4.63 ml, 42.65 mmol) were successively added to a solution of alcohol **248** (6.19 g, 18.96 mmol) in DCM (125 ml) at room temperature and the mixture was stirred overnight. After completion of the reaction (indicated by TLC), the reaction mixture was quenched with saturated NaHCO$_3$ solution and diluted with DCM. After separation of the phases, the aqueous phase was extracted with DCM and the combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to obtain compound **246** as a colourless oil (6.73 g, 96%).

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 6.05 (ddd, *J* = 10.2, 5.4, 2.1 Hz, 1H), 5.95 (dd, *J* = 10.2, 3.0 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.13 – 5.05 (m, 2H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.72 (d, *J* = 6.7 Hz, 1H), 4.33 – 4.29 (m, 1H), 3.94 (dd, *J* = 5.4, 2.2 Hz, 1H), 3.92 – 3.76 (m, 3H), 3.38 (s, 3H), 2.47 – 2.40 (m, 1H), 2.31 – 2.25 (m, 1H), 1.14 – 1.04 (m, 21H)

^{13}C-NMR (CDCl$_3$, 150 MHz): δ = 134.7, 133.3, 125.0, 117.3, 96.4, 72.6, 72.0, 67.0, 62.3, 55.6, 37.3, 18.1, 12.0

IR (ATR): ṽ = 3078 (w), 3037 (w), 2941 (w), 2887 (w), 2866 (w), 2823 (w), 2774 (w), 1642 (w), 1464 (w), 1385 (w), 1367 (w), 1326 (w), 1251 (w), 1212 (w), 1150 (m), 1103 (m), 1088 (m), 1037 (s), 995 (m), 936 (w), 915 (m), 881 (m), 844 (w), 785 (m), 740 (w), 681 (m), 658 (m), 567 (w), 550 (w), 523 (w), 494 (w), 458 (w), 443 (w), 419 (w)

HRMS (ESI) (m/z) $[C_{20}H_{38}O_4SiNa]^+ = [M+Na]^+$: calcd. 393.2437, found 393.2424

$[\alpha]_D^{20} = -124°$ (c = 1.1 in CHCl$_3$)

Synthesis of [(2*R*,3*R*,6*R*)-6-allyl-3-(methoxymethoxy)-3,6-dihydro-2*H*-pyran-2-yl]methanol 244
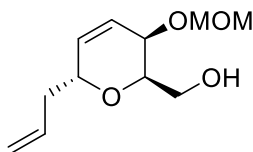
Method A: A 1 M solution of TBAF in THF (45.29 ml, 45.29 mmol) was added dropwise to a solution of compound **245** (7.44 g, 22.65 mmol) in THF (100 ml) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C before it was slowly warmed to room temperature and stirred for another 1 h. Upon completion of the reaction (indicated by a TLC), the reaction mixture was quenched with water and diluted with ethyl acetate. After separation of the phases, the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (pentane/diethyl ether 1:2) to afford alcohol **244** as a colourless oil (4.64 g, 96%).

Method B: A 1 M solution of TBAF in THF (35.19 ml, 35.19 mmol) was added dropwise to a solution of compound **246** (6.52 g, 17.59 mmol) in THF (75 ml) at 0 °C. The reaction mixture was stirred for 2.5 h at 0 °C, and quenched with a freshly prepared NH_4Cl solution before it was diluted with water and diethyl ether. After separation of the phases, the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (pentane/diethyl ether 1:3) to yield alcohol **244** as a colourless oil (3.55 g, 94%).

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 6.02 (ddd, *J* = 10.3, 4.6, 1.8 Hz, 1H), 5.98 (dd, *J* = 10.3, 2.7 Hz, 1H), 5.84 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.15 – 5.08 (m, 2H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.36 – 4.32 (m, 1H), 3.95 – 3.90 (m, 2H), 3.86 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.74 (dd, *J* = 11.4, 7.3 Hz, 1H), 3.39 (s, 3H), 2.46 – 2.40 (m, 1H), 2.31 – 2.25 (m, 1H), 2.08 (s br, 1H)

^{13}C-NMR (CDCl$_3$, 150 MHz): δ = 134.5, 133.6, 124.0, 117.7, 96.0, 72.1, 71.7, 67.9, 62.3, 55.9, 37.2
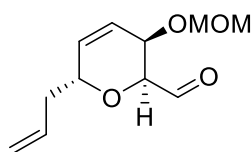
IR (ATR): ṽ = 3446 (w br), 3076 (w), 3037 (w), 2932 (w), 2889 (w), 2848 (w), 2824 (w), 2780 (w), 1641 (w), 1468 (w), 1439 (w), 1395 (w), 1349 (w), 1300 (w), 1212 (w), 1188 (w), 1148 (m), 1080 (m), 1029 (s), 984 (m), 913 (m), 875 (w), 840 (w), 790 (w), 741 (w), 716 (w), 685 (w), 637 (w), 518 (w)

HRMS (ESI) (m/z) $[C_{11}H_{18}O_4Na]^+$ = $[M+Na]^+$: calcd. 237.1103, found 237.1098

$[\alpha]_D^{20}$ = -191° (c = 1.1 in CHCl$_3$)

Synthesis of (2S,3R,6R)-6-allyl-3-(methoxymethoxy)-3,6-dihydro-2H-pyran-2-carb-aldehyde 243

Oxalyl chloride (2.05 ml, 23.94 mmol) was dissolved in DCM (30 ml) and the solution was cooled to –78 °C. DMSO (2.27 ml, 31.92 mmol) dissolved in DCM (15 ml) was added dropwise to this solution and the reaction mixture was stirred for 45 min at –78 °C. A solution of alcohol **244** (3.42 g, 15.96 mmol) in DCM (30 ml) was subsequently added dropwise and the stirring was continued for 1 h at –78 °C. Finally, triethylamine (15.57 ml, 0.11 mol) was added dropwise and the solution was stirred for 20 min at –78 °C before it was slowly warmed to room temperature. The reaction was then quenched with 6% KHSO$_4$ solution and the aqueous layer was extracted with DCM. The organic layer was dried over MgSO$_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 2:1) to give aldehyde **243** as a colourless oil (2.96 g, 87%).

Note: In order to fully characterize the product, the crude mixture was purified as described above. However, it is better to omit this purification step, since the compound has been observed to decompose during both purification and storage.

¹H-NMR (CDCl$_3$, 400 MHz): δ = 9.71 (s, 1H), 6.05 (ddd, J = 10.4, 4.4, 2.1 Hz, 1H), 5.98 (ddd, J = 10.4, 2.8, 0.4 Hz, 1H), 5.84 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.17 – 5.08 (m, 2H), 4.71 (d, J = 6.9 Hz, 1H), 4.64 (d, J = 6.9 Hz, 1H), 4.57 – 4.50 (m, 1H), 4.30 – 4.24 (m, 2H), 3.34 (s, 3H), 2.47 – 2.27 (m, 2H)

¹³C-NMR (CDCl₃, 100 MHz): δ = 201.6, 133.8, 133.3, 123.9, 118.0, 95.9, 76.5, 72.5, 67.8, 55.9, 37.6

IR (ATR): ṽ = 3077 (w), 3041 (w), 2930 (w), 2893 (w), 2847 (w), 2825 (w), 2780 (w), 1736 (m), 1642 (w), 1466 (w), 1440 (w), 1392 (w), 1378 (w), 1322 (w), 1292 (w), 1274 (w), 1213 (w), 1190 (w), 1149 (m), 1090 (m), 1032 (s), 995 (m), 916 (m), 876 (w), 851 (w), 817 (w), 790 (w), 741 (w), 639 (w), 601 (w), 557 (w), 485 (w), 440 (w), 419 (w)

HRMS (ESI) (m/z) [C₁₁H₁₆O₄Na]⁺ = [M+Na]⁺: calcd. 235.0946, found 235.0940

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -215° (c = 0.8 in CHCl₃)

Synthesis of (2R,3R,6R)-6-allyl-2-ethynyl-3-(methoxymethoxy)-3,6-dihydro-2H-pyran 178
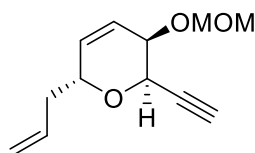
Method A: Trimethylsilyldiazomethane (2.0 M in hexane) (0.53 ml, 1.06 mmol) was dissolved in THF (5 ml) and the solution was cooled to −78 °C. A 2.5 M solution of *n*-BuLi in hexane (0.42 ml, 1.06 mmol) was added dropwise and the mixture was stirred for 30 min at −78 °C. A solution of aldehyde **243** (150 mg, 0.71 mmol) in THF (5 ml) was added and the stirring was continued for 1 h. The mixture was slowly warmed to room temperature and was stirred for an additional 3 h. The reaction was quenched with a freshly prepared saturated NH₄Cl solution before the aqueous layer was extracted with ethyl acetate. The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. After purification by column chromatography on silica gel (pentane/diethyl ether 5:1) alkyne **178** was obtained as a colourless oil (39 mg, 27%).

Method B: A solution of aldehyde **243** (1.56 g, 7.35 mmol) in MeOH (60 ml) was added to a solution of Bestmann reagent (10% solution in acetonitrile) (21.18 ml, 8.82 mmol) and K₂CO₃ (2.03 g, 14.70 mmol) in MeOH. The reaction mixture was stirred for 2.5 h at room temperature and was then quenched with saturated NaHCO₃ solution and extracted with diethyl ether. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude

material was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to obtain alkyne **178** as a colourless oil (901 mg, 59%).

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 5.86 – 5.73 (m, 3H), 5.15 – 5.06 (m, 2H), 4.95 (dd, J = 5.7, 2.0 Hz, 1H), 4.77 (d, J = 7.3 Hz, 1H), 4.73 (d, J = 7.0 Hz, 1H), 4.49 – 4.44 (m, 1H), 4.31 – 4.26 (m, 1H), 3.43 (s, 3H), 2.44 (d, J = 2.2 Hz, 1H), 2.37 – 2.27 (m, 2H)

^{13}C-NMR (CDCl$_3$, 150 MHz): δ = 133.9, 130.8, 125.8, 117.7, 96.9, 79.5, 74.8, 70.6, 69.9, 66.1, 56.2, 39.1

IR (ATR): ṽ = 3288 (w), 3077 (w), 3041 (w), 3002 (w), 2935 (w), 2891 (w), 2846 (w), 2827 (w), 2781 (w), 1641 (w), 1469 (w), 1441 (w), 1392 (w), 1353 (w), 1305 (w), 1263 (w), 1215 (w), 1150 (m), 1106 (m), 1042 (s), 988 (m), 959 (w), 915 (m), 889 (w), 872 (w), 825 (w), 799 (w), 710 (w), 656 (m), 630 (m), 521 (w), 442 (w), 419 (w)

HRMS (ESI) (m/z) [C$_{12}$H$_{16}$O$_3$Na]$^+$ = [M+Na]$^+$: calcd. 231.0997, found 231.0996

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -102° (c = 1.2 in CHCl$_3$)

Synthesis of 1-((2R,3R,6R)-6-allyl-3-(methoxymethoxy)-3,6-dihydro-2H-pyran--2-yl)ethan-1-ol 216
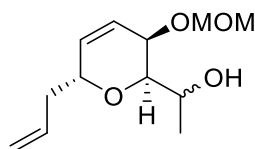
A 3 M solution of MeMgBr in diethyl ether (6.60 ml, 19.79 mmol) was added to a solution of aldehyde **243** (1.40 g, 6.60 mmol) in THF (50 ml) at −78 °C. The solution was stirred at −78°C for 1 h, before it was allowed to slowly warm to room temperature. The reaction mixture was stirred overnight and quenched with saturated NaHCO$_3$ solution and extracted with diethyl ether. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (pentane/diethyl ether 2:1) to yield alcohol **216** as a colourless oil (1.43 g, 95%, 4:1 dr).

The analytical data for the major isomer is as follows:

¹H-NMR (CDCl₃, 400 MHz): δ = 6.08 (ddd, *J* = 10.3, 5.4, 2.0 Hz, 1H), 6.00 (dd, *J* = 10.2, 2.9 Hz, 1H), 5.84 (ddt, *J* = 17.0, 10.2, 7.0 Hz, 1H), 5.18 – 5.09 (m, 2H), 4.79 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 7.0 Hz, 1H), 4.45 – 4.39 (m, 1H), 4.04 (dd, *J* = 7.5, 6.3 Hz, 1H), 3.87 (dd, *J* = 5.4, 2.1 Hz, 1H), 3.41 (dd, *J* = 7.4, 2.1 Hz, 1H), 3.37 (s, 3H), 2.87 (s br, 1H), 2.49 – 2.36 (m, 1H), 2.31 – 2.19 (m, 1H), 1.24 – 1.20 (d, 3H)

¹³C-NMR (CDCl₃, 100 MHz): δ = 134.6, 134.1, 124.1, 117.8, 95.3, 75.6, 72.9, 66.9, 66.8, 55.9, 36.6, 17.7

IR (ATR): ṽ = 3491 (w br), 3075 (w), 3038 (w), 2975 (w), 2931 (w), 2891 (w), 2824 (w), 1641 (w), 1439 (w), 1402 (w), 1375 (w), 1362 (w), 1341 (w), 1320 (w), 1262 (w), 1230 (w), 1212 (w), 1189 (w), 1148 (m), 1078 (m), 1030 (s), 1001 (m), 985 (m), 914 (m), 895 (m), 848 (w), 825 (w), 803 (w), 744 (w), 715 (w), 636 (w), 612 (w), 573 (w), 556 (w), 497 (w), 478 (w), 463 (w), 447 (w), 412 (w)

HRMS (ESI) (m/z) [C₁₂H₂₀O₄Na]⁺ = [M+Na]⁺: calcd. 251.1259, found 251.1258

$[\alpha]_D^{20}$ = -284° (c = 1.1 in CHCl₃, 4:1 dr)

Synthesis of 1-[(2*S*,3*R*,6*R*)-6-allyl-3-(methoxymethoxy)-3,6-dihydro-2*H*-pyran--2-yl]ethan-1-one 206
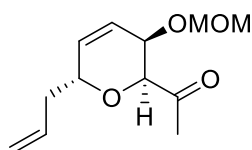
Alcohol **216** (1.30 g, 5.69 mmol) was dissolved in DCM (60 ml) at room temperature. NaHCO₃ (1.91 g, 22.78 mmol) and DMP (4.83 g, 11.39 mmol) were added to this solution and the mixture was stirred for 4 h at room temperature. The reaction was quenched with a saturated Na₂S₂O₃ solution and stirred for another 10 min. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with saturated NaHCO₃ solution and brine, dried over MgSO₄ and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (pentane/diethyl ether 6:1) gave ketone **206** as a colourless oil (1.12 g, 87%).

¹H-NMR (CDCl₃, 600 MHz): δ = 6.06 (ddd, J = 10.3, 5.0, 2.0 Hz, 1H), 6.00 (dd, J = 10.3, 3.1 Hz, 1H), 5.84 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.14 – 5.07 (m, 2H), 4.64 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.51 – 4.46 (m, 1H), 4.18 – 4.14 (m, 2H), 3.30 (s , 3H), 2.45 – 2.38 (m, 1H), 2.30 – 2.25 (m, 1H), 2.27 (s , 3H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 209.0, 134.2, 133.7, 123.9, 117.7, 95.9, 76.9, 73.2, 67.5, 55.7, 36.7, 27.7

IR (ATR): ṽ = 3659 (w), 3077 (w), 3039 (w), 2980 (w), 2930 (w), 2890 (w), 2845 (w), 2825 (w), 2778 (w), 1715 (m), 1641 (w), 1470 (w), 1438 (w), 1417 (w), 1394 (w), 1352 (w), 1323 (w), 1273 (w), 1210 (w), 1187 (w), 1149 (m), 1105 (m), 1089 (m), 1029 (s), 989 (m), 955 (m), 915 (m), 869 (w), 850 (w), 816 (w), 742 (m), 708 (w), 638 (w), 615 (w), 592 (w), 545 (w), 495 (w), 467 (w), 448 (w), 414 (w)

HRMS (ESI) (m/z) $[C_{12}H_{18}O_4Na]^+$ = $[M+Na]^+$: calcd. 249.1103, found 249.1094

$[\alpha]_D^{20}$ = -283° (c = 1.1 in CHCl₃)

Synthesis of (2R,3R,6R)-6-allyl-2-[(Z)-1-iodoprop-1-en-2-yl]-3-(methoxymethoxy)-3,6-di-hydro-2H-pyran 228
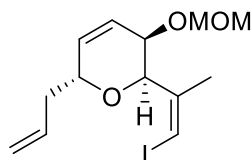
A solution of ketone **206** (150 mg, 0.66 mmol) and iodoform (600 mg, 1.52 mmol) in THF (4 ml) was added to a solution of chromium(II) chloride (693 mg, 5.63 mmol) in THF (4 ml). The reaction mixture was stirred overnight at room temperature. Upon completion of the reaction (indicated by TLC), it was quenched with water and stirred for another 10 min before it was diluted with diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over MgSO₄ and the volatiles were removed *in vacuo*. The crude mixture (E/Z = 1:10, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 10:1) in order to obtain Z-vinyl iodide **228** as a pale-yellow oil (118 mg, 51%).

¹H-NMR ((CD₃)₂CO, 600 MHz): δ = 6.39 – 6.37 (m, 1H), 6.04 (ddd, J = 10.3, 5.0, 2.0 Hz, 1H), 5.99 (dd, J = 10.4, 2.9 Hz, 1H), 5.86 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.11 – 5.01 (m, 2H), 4.68 (d, J = 6.8 Hz, 1H), 4.52 (d, J = 6.8 Hz, 1H), 4.41 (d, J = 2.1 Hz, 1H), 4.32 – 4.27 (m, 1H), 4.03 (dd, J = 4.9, 2.8 Hz, 1H), 3.26 (s, 3H), 2.44 – 2.38 (m, 1H), 2.32 – 2.25 (m, 1H), 1.89 (s, 3H)

¹³C-NMR ((CD₃)₂CO, 150 MHz): δ = 145.7, 135.9, 133.6, 125.4, 117.2, 96.0, 78.6, 75.3, 73.7, 68.7, 55.6, 37.6, 22.2

IR (ATR): ṽ = 3075 (w), 3038 (w), 2979 (w), 2927 (w), 2888 (w), 2851 (w), 2845 (w), 2823 (w), 2776 (w), 1727 (w), 1640 (w), 1625 (w), 1465 (w), 1438 (w), 1415 (w), 1376 (w), 1355 (w), 1327 (w), 1281 (w), 1251 (w), 1228 (w), 1211 (w), 1190 (w), 1148 (m), 1101 (m), 1081 (m), 1033 (m), 995 (m), 963 (w), 915 (m), 874 (w), 848 (w), 841 (w), 799 (w), 742 (w), 678 (w), 641 (w), 621 (w), 610 (w), 590 (w), 580 (w), 543 (w), 524 (w), 487 (w), 454 (w), 444 (w), 418 (w), 412 (w)

HRMS (ESI) (m/z) $[C_{13}H_{19}IO_3NH_4]^+$ = $[M+NH_4]^+$: calcd. 368.0723, found 368.0720

$[\alpha]_D^{20}$ = -219° (c = 1.2 in CHCl₃)

Synthesis of {[(2*S*,3*S*,*Z*)-5-[(2*R*,3*R*,6*R*)-6-allyl-3-(methoxymethoxy)-3,6-dihydro-2*H*-py-ran-2-yl]-3-methylhex-4-en-2-yl]oxy}(*tert*-butyl)dimethylsilane 212
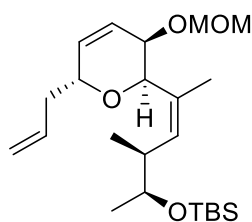
Method A: LiHMDS (1 M in THF) (0.17 ml, 0.17 mmol) was slowly added at –42 °C to a solution of sulfone **210** (49 mg, 0.12 mmol) in DCM (2 ml). After 30 min cerium(III) chloride (12 mg, 0.05 mmol) was added and subsequently a solution of ketone **206** (28 mg, 0.012 mmol) in DCM (3 ml) was added dropwise. The reaction mixture was stirred for 1 h and was allowed to slowly warm to room temperature. The reaction was quenched with a freshly prepared saturated NH₄Cl solution and the mixture was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The

crude mixture (E/Z = 1:12, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 20:1) to yield compound **212** as a colourless oil (17 mg, 34%).

Method B: LiHMDS (1 M in THF) (0.15 ml, 0.15 mmol) was slowly added at −78 °C to a solution of sulfone **210** (51 mg, 0.13 mmol) in THF (2 ml). A solution of ketone **206** (24 mg, 0.11 mmol) in THF (3 ml) was added dropwise after 1 h. The reaction mixture was stirred for 3 h before it was allowed to slowly warm to room temperature. Water was subsequently added and the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture (E/Z = 1:14, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 20:1) to yield compound **212** as a colourless oil (20 mg, 46%).

Method C: LiHMDS (1 M in THF) (0.27 ml, 0.27 mmol) was added dropwise at −78 °C to a solution of sulfone **210** (76 mg, 0.19 mmol) and ketone **206** (60 mg, 0.27 mmol) in THF (5 ml). The reaction mixture was warmed to room temperature after 4 h and water was added. The mixture was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture (E/Z = 1:14, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to yield compound **212** as a colourless oil (41 mg, 53%).

^{1}H-NMR ((CD$_3$)$_2$CO, 600 MHz): δ = 6.02 (ddd, J = 10.3, 5.1, 1.9 Hz, 1H), 5.98 (dd, J = 10.3, 3.2 Hz, 1H), 5.87 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.19 – 5.15 (m, 1H), 5.11 – 5.00 (m, 2H), 4.65 (d, J = 2.9 Hz, 1H), 4.65 (d, J = 6.6 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.30 – 4.25 (m, 1H), 3.87 (dd, J = 5.1, 2.9 Hz, 1H), 3.69 – 3.64 (m, 1H), 3.29 (s, 3H), 2.48 – 2.39 (m, 2H), 2.33 – 2.27 (m, 1H), 1.82 (d, J = 1.4 Hz, 3H), 1.12 (d, J = 6.2 Hz, 3H), 0.94 (d, J = 6.72 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H)

^{13}C-NMR ((CD$_3$)$_2$CO, 150 MHz): δ = 136.2, 134.4, 133.5, 131.9, 126.0, 117.0, 96.4, 73.4, 73.4, 70.7, 70.6, 55.4, 40.9, 37.5, 26.3, 22.9, 21.2, 18.7, 17.0, -4.0, -4.6

IR (ATR): ṽ = 3077 (w), 3037 (w), 2955 (w), 2928 (w), 2888 (w), 2857 (w), 2822 (w), 2774 (w), 1738 (w), 1641 (w), 1462 (w), 1448 (w), 1371 (w), 1296 (w), 1253 (w), 1212 (w), 1187 (w), 1150 (w), 1126 (w), 1096 (m), 1034 (m), 1004 (w), 984 (w), 960 (w), 939 (w), 916 (w), 889 (w), 835 (m), 808 (w), 773 (m), 741 (w), 711 (w), 665 (w), 641 (w), 612 (w), 590 (w), 560 (w), 494 (w), 482 (w), 438 (w)

HRMS (ESI) (m/z) [C$_{23}$H$_{42}$O$_4$SiNH$_4$]$^+$ = [M+NH$_4$]$^+$: calcd. 428.3196, found 428.3196

$[\alpha]_D^{20}$ = -109° (c = 0.5 in CHCl₃)

Synthesis of 3-[(2*R*,5*R*,6*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethyl-silyl)oxy]methyl}-5,6-dihydro-2*H*-pyran-2-yl]propane-1,2-diol 260
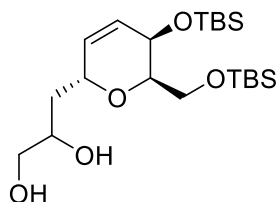
Compound **233** (12.38 g, 0.03 mol) was dissolved in a 1:1 mixture of *tert*-butanol (140 ml) and water (140 ml). AD-mix-*β* (48.37 g, 0.06 mol) was added to this solution and the reaction mixture was stirred for 26 h at room temperature. Upon completion of the reaction (indicated by TLC), Na₂SO₃ (7.04 g, 0.06 mol) was added and the reaction mixture was stirred for another 1 h at room temperature. The solution was subsequently diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue (14.84 g) was used without any further purification in the next step.

¹H-NMR (CDCl₃, 400 MHz): δ = 5.86 – 5.74 (m, 2H), 4.53 – 4.43 (m, 1H), 4.07 – 4.03 (m, 1H), 4.01 – 3.95 (m, 1H), 3.93 – 3.86 (m, 1H), 3.85 – 3.68 (m, 3H), 3.67 – 3.55 (m, 1H), 2.38 (s br, 2H), 1.93 – 1.77 (m, 1H), 1.66 – 1.58 (m, 1H), 0.91 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.07 (s, 6H)

¹³C-NMR (CDCl₃, 100 MHz): δ = 132.2, 126.8, 73.7, 70.5, 69.2, 65.9, 63.6, 62.9, 34.6, 26.2, 25.9, 18.7, -4.0, -4.6, -5.2, -5.3

Synthesis of 2-[(2*R*,5*R*,6*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethyl-silyl)oxy]methyl}-5,6-dihydro-2*H*-pyran-2-yl]acetaldehyde 259

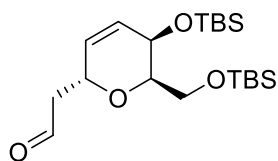2,6-lutidine (8.04 ml, 0.07 mol) and NaIO$_4$ (29.30 g, 0.014 mol) were added to a solution of diol **260** (14.84 g, 0.03 mol) in a 1:1 mixture of *tert*-butanol (100 ml) and water (100 ml). The reaction mixture was stirred for 3 h at room temperature before water and DCM were added. After separation of the organic layer, the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (pentane/diethyl ether 15:1) gave aldehyde **259** as a colourless oil (9.90 g, 80% over two steps).

¹H-NMR (CDCl$_3$, 400 MHz): δ = 9.81 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.87 (ddd, *J* = 10.2, 4.2, 2.0 Hz, 1H), 5.80 (ddd, *J* = 10.2, 2.7, 0.8 Hz, 1H), 4.83 – 4.77 (m, 1H), 4.14 – 4.11 (m, 1H), 3.82 – 3.70 (m, 3H), 2.73 (ddd, *J* = 16.3, 8.7, 2.8 Hz, 1H), 2.52 (ddd, *J* = 16.3, 4.9, 1.8 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 6H), 0.06 (s, 6H)

¹³C-NMR (CDCl$_3$, 100 MHz): δ = 201.0, 130.3, 128.3, 74.3, 67.3, 63.1, 61.6, 46.7, 26.1, 26.0, 18.5, 18.3, -4.1, -4.5, -5.1, -5.2

IR (ATR): ṽ = 3037 (w), 2954 (w), 2929 (w), 2886 (w), 2857 (w), 2721 (w), 1728 (w), 1470 (w), 1389 (w), 1361 (w), 1327 (w), 1253 (m), 1217 (w), 1188 (w), 1143 (w), 1095 (m), 1060 (m), 1006 (w), 937 (w), 870 (m), 833 (m), 774 (m), 668 (w), 566 (w), 500 (w), 472 (w), 418 (w)

HRMS (ESI) (m/z) [C$_{20}$H$_{40}$O$_4$Si$_2$Na]$^+$ = [M+Na]$^+$: calcd. 423.2363, found 423.2362

$[\alpha]_D^{20}$ = -125° (c = 1.2 in CHCl$_3$)

Synthesis of *tert*-butyl{[(2*R*,3*R*,6*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-6-(2,2-dimethoxy-ethyl)-3,6-dihydro-2*H*-pyran-2-yl]methoxy}dimethylsilane 258
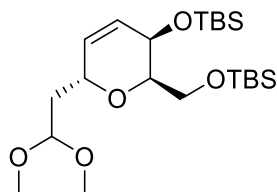
TMOF (18.96 ml, 0.17 mol) was added to a solution of aldehyde **259** (9.90 g, 24.71 mmol) and PTSA (470 mg, 2.47 mmol) in DCM (100 ml) in the presence of 3 Å molecular sieves. After stirring 3 h at room temperature, the reaction mixture was quenched with NaHCO$_3$ (830 mg, 9.88 mmol). After 30 min of vigorous stirring, the solution was filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 15:1) to obtain acetal **258** as a colourless oil (10.79 g, 98%).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 5.84 – 5.76 (m, 2H), 4.62 (dd, *J* = 8.3, 3.2 Hz, 1H), 4.41 – 4.35 (m, 1H), 4.07 – 4.03 (m, 1H), 3.82 – 3.71 (m, 3H), 3.40 (s, 3H), 3.30 (s, 3H), 1.90 (ddd, *J* = 14.1, 10.2, 3.2 Hz, 1H), 1.69 (ddd, *J* = 14.1, 8.3, 3.8 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.07 (s, 12H)

^{13}C-NMR (CDCl$_3$, 100 MHz): δ = 132.3, 126.8, 102.5, 73.8, 68.7, 63.4, 62.4, 54.7, 52.9, 36.0, 26.1, 26.0, 18.5, 18.4, -4.0, -4.5, -5.1, -5.2

IR (ATR): ṽ = 3035 (w), 2953 (w), 2929 (w), 2887 (w), 2857 (w), 1469 (w), 1388 (w), 1362 (w), 1327 (w), 1253 (w), 1191 (w), 1095 (m), 1060 (m), 1016 (w), 1006 (m), 964 (w), 937 (w), 903 (w), 870 (w), 833 (m), 773 (m), 729 (w), 676 (w), 628 (w), 591 (w), 569 (w), 519 (w), 492 (w), 455 (w)

HRMS (ESI) (m/z) [C$_{22}$H$_{46}$O$_5$Si$_2$NH$_4$]$^+$ = [M+NH$_4$]$^+$: calcd. 464.3228, found 464.3225

$[\alpha]_D^{20}$ = -97° (c = 0.9 in CHCl$_3$)

Synthesis of [(2R,3R,6R)-3-[(tert-butyldimethylsilyl)oxy]-6-(2,2-dimethoxyethyl)-3,6-di-hydro-2H-pyran-2-yl]methanol 257
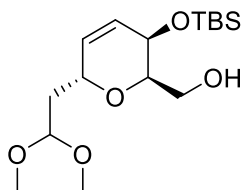
Method A: Iodine (16 mg, 0.06 mmol) was added to a solution of aldehyde **259** (250 mg, 0.62 mmol) in MeOH (7 ml). The reaction mixture was stirred for 3.5 h at room temperature before it was diluted with diethyl ether and the phases separated. The combined organic layers were washed with 5% $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 1:1) to afford alcohol **257** as a colourless oil (98 mg, 47%).

Method B: Compound **258** (10.75 g, 24.06 mmol) was dissolved in a 1:1 mixture of DCM (100 ml) and methanol (100 ml). The solution was cooled to 0 °C and CSA (3.35 g, 14.44 mmol) was added. After 30 min the reaction was quenched with triethylamine (134.15 ml, 0.96 mol). The reaction mixture was subsequently concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 1:1) to yield alcohol **257** as a colourless oil (5.46 g, 68%).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 5.85 – 5.75 (m, 2H), 4.58 (dd, J = 7.1, 4.0 Hz, 1H), 4.38 (dt, J = 9.8, 3.3 Hz, 1H), 4.17 – 4.13 (m, 1H), 3.89 – 3.81 (m, 2H), 3.78 – 3.71 (m, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 2.04 (s br, 1H), 1.90 (ddd, J = 14.1, 9.9, 4.1 Hz, 1H), 1.73 (ddd, J = 14.3, 7.2, 4.0 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 6H)

^{13}C-NMR (CDCl$_3$, 100 MHz): δ = 131.9, 126.6, 102.4, 73.0, 68.5, 64.4, 62.4, 53.7, 51.0, 35.9, 25.9, 18.3, -4.1, -4.6

IR (ATR): ṽ = 3446 (w), 3035 (w), 2953 (w), 2930 (w), 2887 (w), 2857 (w), 2834 (w), 1468 (w), 1447 (w), 1389 (w), 1362 (w), 1327 (w), 1253 (w), 1192 (w), 1122 (m), 1101 (m), 1056 (m), 1004 (m), 966 (w), 928 (m), 879 (w), 834 (m), 795 (w), 774 (m), 729 (w), 678 (w), 623 (w), 594 (w), 569 (w), 509 (w), 494 (w), 459 (w), 446 (w)

HRMS (ESI) (m/z) [C$_{16}$H$_{32}$O$_5$SiNa]$^+$ = [M+Na]$^+$: calcd. 355.1917, found 355.1918

$[\alpha]_D^{20}$ = -147° (c = 1.0 in CHCl$_3$)

Synthesis of (2S,3R,6R)-3-[(*tert*-butyldimethylsilyl)oxy]-6-(2,2-dimethoxyethyl)-3,6-di-hydro-2H-pyran-2-carbaldehyde 256
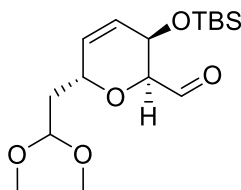
A solution of DMSO (2.56 ml, 36.09 mmol) in DCM (15 ml) was added at –78 °C to a solution of oxalyl chloride (2.32 ml, 27.07 mmol) in DCM (50 ml). After 45 min, a solution of alcohol **257** (5.00 g, 15.04 mmol) in DCM (30 ml) was added dropwise. The reaction mixture was stirred for 1 h at –78 °C before triethylamine (16.77 ml, 0.12 mol) was added. The stirring was continued for 20 min before the mixture was allowed to slowly warm to room temperature. The reaction was quenched with 6% KHSO$_4$ solution and extracted with DCM. The combined organic layers were dried over MgSO$_4$ and the volatiles were evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 3:1) to obtain aldehyde **256** as a colourless oil (3.37 g, 68%).

Note: In order to fully characterize the product, the crude mixture was purified as described above. However, it is better to omit this purification step, since the compound has been observed to decompose during both purification and storage.

¹H-NMR (CDCl$_3$, 600 MHz): δ = 9.73 (s, 1H), 5.85 (dt, *J* = 10.4, 1.8 Hz, 1H), 5.80 (dd, *J* = 10.4, 1.9 Hz, 1H), 4.61 – 4.56 (m, 2H), 4.43 (t, *J* = 3.7 Hz, 1H), 4.13 (d, *J* = 3.8 Hz, 1H), 3.40 (s, 3H), 3.32 (s, 3H), 1.87 – 1.80 (m, 1H), 1.80 – 1.74 (m, 1H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H)

¹³C-NMR (CDCl$_3$, 150 MHz): δ = 201.9, 131.8, 126.3, 102.1, 77.7, 69.2, 64.2, 54.3, 52.9, 36.6, 25.8, 18.2, -4.2, -4.7

IR (ATR): ṽ = 3038 (w), 2990 (w), 2953 (w), 2930 (w), 2896 (w), 2857 (w), 2831 (w), 1738 (m), 1696 (w), 1469 (w), 1446 (w), 1388 (w), 1364 (w), 1323 (w), 1254 (w), 1192 (w), 1100 (m), 1061 (m), 988 (m), 937 (w), 905 (w), 856 (m), 836 (m), 776 (m), 728 (w), 677 (w), 624 (w), 607 (w), 572 (w), 557 (w), 498 (w), 480 (w), 445 (w)

HRMS (ESI) (m/z) [C$_{16}$H$_{30}$O$_5$SiNH$_4$]$^+$ = [M+NH$_4$]$^+$: calcd. 348.2206, found 348.2203

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -119° (c = 1.2 in CHCl$_3$)

Synthesis of *tert*-butyl{[(2*R*,3*R*,6*R*)-6-(2,2-dimethoxyethyl)-2-ethynyl-3,6-dihydro-2*H*-py-ran-3-yl]oxy}dimethylsilane 179
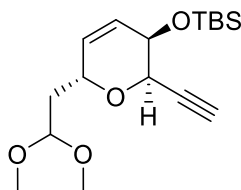
Method A: Trimethylsilyldiazomethane (2.0 M in hexane) (0.34 ml, 0.68 mmol) was dissolved in THF (10 ml) and the solution was cooled to –78 °C. A 2.5 M solution of *n*-BuLi in hexane (0.27 ml, 0.68 mmol) was added dropwise and the mixture was stirred for 30 min at –78 °C. Subsequently, a solution of aldehyde **256** (150 mg, 0.45 mmol) in THF (5 ml) was added. After 1 h, the mixture was slowly warmed to room temperature and was stirred for another 3 h. Finally, the reaction was quenched with a freshly prepared saturated NH$_4$Cl solution and the aqueous layer was extracted with ethyl acetate. The combined organic phases were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. After purification by column chromatography on silica gel (pentane/diethyl ether 10:1) alkyne **179** was obtained as a colourless oil (86 mg, 58%).

Method B: A solution of aldehyde **256** (1.00 g, 3.03 mmol) in MeOH (10 ml) was added at room temperature to a solution of Bestmann reagent (10% solution in acetonitrile) (8.72 ml, 3.63 mmol) and K$_2$CO$_3$ (836 mg, 6.05 mmol) in MeOH (20 ml). After 1.5 h, the reaction was quenched with saturated NaHCO$_3$ solution and extracted with diethyl ether. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. After purification by column chromatography on silica gel (pentane/diethyl ether 10:1) alkyne **179** was obtained as a colourless oil (710 mg, 72%).

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 5.71 (dt, *J* = 10.6, 1.7 Hz, 1H), 5.67 – 5.62 (m, 1H), 4.72 (dd, *J* = 5.8, 2.0 Hz, 1H), 4.56 (dd, *J* = 7.0, 4.3 Hz, 1H), 4.53 – 4.47 (m, 1H), 4.42 – 4.38 (m, 1H), 3.38 (s, 3H), 3.33 (s, 3H), 2.37 (d, *J* = 2.3 Hz, 1H), 1.86 – 1.74 (m, 2H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H)

^{13}C-NMR (CDCl$_3$, 150 MHz): δ = 130.2, 128.1, 102.1, 79.3, 74.7, 67.5, 67.3, 64.9, 54.1, 53.2, 38.3, 25.9, 18.3, -4.5, -4.6

IR (ATR): ṽ = 3311 (w), 3279 (w), 3039 (w), 2954 (w), 2930 (w), 2895 (w), 2857 (w), 2832 (w), 1469 (w), 1447 (w), 1390 (w), 1362 (w), 1345 (w), 1322 (w), 1253 (w), 1189 (w), 1109 (m), 1074 (m), 1060 (m), 1006 (w), 987 (w), 971 (w), 940 (w), 900 (w), 866 (m), 837 (m), 808 (w), 774 (m), 723 (w), 680 (w), 656 (w), 629 (w), 571 (w), 553 (w), 515 (w), 463 (w), 439 (w)

HRMS (ESI) (m/z) $[C_{17}H_{30}O_4SiNH_4]^+ = [M+NH_4]^+$: calcd. 344.2257, found 344.2257

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -49° (c = 1.1 in CHCl$_3$)

Synthesis of 1-[(2*R*,3*R*,6*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-6-(2,2-dimethoxyethyl)-3,6-dihydro-2*H*-pyran-2-yl]ethan-1-ol 269
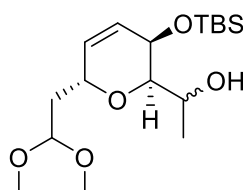
A 3 M solution of MeMgBr in diethyl ether (8.07 ml, 24.21 mmol) was added dropwise to a solution of aldehyde **256** (2.00 g, 6.05 mmol) in THF (20 ml) at –78 °C. The mixture was stirred for 1 h at –78 °C before it was slowly warmed to room temperature. The reaction was quenched with 5% KHSO$_4$ solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated under reduced pressure. After purification by column chromatography on silica gel (pentane/diethyl ether 2:1) alcohol **269** was obtained as a colourless oil (1.53 g, 73%, 1.1:1 dr).

¹H-NMR (CDCl$_3$, 600 MHz): δ = 5.91 – 5.76 (m, 4H), 4.61 – 4.55 (m, 2H), 4.54 – 4.49 (m, 1H), 4.44 – 4.40 (m, 1H), 4.32 – 4.27 (m, 1H), 4.15 – 4.00 (m, 3H), 3.44 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.34 (s, 3H), 3.32 (s, 3H), 3.16 – 3.11 (m, 1H), 2.00 – 1.94 (m, 1H), 1.84 – 1.77 (m, 1H), 1.76 – 1.65 (m, 2H), 1.58 (s br, 2H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H)

¹³C-NMR (CDCl$_3$, 150 MHz): δ = 133.0, 132.0, 126.5, 126.1, 102.8, 102.2, 75.8, 75.8, 70.1, 68.4, 67.5, 66.7, 65.3, 64.1, 54.3, 53.8, 53.2, 52.8, 36.6, 34.8, 26.0, 25.9, 20.0, 18.3, 18.2, 18.2, -3.3, -3.8, -4.3, -4.4

IR (ATR): ṽ = 3500 (w), 3035 (w), 2955 (w), 2930 (w), 2895 (w), 2887 (w), 2857 (w), 2833 (w), 1739 (w), 1657 (w), 1610 (w), 1469 (w), 1389 (w), 1362 (w), 1323 (w), 1253 (w), 1193 (w), 1122 (m), 1050 (m), 1006 (w), 991 (w), 965 (w), 939 (w), 906 (w), 887 (w), 854 (w), 835 (m), 808 (w), 774 (m), 729 (w), 681 (w), 645 (w), 598 (w), 568 (w), 545 (w), 510 (w), 492 (w), 458 (w), 419 (w)

HRMS (ESI) (m/z) $[C_{17}H_{34}O_5SiNa]^+ = [M+Na]^+$: calcd. 369.2073, found 369.2075

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -145° (c = 0.7 in CHCl$_3$, 1.1:1 dr)

Synthesis of 1-[(2*S*,3*R*,6*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-6-(2,2-dimethoxyethyl)-3,6-dihydro-2*H*-pyran-2-yl]ethan-1-one 207
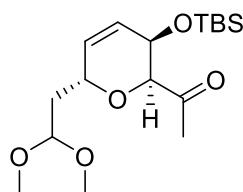
Alcohol **269** (1.50 g, 4.33 mmol) was dissolved in DCM (40 ml). NaHCO$_3$ (1.45 g, 17.31 mmol) and DMP (3.67 g, 8.66 mmol) were added to this solution and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with saturated Na$_2$S$_2$O$_3$ solution and after 10 min it was extracted with DCM. The combined organic layers were washed with saturated NaHCO$_3$ solution and brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to yield ketone **207** as a colourless oil (1.31 g, 88%).

¹H-NMR (CDCl$_3$, 600 MHz): δ = 5.90 – 5.84 (m, 2H), 4.58 – 4.54 (m, 2H), 4.24 (dd, *J* = 4.6, 2.6 Hz, 1H), 4.04 (d, *J* = 2.6 Hz, 1H), 3.38 (s, 3H), 3.30 (s, 3H), 2.25 (s, 3H), 1.90 – 1.84 (m, 1H), 1.75 – 1.69 (m, 1H), 0.84 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H)

¹³C-NMR (CDCl$_3$, 150 MHz): δ = 209.4, 132.5, 125.7, 102.2, 78.1, 70.0, 64.0, 54.1, 52.7, 35.0, 28.1, 25.9, 18.2, -4.1, -4.7

IR (ATR): ṽ = 3038 (w), 2955 (w), 2930 (w), 2895 (w), 2857 (w), 2832 (w), 1720 (w), 1471 (w), 1416 (w), 1389 (w), 1352 (w), 1316 (w), 1254 (w), 1226 (w), 1192 (w), 1111 (m), 1061 (m), 1031 (m), 993 (w), 966 (w), 938 (w), 900 (m), 850 (m), 835 (m), 804 (w), 776 (m), 748 (m), 726 (w), 682 (w), 645 (w), 607 (w), 564 (w), 547 (w), 496 (w), 471 (w), 441 (w)

HRMS (ESI) (m/z) $[C_{17}H_{32}O_5SiNH_4]^+ = [M+NH_4]^+$: calcd. 362.2363, found 362.2364

$[\alpha]_D^{20}$ = -223° (c = 0.7 in CHCl$_3$)

Synthesis of *tert*-butyl{[(2*R*,3*R*,6*R*)-6-(2,2-dimethoxyethyl)-2-[(*Z*)-1-iodoprop-1-en-2-yl]--3,6-dihydro-2*H*-pyran-3-yl]oxy}dimethylsilane 229
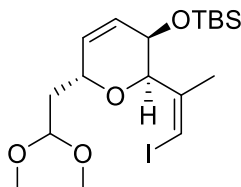
A solution of ketone **207** (150 mg, 0.44 mmol) and iodoform (514 mg, 1.31 mmol) in THF (4 ml) was added to a solution of chromium(II) chloride (589 mg, 4.79 mmol) in THF (3 ml). The reaction mixture was stirred overnight at room temperature. Upon completion of the reaction (indicated by TLC), it was quenched with water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated under reduced pressure. The crude mixture (*E/Z* = 1:12, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to afford vinyl iodide **229** as a colourless oil (126 mg, 62%).

^{1}H-NMR ((CD$_3$)$_2$CO, 600 MHz): δ = 6.35 – 6.33 (m, 1H), 5.96 – 5.90 (m, 2H), 4.52 (dd, *J* = 8.0, 3.7 Hz, 1H), 4.38 – 4.34 (m, 1H), 4.30 (d, *J* = 2.6 Hz, 1H), 4.19 (dd, *J* = 4.4, 2.6 Hz, 1H), 3.31 (s, 3H), 3.24 (s, 3H), 1.89 – 1.83 (m, 4H), 1.77 – 1.71 (m, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H)

^{13}C-NMR ((CD$_3$)$_2$CO, 150 MHz): δ = 145.8, 133.1, 127.1, 102.8, 78.7, 76.2, 70.7, 64.9, 53.6, 52.7, 35.7, 26.3, 22.5, 18.6, -3.7, -4.3

IR (ATR): ṽ = 3035 (w), 2989 (w), 2952 (w), 2928 (w), 2896 (w), 2886 (w), 2856 (w), 2831 (w), 1624 (w), 1464 (w), 1444 (w), 1389 (w), 1361 (w), 1327 (w), 1282 (w), 1252 (w), 1192 (w), 1111 (m), 1059 (m), 1006 (w), 919 (w), 887 (w), 855 (w), 835 (m), 809 (m), 773 (m), 749 (m), 730 (w), 676 (w), 568 (w), 550 (w), 474 (w), 443 (w)

HRMS (ESI) (m/z) $[C_{18}H_{33}IO_4SiNa]^+ = [M+Na]^+$: calcd. 491.1090, found 491.1088

$[\alpha]_D^{20}$ = -143° (c = 1.0 in CHCl$_3$)

Synthesis of *tert*-butyl{[(2*R*,3*R*,6*R*)-2-[(4*S*,5*S*,*Z*)-5-[(*tert*-butyldimethylsilyl)oxy]- -4-methylhex-2-en-2-yl]-6-(2,2-dimethoxyethyl)-3,6-dihydro-2*H*-pyran-3-yl]oxy}di- methylsilane 213
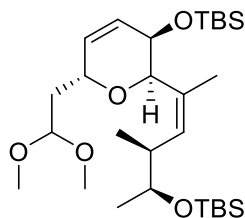
Method A: LiHMDS (1 M in THF) (0.17 ml, 0.17 mmol) was slowly added at –42 °C to a solution of sulfone **210** (50 mg, 0.12 mmol) in DCM (2 ml). After 30 min, cerium(III) chloride (12 mg, 0.05 mmol) was added and a solution of ketone **207** (43 mg, 0.12 mmol) in DCM (3 ml) was subsequently added dropwise. The reaction mixture was stirred for 1 h and allowed to slowly warm to room temperature. The reaction was quenched with a freshly prepared saturated NH$_4$Cl solution and the mixture was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture (*E/Z* = 1:20, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 8:1) to yield compound **213** as a colourless oil (3 mg, 5%).

Method B: LiHMDS (1 M in THF) (0.17 ml, 0.17 mmol) was slowly added at –78 °C to a solution of sulfone **210** (50 mg, 0.12 mmol) in THF (3 ml). A solution of ketone **207** (43 mg, 0.12 mmol) in THF (4 ml) was added dropwise after 1 h. The reaction mixture was stirred for 4 h before it was allowed to slowly warm to room temperature. Water was subsequently added and the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture (*E/Z* = 1:20, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 8:1) to yield compound **213** as a colourless oil (25 mg, 38%).

¹H-NMR ((CD$_3$)$_2$CO, 600 MHz): δ = 5.93 (ddd, *J* = 10.3, 4.7, 1.8 Hz, 1H), 5.89 (dd, *J* = 10.3, 2.9 Hz, 1H), 5.21 – 5.17 (m, 1H), 4.57 (d, *J* = 2.7 Hz, 1H), 4.51 (dd, *J* = 7.9, 3.5 Hz, 1H), 4.35 – 4.30 (m, 1H), 4.07 (dd, *J* = 4.7, 2.7 Hz, 1H), 3.70 – 3.64 (m, 1H), 3.31 (s, 3H), 3.26 (s, 3H), 2.44 – 2.37 (m, 1H), 1.94 – 1.88 (m, 1H), 1.85 (d, *J* = 1.4 Hz, 3H), 1.75 – 1.69 (m, 1H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 6H)

¹³C-NMR ((CD₃)₂CO, 150 MHz): δ = 134.82, 132.85, 131.73, 127.86, 103.19, 73.28, 71.41, 70.23, 67.26, 53.75, 52.81, 40.87, 35.73, 26.31, 23.13, 21.69, 18.70, 18.69, 16.97, -3.81, -3.95, -4.33, -4.52
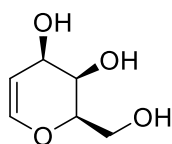
IR (ATR): ṽ = 3032 (w), 2955 (w), 2928 (w), 2897 (w), 2857 (w), 1730 (w), 1692 (w), 1659 (w), 1463 (w), 1386 (w), 1370 (w), 1323 (w), 1253 (w), 1192 (w), 1154 (w), 1112 (m), 1096 (m), 1057 (m), 1033 (m), 1025 (m), 984 (w), 961 (w), 933 (m), 834 (m), 806 (m), 773 (m), 750 (m), 684 (w), 665 (w), 606 (w), 566 (w), 544 (w), 502 (w), 485 (w), 459 (w), 441 (w), 419 (w)

HRMS (ESI) (m/z) $[C_{28}H_{56}O_5Si_2Na]^+$ = $[M+Na]^+$: calcd. 551.3564, found 551.3564

$[\alpha]_D^{20}$ = -77° (c = 0.6 in CHCl₃)

Synthesis of (2R,3R,4R)-2-(hydroxymethyl)-3,4-dihydro-2H-pyran-3,4-diol 274

Compound **236** (18.20 g, 0.07 mol) was dissolved in methanol (100 ml) and K₂CO₃ (2.77 g, 20.06 mmol) was added. The solution was stirred overnight at room temperature. Upon completion of the reaction (indicated by TLC), the volatiles were evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (ethyl acetate/methanol 95:5) to obtain triol **274** as white crystals (9.64 g, 99%).

Note: In order to fully characterize the product, the crude mixture was purified as described above. However, this purification step can be omitted, since the purity of the crude compound was high enough to be directly used in the following reaction.

¹H-NMR (CD₃OD, 600 MHz): δ = 6.35 (dd, *J* = 6.2, 1.6 Hz, 1H), 4.62 (dt, *J* = 6.3, 1.9 Hz, 1H), 4.35 – 4.32 (m, 1H), 3.93 – 3.87 (m, 2H), 3.82 (dd, *J* = 11.4, 6.9 Hz, 1H), 3.75 (dd, *J* = 11.4, 5.4 Hz, 1H)

**¹³C-NMR** (CD₃OD, 150 MHz): δ = 145.2, 103.8, 78.7, 66.5, 65.4, 62.4

IR (ATR): ṽ = 3423 (w br), 3318 (w br), 3195 (w br), 3061 (w), 2980 (w), 2955 (w), 2927 (w),
2892 (w), 2883 (w), 2326 (w), 2064 (w), 1747 (w), 1642 (w), 1453 (w), 1397 (w), 1378 (w),
1358 (w), 1333 (w), 1250 (w), 1236 (w), 1219 (w), 1148 (w), 1115 (w), 1068 (w), 1054 (w),
1017 (m), 967 (w), 957 (w), 929 (w), 903 (w), 859 (w), 809 (w), 757 (w), 684 (w), 613 (w),
565 (w), 551 (w), 511 (w), 492 (w), 459 (w), 436 (w), 420 (w)

HRMS (ESI) (m/z) $[C_6H_{10}O_4Na]^+ = [M+Na]^+$: calcd. 169.0477, found 169.0470

Mp = 98 – 104 °C

$[\alpha]_D^{20}$ = -21° (c = 0.9 in CH_3OH)

Synthesis of (2*R*,3*R*,4*R*)-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-3,4-dihydro-2*H*-pyran--3,4-diol 273
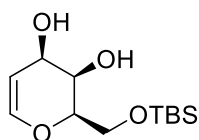
Method A: Imidazole (205 mg, 3.01 mmol) was added to a solution of triol **274** (200 mg, 1.37 mmol) in DMF (5 ml) and the solution was cooled to 0 °C. TBSCl (206 mg, 1.37 mmol) was added dropwise and after 30 min the reaction was allowed to warm to room temperature. The reaction was quenched with water and diluted with ethyl acetate after 8 h. After separation of the phases, the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄ and the volatiles were evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 1:3) to yield diol **273** as a colourless oil (175 mg, 49%).

Method B: Triol **274** (9.50 g, 0.07 mol) was dissolved in a 10:1 mixture of acetonitrile (200 ml) and DMF (20 ml). Triethylamine (16.31 ml, 0.12 mol) and TBSCl (14.70 g, 0.10 mol) were added to the above solution. After stirring for 40 min at room temperature the reaction mixture was directly purified by column chromatography on silica gel (pentane/diethyl ether 1:3) in order to afford diol **273** as a colourless oil (11.80 g, 70%).

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 6.38 (dd, J = 6.2, 1.4 Hz, 1H), 4.71 (dt, J = 6.2, 2.0 Hz, 1H), 4.33 – 4.29 (m, 1H), 4.10 (dd, J = 3.2, 1.4 Hz, 1H), 3.97 (dd, J = 10.9, 5.0 Hz, 1H), 3.91 (dd, J = 10.9, 3.8 Hz, 1H), 3.89 – 3.86 (m, 1H), 3.22 (s br, 1H), 2.77 (s br, 1H), 0.91 (s, 9H), 0.10 (s, 6H)

**^{13}C-NMR** (CDCl$_3$, 150 MHz): δ = 144.7, 103.2, 75.9, 66.2, 64.3, 63.6, 25.9, 18.4, -5.3, -5.4

IR (ATR): ṽ = 3374 (w br), 3068 (w), 2953 (w), 2929 (w), 2885 (w), 2857 (w), 1646 (w), 1469 (w), 1406 (w), 1392 (w), 1361 (w), 1252 (m), 1233 (m), 1189 (w), 1142 (w), 1102 (m), 1066 (m), 1030 (m), 1006 (w), 973 (w), 938 (w), 910 (w), 834 (s), 775 (m), 686 (w), 664 (w), 623 (w), 571 (w), 516 (w), 477 (w), 432 (w)

HRMS (ESI) (m/z) [C$_{12}$H$_{24}$O$_4$SiNa]$^+$ = [M+Na]$^+$: calcd. 283.1342, found 283.1343

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = 6° (c = 1.2 in CHCl$_3$)

The analytical data agree with those in the literature[127].

Synthesis of {[(2R,3R,4R)-3,4-bis(methoxymethoxy)-3,4-dihydro-2H-pyran-2-yl]methoxy}(tert-butyl)dimethylsilane 272
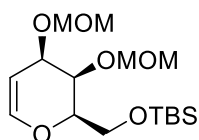
Diol **273** (11.50 g, 0.04 mol) was dissolved in DCM (130 ml). DMAP (1.08 g, 8.83 mmol), DIPEA (29.63 ml, 0.24 mol) and MOMCl (23.96 ml, 0.22 mol) were consecutively added to this solution. The reaction mixture was stirred overnight at room temperature and upon completion (indicated by TLC) it was concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to yield compound **272** as a colourless oil (15.02 g, 98%).

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 6.37 (dd, J = 6.2, 1.7 Hz, 1H), 4.89 (d, J = 6.8 Hz, 1H), 4.78 – 4.74 (m, 3H), 4.71 (d, J = 6.8 Hz, 1H), 4.40 – 4.37 (m, 1H), 4.13 – 4.11 (m, 1H), 4.04 – 4.00 (m, 1H), 3.89 (dd, J = 10.7, 6.8 Hz, 1H), 3.84 (dd, J = 10.7, 6.1 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 144.3, 100.8, 97.2, 95.1, 77.7, 69.0, 68.9, 61.5, 56.1, 55.7, 26.0, 18.5, -5.1, -5.2

IR (ATR): ṽ = 2980 (w), 2930 (w), 2887 (w), 2857 (w), 2823 (w), 1644 (w), 1469 (w), 1444 (w), 1396 (w), 1362 (w), 1299 (w), 1253 (w), 1236 (w), 1215 (w), 1148 (m), 1098 (m), 1071 (m), 1030 (s), 1006 (m), 958 (m), 917 (m), 835 (s), 775 (m), 729 (w), 695 (w), 664 (w), 598 (w), 574 (w), 536 (w), 504 (w), 473 (w), 458 (w), 441 (w), 419 (w)

HRMS (ESI) (m/z) $[C_{16}H_{32}O_6SiNa]^+$ = $[M+Na]^+$: calcd. 371.1866, found 371.1861

$[\alpha]_D^{20}$ = -21° (c = 1.0 in CHCl₃)

Synthesis of [(2R,3R,4R)-3,4-bis(methoxymethoxy)-3,4-dihydro-2H-pyran-2-yl]methan-ol 271
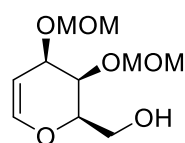
Compound **272** (12.50 g, 0.04 mol) was dissolved in THF (75 ml) and the solution was cooled to 0 °C. A 1 M solution of TBAF in THF (71.73 ml, 0.07 mol) was slowly added before stirring for another 2 h. The reaction was quenched with a freshly prepared saturated NH₄Cl solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 1:2) to obtain alcohol **271** as white crystals (7.25 g, 86%).

¹H-NMR (CDCl₃, 400 MHz): δ = 6.37 (dd, J = 6.2, 1.5 Hz, 1H), 4.87 (d, J = 6.8 Hz, 1H), 4.79 − 4.75 (m, 1H), 4.72 (d, J = 7.4 Hz, 3H), 4.38 − 4.34 (m, 1H), 4.14 − 4.08 (m, 2H), 3.93 (dd, J = 11.9, 6.5 Hz, 1H), 3.79 (dd, J = 11.9, 5.8 Hz, 1H), 3.43 (s, 3H), 3.38 (s, 3H), 2.72 (s br, 1H)

¹³C-NMR (CDCl₃, 100 MHz): δ = 144.6, 100.1, 97.7, 95.5, 76.2, 70.6, 68.4, 61.0, 56.4, 55.8

IR (ATR): ṽ = 3259 (w br), 3069 (w), 2985 (w), 2954 (w), 2937 (w), 2897 (w), 2827 (w), 1642 (w), 1474 (w), 1442 (w), 1397 (w), 1362 (w), 1332 (w), 1301 (w), 1259 (w), 1230 (w), 1212 (w), 1140 (w), 1118 (w), 1098 (w), 1080 (w), 1021 (w), 978 (w), 935 (w), 910 (w), 844 (w), 804 (w), 731 (w), 693 (w), 667 (w), 615 (w), 599 (w), 574 (w), 506 (w), 487 (w), 444 (w), 415 (w)

HRMS (ESI) (m/z) $[C_{10}H_{18}O_6Na]^+$ = $[M+Na]^+$: calcd. 257.1001, found 257.1001

Mp = 71 – 74 °C

$[\alpha]_D^{20}$ = -87° (c = 0.9 in $CHCl_3$)

Synthesis of (2S,3R,4R)-3,4-bis(methoxymethoxy)-3,4-dihydro-2H-pyran-2-carb-aldehyde 270
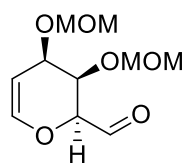
Alcohol **271** (7.00 g, 0.03 mol) was dissolved in DCM (100 ml) before $NaHCO_3$ (10.04 g, 0.12 mol) and DMP (25.35 g, 0.06 mol) were added to the solution. The reaction was stirred overnight at room temperature and quenched with saturated $Na_2S_2O_3$ solution. The mixture was stirred for another 10 min before it was extracted with DCM. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 1:1) to afford aldehyde **270** as a colourless oil (4.70 g, 68%).

Note: In order to fully characterize the product, the crude mixture was purified as described above. However, it is better to omit this purification step, since the compound has been observed to decompose during both purification and storage.

¹H-NMR (CDCl₃, 600 MHz): δ = 9.75 (s, 1H), 6.50 (dd, *J* = 6.1, 0.8 Hz, 1H), 4.92 (dd, *J* = 6.1, 4.7 Hz, 1H), 4.85 (d, *J* = 6.9 Hz, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 4.70 (s, 2H), 4.47 (d, *J* = 4.5 Hz, 1H), 4.38 (t, *J* = 4.1 Hz, 1H), 4.28 (dd, *J* = 4.4, 4.0 Hz, 1H), 3.42 (s, 3H), 3.36 (s, 3H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 197.7, 144.8, 100.3, 96.7, 95.3, 78.9, 72.8, 66.7, 56.2, 55.8

IR (ATR): ṽ = 3072 (w), 2945 (w), 2894 (w), 2846 (w), 2826 (w), 2789 (w), 1735 (w), 1681 (w), 1644 (w), 1598 (w), 1468 (w), 1444 (w), 1396 (w), 1377 (w), 1235 (w), 1215 (w), 1147 (m), 1099 (m), 1020 (s), 972 (m), 948 (m), 914 (m), 818 (w), 782 (w), 754 (w), 735 (w), 693 (w), 583 (w), 429 (w)

HRMS (ESI) (m/z) $[C_{10}H_{16}O_6Na]^+$ = $[M+Na]^+$: calcd. 255.0845, found 255.0844

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -35° (c = 0.7 in CHCl₃)

Synthesis of 1-[(2R,3R,4R)-3,4-bis(methoxymethoxy)-3,4-dihydro-2H-pyran-2-yl]ethan--1-ol 217
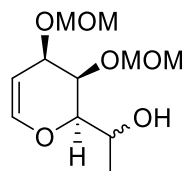
A 3 M solution of MeMgBr in diethyl ether (12.14 ml, 36.43 mmol) was added dropwise to a solution of aldehyde **270** (4.23 g, 18.21 mmol) in THF (75 ml) at −78 °C. The mixture was stirred for 2 h before it was slowly warmed to room temperature. The reaction was quenched with 5% KHSO₄ solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over MgSO₄ and the volatiles were evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 1:1) to obtain alcohol **217** as a colourless oil (2.54 g, 56%, 1.5:1 dr).

¹H-NMR (CDCl₃, 400 MHz): δ = 6.46 (dd, J = 6.2, 1.6 Hz, 1H), 6.36 (dd, J = 6.2, 1.8 Hz, 1H), 4.97 (d, J = 7.0 Hz, 1H), 4.92 (d, J = 6.6 Hz, 1H), 4.78 (d, J = 6.6 Hz, 1H), 4.76 – 4.70 (m, 6H), 4.68 (d, J = 7.0 Hz, 1H), 4.44 – 4.39 (m, 2H), 4.25 – 4.22 (m, 1H), 4.21 – 4.15 (m, 1H), 4.11 – 4.08 (m, 1H), 4.05 – 3.96 (m, 1H), 3.70 – 3.66 (m, 1H), 3.59 – 3.55 (m, 1H), 3.47 (s, 3H), 3.41 (s, 3H), 3.39 (s, 6H), 3.00 (s br, 1H), 2.81 (s br, 1H), 1.30 (d, J = 6.2 Hz, 3H), 1.27 (d, J = 6.4 Hz, 3H)

¹³C-NMR (CDCl₃, 100 MHz): δ = 144.8, 144.5, 100.2, 100.1, 98.6, 97.4, 95.4, 95.3, 80.9, 80.5, 70.4, 69.7, 69.4, 69.3, 66.5, 65.1, 56.5, 56.3, 55.8, 55.7, 19.8, 17.9

IR (ATR): ṽ = 3458 (w br), 3071 (w), 2987 (w), 2935 (w), 2894 (w), 2849 (w), 2825 (w), 2785 (w), 1648 (w), 1466 (w), 1445 (w), 1398 (w), 1368 (w), 1307 (w), 1267 (w), 1233 (w), 1214 (w), 1146 (m), 1097 (m), 1024 (s), 1008 (s), 915 (m), 882 (w), 860 (w), 819 (w), 746 (w), 721 (w), 693 (w), 614 (w), 595 (w), 579 (w), 499 (w), 467 (w), 432 (w)

HRMS (ESI) (m/z) [C₁₁H₂₀O₆Na]⁺ = [M+Na]⁺: calcd. 271.1158, found 271.1163

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -90° (c = 1.2 in CHCl₃, 1.5:1 dr)

Synthesis of 1-((2*S*,3*R*,4*R*)-3,4-bis(methoxymethoxy)-3,4-dihydro-2*H*-pyran-2-yl)ethan--1-one 208
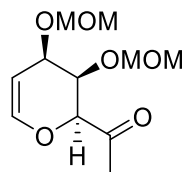
DMP (8.23 g, 19.41 mmol) and NaHCO$_3$ (3.26 g, 38.83 mmol) were added to a solution of alcohol **217** (2.41 g, 9.71 mmol) in DCM (50 ml). The reaction was stirred overnight at room temperature and was quenched with saturated Na$_2$S$_2$O$_3$ solution. The mixture was stirred for another 10 min before it was extracted with DCM. The combined organic extracts were washed with saturated NaHCO$_3$ solution and brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 1:1) to yield ketone **208** as a colourless oil (1.57 g, 66%).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 6.48 (dd, *J* = 6.2, 1.7 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 4.82 (dt, *J* = 6.2, 2.0 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.47 – 4.44 (m, 1H), 4.44 – 4.40 (m, 1H), 4.31 (dd, *J* = 1.7, 0.7 Hz, 1H), 3.38 (s, 3H), 3.33 (s, 3H), 2.33 (s, 3H)

^{13}C-NMR (CDCl$_3$, 100 MHz): δ = 206.2, 144.0, 101.4, 97.2, 95.1, 81.3, 70.3, 69.1, 56.3, 55.8, 28.0

IR (ATR): ṽ = 3074 (w), 2980 (w), 2951 (w), 2934 (w), 2894 (w), 2848 (w), 2825 (w), 1722 (m), 1648 (w), 1584 (w), 1469 (w), 1443 (w), 1417 (w), 1395 (w), 1356 (w), 1295 (w), 1235 (w), 1215 (m), 1148 (m), 1099 (m), 1020 (s), 978 (m), 964 (m), 915 (m), 890 (w), 837 (w), 785 (w), 744 (w), 720 (w), 691 (w), 666 (w), 631 (w), 564 (w), 495 (w), 482 (w), 429 (w)

HRMS (ESI) (m/z) [C$_{11}$H$_{18}$O$_6$Na]$^+$ = [M+Na]$^+$: calcd. 269.1001, found 269.1000

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = -90° (c = 1.2 in CHCl$_3$)

Synthesis of (2*R*,3*R*,4*R*)-2-[(*E*)-1-iodoprop-1-en-2-yl]-3,4-bis(methoxymethoxy)-3,4-dihydro-2*H*-pyran 230
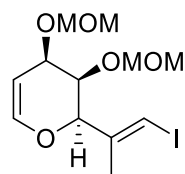
A solution of ketone **208** (100 mg, 0.41 mmol) and iodoform (480 mg, 1.22 mmol) in THF (4 ml) was added to a solution of chromium(II) chloride (549 mg, 4.47 mmol) in THF (3 ml). The reaction mixture was stirred overnight at room temperature. The mixture was quenched with water upon completion of the reaction (indicated by TLC) and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture (*E/Z* = 9:1, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 2:1) to yield *E*-vinyl iodide **230** as a colourless oil (71 mg, 47%).

^{1}H-NMR ((CD_3)$_2$CO, 600 MHz): δ = 6.44 – 6.43 (m, 1H), 6.38 (dd, *J* = 6.3, 2.1 Hz, 1H), 4.84 (d, *J* = 6.9 Hz, 1H), 4.74 – 4.72 (m, 2H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.57 – 4.54 (m, 2H), 4.51 (d, *J* = 6.9 Hz, 1H), 4.20 – 4.18 (m, 1H), 3.34 (s, 3H), 3.27 (s, 3H), 1.90 (dd, *J* = 1.07, 0.70 Hz, 3H)

^{13}C-NMR ((CD_3)$_2$CO, 150 MHz): δ = 144.3, 144.1, 102.3, 97.7, 95.6, 80.3, 79.2, 71.1, 69.0, 56.0, 55.5, 22.0

IR (ATR): $\tilde{\nu}$ = 3092 (w), 3072 (w), 2989 (w), 2947 (w), 2929 (w), 2891 (w), 2844 (w), 2823 (w), 2781 (w), 1650 (m), 1467 (w), 1442 (w), 1396 (w), 1363 (w), 1349 (w), 1297 (w), 1234 (m), 1213 (m), 1140 (m), 1099 (m), 1015 (s), 947 (m), 914 (m), 889 (m), 862 (w), 820 (w), 797 (w), 737 (w), 717 (m), 694 (w), 679 (w), 600 (w), 579 (w), 534 (w), 507 (w), 478 (w), 441 (w), 417 (w)

HRMS (ESI) (m/z) [$C_{12}H_{19}IO_5Na$]$^+$ = [M+Na]$^+$: calcd. 393.0175, found 393.0175

$[\boldsymbol{\alpha}]_D^{20}$ = -19° (c = 1.1 in $CHCl_3$)

Synthesis of {[(2S,3S,Z)-5-[(2R,3R,4R)-3,4-bis(methoxymethoxy)-3,4-dihydro-2H-pyran--2-yl]-3-methylhex-4-en-2-yl]oxy}(tert-butyl)dimethylsilane 214
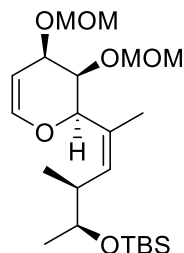
Method A: LiHMDS (1 M in THF) (0.18 ml, 0.18 mmol) was slowly added at −78 °C to a solution of sulfone **210** (50 mg, 0.13 mmol) in THF (3 ml). After 1 h a solution of ketone **208** (31 mg, 0.13 mmol) in THF (4 ml) was added dropwise. The reaction mixture was stirred for 4 h and was allowed to slowly warm to room temperature. Water was subsequently added and the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture (*E/Z* = 1:23, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to yield compound **214** as a colourless oil (3 mg, 6%).

Method B: LiHMDS (1 M in THF) (0.20 ml, 0.20 mmol) was added dropwise at −78 °C to a stirred solution of sulfone **210** (56 mg, 0.14 mmol) and ketone **208** (48 mg, 0.20 mmol) in THF (5 ml). The reaction mixture was warmed to room temperature after 4 h and water was added. The mixture was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. The crude mixture (*E/Z* = 1:25, determined by NMR) was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to yield compound **214** as a colourless oil (15 mg, 25%).

¹H-NMR ((CD$_3$)$_2$CO, 600 MHz): δ = 6.37 (dd, *J* = 6.4, 2.1 Hz, 1H), 5.26 – 5.23 (m, 1H), 4.86 (d, *J* = 6.6 Hz, 1H), 4.83 (d, *J* = 0.6 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.69 – 4.67 (m, 2H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.63 – 4.60 (m, 1H), 4.08 – 4.06 (m, 1H), 3.72 – 3.67 (m, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 2.43 – 2.36 (m, 1H), 1.85 (d, *J* = 1.4 Hz, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H)

¹³C-NMR ((CD$_3$)$_2$CO, 150 MHz): δ = 144.9, 133.3, 132.9, 101.9, 97.9, 95.6, 76.7, 73.3, 72.2, 71.0, 56.2, 55.4, 40.6, 26.3, 23.0, 21.2, 18.7, 16.5, -4.0, -4.6

IR (ATR): ṽ = 3070 (w), 2956 (w), 2929 (w), 2890 (w), 2857 (w), 2824 (w), 1649 (w), 1462 (w), 1394 (w), 1371 (w), 1300 (w), 1252 (w), 1234 (w), 1214 (w), 1151 (w), 1096 (w), 1023 (m), 982 (w), 963 (w), 940 (w), 919 (w), 888 (w), 836 (m), 808 (w), 774 (w), 750 (w), 722 (w), 691 (w), 666 (w), 614 (w), 600 (w), 582 (w), 554 (w), 518 (w), 478 (w), 437 (w), 420 (w)

HRMS (ESI) (m/z) $[C_{22}H_{42}O_6SiNa]^+$ = $[M+Na]^+$: calcd. 453.2648, found 453.2646

$[\alpha]_D^{20}$ = -46° (c = 0.3 in CHCl$_3$)

Synthesis of (2S,3S)-3-methylpent-4-en-2-ol 277
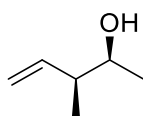
Cis-2-butene **278** (6.51 ml, 74.32 mmol) and *n*-BuLi (2.5 M in hexane) (17.84 ml, 44.59 mmol) were slowly added to a suspension of *t*-BuOK (5.00 g, 44.59 mmol) in THF (30 ml) at −78 °C. The mixture was stirred for 1 h at −42 °C and then it was recooled to −78 °C. A solution of (+)-methoxydiisopinocamphenylborane (16.46 g, 52.02 mmol) in diethyl ether (30 ml) was added dropwise. After stirring the reaction for 30 min at −78 °C, BF$_3$·Et$_2$O (6.42 ml, 52.02 mmol) was added dropwise, followed by a dropwise addition of acetaldehyde **279** (3.34 ml, 59.45 mmol) in diethyl ether (3 ml). After 3 h, the reaction was quenched with a 2 M NaOH solution and 30% aqueous H$_2$O$_2$. The reaction mixture was subsequently stirred for 1 h under reflux. The layers were then separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with water and brine, dried over MgSO$_4$ and concentrated *in vacuo* (500 mbar, 40 °C water bath). The residual liquid was carefully fractionated to give 6.04 g (bp 50-75 °C/94 mbar, 81% yield, >96% purity by ^{1}H-/^{13}C-NMR) of alcohol **277** as a colourless liquid.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 5.82 – 5.71 (m, 1H), 5.11 – 5.04 (m, 2H), 3.71 – 3.64 (m, 1H), 2.27 – 2.17 (m, 1H), 1.69 (s, 1H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H)

**^{13}C-NMR** (CDCl$_3$, 100 MHz): δ = 140.6, 115.6, 70.9, 44.9, 20.0, 14.8

IR (ATR): ṽ = 3358 (w), 3080 (w), 2971 (w), 2931 (w), 2878 (w), 1640 (w), 1454 (w), 1417 (w), 1398 (w), 1373 (w), 1345 (w), 1307 (w), 1270 (w), 1247 (w), 1176 (w), 1141 (w), 1087 (w), 1040 (w), 996 (w), 968 (w), 913 (m), 871 (w), 839 (w), 816 (w), 776 (w), 745 (w), 697 (w), 672 (w), 640 (w), 610 (w), 598 (w), 569 (w), 558 (w), 550 (w), 520 (w), 492 (w), 474 (w), 442 (w), 422 (w)

HRMS (ESI) (m/z) $[C_6H_{12}ONH_4]^+ = [M+NH_4]^+$: calcd. 118.1232, found 118.1226

$[\alpha]_D^{20}$ = -18° (c = 1.1 in CHCl$_3$)

The analytical data agree with those in the literature[161].

Synthesis of *tert*-butyldimethyl{[(2*S*,3*S*)-3-methylpent-4-en-2-yl]oxy}silane 276
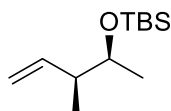
Alcohol **277** (5.00 g, 49.92 mmol) was dissolved in DCM (30 ml). Imidazole (6.12 g, 89.86 mmol) and TBSCl (11.29 g, 74.88 mmol) were added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (pentane) to yield compound **276** as a colourless liquid (9.17 g, 86%).

^{1}H-NMR (CDCl$_3$, 400 MHz): δ = 5.80 (ddd, *J* = 17.6, 10.2, 7.1 Hz, 1H), 5.03 – 4.96 (m, 2H), 3.67 – 3.60 (m, 1H), 2.21 – 2.11 (m, 1H), 1.07 (d, *J* = 6.1 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H)

^{13}C-NMR (CDCl$_3$, 100 MHz): δ = 141.7, 114.1, 72.1, 45.7, 26.0, 21.1, 18.3, 15.6, -4.2, -4.6

IR (ATR): ṽ = 3080 (w), 2957 (w), 2930 (w), 2886 (w), 2858 (w), 1641 (w), 1463 (w), 1416 (w), 1373 (w), 1294 (w), 1253 (w), 1217 (w), 1187 (w), 1172 (w), 1142 (w), 1097 (w), 1057 (w), 1040 (w), 1006 (w), 977 (w), 956 (w), 940 (w), 912 (w), 896 (w), 832 (m), 811 (w), 772 (m), 669 (w), 602 (w), 575 (w), 517 (w), 505 (w), 486 (w), 457 (w), 418 (w)

HRMS (EI, 70 eV) (m/z) $[C_{12}H_{27}OSi]^+ = [M+H]^+$: calcd. 215.4320, found 215.4317

$[\alpha]_D^{20}$ = -7° (c = 1.1 in CHCl$_3$)

The analytical data agree with those in the literature[147].

Synthesis of (2*S*,3*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylbutan-1-ol 275
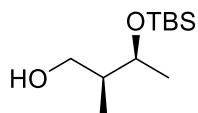
Compound **276** (7.00 g, 32.65 mmol) was dissolved in a 1:1 mixture of DCM (40 ml) and methanol (40 ml), and the solution was cooled to –78 °C. Ozone was bubbled through the solution until it turned blue, and the excess ozone was purged with oxygen until the solution became colourless again. The solution was warmed to 0 °C before NaBH$_4$ (3.71 g, 97.94 mmol) was added portion-wise. After 3 h, the reaction was quenched with water and extracted with DCM. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane/diethyl ether 5:1) to obtain alcohol **275** as a colourless liquid (5.58 g, 78%).

^{1}H-NMR (CDCl$_3$, 600 MHz): δ = 4.02 – 3.97 (m, 1H), 3.71 (dd, *J* = 10.7, 9.0 Hz, 1H), 3.50 (dd, *J* = 10.7, 4.5 Hz, 1H), 2.92 (s br, 1H), 1.99 – 1.91 (m, 1H), 1.14 (dd, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.78 (d, *J* = 7.1 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H)

^{13}C-NMR (CDCl$_3$, 150 MHz): δ = 72.4, 65.8, 40.9, 25.9, 18.4, 18.1, 12.5, -4.4, -5.0

IR (ATR): ṽ = 3299 (w), 2957 (w), 2930 (w), 2885 (w), 2858 (w), 1651 (w), 1534 (w), 1451 (w), 1409 (w), 1388 (w), 1253 (w), 1187 (w), 1157 (w), 1108 (w), 1092 (w), 1043 (w), 961 (w), 942 (w), 901 (w), 835 (w), 814 (w), 774 (w), 742 (w), 677 (w), 600 (w), 551 (w), 478 (w), 467 (w), 419 (w)

HRMS (EI, 70 eV) (m/z) [C$_{11}$H$_{27}$O$_2$Si]$^+$ = [M+H]$^+$: calcd. 219.1780, found 219.1785

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = 11° (c = 1.0 in CHCl$_3$)

The analytical data agree with those in the literature[162].

Synthesis of 5-(((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylbutyl)sulfonyl)-1-phenyl-1*H*-tetrazole 209
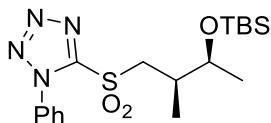
1-phenyl-1*H*-tetrazol-5-thiol (1.47 g, 8.24 mmol) and triphenylphosphine (2.16 g, 8.24 mmol) were added to a solution of alcohol **275** (1.50 g, 6.87 mmol) in THF (40 ml). The reaction mixture was cooled to 0 °C and DEAD (1.28 ml, 8.24 mmol) was added dropwise. After 1 h the reaction was warmed to room temperature and ethanol (10 ml) was added. A solution of ammonium molybdate tetrahydrate (1.70 g, 1.37 mmol) and 30% aqueous H_2O_2 (14.03 ml, 0.14 mol) in ethanol (25 ml) was subsequently added, and the reaction was stirred overnight at room temperature. After completion of the reaction (indicated by TLC), it was diluted with water and DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 8:1) to yield phenyltetrazolyl sulfone **209** as a colourless oil (2.50 g, 89%).

¹H-NMR (CDCl₃, 600 MHz): δ = 7.70 – 7.57 (m, 5H), 4.03 (dd, *J* = 14.4, 3.8 Hz, 1H), 4.01 – 3.97 (m, 1H), 3.54 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.42 – 2.35 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 154.2, 133.3, 131.6, 129.8, 125.3, 70.2, 58.8, 35.1, 25.9, 19.6, 18.1, 14.5, -4.2, -4.8

IR (ATR): ṽ = 3435 (w), 3412 (w), 3314 (w), 3073 (w), 2976 (w), 2950 (w), 2930 (w), 2886 (w), 2857 (w), 1733 (w), 1594 (w), 1496 (w), 1467 (w), 1408 (w), 1389 (w), 1371 (w), 1339 (w), 1319 (w), 1250 (w), 1207 (w), 1155 (w), 1126 (w), 1109 (w), 1087 (w), 1075 (w), 1040 (w), 1028 (w), 1010 (w), 985 (w), 963 (w), 955 (w), 942 (w), 926 (w), 904 (w), 833 (w), 801 (w), 767 (m), 722 (w), 708 (w), 689 (w), 670 (w), 632 (w), 603 (w), 571 (w), 558 (w), 538 (w), 519 (w), 504 (w), 471 (w), 448 (w)

HRMS (ESI) (m/z) $[C_{18}H_{31}N_4O_3SSi]^+$ = $[M+H]^+$: calcd. 411.1886, found 411.1877

$[\alpha]_D^{20}$ = -3° (c = 1.0 in CHCl₃)

Synthesis of 2-{[(2*R*,3*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylbutyl]sulfonyl}benzo[*d*]thiazole 210
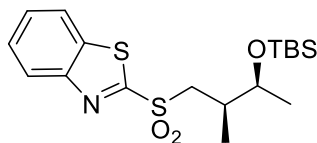
1,3-benzothiazole-2-thiol (1.84 g, 10.99 mmol) and triphenylphosphine (2.88 g, 10.99 mmol) were added to a solution of alcohol **275** (2.00 g, 9.16 mmol) in THF (60 ml). The reaction mixture was cooled to 0 °C and DEAD (1.71 ml, 10.99 mmol) was added dropwise. After 1 h, the reaction was warmed to room temperature and ethanol (15 ml) was added. A solution of ammonium molybdate tetrahydrate (2.26 g, 1.83 mmol) and 30% aqueous H_2O_2 (18.71 ml, 0.18 mol) in ethanol (40 ml) was subsequently added. The reaction was stirred overnight at room temperature, and upon completion of the reaction (indicated by TLC), it was diluted with water and DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (pentane/diethyl ether 8:1) to yield benzothiazolyl sulfone **210** as a colourless oil (2.84 g, 78%).

¹H-NMR (CDCl₃, 600 MHz): δ = 8.23 – 8.20 (m, 1H), 8.03 – 8.00 (m, 1H), 7.65 – 7.62 (m, 1H), 7.61 – 7.57 (m, 1H), 3.93 – 3.89 (m, 1H), 3.80 (dd, *J* = 14.4, 3.5 Hz, 1H), 3.27 (dd, *J* = 14.4, 9.1 Hz, 1H), 2.38 – 2.31 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.79 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H)

¹³C-NMR (CDCl₃, 150 MHz): δ = 166.6, 152.9, 137.0, 128.1, 127.7, 125.7, 122.4, 70.4, 57.3, 35.6, 25.8, 19.2, 18.1, 15.0, -4.4, -4.9

IR (ATR): ṽ = 2954 (w), 2929 (w), 2884 (w), 2856 (w), 1555 (w), 1471 (w), 1423 (w), 1405 (w), 1385 (w), 1330 (m), 1252 (w), 1206 (w), 1180 (w), 1146 (m), 1124 (w), 1102 (m), 1085 (m), 1066 (w), 1027 (m), 1007 (w), 956 (w), 914 (w), 833 (m), 799 (w), 774 (m), 760 (m), 729 (m), 688 (w), 667 (w), 631 (m), 617 (m), 592 (w), 569 (w), 533 (w), 520 (w), 494 (w), 475 (w), 432 (m)

HRMS (ESI) (m/z) $[C_{18}H_{30}NO_3S_2Si]^+ = [M+H]^+$: calcd. 400.1436, found 400.1437

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\textbf{20}}$ = -8° (c = 0.7 in CHCl₃)

6. References

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# 7. Appendix – NOESY NMR spectra for confirmation of stereochemistry

{[(2*R*,3*R*,6*R*)-6-allyl-2-[(4*S*,5*S*,*Z*)-5-[(*tert*-butyldimethylsilyl)oxy]-4-methylhex-2-en-2-yl]-3,6-dihydro-2*H*-pyran-3-yl]oxy}(*tert*-butyl)dimethylsilane **211**
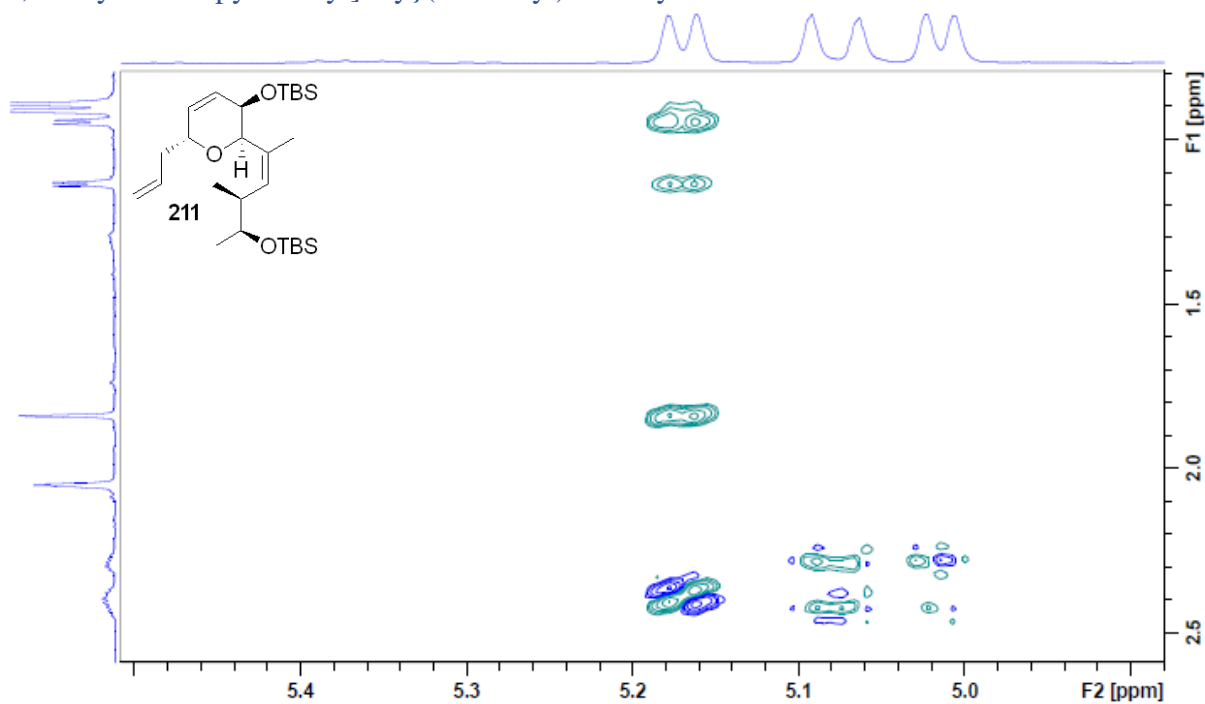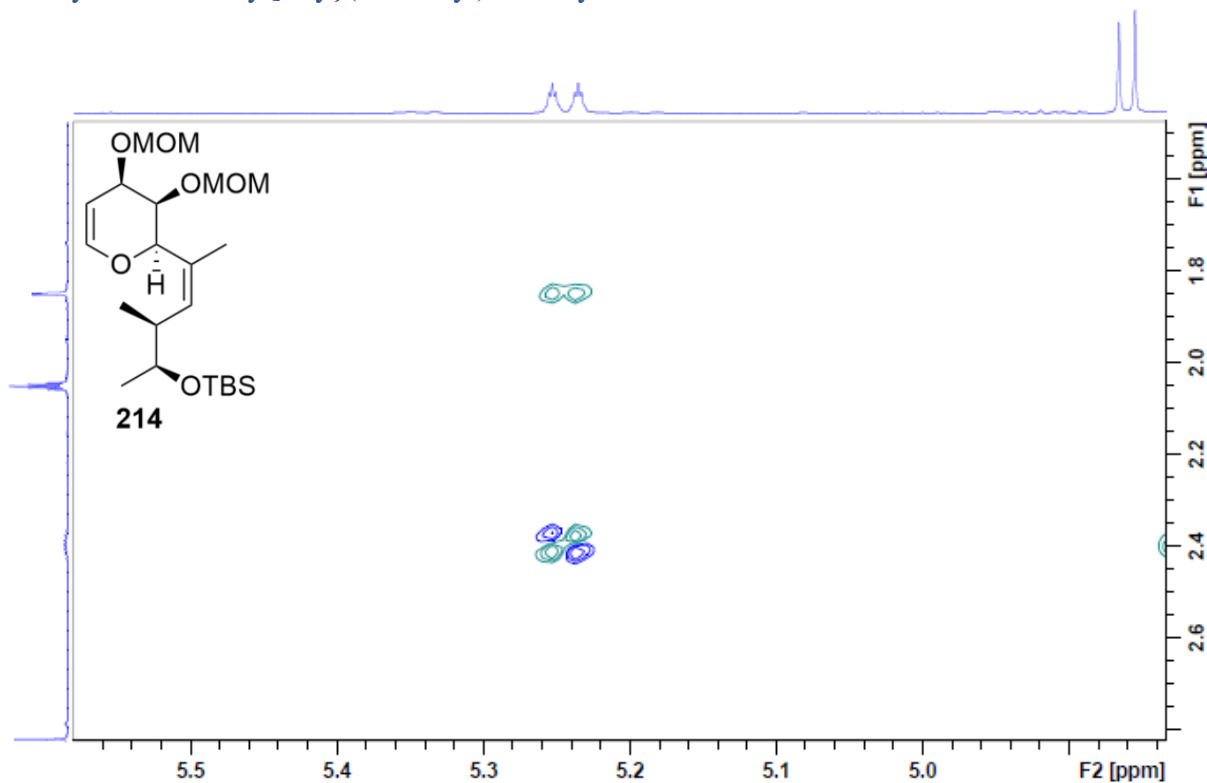

{[(2*S*,3*S*,*Z*)-5-[(2*R*,3*R*,6*R*)-6-allyl-3-(methoxymethoxy)-3,6-dihydro-2*H*-pyran-2-yl]-3-methylhex-4-en-2-yl]oxy}(*tert*-butyl)dimethylsilane **212**
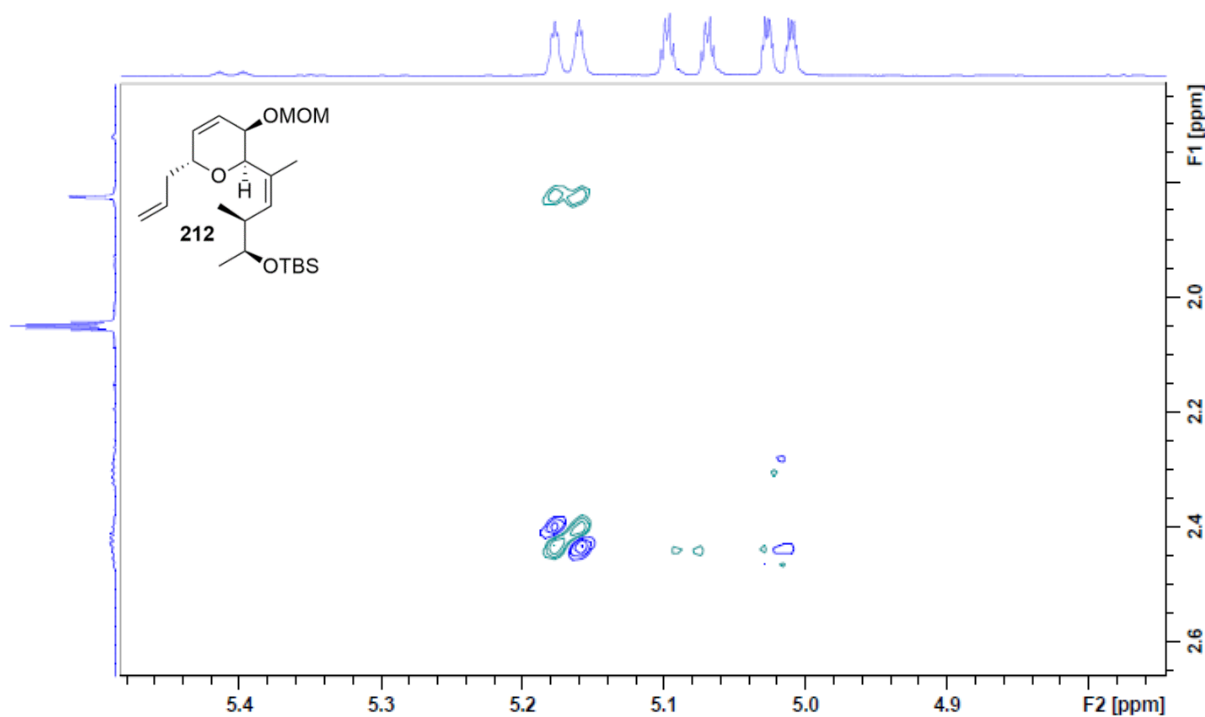
tert-butyl{[(2*R*,3*R*,6*R*)-2-[(4*S*,5*S*,*Z*)-5-[(*tert*-butyldimethylsilyl)oxy]-4-methylhex-2-en-2-yl]-6-(2,2-dimethoxyethyl)-3,6-dihydro-2*H*-pyran-3-yl]oxy}dimethylsilane **213**
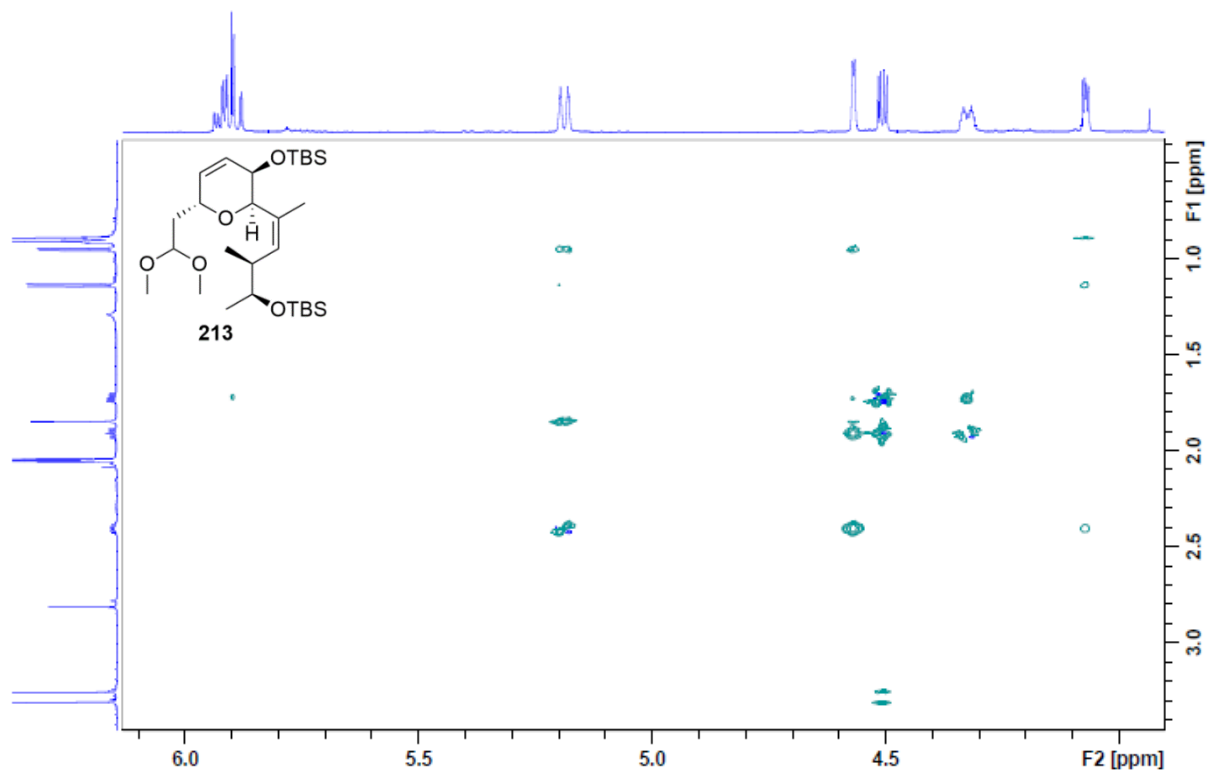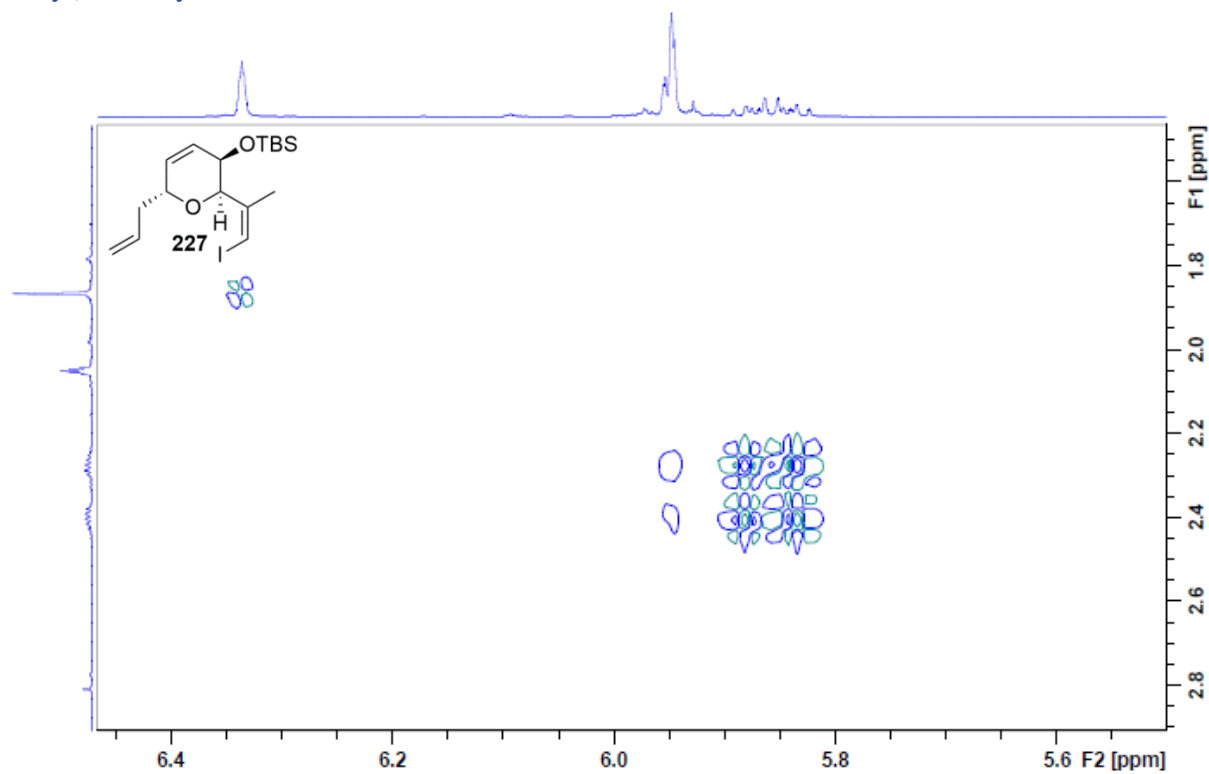

{[(2*S*,3*S*,*Z*)-5-[(2*R*,3*R*,4*R*)-3,4-bis(methoxymethoxy)-3,4-dihydro-2*H*-pyran-2-yl]-3-methylhex-4-en-2-yl]oxy}(*tert*-butyl)dimethylsilane **214**
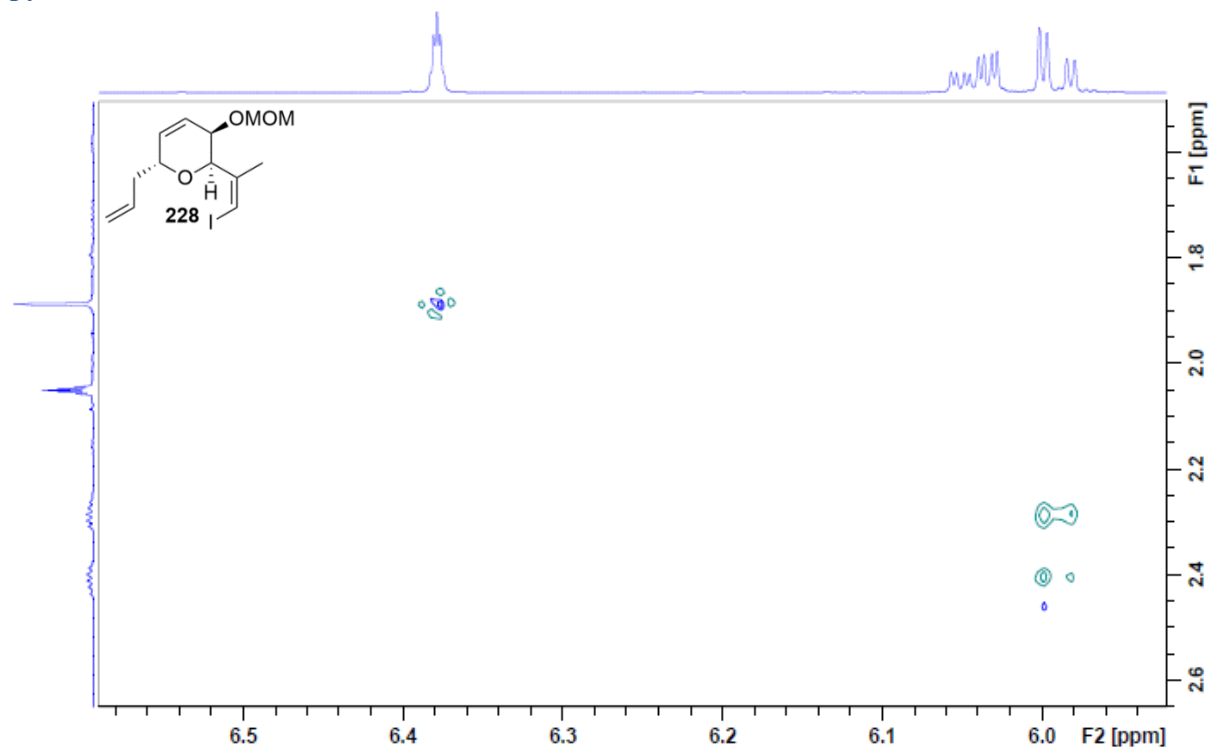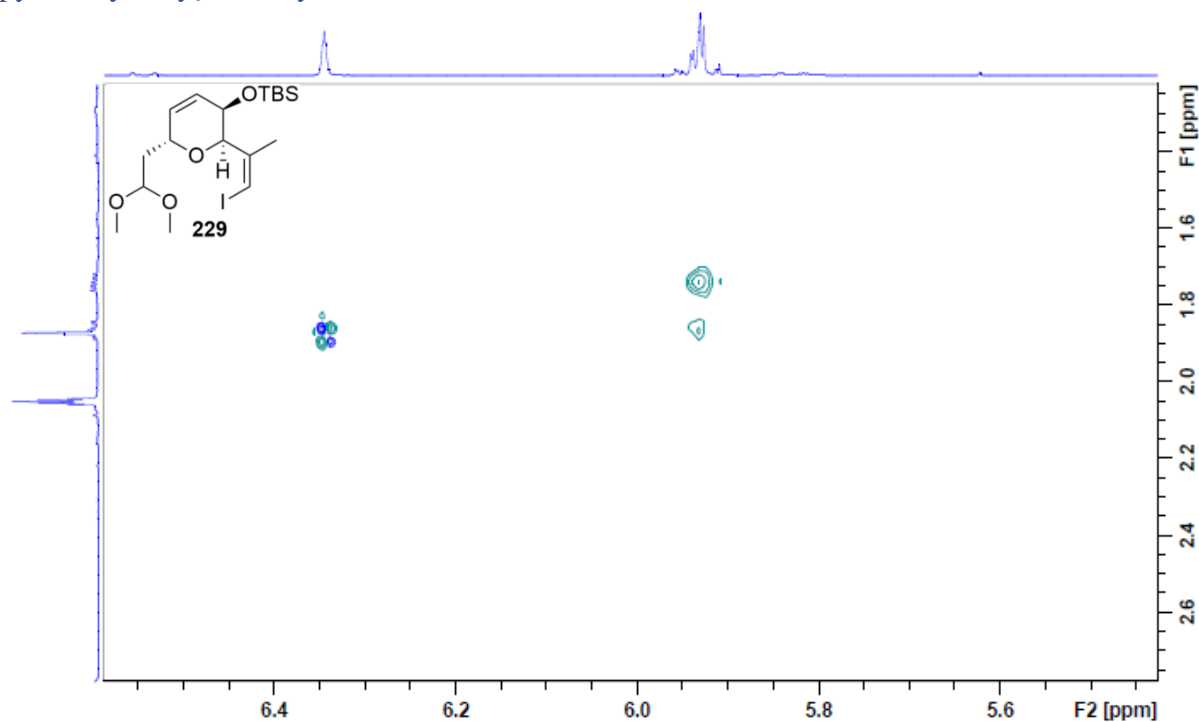
{[(2R,3R,6R)-6-allyl-2-[(Z)-1-iodoprop-1-en-2-yl]-3,6-dihydro-2H-pyran-3-yl]oxy}(*tert*-butyl)dimethylsilane **227**

(2R,3R,6R)-6-allyl-2-[(Z)-1-iodoprop-1-en-2-yl]-3-(methoxymethoxy)-3,6-dihydro-2H-pyran **228**

tert-butyl{[(2*R*,3*R*,6*R*)-6-(2,2-dimethoxyethyl)-2-[(*Z*)-1-iodoprop-1-en-2-yl]-3,6-dihydro-2*H*-pyran-3-yl]oxy}dimethylsilane **229**

(2*R*,3*R*,4*R*)-2-[(*E*)-1-iodoprop-1-en-2-yl]-3,4-bis(methoxymethoxy)-3,4-dihydro-2*H*-pyran **230**