Synthesis of Highly Functionalised Furo[3,4-*b*]pyrans: Towards the Fungal Metabolite (−)-TAN-2483B

by

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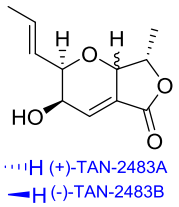
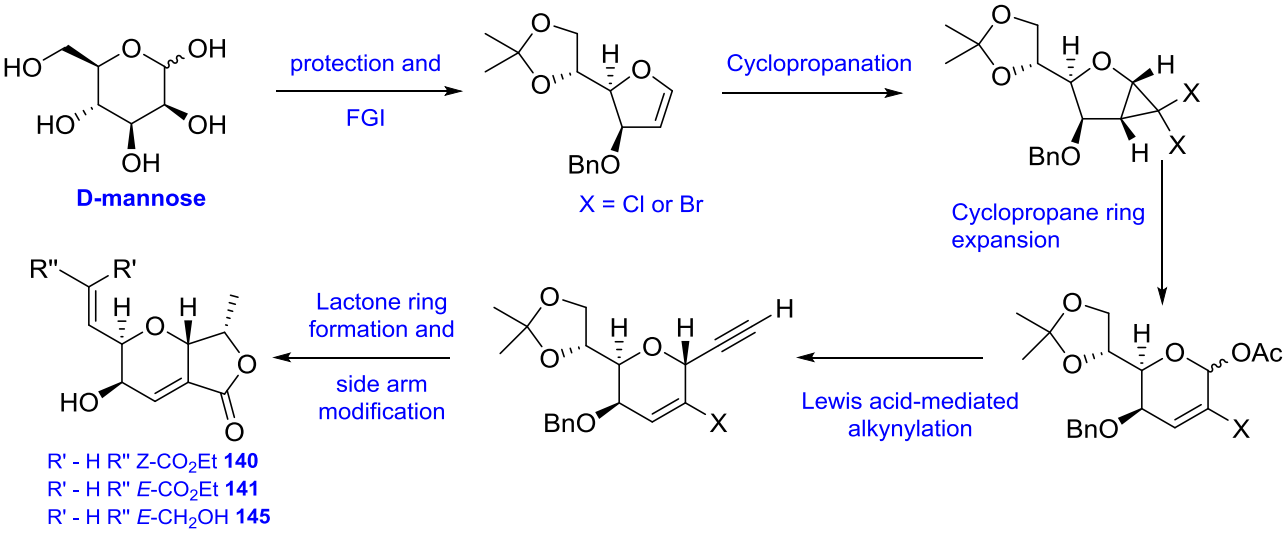
Abstract

Carbohydrate-derived cyclopropanes combine both the stereochemical wealth of carbohydrates and the reactivity of cyclopropanes. A diverse variety of reaction modes for these cyclopropyl carbohydrates can be harnessed for the synthesis of natural products and other targets.

The natural products (−)-TAN-2483A and (−)-TAN-2483B are fungal secondary metabolites displaying a variety of bioactivities such as inhibition of *c*-src kinase action and parathyroid hormone-induced bone resorption. This thesis described several synthetic approaches to the natural product (−)-TAN-2483B and analogues of (−)-TAN-2483B employing cyclopropane ring expansion.



The synthetic route to (−)-TAN-2483B began with the readily available substrate D-mannose. The pyran ring unsaturation of the natural product was established by a cyclopropanation-ring expansion sequence. A synthetic strategy via dichlorocyclopropane-based intermediates is described in chapter 2. This being unsuccessful, an alternative approach via 2-fomyl-glycal was developed in chapter 3. The chapter 2 and 3 provided a solid background for the achievement of the analogues synthesis illustrated in chapter 4 via dibromocyclopropane. Lewis acid-mediated alkynylation followed by Pd-catalysed carbonylative lactonisation was successfully utilised in the revelation of the furo[3,4-*b*]pyran ring skeleton. This route afforded analogues of TAN-2483B; the *Z*-and *E*-unsaturated ethyl esters **140** and **141** and hydroxy(−)-TAN-2483B **145**. The total synthesis of (−)-TAN-2483B was not achieved due to unforeseen obstacles encountered in the deoxygenation of the side arm of **335** (Chapter 4) into the *E*-propenyl side arm of (−)-TAN-2483B.



To my dearest parents

and

loving husband…

Thus go with the steadfast, wise, well-versed,

firm of virtue, practice-pure,

Ennobled 'Such', who's sound, sincere,

as moon in wake of the Milky Way.

Verse 208. The Good And The Wise

From **Dhammapada**

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Special thanks to Ian Vorster for all his dedication to keep NMR machines healthy and his great help in running overnight experiments for me. Further for Jonathan Singh running NMR on 600 NMR for me. Then my best lab mate Jingjing Wang for running HRMS during her busy working hours in the lab.

I was so lucky to work with such amazing group of lab mates. Hemi and Mark you both are such a brilliant chemists. Thank you very much for the useful discussions had with me on TAN. Peter, Jingjing, Scott, Dylan, Claire, Thomas, Jhonny, Rhia, Ben, Tat, Sarah and Loic you all made our AM205 extremely lovely and enjoyable place to work.

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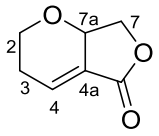
Glossary

AIBN	2,2’-azo-bis-isobutyronitrile
br.S	broad singlet
brsm	based on recovered starting material
conc.	concentration
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicycloundec-7-ene
DMAP	*N,N*-dimethyl-4-aminopyridine
DMF	*N,N*-dimethylformamide
DMF.DMA	*N,N*-dimethyl formamide dimethyl acetal
DIPEA	*N,N*-Diisopropylethylamine
Dppf	1,1’-bis(diphenylphosphino)ferrocene
eq.	equivalents
FGI	functional group interchange
HMBC	heteronuclear multi bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear Single Quantum Coherence
HWE	Horner-Wadsworth-Emmons
IR	infrared
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m.p.	melting point

***m*-CPBA**	*m*-chloroperbenzoic acid
MOM	methoxy methyl acetal
Ms	methanesulfonyl (a.k.a. mesyl)
NBS	*N*-Bromosuccinimide
NMR	nuclear magnetic resonance
NMO	*N*-Methylmorpholine-*N*-Oxide
n*Oe*	nuclear Overhauser effect
Nuc	nucleophile
PTSA	*p*-toluene sulfonic acid
PPTS	pyridinium p-toluenesulfonate
PMP	*p*-methoxy phenyl
q	quartet
r.t.	room temperature
R_f	retention factor
s	singlet
sat.	saturated
t	triplet
TBAI	tetrabutylammonium iodide
TBS	^{t}butyldimethylsilyl
TBAB	tetrabutylammonium bromide
TEBAC	benzyltriethylammonium chloride
TPAP	Tetrapropylammonium perruthenate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl (a.k.a. tosyl)

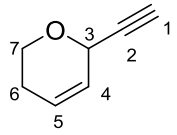
Compound naming and numbering

- All the compounds include in this thesis were named according to the IUPAC recommendations.



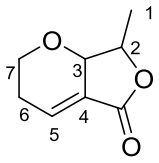
Numbering system used in IUPAC naming compound

- In the experimental section for *C*-glycosides, compound numbering started from the terminal end of the aglycon unit.



Numbering system used in *C*-glycosides

- Compounds incorporating the furo[3,4-*b*]pyran ring system are numbered starting from the methyl end of the lactone ring.



Numbering system used in experimental section

1 Introduction

The joy of
'The art and science of constructing the
molecules of nature in the laboratory'[1]
K. C. Nicolaou

The preparation of urea by Friedrich Wöhler from ammonium cyanate in 1828 represents the origin of natural product synthesis. This was one of the turning points in chemistry because it is considered as the first synthesis of an organic compound from inorganic starting materials. Total and partial (semi) synthesis of natural products are the two main fields of investigation, which allowed the expansion of new scientific knowledge into practical applications.[1]There are many reasons for development of chemical methods for the synthesis of natural products. Designing strategies and artificial creation of challenging molecular architectures present in nature encourages the invention of new synthetic strategies. It can be beneficial to synthesise scarce, biologically active natural products on a large scale and in a cost effective manner for further biological and medicinal experiments. Another benefit of synthesis is the ability to make analogues of the naturally occurring compounds that have enhanced potency, improved selectivity and/or more suitable physical and chemical properties, leading to superior pharmaceuticals.

The vast chemical and biological diversity in nature provides an extraordinary resource for finding drugs to treat various diseases. The structure of these compounds varies from simple linear peptides to complex macrocyclic polyethers.[2] The isolation and identification of anti-cancer drugs from organisms found in nature is often followed by synthetic endeavours towards the natural products themselves and structural analogues. Structure-activity relationships can then be identified, which allow further structural modifications for therapeutic applications

The main goal of this study was the total synthesis of (−)-TAN-2483B and its side arm variants as potential analogues. (−)-TAN-2483B is a member of the group of natural products incorporating the furo[3,4-*b*]pyran-5-one motif. These fungal secondary metabolites exhibit a variety of bioactivities ranging from antibacterial to antitumor activites. (−)-TAN-2483A and (−)-TAN-2483B were reported to inhibit *c*-src kinase and PTH (parathayroid hormone) induced bone resorption,[3] with potential application in cancer and osteoporosis treatment.

1.1 Furopyrans and furopyran containing natural products

An organic compound containing fused pyran and furan rings is known as a furopyran. It is a relatively unexplored moiety synthetically and biosynthetically, and yet encompasses great structural diversity. The substitution pattern, position of the ring fusion and oxidation state are the key factors contributing to the structural diversity. The following figure illustrates the various positions of the ring fusion.

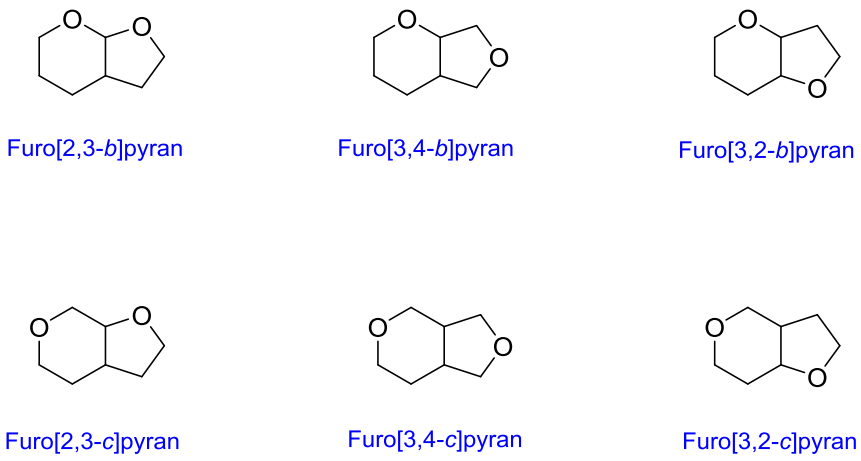


Figure 1.1: Furopyran diversity based on position of the ring fusion

Natural products containing a furopyran motif have been the synthetic targets of few publications in the scientific literature. The origin of these furopyran-containing natural products is diverse, ranging from prokaryotic to eukaryotic sources. Labillarides *E-H* (**1**) were isolated from red algae,[4] while the antibiotic (−)-okilactomycin (**2**) was isolated from the culture filtrate of a strain of actinomycetes.[5] Patulin (**3**) is a mycotoxin produced by a variety of moulds, in particular, *Aspergillus*, *Penicillium* and *Byssochlamys* (Figure 1.2).[6] Most of the natural products containing furopyran ring systems are biologically active, with activities ranging from antifungal to anticancer.

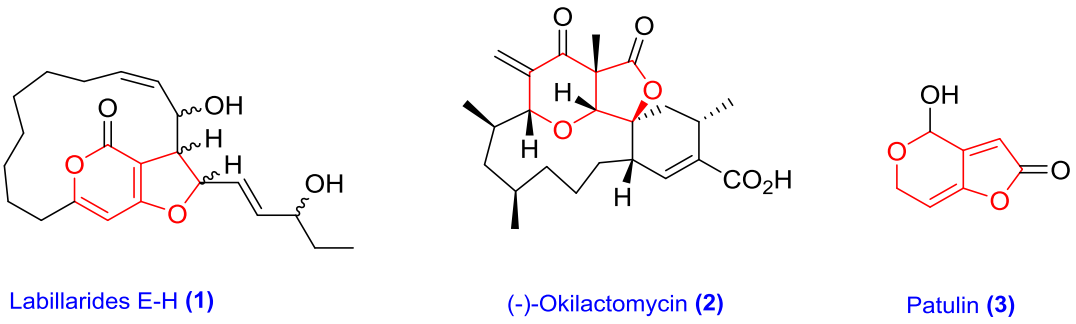


Figure 1.2: Selected natural products containing a furopyran motif

1.1.1 Furo[3,4-*b*]pyran

Of particular interest to this research is the furo[3,4-*b*]pyran motif contained in several natural products. Various strategies can be identified for the synthesis of this heterocyclic ring system according to the chemical environment required.

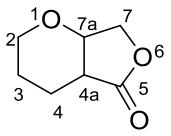
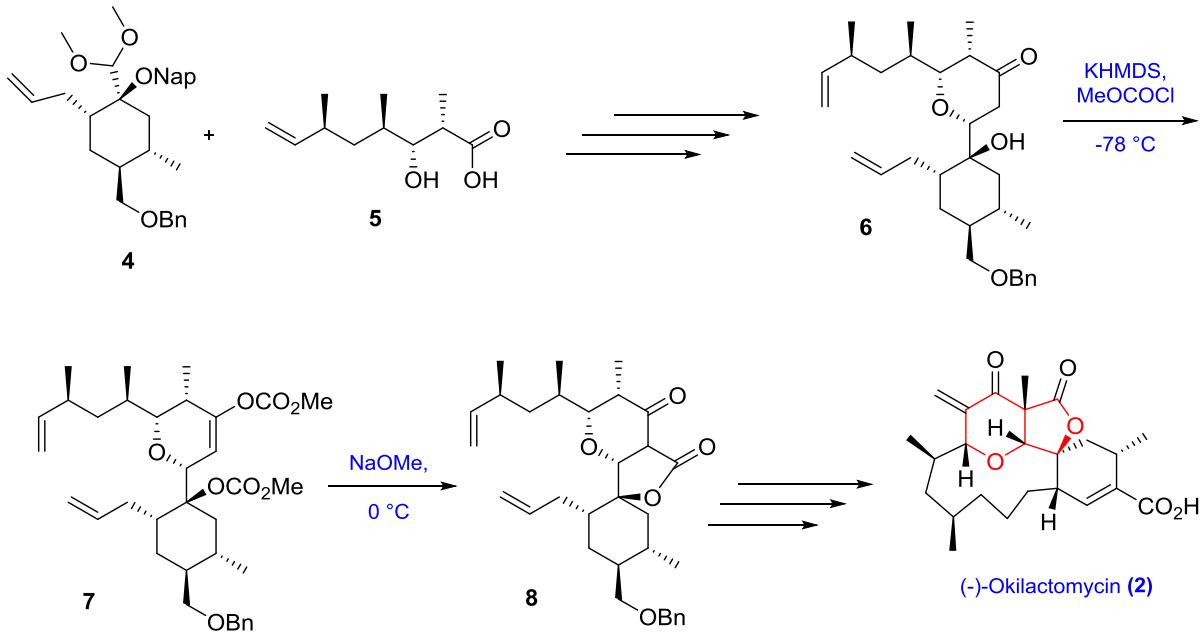


Figure 1.3: Furo[3,4-*b*]pyran

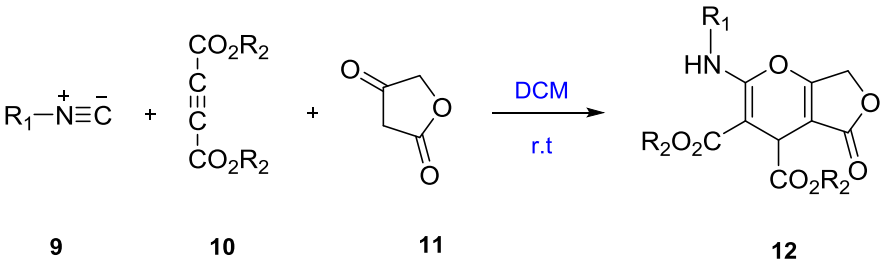
1.1.2 Synthetic strategies for furo[3,4-*b*]pyrans

Okilactomycin is a 13-membered macrocycle containing a highly functionalised cyclohexene, a quaternary spirocyclic centre and an embedded furo[3,4-*b*]pyran moiety. Tetrahydropyranone **6** was furnished from α-hydroxy acid **5**, and dimethyl acetal **4**, exploiting the powerful Petasis-Ferrier union/rearrangement strategy (Scheme 1.1).[7] Smith *et al.* synthesised the furo[3,4-*b*]pyran by manipulating the tetrahydropyranone **8** through formation of the enol carbonate **7** and a Dieckmann ring closure.[7] In the formation of lactone **8**, biscarbonate **7**, was subjected to chemoselective methanolysis to form an intermediate sodium enolate, derived from the enol carbonate, then it underwent cyclisation with the tertiary carbonate to furnish furopyran as a single diastereomer.



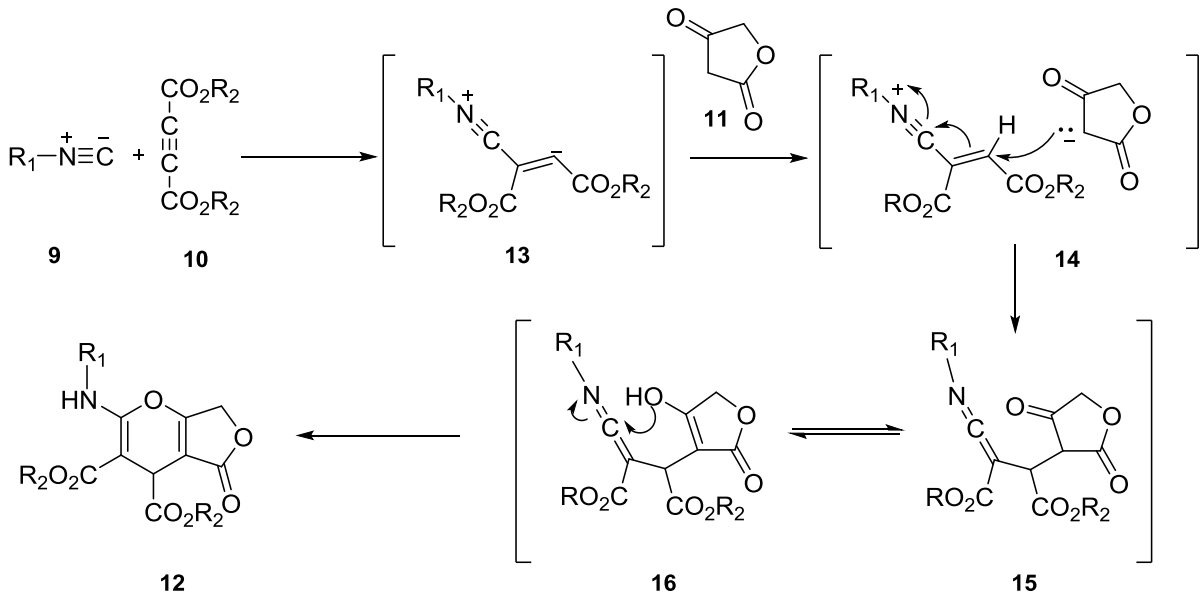
Scheme 1.1: Synthesis of (−)-okilactomycin [7]

In 2008, the Shabaani group reported a method to synthesise the *4H*-furo[3,4-*b*]pyran ring system via a multi-component reaction strategy (Scheme 1.2).[8] Isocyanide **9**, dialkyl acetylenedicarboxylate **10**, and tetronic acid **11**, undergo a 1:1:1 addition reaction to form the ring system at ambient temperature. A mechanism was tentatively proposed as shown in scheme 1.3. Addition of isocyanide **9** to an acetylene dicarboxylate **10** would afford zwitterion **14**. Proton transfer with tetronic acid (**11**) and subsequent Michael addition would give iminoketene **15**. Tautomerism would then lead to cyclisation to produce the furo[3,4-*b*]pyran ring system **12**.



9 **10** **11** **12**

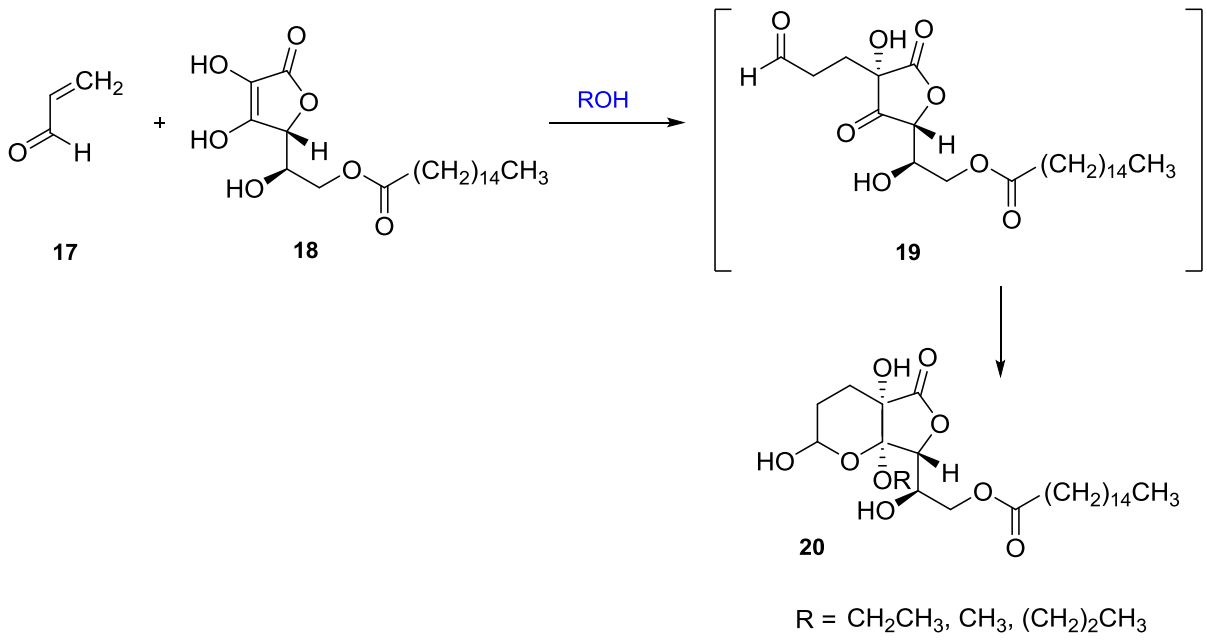
Scheme 1.2: Synthesis of furo[3,4-*b*]pyran **12** via multi-component reaction[8]



9 **10** **13** **11** **14** **12** **16** **15**

Scheme 1.3: Proposed mechanism for three component coupling reaction[8]

A series of protein phosphatase inhibitors containing the furo[3,4-*b*]pyran system has been synthesised from Michael donor, 6-*O*-palmetoyl ascorbic acid (**18**) and acrolein (**17**) in nucleophilic alcoholic solvents (Scheme 1.4).[9] The initial Michael addition of ascorbic acid (**18**) to acrolein leads to intermediate **19**. In the presence of nucleophilic solvents, the aldehyde intermediate **19** is attacked by the internal alcohol, forming a hemiacetal, followed by intramolecular cyclisation to the stable furo[3,4-*b*]pyran product.



Scheme 1.4: Protein phosphatase inhibitors synthesis via Michael addition[9]

1.1.3 Furo[3,4-*b*]pyran based natural products

The furo[3,4-*b*]pyran-5-one heteroatomic bicycle is present in several natural products and has been the synthetic target of several publications. Fusidilactone, massarilactone, (−)-TAN-2483A, (−)-TAN-2483B, and waol A, share the furo[3,4-*b*]pyran-5-one ring system. All of these compounds are of fungal origin, and display numerous structural similarities leading to related bioactivities.

Waol compounds

In 1994, Mizoue and co-workers carried out screening programmes for low molecular weight compounds effective against multidrug resistant tumour cells using human promyelocytic (cancer cells in blood or bone marrow) leukaemia cells. During this study, they discovered a new five-membered lactone FD-211 (waol A) in the fermentation broth of *Myceliophthora lutea* TF-0409. The structure **21** proposed in 1994 (Figure 1.4) was revised by Barry B. Snider in 2002 through synthesis.[10]

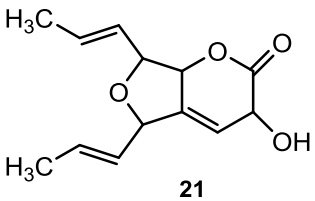
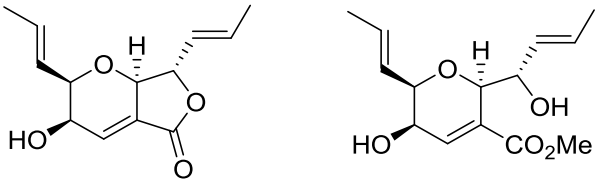


Figure 1.4 Initially proposed structure for waol A[10b]

FTIR and NMR spectroscopic evidence indicated to the Snider's team that the structure initially proposed by Mizoue was incorrect. The IR carbonyl stretch of the isolated waol A is 1767 cm^{-1}, characteristic of a γ-lactone. The endocyclic alkene hydrogen of the proposed waol A should be between 5—6 ppm while, in the isolated waol A, it is at 6.90 ppm, which is characteristic of an α,β-unsaturated lactone. By considering this information together, Snider's group revised the waol A structure as 2,3,7,7a-tetrahydro-*5H*-furo[3,4-*b*]pyran-5-one (**22**) (Figure 1.5). Their predictions were confirmed by synthesis of these natural products (**section 1.3**). Waol B (**23**) is the ring opened methyl ester variant of Waol A.[10a]

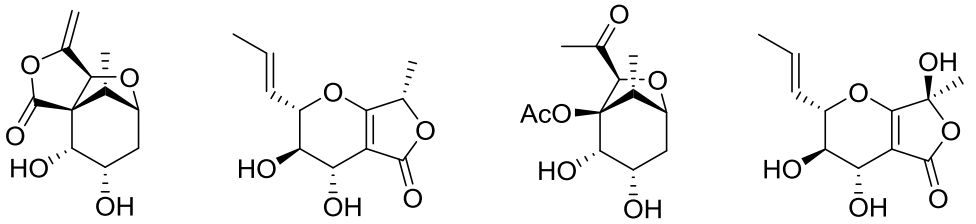


(-)-Waol A (**22**) Waol B (**23**)

Figure 1.5: Revised structures of waol A and B[10a]

Massarilactones

In 2000, the polyketide-derived antibacterial compounds massarilactones A (**24**) and B (**25**) were isolated from cultures of the freshwater aquatic fungus *Massarina tunicata*.[11] Both massarilactone A and B showed inhibition activity against *Bacillus subtilis* and massarilactone B was active against *Staphylococus aureus*. Massarilactones C (**26**), and D (**27**) were later isolated from the endophytic fungus *Coniothyrium sp.*[12] These compounds were inactive against *Bacillus subtilis* and *Staphylococus aureus*.[12]



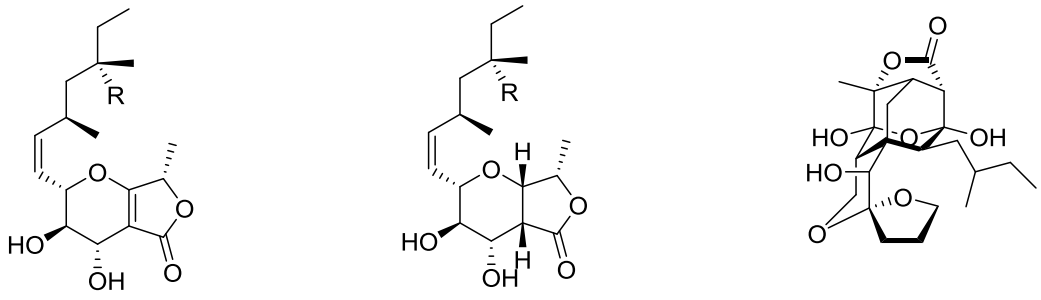
(+)-massarilactone A (**24**) (+)-massarilactone C (**26**)

(-)-massarilactone B (**25**) (-)-massarilactone D (**27**)

Figure 1.6: Massarilactone A—D [12-13]

Fusidilactones

In 2002, fusidilactones A (**28**) and B (**29**) were isolated from an endophytic *Fusidium* species by Krohn and co-workers in Germany.[14] These compounds exhibited good antifungal activity against *Eurotium repense* and *Fusarium oxyporum*, while weak antibacterial activity was displayed against *Escherichia coli* and *Bacillus megaterium*. The new bicyclic fusidilactone D (**31**) and E (**32**) were isolated along with the known fusidilactone B.[15] Fusidilactone C (**30**) is an unusual complex molecule having a rare architectural design. Structural properties including two ether bridged hemiacetals, a rigid oxadamantane ring and spiroacetal structure make fusidilactone C a structurally fascinating natural product.



R = H (+)-fusidilactone A (**28**)
R = OH (+)-fusidilactone D (**31**)

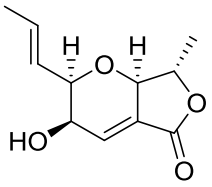
R = OH (+)-fusidilactone B (**29**)
R = H (+)-fusidilactone E (**32**)

(+)-fusidilactone C (**30**)

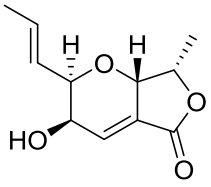
Figure 1.7: Fusidilactones A-E

(–)-TAN-2483A and (–)-TAN-2483B

In 1998 Hayashi *et al.* reported two novel compounds (–)-TAN-2483A (**33**) and (–)-TAN-2483B (**34**), the latter being the primary synthetic target of this thesis. The group of scientists from Takeda Chemical Industries isolated these natural products from a culture of the filamentous fungus NF 2329.[3] (–)-TAN-2483A has a very similar structure to that of waol A except for a methyl group replacing the propenyl group at C7. Full characterisation and initial biological data for the (–)-TAN-2483B were reported in the patent, while in contrast (–)-TAN-2483B was poorly characterised and reported.



(-)-TAN-2483A (**33**)



(-)-TAN-2483B (**34**)

Figure 1.8: Structures of (−)-TAN-2483A and (−)-TAN-2483B

According to the patent data, (−)-TAN-2483A shows strong *c*-src kinase inhibitory action and PTH-induced bone resorption. Thus, it may be useful as a therapeutic or preventive agent for osteoporosis or cancer.[3]

c-Src is a non-receptor tyrosine kinase that is abundant in platelets, osteoclasts and neural tissues. *c*-Src kinases are proto-oncogenic proteins (enzymes) that regulate cell growth, migration and survival by phosphorylation of proteins in the cell using phosphate donors like ATP. Protein kinases can mutate and can cause unregulated cell division, which is a necessary step in developing cancer. Thus, kinase inhibitors have been considered as putative cancer therapeutics.[16] *c*-Src kinase inhibitors can be classified into two major groups according to their modes of action. The first group contains inhibitors of tyrosine kinase activity and the second group comprises inhibitors of protein-protein interaction. Inhibitors of tyrosine kinase activity are the most promising group in terms of potency, selectivity and therapeutic applications.[16] This group includes heterocyclic materials that act as ATP analogues. One of the first compounds employed to inhibit *c*-src kinase activity was the antibiotic herbimycin A. Numerous other compounds have now been synthesised and tested in vitro and in vivo; for some of them, clinical trials are in progress.[16]

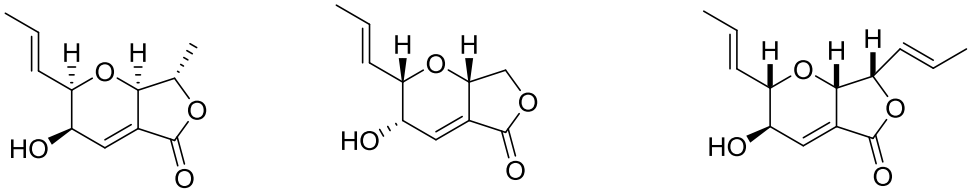
The second physiological role of TAN-2483A is the inhibition of PTH (Para-thyroid hormone)-induced bone resorption. Para-thyroid glands release PTH when the blood calcium level falls. PTH acts on osteoclasts and triggers break-down of bone with release of minerals, and transfer of calcium from bone fluid to the blood. *c*-src kinase plays a crucial role in osteoclast physiology and therefore it is conceivable that *c*-Src is a potential pharmacological target for the treatment of bone loss.

TAN-2483A inhibited human recombinant *c*-src kinase activity with an IC_{50} of 4 μM and it showed 76% inhibition of PTH-induced bone resorption of a mouse femur.[3] Later on Snider's group synthesised (−)-TAN-2483A and conducted biological studies. Apart from those studies, there is no published data regarding the biological and clinical significance of TAN compounds. Comprehensive biological studies are necessary to establish the pharmacological value of the TAN compounds.

1.2 Biological evaluations of furo[3,4-*b*]pyran based natural products

The biological activity of furo[3,4-*b*]pyran based natural products has been reported in two instances in the literature by comparing their stereochemistry and their ability to act as Michael acceptors. The first study was done by Snider's group based on Waol compounds and (−)-TAN-2483A. The main focus of their biological study was investigation of the impact of stereochemistry on biological activity.

Waol A was reported to have broad anti-tumour activity.[10b] Snider *et al*. investigated the anti-tumour activity of waol A, (−)-TAN-2483A and two other related compounds in 2004.[17] They submitted synthetic (−)-TAN-2483A (**33**), (+)-desmethyl-TAN-2483A (**35**) and racemic waol A (**22**) (Figure 1.9) to the NCI (National Cancer Institute) human disease-oriented 60-cell line trial, which provides an *in vitro* anti-tumour screening protocol. All three compounds behaved similarly, showing GI_{50} activity values[1] ranging from 10^{-5} to 10^{-6} M. This suggested that the stereochemistry of the subjected compounds may not determine their biological activity because compounds **33** and **35** have the opposite stereochemistry and waol A is racemic. The observed similarity of their biological behaviour suggests that the antitumor activity may result from their ability to act as Michael acceptors in biological systems, rather than more specific binding to certain protein factors.

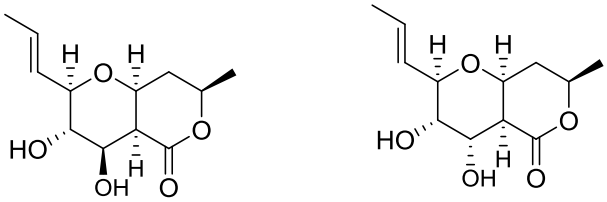


(-)-TAN-2483A (**33**) (+)-desmethyl TAN-2483A (**35**) (±)-waol A

Figure 1.9: Compounds subjected to NCI screening

The proposed hypothesis was tested by the same group with a related natural product called dinemasone, which contains a pyran ring fused with a six membered lactone ring (Figure 1.10).[18]This compound differs from the waol, massarilactone and TAN compounds in the size of the lactone ring and the ring unsaturation.

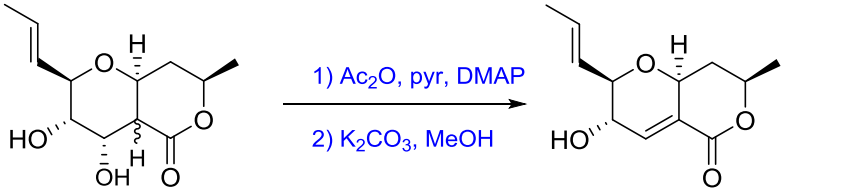
[1] Growth inhibition of 50% (GI_{50}) is the drug concentration resulting in a 50% reduction in the net protein increase in control cells during the drug incubation.



dinemasone B (**36**) dinemasone C (**37**)

Figure 1.10: Structures of dinemason B and C

After the total syntheses of dinemasone B (**36**) and dinemasone C (**37**) were completed, they were converted to anhydrodinemason BC (**39**) as depicted in Scheme 1.5 via anhydrodinemasone BC acetate. Then this was eliminated with K_2CO_3 in MeOH to provide anhydrodinemasone BC (**39**).[18]



dinemasone BC (**38**) anhydrodinemasone BC (**39**)

Scheme 1.5: Synthesis of anhydrodinemasone BC for biological evaluations[18]

The activities of *nor*-dinemasone B (**40**), and dinemasone C (**37**), along with the synthetic intermediate compound **41**, *epi*-dinemasone C (**42**), and anhydrodinemasone BC (**39**) were tested in an agar diffusion assay for antibacterial (*Bacillus megaterium* and *Escherichia coli*), antifungal (*Microbotryum violaceum*), and antialgal activity (*Chlorella fusca*). All five compounds were observed to be active against the four test organisms, but anhydrodinemasone BC (**39**), having a conjugated double bond, did not lead to improved biological activity (Table 1.1). This suggests another hypothesis, that the size of the lactone ring may be crucial in the activity of these related compounds for their specific binding patterns and their kinetics. Thus, it was proposed that the compounds having furan and pyran lactones might be good lead structures for further investigation of structure-activity relationships.

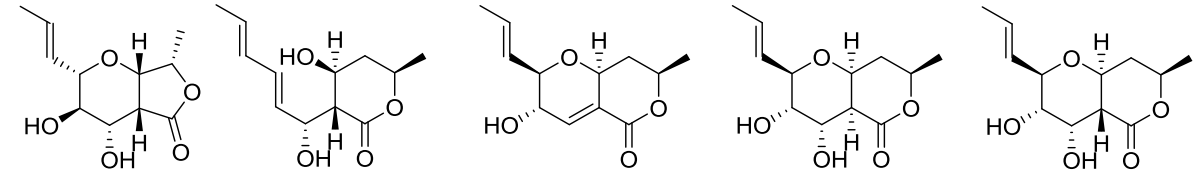


Figure 1.11: Dinemasone C and related compounds subjected for agar diffusion assay[18]

Compound	Zone of inhibition (mm)[a]			
	Escherichia coli	*Bacillus megaterium*	*Microbotryum violaceum*	*Chlorella fusca*
nor-dinemasone B	10	10	10	10
40	9	7	7	7
epi-dinemasone C	10	7	7	9
dinemasone C	12	6	9	10
anhydrodinemasone BC	9	7	7	9
penicillin	14	18	0	0
tetracycline	18	18	0	10
nystatin	0	0	20	0
actidione	0	0	50	35
acetone	0	0	0	0

[a] Values given are the radius of the zone of inhibition in mm

Table 1.1: Antibacterial, antifungal and antialgal activities of nor-Dinemasone B (**41**), compound **40**, *epi*-Dinemasone C (**37**), and anhydrodinemasone BC (**39**) against microbial test organisms in an agar diffusion assay at a concentration of 50 µg per filter disc.

1.3 Early synthetic attempts of furo[3,4-*b*]pyran-based natural products

Only two research groups have reported total syntheses of furo[3,4-*b*]pyran-based natural products. The earliest one, reported in 2004, was from Snider's group after revising the structures of waol A (**22**) and B (**23**).[10a, 17] The synthetic methodology was applied successfully to the total syntheses of waol A (**22**), (−)-TAN-2483A (**33**) and massarilactone B (**25**). Significantly, Snider's methodology invariably generated products with a *cis*-configuration across the pyran ring (Figure 1.12). Therefore,

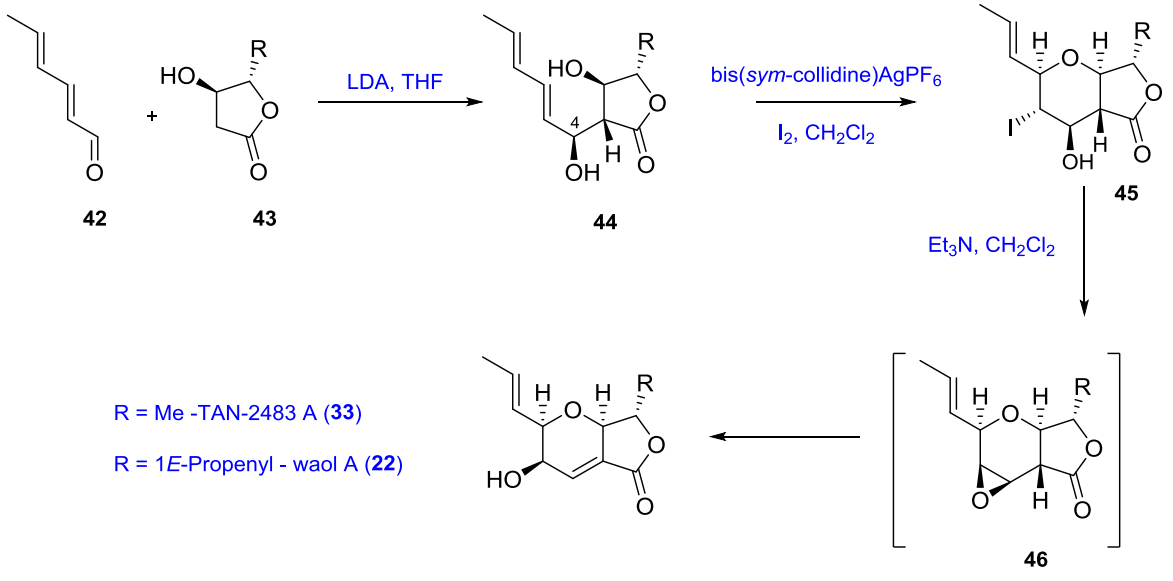
the total synthesis of (−)-TAN-2483B (**34**) was unsuccessful via his methodology since it contains a *trans*-relationship.

R = Me (-)-TAN-2483A (**33**)
R = (1*E*)-propenyl (-)-waol (**22**)

(-)-TAN-2483B (**34**)

Figure 1.12: Stereochemistry of the pyran ring in (−)-TAN-2483A (−)-waol A and (−)-TAN-2483B

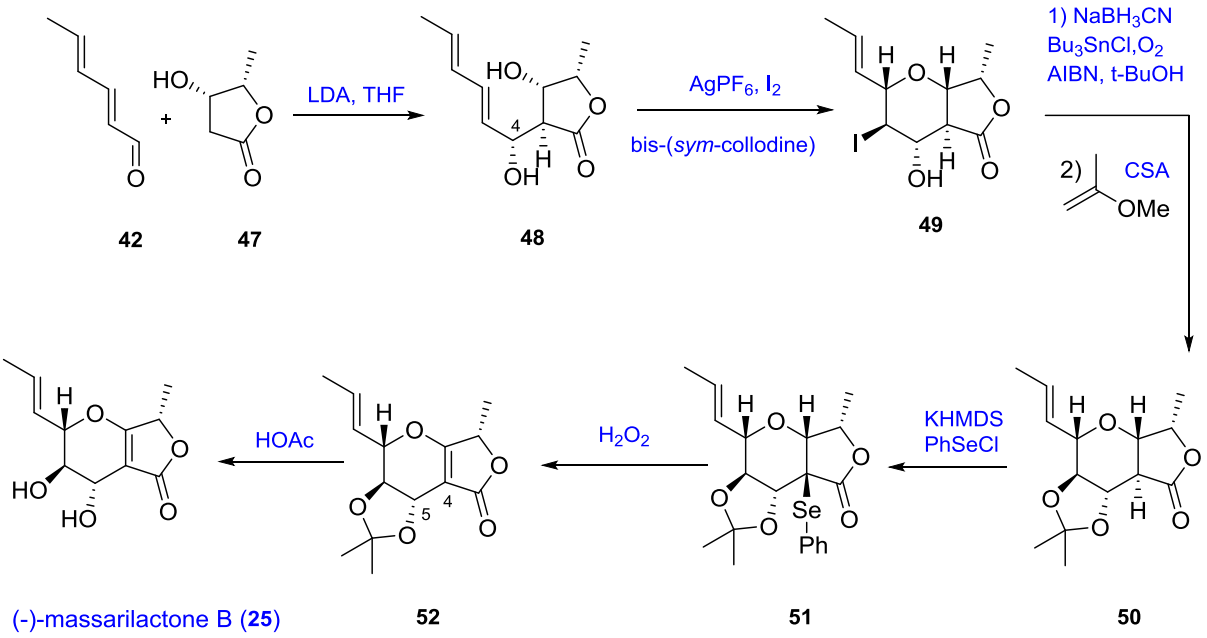
TAN-2483A (**33**) and waol A (**22**) were synthesised by the Snider's group using a convergent methodology starting with aldol condensation of commercially available 2,4-hexadienal (**42**) and hydroxyfuranone **43** (Scheme 1.6). In this way, diene **44** was generated as a mixture with its C4 epimer. Formation of the bicyclic core of the furo[3,4-*b*]pyran skeleton was completed by iodoetherification of the allylic alcohol **44** to give iodohydrin **45**. This species was subjected to base-induced substitution to form epoxide **46**. Eliminative epoxide ring opening introduced the required unsaturation into the pyran ring and completed the total syntheses of (−)-TAN-2483A (**33**) and waol (**22**).



Scheme 1.6: Synthesis of (−)-TAN-2483A and waol A[17]

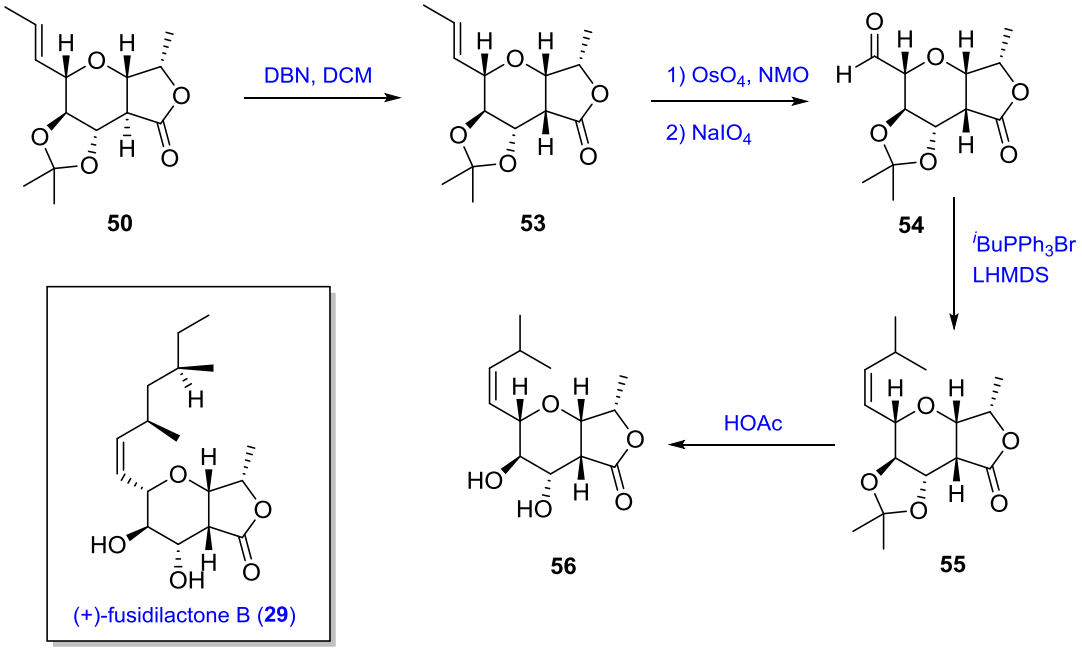
Snider applied similar methodology to synthesise (−)-massarilactone B, beginning from the lactone **47.** Repetition of the above described aldol reaction provided **48** and the C4 epimer. Compound **48** was converted to massarilactone precursor **49** (Scheme 1.7) by iodoetherification. Then

massarilactone B was prepared by dehydrogenation of protected dihydromassarilactone B **50**, derived from **49** by radical oxygen substitution. *cis*-Fused phenylselenide **51** was obtained by acetonide protection and subsequent phenylselenation with KHMDS and PhSeCl. Oxidation with H_2O_2 led to the desired unsaturated acetonide **52** along with the Δ-4,5 regioisomer. Acid-mediated cleavage of the acetonide group of **52** gave (−) -massarilactone B (**25**).



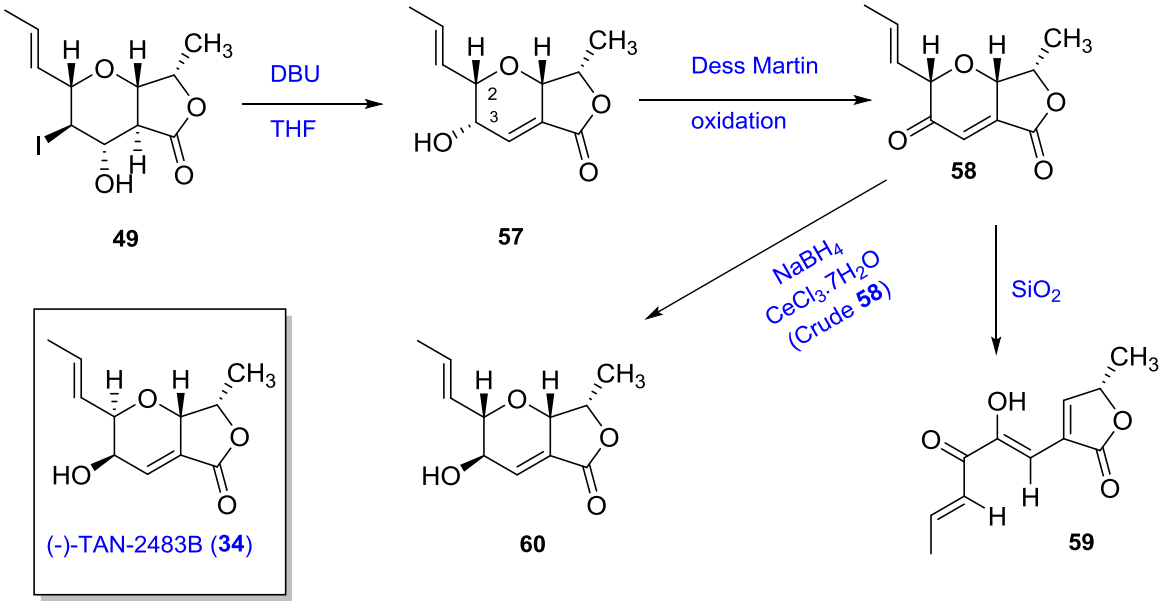
Scheme 1.7: Synthesis of (−)-massarilactone B[17]

In the synthesis of the main skeleton of fusidilactone, acetonide-protected intermediate **50** from the massarilactone synthesis was used. The *trans*-fused lactone **50** was epimerised to the more stable *cis*-fused lactone **53** with DBN (Scheme 1.8). Then, oxidative cleavage of the alkene followed by $NaIO_4$ oxidation afforded the desired aldehyde **54**. Wittig olefination using isobutyl-triphenylphosphonium bromide and LHMDS afforded the *cis*-alkene **55** which incorporated half of the carbon skeleton of the side arm of (+)-fusidilactone B (**29**), Hydrolysis of the acetonide provided truncated fusidilactone B **56**.



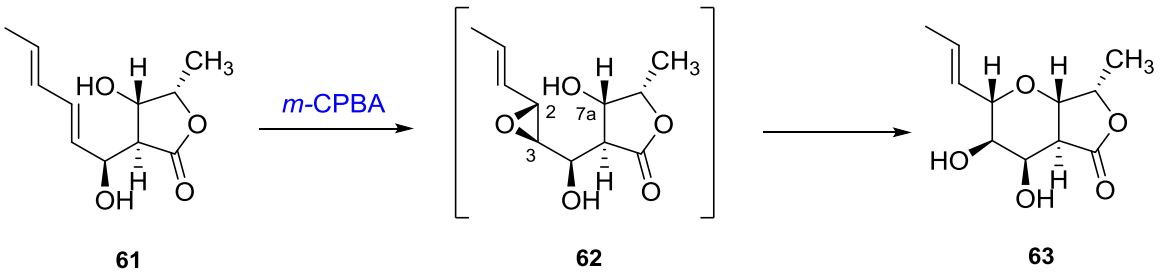
Scheme 1.8: Synthesis of fusidilactone ring skeleton[17]

Finally, the same protocol was applied to the attempted synthesis of TAN-2483B using lactone **47** and 2,4-hexadienal (**42**). Base treatment of bicyclic iodolactone **49** provided the stereoisomer of TAN-2483B (**57**) which has the non-natural configuration at C2 and C3 (Scheme 1.9). The planned strategy for epimerisation of C3 involved oxidation followed by reduction to give 2-*epi*-TAN-2483B (**60**). Unfortunately, the enone **58** was unstable to silica gel and gave the more stable enol **59** via electrocyclic ring opening of a tautomer of **58**. This led to the investigation of alternative methods to form the pyran ring (*vide infra*).



Scheme 1.9: Attempted synthesis of (−)-TAN-2483B [10a, 17]

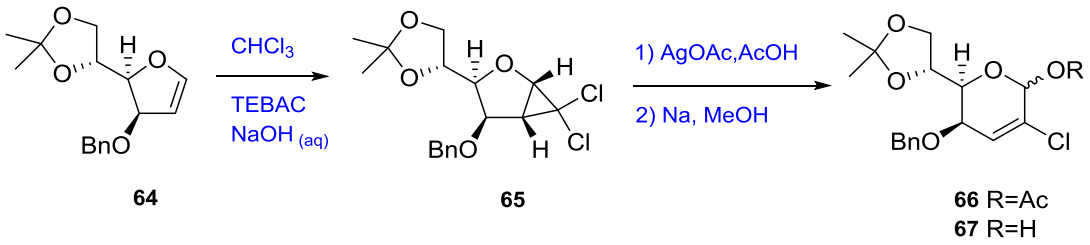
As a final attempt of the synthesis of (−)-TAN-2483B, the minor aldol adduct **61**, from the synthesis of massarilactone B, was used (Scheme 1.10). It was planned that epoxidation of the 2,3 bond in **61** and subsequent attack by the C7a alcohol would provide access to (−)-TAN-2483B. The obtained epoxide **62** underwent cyclisation to provide diol **63** having a *cis*-configuration across the pyran ring oxygen. Snider's several unsuccessful approaches to synthesise (−)-TAN-2483B indicate that an alternative strategy is needed for the synthesis of this natural product.



Scheme 1.10: Attempted epoxy alcohol directed synthesis of (−)-TAN-2483B[17]

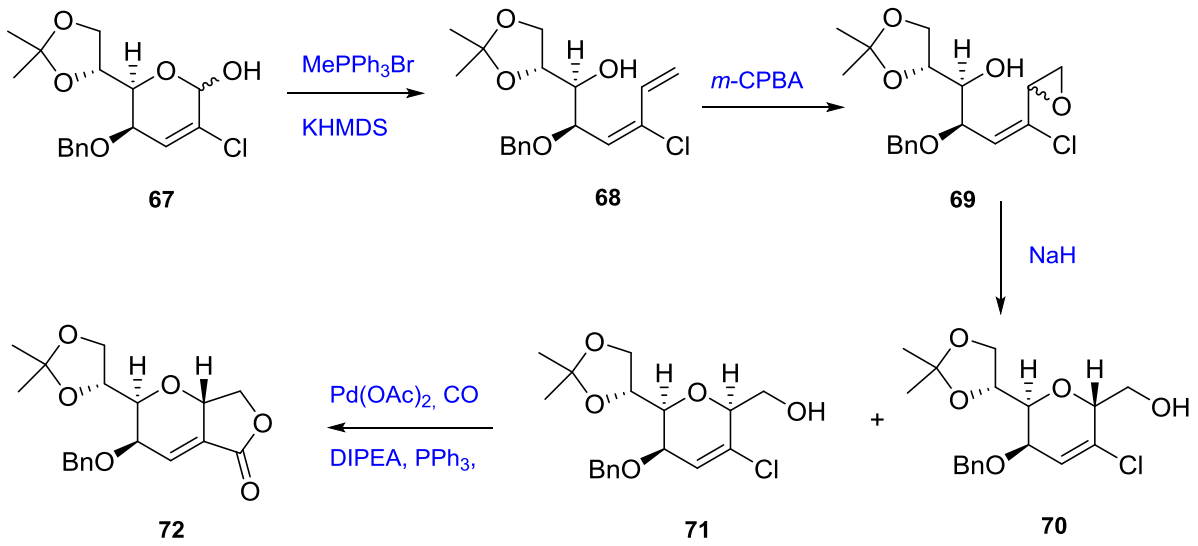
In 2010, Hewitt and Harvey reported the first stereoselective synthesis of the ring system of (–)-TAN-2483B, which proceeds from D-mannose through a cyclopropanation and ring expansion sequence (Scheme 1.11).[19] Installation of the ring unsaturation was achieved by ring expansion of a *gem*-dihalocyclopropane. The glycal substrate for the cyclopropanation, **64** was synthesised from D-mannose by the procedure developed by Theodorakis.[20] The cyclopropanation of glycal **64** using

dichlorocarbene afforded a single isomer **65**, resulting from attack of dichlorocarbene from the less hindered side. The hemiacetal intermediate **67** was obtained by treating the crude cyclopropane with silver acetate in acetic acid followed by methanolysis of the resultant acetate **66**. The hemiacetal **67**, was a versatile intermediate which contains the functionalities deemed necessary to build the lactone ring and the side arm of (−)-TAN-2483B.



Scheme 1.11: Cyclopropane ring opening approach to pyrans **66** and **67**

Construction of the lactone ring was achieved through Wittig homologation of hemiacetal **67** with the anion derived from methyltriphenylphosphonium bromide to form **68**, followed by *m*-CPBA-mediated epoxidation (Scheme 1.12). Intramolecular attack on the resulting epoxide **69** was achieved by treatment with base. The functionalised pyran ring was obtained in a modest 42% yield as a 1:3.3 mixture of epimers **70** and **71**. The complete bicyclic system of TAN-2483B was synthesised by a palladium-catalysed carbonylation/lactonisation sequence under a carbon monoxide atmosphere. It was found that alkenyl chloride in **70** is poorly reactive towards carbonylation under these conditions and therefore the yield of **72** was low (18%). The low yield is also due to the fact that only the minor alcohol isomer **70**, with the correct stereochemistry, reacted.

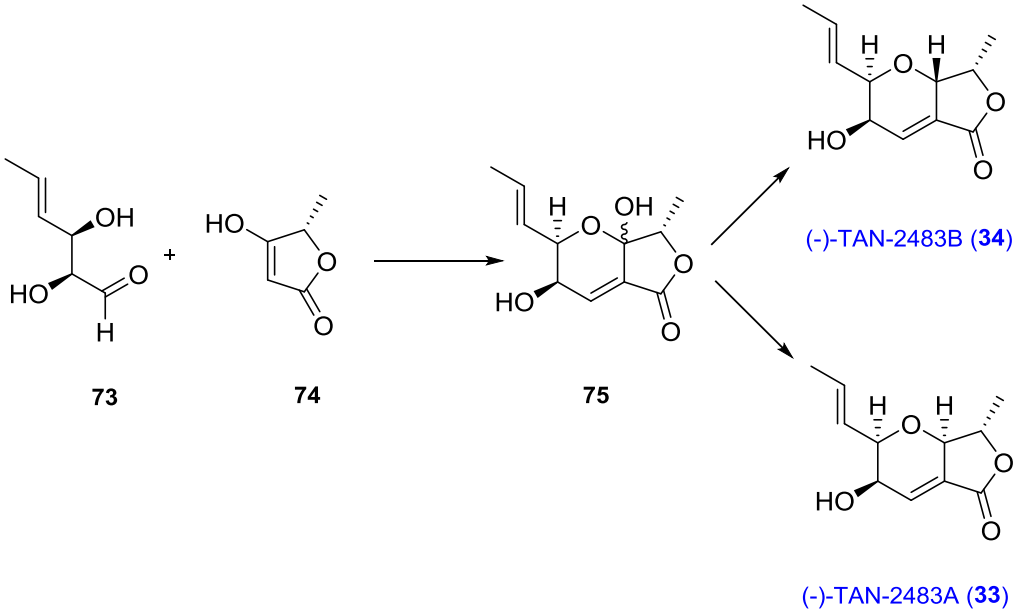


Scheme 1.12: Synthesis of the (−)-TAN-2483B ring system[19]

1.4 Biosynthesis of (−)-TAN-2483A and (−)-TAN-2483B

Direct studies exploring the biosynthesis of (−)-TAN-2483A and (−)-TAN-2483B have not been reported. The shared biological origin of these compounds and strong structural similarities imply that these metabolites are produced via related pathways, perhaps from the same starting material.

Snider *et al*. suggested that both (−)-TAN-2483A and (−)-TAN-2483B might be biosynthesised by reduction of a common intermediate **75**, which could be formed by condensation of an aldehyde **73** or a surrogate with the ubiquitous natural product α-methyltetronic acid (**74**) (Scheme 1.13).[17]However, they reported that model studies invoking such a biomimetic strategy, through the attempted condensation of tetronic acid **43/47** with 2,4-hexadienal (**42**) and other aldehydes were unsuccessful.



73 74 75

Scheme 1.13: Proposed biosynthesis of (−)-TAN-2483A and (−)-TAN-2483B[17]

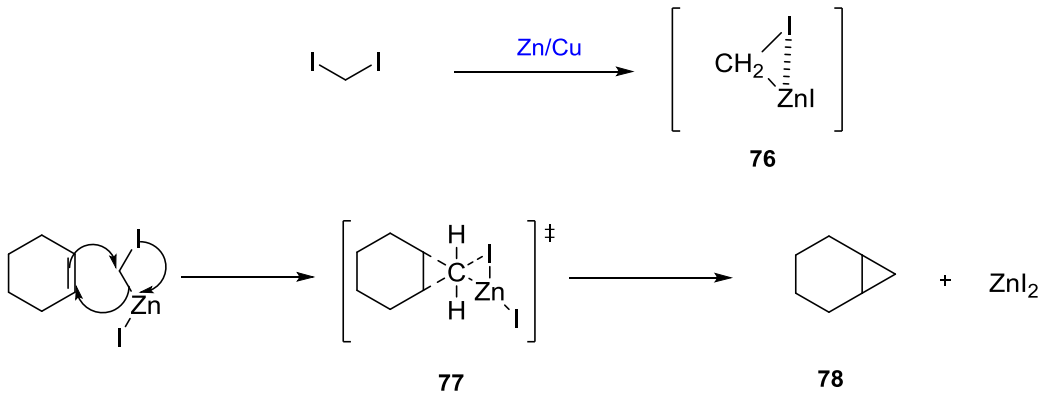
1.5 Introduction to key reactions involved in synthetic plans

Several reactions are key to the synthetic strategy which will be outlined in Section 1.6 namely cyclopropane formation and ring opening, synthesis of sugar acetylenes and palladium-catalysed carbonylation. The main purpose of this section is to introduce these featured reactions.

1.5.1 Cyclopropanation and ring opening reactions

Cyclopropane and its substituted variants (e.g. *gem*-dihalocyclopropanes) are popular reactive intermediates in organic chemistry. There are many methods for synthesis of substituted cyclopropanes. Addition of a carbene to an alkene is one of the most common methods for the synthesis of cyclopropanes and involves a concerted reaction that is often stereoselective. A variety of methods for formation of the carbene and its addition to alkenes have been successful, including Simmons–Smith and Mäkosza cyclopropanation methods.

The Simmons-Smith reaction, reported in 1959, is a powerful method for cyclopropanation of olefins.[21] It involves treatment of the alkene with iodomethyl zinc iodide, which is effectively a complex of the carbenoid CH_2 and zinc iodide (Scheme 1.14). It can be formed either by reaction of diiodomethane with a zinc/copper couple (original conditions) or with dialkylzinc (Furakawa modification).[22] The reaction is believed to proceed via a five-centre transition state **77** through a process that involves transfer of a methylene group from the $IZnCH_2I$ to the double bond.



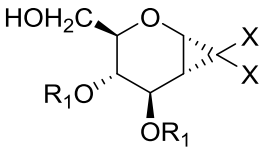
Scheme 1.14: Simmons-Smith cyclopropanation

In 1954, Doering and Hofmann showed the capacity to form dihalocyclopropanes by reaction of an alkene with dihalocarbene generated by α–elimination of HX from a haloform under anhydrous conditions.[23] However, the necessity for strictly anhydrous conditions made it of limited application in synthesis.

In 1969, Mąkosza made a tremendous improvement in the synthesis of dihalocyclopropanes by using aqueous base and a phase transfer catalyst.[24] α-Elimination of the haloform and then carbene addition could be achieved selectively in a two-phase system using highly concentrated sodium hydroxide in the presence of a quaternary ammonium salt. The use of readily available reagents and generally high yields made this procedure a popular reaction for synthetic chemistry.

In 1974, Mąkosza formulated the interfacial mechanism to explain the generation and trapping of dihalocarbene in the biphasic system. According to his model, deprotonation of the haloform (CHX_3, X = Cl/Br) occurs in the interphase region with NaOH.[25] The resulting sodium salt of the trihaloform anion undergoes ion exchange with the more lipophilic tetraalkylammonium (TAA) salt. The TAA^+ and CX_3^- ion pair enters the organic phase where it decomposes to dihalocarbene, which reacts with the alkene to produce *gem*-dihalocyclopropane. The two phase system ensures that hydrolysis of the product dihalocyclopropane is minimised, despite the presence of water. As a result, substrates with groups susceptible to aqueous base have been successfully cyclopropanated using this methodology.[25]

Dihalocyclopropanation has been widely exploited to make carbohydrate-fused cyclopropanes. Stereoselectivity of cyclopropanation is mainly dependent on the steric demand of the substrate. The history of dihalocyclopropyl carbohydrates began in 1967, when Brimacombe and co-workers published the synthesis of **79** using dichloromethylene (Figure 1.13).[26] They assumed that the *in situ* dihalocarbene addition preferentially occurred on the less sterically hindered face.



79

a. X = Cl ; R_1 = Me

b. X = Cl ; R_1 = H

c. X = Cl ; R_1 = Bz

Figure 1.13: The first carbohydrate-derived cyclopropanes

Even though the reaction has been known since 1967, further use of this strategy was not realised until Nagarajan and co-workers reported their studies on a series of protected glycals (Table 1.2).[27] They used as substrates 3,4,6-tri-*O*-benzyl-D-glucal (**80**), 3,4,6-tri-*O*-benzyl-D-galactal (**81**), 3,4,6-tri-*O*-benzyl-D-rhamnal (**82**) and 3,4,-di-*O*-benzyl-D-xylal (**83**), reacting them in $CHCl_3$ in the presence of 50% aqueous NaOH solution and a catalytic amount of benzyl triethylammonium chloride as phase transfer catalyst. According to the isolated adducts **84**, **85**, **86** and **87**, dichlorocyclopropanation occurred predominately on the face of the double bond away from the C3 substituent, presumed to be due to steric reasons.

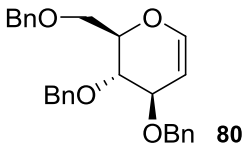
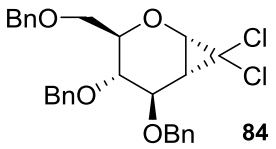
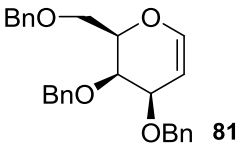
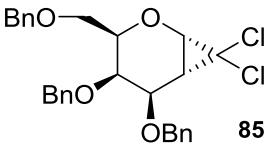
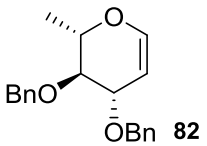
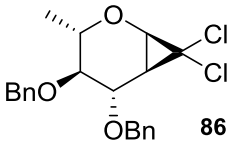
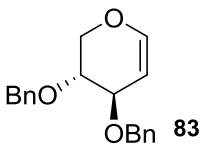
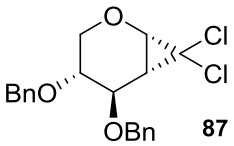
Substrate	Time	Product	Yield %
 **80**	4h	 **84**	84
 **81**	24h	 **85**	92
 **82**	18h	 **86**	95
 **83**	18h	 **87**	55

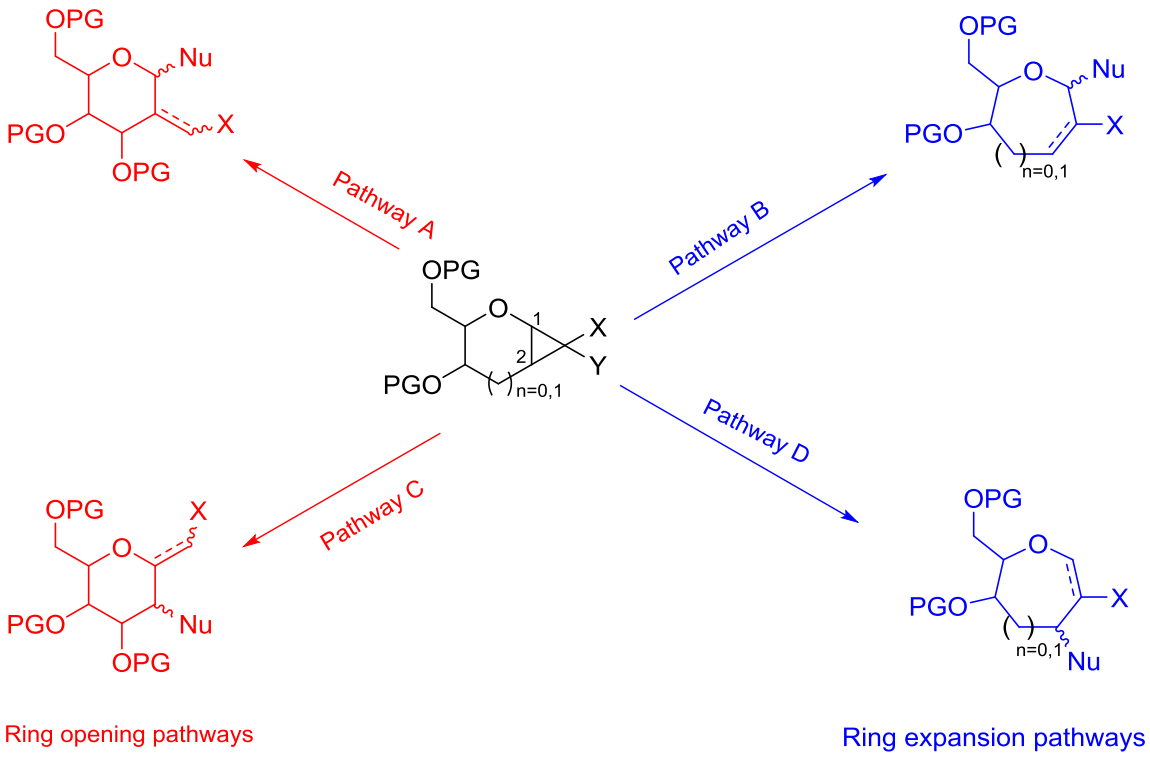
Table 1.2: Results of cyclopropanation of benzyl-protected glycals by Nagarajan[27]

Reactions of ring fused cyclopropanes

Reactions of ring-fused cyclopropanes are diverse and an interesting area for study. For example, some ring opening reactions proceed through a ring expansion process to afford a product larger by a one-carbon unit while others generate a one-carbon branch on the existing ring. The halogen functionality on carbohydrate-derived *gem*-dihalocyclopropanes creates additional functionality for a variety of synthetic transformations such as cross-coupling reactions.[28]

Cyclopropane ring opening reactions

The ring cleavage of six-membered carbohydrate-derived cyclopropanes mainly produces either ring- expanded products or branched products (Scheme 1.15). Mechanistically, the reaction can take different routes depending on the conditions (Pathways A-D). Cleavage of the exocyclic bond at C1 is highly favoured over that at C2, due to the formation of an oxonium resonance structure involving the adjacent oxygen. The ring cleavage reaction is usually selective towards C2 branched sugars and pathway C is not favoured for such cyclopropanes. Similarly, with ring expansion, pathway D is also not favoured; therefore ring expansion proceeds principally via pathway B.



X, Y = Cl, Br, CO_2Et and /or H

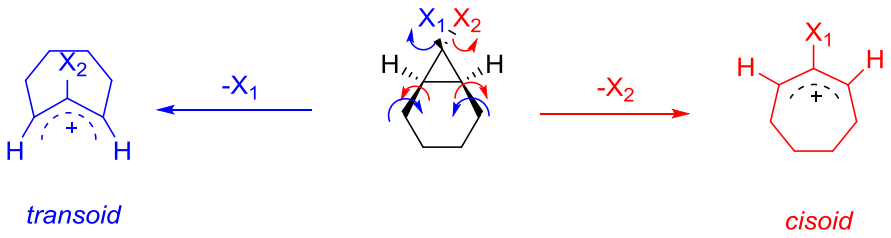
PG = Protecting Group

Scheme 1.15: Possible paths for reactions of 1,2-cyclopropyl carbohydrates

The more relevant carbohydrate cyclopropane ring opening reaction for this thesis is the ring expansion reaction denoted by Pathway B.

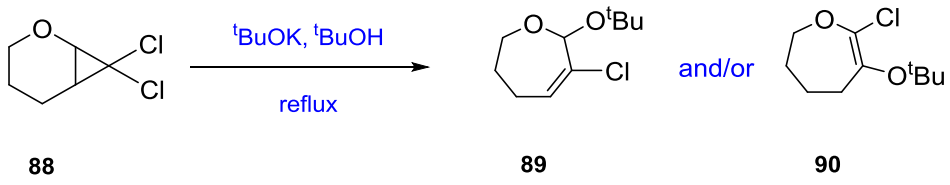
Ring expansion of cyclopropyl carbohydrates

Pathway B (Scheme 1.15) involves ring expansion of pyran-fused cyclopropanes to give oxepines by releasing ring strain in the three membered cyclopropane rings. According to the Woodward-Hoffmann-DePuy rule,[29] the substituents in a fused-bicyclic system *trans* to the departing halogen rotate outwards in a disrotatory fashion (Scheme 1.16). Thus, loss of the *exo*-halogen would lead to the strained *transoid* allylic cation intermediate. The *transoid* configuration cannot be accommodated in a ring with fewer than eight carbons. In contrast, loss of the *endo*-halogen produces a *cisoid* intermediate through inward rotation of the ring carbons. In medium-sized ring-fused dihalocyclopropanes, only the *cisoid* ring intermediate is possible and ring-expanded cycloalkenes are formed by eliminating the *endo*-halogen atom.[29b]



Scheme 1.16: Woodward-Hoffmann-Depuy rule for ring expansion of ring-fused cyclopropane

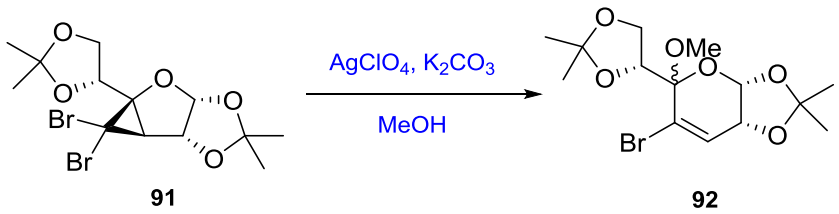
In 1969 Skattebøl [30]reported ring opening of the dihydropyran derived cyclopropane 7,7-dichloro-2-oxabicyclo[4.1.0]heptane (**88**) under basic conditions (Scheme 1.17). According to his arguments the ring expanded structure **89** was formed as the sole product based on NMR evidence.



Scheme 1.17: Skattebøl's studies on ring expansion of ring-fused cyclopropane[30]

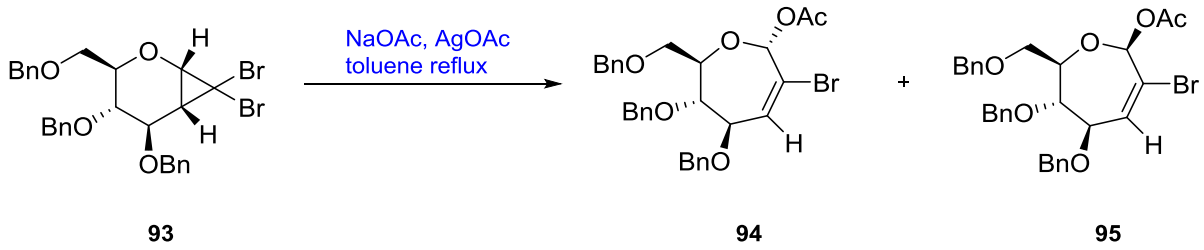
Various examples of the ring-expansion reaction of *gem*-dihalocyclopropanes in the presence of silver salts acting as Lewis acids have been noted. Silver salts promote the dissociation of the halide, resulting in disrotatory electrocyclic ring opening of the three-membered ring and formation of an allylic cation. The allylic cation can be trapped by the anion of the silver salt or an exogenous nucleophile.

Gross and co-workers implemented this strategy on the ring expansion of cyclopropane carbohydrates in 1979 (Scheme 1.18).[31] The dibromocyclopropyl sugar **91** underwent a ring expansion reaction with silver perchlorate in methanol, producing bromoalkene **92**. A similar reaction was seen with the corresponding dichlorocyclopropane.



Scheme 1.18: Ring expansion of ring-fused cyclopropane with silver ions

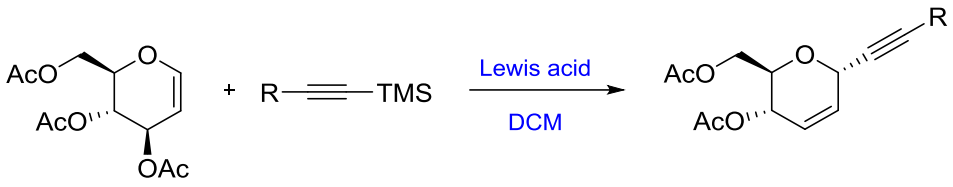
In 2010, Hewitt and Harvey reported a cyclopropane ring expansion using silver ions.[32] Careful investigation of the experimental conditions led them to find that the reaction of cyclopropanated carbohydrate **93** with silver tetrafluoroborate or silver acetate was extremely slow at ambient temperatures, yet eventually produced a mixture of oxepines **94** and **95** (Scheme 1.19). The conditions were optimised to obtain a 65% combined yield of α- and β-anomers using NaOAc and AgOAc in toluene.



Scheme 1.19: Silver promoted ring expansion of pyran ring-fused cyclopropane[32]

1.5.2 Synthesis of sugar acetylenes

Carbohydrates were used as a chirons that act as a source of the carbon atoms of the TAN-2483B core.[19] *C*-Glycosidation (such as alkynylation) is a key reaction for the introduction of carbon chains (e.g. acetylene) into sugars (Scheme 1.20). The resulting *C*-alkynylated compounds are called 'sugar acetylenes'.[33] *C*-Glycosidation with a silylacetylene allows for introduction of a wide variety of substituents onto the other end of the acetylene, and the resulting alkynylated sugar derivatives are of great potential utility as starting materials for natural product synthesis in optically active form.



96 **97**

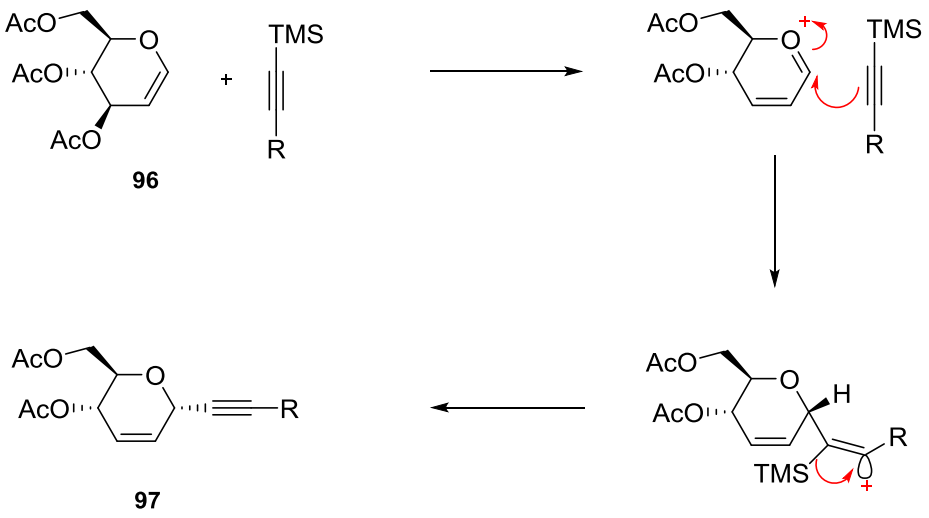
Scheme 1.20: *C*-Glycosidation of tri-*O*-acetyl-D-glucal with acetylene

R	Lewis acid	Yield (%)
H	$TiCl_4$	0
Me	$SnCl_4$	99
TMS	$TiCl_4$	75

Table 1.3: *C*-Alkynylation of tri-*O*-acetyl-D-glucal

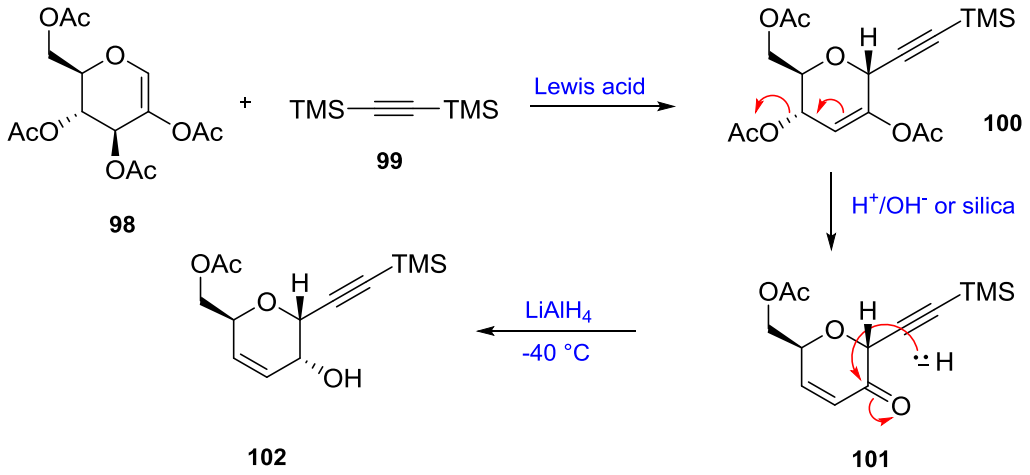
In the *C*-alkynylation of tri-*O*-acetyl-D-glucal (**96**) (Table 1.3) with various acetylenes, R has to be larger than a methyl group to afford *C*-glycosides **97** in good yield.[33b] When TMS-acetylene was used (R=H) no reaction was observed. On the other hand it is necessary to use stronger Lewis acids such as $SnCl_4$ to afford good yields with bulky R groups such as TMS.

The mechanism is proposed to involve eliminative formation of the enonium ion followed by coordination of silyl acetylene from the less hindered α side, leading to the α-glycoside exclusively (Scheme 1.21).[33b] The stereochemistry is largely determined by the coordination of π-orbitals of the onium ion with acetylene which allows the α-pseudo-axial orbital to participate in making the glycosidic bond.



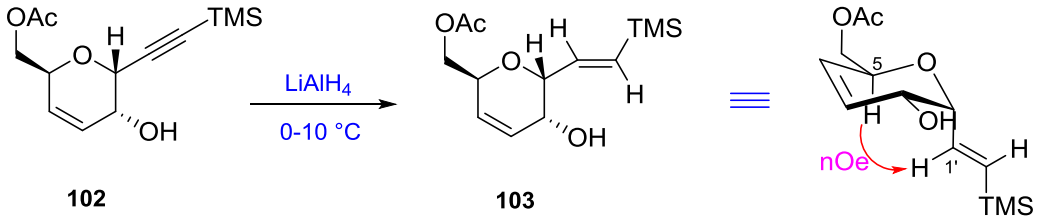
Scheme 1.21: Possible mechanism of *C*-alkynylation[33b]

C-Alkynylation of 2-oxy-glucal **98** initially afforded sugar acetylene **100**, which is unstable under the work-up conditions and/or silica gel chromatography (Scheme 1.22).[33b] The resultant ketone **101** was formed from the elimination of the 4-OAc group and immediately subjected to reduction with $LiAlH_4$ at low temperature. During the reaction, hydride attacked from the side opposite to the axially oriented α-alkynyl group, thus affording the 2α-hydroxy product **102** exclusively.



Scheme 1.22: Proposed mechanism for the α-selective *C*-alkynylation[33b]

Further evidence of the selectivity was provided by reduction of sugar acetylene **102** with $LiAlH_4$, forming *trans*-alkene **103** (Scheme 1.23). The n*O*e correlation between H-5 and H-1' confirmed the α-orientation of the original acetylene.[33b]



Scheme 1.23: n*O*e evidence for the α-selectivity[33b]

On the other hand, steric demand of the substrate also plays a role in the selectivity of sugar alkynes, favouring 1,4-*anti*-selectivity. For example, addition of silylacetylene to pentopyranoglycal diacetates **104, 105** and **106** affords the 1,4-*anti*-stereochemistry exclusively (Table 1.4)

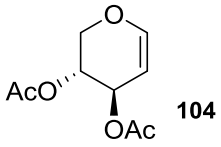
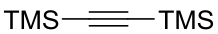
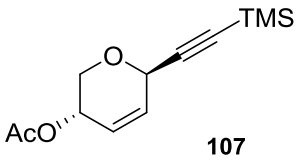
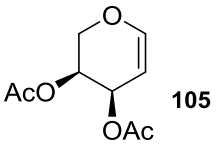
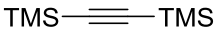
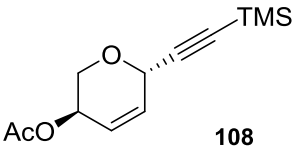
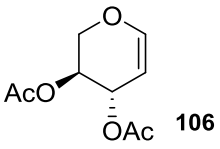
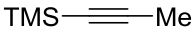
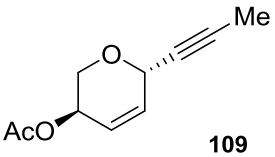
Glycal	Nucleophile	Lewis acid	Major product	Yield (%)
 **104**		$TiCl_4$	 **107**	73
 **105**		$TiCl_4$	 **108**	93
 **106**		$TiCl_4$	 **109**	99

Table 1.4 1,4-*anti*-stereochemistry in *C*-glycosidation[33b]

The observed 1,4-*anti*-selectivity of the above compounds can be explained by the nucleophile silylacetylene approaching from the side anti to the 4-acetyl group (Figure 1.14). On the point of orbital interaction, an axially oriented acetyl group reduces the electron density in the π electron system on the β face, making the anti-lobe at C1 more reactive by withdrawing electron density.

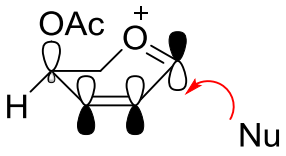
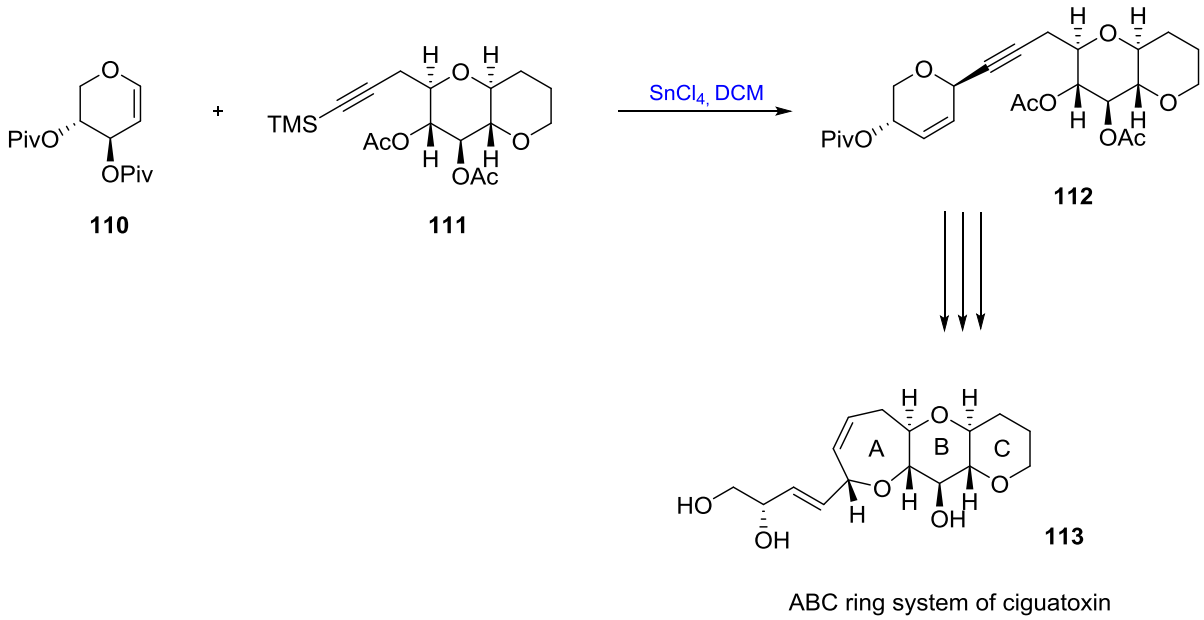


Figure 1.14: Orbital diagram of stereoselective nucleophilic attack[33b]

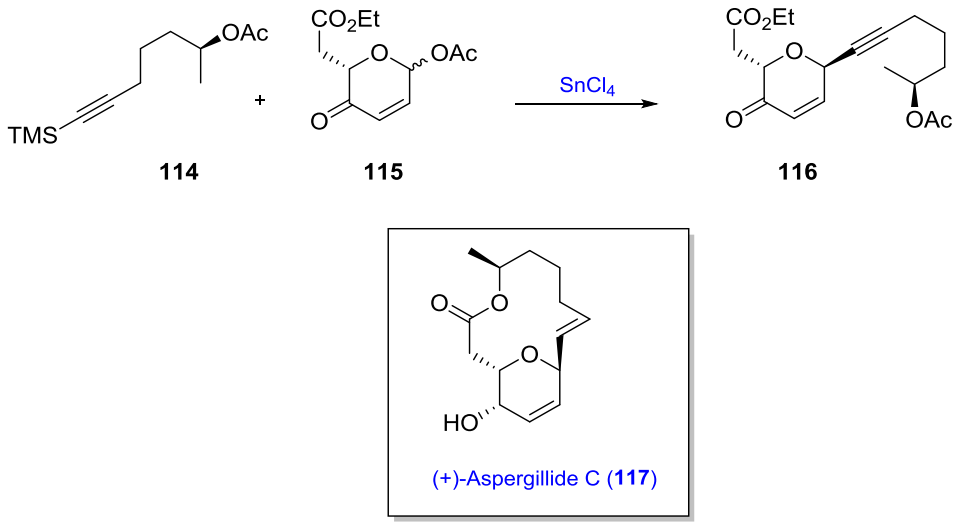
This methodology has been developed and used in the synthesis of natural products. The earliest application is the synthesis of the ABC ring system of ciguatoxin by Isobe *et al. (* scheme 1.24).[33b]



Scheme 1.24: *C*-glycosidation in ciguatoxin synthesis

Silylated bicyclic compound **111** was coupled with the xylal **110** to form alkyne **112** as single diastereoisomer. The alkyne nucleophile attacks the oxonium intermediate derived from xylal **110** from the opposite side to the C4 group, leading to the 1,4-*anti*-glycoside.

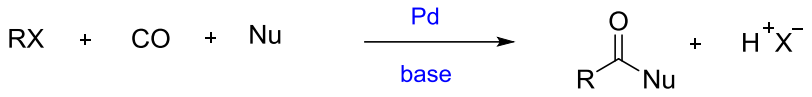
The recent literature reports a sterically dominated *C*-glycosidation reaction in synthesis of (+)-aspergillide C (Scheme 1.25).[34] Ferrier-type *C*-glycosidation of activated acetate **115** with silylated alkyne **114** in the presence of $SnCl_4$ affords alkyne **116** in 85% yield as a single diastereoisomer. The high diastereoselectivity was rationalised by preferential attack of the nucleophile from the opposite face (β-face) to the C6 substituent oriented on the α-face.



Scheme 1.25: Lewis acid-mediated alkynylation in (+)-aspergillide synthesis

1.5.3 Pd-catalysed carbonylation

Carbonylative versions of cross-coupling reactions were developed in parallel to the progress of other palladium-catalysed-cross coupling reactions since their first report by Heck and co-workers in the 1970s.[35] It was reported that various vinyl and aryl halides can form an acylpalladium species, which can react with various nucleophile to form acids, esters, amides and aldehydes. After this discovery, the carbonylation reaction was used in industrial production of a diverse range of products from readily available chemicals.



R = aryl, vinyl, aryl; X = I, Br, Cl, OTf; Nu = Nucleophile

Scheme 1.26 General palladium-catalysed carbonylative cross coupling reaction

There are many commercially available mono- and polydentate ligands which can finely tune the catalytic properties of palladium. The electronic and steric properties of the ligands play a major role in the catalytic activity of the palladium. The active catalyst is usually generated *in situ* from a storable precatalyst.

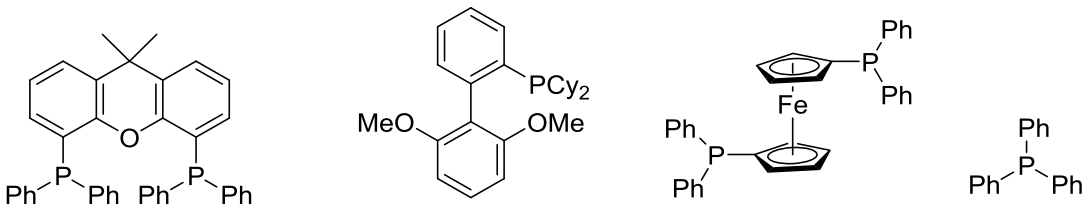


Figure 1.15: Different ligands employed in the work presented in this thesis

The mechanism of carbonylation is still accompanied by some disagreements and uncertainties regarding the later steps of the mechanism.[35] This is partly because several steps of the reaction offer alternative pathways. The relative rate or kinetics of the reaction depends on the choice of catalyst precursor, plus the electronic and steric effects of ligands. The strength of base determines the concentration of the nucleophile and influences the reductive elimination step. The choice of halide in the substrate determines the electronic and steric factors. In carbonylation reactions, as in any other reaction, the solvent influences the stabilisation of charge separated transition states. The

palladium catalysed carbonylation mechanism proposed by Yamamoto [36] and Heck [37]is used as a generalised model to describe the mechanism herein.

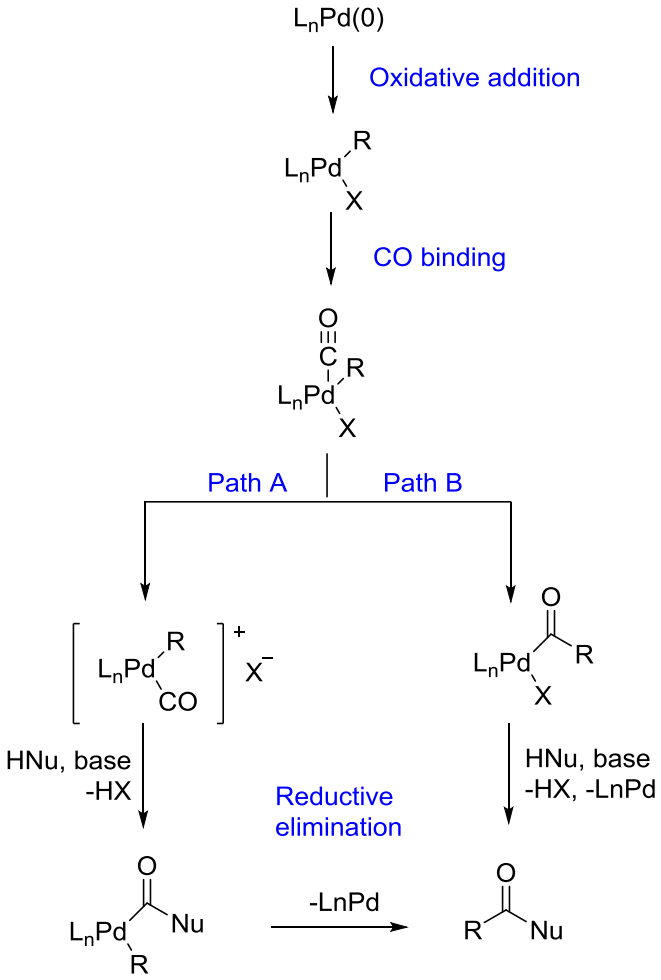
Mechanism of the palladium-catalysed carbonylation

The most popular catalyst precursors for the carbonylation are $Pd^{(II)}$ species which are reduced to the active $Pd^{(0)}$ catalyst *in situ*. Active catalyst formation is influenced by the base or choice of the ligand. In some cases, the availability of the active palladium species is diminished by undesirable equilibria involving complexation with CO. CO tends to reduce electron density at the metal centre via back donation,[38] affording inactive species for the oxidative addition,[38] which is the first step in the catalytic cycle. Moreover, bidentate ligands are often superior to the corresponding monodentate ligands due to their greater ability to prevent catalyst poisoning via ligation of multiple CO ligands during the formation of the active catalyst.[39]

Oxidative addition is commonly the first step for most organometallic coupling reactions (Scheme 1.27). An increase in electron density on the palladium species reduces the activation energy of the oxidative addition of palladium to an alkenyl or aryl halide. Therefore careful selection of ligand can facilitate the oxidative addition. Generally, σ-donating ligands such as triphenylphosphine increase the electron density around the metal atom, accelerating oxidative addition of the catalyst to the substrate.[39]

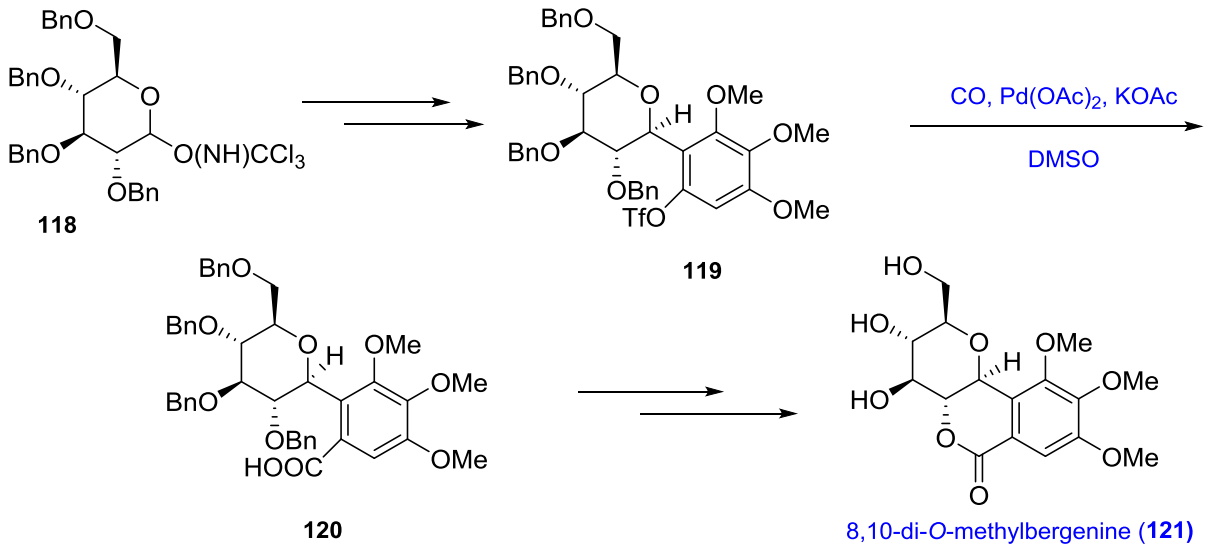
On the other hand, the nature of the substrate also affects the oxidative addition. The order of reactivity of X is I>Br~OTf>>>Cl.[39] In some cases where the substrate is a poorly active alkenyl or aryl halide, oxidative addition is the rate determining step.

The next accepted step in Pd-catalysed carbonylation is the insertion of CO into the organopalladium halide. This step is sensitive to the steric features of the substrate. The reaction of the resulting acyl complex with the nucleophile can then occur either by direct attack of the nucleophile at the acyl carbon (path A) as proposed by Heck in his initial work or by initial bonding to palladium followed by reductive elimination (path B), affording the carbonylated product. A full understanding of the final step remains to be achieved with more experimental evidence.



Scheme 1.27: Mechanism for the palladium-catalysed carbonylation

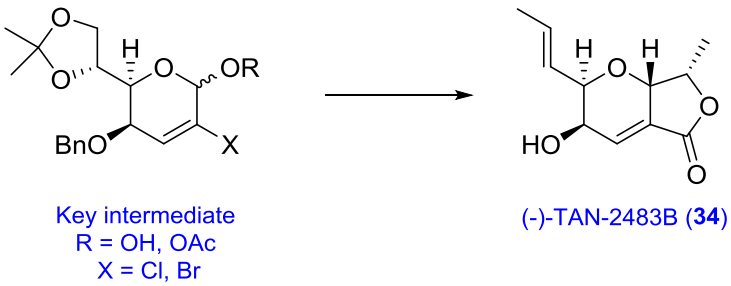
Palladium-catalysed carbonylation has been used in many instances where synthesising natural products and other drug related compounds. 8,10-Di-*O*-methylbergenine (**121**) is a gallic acid derived *C*-glycoside isolated from variety of plants (Scheme 1.28).[40] Palladium$^{(0)}$-catalysed carbonylation was employed at ambient pressure with water as a nucleophile to yield *C*-glycosyl benzoic acid derivative **119**. In this example the use of ligand was avoided as the substrate is really active towards the oxidative addition.



Scheme 1.28: Synthesis of 8,10-di-*O*-methylbergenine via carbonylation[40]

1.6 Strategies for the total synthesis of (−)-TAN-2483B

The research discussed in this thesis is mainly on studies towards the synthesis of (−)-TAN-2483B through *gem*-dihalocyclopropane ring-opening reactions. A short deviation to investigate a 2-*C*-formylated glycal is also described. The project involves significant extension of the methodology developed by Harvey and Hewitt in their efforts towards the synthesis of (−)-TAN-2483B via a cyclopropanation-ring expansion sequence.[19] The pyran key intermediate (Scheme 1.29) provides all the necessary functionalities to make the bicyclic lactone ring and attach the side arm. The major objectives of this research were to functionalise the key intermediate by constructing the methylated ring-fused γ-lactone and to install the side arm of (−)-TAN-2483B.



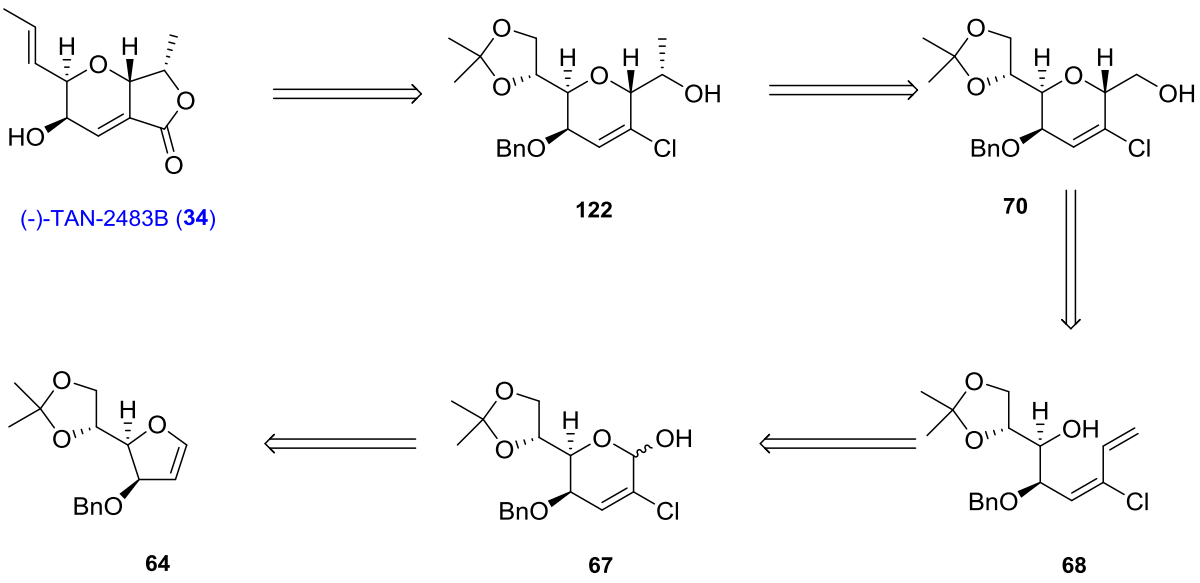
Scheme 1.29: Major transformations from key intermediates

The main hurdle here was the manipulation of highly competitive functionalities in key intermediates in a chemoselective manner. In other words, to maintain the orthogonality of functional groups throughout the synthesis was important to its ultimate success. This resulted in

investigation of a number of different strategies, mainly involving cyclopropanation, but also including non-cyclopropanated routes. These approaches should be able to avoid the main difficulties of previous synthetic attempts and develop more optimised conditions. The comparison of the new strategies and optimised conditions with previous synthetic studies will be discussed accordingly throughout this thesis. An introduction to the various approaches initiated for solving the synthetic challenges are outlined below.

1.6.1 Extension of the synthetic procedure reported by Harvey and Hewitt

The main carbon skeleton of (−)-TAN-2483B core was synthesised by Harvey and Hewitt in 2010 via a cyclopropanation-ring expansion sequence.[19] Side chain elaboration and installing the methyl group of the γ-lactone remained as obstacles to complete the total synthesis of the natural product. This retrosynthetic approach (Scheme 1.30) was initially explored for the total synthesis of (−)-TAN-2483B. The retrosynthetic strategy would involve preparation of **70** as before (section 1.3) followed by installation of the methyl group, deprotection of the acetonide group and stereoselective attachement of the unsaturated side chain by Julia-Kocienski homologation. The ultimate target of (−)-TAN-2483B can be achieved by the deprotection of the benzyl ether. There are various methods to deprotect benzyl ethers. The most suitable method should be selected by considering the acid/base labile functional groups and the unsaturation on the substrate.

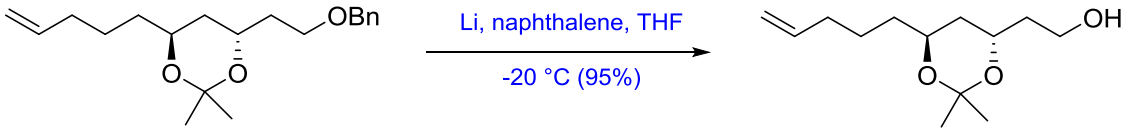


Scheme 1.30: Extension to the retrosynthetic strategy proposed by Harvey and Hewitt[19]

Benzyl ether protecting groups can be conveniently removed by using hydrogenolysis under neutral conditions or by acid hydrolysis. Hydrogenolysis with Raney nickel or palladium might affect the

endocyclic alkene functionality, therefore acid hydrolysis or alternative methods like free-radical initiated benzyl deprotection could be more appropriate.

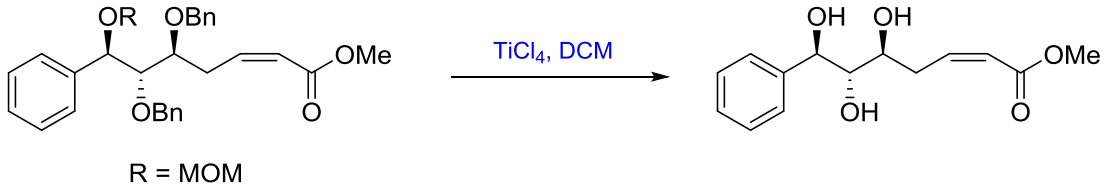
The olefinic compound **123** containing a benzyl group has been successfully debenzylated by a free radical-induced mechanism with Li/naphthalene to obtain **124** in excellent yield (Scheme 1.31).[41] The product **124** retained the double bond, which was considered a promising precedent for the related group in (−)-TAN-2483B.



123 **124**

Scheme 1.31: Debenzylation of **123** by Li/naphthalene in the total synthesis of attenols A and B[41]

In addition to hydrogenolysis of benzyl group, cleavage with strong Lewis acids was reported for molecules containing unsaturated C-C double bonds. Sabitha *et al.* (Scheme 1.32)[42] reported the use of $TiCl_4$ in deprotection of benzyl protecting groups in **125** during the total synthesis of leiocarpin A.[42]



R = MOM

125 Leiocarpin A **(126)**

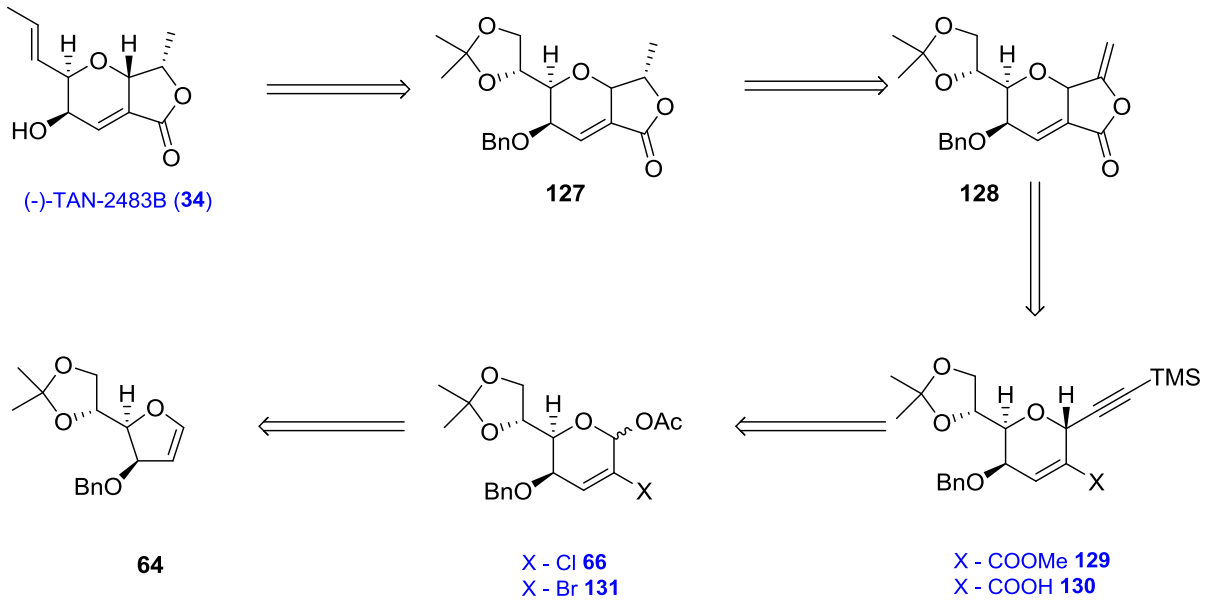
Scheme 1.32: Lewis acid-mediated debenzylation in the synthesis of leiocarpin A[42]

According to the retrosynthetic strategy (Scheme 1.30) γ-lactone formation may be achieved from the advanced secondary alcohol **122** via Pd-catalysed carbonylation. Secondary alcohol **122** could be synthesised by oxidation of primary alcohol **70** followed by Grignard reaction with an appropriate methyl nucleophile. Controlling the stereochemistry of this Grignard reaction might be challenging and could result in an inseparable alcohol mixture. Primary alcohol **70** can be prepared by the reported procedure by Harvey and Hewitt through Wittig olefination, epoxidation and epoxide ring opening. Optimisation of the original sequence would be necessary for pursuing this route due to the poor yields and poor diastereoselectivity obtained previously. Cyclopropanation of glycal **64** under Mąkosza condition, followed by silver-mediated intermolecular ring expansion of cyclopropane would provide the key intermediate **67** as discussed in section 1.3 for the synthesis of

the (−)-TAN-2483B core by Harvey and Hewitt in 2010. The glycal can be easily prepared by a procedure reported by Theodarakis.[20] The strategic disadvantages of the above retrosynthetic approach are the creation of a linear structure **68** by Wittig homologation, thus destroying the dihydropyran ring already made by cyclopropane ring opening, and installation of the methyl group of the γ-lactone in a separate step.

1.6.2 Retrosynthetic route with *C*-glycosidation

An alternative plan was devised that would use alkynylated glycoside **129** as an advanced intermediate (Scheme 1.33). This strategy allows the installation of the two carbon unit in a single step without affecting the pyran ring. Side arm installation of (−)-TAN-2483B was planned to be exactly the same as the previous route (scheme 1.33).

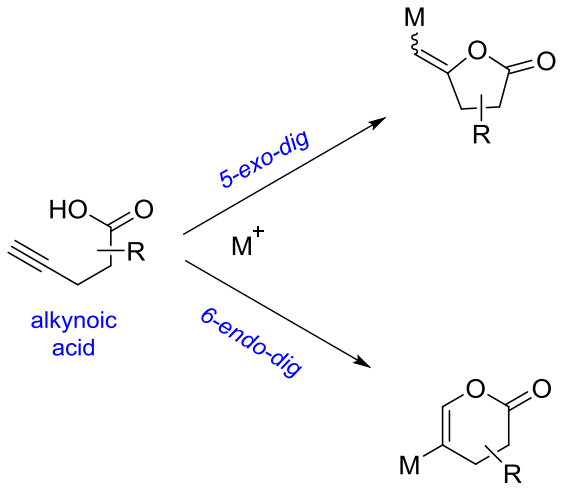


Scheme 1.33: Retrosynthetic strategy via *C*-glycosidation

Minoru Isobe and co-workers showed that silylacetylenes are sufficiently reactive to substitute acetyl glycosides in the presence of $SnCl_4$, forming sugar acetylenes in an α-selective manner.[33b] The acetate **66/131**, resulting from cyclopropane ring opening, can therefore be directly utilised in the two-carbon installation to synthesise sugar acetylene in a more step economic manner.

Palladium-catalysed carbonylation can be used to synthesise alkynoic acid **130** via its methyl ester **129**. The metal-catalysed intramolecular cyclisation of an alkynoic acid **130** is probably the most convenient and flexible method to form the lactone ring. Among the metals used for such cyclisations, silver and gold have proved to be the most effective as well as the most

regioselective.[43] The π-coordination of alkynes with metals such as $Ag^{(I)}$ and $Au^{(I)}$ has a dramatic consequence on the behaviour of the alkyne π-system. If a molecule possesses a heteronucleophile, the metal-complexed alkyne becomes prone to nucleophilic addition. However, depending on the complexed metal and the conditions, both 5-*exo*- and 6-*endo*-dig cyclisation processes could occur, leading to mixtures of ring sizes.[43b]

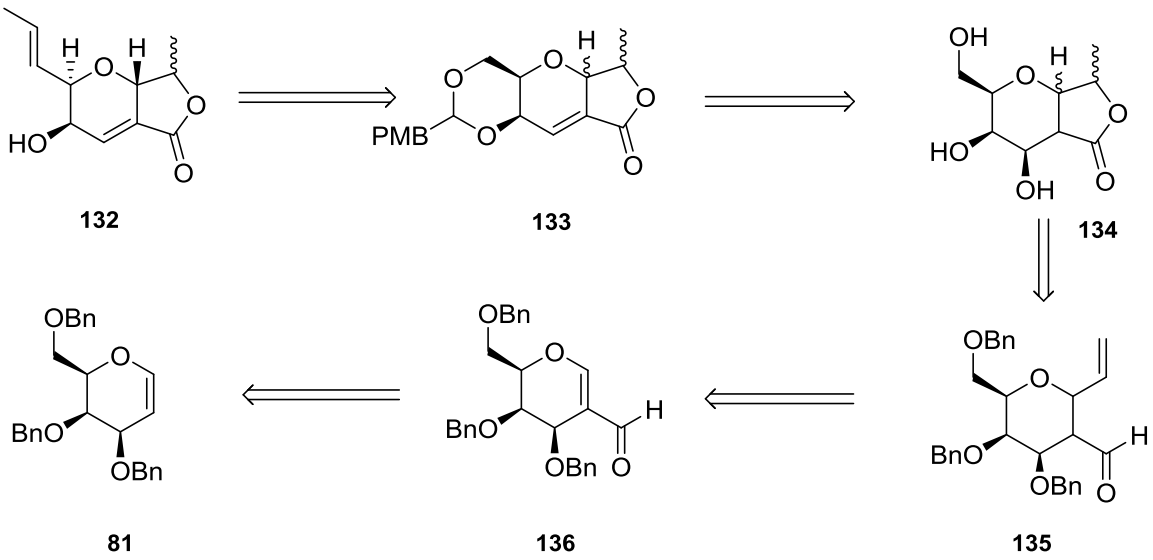


Scheme 1.34: *endo*- vs *exo*-dig cylisation leading to alkylidene lactones

Desilylation before the alkyne lactonisation is essential, because a silyl group attached to the triple bond is known to decrease electron density of the alkyne through d-π conjugation.[43b] As a result, the coordination of the silyl alkyne with an electrophilic metal ion is diminished. Meanwhile, metal-catalysed lactone ring formation via a 5-*exo*-dig mechanism and the selective reduction of the less sterically hindered (exocyclic) double bond are likely to be the most challenging steps of this synthetic route.

1.6.3 Non-cyclopropanated route based on 2-formylglycal

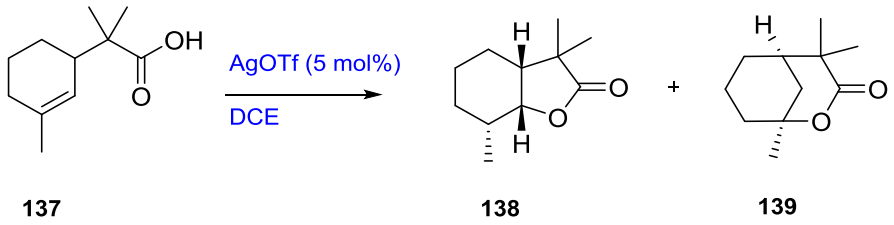
Due to the expected lack of reactivity of the chloroalkene intermediates in carbonylation and the difficulties encountered by Hewitt in preparing the bromoalkene **131**, an alternative strategy was investigated. The key steps of this retrosynthetic plan are Vilsmeier-Haack reaction of the glycal **81** and Michael addition of vinyl magnesium bromide to the conjugated aldehyde **136** to complete the essential number of carbons in the γ-lactone (Scheme 1.35). Consequently this strategy leads to synthesising the full carbon skeleton of the furopyran ring system without the ring unsaturation of the pyran.



Scheme 1.35: Retrosynthetic strategy via Vilsmeier-Haack reaction

(−)-TAN-2483B could be formed via advanced intermediate **133**, through regioselective protection of the *p*-methoxybenzylidene acetal. Unsaturation of the pyran ring can be realised through elimination of a good leaving group under alkaline conditions. Lactone ring formation can be achieved by metal-catalysed intramolecular acyloxylation. In 2005, Yang *et al.* discovered that silver$^{(I)}$ triflate is an excellent catalyst for intramolecular hydroalkoxylation and hydroacyloxylation of inert olefins (Scheme 1.36).[43a] Recently, platinum, gold, tin, ruthenium, and iridium have been shown to act as good catalysts for intramolecular and intermolecular hydroalkoxylation of unactivated olefins.

The stereoselectivity of the silver$^{(I)}$-catalysed cyclisation with olefin is revealed by the reaction with substrate **137** by Yang *et al*. Products **138** and **139** were isolated in a 2:1 ratio under the standard reaction conditions with substrate **137**. The *cis*-geometry of the substituents on the bridgehead carbons of products **138** and **139** was observed. [43a]



137 138 139

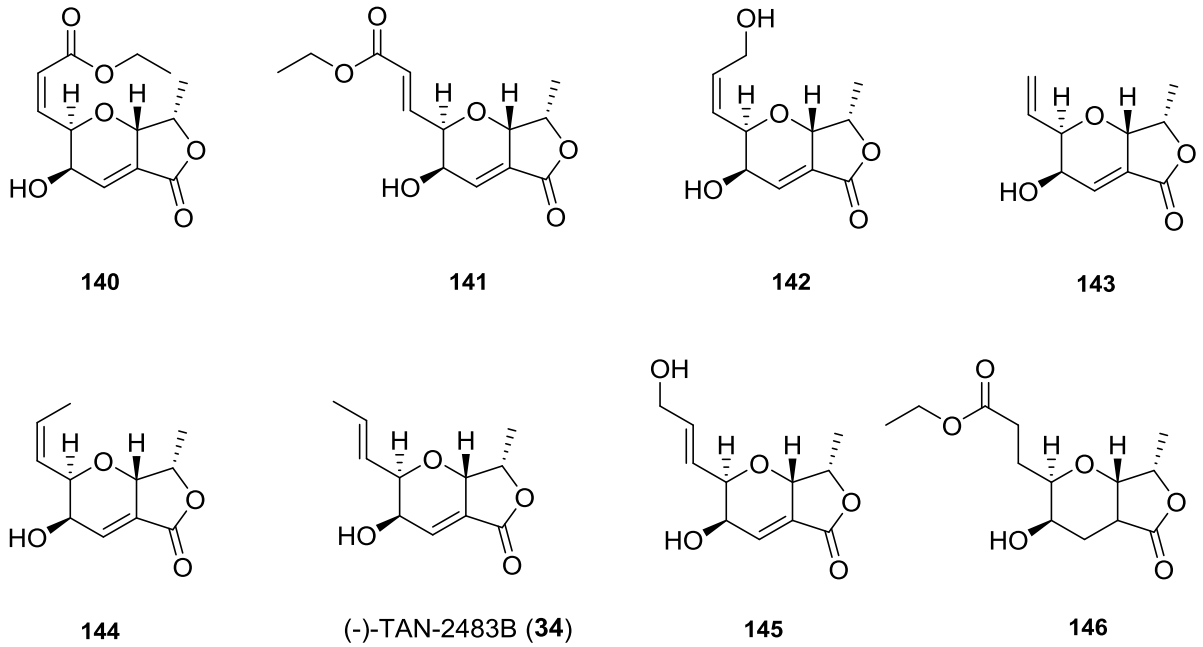
Scheme 1.36: AgOTf-mediated hydroacyloxylation[43a]

The two-carbon unit of the γ-lactone can be installed by Michael addition of **136** to the Vilsmeier-Haack aldehyde. Tribenzylated galactal (**81**) is reported to be a good substrate for the Vilsmeier-Haack reaction, which can be synthesised from readily available galactose via a well precedented

procedure.[44] The use of galactose as a primary starting material is beneficial, because the stereochemistry at the C4 and C5 positions maps onto that of the natural product (−)-TAN-2483B.

1.7 Research aim

The main research aim of the project presented in this thesis was to study the total synthesis of (−)-TAN-2483B and generation of several analogues of (−)-TAN-2483B (Figure 1.16). Cyclopropanation, *C*-glycosidation, Vilsmeier-Haack chemistry and Pd-catalysed carbonylation would be key reactions.



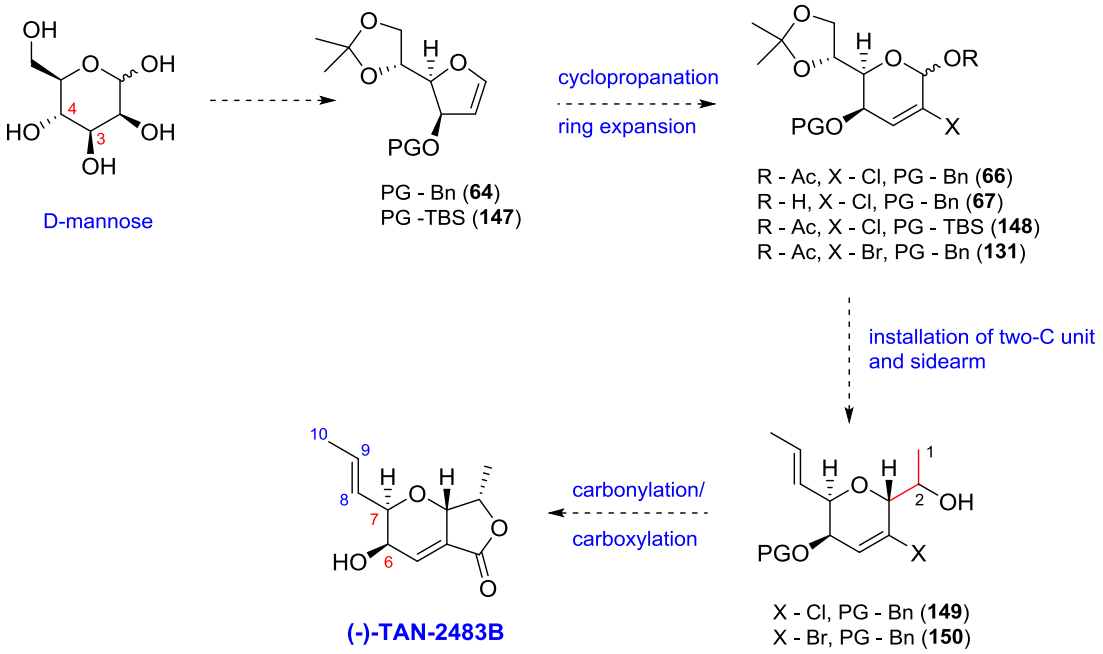
Fugure 1.16: Synthetic targets of this project: Natural product (−)-TAN-2483B and analogues

2 Dichlorocyclopropane Approaches to (−)-TAN-2483B

2.1 Introduction

A cyclopropane ring expansion sequence was identified as a viable route for the synthesis of the (−)-TAN-2483B ring system by Hewitt and Harvey in 2011.[19] This incentive encouraged the author to pursue a related strategy for the synthesis of the target natural product. The haloalkene functionality generated in the process of a *gem*-dihalocyclopropane ring expansion may be exploited in the synthesis of natural products sharing the furo[3,4-*b*]pyran ring system.

Commercially available D-mannose was identified as a suitable starting material for synthesis of the natural product, as for the ring system produced by Hewitt and Harvey.[19, 45] D-Mannose provides an excellent feedstock because its configurations at C3 and C4 correlate with those at positions C6 and C7 of (−)-TAN-2483B (Scheme 2.1). Synthesis of protected glycals **64** or **147** followed by a *gem*-dihalocyclo- propanation-ring expansion sequence would afford the key dihydropyran intermediates **66, 67, 148** or **131** as established previously by Hewitt and Harvey.[19] One key feature of this route is the revelation of the required unsaturation in the pyran ring by a cyclopropanation ring-expansion sequence.



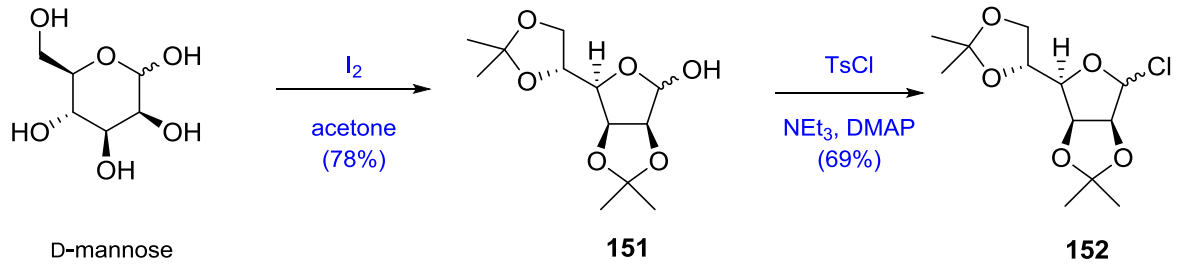
Scheme 2.1: Proposed plan for the synthesis (−)-TAN-2483B

The two-carbon fragment (C1−C2) of the lactone ring (highlighted in red Scheme 2.1) of compounds **149 and 150** could be installed by Wittig olefination, Seyferth–Gilbert homologation (using the Ohira-Bestmann reagent) or Lewis acid-mediated alkynylation. Stereoselective installation of this two-carbon unit would provide the remaining two stereogenic centres of the natural product. Acetonide deprotection and diol cleavage would provide the aldehyde required for the Julia-Kocienski olefination to append the side arm (C8−C10) of (−)-TAN-2483B. Subsequently, Pd-catalysed carbonylation or carboxylation followed by lactonisation would realise the furo[3,4-*b*]pyran ring skeleton of (−)-TAN-2483B. Finally, removal of the benzyl group would provide the natural product.

2.2 Synthesis of benzylated glycal 64

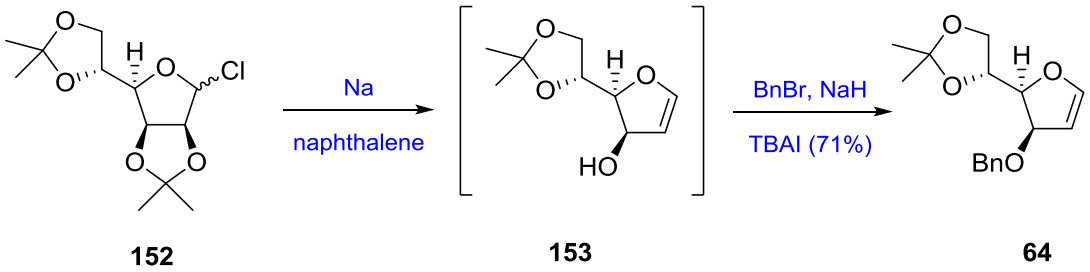
Synthetic ventures began with the transformation of commercially available D-mannose into furanose glycal **64** (Scheme 2.2) using the four-step sequence reported by Theodorakis.[20] First, D-mannose was converted to diacetonide mannose **151** by reacting with acetone and a catalytic amount of iodine. Acetone selectively generates five-membered acetonide rings linking adjacent *cis*-oriented hydroxyl groups. Protected mannofuranose **151** was thus obtained in 79% yield as white crystals after recrystallisation from acetone and petroleum ether. Treatment of diacetonide

mannose **151** with tosyl chloride, DMAP and triethylamine afforded the desired glycosyl chloride **152** as colourless viscous oil in 68% yield.

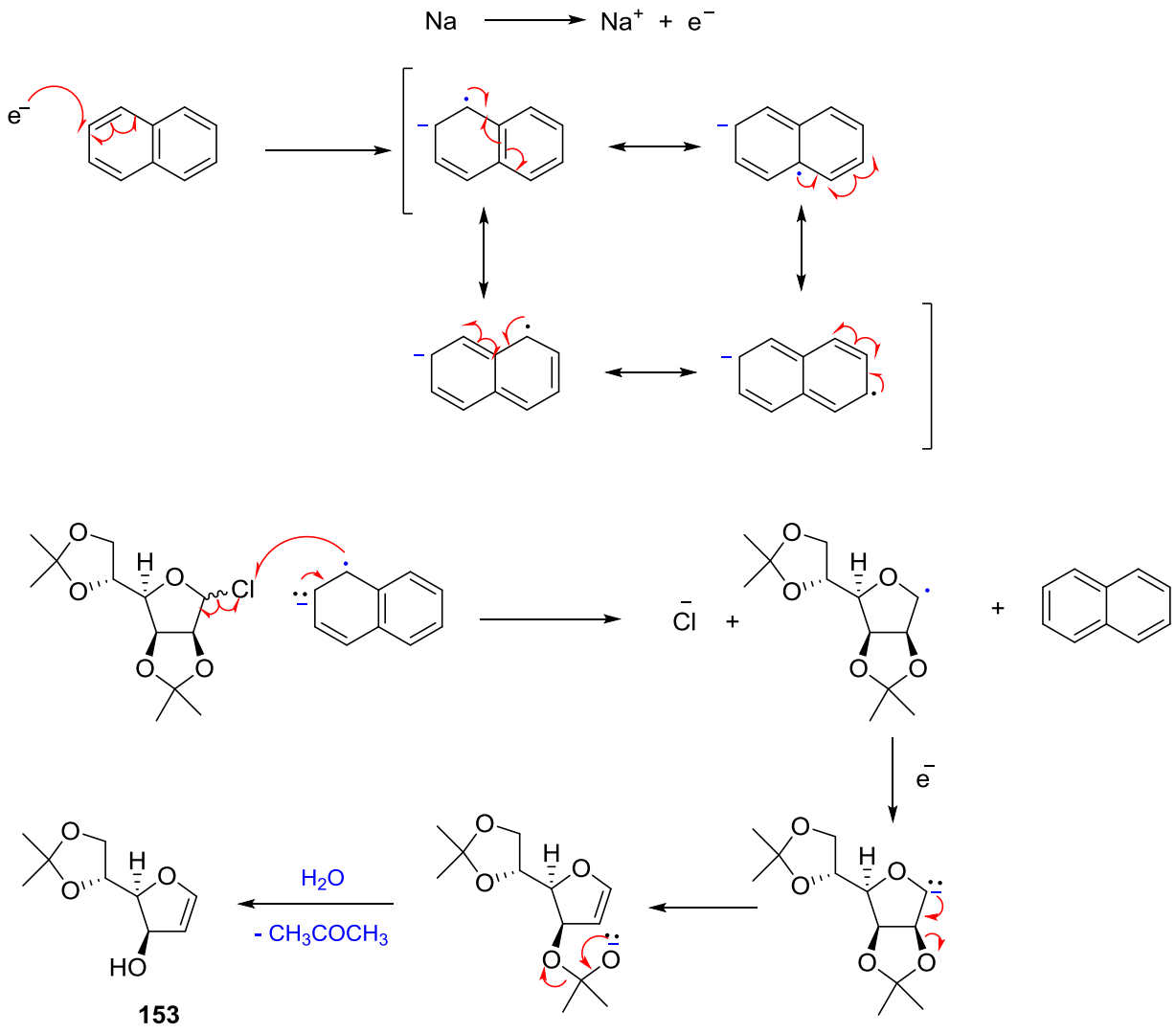


Scheme 2.2: Synthesis of glycosyl chloride **152**

Addition of freshly cut sodium into a solution of naphthalene in THF under an inert atmosphere produced an intensely green coloured solution due to formation of the sodium naphthalenide radical anion through the acceptance of one electron from sodium metal by naphthalene (Scheme 2.3). Glycosyl chloride **152** was added to this sodium naphthalenide solution at 0 °C to form glycal **153** through a radical initiated process (Scheme 2.4).[20]

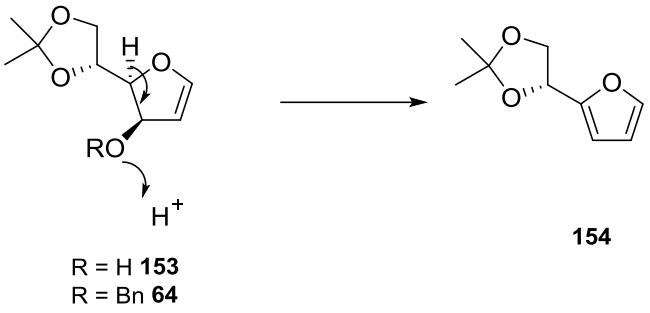


Scheme 2.3: Synthesis of benzylated glycal **64**



Scheme 2.4: Proposed mechanism of formation of **153** through free radical process

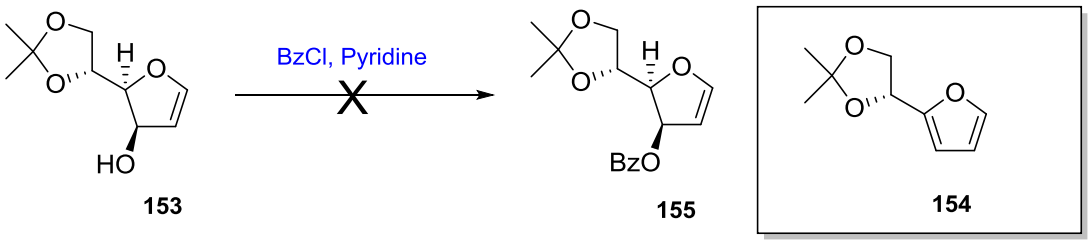
The glycal **153** was found to be very unstable as it tends to degrade in the acidic or basic medium. Glycal **153** was subjected to benzylation as soon as possible to provide fully protected glycal **64** (Scheme 2.3). Degradation of this benzylated glycal **64** into the known acetonide furan compound **154** was observed upon purification on a silica gel column and standing in unneutralised $CDCl_3$ solution. Both acid- and base-catalysed degradation of **64** is possible to afford **154**. In acid-mediated degradation, a catalytic amount of a proton source is sufficient as the proton is regenerated during the elimination process (Scheme 2.5).



Scheme 2.5: Acid-catalysed side reaction forming furan **154**

The acidity of the silica could be promoting the elimination of benzyl alcohol by establishing the aromaticity of the furan ring. Rapid column chromatography was necessary to minimise this degradation and to recover the desired compound.

Accidental formation of furan **154** was reported by Van Boom *et al.*[46] during the installation of a benzoyl protecting group into compound **153** with benzoyl chloride and pyridine (Scheme 2.6). This indicates that base-promoted elimination is also possible in these systems, although it should be noted that compound **155** contains a good leaving group. Similar base-promoted degradation of **64** was also observed in this research (details in section 4.2). The observations and reported data suggested that the both protected glycal **64** and unprotected glycal **153** are sensitive to acidic and basic environments, forming aromatic furan **154**.

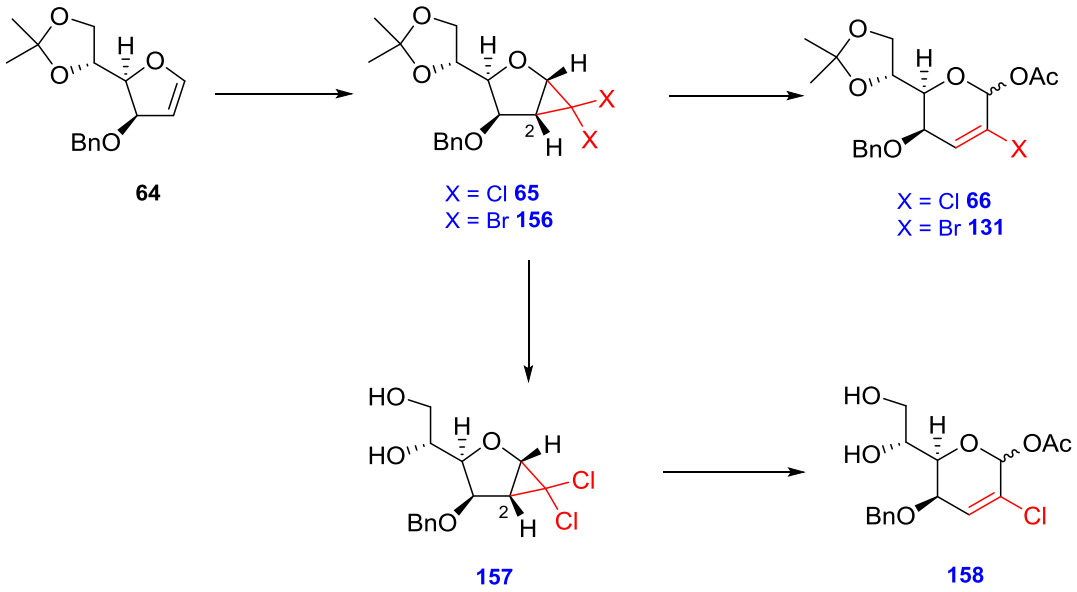


Scheme 2.6: Reported formation of furan **154** in benzoyl protection[46]

2.3 Cyclopropanation-ring expansion of benzylated glycal 64

The chosen strategy for synthesis of the pyran-based intermediates **66, 131** and **158** was cyclopropanation followed by cyclopropyl ring expansion, as established by Hewitt and Harvey for the synthesis of the bicyclic carbon skeleton of (−)-TAN-2483B (Scheme 2.7).[19] Cyclopropanation of

benzylated glycal **64** under Mąkosza conditions would provide the furanose-fused cyclopropanes **65** and **156**. Cyclopropane ring expansion in the presence of acetate nucleophile would provide the acetyl glycosides **66** and **131.** Ring expansion of acetonide-cleaved cyclopropane **157** would provide acetyl glycoside **158** (Scheme 2.7).



Scheme 2.7: Key cyclopropanation-ring expansion sequence in the synthesis of acetates **66, 131** and **158**

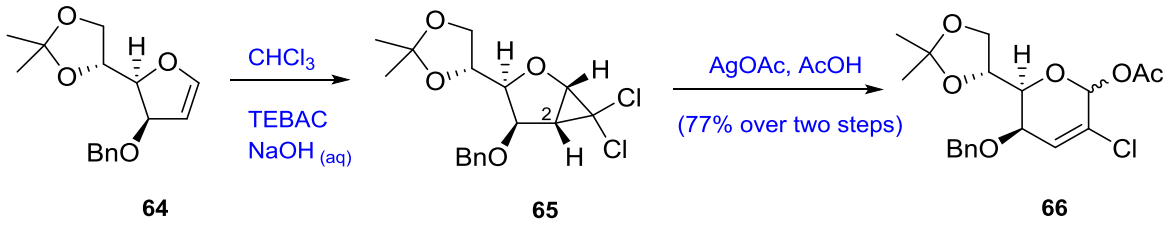
2.3.1 Cyclopropanation-ring expansion of 64 in the synthesis of key intermediates 66, 67 and 158

Cyclopropanation of benzylated glycal **64** with dibromocarbene and dichlorocarbene were tested by Hewitt.[45] Unfortunately, dibromocyclopropanation to afford **156** was unsuccessful (details in section 4.2), while dichlorocylopropanation was a facile process. Thus, the dichlorocyclopropane **65** was carried forward by Hewitt in the synthesis of the bicyclic furo[3,4-*b*]pyran core of TAN-2483B.[45] Consequently, dichlorocyclopropanation became the primary strategy for the synthesis of the natural product and analogues.

Cyclopropanation of glycal **64** with dichlorocarbene, generated from chloroform in the presence of 50% (w/w) sodium hydroxide, proceeded smoothly to form desired cyclopropane **65** in sufficient purity. None of the stereoisomeric cyclopropane was observed. The stereoselectivity of this

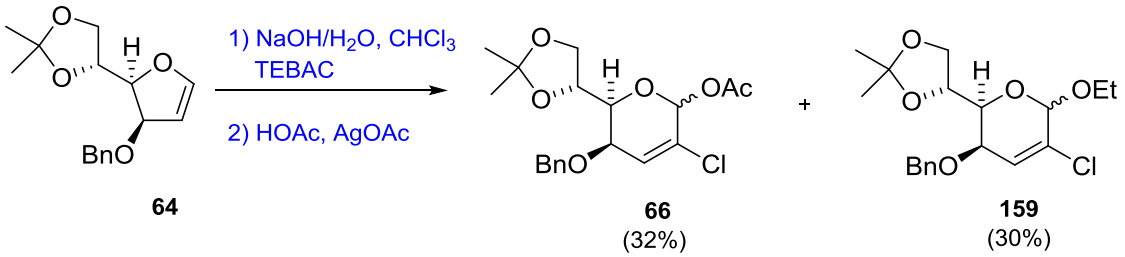
cyclopropanation is controlled by the steric hindrance exerted from the benzyl and isopropylidene protecting groups on the top face. As a result, the carbene attacks from the bottom face, affording the dichlorocyclopropane **65** (Scheme 2.8).

The dichlorocyclopropane **65** was used for the ring expansion reaction directly after aqueous work-up, without performing silica column purification, as determined to be beneficial by Hewitt and Harvey.[19] Furan-fused *gem*-dichlorocyclopropane **65** was easily ring expanded in the presence of silver acetate and glacial acetic acid as reported by Hewitt and Harvey.[19] The ring expansion reaction proceeded cleanly within two hours at 90 °C in glacial acetic acid (Scheme 2.8), yielding the desired acetyl glycoside **66** (3:1 ratio of anomeric mixture, 77% over two steps). Surprisingly, the other regioisomeric glycal, originating from acetate attack at the C2 position, was not observed at 90 °C in neat glacial acetic acid. Usually ring expansions of pyran-fused cyclopropanes need high temperature as well as prolonged reaction time.[32, 45] A relatively lower temperature and shorter reaction time were sufficient for the ring expansion of furan-fused cyclopropane **65** due to comparatively greater ring strain in the bicyclo[3.1.0] system. Further, the presence of the adjacent ring oxygen also facilitates ring expansion by electron donation.



Scheme 2.8: Cyclopropanation and ring expansion of benzylated-glycal **64**

Upon scale-up (using 1.2 g of **64**) of the cyclopropanation-ring expansion process, two products were detected by TLC. Ethyl glycoside **159** (5:1 anomeric mixture in 30% yield) was isolated in addition to the desired acetate **66** after silica gel chromatography (Scheme 2.9). Ethyl glycoside **159** might be formed by spontaneous ring expansion during the cyclopropanation reaction in chloroform by ethanol. Ethanol is present as a stabiliser in chloroform (3−5% w/w) and presumably acts as a nucleophile to afford undesired ethyl glycoside **159**. Formation of **159** during the cyclopropane ring expansion is not possible as no source of ethanol is present in that reaction mixture. Such a cyclopropane ring opening reinforces the observations throughout this work of the high reactivity of the furocyclopropane **65** moiety towards ring expansion, presumably due to its inherent ring strain.

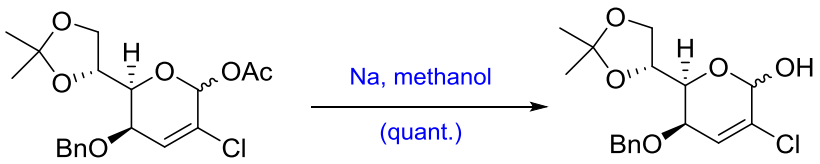


64 **66** (32%) **159** (30%)

Scheme 2.9: Formation of ethyl glycoside **159** during the cyclopropanation

The formation of the undesired ethyl glycoside **159** was completely suppressed by addition of the aqueous NaOH 50% solution into a 0 °C solution of the glycal **64** in chloroform and performing the reaction at low temperature. Heat generated upon addition of aqueous NaOH mixture to the glycal solution may have been been promoting thermal ring expansion and concomitant formation of ethyl glycoside **159**. The temperature increment would be insignificant in small scale cyclopropanation reactions but at larger-scale it could become significant. Thus, it was deemed necessary to perform subsequent cyclopropanation reactions at low temperature.

The masked aldehyde in hemiacetal **67** which is generated by the hydrolysis of acetyl glycoside **66** can be utilised in installation of the two-carbon unit of the methyl furo[3,4-*b*]pyran. Acetyl glycoside **66** was subjected to methanolysis in the presence of a catalytic amount of sodium metal (Scheme 2.10). Complete consumption of starting material was observed within one hour at room temperature. The crude material was passed through a silica plug and eluted with dichloromethane in order to obtain the purified hemiacetal **67**. The hemiacetal **67** was obtained in a quantitative yield and sufficient purity to carry out the further transformations described in the Section 2.5.

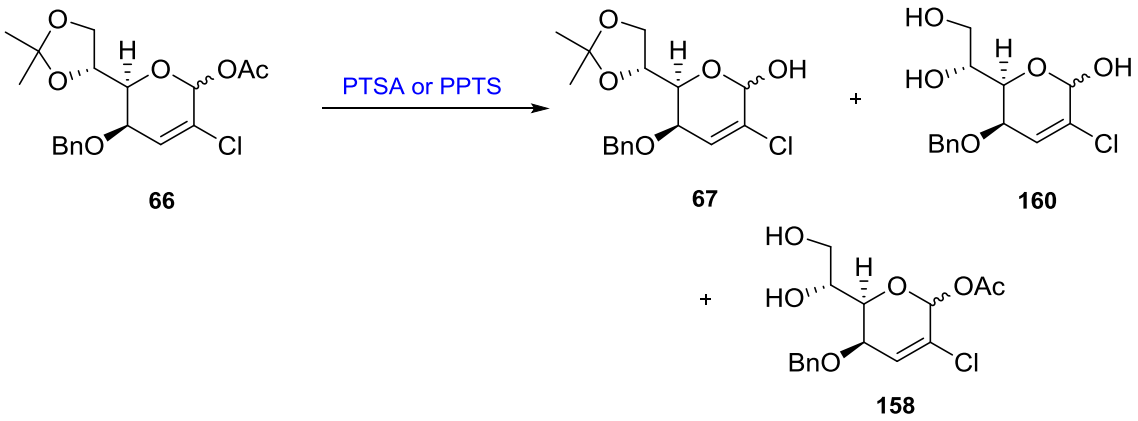


66 **67**

Scheme 2.10: Synthesis of hemiacetal **67**

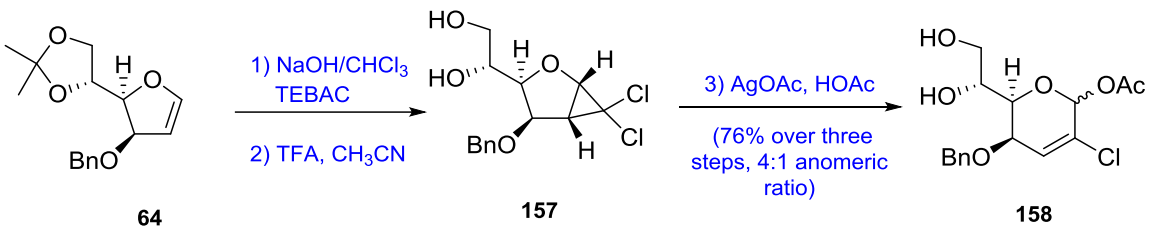
2.3.2 Deprotection of acetonide group on 66 and synthesis of diol acetate 158

The acetonide protecting group in **66** needed to be cleaved at some stage in order to install the side arm (C8-C9 fragment) of the natural product. The acetate **66** is the earliest intermediate on which it would be possible to study side arm installation (see Section 2.7). Doing so prior to cyclopropanation could lead to a cyclopropyl side arm. Attempted selective removal of the isopropylidene group in **66** in the presence of an acetate group with PTSA and PPTS resulted in complicated mixture of hemiacetals **67** and **160** along with the desired acetate **158** (Scheme 2.11).



Scheme 2.11: Unsuccessful selective deprotection of acetonide group n **66**

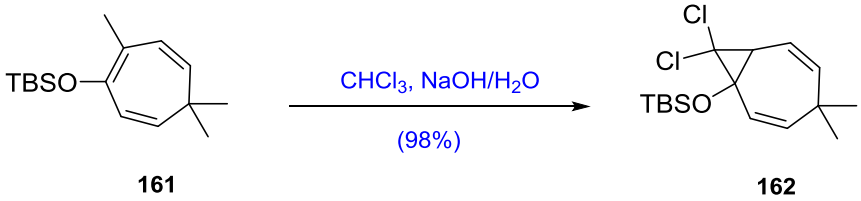
Consequently, acetonide deprotection at the cyclopropane **65** stage was tried. Delightfully, acetonide deprotection with TFA at 0 °C went smoothly without any side reactions. The crude cyclopropane **157** was immediately reacted with AgOAc and glacial acetic acid to afford ring-opened acetate **158** (Scheme 2.12). Cyclopropanation, acetonide deprotection and ring expansion was done in a sequence without performing silica column purification. Diol acetate **158** was obtained in 76% (4:1 anomeric ratio) yield over a three step sequence from the cyclopropane **65**. The diol acetate **158** was used in the study of side arm installation which will be discussed in section 2.7**.**



Scheme 2.12: Synthesis of diol acetate **158**

2.4 Cyclopropanation-ring expansion of TBS-protected glycal 147

Benzyl ethers are robust protecting groups due to their capacity to withstand many reaction conditions including the highly basic environment of Mąkosza cyclopropanation. Nonetheless, synthesis and isolation of benzylated glycal **64** presented a few difficulties (see section 2.2). The choice of benzyl protecting group for the research presented here was based on the great deal of precedent for this protecting group in cyclopropanation of glycals. Silyl protection has limited popularity as a protecting group in cyclopropanation of glycals under Mąkosza conditions.[25] The trimethylsilyl (TMS) protecting group is very sensitive to aqueous basic conditions; thus, the strongly basic aqueous conditions of Mąkosza cyclopropanation cannot be used with them.[25] Nevertheless, *tert*-butyldimethylsilyl (TBS) derivatives were shown to withstand these conditions[47] by Takashi *et al.,* who reported cyclopropanation of substrate **161** containing a TBS protecting group in an excellent yield (Scheme 2.13).[47]

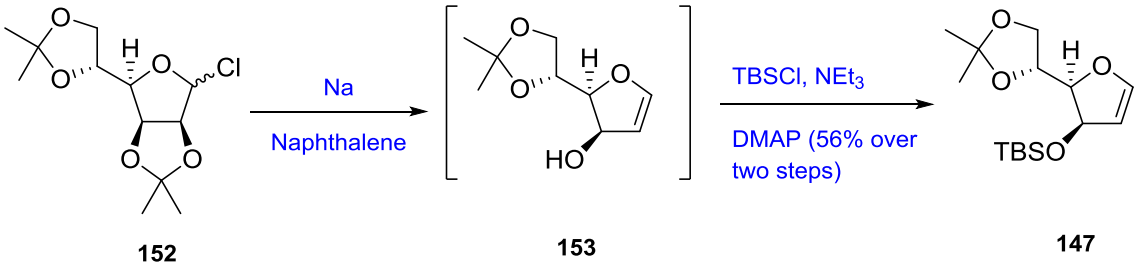


Scheme 2.13: Reported Mąkosza cyclopropanation of substrate **161** containing a TBS protecting group[47]

The lability of the TBS protecting group in the present setting was tested with the TBS-protected glycal **147** (Scheme 2.14). The main advantage of TBS protection over benzyl protection is the

orthogonality of deprotection, because the planned hydrogenolysis of the benzyl ether is a concern with respect to the ring unsaturation.

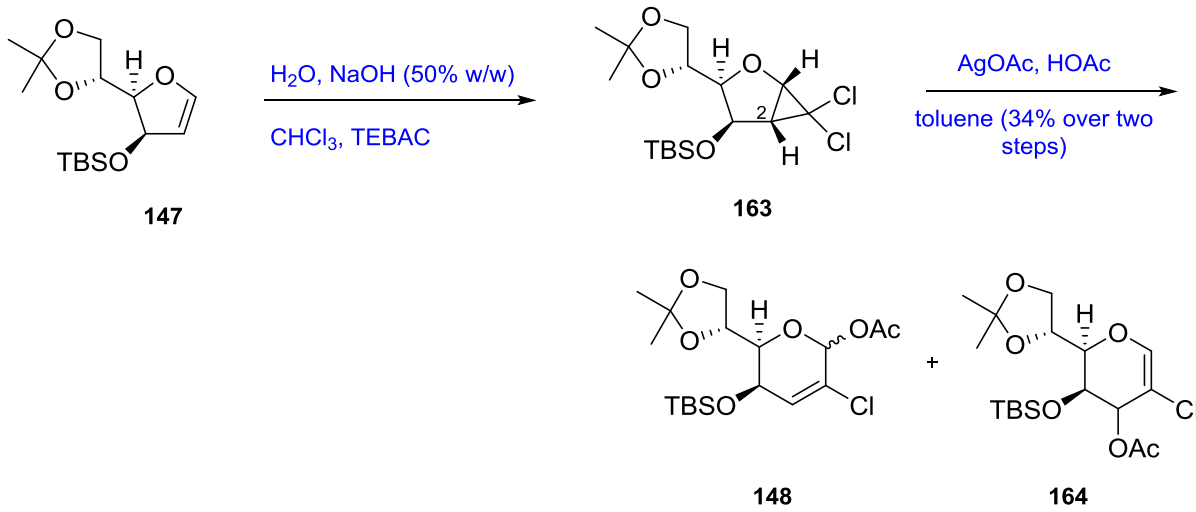
TBS-protected glycal **147** was synthesised in two step starting from chloride **152**. The glycal obtained from sodium naphthalenide reaction was protected with a TBS group by reacting with TBSCl, NEt_3 and DMAP. TBS-protected glycal was obtained in 56% yield which is comparatively low yield relative to that obtained for the benzyl protected glycal **64** (Table 2.1).



152 **153** **147**

Scheme 2.14: Synthesis of TBS protected-glycal **147**

The TBS-protected glycal **147** was subjected to Mąkosza cyclopropanation conditions. The reaction progressed cleanly to give desired cyclopropane **163** with sufficient purity (Scheme 2.15). The cyclopropane **163** was used immediately in the cyclopropane ring expansion reaction due to its low stability.



147 **163** **148** **164**

Scheme 2.15: Cyclopropanation of TBS protected-glycal **147** and it ring expansion

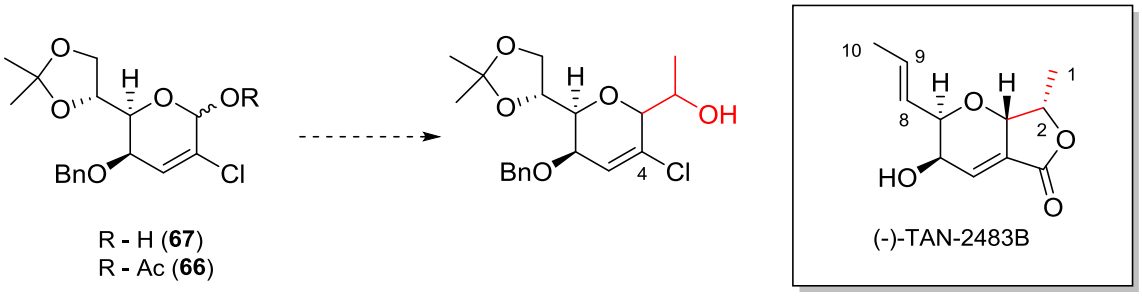
The most successful conditions for cyclopropane ring expansion of benzyl-protected **65** involve use of silver acetate and glacial acetic acid at 90 °C.[45] The use of glacial acetic acid at elevated temperature was anticipated to cause cleavage of the TBS protecting group of the cyclopropane **163**. Ring expansion of **163** was attempted with NaOAc and AgOAc in toluene at reflux (Scheme 2.15). Full consumption of starting material was observed after one hour; upon purification an inseparable mixture of desired acetyl glycoside **148** was obtained along with regioisomeric glycal **164** in a relatively low yield (34% as a 3:1 ratio). Glycal **164** is formed by acetate attack at C2 of cyclopropane **163**. The low yield (see table 2.1) and synthesis of significant amounts of the undesired ring expanded regioisomer as an inseparable mixture with desired acetyl glycoside **148** led to abandonment of further use of a TBS-protected glycal.

Reaction	**Yield (with Benzyl)**	**Yield (with TBS)**
Glycal **153** protection	71%	56%
Cyclopropanation and cyclopropane ring expansion	77%	34% (mixture of **148**:**164**, 3:1 ratio)

Table 2.1: Comparison of benzyl vs TBS protecting groups in cyclopropanation and ring expansion

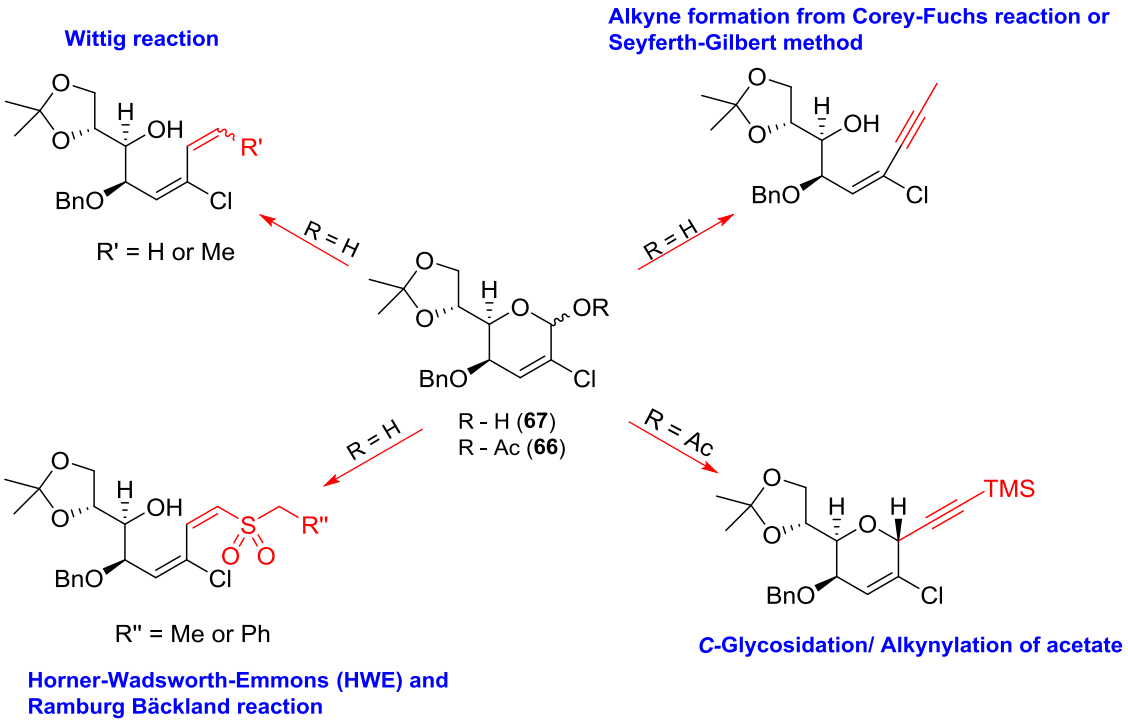
2.5 Attachment of two carbon unit (C1-C2) to the pyran intermediates 66 and 67

As illustrated in Scheme 2.16, the planned synthetic strategy involved introduction of a two carbon unit (C1-C2) onto pyran intermediates **66** or **67**. Subsequent cyclisation of the C2 oxygen with the appropriate carbonyl functionality branched at C4 would reveal the furo[3,4-*b*]pyran ring skeleton. The following sections describe attempts to elaborate the chloroalkenes **66** and **67** to the methylated furo[3,4-*b*]pyran ring skeleton.



Scheme 2.16: Installation of two carbon unit in the formation of furo[3,4-*b*]pyran ring skeleton

The potential strategies for installation of the two-carbon unit of the methylated lactone ring are summarised below (Scheme 2.17). Alkyne formation through a Corey-Fuchs reaction, a Seyferth-Gilberet reaction or with the Ohira Bestmann reagent and alkene formation through olefination reactions with hemiacetal **67** will be discussed**.** Alkynylation of acetyl glycoside **66** will be also discussed in the installation of two-carbon fragment. Consideration of the functional group tolerance and stereoselectivity must be made when choosing methods for installation of the two-carbon unit to key intermediates **66** and **67** as one stereocentre of the target natural product is generated in this process. The following section describes the attempts to introduce two-carbon unit of the γ-lactone utilising the methods mentioned in Scheme 2.17.

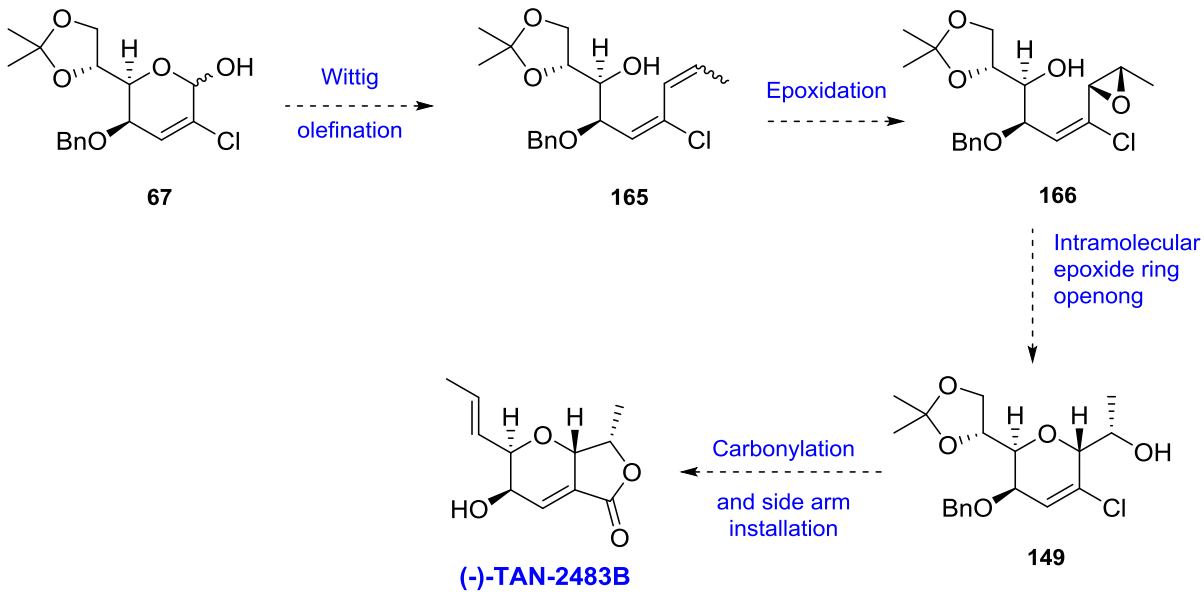


Scheme 2.17: Planned strategies for installation of the two-carbon unit to the intermediates **66** and **67**

2.5.1 Olefination reactions of hemiacetal 67

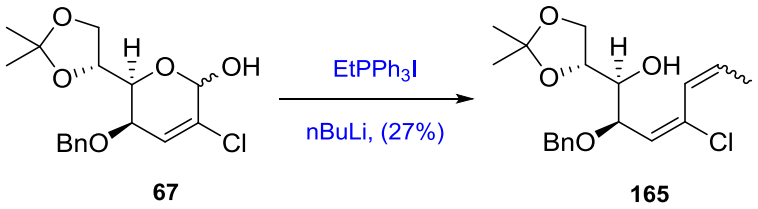
Wittig and Julia-Kocienski olefination of hemiacetal 67

As illustrated in Scheme 2.18, Hewitt planned to synthesise (−)-TAN-2483B via formation and subsequent reaction of epoxide **166**.[45] Epoxide **166** can be accessed from the olefin **165** that may be synthesised by Wittig olefination of masked aldehyde **67**. Poor *Z*-/*E*-selectivity in the Wittig olefination was found to be the main drawback of the Wittig approach.[45] Nevertheless, the same synthetic plan was repeated in this project with the intention of optimising stereoselectivity in the olefination.



Scheme 2.18: Attempted (−)-TAN-2483B synthesis via ethylidene Wittig olefination

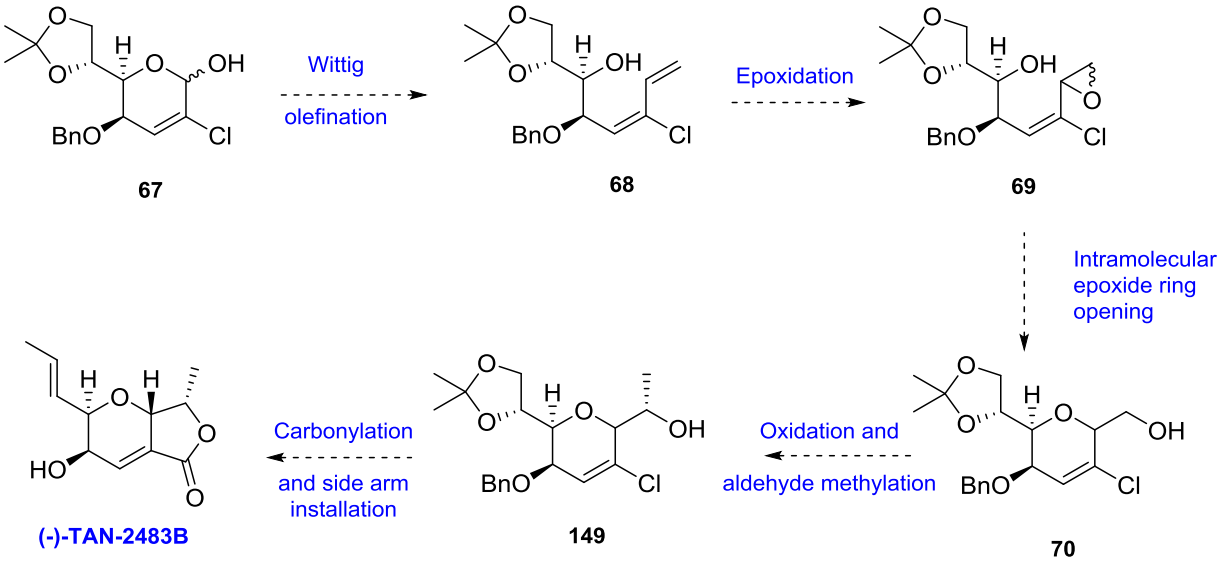
Generally, the *Z*-selective Wittig reaction is favoured with an unstabilised phosphonium ylide. First, a Wittig olefination between hemiacetal **67** and ethyltriphenylphosphonium iodide was attempted using n-butyllithium as the base (Scheme 2.19). After five hours in refluxing THF, an inseparable mixture of alkene isomers **165** was obtained in 27% yield in favour of the *cis*-alkene (1:2 *E*:*Z*).



Scheme 2.19: Ethylidene Wittig olefination to form compound **165**

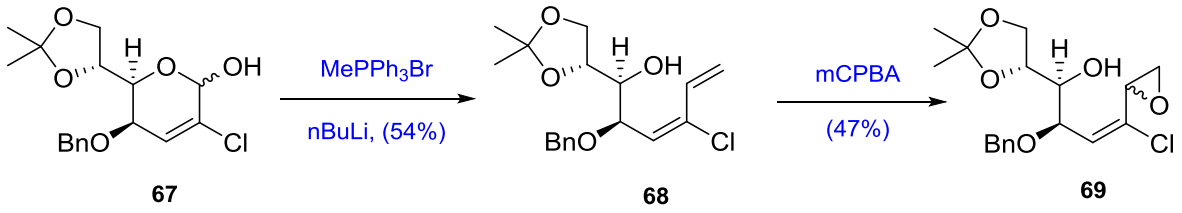
Formation of the *E*-alkene may arise from the large chlorine atom at the sp^2-hydridised α-position. The reaction was replicated using alternative bases such as KHMDS and ^{t}BuOK in the presence of 18-crown-6. Improvement in the *Z*-selectivity was not observed. When the reaction was performed with ^{t}BuOK, a 2:3 mixture of *E:Z* isomers was obtained. With KHMDS, the reaction was not completed after 5 hours of refluxing in THF containing 10% v/v DMPU and a 1:2 *E:Z* ratio was observed in the product. Moreover, the reaction was very sluggish at room temperature. Starting material was recovered from the reaction between ethyltriphenylphosphonium iodide and n-butyllithium after two days of stirring at room temperature. Trying to trap the aldehyde form by silylating the 5-hydroxyl position by premixing hemiacetal **67** with trimethylsilyl chloride and triethylamine gave complete degradation. In a related vein, a Julia-Kocienski olefination with LHMDS at reflux in THF gave a TMS-protected hemiacetal. Presumably, LHMDS acts as a source of TMS and leads to trapping of **67** as the corresponding TMS-protected hemiacetal. The silylating ability of KHMDS was reported previously by our group in the synthesis of sulfone analogues of aigialomycin D.[48]

Due to difficulties in improving the *Z*-selectivity of the ethylidene Wittig reaction, it was decided to pursue a Wittig olefination with the lower (methylidene) homologue, to synthesise diene **68** with the intention of installing the second carbon at a later stage, possibly through methylation of aldehyde as depicted in Scheme 2.20.



Scheme 2.20: Attempted synthetic route to (−)-TAN-2483B via methylidene Wittig olefination

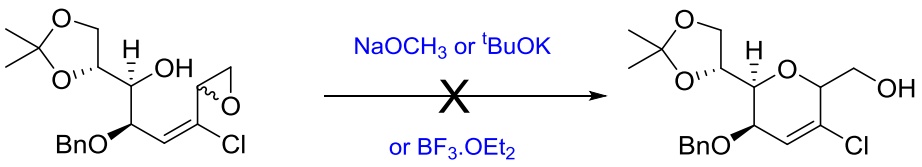
Synthesis of the methylidene Wittig-derived diene **68** was repeated in this work by treatment of a solution of commercially available methyltriphenylphosphonium bromide with n-butyllithium (Scheme 2.21). The masked aldehyde **67**, was added and the mixture heated at reflux in THF for 45 minutes. This provided diene **68** in 54% yield, which was converted to the corresponding epoxide **69** by treatment with *m*-CPBA. After two days, the reaction was completed and a mixture of epoxides was obtained (47%, 1:1 d.r.).



Scheme 2.21: Methylidene Wittig olefination and epoxidation of hemiacetal **67**

Pyran ring closure through substitution is possible under a base-mediated process as well as a Lewis acid-mediated process. Hewitt reported formation of the desired pyran ring in 42% yield together with minor unidentified product through a base-mediated process with sodium methoxide.[45]

Epoxide **69** was treated with a solution of sodium methoxide in methanol at room temperature (Scheme 2.22). Unfortunately, it provided a complicated mixture of compounds including recovered starting material. In another attempt, no reaction was observed with treatment of ^{t}BuOK at room temperature for one day. Epoxide ring opening with Lewis acidic conditions was tried as base-mediated pyran ring closure was unsuccessful. Acetonide deprotection was observed predominantly when the epoxide **69** was treated with freshly distilled $BF_3.OEt_2$.



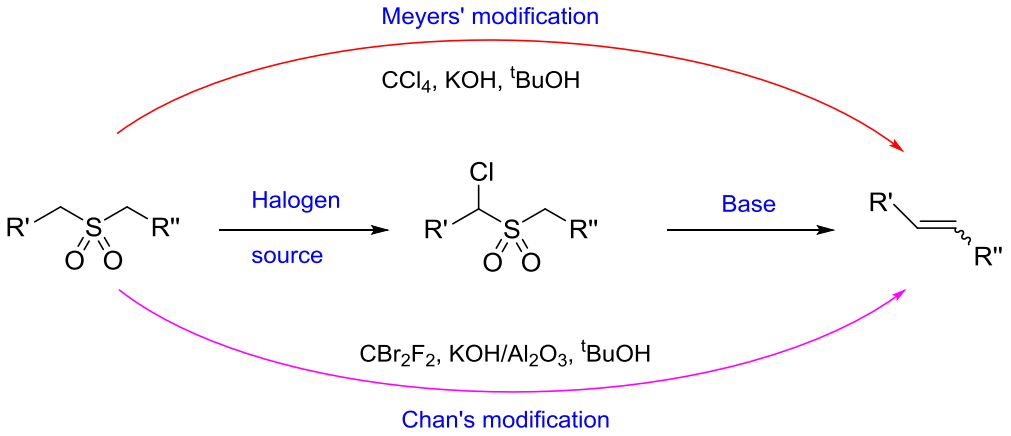
69 **70**

Scheme 2.22: Attempted pyran **70** formation via epoxide **69**

Due to the unreactivity of base-catalysed intramolecular epoxide ring opening and the sensitivity of the acetonide group towards the Lewis acidic conditions, pyran ring cyclisation through epoxide ring opening was abandoned.

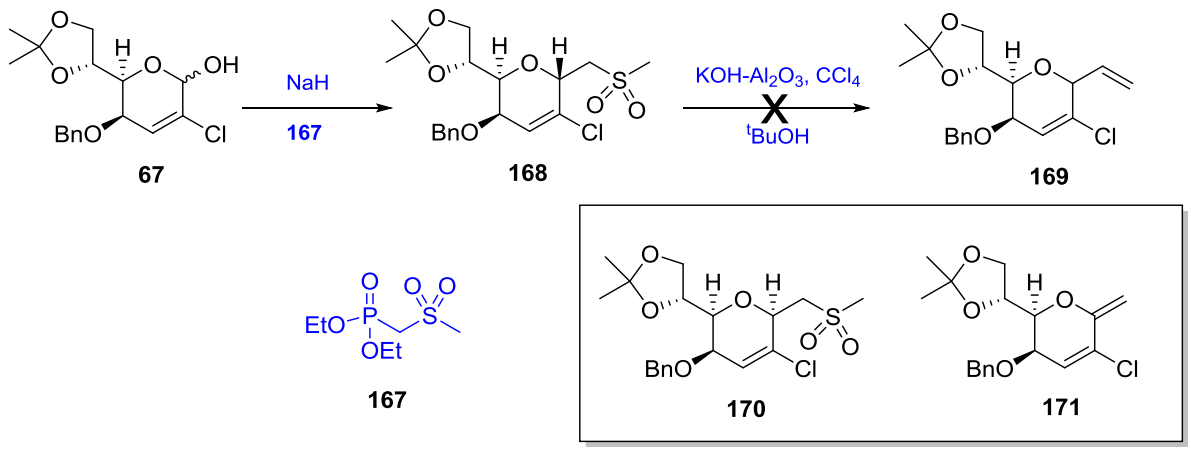
Horner-Wadsworth-Emmons /Ramburg Bäckland olefination approaches from hemiacetal 67

The Ramberg–Bäcklund (RB) reaction is an olefination reaction that converts an α-halosulfone into an alkene in the presence of a base with extrusion of sulfur dioxide.[49] Meyers' and Chan's modifications of the RB reaction directly convert a sulfone, via an α-halosulfone, to the product olefin, improving the synthetic efficiency through the one-pot conditions (Scheme 2.23).[49] Myers' modification of the RB reaction uses an *in situ* halogenation sequence in the presence of CCl_4, which acts as both solvent and electrophilic halogenating reagent. After halogenation, the α-halosulfone undergoes cyclisation to an episulfone and olefin formation as with unmodified RB reaction. In Chan's modification, dibromodifluoromethane in the presence of KOH adsorbed onto an alumina support provides the halogen source.[49]



Scheme 2.23: Classical RB reaction and its single step modifications

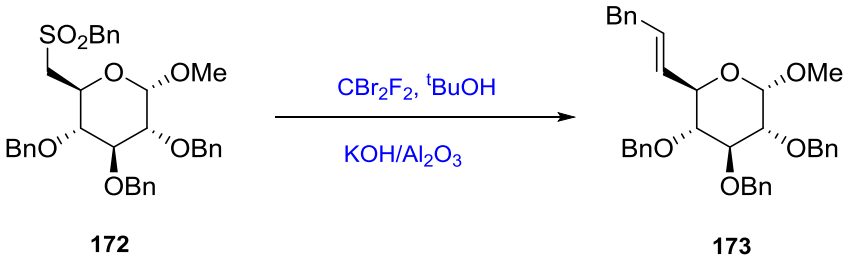
The RB reaction has been successfully used in the formation of *C*-glycosides and *C*-linked disaccharides by Taylor *et al*.[51] Hewitt made several attempts to synthesise a vinyl-substituted sugar **169** by Horner-Wadsworth-Emmons (HWE) reaction with diethyl (methylsulfonyl)methyl-phosphonate (**167**) followed by a RB reaction (Scheme 2.24).[45] Attempts using both Meyers' modification and Chan's modification were unsuccessful due to epimerisation, giving **170** and elimination of the sulfonyl group to form **171**.



Scheme 2.24: Previously attempted HWE/RB reaction sequence to afford **169**[45]

A stepwise sequence involving separate halogenation and RB reactions was also attempted in several different ways by changing reaction conditions such as base, halogen source and temperature.[45] However, due to the undesired reactivity of the sulfone **168**, the RB reaction route

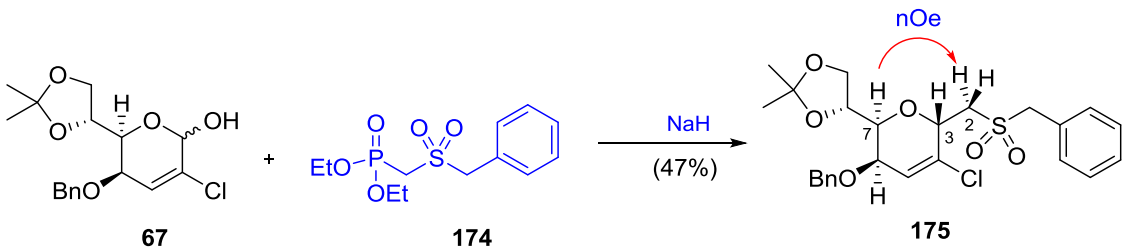
was abandoned by Hewitt. However, another research group reported a related system **172** benefitted from replacement of the terminal methylsulfonyl group with a benzylsulfonyl group, providing desired reactivity under RB reaction conditions (Scheme 2.25).[52]



172 **173**

Scheme 2.25: Reported RB reaction with benzyl sulfone to afford **173**[52]

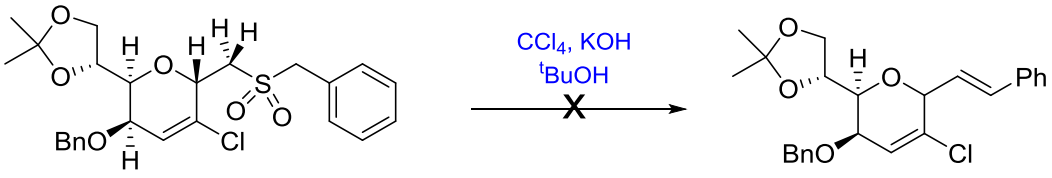
With this encouragement, diethyl (phenylsulfonyl)methylphosphonate (**174**) was synthesised in order to test the RB reaction with the benzylsulfone; this would lead to formation of the benzyl analogue of the target natural product. The required phosphonate was prepared in three known steps starting from commercially available benzyl mercaptan.[53] A HWE reaction with hemiacetal **67** was then performed. After deprotonation of the HWE reagent **174** with sodium hydride, hemiacetal **67** was added at 0 °C. After one day, TLC analysis showed that the starting material was fully consumed and upon purification, sulfonated sugar **175** was obtained in 47% yield (Scheme 2.26). The intermediate α,β-unsaturated sulfone was not isolated, because of the facile *in situ* cyclisation to the dihydropyran **175**. This was not surprising as both Taylor and Hewitt isolated similar cyclised products directly during the coupling of sulfonylphosphonates to carbohydrates.[45, 51]Then with cyclic sulfone **175** in hand, the configuration at C3 was determined by n*O*e correlations. Irradiation of the hydrogen at the C7 position caused enhancement of the signals at C2 and C6. The positive correlation between C2 and C7 confirms that the C3 branch is α oriented, which is the same configuration as the natural product.



67 **174** **175**

Scheme 2.26: HWE reaction of hemiacetal **67** with benzylsulfone **174**

With the desired sulfone **175** in hand, the key RB reaction was attempted using Meyers' conditions to afford **176** (Scheme 2.27). Consumption of starting material was observed within two and a half hours, according to TLC analysis, with an array of new spots being observed on TLC of the reaction mixture. The crude mixture was separated by silica gel column chromatography and the products investigated by ^{1}H-NMR spectroscopy. One isolated fraction provided evidence of a minute amount of a compound having an olefin functionality based on the the new signals appearing in the alkene region at 5.5 ppm-6.0 ppm. However, the structure of the isolated product could not be confirmed due to the presence of a complicated mixture of compounds. This unsuccessful RB reaction led the author to investigate alternative routes for the installation of the two-carbon unit of the lactone in (−)-TAN-2483B.



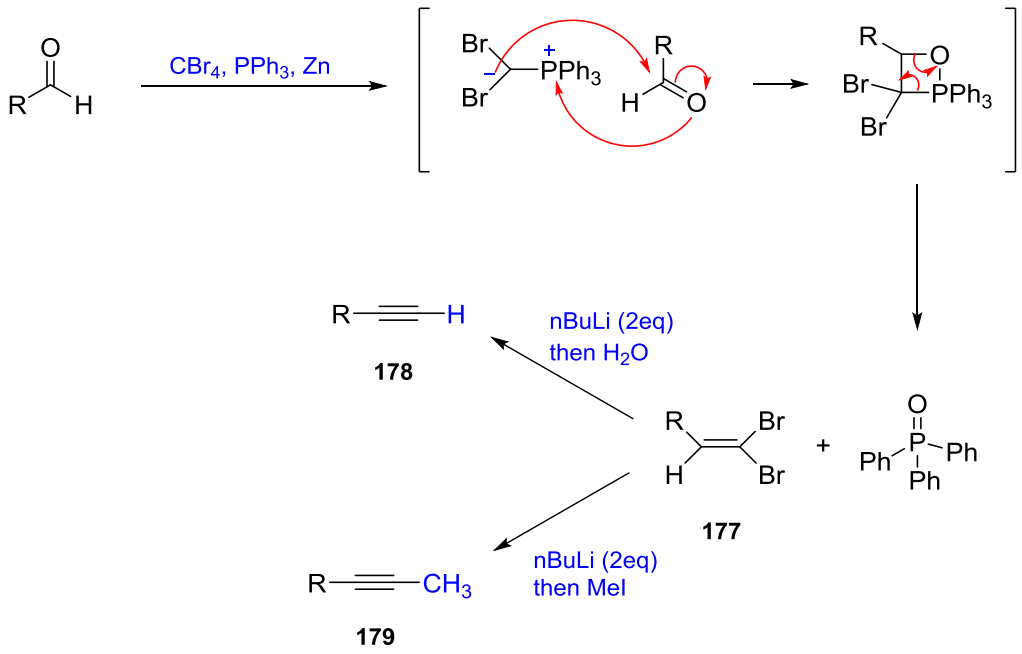
175 **176**

Scheme 2.27: Attempted Ramberg–Bäcklund reaction of sulfone **175**

2.5.2 Alkyne formation from hemiacetal 67

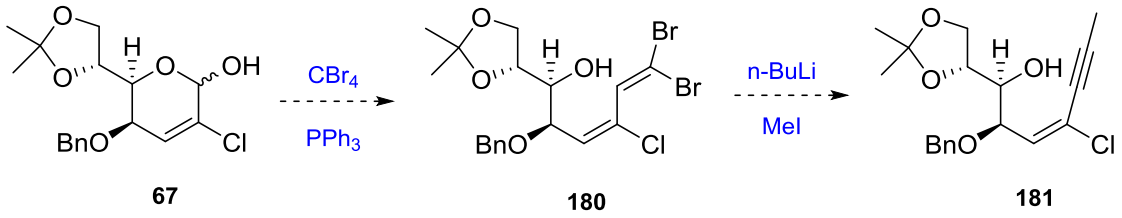
Corey-Fuchs approach

Homologation reactions of carbonyl compounds are widely used in total synthesis due to the ease of preparation and versatility of the substrates.[54] The Corey-Fuchs reaction is a simple and expeditious method for the transformation of aldehydes to alkynes in two steps. The Corey-Fuchs reaction requires a dibromomethyl phosphonium ylide, which can be prepared from carbon tetrabromide and triphenylphosphine, and has similar reactivity to Wittig reagents. Isolable *gem*-dibromoalkene **177** is formed by the condensation of aldehyde with dibromomethylene-triphenylphosphorane. Two equivalents of n-butyllithium are added to this material to eliminate HBr and debrominate the resulting bromoalkyne. This affords the terminal alkyne **178** after quenching with water (Scheme 2.28). Alternatively, quenching the lithium acetylide with methyl iodide affords a methylated alkyne **179.**



Scheme 2.28: The two step Corey-Fuchs reaction

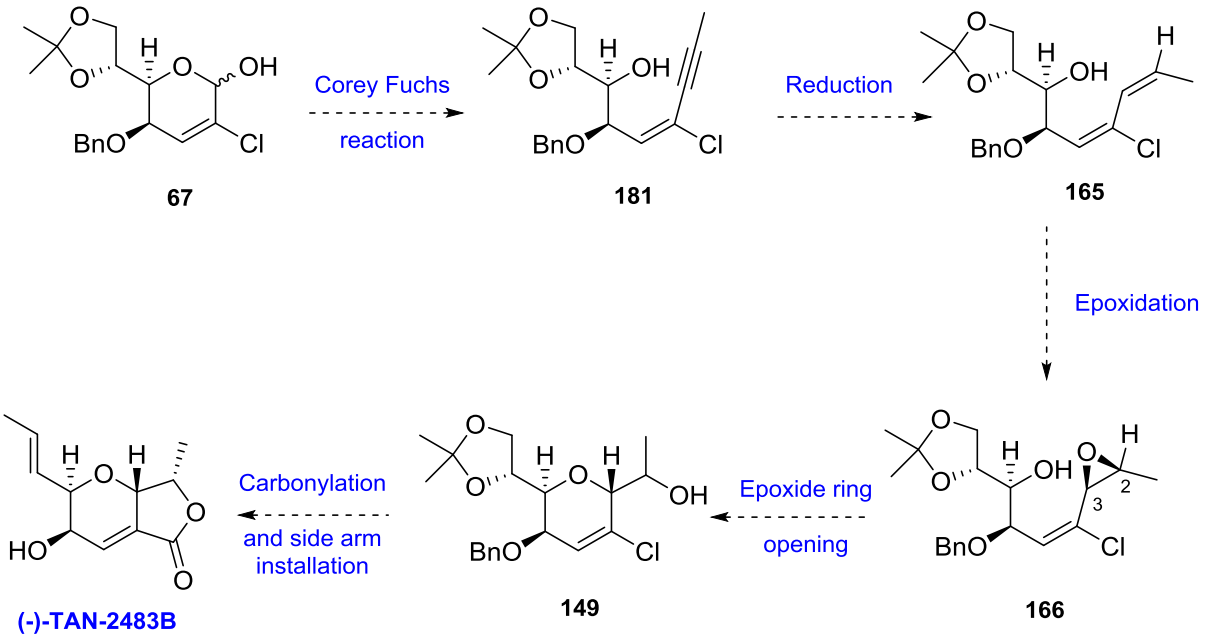
The planned strategy for installation of the two-carbon fragment of the γ-lactone involved Corey-Fuchs reaction of hemiacetal **67** followed by methylation. The first step was the formation of homologated dibromoolefin **180** under the Corey-Fuchs reaction conditions with hemiacetal **67**. The second step involves treatment of **180** with n-butyllithium to form the lithium acetylide followed by methylation with methyl iodide to obtain methylated alkyne **181** (Scheme 2.29).



Scheme 2.29: Corey-Fuchs approach to the installation of the two-carbon unit for **67**

As illustrated in Scheme 2.30, *cis*-selective reduction of alkyne **181** followed by epoxidation and cyclisation would reassemble the pyran ring with the essential functionalities for the formation of the lactone ring of (−)-TAN-2483B by carbonylation of chloroalkene **149**. The stereoselectivity of the

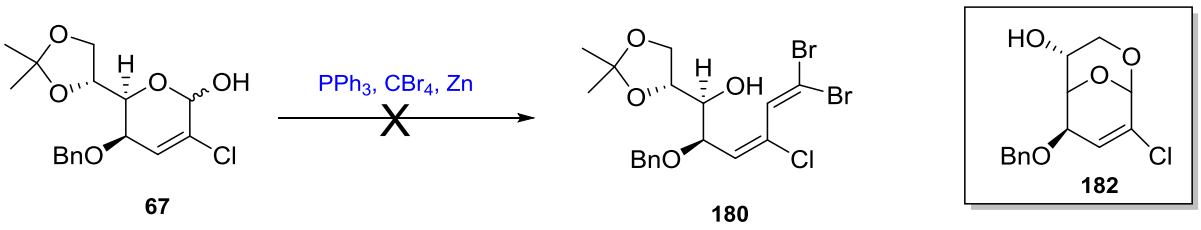
epoxidation would need to be controlled in order to obtain the correct configurations at positions C2 and C3.



Scheme 2.30: Corey-Fuchs approach to total synthesis of (−)-TAN-2483B

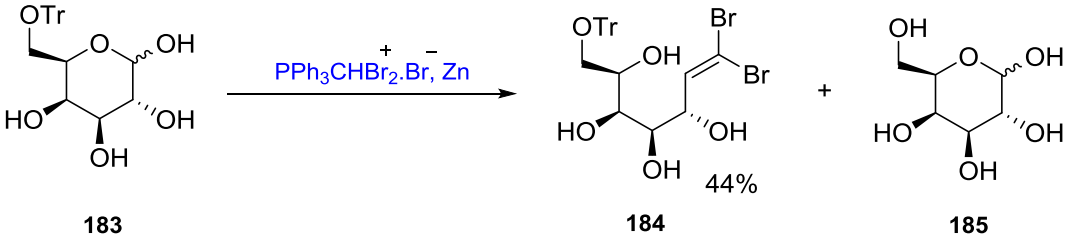
Routinely, two methods are used in the Corey-Fuchs reaction; the first one involves the addition of the aldehyde (1 eq) to a mixture of triphenylphosphine (4 eq) and carbon tetrabromide (2 eq) in a solvent. The second method is the addition of the aldehyde (1 eq) to the reagent prepared from the reaction between Zn dust (2 eq), triphenylphosphine (2 eq) and carbon tetrabromide (2 eq) in a solvent.[55] Generally the use of Zn with 1:1 ratio of carbon tetrabromide and triphenylphosphine is preferred for several reasons; 1) It requires less phosphine 2) the isolation of the dibromoolefin is easier and the yields tend to be somewhat higher than using 2:1 ratio of carbon tetrabromide and triphenylphosphine.[55]Hemiacetal **67** was introduced to a premixed suspension of carbon tetrabromide, triphenylphosphine and zinc dust (Scheme 2.31). The solution turned from dark orange into a light-yellow colour. After six hours the starting material had been completely consumed; therefore silica gel column chromatography was done. ^{1}H-NMR spectroscopic analysis of the obtained compound revealed that the proton signals attributed to the two methyl groups on the acetonide protecting group were missing and the proton signal corresponding to the anomeric centre had moved to 4.97 ppm from 5.34 ppm. ^{1}H-NMR spectroscopic analysis revealed that an unexpected compound had been produced instead of desired *gem*-dibromoolefin **180**. The structure

of the unknown compound was recognised as bicyclic acetal **182** by the aid of 2D-spectroscopic data and mass confirmed by the HRMS data ($C_{14}H_{19}ClO_4N^+$ $[M+NH_4]^+$ calculated value 300.0997 found 300.0999).



Scheme 2.31: Attempted Corey-Fuchs reaction of hemiacetal **67**

The bicyclic compound **182** presumably resulted from deprotection of the isopropylidene and subsequent cyclisation onto the anomeric centre. Deprotection of the isopropylidene group could have occurred by the reaction of *in situ* generated Lewis acid $ZnBr_2$ during the formation of dibromomethylenetriphenylphosphorane. A similar acid-mediated deprotection of a trityl protecting group was observed by F. Dolhem *et al*. in the attempted Corey-Fuchs reaction of 6-*O*-trityl-D-galactose (**183**) with ylide generated *in situ* from pre-synthesised dibromomethylenetriphenyl-phosphonium bromide in the presence of Zn (Scheme 2.32).[56]



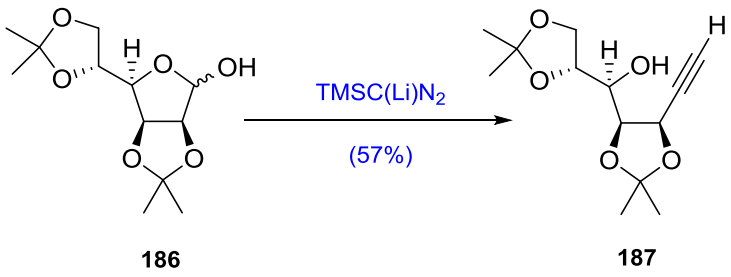
Scheme 2.32: Reported trityl deprotection under Corey-Fuchs reaction conditions[56]

The major role of Zn in this process is the ability to regenerate PPh_3 during the formation of dibromomethylphosphorane ylide. The use of Zn dust can be avoided by using two equivalents of PPh_3. This was deemed to be beneficial in the case of **67** with the acid-sensitive acetonide. Hence, an experiment was performed with a 2:1 ratio of PPh_3:CBr_4 in the absence of Zn dust. Unfortunately, the same bicyclic compound **182** was again obtained even without using Zn. This observation

suggested that another mechanism might operate in the formation of compound **182** from hemiacetal **67**.

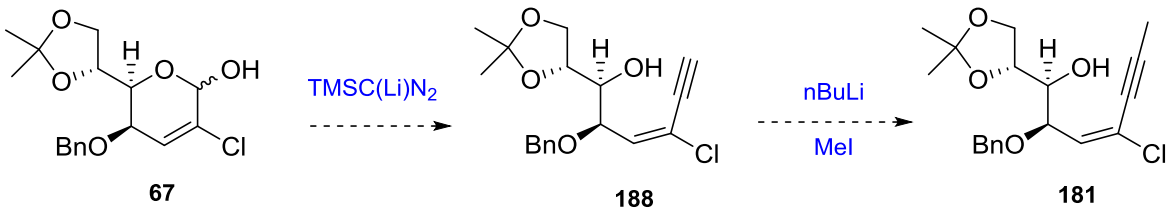
Colvin reaction approach

As an alternative route to the acetylene **181,** reaction of the masked aldehyde, *viz.* hemiacetal **67**, with trimethylsilyldiazomethane was tried as reported by Colvin *et al.* [57] This procedure has found application in many recent total syntheses. For example, in Furstner's approach to hikizimycin, mannofuranose **186** is turned into terminal alkyne **187** via Colvin rearrangement in 57% yield (Scheme 2.33).[58]



Scheme 2.33: Colvin rearrangement in total synthesis of hikizimycin[58]

According to the Scheme 2.34 the terminal alkyne **188** can be accessed from trimethylsilyl-diazomethane. It can be homologated by another carbon unit by reaction with base and methyl iodide.

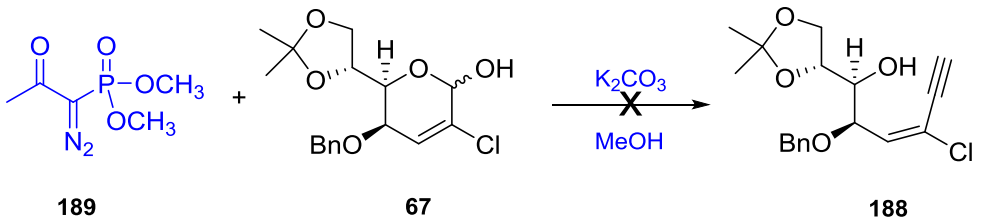


Scheme 2.34: Installation of two-carbon unit of lactone with trimethylsilyldiazomethane followed by methylation of **188**

With this idea in mind, the hemiacetal **67** was added into *in situ*-generated lithium trimethylsilyldiazomethylide solution at -78 °C in the hope of synthesising terminal alkyne **188**. Starting materials disappeared within one hour according to TLC analysis without any distinguishable formation of new products. The ^{1}H-NMR spectrum taken from the crude reaction mixture was very complicated and showed a complex mixture of degraded materials; therefore, this method was abandoned.

Seyferth-Gilbert homologation

The Ohira-Bestmann reagent (**189**) was next investigated for its ability to convert an aldehyde into an alkyne in one step. This reagent is a variant of the Seyferth-Gilbert reagent, with many advantages such as great substrate scope and milder conditions.[55] The reaction was carried out with premade Ohira-Bestmann reagent (**189**) and potassium carbonate in methanol with hemiacetal **67** (Scheme 2.35). The reaction mixture was stirred at room temperature until starting material had disappeared according to TLC (2 hours). A series of newly formed products were observed by TLC and the ^{1}H-NMR spectrum of the crude reaction mixture was very complicated. Furthermore, the characteristic proton signals for the terminal alkyne around 2.5 ppm was not observed, which reflects that desired alkyne **188** has not been formed.



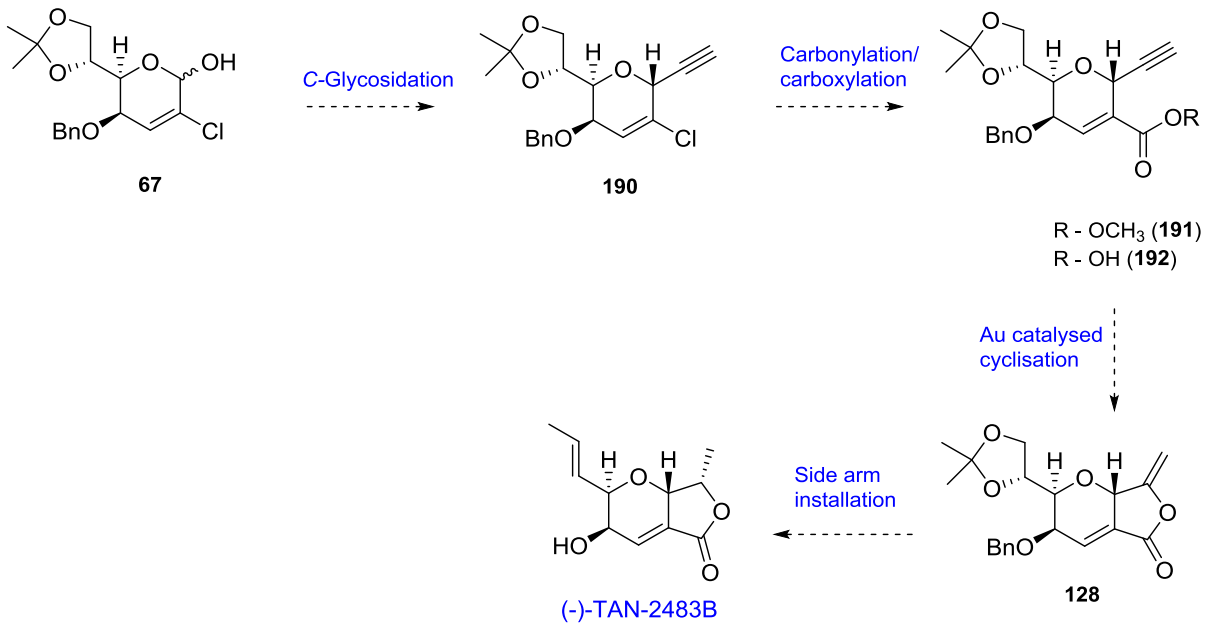
189 **67** **188**

Scheme 2.35: Terminal alkyne formation with Ohira-Bestmann reagent **189**

Bestmann *et al.* reported that homopropargylic methyl ether formation can be observed instead of the desired enynes with similar substrates having α, β-unsaturated aldehydes. (see Section 2.7.3).[59] However, no methoxy peak was noted in the ^{1}H-NMR spectrum. Alternatively, transformations of hemiacetals to homologated alkynes can be substrate dependant and probably rely on the position of the hemiacetal-aldehyde equilibrium. Due to all of these unsuccessful results and observations described above, the route illustrated in Scheme 2.30 was abandoned.

2.5.3 *C*-glycosidation of 66 with *bis*(trimethylsilyl)acetylene

The next strategy investigated to install the two-carbon unit of the lactone ring was the use of *C*-glycosidation, which is considered to be a very useful reaction in carbohydrate chemistry. The primary plan was to synthesise sugar alkyne **190** and then perform carbonylation or carboxylation of the vinyl chloride to obtain the carboxyl functionality of the furan ring (Scheme 2.36). Next, the recently developed $Au^{(I \text{ or } III)}$-catalysed alkynoic acid **192** cyclisation[43b] would provide the furo[3,4-*b*]pyran ring system of (−)-TAN-2483B (see Section 1.8.2). The major significance of this route compared to the previous approaches is the ability to append the two-carbon unit while keeping the six-membered ring intact.

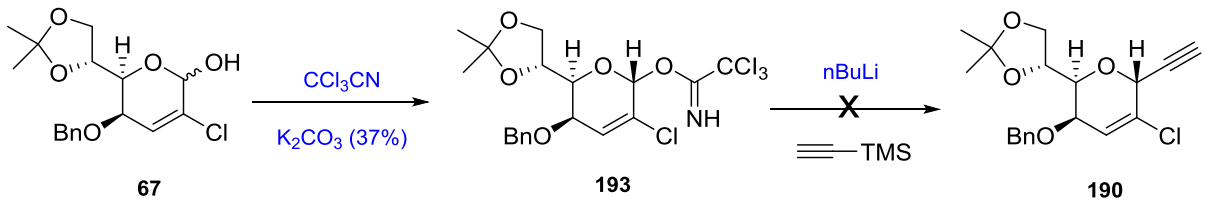


Scheme 2.36: *C*-Glycosidation approach to the synthesis of (−)-TAN-2483B

Schmidt developed a glycosidation protocol using a trichloroacetimidate donor in the 1980s. Since then, it has been used widely for glycosidation.[60]Trichloroacetimidate donors are convenient to prepare via base-catalysed addition of trichloroacetonitrile to the anomeric hydroxyl group. The main drawback of the glycosyl trichloroacetimidate in *C*-glycosidation is the need for activation with strong and moisture-sensitive Lewis acids.[61]

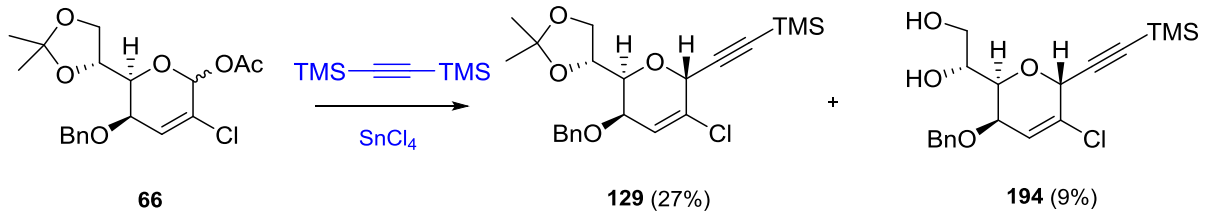
The hemiacetal **67** was converted to its trichloroacetimidate derivative **193** using potassium carbonate and trichloroacetonitrile (Scheme 2.37). The product **193** was quickly purified on a silica

column (yield 37%) and used for the glycosidation reaction as soon as possible. The carbon nucleophile was prepared by pre-mixing n-butyllithium with trimethysilyl acetylene. The trichloroacetimidate derivative **193** was cannulated into the carbon nucleophile mixture at -78 °C. After one hour, the starting material had disappeared, leaving a complicated mixture of compounds according to TLC analysis. The desired alkyne **190** was not isolated upon purification of the complicated mixture of compounds.



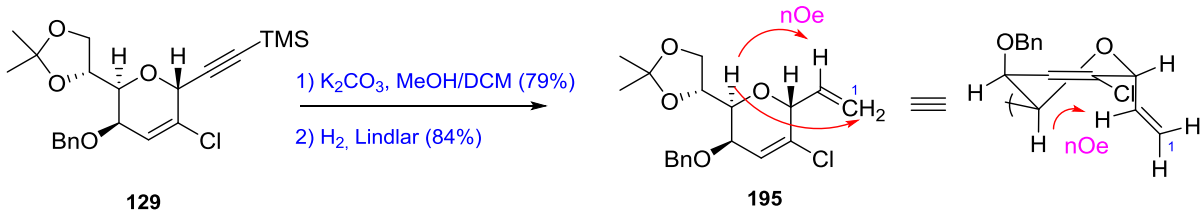
Scheme 2.37: *C*-glycosidation via trichloroacetimidate derivative **193**

After several efforts to perform the homologation reaction by *C*-glycosidation to attach the two carbon unit to hemiacetal intermediate **67**, Lewis acid-mediated alkynylation was performed in the presence of *bis*(trimethylsilyl)acetylene with the precursor acetate **66** (Scheme 2.38). Gratifyingly, reaction of *bis*(trimethylsilyl)acetylene with the acetate **66** with the Lewis acid tin tetrachloride (1 eq) yielded the expected TMS-alkynyl sugar **129** (27%) and its acetonide-cleaved variant diol **194** (9%) within half an hour at room temperature. Although the yield of the reaction was quite insufficient (36% combined yield), it was able to install the two carbon unit of the furan ring while keeping the ring structure intact. Furthermore, only a single isomer of each product was obtained. The reaction was repeated with $BF_3.OEt_2$ under similar conditions. The yields of the TMS-alkynes **129** and **194** were not improved and a lower combined yield (8%) of products was obtained compared to $SnCl_4$.



Scheme 2.38: Lewis acid-mediated alkynylation of **66**

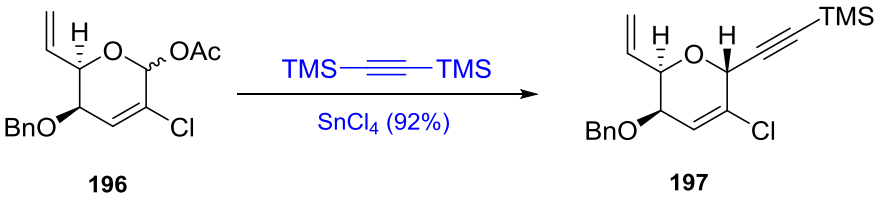
Minoru *et al.* reported that $SnCl_4$-mediated alkynylation is α-selective due to stereoelectronic and/or steric factors (see section 1.6).[33b] Moreover, in this reaction of **66** the steric demand of the upper face due to the presence of the bulky benzyl group and the isopropylidine-containing side-chain, the nucleophile should attack from the α-face. The configuration at the C1 position was established by an n*O*e correlation of the terminal alkene **195**, generated from alkyne **129** by desilylation with methanolic potassium carbonate and reduction with Lindlar catalyst (more details about the synthesis of alkene **195** will be given in Section 2.6.2). Irradiation of the proton at C7 afforded a correlation with the protons at C1 and C2 (Scheme 2.39). Pleasingly, this positive n*O*e correlation between the protons attached to C7 and C2/C1 confirmed the expected and desired α-selectivity.



Scheme 2.39: Key n*O*e correlations in compound **195**

The main drawback of this reaction was the partial cleavage of the isopropylidene group caused by the strong Lewis acid $SnCl_4$, leading to a mixture of products. The decrease in yield might be due to the solubility of polar diol **194** in the aqueous layer which would therefore not be isolated completely from the workup. Furthermore complexation of the $SnCl_4$ with the generated diol **194** may inhibit the catalytic activity of $SnCl_4$ in the alkynylation. Nevertheless the undesired complex would not be isolated as they react with water during the work-up to afford diol **194**. Lewis acidic $SnCl_4$ has dual competitive functions: both acetonide deprotection and alkynylation reaction can occur with substrate **66**. Thus the use of a super-stoichiometric amount of $SnCl_4$ might help in improving the yield of **129**. However, the use of excess $SnCl_4$ (2 eq) did not fix the problem (25% combined yield). Usually, acetonide deprotection requires the presence of water. Therefore 4Å molecular sieves were used to remove water from the reaction, but no significant improvement in yield of **129** was observed. The reaction was then performed with the acetate **196** which lacks an acid labile protecting group. The alkene acetate **196** was synthesised by acetonide deprotection of **66** followed by deoxygenation of the resulting diol (synthesis of **196** will be discussed in Section 2.7.3).This was a good substrate for the $SnCl_4$-mediated alkynylation as it is free of the acid-sensitive

isopropylidene group (Scheme 2.40). It was pleasing that TMS-alkyne **197** was obtained in 92% yield from the reaction between **196** and *bis*(trimethylsilyl)acetylene, mediated by $SnCl_4$.



196 **197**

Scheme 2.40: *C*-glycosidation with acetate **196**

The compounds afforded through the successful installation of two carbon unit (C1-C2 fragment) to the pyran ring were used further during this research to study various synthetic strategies towards natural product (−)-TAN-2483B.

2.6 Functionalisation of sugar acetylenes

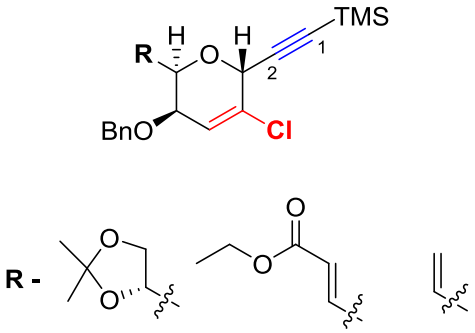
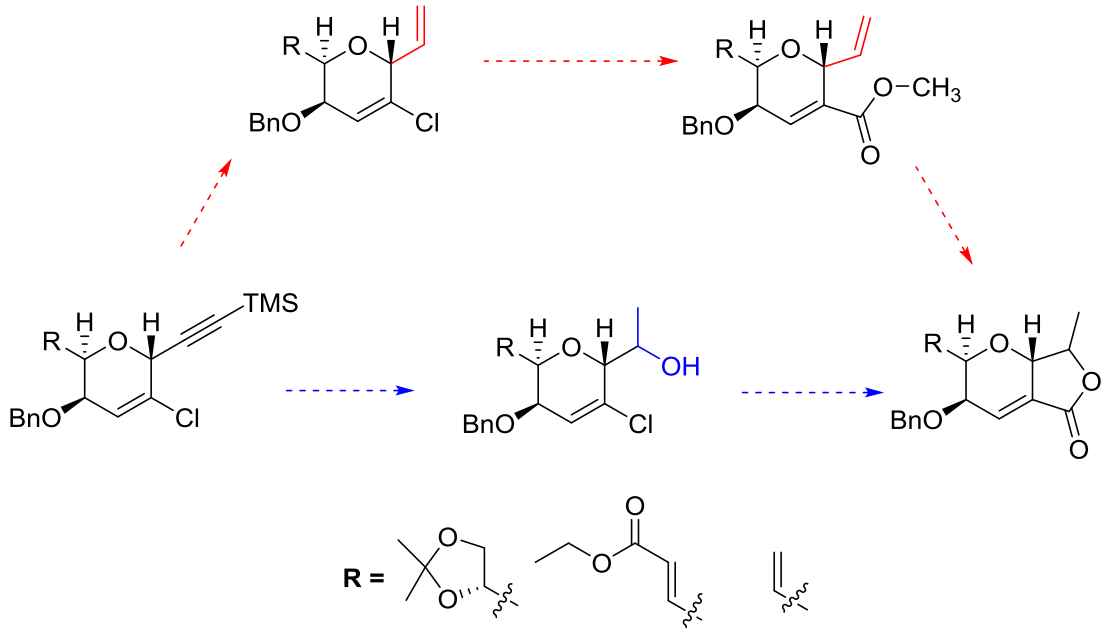


Figure 2.1: Different sugar acetylenes synthesised in this project

The coordination affinity of alkynes to Pd species is stronger than that of alkenes.[62] The sugar acetylenes generated in this project (Figure 2.1) contain two reactive centres towards palladium: the alkyne and chloroalkene. Thus the presence of a competitive π-electron centre might cause problems in palladium-catalysed carbonylation of the chloroalkene. Further, formation of an α,β-unsaturated methyl ester was observed in the attempted carbonylation of sugar acetylene **129** by reacting with the triple bond (will be discussed further in Section 2.8.2.). The observed undesired reactivity of the alkyne led the author to identify the benefit of converting the TMS alkyne into

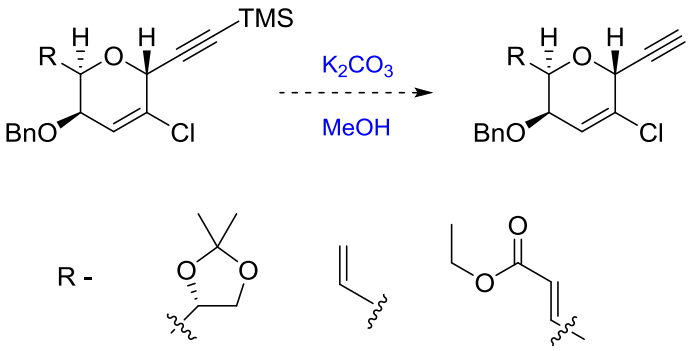
another, less reactive functionality prior to the Pd-catalysed carbonylation of the chloroalkene. Reduction to a terminal alkene and hydration to afford a secondary alcohol were explored as potential strategies (Scheme 2.41). Both strategies involve desilylation of the TMS acetylene. Terminal alkene formation passes through a Lindlar reduction (red route) and secondary alcohol formation involves alkyne hydration followed by reduction (blue route). While both routes were explored, that via secondary alcohol (blue route) provided a more convenient synthesis of the furo[3,4-*b*]pyran ring system. Only a single step Pd-catalysed carbonylative lactonisation sequence is required in this case, which is more expedient than the pathway involving alkene carbolactonisation.



Scheme 2.41: Routes considered for furo[3,4-*b*]pyran synthesi from various sugar acetylenes

2.6.1 TMS deprotection of sugar acetylenes

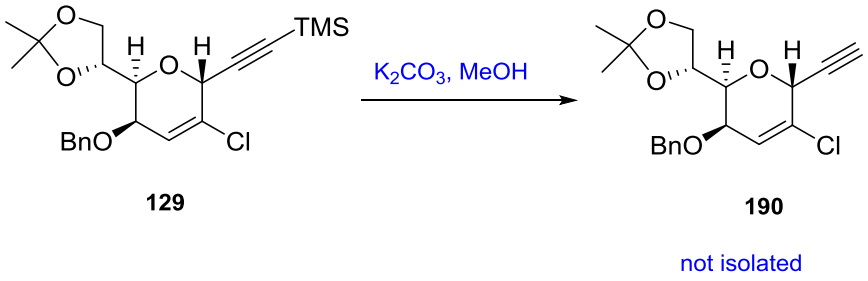
Desilylation of a variety of TMS-acetylenes was explored for the formation of potential substrates that would be used in subsequent carbonylation reaction to afford the five-membered lactone ring of TAN-2483B.



Scheme 2.42: Proposed TMS deprotection of sugar acetylenes

TMS deprotection of sugar acetylene 190

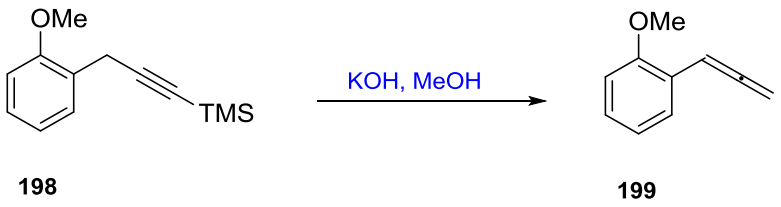
The deprotection of silylalkynes is routinely carried out by treatment with a weak base in a protic solvent.[63] The conventional method employing potassium carbonate in methanol was used with sugar acetylene **129** (Scheme 2.43). The reaction was completed within 15 minutes by TLC analysis. Surprisingly, the R_f values of the TLC spots observed after the work-up and after the evaporation of solvents from the rotary evaporator were significantly different in the same mobile phase. A totally new, more polar spot appeared after the evaporation of excess solvent via rotary evaporation. It was noted that the temperature of the rotary evaporator bath (40 °C) and the time taken for the evaporation of the excess solvent significantly affected the formation of the new compound.



Scheme 2.43: Attempted TMS deprotection of sugar acetylene **129**

The new product was purified by silica gel chromatography. ^{1}H-NMR spectroscopy showed an absence of the characteristic proton signal for a terminal alkyne (around 2.50 ppm) and the loss of the singlet for theTMS group. Two distinctive singlets at 5.56 ppm and at 5.30 ppm were observed in the ^{1}H-NMR spectrum of the isolated new compound, in addition to peaks attributed to the alkene

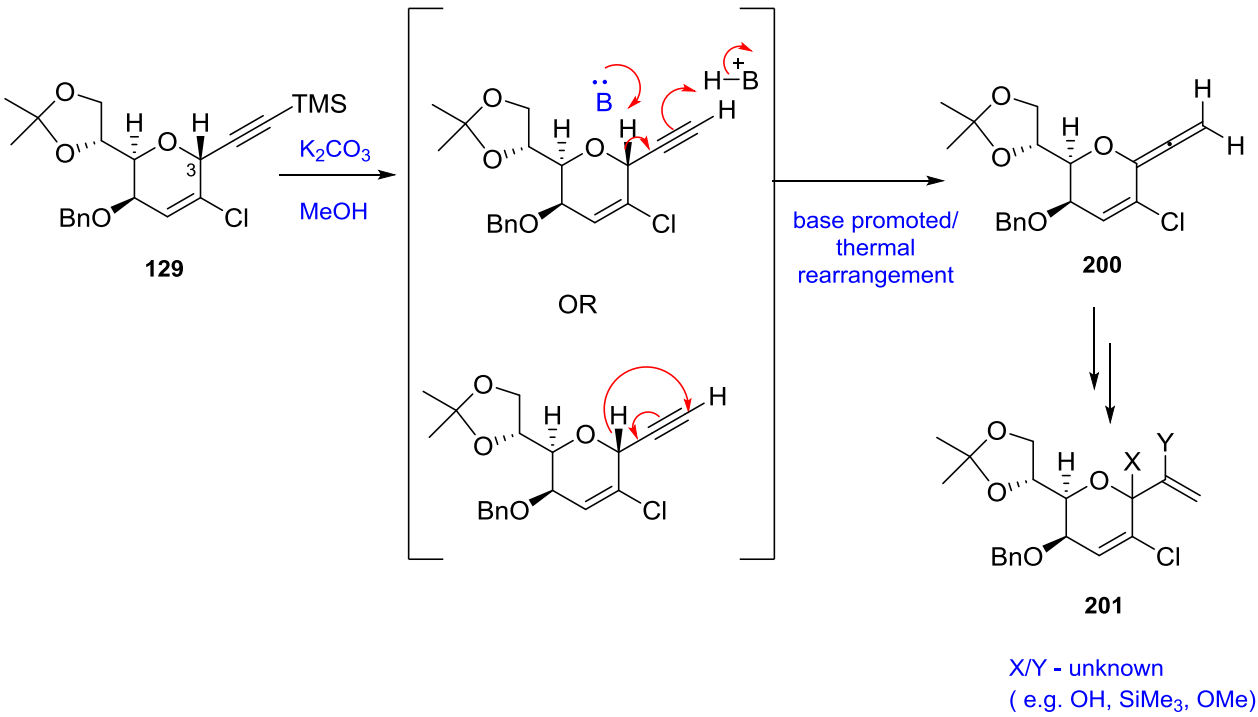
proton in the pyran ring. HSQC correlations revealed that the olefinic protons at 5.56 ppm and 5.30 ppm (singlets) were attached to the same carbon at 108 ppm indicating a *gem*-disubstituted terminal alkene. It is proposed that degradation of alkyne had occurred due to the instability of the terminal alkyne **190** in basic condition at elevated temperature. Hagenah *et al*. reported the degradation of alkyne **198** into undesired allene **199** upon deprotection with methanolic KOH (Scheme 2.44).[64]



198 **199**

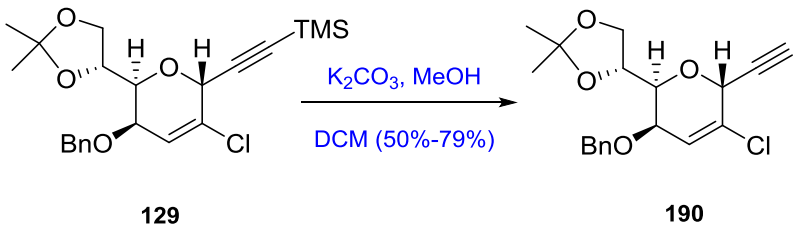
Scheme 2.44: Reported degradation of TMS alkyne **198** into allene **199**[64]

A similar type of degradation is possible with the terminal alkyne **190,** produced from the silyl acetylene **129** by abstraction of the proton at C3 in the basic medium. On the other hand, concerted thermal rearrangement/isomerisation (through a 1,3-hydride shift) is possible due to the migration of the π-bond into conjugation with the neighbouring alkene in the pyran ring (Scheme 2.45). These kinds of migration of a π-bond into conjugation with a neighbouring alkene or arene system have been reported several times in the literature.[65] Nevertheless, ^{13}C-NMR analysis was not compatible with the presence of allene **200**, due to the absence of the expected distinctive ^{13}C-NMR shift (200 ppm-210 ppm) for the central allene carbon in **200.** Possibly **200** was further degraded into an alkene similar to **201** by addition of unknown substituent (e.g. OMe) to the enol moiety of the allene. Further, the observed quaternary carbon signals at 146 ppm and 89 ppm are consistent with alkenic and acetal carbons as in a compound with structure **201**. According to the reaction conditions the unknown substituent (X) might be OH, OMe or $SiMe_3$. Nevertheless, the presence of OMe and $SiMe_3$ was not evident in ^{1}H-NMR or ^{13}C-NMR spectra. HRMS data revealed a major ion at m/z 419.1235 ($C_{20}H_{25}O_6ClNa^+$; Δ=0.5 ppm) which corresponds to the structure having X/Y = OH and X/Y = OMe. Full characterisation of unknown degraded compound was not achieved due to the incompatibility of the spectroscopic data with HRMS data (^{1}H-NMR and ^{13}C-NMR spectra of the unknown compound **201** were attached in the Appendix page 209).



Scheme 2.45: Plausible degradation pathways for **129** in K_2CO_3/MeOH

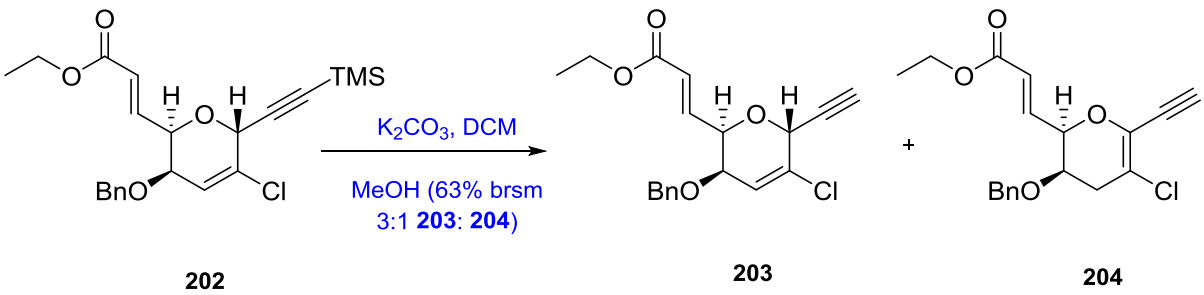
It was realised that rapid evaporation of the excess solvent at lower temperature was necessary to isolate the desired TMS-deprotected terminal alkyne **190**. If methanol is used as the solvent for the reaction, rapid evaporation at low temperature is difficult. Readily evaporating dichloromethane was used in the next attempt using methanol as a co-solvent. Then, the original method was changed by using potassium carbonate (5 eq) in a solution of 20% methanol in dichloromethane. The reaction was quenched with brine before the disappearance of all the starting materials. Extra care was taken when evaporating the organic layer, with the temperature of the water bath of the rotary evaporator kept close to room temperature. The desired terminal alkyne **190** was then obtained in 50%−78% yield.



Scheme 2.46: Successful TMS deprotection of sugar acetylene **129**

TMS deprotection of sugar acetylene 202

TMS deprotection of the sugar acetylene **202** containing an ethyl ester side arm (synthesis will be discussed in Section 2.7.2) was tried with potassium carbonate in 20% methanol in dichloromethane. Excess solvents were evaporated rapidly at relatively low temperature (evaporator water bath 28 °C). The degradation into an unknown alkenic material was still observed in addition to the formation of compound **203**. As a precaution, the reaction was stopped before all starting material had reacted. In this case, conjugated enyne **204** was observed along with the desired skipped enyne **203** (Scheme 2.47). The isomerised product possessed the same R_f as the desired alkyne **203** and it was hard to separate by silica gel column purification. The inseparable mixture of terminal alkyne **203** and by-product **204** was isolated (3:1 product ratio according to the ^{1}H-NMR integration) and used for the subsequent reactions.

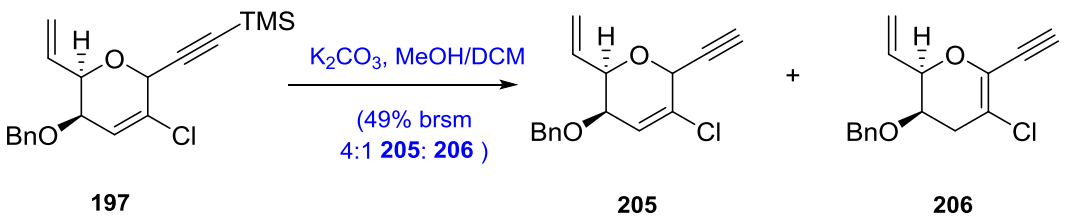


202 **203** **204**

Scheme 2.47: TMS deprotection in ethyl ester **202**

TMS deprotection of sugar acetylene 197

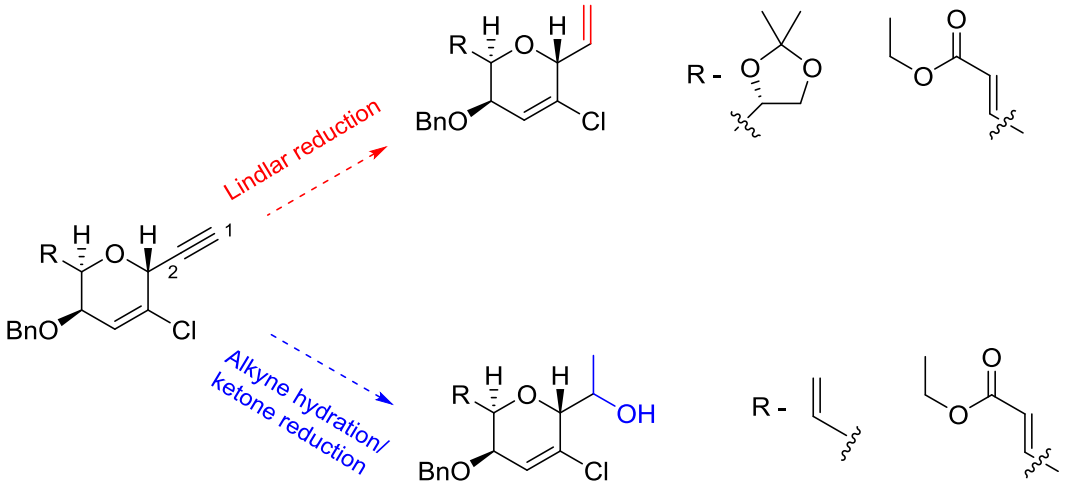
The alkyne **197**, synthesised by alkynylation of **196**, was subjected to TMS deprotection with K_2CO_3 in 20% methanol in dichloromethane (Scheme 2.48). The degradation of terminal alkyne into unknown compound was still observed in the methanolic K_2CO_3. Thus, the reaction was quenched before complete TMS deprotection. In addition to degradation, a by-product formed by migration of the internal double bond was detected in the ^{1}H-NMR spectrum and was inseparable from the desired terminal alkyne **205** (**205:206** 4:1 product ratio was calculated by ^{1}H-NMR integration). Futher chemistry was conducted with the mixture of compounds, with the intention of separating the desired material in a future step.



Scheme 2.48: TMS deprotection of alkene **197**

2.6.2 Functionalisation of C1-C2 fragment of alkynes 190, 203 and 205

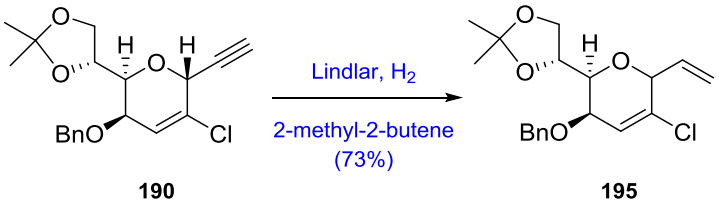
With terminal alkyne substrates in hand, Lindlar reduction and alkyne hydration followed by ketone reduction were attempted in the formation of the terminal alkene and secondary alcohol based chloroalkenes (Scheme 2.49).



Scheme 2.49: Formation of potential substrates for carbonylation/carboxylation of chloroalkenes

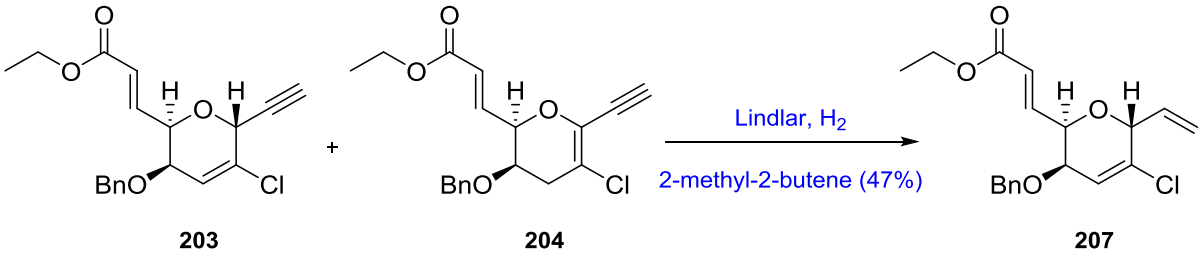
Lindlar reduction of alkynes 190 and 203

Lindlar catalyst is a mild heterogenous catalyst, which is a mixture of Pd, $CaCO_3$, and lead salts. It is the catalyst of choice in catalytic hydrogenation of alkynes to give alkenes. Terminal alkyne **190** was subjected to Lindlar reduction in the presence of the scavenger alkene 2-methyl-2-butene (Scheme 2.50). Partial hydrogenation progressed smoothly to afford the alkene **195** in 73% yield.



Scheme 2.50: Lindlar reduction of terminal alkyne **190**

The mixture of ethyl esters **203** and **204** was also subjected to Lindlar reduction in the presence of 2-methyl-2-butene as a scavenger (Scheme 2.51). This reaction also progressed smoothly and the partially hydrogenated product **207** was obtained in 47% yield. The corresponding product from reduction of the isomerised terminal alkyne **204** was not isolated; presumably this is due to it being a minor component of a small scale reaction (48 mg).



Scheme 2.51: Lindlar reduction of mixture of terminal alkynes **203** and **204** to alkene **207**

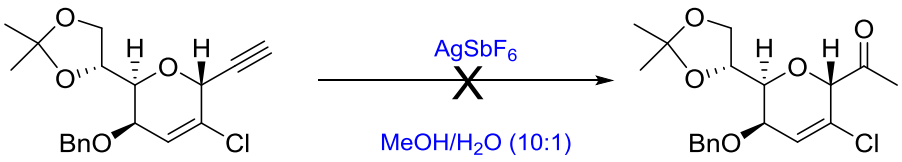
Hydration of alkynes 190, 203 and 205

In parallel to the exploration of the chemistry towards the terminal alkenes, formation of secondary alcohol substrate (blue route in Scheme 2.49) was investigated. The chloroalkene functionality could then be used in a single-step carbonylative lactonisation process to obtain the bicyclic core of the natural product. The strategy behind the synthesis of these compounds involves alkyne hydration followed by methyl ketone reduction.

Alkyne hydration permits simple access to the carbonyl function and has been used as a tool in total synthesis. Starting with Kucherov's (in 1881) discovery of oxymercuration, acid-catalysed alkyne hydration has been achieved with a variety of transition metals including palladium, rhodium,

iridium, copper, silver and gold. Since its first discovery, oxymercuration has been widely used, despite the toxicity of the mercuric salts. Gold and mercury display high affinity to alkynes. Gold compounds have gradually taken a prominent place in alkyne hydroxylation, beneficially replacing toxic mercury$^{(II)}$ salts. Notably, in 2002, Hayashi and Tanaka reported the use of a [$(Ph_3P)AuMe]/H^+$ catalytic system allowing for a high turnover frequency in the hydration of terminal alkynes.[66] Nevertheless this catalyst suffers from some drawbacks including the use of concentrated solutions of strong acids (H_2SO_4, CF_3SO_3H) which leads to limited substrate scope. In 2009, Nolan *et al*. reported [(NHC)AuI]-catalysed hydration of a wide range of alkynes at part-per-million loadings using silver as a co-catalyst.[67] Recently Nun *et al.* reported gold$^{(I)}$ catalysed alkyne hydration without using any other Brønsted acids, with or without $Ag^{(I)}$ source.[68] A gradual improvement of the catalyst system used in the alkyne hydration reached a great milestone in 2012 with the exploitation of non-expensive $AgSbF_6$ without using any source of acid or any other co-catalyst.[69]

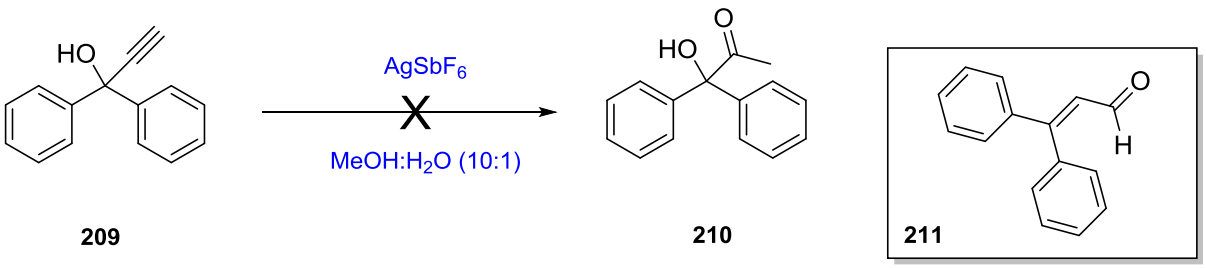
With the encouragement of the recently reported procedure, hydration of terminal alkyne **190** was explored using $AgSbF_6$ in methanol (Scheme 2.52).[69] After overnight stirring, ^{1}H-NMR data revealed that cleavage of the isopropylidene group had predominantly occurred without formation of the desired methyl ketone.



190 **208**

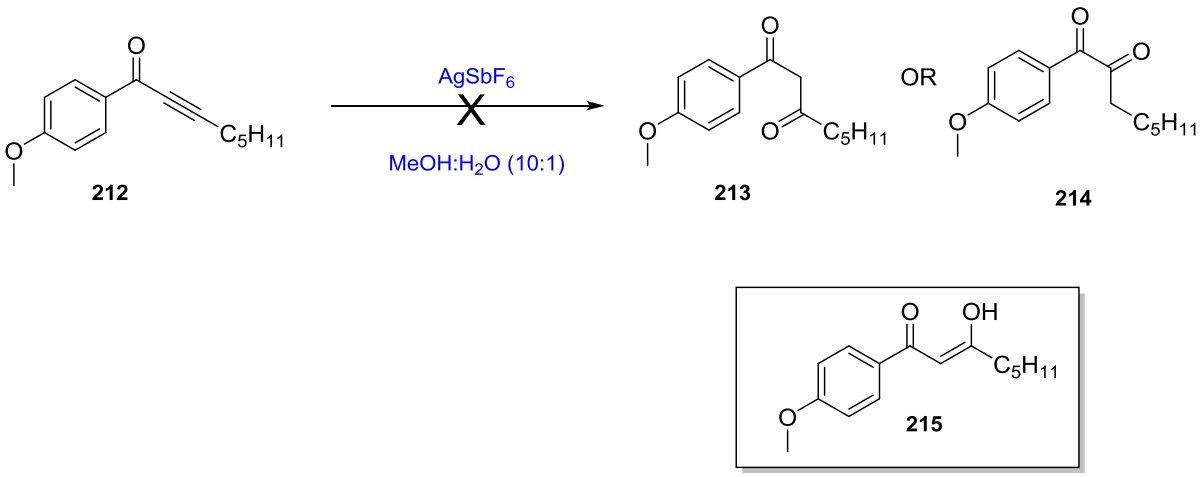
Scheme 2.52: Attempted hydration of alkyne **190** with $AgSbF_6$

This observation reflects the acidic nature of the catalyst $AgSbF_6$ which leads to deprotection of the acetonide group instead of alkyne hydration. These acidic properties of $AgSbF_6$ have been seen before in the attempted hydration of alkyne **209** by Wagner *et al.* (Scheme 2.53).[69]Propargyl alcohol **209** did not afford the expected methyl ketone **210** in the reaction of $AgSbF_6$, but underwent the acid-catalysed Meyer–Schuster rearrangement instead to afford **211**.



Scheme 2.53: Reported acid-catalysed Meyer–Schuster rearrangement observed during the attempted hydration of alkyne **209**[69]

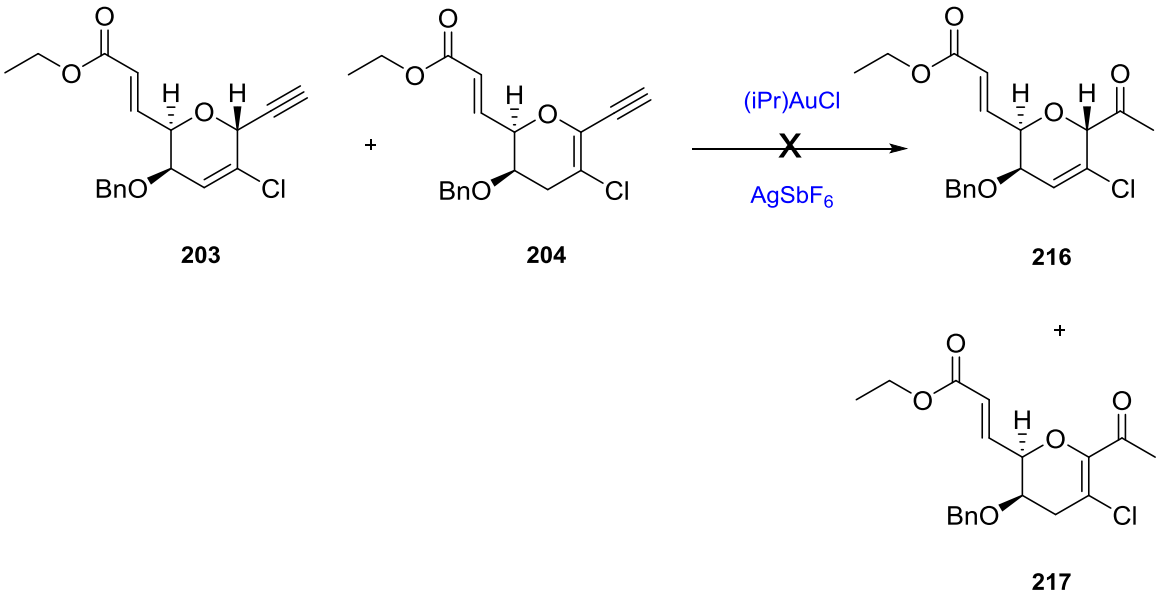
Moreover, enol **215** was obtained in hydration of the internal alkyne **212** with $AgSbF_6$. Enol **215** could result from the enolisation of 1,3-diketone **213** or by Lewis acid-promoted 1,4-nucleophilic addition of water. Wagner *et al.* reported that the formation of enol **215** most likely is due to the acid-catalysed 1,4-addition of water as internal alkynes are inactive towards hydration with $AgSbF_6$ (Scheme 2.54).[69]



Scheme 2.54: Reported acid-catalysed 1,4-addition of water to afford **215**, observed during the attempted hydration of alkyne **212**[69]

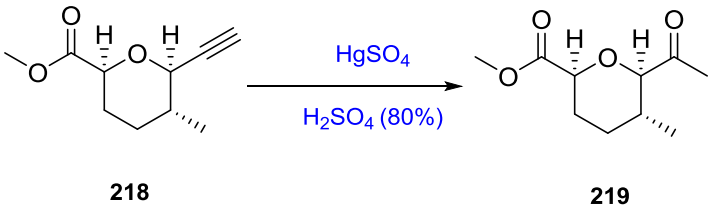
Generally, almost all reagents that are used in alkyne hydration are acidic in nature or use acids; therefore, the acid-sensitive acetonide group might be expected to cause problems with all the proposed methods. Therefore it was deemed necessary to use substrates free of an acetonide group for hydration of alkynes.

Alkyne hydroxylation was examined with the new substrate **203**, which is free of the acid-sensitive isopropylidene group. With the encouragement of recent advancements in gold-alkyne chemistry, alkyne hydroxylation with (iPr)AuCl in a 1:1 mixture of H_2O and 1,4-dioxane was attempted according to the reported procedure (Scheme 2.55).[70] After two hours at room temperature, starting materials had disappeared, but no signs of the desired products **216** and **217** were observed on the basis of TLC and ^{1}H-NMR analysis.



Scheme 2.55: Attempted Au$^{(I)}$-catalysed alkyne hydroxylation of **203/204**

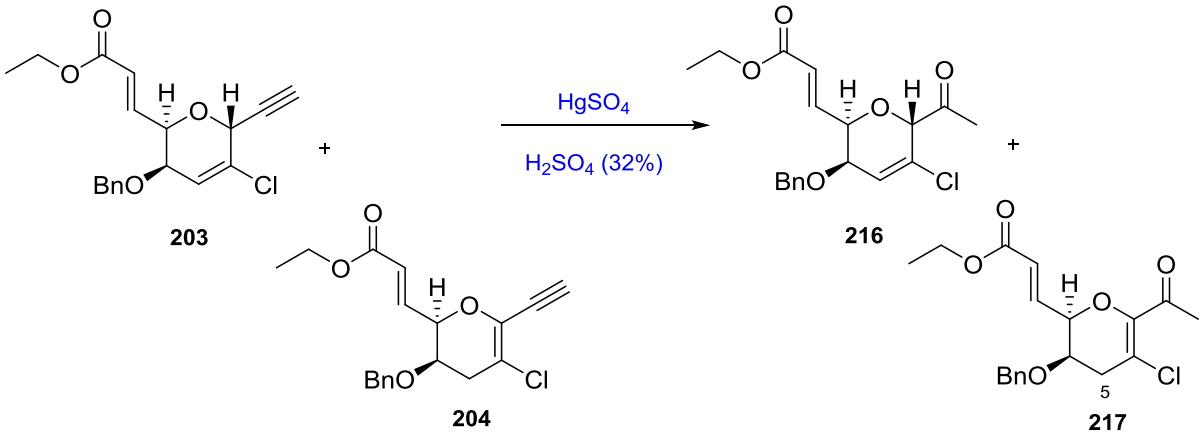
Usually, propargylic alcohols are prone to give side reactions such as Meyer-Schuster or Rupe rearrangement or polymerisation products under gold-catalysed hydroxylation conditions.[70] Even though the alkynes **203** and **204** are not propargylic alcohols, an undesired co-ordination between gold$^{(I)}$ and the propargylic ether system comprising the pyran ring oxygen and alkyne might be possible. Further, there are limited examples of efficient hydroxylation of propagylic alcohols into α-hydroxy ketones except under Kucherov (HgO/H_2SO_4) conditions.[70] In 2011, Ghosh *et al.* successfully performed oxymercuration of alkyne **218** in the total synthesis of (+)-herboxidiene/GEX1A (Scheme 2.56).[71] This recent literature evidence encouraged the author not only for its success but also the similarity of the structural feature of Ghosh's substrate with the alkynes **203** and **204**; therefore, oxymercuration of the mixture of alkynes **203** and **204** was attempted.



218 219

Scheme 2.56: Oxymercuration used in the total synthesis of (+)-herboxidiene/GEX1A[71]

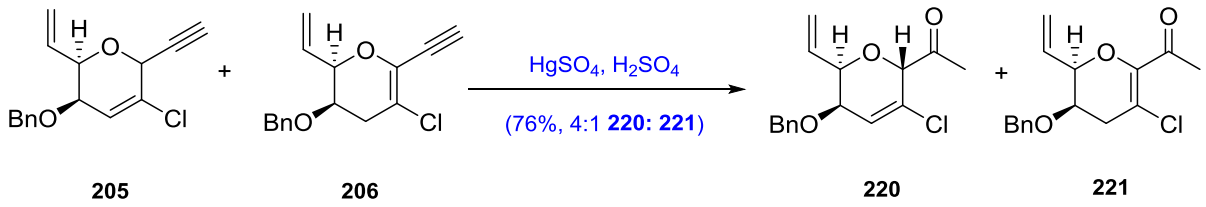
The literature precedented procedure was followed using the mixture of alkynes **203** and **204** with a catalytic amount of $HgSO_4$ in the presence of H_2SO_4 (Scheme 2.57). Gratifyingly, the alkyne functionality of ethyl esters **203/204** was successfully oxymercurated to afford methyl ketone **216** in 32% yield along with enone **217**. The α,β-unsaturated methyl ketone **217** showed a characteristic signal at 2.63 ppm which corresponds to the methylene protons at C5.



203 204 216 217

Scheme 2.57: Oxymercuration of alkyne-ethyl esters **203/204**

Then, the mixture of terminal alkyne **205** and minor impurity **206** was successfully reacted with $HgSO_4$ to afford methyl ketones **220** and **221** in 76% yield (Scheme 2.58). The undesired methyl ketone **221** was detected after silica gel column purification (**220:221** 4:1 product ratio, calculated by ^{1}H-NMR integration).



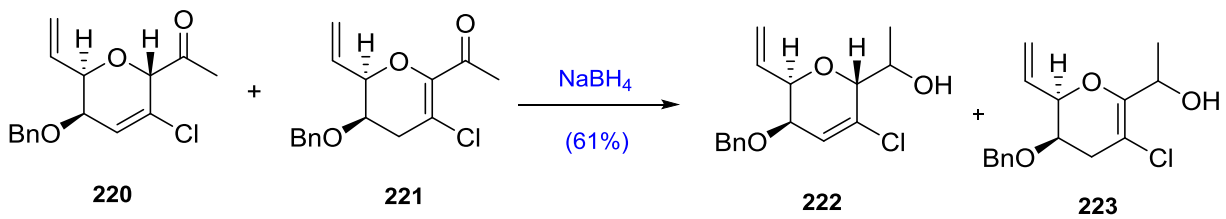
205 206 220 221

Scheme 2.58: Oxymercuration of alkyne mixture **205/206**

Reduction of ketone 220

After successful oxymercuration of the terminal alkynes, the reduction of mixture of methyl ketones **220** and **221** was studied. The secondary alcohol thus obtained was expected to react in the Pd-catalysed carbonylative lactonisation to achieve the furo[3,4-*b*]pyran ring system.

Sodium borohydride is a versatile reducing agent that finds wide a range of applications in chemistry. First, simple reduction with $NaBH_4$ was tried with the mixture of methyl ketones **220** and **221** at 0 °C (Scheme 2.59). Remarkably, only one stereoisomer of **222** was obtained, presumably due to stereo control by the substrate (will be discussed Section in 4.3). The desired alcohol was successfully obtained in pure form by silica gel column purification in moderately good yield (61%). According to the NMR spectra it was evident that the amount of isomerised contaminant **223** was insignificant (Figure 2.2). With the secondary alcohol **222** in hand, the one-step synthesis of the furo[3,4-*b*]pyran skeleton was attempted through Pd-catalysed carbonylation (will be discussed in Section 2.8.3).



220 221 222 223

Scheme 2.59: Reduction of methyl ketone mixture **220** and **221**

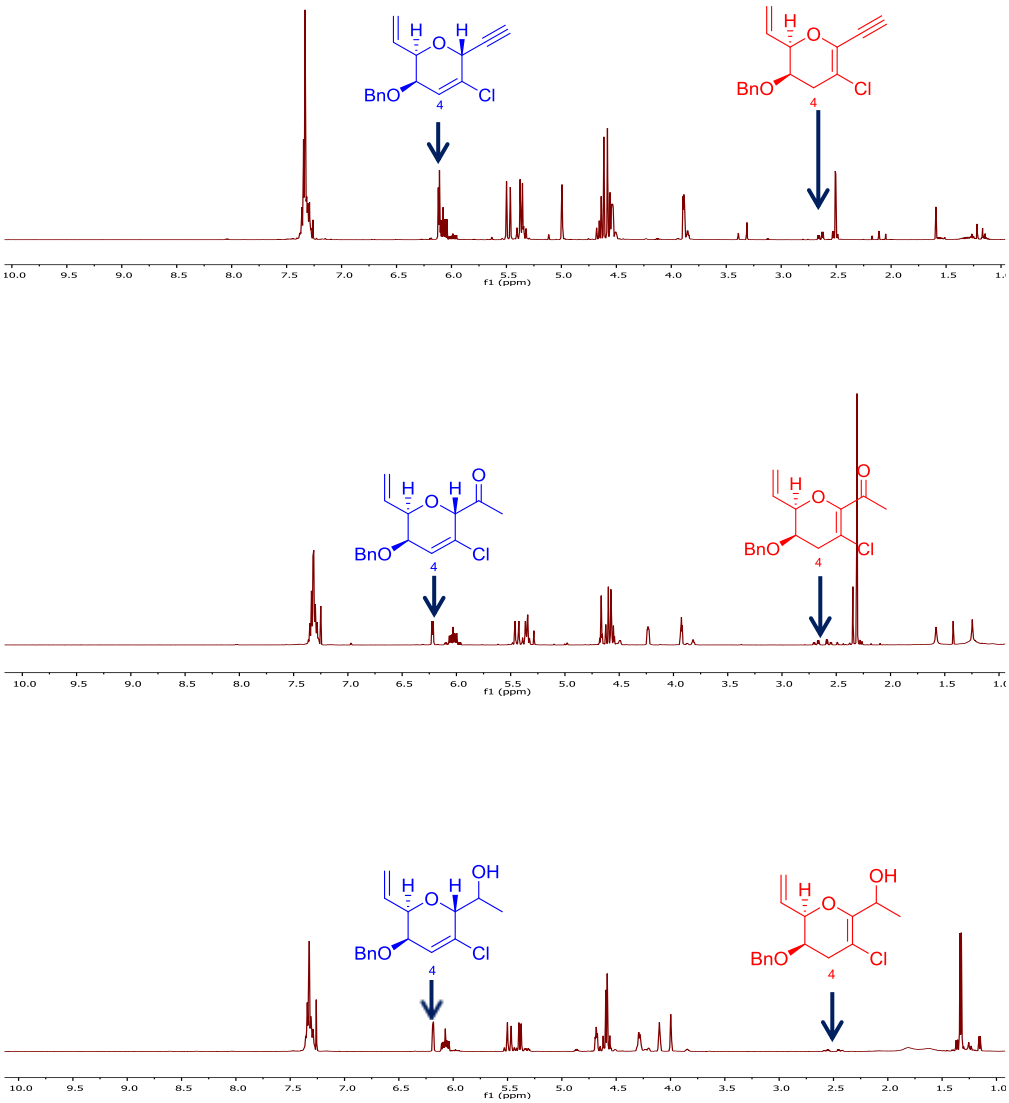
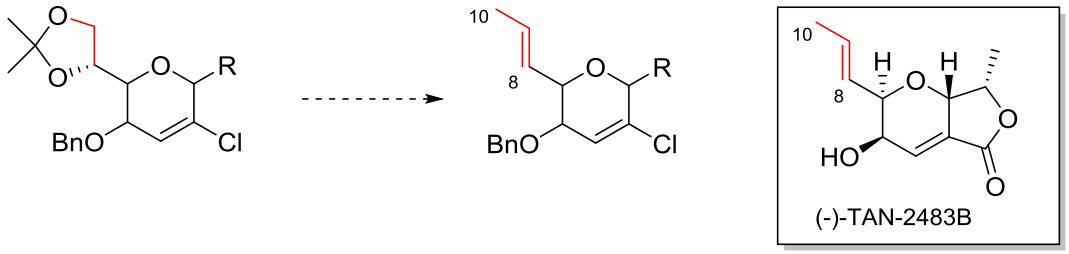


Figure 2.2: NMR spectra of **205, 220, 222** and their isomerised counterpart

2.7 Installation of the side arm (C8-C10 fragment) of (−)-TAN-2483B

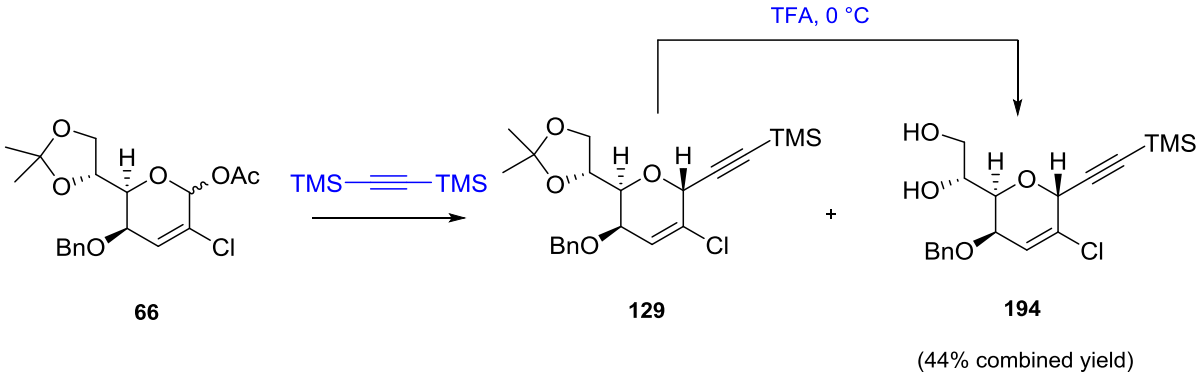
The planned strategy to install the side arm (C8-C10 fragment) of the natural product was deprotection of the acetonide group and the conversion of the diol to an aldehyde which could be functionalised further by olefination reactions (Scheme 2.60). *E*-Selective olefination such as Julia-Kocienski reaction would install the *E*-propenyl side arm.



Scheme 2.60: Intended installation of the side arm of the natural product

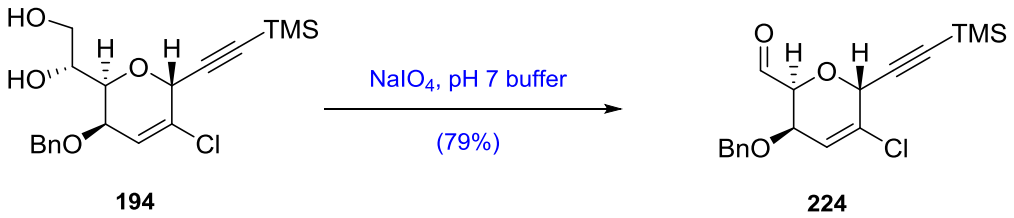
2.7.1 Attempts to install *E*-propenyl side arm by olefination

C-Glycosidation of pyran intermediate **66** with $SnCl_4$ provided some acetonide-deprotected diol **194** along with **129**. The acetonide group in **129** was converted quantitatively to the diol **194** by treatment with trifluoroacetic acid at 0°C (Scheme 2.61).



Scheme 2.61: Synthesis of diol **194** by *C*-glycosidation

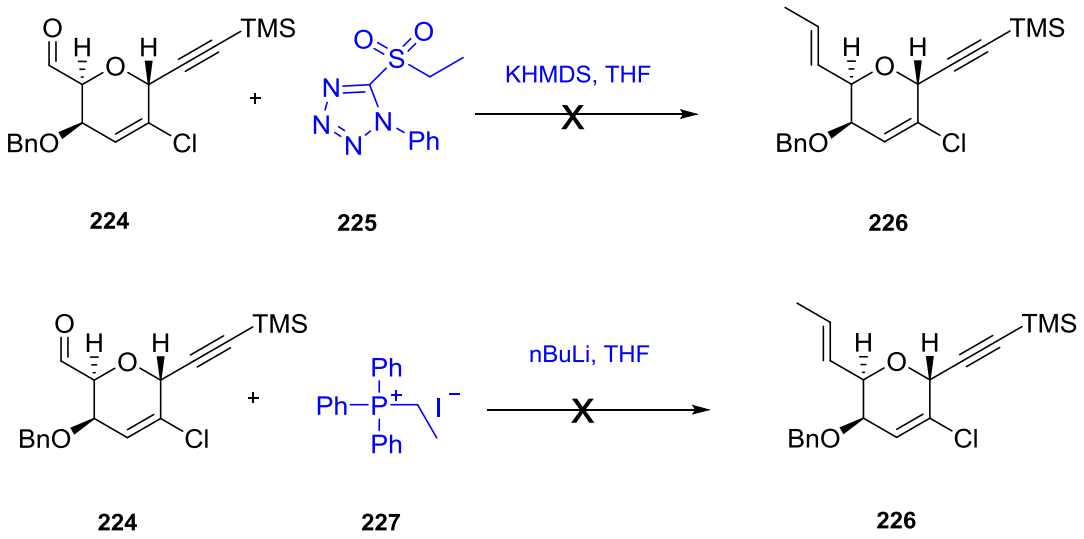
The diol **194** was cleanly transformed to aldehyde **224** with sodium periodate in the presence of phosphate buffer (pH 7) in 78% yield (Scheme 2.62). The aldehyde was not able to be tracked by TLC as the spot displayed as a streak line. Nonetheless, ^{1}H-NMR spectroscopy indicated that the crude aldehyde **224** was pure enough to proceed to olefination without further purification.



194 224

Scheme 2.62: Diol cleavage of **194** with $NaIO_4$

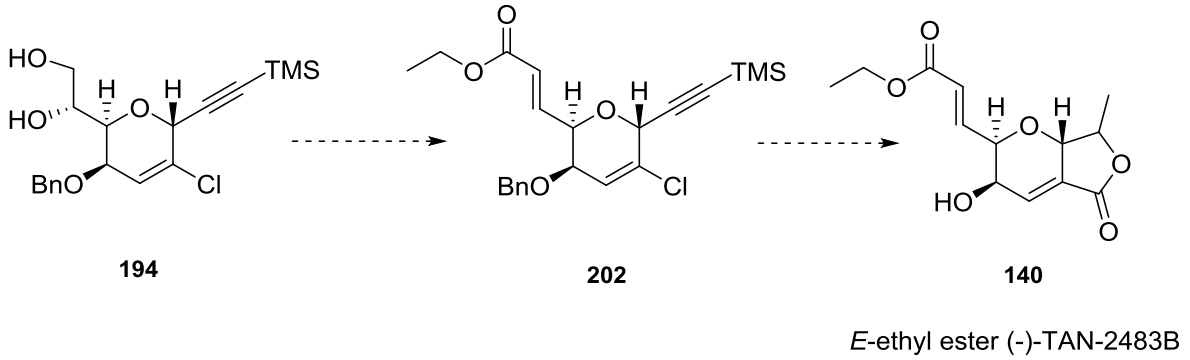
According to the planned retrosynthetic strategy, the aldehyde **224** was first subjected to Julia-Kocienski olefination in an attempt to generate the desired *E*-propenyl side-chain, due to its high *trans*-selectivity (Scheme 2.63). Unfortunately the starting material degraded into a complex mixture in which no products were identifiable. The next strategy was Wittig homologation with ethyltriphenylphosphonium iodide (**227**). That reaction also resulted in a complicated mixture (Scheme 2.63). Presumably the acidic nature of the α-proton of the aldehyde **224** would be the main reason for the degradation. The α-proton of the aldehyde **224** has a pKa of around 17, whereas the pKa of the ylide is about 22.[72] Thus, it was suggested that the ylide itself is strong enough to deprotonate the α-proton of the aldehyde. Very mild conditions without use of any strong bases may be needed to avoid this impediment in appending the side arm onto aldehyde **224**.



Scheme 2.63: Attempted olefinations to install the side arm onto **224**

2.7.2 Installation of ethyl ester model side arm

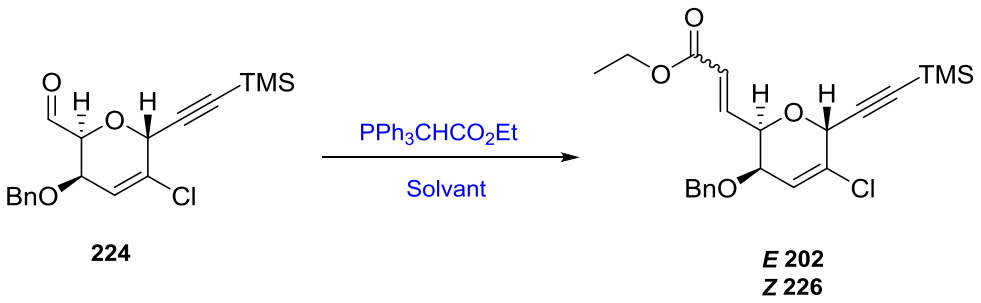
Wittig olefination is the most commonly used reaction to make alkenes from carbonyl compounds. When stabilised ylides are used, the use of external bases can be avoided and high *trans*-selectivity can be expected. Installation of an ethyl ester side arm was investigated with the intention of synthesising the *E*-ethyl ester analogue of (−)-TAN-2483B (**140**).



Scheme 2.64: Intended synthesis of the *E*-ethyl ester analogue of (−)-TAN-2483B

Stabilised Wittig reactions with α-alkoxyaldehydes, especially those derived from carbohydrates, appear inconsistent, as they can proceed with low stereoselectivity.[73] Generally, the use of non-polar solvents,[74] carboxylic acid derived additives[75] and elevated temperatures[76] have been used to improve the *trans*-selectivity in such cases.

The model side arm installation began with reaction of aldehyde **224** and pre-synthesised (ethoxycarbonylethylene)triphenylphosphoranes in THF (Scheme 2.65). The yield of the reaction was pleasing, but the selectivity was poor (1:1 *E:Z,* Table 2.2) . The next aim was the exploration of reaction conditions to improve *trans*-selectivity. First, the reaction was performed in different solvents at room temperature, to screen the best solvent for the reaction. Both THF and DCM gave excellent yields (96% and 90%, respectively) whereas DMF was the best solvent for *trans*-selectivity (3:1 *E*:*Z*, Table 2.2).



224

***E* 202**
***Z* 226**

Scheme 2.65: Installing ethyl ester side arm to **224**

Solvent	**THF**	**DCM**	**$CHCl_3$**	**DMF**	**C_6H_6**	**Toluene**	**CH_3CN**
Yield	96	90	84	57	62	54	49
E:Z	1:1	1:1	1:2	3:1	*Z* only	1:1	1:1

E:Z ratios were calculated by ^{1}H-NMR integrations

All reactions were carried out at room temperature

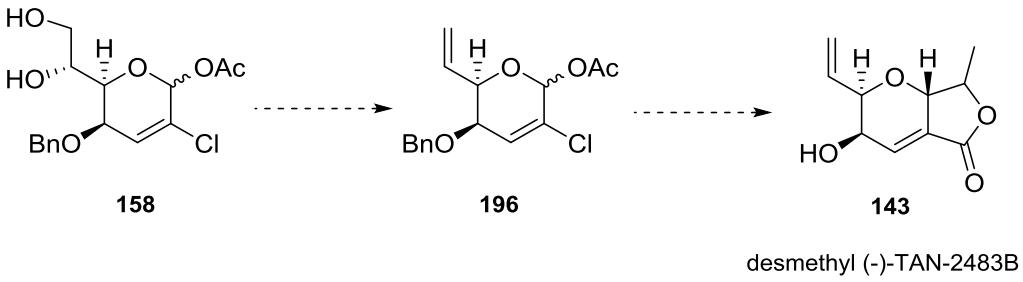
Table 2.2: Table of yield of **202** and **226** and *E:Z* ratio

Martin *et al.* reported that changes in solvent or temperature had little effect upon the product ratio with a similar sugar-derived substrate.[73] However, they reported that the addition of a catalytic amount of benzoic acid dramatically increased the *trans*-selectivity.[73] With this idea in mind, the reaction was repeated in THF in the presence of 0.1 *eq* benzoic acid. Unfortunately, a significantly poorer yield (49%) was obtained with the same selectivity (*E:Z* 1:1). A similar effect was observed with addition of a catalytic amount of acetic acid in DCM (62%, *E:Z* 1:1).

Phosphonate-stabilised carbanions in Horner-Wadsworth-Emmons reactions are more nucleophilic and less basic than the phosphonium ylides and typically produce *trans*-alkenes preferentially.[77] The pre-formed carbanion derived from triethyl phosphonoacetate in LHMDS was treated with aldehyde **224** at -78 °C. The reaction was completed within half an hour after warming to room temperature, yielding the ethyl ester in a 1:1 ratio of *E*- and *Z*- isomers (yield 70%). All the general strategies of optimisation of *E*-stereoselectivity in Wittig-like reactions were unsuccessful. Despite the disappointing selectivity results, further functionalisation of the ethyl ester-derived alkyne was pursued towards the formation *E*-ethyl ester analogue of (−)-TAN-2483B (will be discussed in Section 2.8.3).

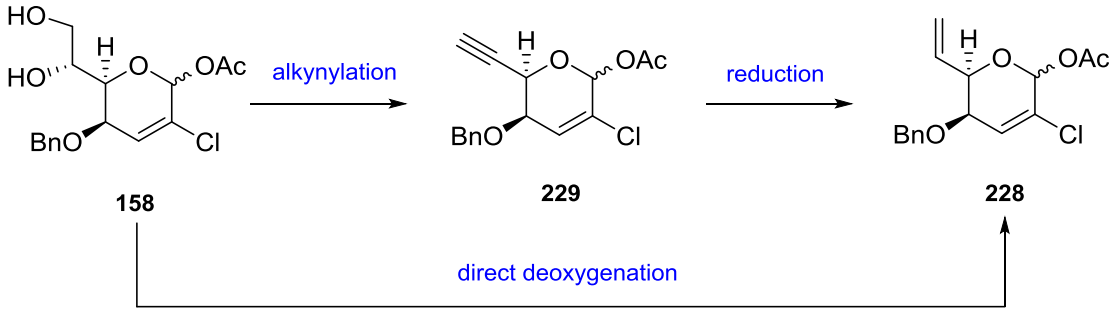
2.7.3 Installation of desmethyl side arm

Due to the lack of stereoselectivity of the stabilised ylide Wittig route, installation of an alternative side arm was investigated. The targeted two-carbon side arm was a terminal alkene, which could be used to form either desmethyl (−)-TAN-2483B (**143**) or (−)-TAN-2483B itself, through a late–stage alkene cross metathesis (Scheme 2.66).



Scheme 2.66: Strategy for the synthesis of des-methyl (−)-TAN-2483B via model side arm

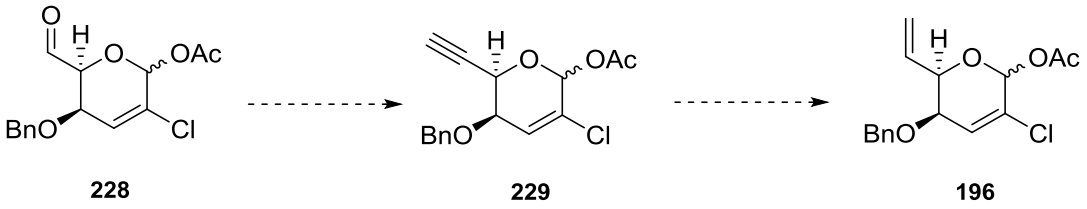
Two approaches were employed in synthesis of the terminal alkene side arm. The first was the formation of terminal alkyne **229** followed by partial reduction (Scheme 2.67) and the second one was the direct deoxygenation of diol **158**. This strategy would be applied at an early stage of the synthesis prior to construction of the furo[3,4-*b*]pyran ring system.



Scheme 2.67: Installation of terminal alkene-based side arm to **158**

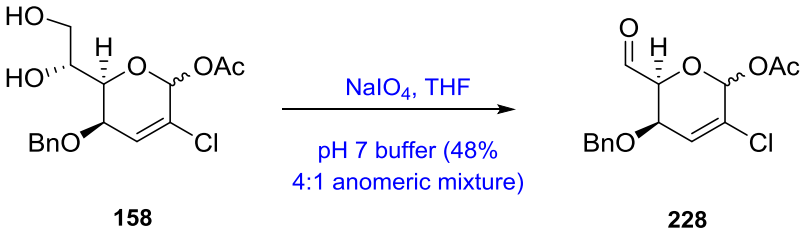
Synthesis of desmethyl side arm from Ohira-Bestmann reagent

Terminal alkyne formation using Ohira-Bestmann reagent would be followed by subsequent reduction (Scheme 2.68). These would lead to attachment of alkene terminated side arm.



Scheme 2.68: Installation of alkene side arm via terminal alkyne **229**

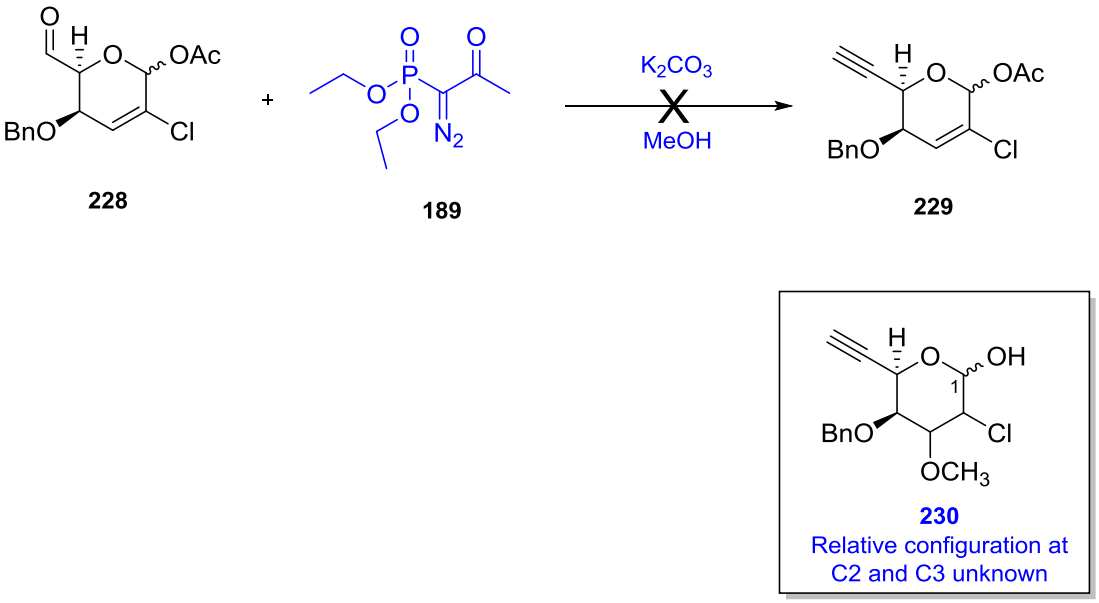
The required starting aldehyde **228** was prepared by the cleavage of diol acetate **158** with $NaIO_4$ (Scheme 2.69). The aldehyde **228** was obtained as an anomeric mixture of acetates (4:1). After aqueous work-up the material was clean according to NMR spectroscopy and therefore used directly without further purification.



Scheme 2.69: Synthesis of aldehyde **228** by diol cleavage with $NaIO_4$

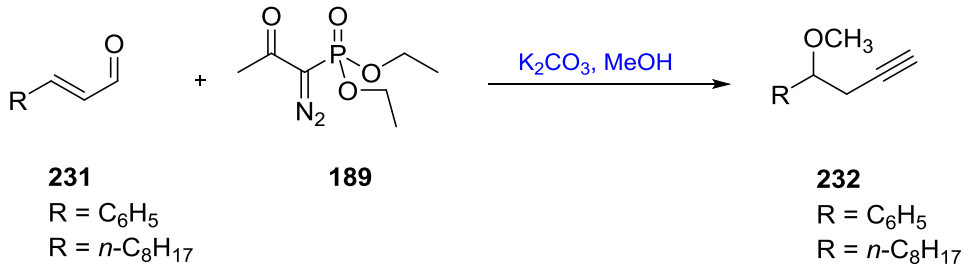
Aldehyde **228** was treated with freshly prepared Ohira-Bestmann reagent and potassium carbonate in methanol. Aldehyde **228** was completely consumed within one hour and a new compound was isolated (Scheme 2.70). ^{1}H-NMR spectroscopy of the isolated material revealed that the signal corresponding to the ring alkene proton at 6.26 ppm had disappeared. It was considered that the double bond might have migrated to make a glycal or reacted through addition. A characteristic singlet which integrated for three protons appeared at 3.42 ppm, which corresponds to an OMe group (^{13}C-NMR 55.8 and 55.3 ppm for the two anomers). A singlet at 2.63 ppm corresponded to the desired terminal alkyne proton. Thus, ^{1}H-NMR data suggested that the desired product **229** further reacted with methanol and potassium carbonate to afford the hemiacetal **230**. Further, the presence of OH in the molecule was confirmed by IR data from the characteristic broad peak at 3500 cm^{-1}. The carbon signals corresponding to C1 were at 110 and 103 ppm in the two anomers. By considering all the data acquired from 1D and 2D-NMR and IR, the major product of the unknown mixture was identified as **230**. The presence of **230** was confirmed by a HRMS peak found at 314.1163 that

corresponds to the $[M+NH_4]^+$ ion (calculated m/z 314.1154). Isolation of this product demonstrates the undesired reactivity of the acetyl glycoside functionality.



Scheme 2.70 Alkyne formation with Ohira-Bestmann reagent **189**

Incorporation of a methyl ether during the reaction of α,β-unsaturated aldehydes **231** with Ohira-Bestmann reagent was reported by Bestmann and co-workers in 1996.[59] Homopropargylic methyl ethers **232** were afforded due to an initial conjugate addition of methanol and subsequent transformation of the aldehyde to the alkyne (Scheme 2.71).



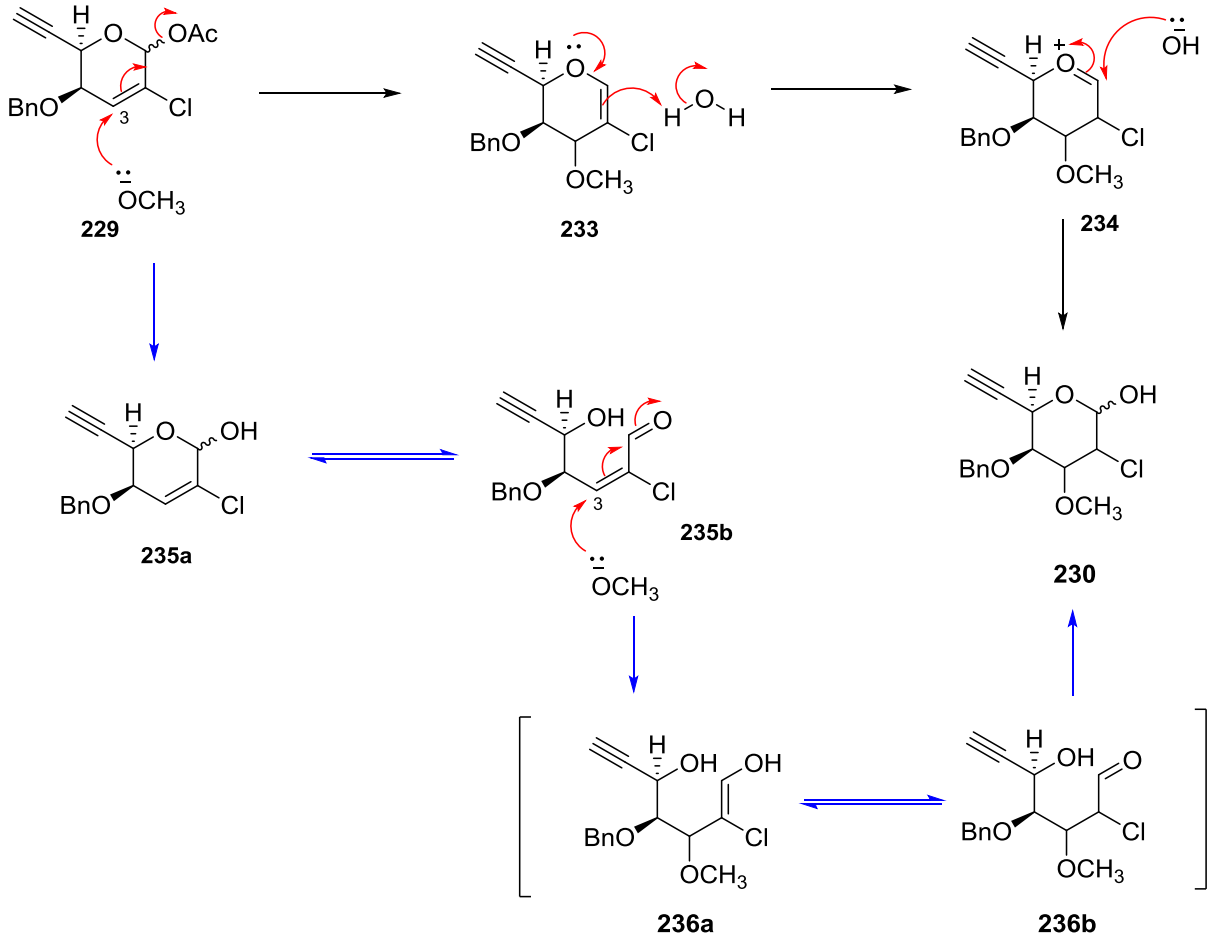
231
R = C_6H_5
R = *n*-C_8H_{17}

189

232
R = C_6H_5
R = *n*-C_8H_{17}

Scheme 2.71: Reported propargylic methyl ether formation during reaction of enal with Ohira-Bestmann reagent[59]

Migration of the double bond in the pyran ring was also observed in the presence of K_2CO_3 and MeOH (see section 2.6.1) with a similar substrate. Moreover, nucleophilic attack by methoxide at the C3 centre could trigger the double bond migration (Scheme 2.72, black route). Migration of the double bond would be facilitated by the presence of an acetate group at the anomeric centre which can act as a leaving group. Isomerised pyran **233** could react with water due to the electron donating ability of the pyran ring oxygen atom. On the other hand, base-promoted hydrolysis of acetate would form the hemiacetal **235a** (Scheme 2.72, blue route). Methoxide attack at the C3 centre of ring opened species **235b** would result in the formation of enol **236a**, which can subsequently form **230**.

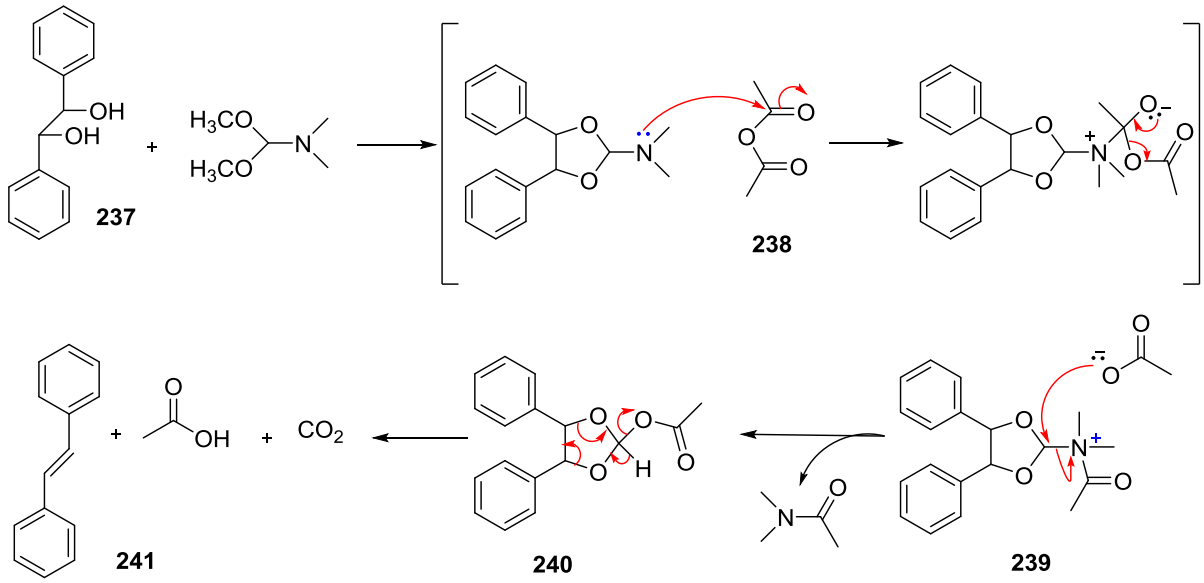


Scheme 2.72: Plausible mechanisms for the formation of **230**

These results indicated that, while the aldehyde **228** reacted with the Ohira-Bestmann reagent to afford alkynes, other moieties within the product were incompatible with the reaction conditions. This encouraged the author to explore the direct deoxygenation of vicinal diol **158** into alkene **196**.

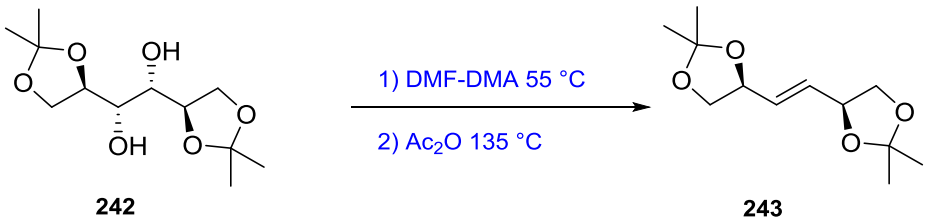
Synthesis of desmethyl side arm from direct deoxygenation of vicinal diol 158

In 1970, deoxygenation of the vicinal diol **237** was reported by Eastwood and co-workers using *N,N*-dimethylformamide dimethylacetal (DMF-DMA) and acetic anhydride.[78] The mechanism of the reaction can be exemplified as in Scheme 2.73. First, the vicinal diol reacts with DMF-DMA to form the dioxolane **238**. Reaction with acetic anhydride will produce alkene, acetic acid, *N,N*-dimethylacetamide and CO_2 through a cyclic elimination process.



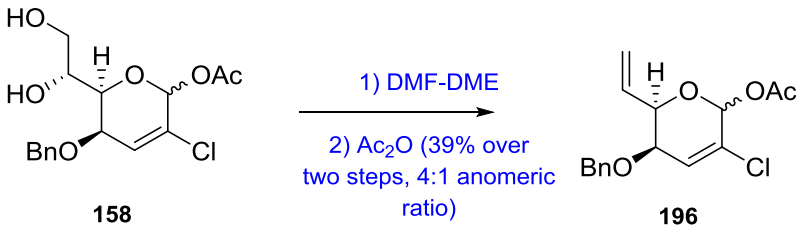
Scheme 2.73: Mechanism for the vicinal alcohol deoxygenation

Direct conversion of a diol into an alkene in this way has been used in many natural product syntheses. For example, Reddy *et al.* reported conversion of internal diol **242** into alkene **243** in the synthesis of dinemason A in recent literature (Scheme 2.74).[79]



Scheme 2.74: Reported alcohol deoxygenation into alkene[79]

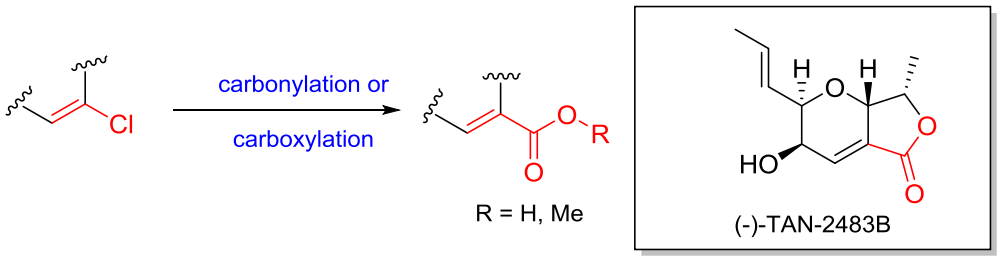
The diol acetate **158** was stirred at 52 °C for one day with DMF-DMA, which has dual functionality as both the solvent and the reagent. The volatile materials were then removed in *vacuo* and the residue was treated with acetic anhydride and heated at 106 °C (Scheme 2.75). The resulting brown viscous material was purified on silica gel to obtain alkene **196** as yellow oil. The yield of terminal alkene formation reaction was not good (yield 39%, 4:1 anomeric ratio) but this provided enough material to proceed with further chemistry.



Scheme 2.75: formation of terminal alkene side armby deoxygenation of **158**

2.8 Functionalisation of chloroalkene

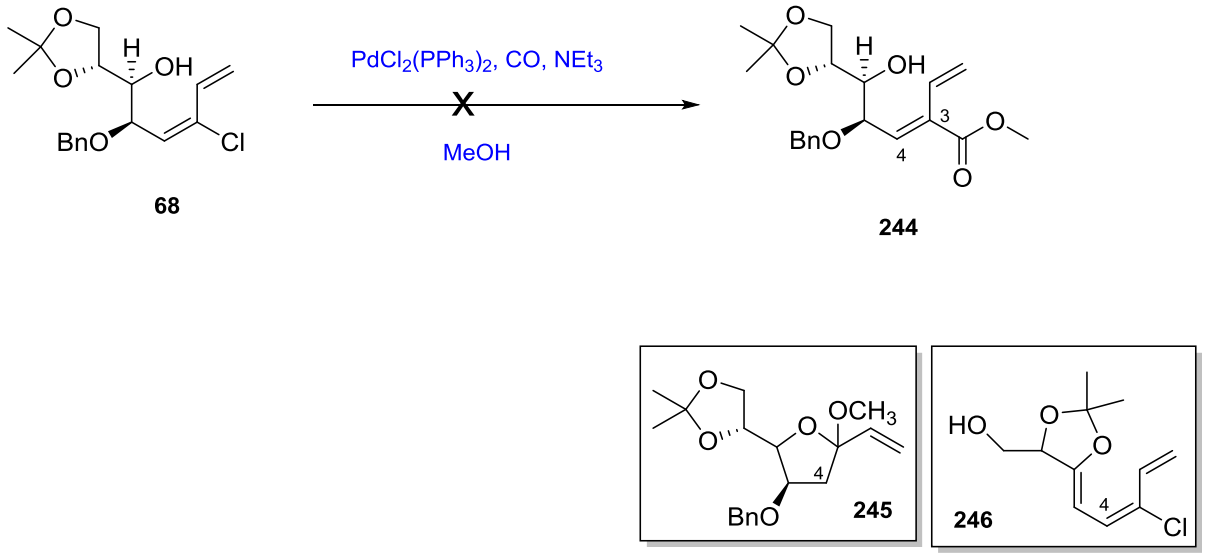
The chloroalkene functionality in advanced intermediates synthesised as described in the previous sections needed to be converted into a carboxylic acid or an ester in the synthesis of the five-membered lactone ring in the natural product/analogues. As discussed in the retrosynthetic strategies Pd-catalysed carbonylation or carboxylation is the most appropriate strategy to use in functionalisation of a chloroalkene. The next section will detail the functionalisation of the chloroalkene by the aforementioned strategies.



Scheme 2.76: Functionalisation of chloroalkene to form the lactone ring of the natural product

2.8.1 Carbonylation of dienyl chloride 68

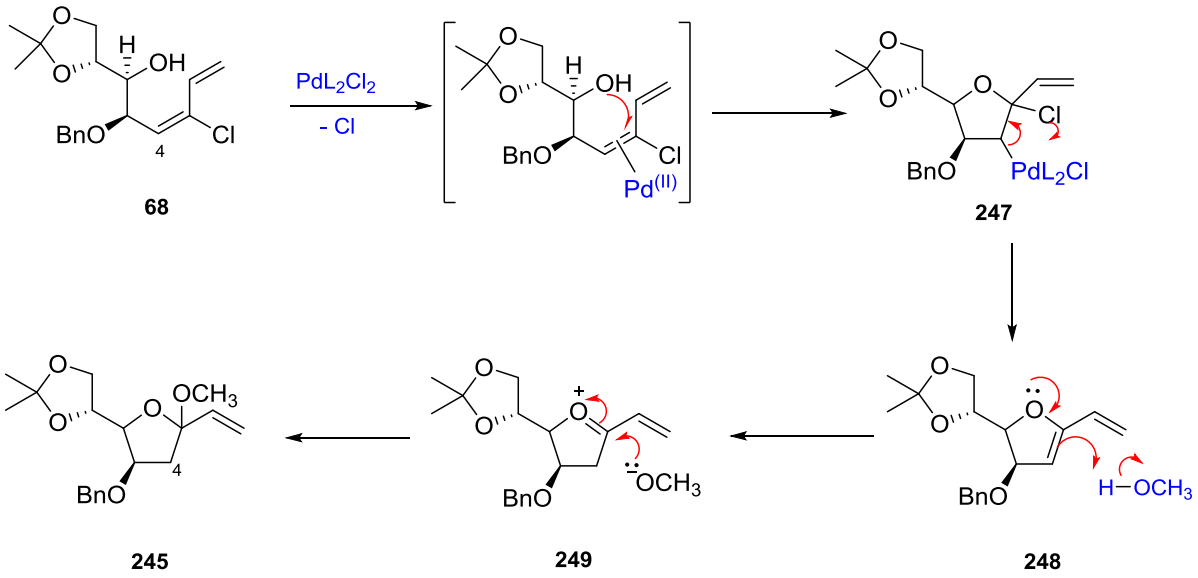
Introduction of a carboxyl derived functionality is needed to make the five-membered lactone ring attached to the pyran ring. Exploration was begun with palladium-catalysed carbonylation of the alkenyl chloride in diene **68**. There are numerous variables associated with the carbonylation conditions such as Pd precatalyst, ligand, solvent and base. However, the choice of the ligand is often the most influential factor among those variables.[39] Most of the previous studies showed that the electron-donating ability of the ligand is a crucial factor in the selection of the ligand for carbonylation.[39] Triphenylphosphine is considered to be a good starting point for carbonylation due to its electron-donating ability. Thus, the first attempt at carbonylation of diene **68** was made using *bis*(triphenylphosphine)dichloropalladium in the polar solvent methanol with triethylamine as base with diene **68**. Consumption of starting material was observed within 6 ½ hours under a CO atmosphere. Upon purification, two compounds **245** and **246** were isolated (Scheme 2.77). Unfortunately, neither of them was the desired methyl ester **244** as they lack the characteristic peak corresponding to H4 (around 6.80 ppm) in the ^{1}H-NMR spectra.



Scheme 2.77: Pd-catalysed carbonylation of diene **68**

A diagnostic set of proton signals at 2.37 ppm (dd, *J*=13.9, 6.6 Hz) and 2.06 ppm (dd *J*=14.0, 3.4 Hz) were seen for furan **245** which were characteristic for the geminal protons at C4. Further evaluation of the 1D and 2D-NMR spectroscopy data led to complete characterisation of **245**. This compound

may result from the complexation of Pd to the C3-C4 alkene of **68** instead of oxidative addition to alkenyl chloride (Scheme 2.78). Intramolecular nucleophilic attack on to the activated alkene followed by reductive elimination of L_2PdCl_2 would provide the vinyl glycal **248**. Further reaction of glycal **248** could conceivably be catalysed by Pd as a Lewis acid in the solvent methanol making the furan **245** containing both *C*-glycosidic and *O*-glycosidic bonds.

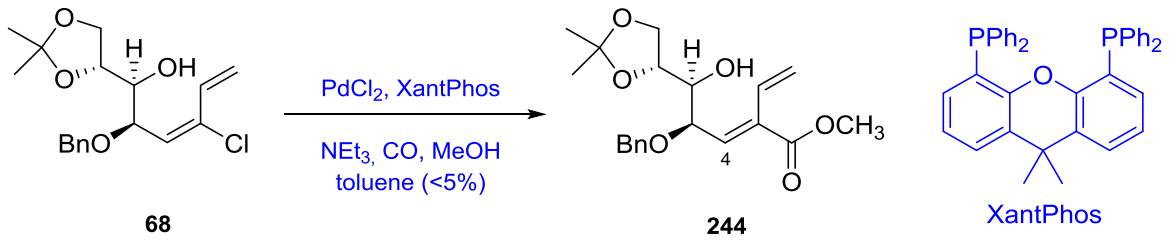


Scheme 2.78: Plausible mechanism for the formation of **245**

^{1}H-NMR spectroscopy of compound **246** revealed that benzyl protecting group was cleaved off as is evident from the absence of any aromatic peaks. A new signal (at 6.34 ppm) appeared in the alkene region in addition to the olefinic signals of starting materials. The new alkene signal correlated in the COSY NMR spectrum with the signal for H4, which revealed the establishment of an extended conjugated system due to the elimination of the benzyl group. Then the structure of the compound **246** was further evaluated by 1D and 2D-NMR spectroscopy. Compound **246** was presumably formed by elimination of benzyl alcohol followed by potential rearrangement of the acetonide group catalysed by Lewis acidic palladium or base-mediated elimination triggered by triethylamine.

Typically, bidentate ligands are superior to monodentate ligands in carbonylation reactions, minimising catalyst poisoning by ligation of multiple CO ligands. Thus, the next ligand chosen for investigation was bidentate XantPhos. The reaction was performed with an excess of methanol in toluene with triethylamine, XantPhos and $Pd(OAc)_2$ (Scheme 2.79). Methanol is necessary for this reaction as it acts as a nucleophile to afford methyl ester **244**. ^{1}H-NMR data obtained from the

crude reaction mixture showed a downfield doublet at 6.78 ppm which corresponds to H4, indicating the presence of a small amount of the desired methyl ester **244**. The presence of **244** was further confirmed by the OMe peak at 3.52 ppm (integrating for three relative protons) in the ^{1}H-NMR spectrum. The crude material was purified to obtain **244** in <5% yield. The reaction was repeated with $Pd^{(0)}$ catalyst precursor $Pd_2(dba)_3$. Unfortunately, only starting material was recovered. Use of $PdCl_2$ as a precursor was next explored with XantPhos ligand in 1,4-dioxane as solvent. The desired methyl ester **244** was obtained in a trace amount. No improvement in yield was observed.

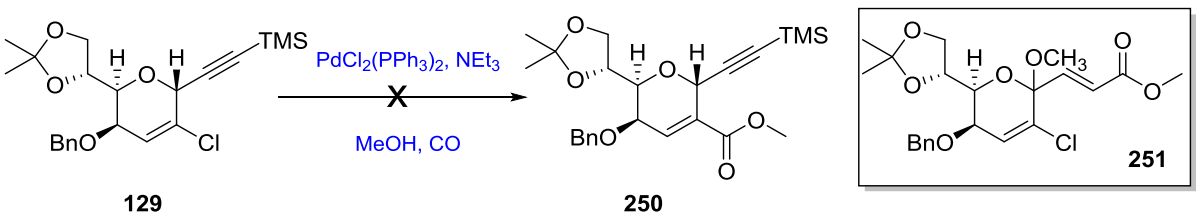


68 244

Scheme 2.79: Pd-catalysed carbonylation of **68** with XantPhos

2.8.2 Carbonylation of alkyne 129 containing chloroalkene

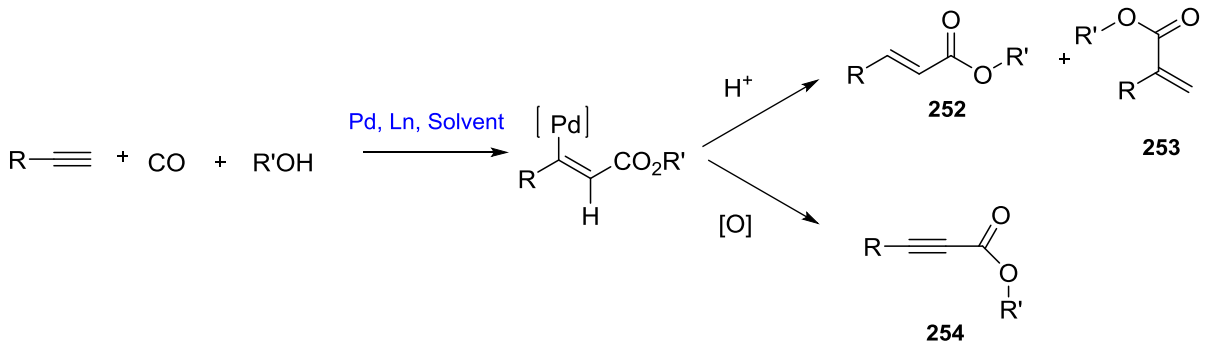
Palladium-catalysed carbonylation was explored with TMS-protected alkyne **129** in methanol using triphenylphospine as a ligand (Scheme 2.80). Starting material was completely consumed after refluxing in methanol overnight and a new product formed, migrating just slower than the starting material on TLC; however, the desired methyl ester **250** derived from carbonylation of chloroalkene was not observed. Instead, *E*-enoate **251** was obtained in 30% yield. Presumably, carbonylation of the chloroalkene is very sluggish compared to the Pd-catalysed carbonylation of the alkyne.



129 250

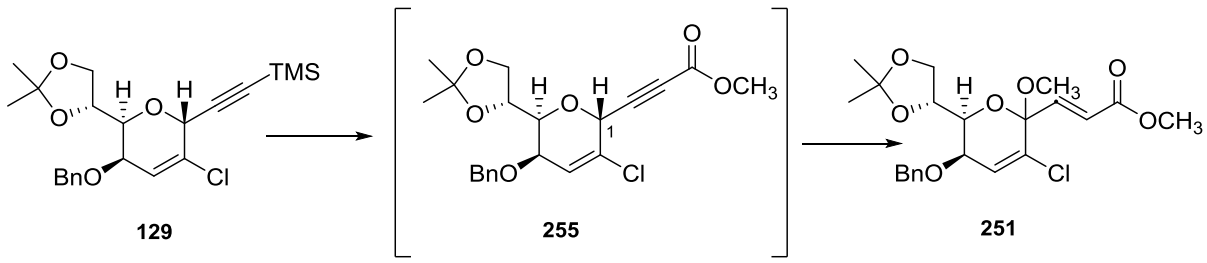
Scheme 2.80: Palladium-catalysed carbonylation of TMS alkyne **129**

Alkoxy carbonylation of terminal alkynes produces a diverse range of compounds dependent upon fine tuning of the reaction conditions. A generic scheme for the alkoxycarbonylation of the terminal alkynes can be produced by considering the reaction conditions (Scheme 2.81). For example α,β-unsaturated esters **252** and **253** are produced in the presence of a catalytic amount of acid source.[80] The linear (**252**) to branched (**253**) ratio is dependent on the substituent R. Alternatively, oxidative or basic conditions are known to deliver α,β-alkynyl esters **254**.[81]



Scheme 2.81: Generic scheme for the alkoxycarbonylation of terminal alkynes

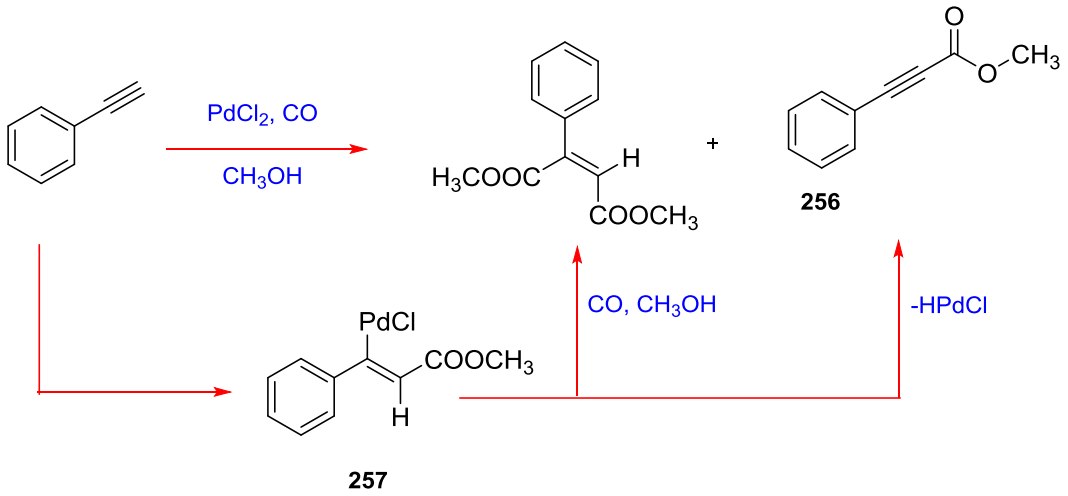
While the presence of the *E*-enoate **251** resembles the products usually obtained under acidic conditions, the extra oxygenation in the resultant acetal **251** cannot be explained by this type of process. Instead it is proposed that an intermediate resembling the α,β-alkynyl ester **255** is involved (Scheme 2.82). Further reaction of this intermediate could produce the isolated ester **251**.



Scheme 2.82: Formation of **251** via α,β-alkynyl ester **255**.

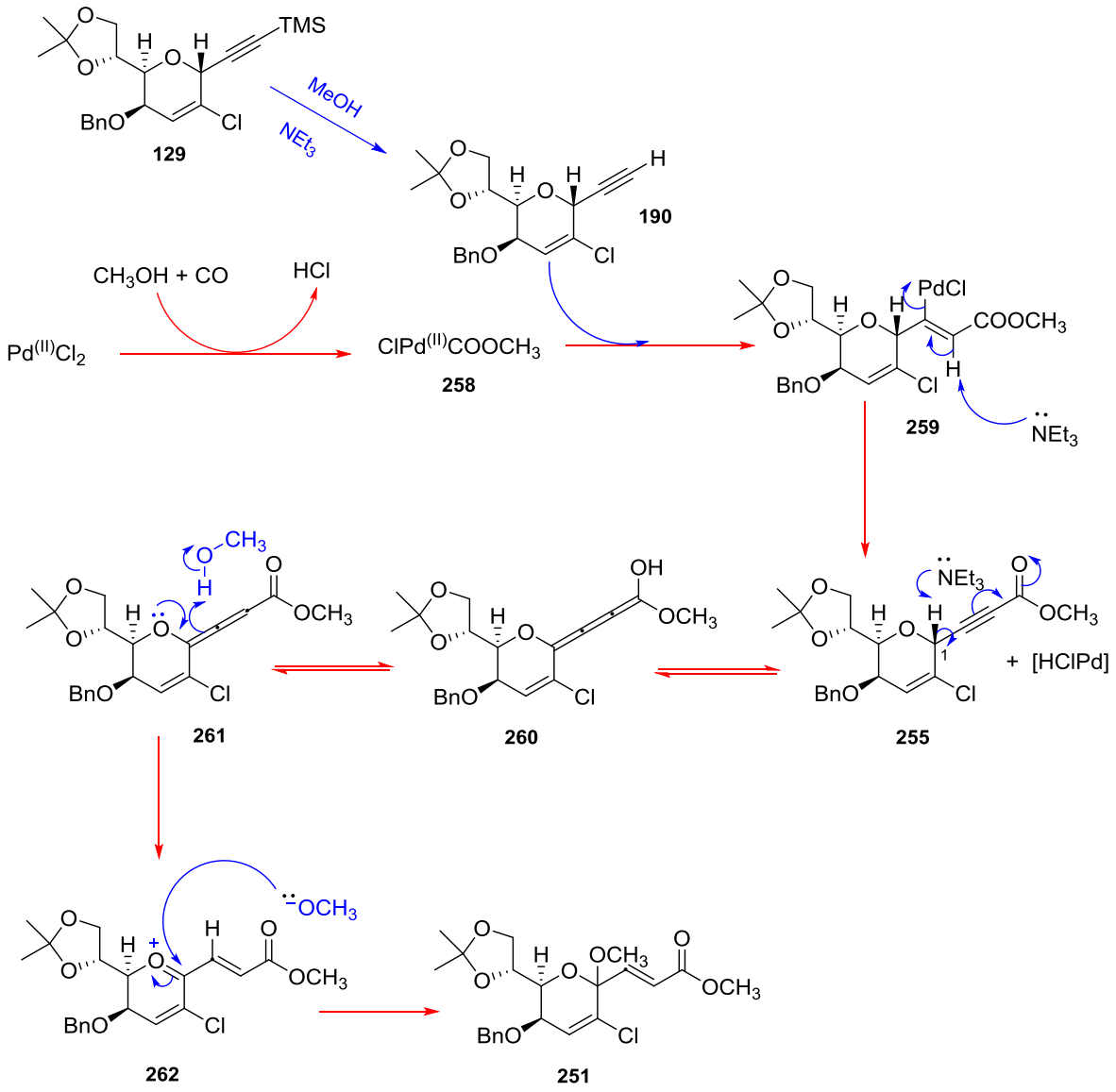
Heck *et al.* reported the formation of minor amounts of methyl phenylpropiolate **256** in the carboalkoxylation of phenylacetylene, which was proposed to proceed via the organopalladium

species **257** (Scheme 2.83).[82] Presumably, similar mechanism will be followed in the formation of **255**.



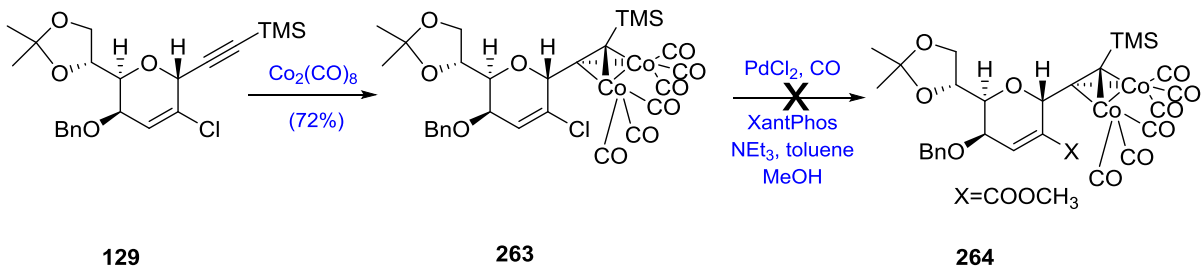
Scheme 2.83: Reported alkoxycarbonylation of alkynes[82]

The conversion of **129** into **255** may proceed via the reactive terminal alkyne **190** by deprotection of TMS group in the presence of methanol and triethylamine (Scheme 2.84). This kind of behaviour of **129** in methanol was also observed accidently, when a solution of TMS alkyne in methanol was left under reduced pressure at elevated temperature (40 °C) on the rotary evaporator for a prolonged time. Based on Heck's proposed mechanism (see above), Pd-acyl complex **258** will coordinate with alkyne **190** to afford organopalladium species **259**. *Trans*-elimination of [HPdCl] from the intermediate carboalkoxylated vinylpalladium compound **259** was proposed to proceed through the action of base.[83] The formation of **255** by a β-hydride *syn*-elimination of [HPdCl] is impossible because of the *syn*-addition of $PdClCOOCH_3$ to the alkyne **190**. The α,β-alkynyl ester **255** might further react with the base and solvent to form the product **251** obtained. Thus, rearrangement of the proton at the C1 centre can occur by base-promoted establishment of an extended allene system to form **260**. Addition of methanol across the double bond attached to the pyran ring may be a stepwise process passing through intermediates **261** and **262,** assisted by the presence of the adjacent pyran ring oxygen. Ultimately the observed product **251** would be formed.



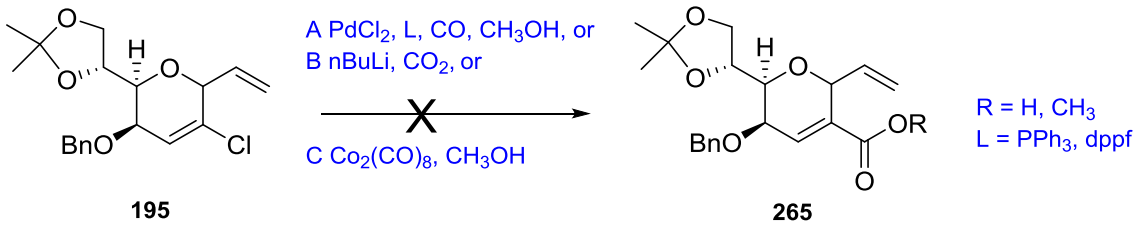
Scheme 2.84: Formation of **251** via σ,β-alkynyl ester **255**

Due to the higher reactivity of the terminal alkyne over the chloroalkene in Pd-cross coupling seen, it was impossible to functionalise compound **129** to the desired methyl ester **250** (Scheme 2.80). In order to decrease the reactivity of the alkyne it was protected by $Co_2(CO)_8$ (Scheme 2.85). The dicobalt complex **263** was obtained in reasonable good yield (72%) as a red-coloured oil, upon reaction with $Co_2(CO)_8$ in dichloromethane. Then the cobalt acetylene complex was used for the carbonylation reaction. Unfortunately, the cobalt complex appeared to be incompatible with the palladium-catalysed reaction conditions, as starting material alkyne **129** was obtained, due to decomplexation of cobalt and the lack of reaction at the alkenyl chloride.



Scheme 2.85: Alkyne protection followed by attempted carbonylation of **129**

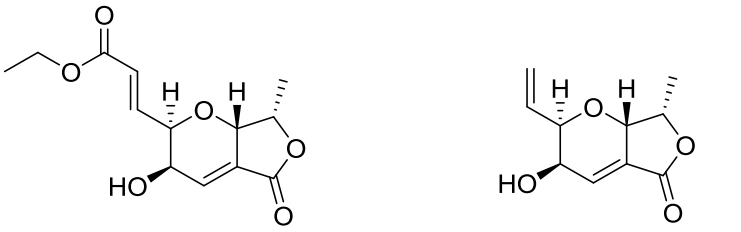
Pd-catalysed carbonylation was next attempted with substrates that lack the competitive alkyne functionality. First, carbonylation of alkene **195** was tried with CO with palladium catalysts containing different ligands (PPh_3, dppf). Carbonylation with $Co_2(CO)_8$ and carboxylation with nBuLi/CO_2 were also tested. Unfortunately all attempts to this end were unsuccessful, demonstrating the poor reactivity of the alkenyl chloride (Scheme 2.86).



Scheme 2.86: Attempted carbonylation and carboxylation reactions with **195**

2.8.3 Attempted lactone formation from various chloroalkenes 207, 220 and 222

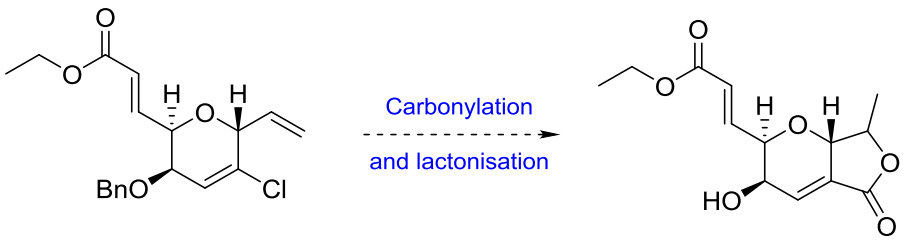
Installation of model side arms (ethyl ester and terminal alkene) to the advanced intermediates **224** and **228** was successful. However the desired *E*-propenyl based side arm could not be obtained, attributed to the unexpected reactivity observed at the α-centre of aldehyde **224** (see section 2.7.1). Consequently, this diverted the project towards the synthesis of analogues of the natural products. This section will discuss the synthetic studies towards the analogues of (−)-TAN-2483B by attempted functionalisation of chloroalkenes and subsequent lactone formation.



E-ethyl ester (-)-TAN-2483B des-methyl (-)-TAN-2483B

Figure 2.3: Target analogues of (−)-TAN-24833 based on successful side arm installation

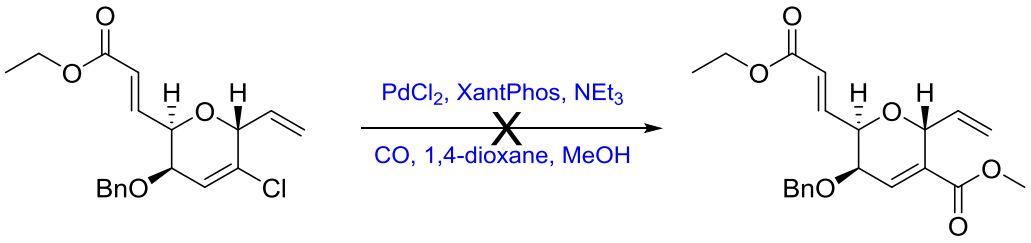
The advanced intermediate **207** was tested in the synthesis of an *E*-ethyl ester analogue of the natural product. Palladium-catalysed carbonylation, lactone ring cyclisation followed by benzyl deprotection would afford the target analogue of the natural product.



207 **141**

Scheme 2.87: Attempted synthesis of *E*-ethyl ester (−)-TAN-2483B (**141**) via alkene **207**

Pd-catalysed carbonylation of the chloroalkene in **207** in the presence of methanol was attempted to make the methyl ester **265** (Scheme 2.88). However, no reaction was observed when using $PdCl_2$ and XantPhos, which were previously identified as the best of the conditions for the carbonylation for chloroalkene substrates.

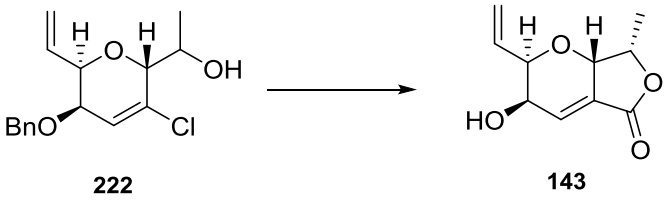


207 **265**

Scheme 2.88: Palladium-catalysed carbonylation of alkene **207**

All the attempts to functionalise the chloroalkene with *E*-ethyl ester side arms were unsuccessful due to the poor reactivity of alkenyl chloride. Consequently, the *E*-ethyl ester analogue of (−)-TAN-2483B was not achieved.

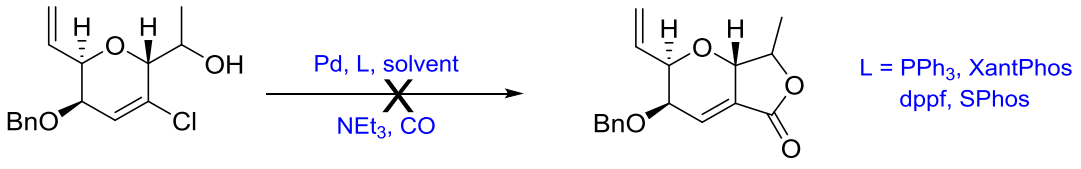
Then, lactone formation towards the synthesis of desmethyl (−)-TAN-4483B (**143**) was begun with the higher intermediate **222** containing the 2-hydroxylethyl fragment. Single step Pd-catalysed carbonylation followed by lactonisation would afford the bicyclic core of the target analogue. A similar type of carbonylation was performed in the synthesis of the desmethyl bicyclic core of the natural product by Hewitt and Harvey in 2010.[19]



222 **143**

Scheme 2.89: Synthesis of desmethyl (−)-TAN-2483B (**143**) via 2-hydroxyethyl **222**

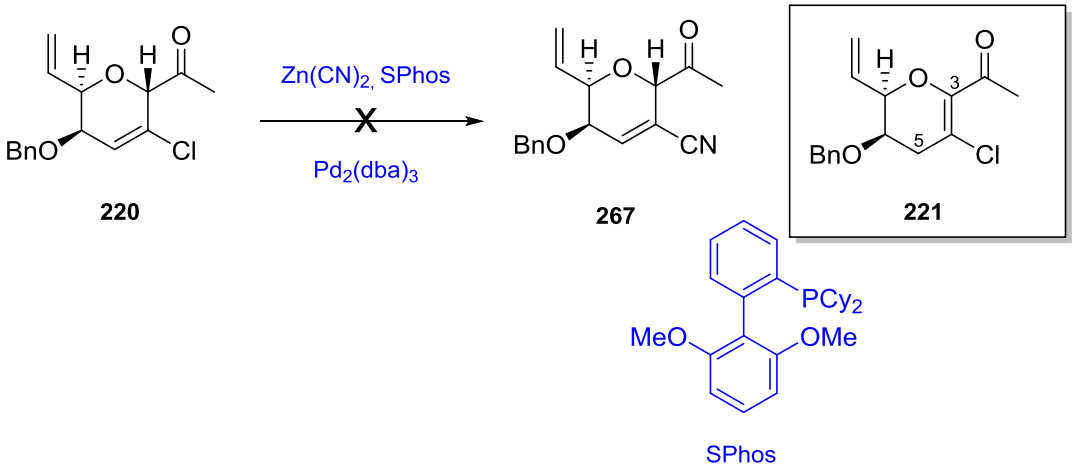
As described in the previous sections, the best ligand for the Pd-catalysed carbonylation with the chloroalkene-based substrates related to this project was XantPhos. Therefore, carbonylation was attempted with intermediate **222** using $PdCl_2$ and XantPhos in toluene (Scheme 2.90). Unfortunately, starting materials were recovered after refluxing overnight in toluene. It has been reported in the literature that Pd complexes with SPhos exhibit high activity for Suzuki coupling reactions involving aryl chlorides.[84] Therefore, the reaction was repeated with $Pd_2(dba)_3$ with SPhos in toluene, which was also unsuccessful. Further, carbonylation attempts with catalysts including $PdCl_2$(dppf) and $PdCl_2(PPh_3)_2$ were fruitless.



222 **266**

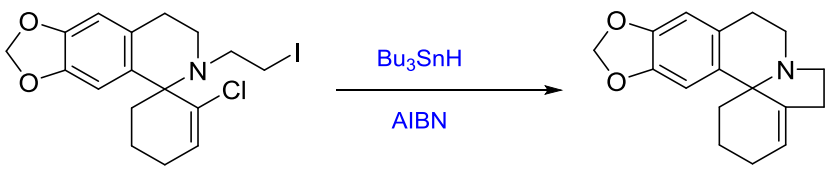
Scheme 2.90: Attempted carbonylations with alcohol **222**

As an another useful alternative for the functionalisation of the chloroalkene, Pd-catalysed cyanation was attempted with the intermediate methyl ketone **220** with $Zn(CN)_2$ as a nitrile source (Scheme 2.91).[85] Typical reaction conditions for the cyanation involve higher temperature in solvents like DMF, because the solubility of $Zn(CN)_2$ is proportional to the reaction temperatures in polar solvents. Refluxing the methyl ketone **220** with $Zn(CN)_2$ and SPhos in DMF turned the colour of reaction mixture into metallic green. Starting materials disappeared within three hours leaving a UV active product which having the same R_f as the methyl ketone **220**. The ^{1}H-NMR spectrum showed that the alkene proton in the ring disappeared and a characteristic pair of doublet of doublets for H5 appeared at 2.69 ppm (dd, *J* = 18.4, 5.3 Hz) and 2.58 ppm (dd, *J* = 18.4, 5.0 Hz). The carbon signal for C3 had moved from 80.2 ppm (for **220**) ppm to 144.9 ppm for the isomerised ketone **221**. Spectroscopic data of the purified product from the Pd-catalysed cyanation indicated that the isolated product was the isomerised methyl ketone **221**.



Scheme 2.91: Attempted Pd-catalysed cyanation of **220**

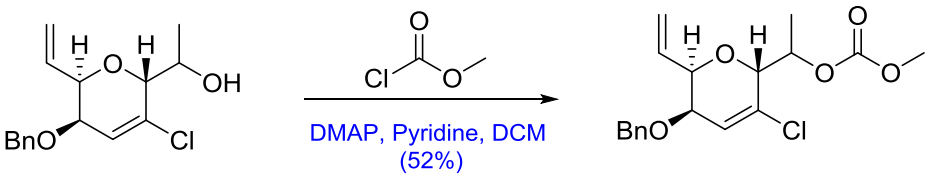
A radical cyclisation/ elimination reaction sequence has been successfully implemented by Banwell's group in synthesis of aromatic erythrina alkaloids.[86] The halogenated alkene in **268** derived from *gem*-dichlorocyclopropane ring expansion was exploited in a C-radical addition/halide elimination processes (Scheme 2.92). This sequence leads to the formation of a carbon-carbon single bond which proceeds with retention of the adjacent carbon-carbon double bond.



268 **269**

Scheme 2.92: C-radical addition/halide elimination process used in the synthesis of erythrina alkaloids[86a]

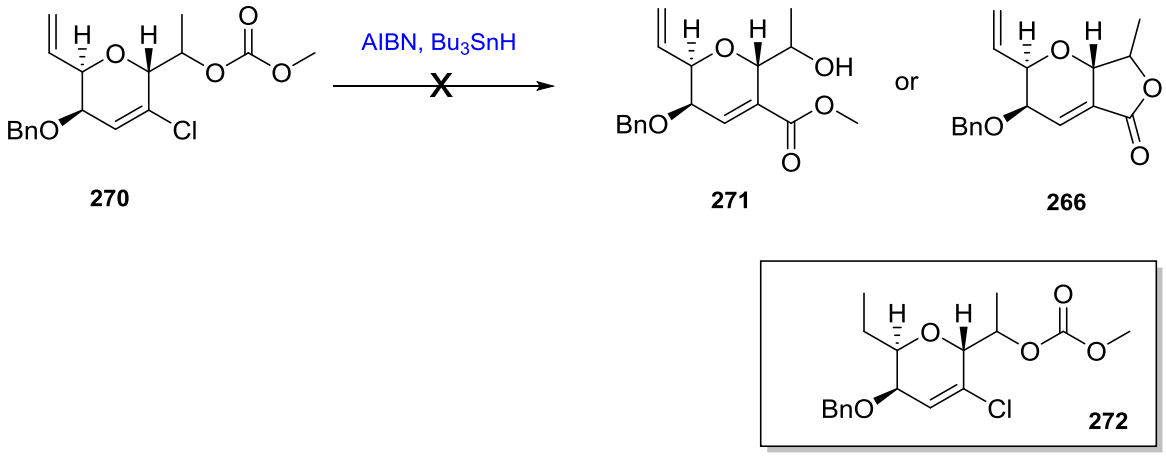
With this idea in mind, alcohol **222** would be converted into **270** as a potential precursor to the acyl radical. Alcohol **222** was converted to its carbonate **270** to connect the methyl ester functionality for the carbon skeleton of the furo[3,4-*b*]pyran ring system. Carbonate **270** was prepared by reaction between alcohol **222** and methyl chloroformate in 52% yield in DCM (Scheme 2.93).



222 **270**

Scheme 2.93: Synthesis of potential free radical precursor **270**

Then, the carbonate **270** was reacted under free radical reaction conditions with AIBN and Bu_3SnH (Scheme 2.94). Unfortunately, hydrogenation of the terminal alkene side arm was the predominant reaction to afford **272** with no sign of the desired free radical addition/Cl elimination sequence.



Scheme 2.94: Attempted free carboxylation of chloroalkene **270**

After extensive studies, the construction of the furo[3,4-*b*]pyran ring system in (−)-TAN-2483 via dichlorocyclopropanation was abandoned, due to the apparent unreactivity of the alkenyl chloride towards Pd-catalysed carbonylation, cyanation and carboxylation conditions.

2.9 Conclusion

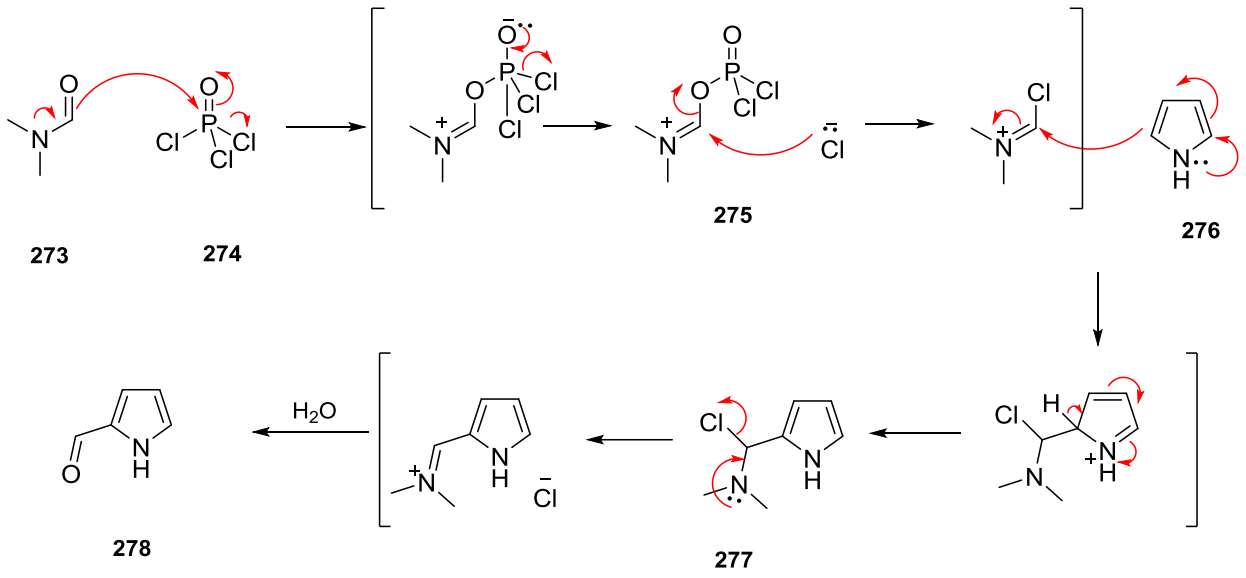
This chapter has reported the use of a dichlorocyclopropane-ring expansion route to afford pyrans with chloroalkene moiety. However attempts to synthesise the (−)-TAN-2483B furo[3,4-*b*]pyran ring system using a variety of strategies were unsucessful. Many olefination methodologies were unsuccessful in achieving the two carbon unit installation for the hemiacetal, whereas *C*-glycosidation under Lewis acid condition proved to be successful. The actual (*E*-propenyl) side arm of the natural product (−)-TAN-2483B was not achievable according to the retrosynthetic analysis proposed. Therefore, a range of model side arms was investigated. The completion of the furo[3,4-*b*]pyran ring system was not achieved due to the low reactivity of the chloroalkene functionality towards the Pd-catalysed cross coupling conditions. An alternative route that circumvents these issues will be discussed in chapters 3 and 4 using Vilsmeier-Haack and dibromocyclopropanation strategies, respectively.

3 Vilsmeier–Haack (V-H) Approaches to (–)-TAN-2483B

3.1 Introduction

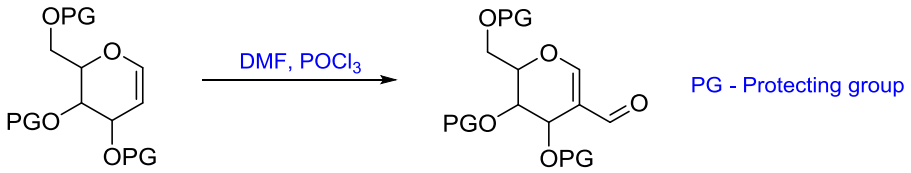
The main focus of this chapter was the exploration of new avenues for the synthesis of the furo[3,4-*b*]pyran ring system towards the synthesis of (–)-TAN-2483B, and was begun because of difficulties being encountered in the dichlorocyclopropane strategy. The biggest challenge encountered in the dichlorocyclopropanation strategy was the difficulty in carbonylation of chloroalkenes into carbonyl or carboxyl functions. One-step direct formylation of glycals through the Vilsmeier–Haack (V-H) reaction and dibromocyclopropanation were identified as potential solutions for the mentioned challenge. This chapter mainly describes attempts at synthesis of the furo[3,4-*b*]pyran ring system based on 2-*C*-formyl glycal through the V-H reaction. This study was mainly done in parallel to the studies towards the total synthesis (–)-TAN-2483B via dibromorocyclopropanation (described in chapter 4).

The application of the Vilsmeier-Haack (V-H) reagent ($POCl_3$/DMF) for the formylation of a variety of both aromatic and heteroaromatic substrates is well documented. The V-H reagent is an efficient, economical and mild reagent for the formylation of reactive aromatic and heteroaromatic substrates.[87] The classical V-H reaction[88] involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt **275** to yield the corresponding iminium **277** species, which facilitates easy entry into various nitrogen and oxygen based heterocycles (Scheme 3.1).[89] V-H product **278** is formed by subsequent hydrolysis of iminium intermediate **277**.



Scheme 3.1: Generic mechanism for the V-H formylation of an aromatic compound

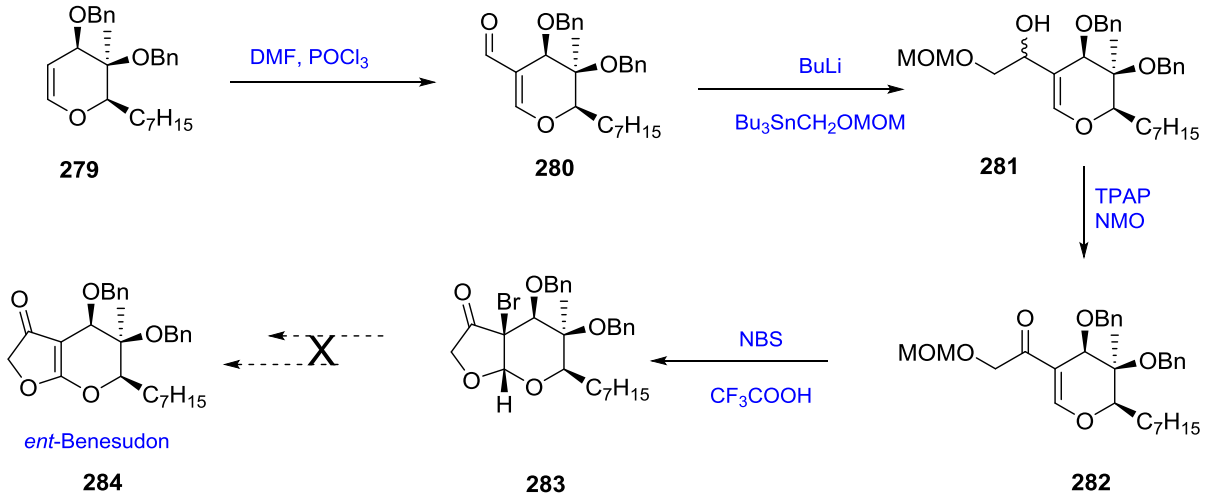
Later, one-step direct formylation of glycals through the V-H reaction was reported by Ramesh and Balasubramanian with a variety of glycals.[44] A generic scheme for the formylation of glycals is shown in below.



Scheme 3.2: Synthesis of 2-*C*-formyl-glycals through V–H reaction

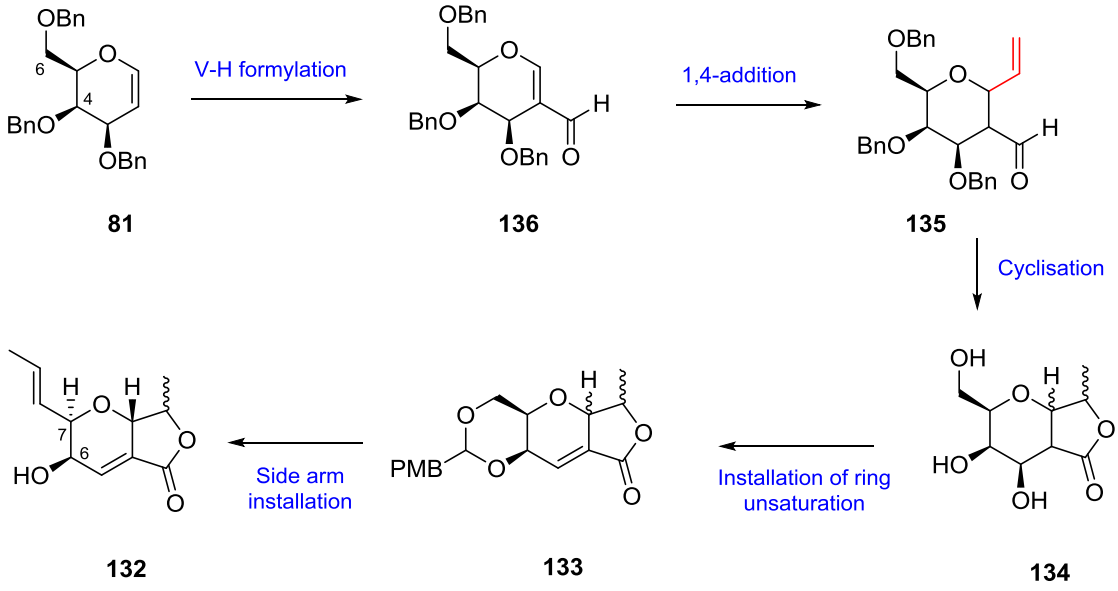
The V-H reaction has been used in the synthesis of natural products containing a fused furopyran bicycle. Benesudon has a ketene acetal function embedded in the bicyclic ring system, and was isolated from a terrestrial fungus.[90] Clive *et al.* utilised the V-H formylation of functionalised galactal **279** as one of the key steps in their initial attempt to synthesise the enantiomer of naturally occurring benesudon (Scheme 3.3).[90] Alcohol **281** was revealed by exposure of aldehyde **280** to *in situ* generated $MeOCH_2OCH_2Li$. Formation of the bicyclic framework of *ent*-benesudon was accomplished by bromination of the enol ether double bond in **282** with concomitant cleavage of the MOM group, followed by cyclisation to afford furo[2,3-*b*]pyran **283**. Attempts to introduce the central double bond through dehydrohalogenation were not successful. Nevertheless, their synthetic effort was a good encouragement for this author to apply the V-H reaction to the synthesis

of a fused furopyran bicyclic skeleton. With this idea in mind, a new synthetic plan was proposed for the synthesis of the furo[3,4-*b*]pyran ring system towards the synthesis of (−)-TAN-2483B.



Scheme 3.3: Reported V-H formylation in synthesis of main bicyclic carbon skeleton of natural product *ent*-benesudon[90]

The major challenge of the dichlorocyclopropane route was the difficulty in functionalisation of the alkenyl chloride functionality to form a carboxyl group. This problem might be circumvented by the use of the 2-*C*-formyl glycal moiety as one of the key intermediates. Thus, a synthetic strategy was devised as shown in Scheme 3.4 through the V-H formylated glycal intermediate **136**. The main drawback of this plan, compared to a route based on cyclopropanation, is the need to install the pyran ring unsaturation at a later stage. Global deprotection of the benzyl groups in **135** followed by selective reprotection of the C4- and C6-hydroxyl groups of **134** as a PMB acetal **133** was the planned strategy to achieve selective introduction of the double bond in the ring system through an elimination sequence.

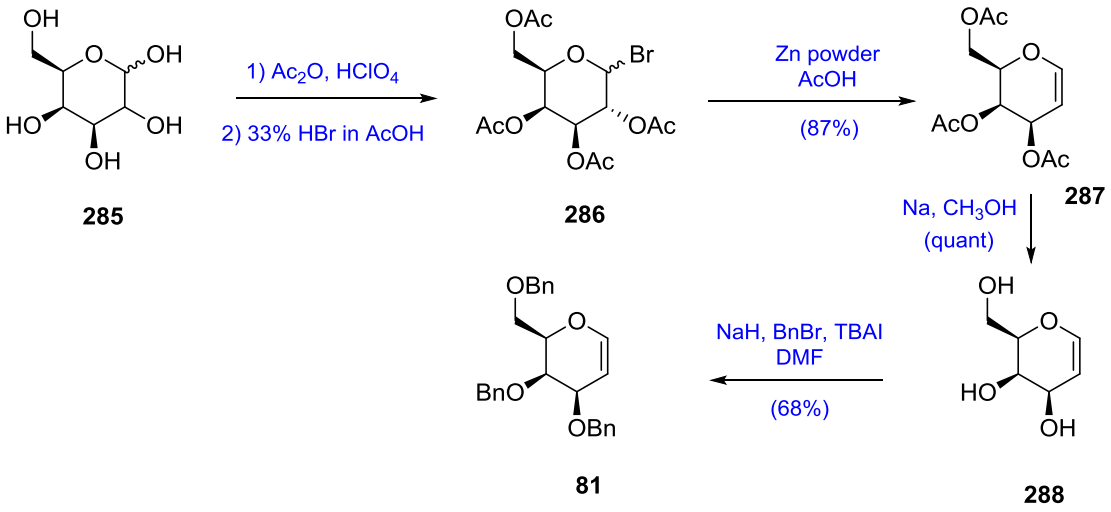


Scheme 3.4: Synthetic plan via 2-*C*-formyl glycal **136**

D-Galactose can serve as the source of many of the carbons of the target while sharing the configuration of (−)-TAN-2483B at C6 and C7. Tribenzylated galactal **81** was reported as a virtuous substrate for the V-H formylation as it is free of sensitive protecting groups.[44] The two- carbon unit of the five-membered lactone ring marked in red on **135** can be revealed by 1,4-addition of a vinyl nucleophile. Metal-catalysed intramolecular acyloxylation would accomplish the formation of the furo[3,4-*b*]pyran ring system in a facile manner as proposed by Yang *et al.* (see Section 1.8.3).[43a] Finally, PMB deprotection of **133** followed by oxidation would provide the essential functionality for the olefination, which leads to the *E*-propenyl side arm of the natural product (−)-TAN-2483B.

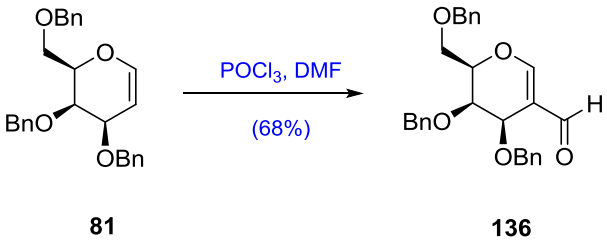
3.2 Synthesis of formylated glycal 136

The synthetic venture began with D-galactose (**285**), a readily available sugar with good precedence for V-H formylation, as demonstrated by Ramesh.[44, 91] Conversion of D-galactose to D-galactal **288** involved the five-step sequence pioneered by Kozikowski, which began with the peracetylation of D-galactose using acetic anhydride and catalytic perchloric acid (Scheme 3.5).[92] Bromoglycoside **286** was obtained by reaction of the peracetate with HBr in acetic acid. Compound **286** was then dissolved in diethyl ether and reacted with zinc dust in the presence of aqueous acetic acid to provide tri-*O*-acetyl-D-galactal (**287**) in 87% over three steps. D-Galactal was revealed by removing all acetyl groups with a catalytic amount of sodium metal in methanol. Finally, D-galactal (**288**) was perbenzylated upon treatment with excess sodium hydride in the presence of benzyl bromide to obtain **81**.



Scheme 3.5: Synthesis of benzylated-galactal **81**

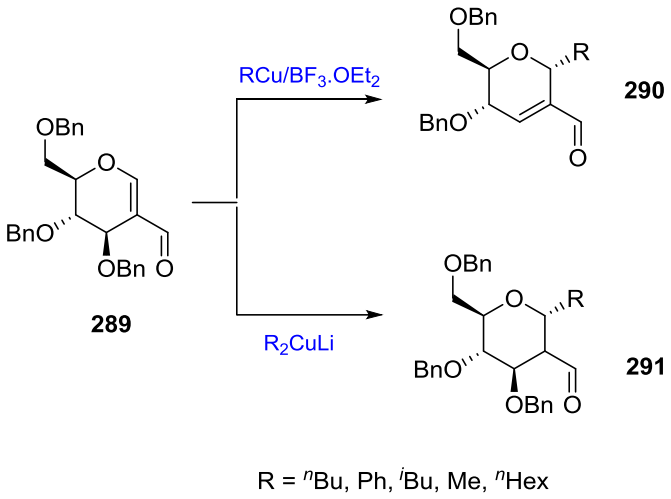
With tri-*O*-benzylated galactal (**81**) in hand, the 2-*C*-formylation was tried by addition of **81** to the pre-mixed solution of phosphorous oxychloride in DMF at 0 °C (Scheme 3.6). 2-*C*-Formylated galactal **136** was obtained in 62% yield after overnight stirring at room temperature.



Scheme 3.6: 2-*C*-Formylation of tri-*O*-benzylated galactal (**136**)

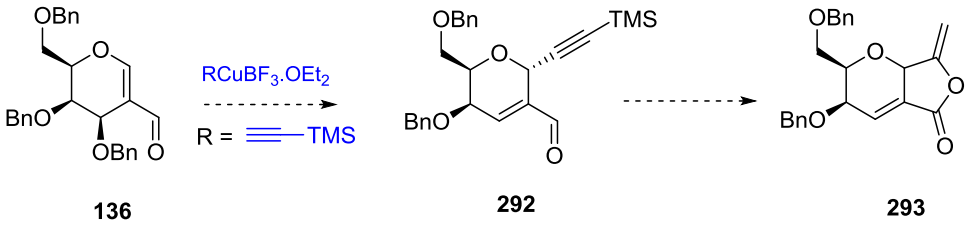
3.3 Attempted two-carbon unit installation to the 2-*C*-formylated galactal 136

With the 2-*C*-formylated galactal in hand, the synthetic ventures to install the two-carbon unit of the five-membered lactone ring began. According to the synthetic plan, 1,4-nucleophilic addition was explored with compound **136**. Cossy *et al*. reported synthesis of *C*-glycosides stereoselectively from 2-*C*-formyl glycal by nucleophilic addition of alkylcopper reagents (RCu) in the presence of $BF_3.OEt_2$ (S_N2 reaction) or by nucleophilic addition of lithium dialkylcuprates (1,4-addition) (Scheme 3.7).[93]



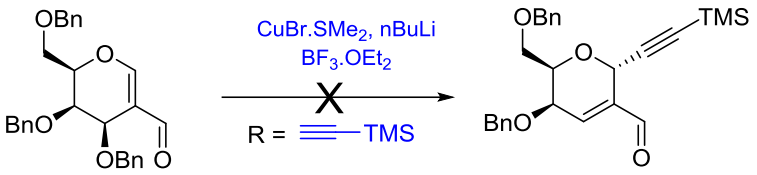
Scheme 3.7: Reported *C*-glycosidation with 2-*C*-Formylated glycal [93]

Formation of the *C*-glycoside **290** from formylated glycal **289** in the presence of $BF_3.OEt_2$, provides an ideal strategy to adapt for this research as it includes migration of the C1-C2 double bond via a Ferrier-type rearrangement. The yield and stereoselectivity are both good as α-glycosides were the only products obtained with all studied nucleophiles (Scheme 3.7).[93] In light of this precedence, installation of a TMS-alkyne was planned with the intention of cyclising with well-documented gold catalysis to reveal the furo[3,4-*b*]pyran ring system (Scheme 3.8).[43b]



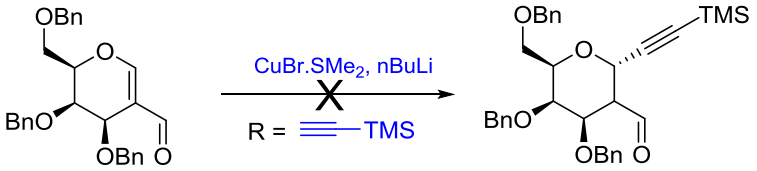
Scheme 3.8: Planned synthesis of furo[3,4-*b*]pyran ring system by *C*-glycosidation of 2-*C*-formylated galactal **136**

With this idea in mind, a reaction was performed with *in situ*-generated lithiated TMS alkyne together with $CuBr.SMe_2$ (Scheme 3.9). The premixed copper solution and lithiated TMS alkyne at -78 °C was treated with $BF_3.OEt_2$ followed by 2-*C*-formylated glycal **136**. Unfortunately, no reaction was observed even after warming to room temperature for three hours.



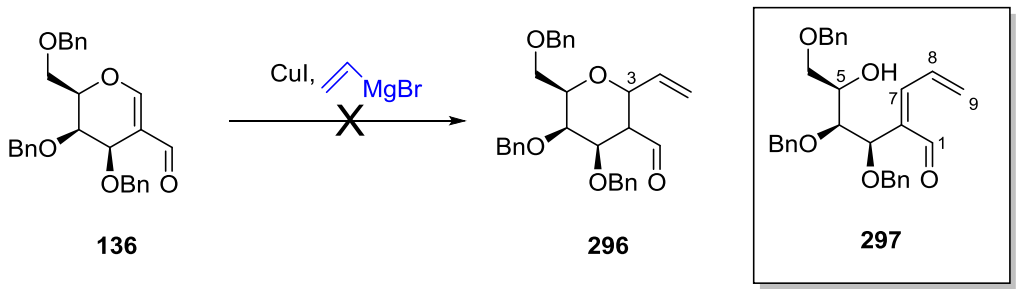
Scheme 3.9: Attempted *C*-glycosidation reaction with TMS alkyne

The reaction was repeated according to the literature procedure, without activation of the glycal by Lewis acid (Scheme 3.10). Unfortunately the desired 1,4-adduct **295** was not observed. The reason for the lack of reactivity may be the use of unprecedented alkynes as nucleophiles, which may be more prone to complexation with the metals used in the reaction.



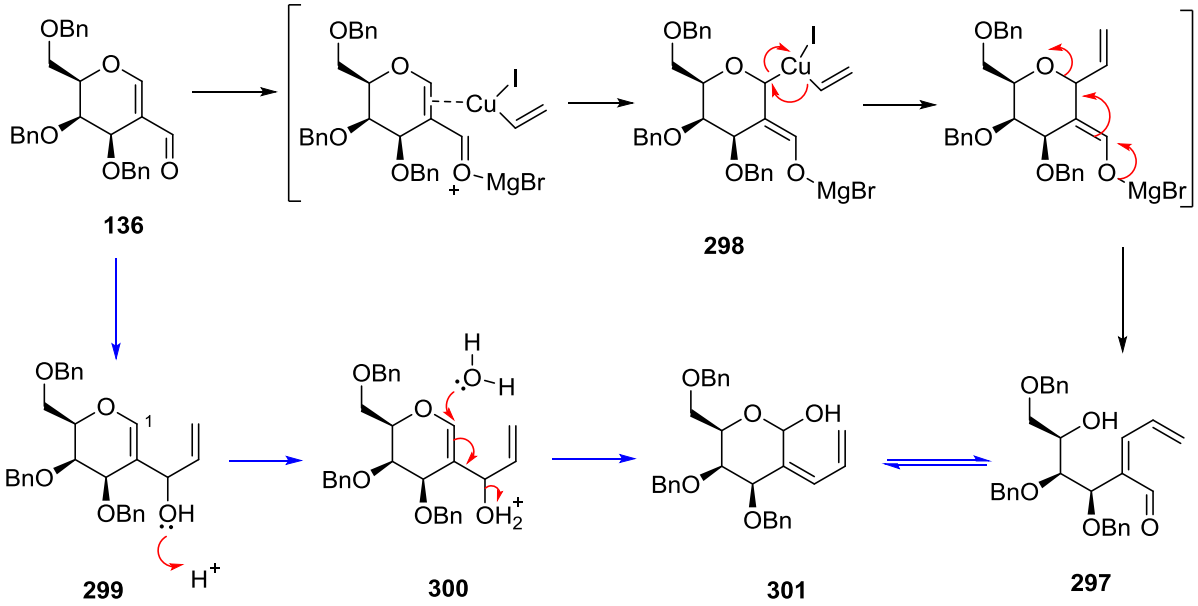
Scheme 3.10: Attempted 1,4-addition of TMS alkyne to 2-*C*-formylated glycal **136**

In a subsequent reaction, a classical 1,4-addition was tried with vinyl magnesium bromide in the presence of CuI. Vinyl magnesium bromide was reacted with a solution of CuI and formylated glycal **136** at -78 °C (Scheme 3.11). The reaction was completed within two hours by TLC analysis. Unfortunately, the most diagnostic ^{1}H-NMR peak of the desired product **296** for H3 (around 5.1 ppm) was not apparent in the isolated product, which reflected that the isolated product was not the expected 1,4-adduct **296**. Instead a characteristic diene system was identified whereby H7, H8 and H9 were confirmed by the COSY and HMBC correlations. The structure of this compound was characterised as ring-opened dienal **297** by further analysis of spectroscopic data.



Scheme 3.11: Attempted 1,4-addition with vinyl magnesium bromide

The compound **297** can be formed by the desired 1,4-addition of vinyl copper iodide complex to **136** as mentioned in Scheme 3.12. Reductive elimination of CuI established the more stable, extended conjugated dienal system of **297** (Scheme 3.12). On the other hand, the compound **297** could be obtained through the 1,2-addition of vinyl magnesium bromide followed by isomerisation of the unconjugated diene **299** in the work-up to **297** (blue route-Scheme 3.12). The second mechanism is more unlikely in the presence of CuI.



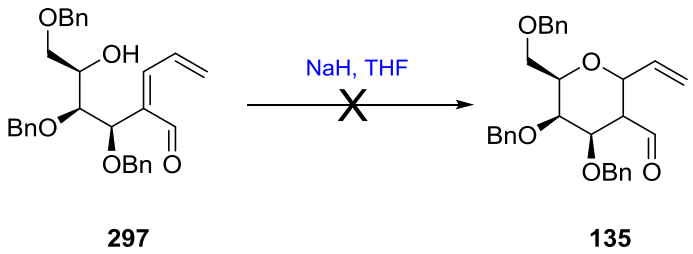
Scheme 3.12: Plausible mechanism for the formation of **297**

In a subsequent reaction, strictly anhydrous conditions were assured by using dry solvents and flame-dried glassware. Further aqueous work-up with NH_4Cl was avoided. The crude reaction mixture was passed through Celite® and ^{1}H-NMR spectroscopy was performed with neutralised $CDCl_3$ solution with potassium carbonate. The same acyclic dienal compound **297** with a characteristic aldehyde peak (9.46 ppm) was detected in the NMR spectrum of the crude mixture. These observations suggest that the 1,4-adduct **298** is more likely to be formed through the 1,4-addition in the presence of CuI. The reaction was repeated in the absence of CuI as a test case. Surprisingly, the same compound **297** was detected by proton NMR of the crude reaction mixture without any sign of formation of the 1,2-adduct. The proton signal for the C1 position in the 1,2-adduct should be characteristically different compared to the 1,4-adduct signal pattern in the alkene region. It is likely that 1,2-addition occurs under these conditions, therefore the second mechanism shown in Scheme 3.12, via **299**, may operate in this case to form the more stable conjugated compound **297**. Thus, it is presumed that the formation of highly stable dienal **297** can be expected under both conditions, in the presence and absence of CuI, possibly through different mechanisms.

3.3.1 *oxa*-Michael addition with compound 297

The addition of stabilised carbon nucleophiles to conjugated acceptor systems is commonly known as Michael addition.[94] The addition of an alcohol to a conjugate acceptor is known as an *oxa*-Michael addition. Major drawbacks of *oxa*-Michael reactions typically are the reversibility of the alcohol addition step as well as the relatively poor nucleophilicity of the employed alcohol. This renders intermolecular *oxa*-Michael reactions especially challenging.[94]

With the compound **297** in hand, an *oxa*-Michael reaction was attempted with NaH in an effort to make the desired cyclic product **135** (Scheme 2.13). The reaction was carried out at 0 °C but a degraded mixture of compounds was obtained. All attempts to this end were unsuccessful under different reaction conditions, even with the relatively mild base K_2CO_3.



297 **135**

Scheme 3.13: Attempted *oxa*-Michael addition of **297**

Although the full conjugated carbon skeleton of the target furo[3,4-*b*]pyran ring system was accomplished in a facile manner by the V-H reaction and conjugate addition, the author's attempts at intramolecular cyclisation via *oxa*-Michael addition with this highly conjugated system was not successful. Hence, the synthesis of furo[3,4-*b*]pyran ring system via V-H formylation followed by 1,4-addition was abandoned.

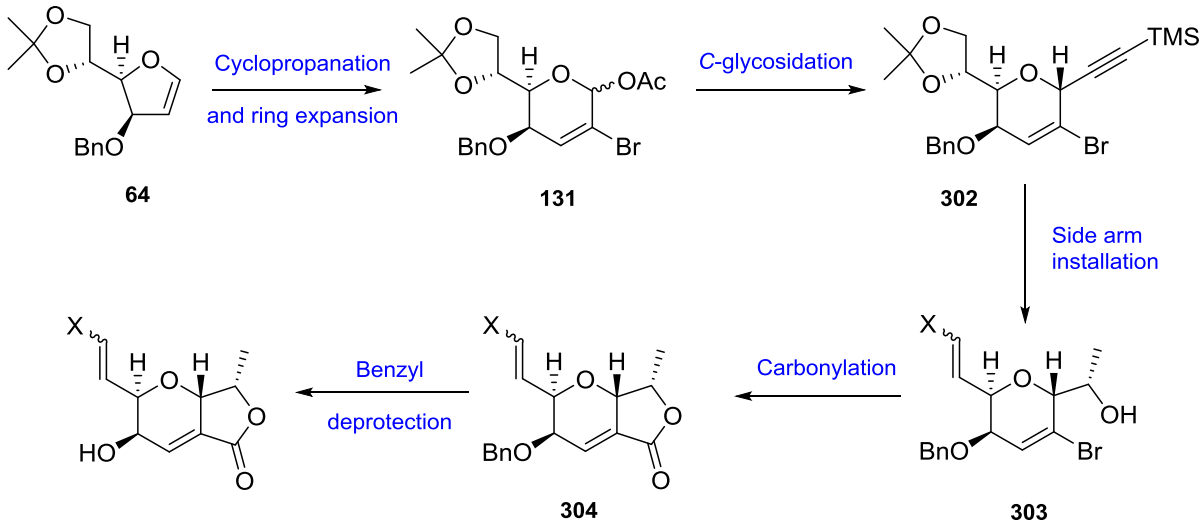
3.4 Conclusion

Synthesis of the carbon skeleton of the furo[3,4-*b*]pyran ring was accomplished via 1,4-addition with 2-*C*-formylated galactal. Conditions for both 1,4- and 1,2-addition to the V-H product **136** were tested. Both conditions were found to lead to formation of the highly conjugated and stable compound **297**. Pyran ring cyclisation of **297** via *oxa*-Michael addition was unsuccessful. As a result of these difficulties, an alternative approach involving more reactive cyclopropyl carbohydrates was investigated in order to complete the synthesis of the furo[3,4-*b*]pyran ring system and the target natural product.

4 Dibromocyclopropane Approaches to (−)-TAN-2483B

4.1 Introduction

The unsuccessful attempts to synthesise the furo[3,4-*b*]pyran ring system via dichlorocyclopropane-derived intermediates **66/67** and Vilsmeier-Haack derived intermediate **136** were discussed in Chapters 2 and 3. The major challenge associated with the dichlorocyclopropane-based strategy was the lack of the reactivity of the chloroalkene, which failed to afford a γ-lactone by carbonylation or other methods. This chapter addresses the synthetic progress towards the natural product (−)-TAN-2483B and its analogues via the more reactive bromoalkene intermediate **131**. The main challenge in the formation of intermediate **131** is dibromocyclopropanation. The remainder of the synthesis would mirror that used with the chloroalkene intermediates (discussed in Chapter 2). The γ-lactone would be generated by the Lewis-acid mediated alkynylation of **131** followed by oxymercuration (Scheme 4.1). Subsequent reduction of the resultant methyl ketone should reveal the required hydroxyl functionality for carbonylative lactonisation to complete the furo[3,4-*b*]pyran ring system. Additionally, functionalisation of the side arm would provide (−)-TAN-2483B and its side arm variants.

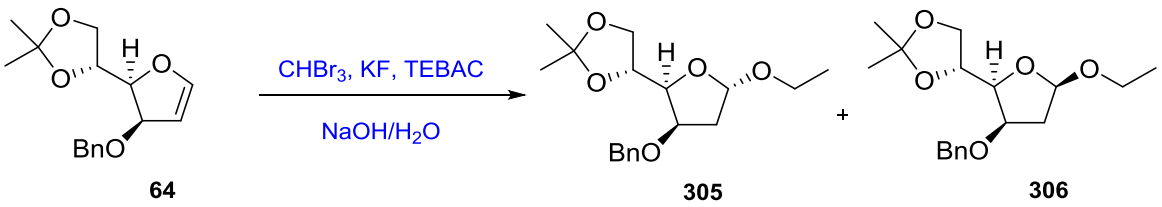


Scheme 4.1: Synthetic plan for the preparation of (−)-TAN-2483 and analogues via dibromo-cyclopropanation-ring expansion

4.2 Dibromocyclopropanation of benzylated glycal 64 and synthesis of bromoalkene 131

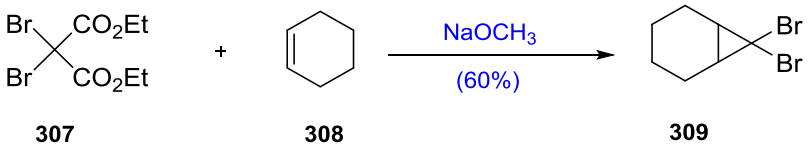
gem-Dibromocyclopropanes are more reactive than the corresponding *gem*-dichlorocyclopropane compounds, therefore *gem*-dibromocyclopropanes are very valuable substrates in organic sunthesis. The bromoalkene-based intermediate which results from the electrocyclic ring opening of the *gem*-dibromocyclopropane should be more reactive towards Pd-catalysed carbonylation than the chloroalkene. Similarly to dichlorocyclopropanation, the most convenient method to make dibromocyclopropanes is through addition of the dibromocarbene to an alkene. The base-induced α-elimination of hydrogen bromide from bromoform is the most common method of formation for dibromocarbene.[25, 29b]

Cyclopropanation of glycal **64** with dibromocarbene was attempted by Hewitt as described in his PhD thesis.[45] Dibromocyclopropanation under modified Mąkosza conditions using an excess amount of KF was unsuccessful and formation of the undesired isomeric ethyl glycosides **305** and **306** was reported (Scheme 4.2).[45] The ethyl glycosides were presumably formed by addition of ethanol (a stabiliser present in bromoform 1–3% v/v) to the glycal bond. Furthermore, the degradation of starting materials was observed when using distilled bromoform to avoid the formation of ethyl glycosides **305** and **306.**[45] These results prompted the exploration of non-aqueous methods for cyclopropane introduction.



Scheme 4.2: Reported ethyl glycosides **305** and **306** formed under modified Mąkosza cyclopropanation conditions[45]

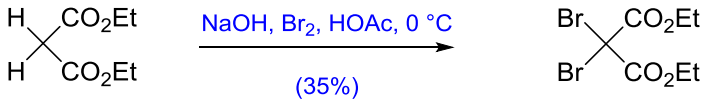
Mebane *et al*. reported a successful dibromocyclopropanation with diethyl dibromomalonate **307** and sodium methoxide,[95] whereby cyclohexene was converted to its ring-fused cyclopropane 7,7-dibromonorcarane (**309**) in 60% yield (Scheme 4.3).



307 308 309

Scheme 4.3: Reported dibromocyclopropanation with diethyl dibromomalonate[95]

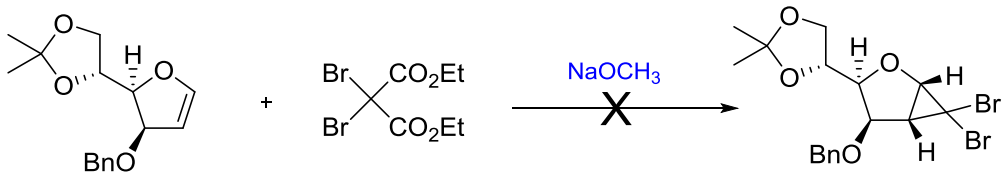
Diethyl dibromomalonate was prepared according to the literature procedure using Br_2, NaOH and diethyl malonate (**310**) (Scheme 4.4).[96]



310 307

Scheme 4.4: Synthesis of **307** from diethyl malonate (**310**)

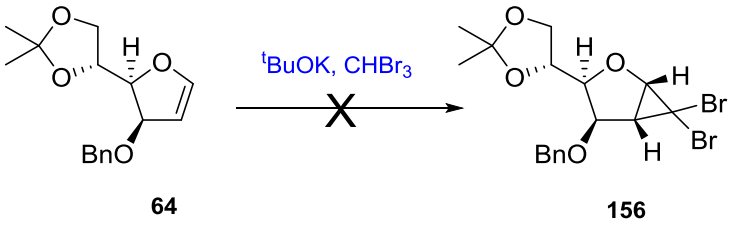
The reported methodology was applied to dibromocyclopropanation of the benzylated glycal **64** (Scheme 4.5). Freshly prepared diethyl dibromomalonate (**307**) was reacted with glycal **64** in the presence of $NaOCH_3$. However, starting material **64** was recovered after two days of stirring at room temperature.



64 307 156

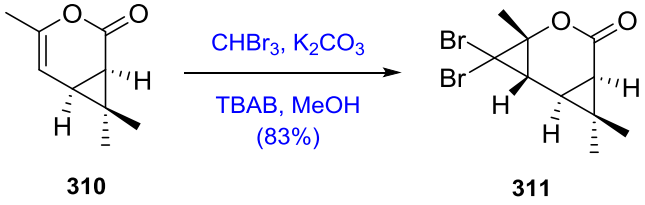
Scheme 4.5: Attempted dibromocyclopropanation with diethyl dibromomalonate **307**

In 2010, another group reported a method of generating dibromocarbene by treatment of the bromoform with potassium *tert*-butoxide and reacting it with the corresponding alkene source at room temperature to make dibromocyclopropane.[97] The same procedure was repeated with glycal **64** using freshly prepared potassium *tert*-butoxide and distilled bromoform (Scheme 4.6). Unfortunately, the glycal **64** was recovered after stirring overnight at room temperature. The temperature was then increased to 68 °C (THF reflux) on the next attempt. However, starting materials degraded into a complex tar-like mixture under these conditions. The glycal substrate **64** may therefore not be compatible with strong bases such as potassium *tert*-butoxide at elevated temperatures.



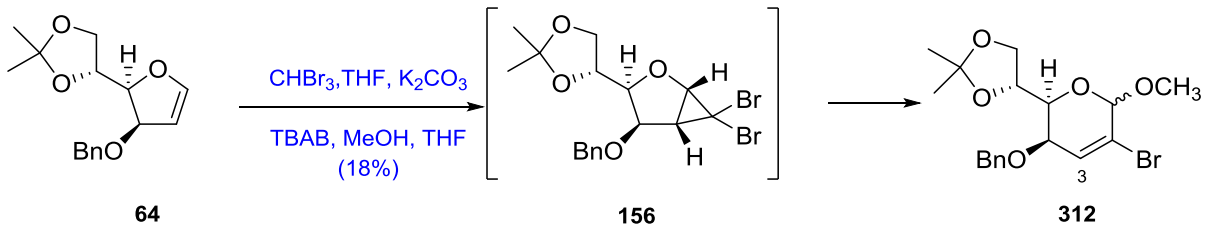
Scheme 4.6: Attempted dibromocyclopropanation of **64** with ^{t}BuOK

In 2007, a group of Russian chemists successfully performed a cyclopropanation reaction with the weak base potassium carbonate in the presence of TBAB (*tetra*-butylammonium bromide) as a phase-transfer catalyst and traces of methanol in bromoform at reflux to obtain **311** in 83% yield (Scheme 4.7).[98]



Scheme 4.7: Reported dibromocyclopropanation with TBAB[98]

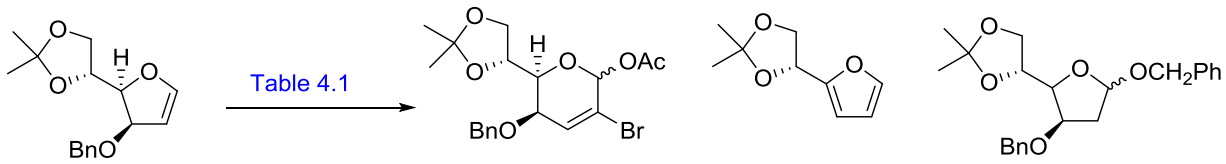
Encouraged by these results, a reaction was performed with glycal **64,** distilled bromoform in the presence of a few drops of methanol and THF as a co-solvent (Scheme 4.8). After 25 hours of refluxing in THF, a new TLC spot was observed below the starting material spot. The ^{1}H-NMR spectrum of the isolated compound showed a diagnostic doublet in the alkene region at 6.39 ppm which resembles the C3 alkene proton in a pyran ring. Furthermore a singlet at 4.89 ppm which displayed an HSQC correlation to a carbon signal at 98.6 ppm is characteristic for the anomeric centre. Then there was a prominent singlet at 3.47 ppm in the ^{1}H-NMR spectrum which is characteristic for the OMe group. Further evaluation of the 1D- and 2D-NMR experiment data led to identification of the isolated product as the methyl glycoside **312** (10:1 anomeric ratio). This was presumably formed by ring-expansion of the intermediate cyclopropane **156**. The higher reactivity of the *gem*-dibromocyclopropane moiety attached to the furan ring evidently results in spontaneous ring opening to make the pyran ring of **312**. It was pleasing to note that the isolated product **312** contains the required bromoalkene functionality to make the furo[3,4-*b*]pyran ring system. However, the methyl glycoside **312** was not the ideal substrate for subsequent transformation to form the acetylene glycoside.



64 **156** **312**

Scheme 4.8: Dibromocyclopropanation of **64** with K_2CO_3

This result stimulated us to carry on further investigation of this reaction. According to the research plan, the desired target was the acetate **131.** This would be obtained by trapping of the cyclopropane ring-expanded intermediate with acetate instead of methoxide. The reaction was adapted to include sodium acetate instead of methanol (Scheme 4.9 and Table 4.1). Gratifyingly, the expected acetate **131** was obtained in 21% yield (4:1 anomeric ratio) along with a series of by-products and starting materials (Table 4.1, entry 1).



64 **131** **154** **313**

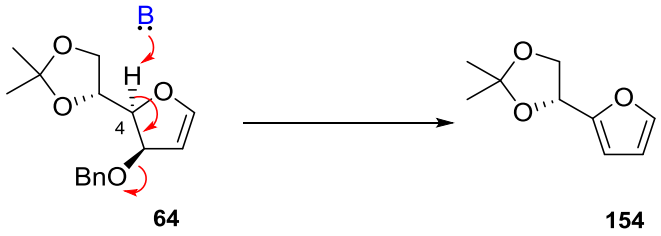
Scheme 4.9: Dibromocyclopropanation and ring expansion of benzylated glycal **64** with NaOAc

Entry	Solvent	Reagents eq: (TBAB : K_2CO_3: NaOAc: 18-C-6)	Product combination
1	$CHBr_3$: THF[a,b]	0.1:6:2:0	21% **131**, 11% **154**, 8% **313** and **64**
2	$CHBr_3$: THF[a,b]	0.1:6:2:0.1	27% **131** and **64**
3	$CHBr_3$[c]	0.1:6:2:0.1	47% **131** and **64**

[a] $CHBr_3$: THF volume ratio is 1:1, [b] 62 °C, overnight, [c] 82 °C, two days

Table 4.1: Table of optimisation for preparation of the acetate **131**

The furan **154** was not an unknown compound in this project as it was observed before in purification of benzylated glycal **64** obtained from the sodium naphthalenide reaction (see section 2.2)**.** The furan **154** might be formed by base-mediated elimination of the proton at C4 and loss of the benzyloxy group (Scheme 4.10).



Scheme 4.10: Base-mediated elimination of benzyl alcohol in the formation of by-product **154**

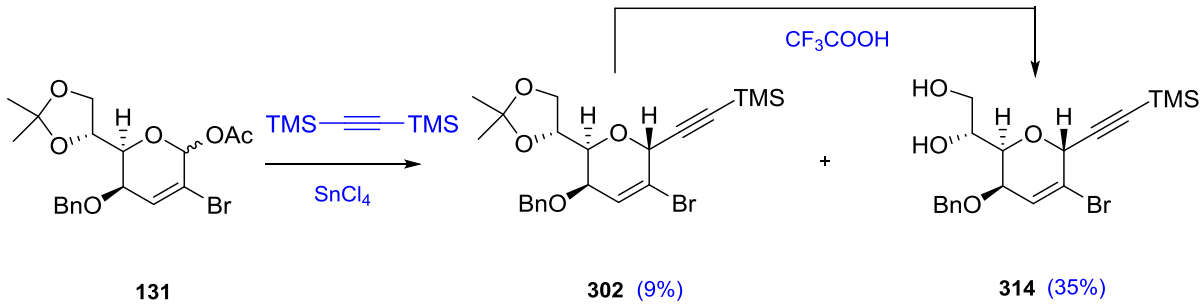
The eliminated benzyl alcohol presumably reacted with the starting material glycal **64** to make benzyl glycoside **313**. A similar kind of glycoside formation was observed by Hewitt in the presence of a trace amount of ethanol in the reaction mixture during the attempt to dibromocyclopropane **64** under Mąkosza conditions (see Scheme 4.2).[45]

18-Crown-6 was then included in the reaction mixture to capture the potassium in order to enhance the basicity and solubility of potassium carbonate (entry 2). No significant improvement in yield of the desired acetate **131** was observed; nevertheless, degradation of starting materials into undesired furan **154** and glycosides **313** was less evident. The yield of the desired product **131** was doubled by heating in neat bromoform at 85–90 °C for two days (entry 3). Still the reaction was sluggish and the maximum yield obtained was 47%. Nonetheless, recovered starting material could be subjected to repeated reaction to increase the crop of the desired acetate **131**. Vigorous stirring was required in order to provide adequate mixing of the solid reagents, which were relatively insoluble despite the phase transfer catalyst and 18-crown-6. Further optimisation was not pursued as the material in hand was sufficient to proceed further with exploration of the chemistry.

4.3 Formation of furo[3,4-*b*]pyran bicycle containing (−)-TAN-2483B *Z*-and *E*-unsaturated ethyl esters 140 and 141

Chapter 2 elaborated various methods to realise the lactone ring of the natural product by *C*-glycosidation with *bis*(trimethylsilyl)acetylene promoted by $SnCl_4$ in the chloroalkene series. The *C*-glycosidic alkyne route seemed to provide the greatest potential for synthesis of the bicyclic skeleton through a one-step Pd-catalysed carbonylative lactonisation. With the benefit of the background study on chloroalkenes discussed in chapter 2, a similar strategy was implemented in the work described in this chapter through the use of bromoalkene intermediate **131**.

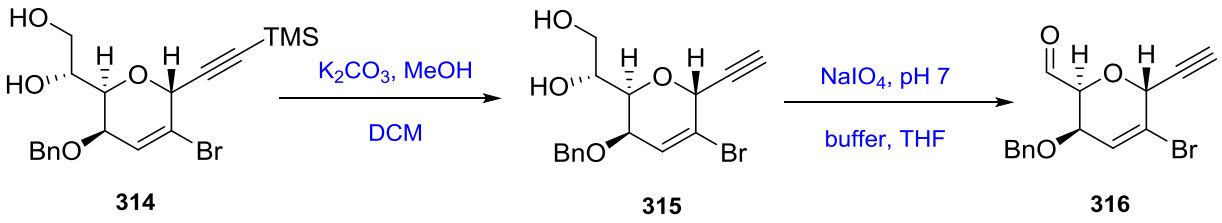
Vinyl bromide intermediate **131** was used in the $SnCl_4$ mediated alkynylation, but unfortunately at 0 °C the solution turned to a black colour upon addition of $SnCl_4$ to the mixture of acetate **131** and *bis*(trimethylsilyl)acetylene. ^{1}H-NMR data showed that reaction resulted in complete degradation. The reaction temperature was reduced to –78 °C in the next trial of the alkynylation reaction (Scheme 4.11). Gratifyingly, the acetonide-protected TMS alkyne **302** was obtained in 9% yield in addition to the diol **314** (35%), which resulted from Lewis acid-promoted hydrolysis of the desired product. The isopropylidene group was removed from the TMS alkyne **302** with TFA at 0 °C to afford TMS diol **314** in a combined yield of 44%. The anomers of the acetate **131** appeared to react at different rates; in one instance, the β-anomer of starting material **131** was isolated due to the partial completion of the TMS-alkynylation reaction. The configuration of the pseudoanomeric position in **314** was assumed at this stage to be the same as that for the analogous reaction of the chloroalkene. This was confirmed as described later in this section.



131 **302** (9%) **314** (35%)

Scheme 4.11: Synthesis of TMS alkyne diol **314**

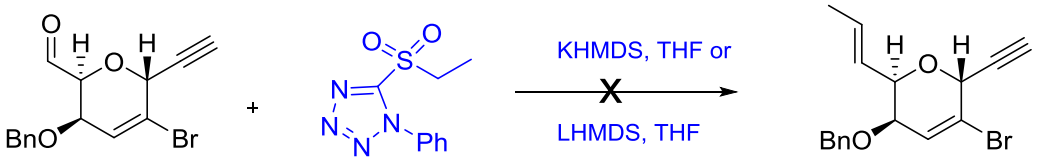
The TMS group of the diol **314** was cleaved with alcoholic K_2CO_3 in DCM to afford the terminal alkyne **315** in 94% yield (crude) without any degradation (Scheme 4.12). Gratifyingly, migration of the double bond in the pyran ring was less evident with this bromoalkene **314** than in the corresponding chloroalkene. Side arm installation was pursued before alkyne hydrolysis because the diol of **315** was not expected to be compatible with the oxymercuration conditions. Diol cleavage of **315** with $NaIO_4$ afforded the aldehyde **316** (62% crude yield) which could not be easily purified as it produces a streak and no distinct spot on the TLC plate was observed. However, the aldehyde **316** was recovered with adequate purity to carry out further transformations.



314 315 316

Scheme 4.12: Alkyne desilylation and diol cleavage to afford aldehyde **316**

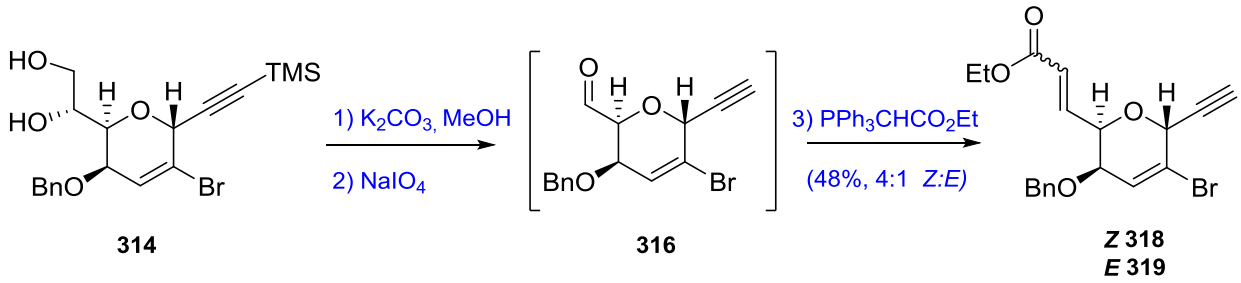
Julia-Kocienski olefination of aldehyde **316** would be the ideal route to install the desired side arm in a single reaction with high *trans*-selectivity. It was not successful with the chloroalkene **224** due to presence of base sensitive α-proton (see section 2.7.1); nevertheless, Julia-Kocienski olefination was attempted with the new aldehyde **316**. First, LHMDS was used as a base and THF as a solvent with tetrazole **225** (Scheme 4.13). Unfortunately, the reaction resulted in complete degradation as for the chloroalkene **224**. Changing the base for KHMDS didn't change the outcome of the Julia-Kocienski olefination. As a result, installation of a model side arm was explored. An ethyl ester-based model side arm was installed in the chloroalkene intermediate **224** using a stabilised phosphorous ylide (see Section 2.7.2). Installation of the same side arm would lead to synthesis of ethyl ester analogues of the natural product.



316 225 317

Scheme 4.13: Attempted Julia-Kocienski olefination of aldehyde **316**

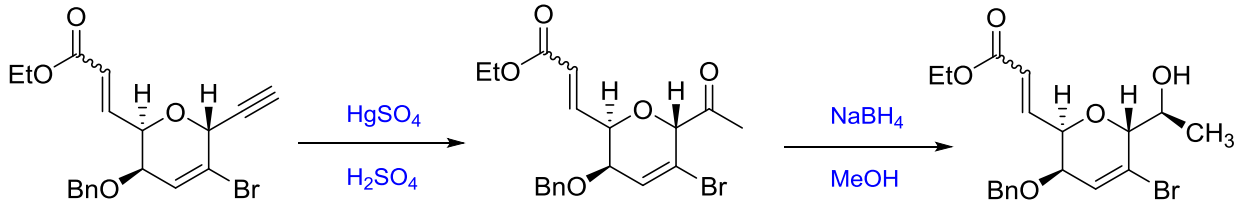
THF was found to be the best solvent for the stabilised Wittig olefination with the chloroalkene based aldehyde (see Section 2.7.2). A Wittig reaction was performed with the stabilised ylide ethyl triphenylphosphorane in THF and the crude aldehyde **316** obtained from the diol cleavage (Scheme 4.14). Pleasingly, *Z*- and *E*-ethyl esters **318** and **319** were obtained after silica gel column purification in a 48% combined yields as a separable 4:1 mixture of *Z*- and *E*-isomers, over three steps. The TMS deprotection, diol cleavage and olefination were carried out in a sequence without performing silica column purification. The Wittig reactions of α-alkoxyaldehydes with stabilised ylides can proceed with low *E*-selectivities as seen here.[73] The reason for the poor selectivity and exact solutions for the improvement of the *E*-selectivity are unknown.[74, 99]



314 **316** ***Z* 318** ***E* 319**

Scheme 4.14: Synthesis of *Z*- and *E*-esters from the diol **314**

With the *Z*- and *E*-ethyl esters **318** and **319** in hand, the key oxymercuration reactions of the alkyne moiety in each were tried. A catalytic amount of $HgSO_4$ was stirred with the major terminal alkyne **318** in a 1:1 (v/v) mixture of THF and 10% aqueous H_2SO_4 solution (Scheme 4.15). The methyl ketone **320** was obtained in 70% in yield. Similarly the reaction of *E*-isomer **319** afforded methyl ketone **321** in 61% yield. The next milestone was the reduction of the methyl ketone functionalites to the secondary alcohols **322** and **323** prior to the single step Pd-catalysed carbonylative lactonisation. The reducing agent $NaBH_4$ selectively reduces aldehydes, ketones and acid chlorides in the presence of esters. $NaBH_4$ reductions of both methyl ketones **320** and **321** were perfomed in methanol at -78 °C. The reductions were successful, with the alcohols **322** and **323** being formed as single isomers in excellent yields. Formation of a single isomer of the alcohol was pleasing and it must be due to substrate control in the methyl ketones **320** and **321**.



***Z* 318** ***E* 319** ***Z* 320** (70%) ***E* 321** (61%) ***Z* 322** (90%) ***E* 323** (91%)

Scheme 4.15: Synthesis of secondary alcohols **322** and **323** via oxymercuration of **320** and **321** followed by reduction

The Felkin-Ahn model is used to explain or predict the stereoselectivity of nuclophilic addition to a carbonyl group with an adjacent stereogenic centre. In the normal Felkin-Ahn model, a Newman projection of the transition state is drawn with the largest substituent (L) perpendicular to the C=O bond (Figure 4.1-a).[100] A nucleophile (Nu) will attack along the Bürgi-Dunitz trajectory passing the least sterically demanding (smallest = S) substituent. When an electronegative substituent is attached to the α-carbon the polar Felkin-Ahn model is considered. The reaction of a conformation

with most electronegative group perpendicular to the C=O bond should be considered (Figure 4.1-b). When the electronegative group is perpendicular to the C=O bond, partial overlap of the nucleophile HOMO and σ* orbital of the C-X bond occurs to favour this reactive conformation.[101]

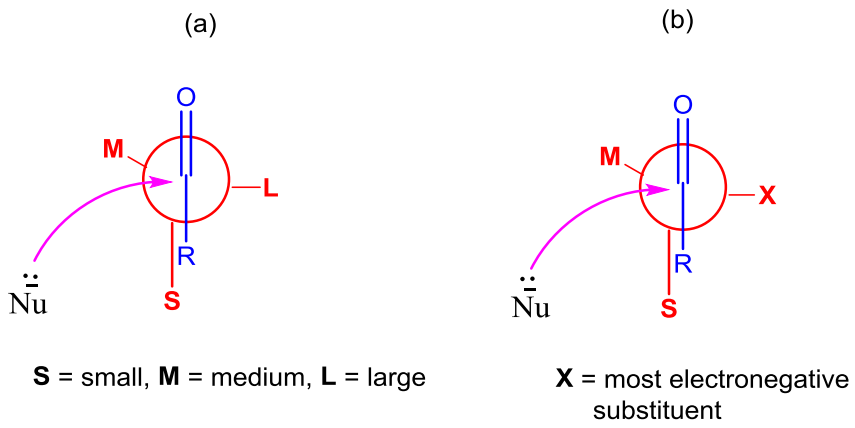
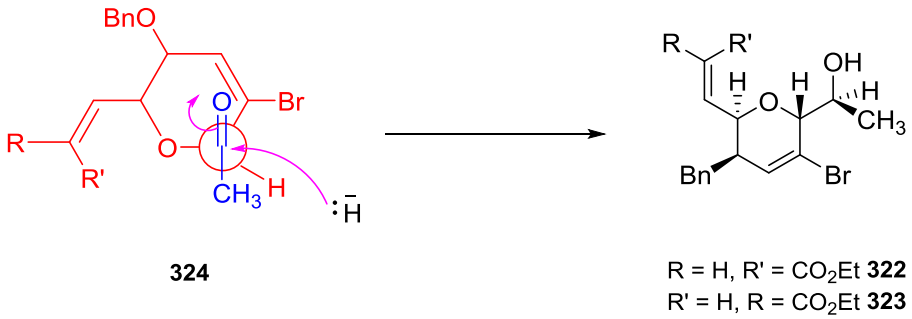


Figure 4.1: Newman projections of transition states for (a) normal Felkin-Ahn model and (b)polar Felkin-Ahn model

The polar Felkin-Ahn model is considered with the reduction of methyl ketones **320** and **321** due to the presence of the pyran ring oxygen at the α-position (Scheme 4.16). According to the polar Felkin-Ahn model, a nucleophile comes from the least hindered side; therefore the borohydride should attack from an angle near the anomeric proton **324** leading to the isomer observed**.** The stereochemistry of the remote side arm as well as the functionality present there is unlikely to affect the configuration generated at C2. As a consequence it was assumed that only the desired isomer was obtained from the $NaBH_4$ reductions of methyl ketones **320** and **321**. This was shown to be correct at the later stage (*vide infra*). The alcohols **322** and **323** contain the necessary functionalities for the single-step synthesis of the furo[3,4-*b*]pyran skeleton by Pd-catalysed carbonylative lactonisation.

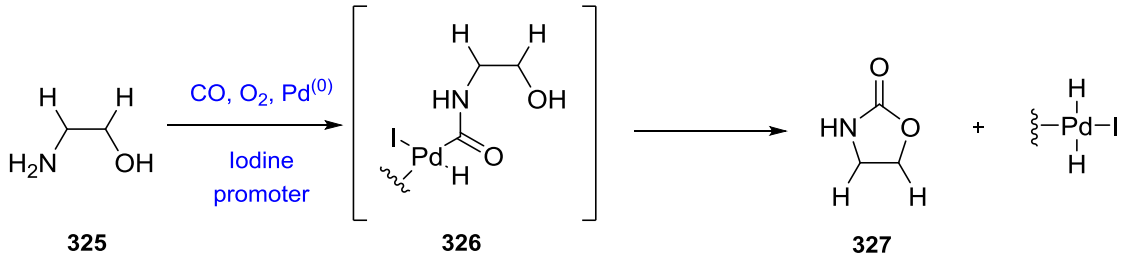


324

R = H, R' = CO_2Et **322**
R' = H, R = CO_2Et **323**

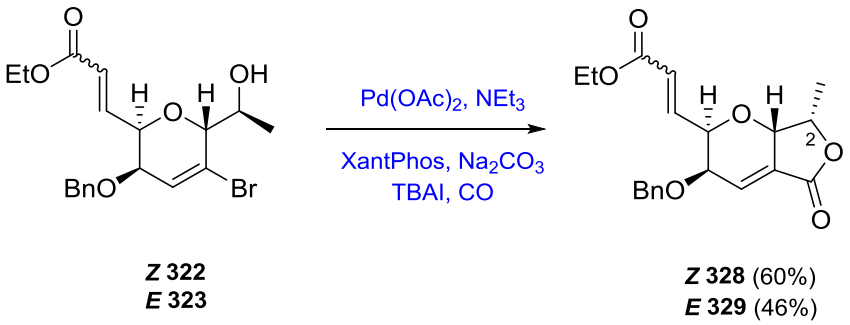
Scheme 4.16: Polar Felkin-Ahn model for the substrate-controled reduction of methyl ketones **320** and **321**

Iodine-based promoters in Pd-catalysed carbonylation of aminoalcohols have been reported in literature.[102] The exact function of the iodine-based activators on the catalytic efficiency on carbonylation is not clear, although it is expected that they participate in the formation of an active Pd-I species **326** in carbonylation with amine (Scheme 4.17).[102] A dramatic change in the yield of 2-oxazolidinone **327** was reported upon addition of I_2 as a promoter.[102] Later, TBAI was found to be the best additive in the alkoxy carbonylation of alkynes after screening of various iodide additives such as KI, TBAI and I_2.[81] Thus, TBAI was used as a promoter in the carbonylation of **322** and **323.**



Scheme 4.17: Palladium-catalysed carbonylation of aminoalcohol **325** with iodine promoter[102]

As described in the Chapter 2, XantPhos was the best ligand in Pd-catalysed carbonylation of diene **68** containing an alkenyl chloride. As a result, Pd-catalysed carbonylation was performed with the robust Pd precursor, $Pd(OAc)_2$, and XantPhos as a ligand in the presence of TBAI, triethylamine and sodium carbonate (Scheme 4.18). It was pleasing that the carbonylation reactions of both **322** and **323** were successful with the aforementioned catalyst system under a CO atmosphere (with a CO balloon) affording furopyrans **328** and **329** in good yields. Unfortunately, lack of time and the scarcity of materials prevented exploration of the necessity or effect of the additive TBAI in these carbonylation of **322** and **323** reactions.



Scheme 4.18: Pd-catalysed carbonylation of bromoalkenes **322** and **323**

At this stage, the stereochemistry of the C3 position of **328** was determined from an n*O*e experiment. The correlations between H3 and benzyl group demonstrated the correct configuration at C3 as the natural product. A strong correlation between H2 and H3 allowed (Figure 4.2) tentative

assignment of the sterogenic C2 centre as similar to the stereochemistry of natural product (−)-TAN-2483B. However this was not taken as proof because n*O*e correlation can be observed between vicinal protons that are *trans*-oriented. Nevertheless, there were a good agreement with the coupling constants between H1 and H2 of **328** with (−)-TAN-2483B acetate (**34a**) and 2-*epi*-TAN-2483B (**60**).

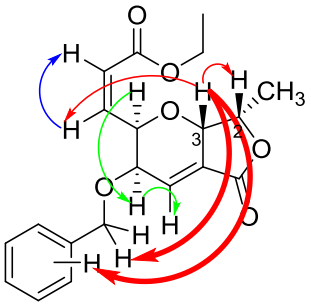
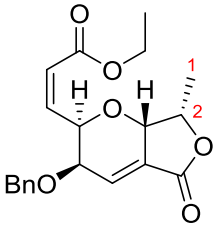
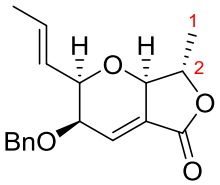


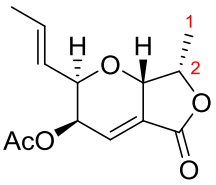
Figure 4.2: Observed n*O*e correlation of compound **328**



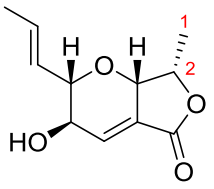
328



(-)-TAN-2483A (**33**)



(-)-TAN-2483B acetate (**34a**)



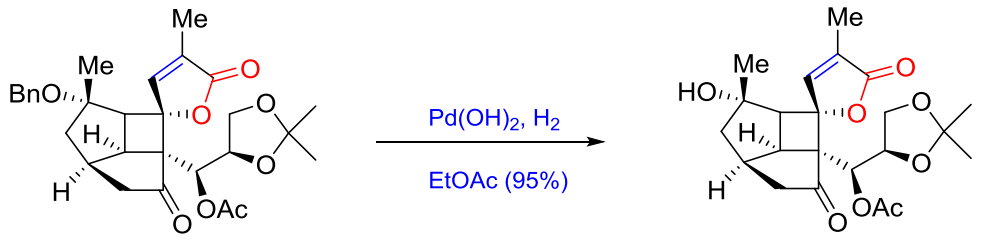
2-*epi*-TAN-2483B (**60**)

Compound	**H1**		**H2**	
	Chemical shift (ppm)	**Coupling constant (Hz)**	**Chemical shift (ppm)**	**Coupling constant (Hz)**
328	1.29	doublet (*J* = 6.7)	4.85	quintet (*J* = 6.8)
33[17]	1.56	doublet (*J* = 6.1)	4.34	dq (*J* = 7.3, 6.1)
34a[3]	1.34	doublet (*J* = 6.9)	4.68	quintet (*J* = 6.9)
60[17]	1.27	doublet (*J* = 6.9)	4.91	dq (*J* = 7.9, 6.7)

Table 4.2: Comparison of chemical shifts and coupling constants of compounds **328, 33, 34a** and **60**

The next crucial step in our retrosynthetic plan was the deprotection of the benzyl group in the presence of highly olefinic functionalities. Hydrogenolysis with Pd is the most popular debenzylation approach described in the literature. It is unlikely to be suitable with the substrates **328** and **329** due

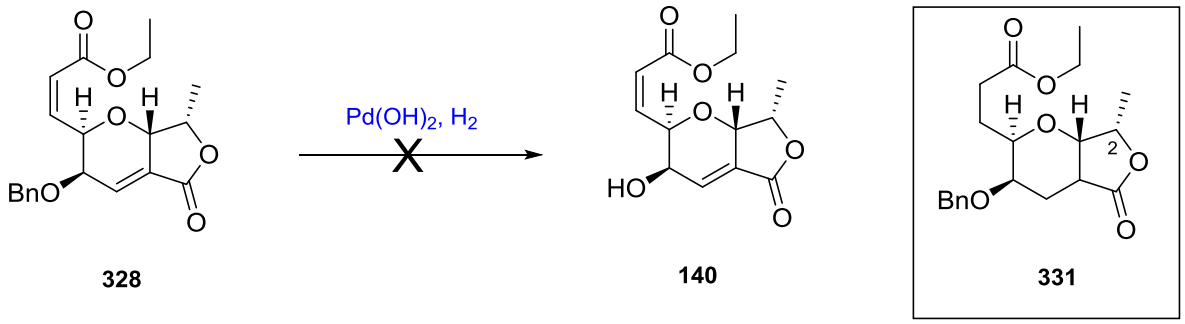
to the high tendency towards hydrogenation of the alkenes. Nevertheless, successful hydrogenolysis of a benzyl protecting group upon brief treatment with H_2 and Pearlman's catalyst was reported in the recent literature (Scheme 4.19). Hydrogenolysis of **330** was successfully carried out in approach to the synthesis of bielschowskysin. The substrate **330** contained similar functionalities to **328** and **329** such as ring unsaturation and lactone functionality.[103]



330 bielschowskysin

Scheme 4.19: Reported benzyl deprotection of **330** with H_2 and Pealman's catalyst[103]

Encouraged by the reported success, hydrogenolysis of **328** with $Pd(OH)_2$, Pearlman's catalyst, was attempted (Scheme 4.20). Unfortunately, the diene **328** was fully hydrogenated even with brief treatement (10 min) of hydrogen, which was bubbled through the solution containing **328**. The benzyl ether was retained in the product **331**. Even though the hydrogenated product **331** was not the desired compound, its formation was fortuitous because it allowed definitive determination of the stereochemistry at C2.

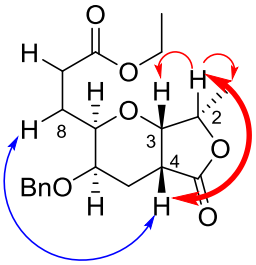


328 **140** **331**

Scheme 4.20: Hydrogenation of **328** with Pearlman's catalyst

Fully hydrogenated product **331** is a concave bicyclic lactone having *cis*-fused ring geometry (figure 4.3). The n*O*e correlation between H4 and H8 at the side chain confirms the *cis*-ring fusion of the furo[3,4-*b*]pyran (figure 4.4). Gratifyingly, the n*O*e correlations between H2 and the ring fused proton H4 confirmed that the orientation of the methyl group resembles that of the natural product (−)-TAN-2483B. The conformational preferences of the **331** were studied by molecular mechanics

measurements and the low-energy conformer appeared to have an orientation amenable to allow the observed n*O*e correlations.



331

Figure 4.3: Main n*O*e correlations in hydrogenated product **331**

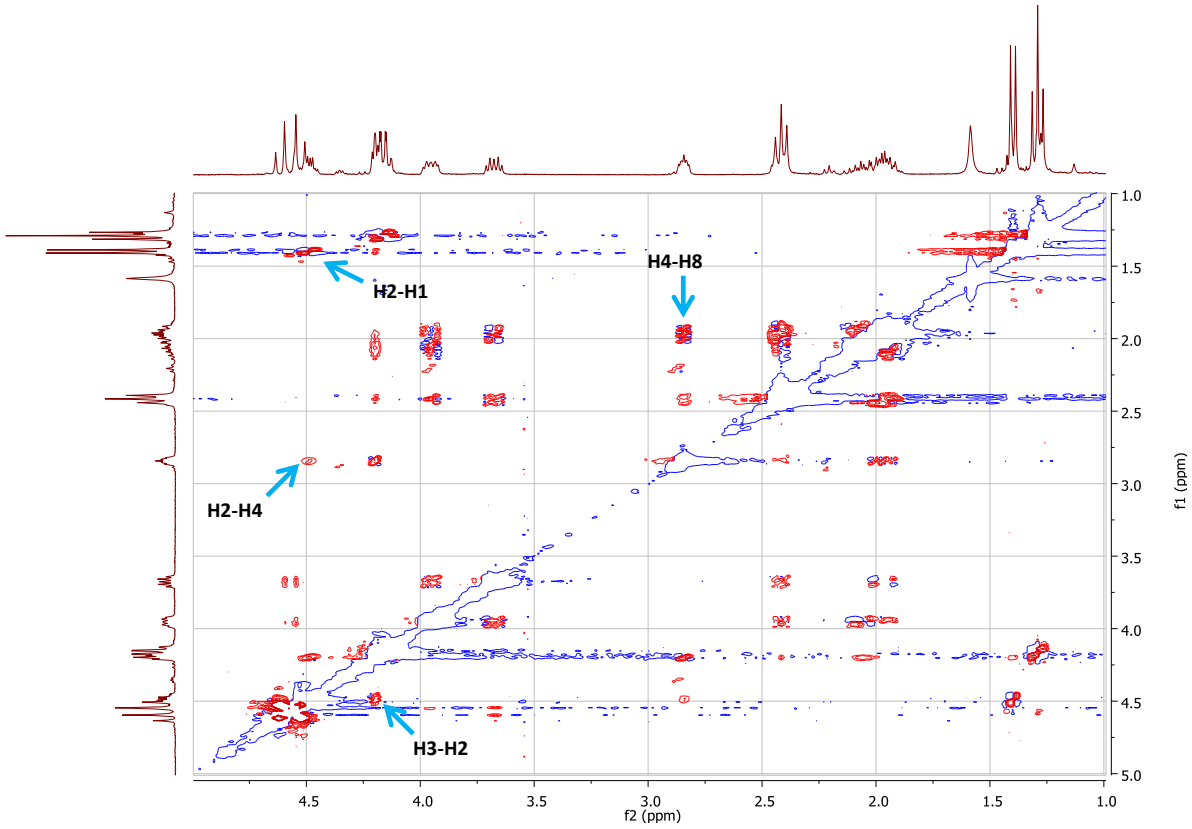
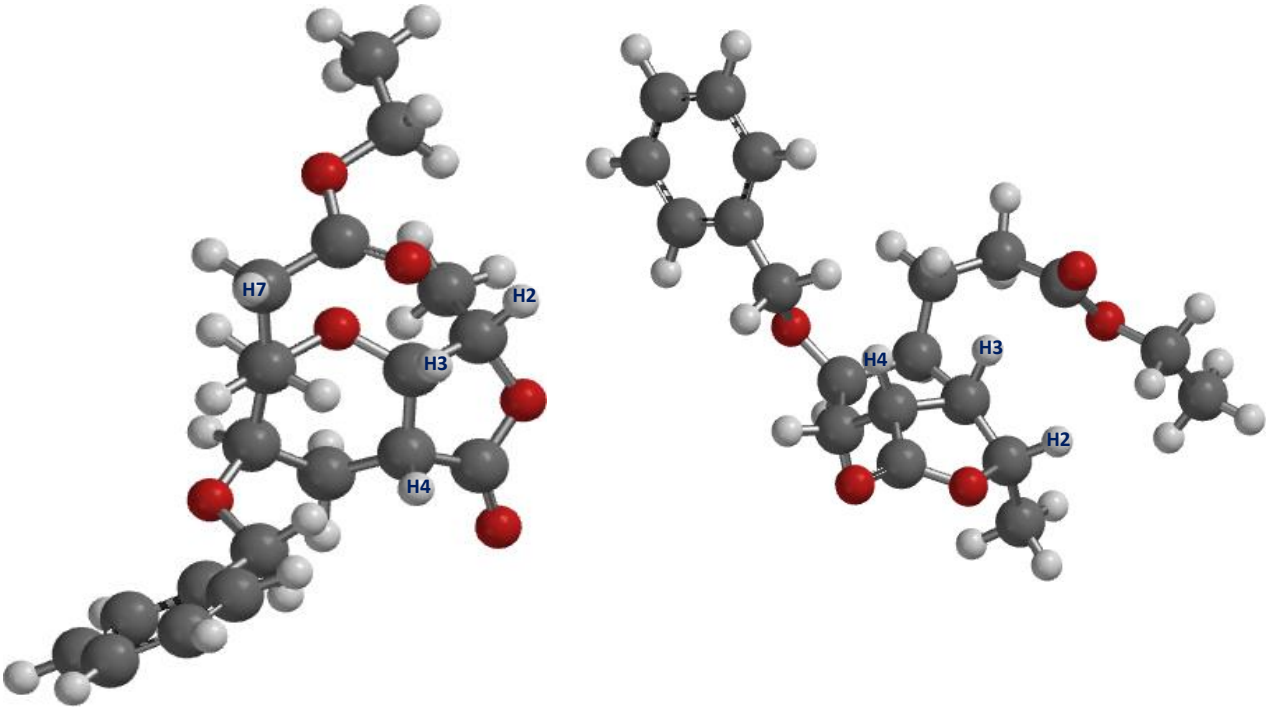


Figure 4.4: 2D-n*O*e spectrum of hydrogenated product **331** and key correlations (in $CDCl_3$, 300 MHz)

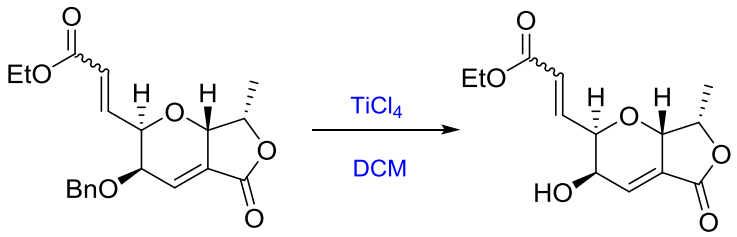


Hydrogenated ethyl ester **331** top view

Hydrogenated ethyl ester **331** side view

Figure 4.5: 3D-structure of hydrogenated product **331**[2]

Benzyl deprotection in substrates containing unsaturated double bonds has been successfully performed with strong Lewis acids like $TiCl_4$.[104] With this encouragement, lactones **328** and **329** were treated with $TiCl_4$ at 0 °C to remove the benzyl group (Scheme 4.21). Starting materials disappeared within 10 minutes of stirring under these conditions. Fortunately, the benzyl-deprotected products **140** and **141** were obtained in yields of 56% and 52%, respectively. These represent the *Z*- and *E*- ethyl ester analogues of (−)-TAN-2483B **140** and **141**



***Z* 328**
***E* 329**

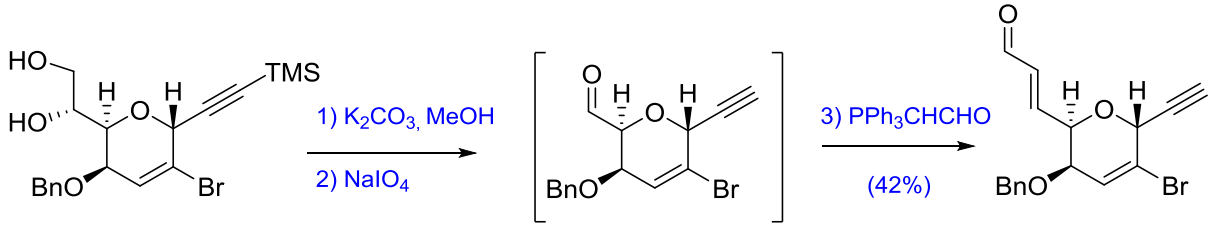
***Z* 140** (56%)
***E* 141** (52%)

Scheme 4.21: Benzyl deprotection with $TiCl_4$ to form *Z*-and *E*-(−)-TAN-2483B ethyl esters

[2] The minimised conformations shown in Figure 4.5 was generated by Spartan© '08, Version 1.2.0. The Merck Molecular Force Field (MMFF) was applied and provided the lowest energy conformer.

4.4 *E*-selective Wittig olefination of towards synthesis of 10-hydroxy(−)-TAN-2483B

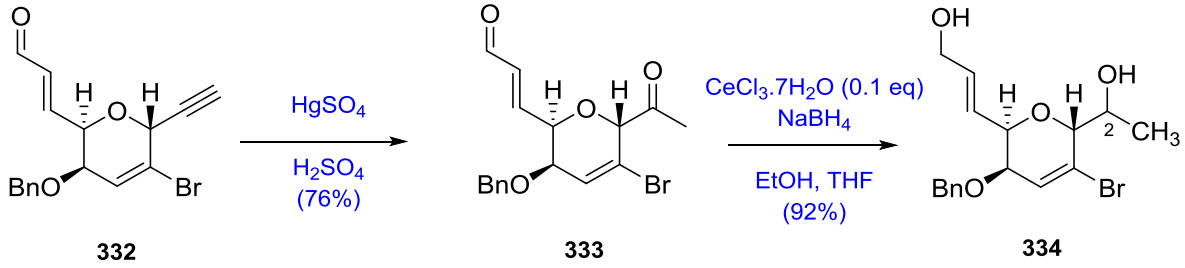
After the poor success with stereoselectivity of products from Wittig olefination of the stabilised ylide (ethoxycarbonylethylene)triphenylphosphoranes in different solvents (**see section 2.7.2**), the olefination was attempted with the alternative ylide (triphenylphosphoranylidene)acetaldehyde, which is commercially available. The reaction was performed in dry THF with the crude aldehyde **316** which was synthesised by $NaIO_4$ diol cleavage (Scheme 4.22). The *E*- isomer **332** was obtained exclusively, in moderately good yield (42%) over the three step reaction sequence from TMS diol **314**.



314 **316** **332**

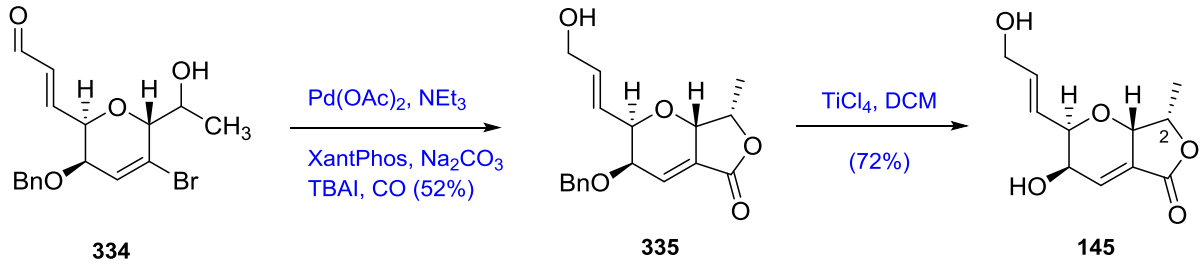
Scheme 4.22: *E*-selective Wittig olefination of **332** with (triphenylphosphoranylidene)acetaldehyde

Then, the terminal alkyne **332** was subjected to oxymercuration to obtain methyl ketone **333** in 76% yield (Scheme 4.23). Luche reduction in the presence of $CeCl_3$ with $NaBH_4$ gives very selective 1,2-reduction of conjugated aldehydes and ketones by coordination between carbonyl and cerium. This effect results in increased hardness and more δ+ character at the carbonyl making it more reactive towards the borohydride. Further, borohydride can be made harder by the replacement of some hydride ligands with alkoxy groups so that high 1,2-selectivity will be expected. Methyl ketone reduction and the conjugated aldehyde reduction were achieved concomitantly under the Luche reduction conditions in the presence of a catalytic amount (0.1 eq) of $CeCl_3.7H_2O$ (Scheme 4.23).[105] The reaction was completed within two hours at -78 °C without any apparent side reactions. However, a significant loss in yield (26%) was observed in this step when an aqueous work-up was conducted. In a subsequent reaction, the aqueous work-up was avoided and the excess borohydride was quenched with acetone and the mixture evaporated to dryness. The crude mixture was then introduced to the silica column and purification afforded diol **334** in 92% yield.



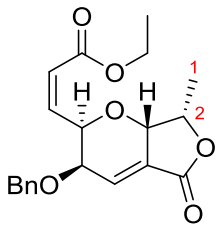
Scheme 4.23: Synthesis of diol **334** via oxymercuration of **333** followed by Luche reduction

The diol **334** was used for the synthesis of the furo[3,4-*b*]pyran ring system via Pd-catalysed carbonylation. The previously most successful catalyst system, XantPhos with $Pd(OAc)_2$,was used for the carbonylation (Scheme 4.24). The determination of reaction progress was difficult, because the starting material diol **334** and lactone **335** possess identical R_f values on silica gel TLC plate. As a result the reaction was carried out for 24 hours to ensure all the starting materials reacted. Moreover, a comparatively dilute reaction mixture was used to avoid intermolecular participation by the side-chain hydroxyl in carbonylation. Fortunately, under these conditions the lactone **335** was obtained with only trace amounts of recovered diol **334**. The product was used in the next reaction, hydrolysis of the benzyl group, with the intention of purifying the final product **145**. The Lewis acid-mediated benzyl deprotection was carried out at 0 °C in CH_2Cl_2 to afford 10-hydroxy-TAN-2483B (**145**). The crude reaction mixture was purified to obtain **145** as colourless oil in 72% yield.

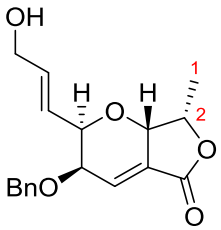


Scheme 4.24: Synthesis of 10-hydroxy-TAN-2483B (**145**) via benzylated lactone **335**

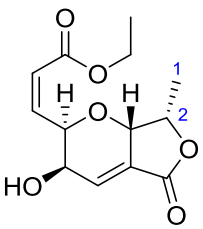
The configuration of the C2 position is taken to be the same as for ethyl ester **140,** which was determined by n*O*e (see Section 4.4). This was based on the similarity of chemical shifts and coupling constants (*J* values) for H1 and H2 (Table 4.2), together with the expectation that the stereoselectivity of the borohydride reduction of the methyl ketone would be unaltered by the identity of the remote side arm substituents. These values indicate that the C2 configuration of 10-hydroxy-TAN-2483B is same as that of the *Z*-ethyl ester (−)-TAN-2483B **140**.



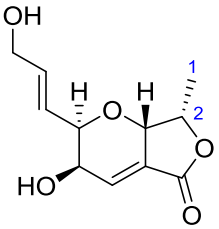
328



335



140



145

Compound	H1		H2	
	Chemical shift (ppm)	**Coupling constant (Hz)**	**Chemical shift (ppm)**	**Coupling constant (Hz)**
328	1.29	doublet (*J* = 6.7)	4.85	quintet (*J* = 6.8)
335	1.24	doublet (*J* = 6.4)	4.83	quintet (*J* = 6.8)
140	1.30	doublet (*J* = 6.4)	4.85	quintet (*J* = 6.8)
145	1.27	doublet (*J* = 6.6)	4.84	quintet (*J* = 6.8)

Table 4.3: Comparison of chemical shifts and coupling constants of compounds

328, 335, 140 and **145**

Further evidence for the desired configuration was able to obtained by an n*O*e experiment of 10-hydroxy-TAN-2483B (figure 4.6). A key correlation between H7 and H1 provided strong evidence in favour of the assigned configuration at C2.

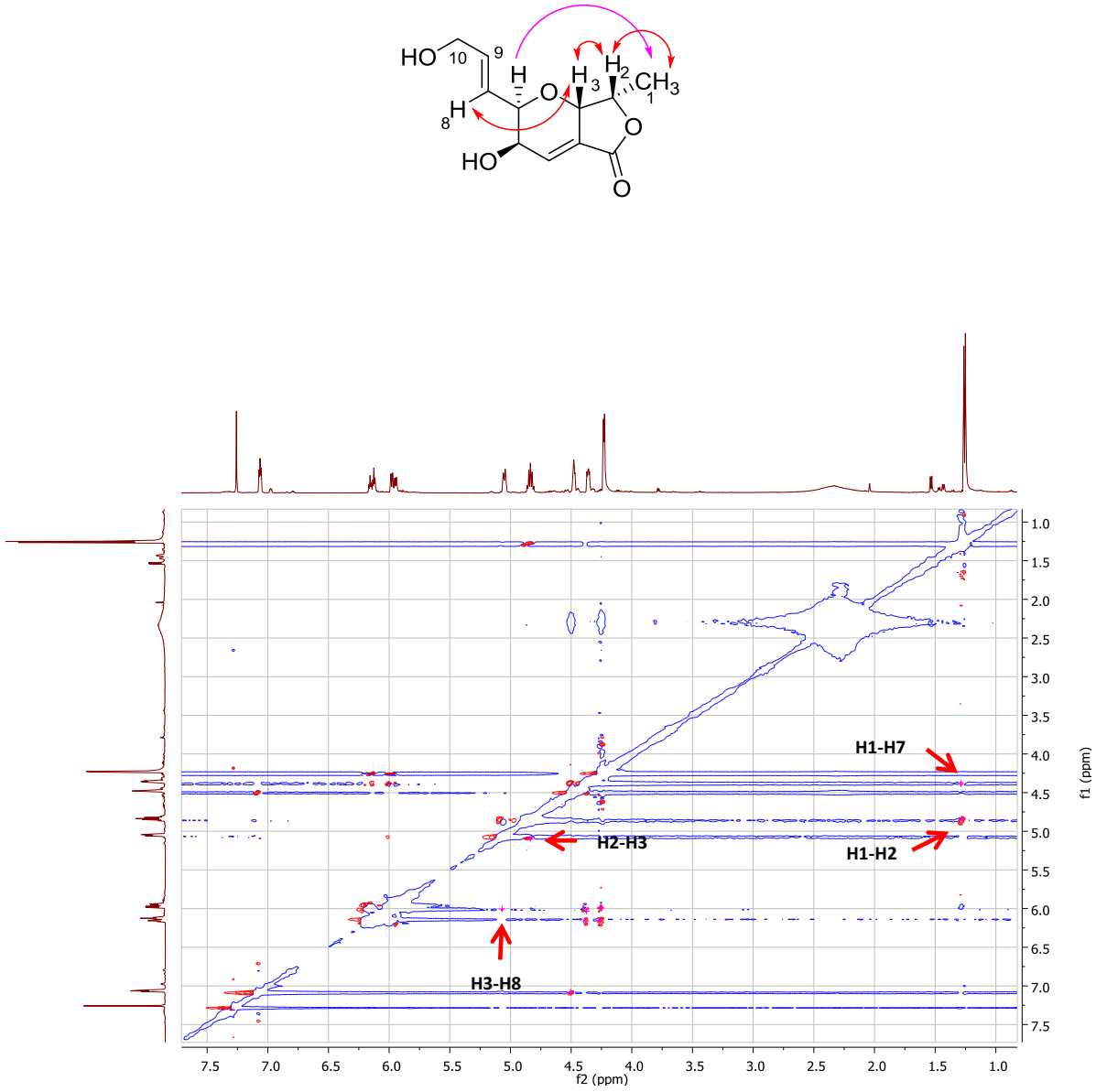
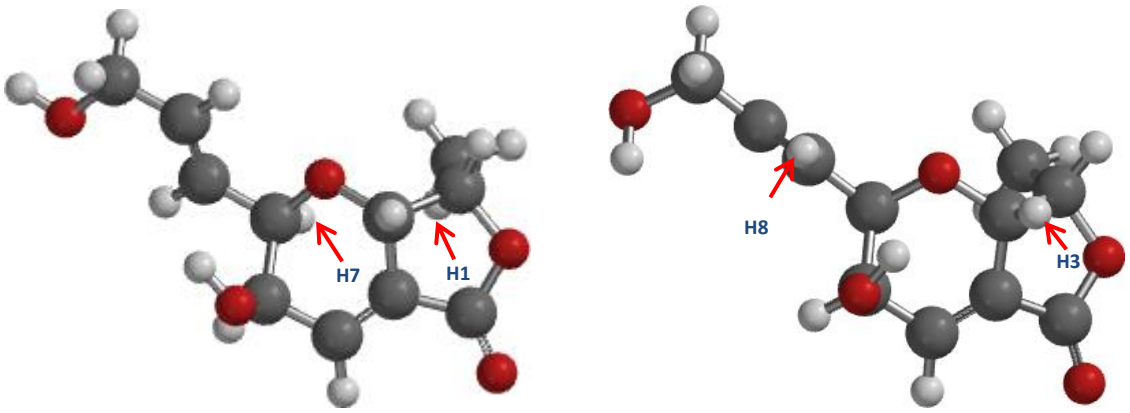


Figure 4.6: 2D-n*O*e spectrum of 10-hydroxy-TAN-2483B **145** (in $CDCl_3$, 300 MHz)

The likelihood of an n*O*e correlation between H1 and H7 protons is visualised promptly in the lowest energy conformer of 10-hydroxy-TAN-2483B (Figure 4.7). The correlation between H3 and H8 is not prominent enough in the lowest energy conformer. Nevertheless it can be expected from the 6th lowest energy conformer (+2.42 kJ/mol) in which the H3-H8 distance is 4.3 Å. The n*O*e correlations together with coupling constant similarities strongly suggest that the configuration at C2 of 10-hydroxy-TAN-2483B is the same as the configuration of the natural product.

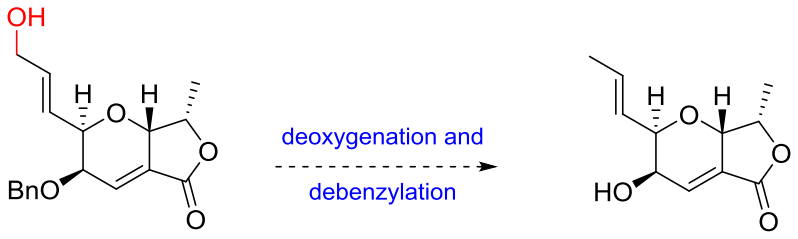


Lowest energy conformer of **145** 6th Lowest energy conformer of **145**

Figure 4.7: The 3D-structure of the 10-hydroxy-TAN-2483B[3]

4.5 Synthetic studies towards the total synthesis of (−)-TAN-2483B

According to Scheme 4.25, deoxygenation of the allylic alcohol **335** followed by debenzylation may reveal the target natural product (−)-TAN-2483B. In the quest for the total synthesis of (−)-TAN-2483B from 10-hydroxy-TAN-2483B, deoxygenation of the allylic alcohol side arm was explored with the advanced intermediate **335.**



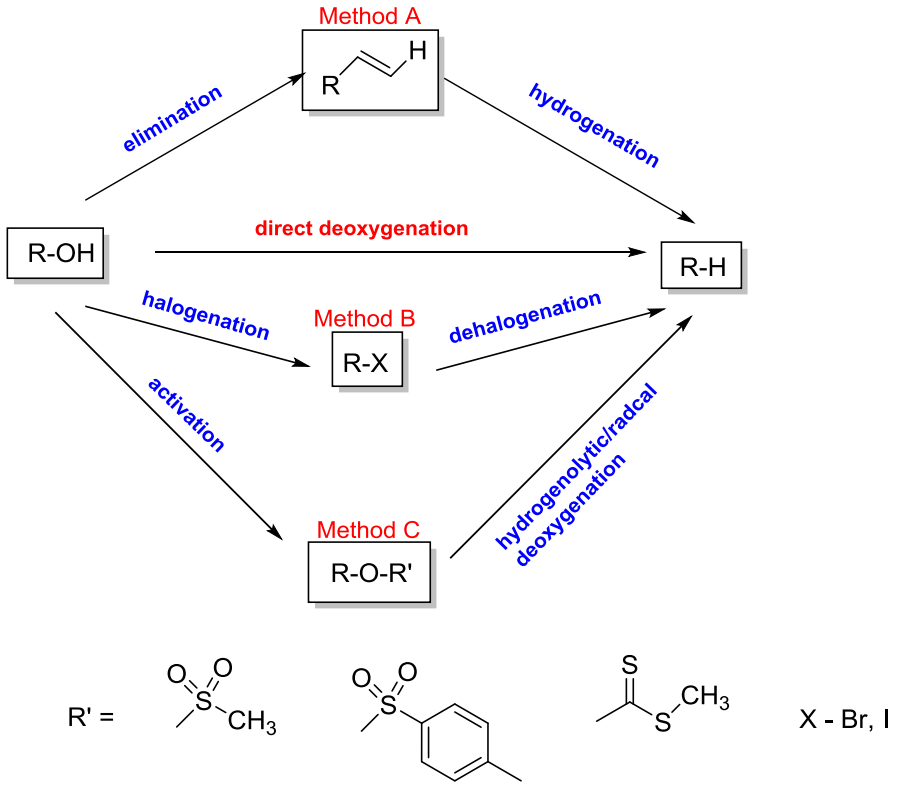
335 (-)-TAN-2483B

Scheme 4.25: Towards the total synthesis of (−)-TAN-2483B by deoxygenation of **335**

[3] The low energy conformer shown in Figure 4.7 were generated by Spartan© '08, Version 1.2.0. The Merck Molecular Force Field (MMFF) delivered a library of conformers. The 6th lowest energy conformer (+2.42 kJ/mol) had an orientation of the side chain that could explain the observation of the n*O*e correlation between H3-H8.

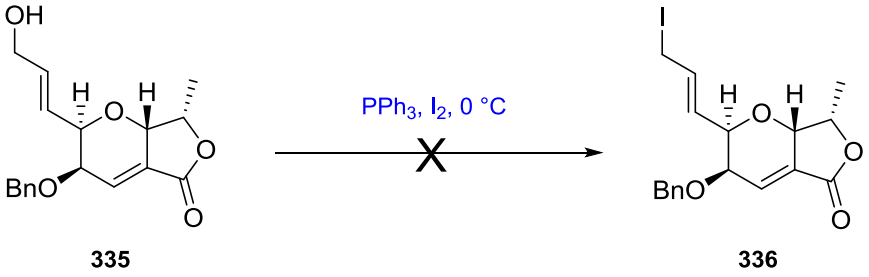
4.5.1 Deoxygenation of alcohol functionality in 335

The deoxygenation of alcohols is an important and rather broad area of research in modern organic chemistry.[106] Mostly nonselective methods are used to convert a mixture of carbohydrate-derived natural resources into biofuel, but organic chemists need more specific deoxygenation techniques which tolerate a variety of functional groups. Several pathways are available for deoxygenation of alcohols, including direct deoxygenation and two step procedures (Scheme 4.26). Direct deoxygenation methods involve hydrogenation with supported metals such as rhenium, platinum and palladium, and Lewis acid-mediated (e.g. $Ca(NTf_2)_2$ and $Bi(OTf)_2$) deoxygenation in the presence of hydride source (e.g. Et_3SiH). Direct deoxygenation methods are deemed to be unsuitable for deoxygenation of **335** due to the presence of lactone functionality and the richness of unsaturated double bonds. A variety of two-step procedures were considered for the deoxygenation of advanced intermediate **335** (Scheme 4.26). Method A involves elimination followed by hydrogenation of the resulting double bond. Dehydration and subsequent hydrogenation is popular in deoxygenation of biomass-derived carbohydrates to form alkene. Method A is unsuitable for the deoxygenation of **335** because the hydroxyl group is allylic and reduction of the newly formed double bond would be unselective. The next possibility is activation of the C-O bond by introducing a suitable leaving group through substitution of the alcohol followed by displacement with hydride source (methods B and C). A halogenation and dehalogenation sequence is the most commonly used protocol (method B). Alternatively, conversion into sufonates or xanthates followed by displacement by stannanes (Barton McCombie deoxygenation) or other hydride sources is a typical methodology used in deoxygenation of alcohols (method C).



Scheme 4.26: Reaction pathways for deoxygenation of alcohols

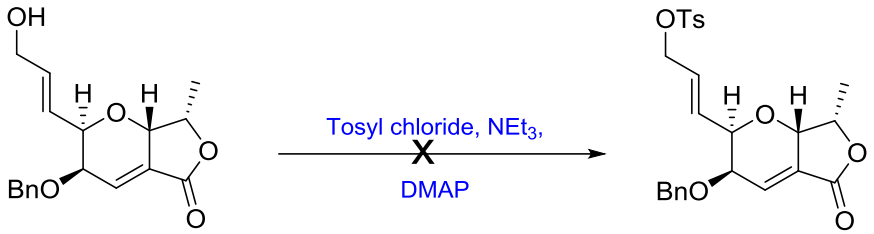
Halogenation and dehalogenation appeared to be most appropriate procedure according to the substrate features of **335**, as it avoids the use of strong bases. Synthesis of allylic iodide **336** from the lactone **335** would be followed by dehalogenation either by a suitable hydride source or a radical process. An experiment was performed using triphenylphosphine and iodine in CH_2Cl_2 at 0 °C (Scheme 4.27). No reaction was observed according to TLC analysis after stirring at room temperature for a prolonged time and starting material was obtained with good recovery. This might be in fact due to difficulty in observing the highly reactive allylic iodide **336** under the moist conditions of the TLC plate. The allylic iodide **336** could be hydrolysed back to the allylic alcohol during the work-up as well as by reacting with silica.



335 **336**

Scheme 4.27: Attempted iodination of allylic alcohol **335**

Installation of a tosyl group was investigated with lactone **335** with the intention of isolating tosylated product **337**. Full consumption of starting material was observed by TLC analysis of the reaction with tosyl chloride and triethylamine in the presence of a catalytic amount of DMAP (Scheme 4.28). Unfortunately, the tosylated **337** was not isolated after the work-up and subsequent silica gel chromatography; instead starting material was recovered. It is possible that the tosylated species **337** was formed but was converted back to the starting material **335** upon work-up.

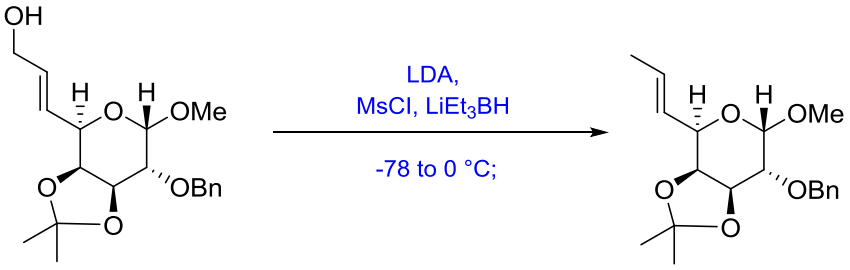


335 **337**

Scheme 4.28: Tosylation of allylic alcohol in **335**

The aforementioned observations revealed that the work-up and/or silica gel purification cause conversion of the activated species (allylic iodide or tosylated) back to starting material. A one-pot reaction comprising activation of alcohol and subsequent substitution with a suitable hydride source might be a good option to circumvent this problem.

Knapp and co-workers reported *in situ* reduction of the allylic alcohol **338** into an *E*-alkene **339** via mesylation and reduction using Super Hydride®(lithium triethylborohydride).[107]

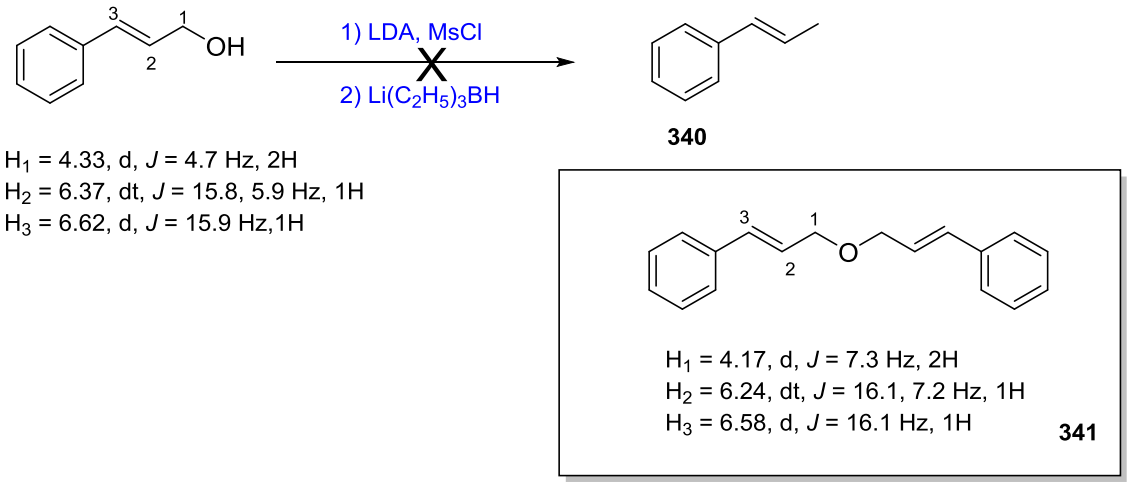


338 **339**

Scheme 4.29: Reported one-pot deoxygenation of allylic alcohol **338**[107]

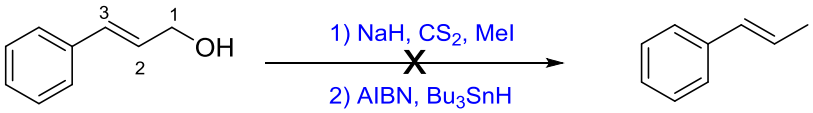
Based on the reported transformation, a one-pot deoxygenation was attempted with a model substrate having an allylic hydroxyl functionality. The reaction of cinnamyl alcohol was performed with *in situ*-generated LDA and mesyl chloride (1.5 eq). Super Hydride® was added after the completion of mesylation as determined by TLC analysis. A new product was isolated which was

characteristically different from the starting material and the desired product **340**. The observed product could not be definitely identified by NMR spectroscopy and HRMS data. Nonetheless, the slight changes of chemical shifts in the alkene region indicated a possible dimer such as **341** (Scheme 4.30). With this idea in mind, the reaction was repeated using an excess of mesyl chloride (5 eq and 10 eq) with a dilute reaction mixture (0.1 M) to minimise the dimerisation. Unfortunately, similar results were observed.



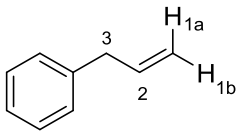
Scheme 4.30: Attempted one-pot mesylation and reduction of cinnamyl alcohol

Barton-McCombie deoxygenation was also attempted with the model substrate cinnamyl alcohol. The xanthate of cinnamyl alcohol was prepared in good yield and sufficient purity using carbon disulfide, NaH and imidazole (Scheme 4.31). The crude xanthate was subjected to radical-mediated reduction with AIBN and tributyltin hydride. None of the desired product **342** was observed. Instead the isomerised alkene **343** was obtained after two hour stirring in 90 °C in toluene. Isomerisation of the double bond might be sensitive to temperature and it was thought that the desired product might isolate at lower temperatures. Unfortunately, lack of time prevented exploration of this hypothesis.



342

H_1 = 4.33, d, *J* = 4.7 Hz, 2H
H_2 = 6.37, dt, *J* = 15.8, 5.9 Hz, 1H
H_3 = 6.62, d, *J* = 15.9 Hz, 1H

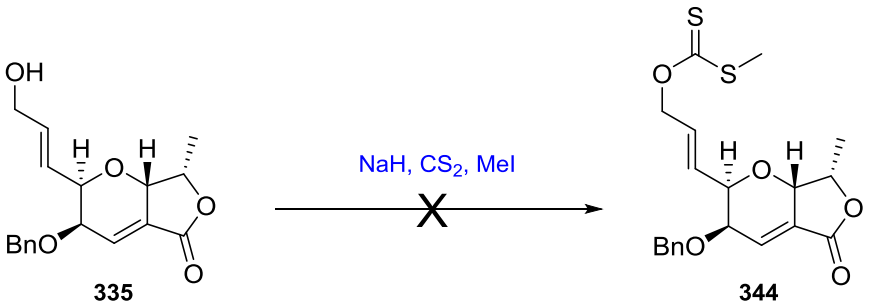


H_{1a} = 5.22, dd, *J* = 17.0, 7.9 Hz, 1H
H_{1b} = 5.41, d, *J* = 8.0 Hz, 1H
H_2 = 6.08, m, 1H

343

Scheme 4.31: Barton-McCombie deoxygenation of cinnamyl alcohol

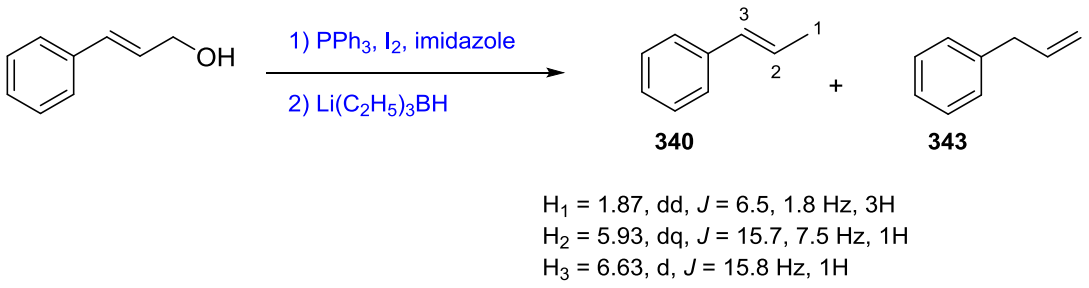
The xanthate formation with lactone **344** was attempted with the same procedure as that applied to model substrate cinnamyl alcohol (Scheme 4.32). Unfortunately, the lactone **335** was completely degraded into a mixture of unidentified compounds. This might be due to the use of a relatively strong base NaH, in the presence of base-sensitive functionalities in **335**.



335 **344**

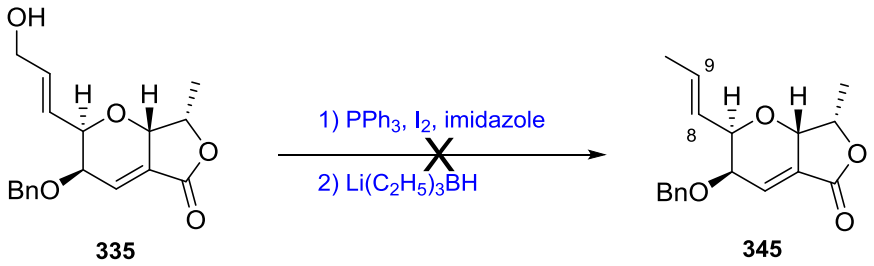
Scheme 4.32: Attempted xanthate formation with the lactone **335**

After this unsuccessful attempt to perform Barton-McCombie deoxygenation with lactone **335**, another one-pot deoxygenation was attempted with cinnamyl alcohol. Cinnamyl alcohol was subjected to halogenation with triphenylphosphine and iodine followed by addition of Super Hydride® to the same pot (Scheme 4.33). ^{1}H-NMR spectral data of the crude reaction mixture revealed the presence of two products, tentatively proposed to be desired *E*-alkene **340** and another product having isomerised double bond **343**.



Scheme 4.33: One-pot iodination and reduction of cinnamyl alcohol

Delighted with the observed results from the one pot iodination/reduction reaction sequence with cinnamyl alcohol, the same protocol was attempted with the lactone **335** (Scheme 4.34).



Scheme 4.34: Attempted one-pot iodination and reduction of lactone **335**

TLC indicated formation of a single product which was isolated in a minute quantity by silica gel chromatography. ^{1}H-NMR of the isolated product had a well resolved alkene region compared to the starting material **335**, but a peak corresponding to the allylic methyl group was absent. The signal for H9 was at 6.18 ppm (dq, *J* = 15.2, 5.8 Hz) whereas it was at 6.09 ppm (dt, *J* = 15.7, 4.7 Hz – overlapping signal with H8), in starting material **335**, moreover the signal for H8 was at 6.00 ppm (dd, *J* = 15.1, 7.2 Hz) whereas it was 6.03 ppm (dd, *J* = 15.7, 6.9 Hz – overlaping with signal for H9) in starting material **335**. The proton signal for the methyl group on the side arm of (−)-TAN-2483A is a doublet at 1.78 ppm,[3] whereas this position was identified as complex multiplet at 3.92 ppm in the observed product (broad doublet, 4.22 ppm in the starting material **335**. These ^{1}H-NMR data indicated that the deoxygenation of the allylic alcohol might have not occurred. On the other hand the isolated product may be the allylic iodide **336** (Scheme 4.27)**.** Nevertheless the HRMS data didn't indicated the presence of iodide **336**, and according to the previous observations iodide **336** is highly reactive species which is impossible to isolate. An alternative hypothesis is the isomerisation of the starting material to form **346**, but this is also ruled out due to the absence of the required pattern and number of protons in the alkene region (Figure 4.8).

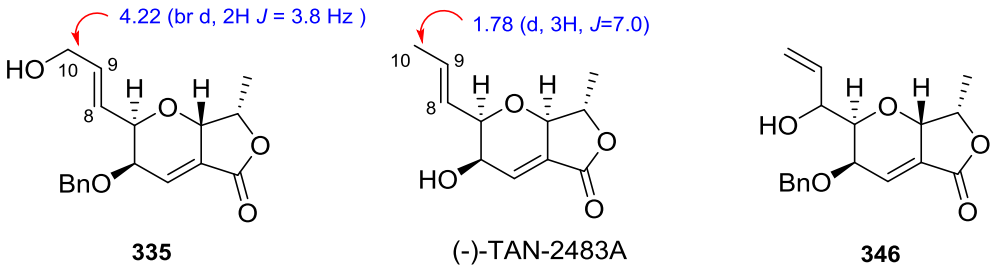


Figure 4.8: ^{1}H-NMR data comparison of **335,** (−)-TAN-2483A and structure of **346**

However, further analysis of the product isolated from the one pot iodination/reduction was not achieved due to the small amount of material obtained. Due to the time constraints, other synthetic strategies on deoxygenation of allylic alcohol towards the total synthesis of (−)-TAN-2483B were not followed.

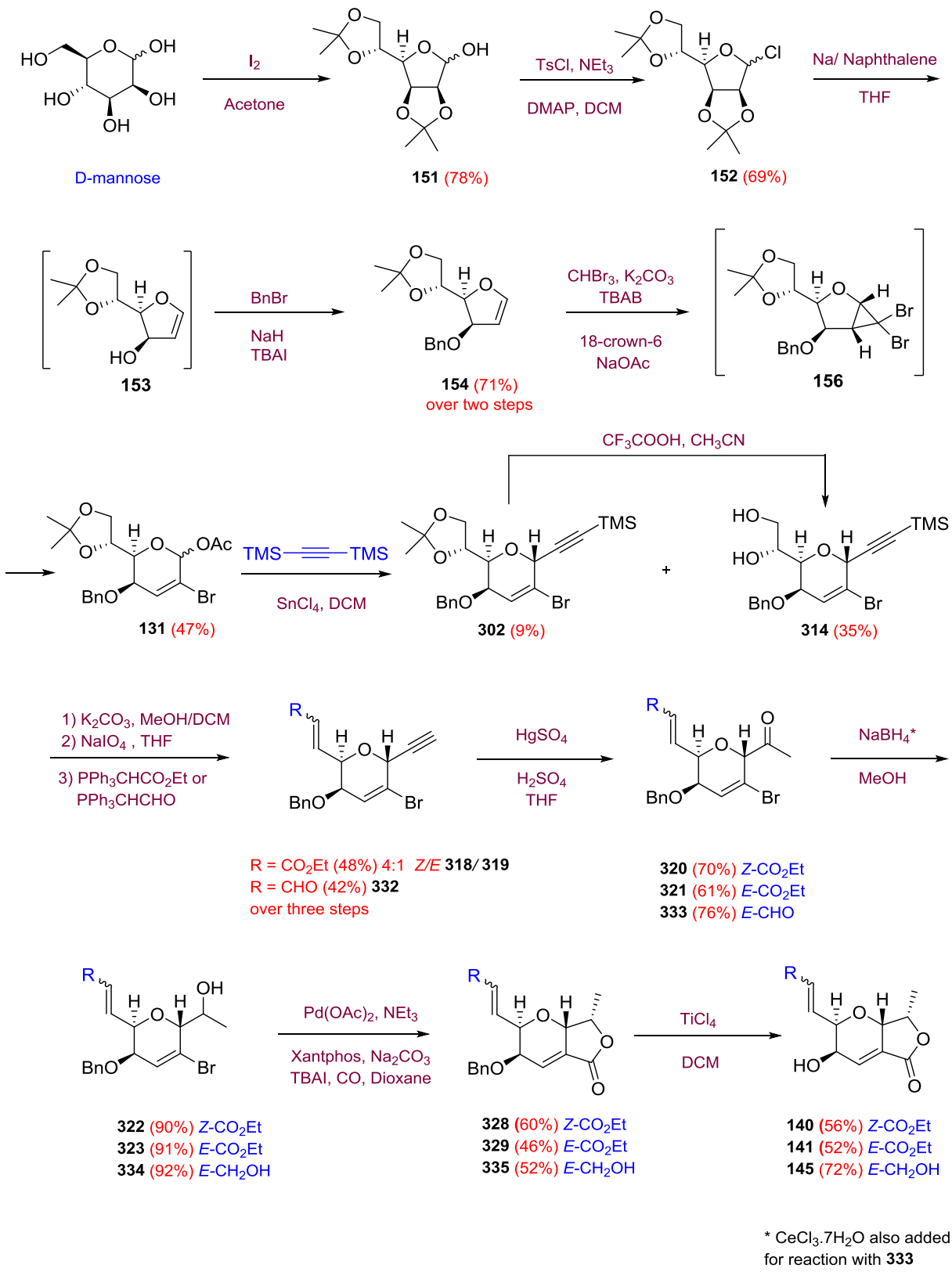
4.6 Conclusion

This chapter described the dibromocyclopropane-based route towards the synthesis of analogues of (−)-TAN-2483B (scheme 4.1). The resulting bromoalkene was very successful in Pd-catalysed carbonylation to form the furo[3,4-*b*]pyran ring system. Lewis acid-mediated debenzylation was able to remove the benzyl group in the presence of unsaturated alkenes during the synthesis of three analogues **140**, **141** and **145.** Deoxygenation of the allylic hydroxyl group was unsuccessful in **335** under the attempted reaction conditions. Thus, (−)-TAN-2483B was not able to be synthesised during the timeframe of this research project. The synthesis of (−)-TAN-2483B could be achievable if the correct side arm was able to be installed at an early stage of the synthesis, such as at the alkyne **316** stage.

4.7 Final comments and outlook

The established synthetic strategy towards the synthesis of analogues of (−)-TAN-2483B has 14 linear steps featuring cyclopropanation/ring expansion and Pd-catalysed carbonylation (Scheme 4.35). The strength of this synthetic route is the use of dibromocyclopropanation/ring expansion sequence to realise the pyran ring unsaturation, with reactive functionalities suited to elaboration to the lactone ring of furo[3,4-*b*]pyran. Establishment of the remaining two stereocentres was achieved by stereoselective *C*-glycosidation and substrate-controled $NaBH_4$ reduction. A final stage

deoxygenation of allylic alcohol **335** towards the total synthesis of (−)-TAN-2483B requires further research due to the unforeseen obstacles encountered. On the other hand it might be beneficial to revise the synthetic plan by introducing the correct *E*-propenyl side arm at an earlier stage of the synthesis. A few potential alternative strategies are reported in Chapter 5. Although the target natural product (−)-TAN-2483B was not achieved here, the synthetic strategy used in the analogue synthesis lays a solid platform to achieve the total synthesis of (−)-TAN-2483B in the near future.



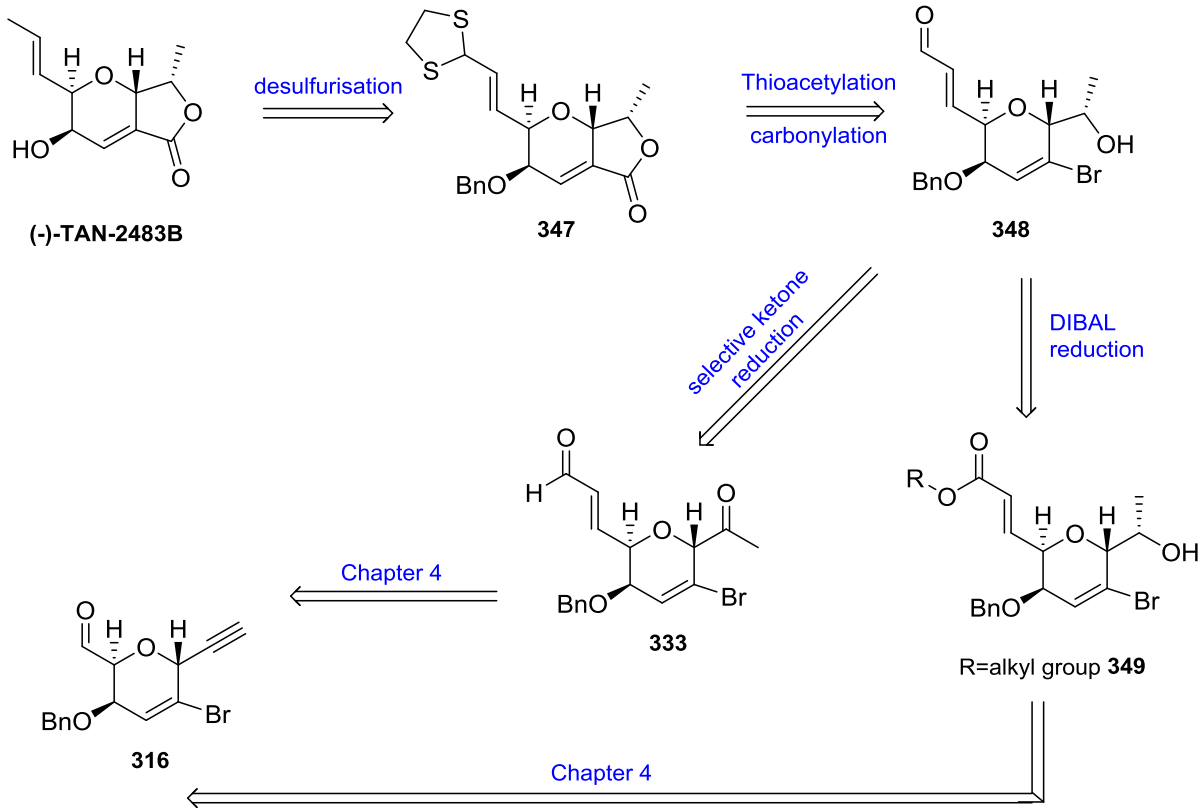
Scheme 4.35: Synthesis of the analogues of (−)-TAN-2483B

5 Future directions towards the total synthesis of (−)-TAN-2483B

The results described in Chapter 2 demonstrated the lack of reactivity of the chloroalkene in the formation of furo[3,4-*b*]pyran ring system through carbonylation and related methods. Synthetic attempts to access the furo[3,4-*b*]pyran core via the dichlorocyclopropane route nonetheless provided a solid background to the dibromocyclopropane route discussed in Chapter 4 resulting in the synthesis of three analogues of (−)-TAN-2483B. Attempts to generate the furo[3,4-*b*]pyran using Vilsmeier-Haack derived 2-formyl glycal were unsuccessful. This route showed great promise for achieving the target natural product. This chapter mainly addresses synthetic strategies proposed to achieve the total synthesis of the natural product through installation of the *E*-propenyl side arm.

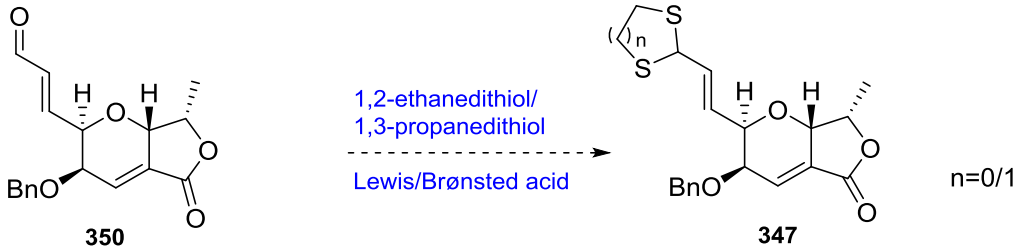
5.1 Proposed retrosynthetic strategy based on thioacetylation, desulfurisation of furo[3,4-*b*]pyran

The new proposed retrosynthetic strategy for (−)-TAN-2483B (Scheme 5.1) might be beneficial in the future to achieve the total synthesis. The new route features thioacetylation, desulfurisation and selective ketone reduction of **333** or otherwise DIBAL reduction of ester **349** (Scheme 5.1).



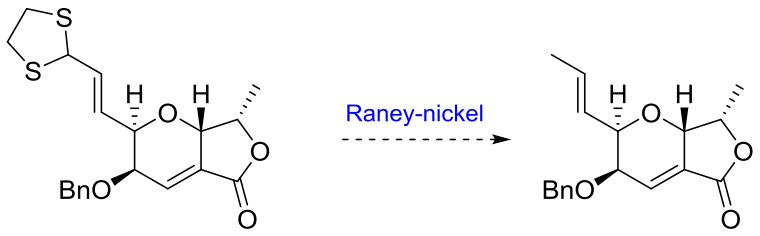
Scheme 5.1: Proposed retrosynthetic strategy for the total synthesis of (−)-TAN-2483B

According to the retrosynthetic strategy a possible intermediate in which to functionalise the α,β-unsaturated aldehyde is the furopyran **350** (Scheme 5.2). A thioacetalisation-desulfurisation sequence may be a useful option to install the *E*-propenyl side arm of (−)-TAN-2483B. Thioacetals, sulfur analogue of acetals, can be prepared in a similar way to acetals by the reaction of dithiol with an aldehyde **350** in the presence of an acid catalyst (Scheme 5.2). Thioacetal formation typically employs either a Lewis or Brønsted acid catalyst.



Scheme 5.2: Thioacetalisation of furopyran **350**

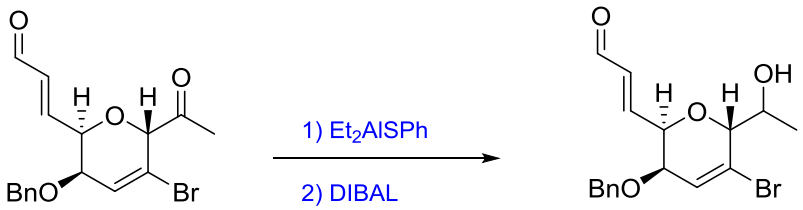
Desulfurisation can be achieved with Raney-nickel and it is hoped that such a reaction with **347** would produce the desired sidearm. Debenzylation of **351** as used in the synthesis of (−)-TAN-2483B analogues **140, 141** and **145** could be employed to achieve the natural product target.



347 **351**

Scheme 5.3: Desulfurisation of **347** towards the total synthesis of (−)-TAN-2483B.

Furopyran **347** can be synthesised by a route similar to that discussed in Chapter 4. The alcohol **348** may be synthesised by DIBAL reduction of ester **349** or chemoselective reduction of ketone moiety in **333** by a two step procedure reported by Marko *et al.* (Scheme 5.4). [108]



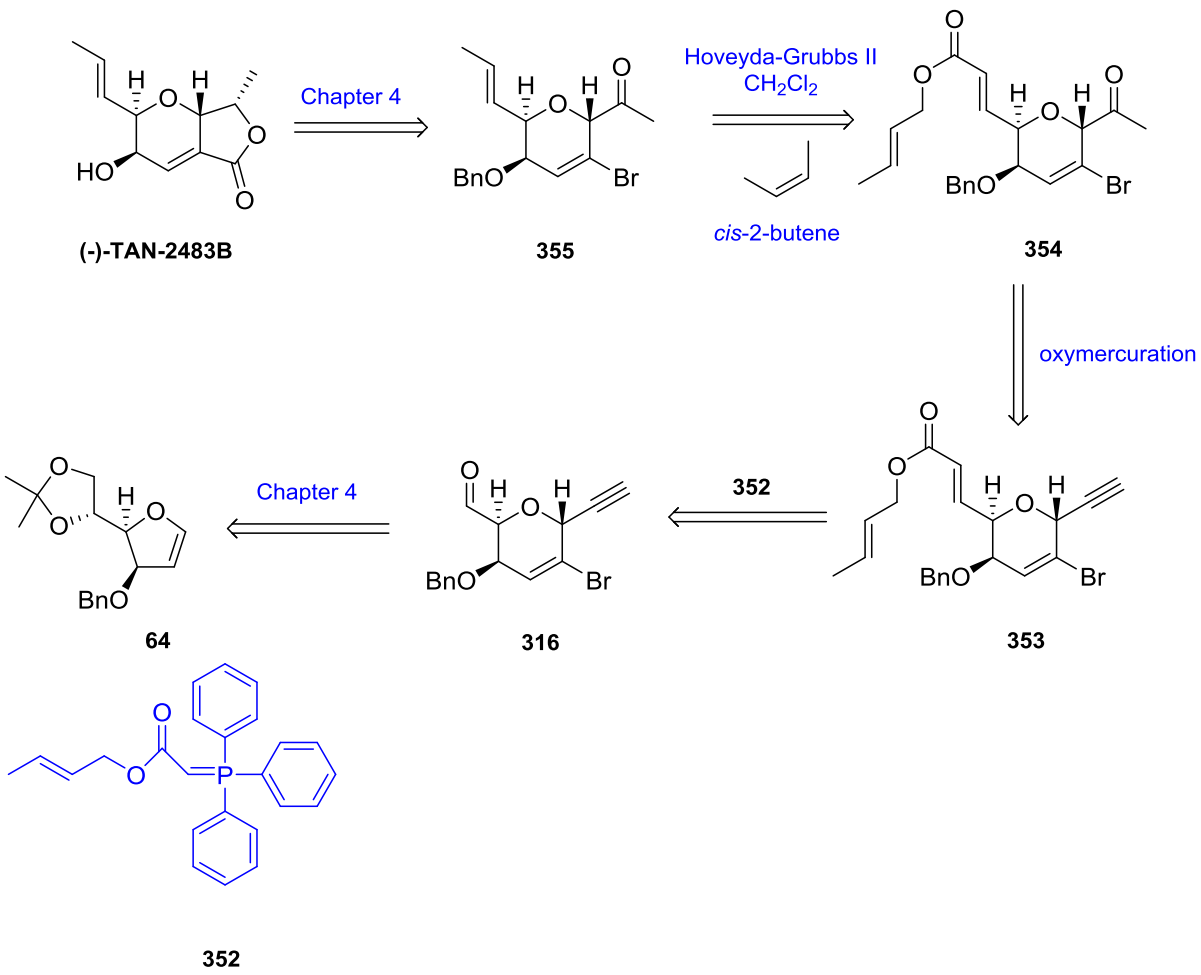
333 **348**

Scheme 5.4: Selective reduction of ketone moiety in **333**

5.2 Proposed retrosynthetic strategy based on relay cross metathesis of 354

An alternative strategy featuring cross metathesis using a relay strategy might provide a useful transformation to reveal the *E*-propenyl side arm of the natural product. The early stage installation of the correct *E*-propenyl-based side arm may therefore be necessary to circumvent the obstacles discussed in Sections 2.7.1 and 4.3. For example, aldehyde precursor **316** might be good substrate to elaborate the correct side arm of the natural product (Scheme 5.5). The stabilised Wittig reaction provided the best strategy for side arm installation in the analogue synthesis described in Sections 2.7.2, 4.3 and 4.4. The crotyl acetate-based phosphorane **352** could be used to afford **353**. Subsequent transformation of the alkyne **353** to ketone **354** would provide the most suitable point to attempt the relay cross metathesis. Relay olefin metathesis with *cis*-2-butene can be effective in installation of the correct side arm.[109] Further functionalisation of the methyl ketone **355** by

reduction, carbonylation and debenzylation may be able to afford the ultimate target natural product (−)-TAN-2483B as mentioned in following retrosynthetic strategy.



Scheme 5.5: Relay cross metathesis towards the total synthesis of (−)-TAN-2483B

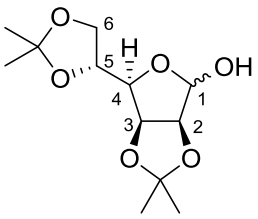
6 Experimental

6.1 General experimental

Unless otherwise stated, the following conditions apply. All reactions were performed under nitrogen in vacuum-dried glassware using dry solvents and standard syringe techniques. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethylether (Et_2O), and toluene ($C_6H_5CH_3$) were either taken from solvent purification system (using Innovative Technology's PureSolv system) or freshly distilled from calcium hydride (for CH_2Cl_2 and toluene) or sodium metal, benzoquinone (for THF). Methanol (MeOH) and 1,4-dioxane were distilled in the presence of sodium. Anhydrous *N,N*-dimethylformamide (DMF) and chloroform used as received (with small amounts of ethanol as stabiliser). Bromoform was fractionally distilled over calcium hydride to remove 3 -5 % (v/v) amounts of ethanol. Sodium hydride (NaH) was obtained as 60% (w/w) dispersion in paraffin oil and was used as obtained. All other reagents were of commercial quality and distilled prior to use if necessary. CO was filled in a helium grade balloon and used in the carbonylation reactions. Reaction progress was monitored using aluminium-backed thin layer chromatography (TLC) plates pre-coated with silica UV254 and visualised by either UV fluorescence quenching (254 nm) or anisaldehyde dip. Purification of products via flash chromatography was conducted using a column filled with Silica Zeoprep 60 (40-63 microns) as the matrix, obtained from Pure Science Ltd, with solvent systems as indicated. ^{1} H- and 13C-NMR spectra were recorded on a Varian Unity Inova 500 (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer, NOESY spectra were recorded on a Varian Unity Inova 300 (300 MHz for ^{1}H). All chemical shifts were referenced to solvent peaks ($CDCl_3$: ^{1}H-7.26 ppm, ^{13}C 77.16, D_2O: ^{1}H 4.79 ppm). Melting points were determined using a Gallenkamp melting point apparatus. Optical rotations were measured on an Autopol II polarimeter from Rudolph Research Analytical. Infrared spectra were obtained on a Brucker Tensor 27 FTIR spectrometer. High-resolution mass spectrometry was recorded on a 6530 Accurate Mass Q-TOF LC/MS instrument (Agilent Technologies). The structure of each compound is presented with the corresponding method of preparation and spectroscopic data.

6.2 Experimental for chapter 2

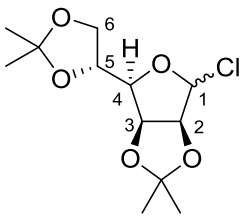
Preparation of (3a*S*,6*R*,6a*S*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (151)



A solution of D-mannose (18.0 g, 100 mmol) in acetone (0.75 L) was treated with iodine (5.14 g, 10.1 mmol), then stirred at room temperature for three hours. The purple colour solution was diluted with sat. sodium thiosulfate solution (300 mL) and sat. sodium bicarbonate solution (300 mL), extracted with chloroform (3x300 mL), then dried, filtered and concentrated to provide a pale–yellow solid. This crude product was recrystallised with acetone to provide **151** as pale off-white crystals (15.1 g, 58**%**). The mother liquor was concentrated further, and recrystallised to obtain another crop of **151** (5.6 g, 20%). The spectral data matched those reported previously.[20, 45]

^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 5.38 (d, *J* = 3.5 Hz, 1H, H-1), 4.82 (dd, *J* = 5.8, 3.6 Hz, 1H, H-3), 4.62 (d, *J* = 5.8 Hz, 1H, H-2), 4.40 (dd, *J* = 11.3, 6.7 Hz, 1H, H-5), 4.19 (dd, *J* = 7.1, 3.6 Hz, 1H, H-4), 4.09 (dd, *J* = 8.7, 6.2 Hz, 1H, H-6a), 4.04 (dd, *J* = 8.7, 4.8 Hz, 1H, H-6b), 2.60 (s, 1H, OH), 1.46 (s, 3H, $(CH_3)_2C$), 1.45 (s, 3H, $(CH_3)_2C$), 1.38 (s, 3H, $(CH_3)_2C$), 1.33 (s, 3H,$(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 112.6 (C, $(CH_3)_2C$), 109.1 (C, $(CH_3)_2C$), 101.3 (CH, C-1), 85.4 (CH, C-2), 80.3 (CH, C-4), 79.6 (CH, C-3), 73.2 (CH, C-5), 66.6 (CH_2, C-6), 26.8 (CH_3, $(CH_3)_2C$), 25.8 (CH_3, $(CH_3)_2C$), 25.1 (CH_3, $(CH_3)_2C$), 24.4 (CH_3, $(CH_3)_2C$).

Preparation of (3a*S*,6*R*,6a*S*)-4-chloro-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole (152)

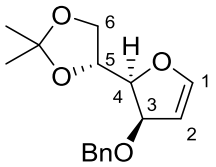


Diacetonide D-mannose **151** (10.2 g, 39.0 mmol) was dissolved in dry dichloromethane (190 mL), then treated with DMAP (2.86 g, 23.4 mmol), tosyl chloride (8.81 g, 46.2 mmol) and triethylamine (5.4 mL, 39 mmol) respectively. The pale yellow colour solution mixture was stirred at room temperature for four hours, then washed sequentially with sat. copper sulfate solution (200 mL), sat.

sodium bicarbonate solution (200 mL) and brine (100 mL). The solution obtained was dried, filtered and concentrated to provide viscous yellow–orange oil. This material was purified by column chromatography (9:1 petroleum ether: ethyl acetate) to provide mannosyl chloride **152** as a colourless oil (7.43 g, 69%). The spectral data matched those reported previously.[20, 45]

R_f 0.34 (9:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 6.07 (d, *J* = 1.9 Hz, 1H, H-1), 4.96 (dd, *J* = 5.6, 2.7 Hz, 1H, H-2), 4.89 (m, 1H, H-3), 4.44 (m, 1H, H-5), 4.21 (dd, *J* = 7.8, 3.0 Hz, 1H, H-4), 4.10 (ddd, *J* = 8.9, 6.3, 2.7 Hz, 1H, H-6a), 4.02 (ddd, *J* = 8.8, 4.4, 2.7 Hz, 1H, H-6b), 1.47 (s, 6H, $(CH_3)_2C$), 1.39 (s, 3H, $(CH_3)_2C$), 1.33 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 113.3 (C, $(CH_3)_2C$), 109.5 (C, $(CH_3)_2C$), 97.6 (CH, C-1), 89.1 (CH, C-2), 82.3 (CH, C-4), 78.5 (CH,C-3), 72.3 (CH, C-5), 66.7 (CH_2, C-6), 26.9 (CH_3, $(CH_3)_2C$), 25.8 (CH_3, $(CH_3)_2C$), 25.1 (CH_3, $(CH_3)_2C$), 24.6 (CH_3, $(CH_3)_2C$).

Preparation of (*R*)-4-((2*S*,3*R*)-3-(benzyloxy)-2,3-dihydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane (64)



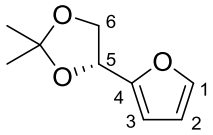
A solution of naphthalene (38.4 g, 299 mmol) in dry tetrahydrofuran (100 mL) was treated with freshly cut sodium (2.71 g, 118 mmol) and stirred at room temperature for two hours to generate the deep–green coloured sodium naphthalenide radical. The mixture was cooled to 0 °C, then treated with cold mannosyl chloride **152** (7.54 g, 27.1 mmol) as a solution in tetrahydrofuran (60 mL) via cannula. The reaction mixture was allowed to stir for ten minutes at 0 °C and 15 minutes at room temperature, then quenched with sat. ammonium chloride solution (100 mL), followed by dilution with water (100 mL). The phases were separated, then the aqueous layer was extracted with diethyl ether (2x100 mL). The combined organic fractions were washed with brine (100 mL), then dried, filtered and concentrated to provide a mixture of naphthalene and furanoglycal **153** as pale yellow solid. This mixture was immediately dissolved in a minimum volume of tetrahydrofuran (100 mL), cooled to 0 °C, then treated successively with tetrabutylammonium iodide (506 mg, 1.37 mmol), sodium hydride (1.43 g, 35.8 mmol) and benzyl bromide (4.0 mL, 33 mmol). The mixture was allowed to warm to room temperature, then stirred overnight. The reaction was quenched with brine (100 mL) and water (100 mL), then the mixture was extracted with diethyl ether (3x100 mL). The combined organic fractions were washed with brine (100 mL), then dried, filtered and concentrated to provide a mixture of naphthalene and glycal **64** as pale yellow solid. This crude product was dissolved in petroleum ether and flushed through the silica column to get rid of naphthalene then

column chromatographed (20:1 petroleum ether: ethyl acetate) to provide glycal **64** as a pale–yellow oil (5.30 g, 71%). The spectral data matched those reported previously.[20, 45]

R_f 0.29 (20:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.27 (complex m, 5H, Bn), 6.62 (d, *J* = 2.7 Hz, 1H, H-1), 5.29 (apparent t, *J* = 2.5 Hz, 1H, H-2), 4.65 (dd, *J* = 7.1, 2.4 Hz, 1H, H-3), 4.59 (dd, *J* = 11.6, 6.5 Hz, 1H, H-5), 4.57 (d, *J* = 11.4 Hz, 1H, $PhCH_2$), 4.51 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.44 (dd, *J* = 6.8, 5.4 Hz, 1H, H-4), 4.11 (dd, *J* = 8.6, 6.8 Hz, 1H, H-6a), 3.99 (dd, *J* = 8.5, 6.4 Hz, 1H, H-6b), 1.48 (s, 3H,$(CH_3)_2C$), 1.40 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 150.6 (CH, C-1), 138.4 (C, 156, Bn), 128.4 (CH, Bn), 127.6 (CH, Bn), 127.5 (CH, Bn), 108.7 (C, $(CH_3)_2C$), 101.9 (CH, C-2), 84.1 (CH, C-4), 79.2 (CH, C-3), 73.1 (CH, C-5), 71.0 (CH_2, $PhCH_2$), 65.9 (CH_2, C-6), 26.5 (CH_3, $(CH_3)_2C$), 25.2 (CH_3, $(CH_3)_2C$).

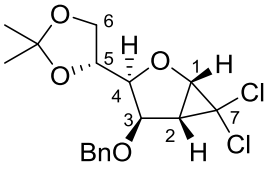
In a separate reaction benzylated gycal **64** was completely degraded on silica gel to afford **154**. The spectral data for **154** matched those reported previously.[110]

Characterisation of 4*R*-(2-furanyl)-2,2-dimethyl-1,3-dioxolane 154[110]

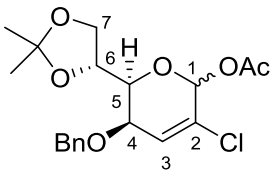


R_f 0.34 (20:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.43 (dd, *J* = 1.8, 0.9 Hz, 1H, H-1), 6.37 (complex m, 2H, H-2, H-3), 5.11 (t, *J* = 6.9, Hz, 1H, H-5), 4.24 (dd, *J* = 8.3, 6.6 Hz, 1H, H-6a), 4.11 (dd, *J* = 8.3, 6.9 Hz, 1H, H-6b), 1.51 (s, 3H, $(CH_3)_2C$), 1.46 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 152.0 (C, C-4), 143.0 (CH, C-1), 110.1 (CH, C-2), 110.0 (C, $(CH_3)_2C$), 108.0 (CH, C-3), 71.3 (CH, C-5), 67.9 (CH_2, C-6), 26.4 (CH_3, $(CH_3)_2C$), 26.0 (CH_3, $(CH_3)_2C$); IR (film from CH_2Cl_2) ν_{max} 3063, 3032, 2986, 2959, 2898, 1650, 1455, 1380, 1373, 1261, 1113, 889, 843 cm $^{-1}$; HRMS: m/z $C_9H_{16}NO_3^+$ $[M+NH_4]^+$ calcd 186.1125, found 186.1127.

Preparation of 1,4-Anhydro-3-*O*-benzyl-2-deoxy-1,2-*C*-(dichloromethylene)-5,6-*O*-isopropylidene-D-glycero-D-gulohexitol (65) and acetyl 4-*O*-benzyl-2-chloro-2,3-dideoxy-6,7-*O*-isopropylidene-D-arabino-hept-2-enopyranoside (66)



65



66

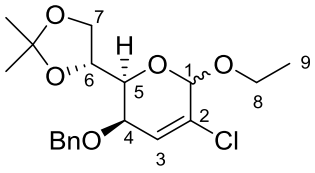
Glycal **64** (462 mg, 1.67 mmol) was dissolved in chloroform (3 mL), treated with TEBAC (8 mg, 0.04 mmol), then a solution of sodium hydroxide (3.00 g, 75.3 mmol) in water (3.0 mL) and allowed to stir under air at room temperature for 3 hours. The brown colour reaction mixture was dissolved in water (20 mL), then extracted with diethyl ether (3x20 mL). The ethereal fractions were combined, dried, filtered and concentrated to afford cyclopropane **65** as brown oil. This oil was dissolved in dry acetic acid (17 mL), treated with silver acetate (435 mg, 2.61 mmol), then stirred at 90 °C for two hours. The solution was filtered through Celite® and eluted with diethyl ether (20 mL). The brown colour crude was purified by column chromatography (5:1 petroleum ether: ethyl acetate), to provide α- and β-acetyl pyranosides **66** (3:1 ratio, 495 mg, 77%), as an inseparable mixture. The spectral data matched that reported previously.[45]

(**65**) R_f 0.44 (9:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.39–7.31 (complex m, 5H, Bn), 4.67 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.61 (d, *J* = 11.5 Hz, 1H, $PhCH_2$), 4.48 (apparent t, *J* = 5.9 Hz, 1H, H-5), 4.33 (d, *J* = 6.4 Hz, 1H, H-3), 4.31 (d, *J* = 5.9 Hz, 1H, H-4), 4.27 (dd, *J* = 5.9, 0.8 Hz, 1H, H-1), 4.05 (dd, *J* = 8.3, 6.9 Hz, 1H, H-6a), 3.93 (dd, *J* = 7.9, 6.5 Hz, 1H, H-6b), 2.47 (d, *J* = 5.9 Hz, 1H, H-2), 1.44 (s, 3H, $(CH_3)_2C$), 1.36 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.2 (C, Bn), 128.5 (CH, Bn), 128.0 (CH, Bn), 127.6 (CH, Bn), 108.8 (C, $(CH_3)_2C$), 87.6 (CH, C-5), 80.0 (CH, C-3), 73.5 (CH, C-4), 73.2 (CH_2, $PhCH_2$), 67.9 (CH, C-1), 66.2 (CH_2, C-6), 61.2 (C, C-7), 39.3 (CH, C-2),26.5 (CH_3, $(CH_3)_2C$), 25.3 (CH_3, $(CH_3)_2C$).

(**66**) R_f 0.38 (5:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.42–7.30 (complex m, 5H, Bn), 6.28–6.24 (complex m, 2H, H-1,H-3), 4.70 (s, 1.5H, $PhCH_2$), 4.68 (s, 0.5H, $PhCH_2$), 4.39 (m, 0.75H, H-6), 4.38 (m, 0.25H, H-6), 4.12 (dd, *J* = 8.8, 6.3 Hz, 0.75H, H-7a), 4.10 (m, 0.25H, H-7a), 4.04 (dd, *J* = 8.8, 4.7 Hz, 0.25H, H-7b), 4.00 (m, 0.25H, H-4), 3.98 (dd, *J* = 5.9, 2.5 Hz, 0.75H, H-4), 3.88 (dd, *J* = 8.8, 4.7 Hz, 0.75H, H-7b), 3.84 (dd, *J* = 8.5, 2.4 Hz, 0.75H, H-5), 3.67 (dd, *J* = 8.6, 1.9 Hz, 0.25H, H-5), 2.16 (s, 0.75H, Ac), 2.13 (s, 2.25H, Ac), 1.41 (s, 2.25H, $(CH_3)_2C$), 1.40 (s, 0.75H, $(CH_3)_2C$), 1.38 (s, 2.25H, $(CH_3)_2C$), 1.37 (s, 0.75H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 169.5 (C, $CH_3CO)_{66\alpha}$, 169.2 (C, $CH_3CO)_{66\beta}$, 138.0 (C, Bn) $_{66\beta}$, 137.8 (C, Bn) $_{66\alpha}$, 133.7 (C, C-2) $_{66\beta}$, 132.4 (C, C-2) $_{66\alpha}$, 127.94 (CH, Bn) $_{66\alpha}$, 128.35 (CH, Bn), 128.02 (CH, Bn), 127.96 (CH, Bn), 127.85 (CH, Bn), 127.83 (CH, Bn), 127.2 (CH, C-3) $_{66\beta}$, 125.9 (CH, C-3) $_{66\alpha}$, 109.4 (C, $(CH_3)_2C$) $_{66\beta}$, 90.0 (CH, C-1) $_{66\beta}$, 89.0 (CH, C-1) $_{66\alpha}$, 76.8 (CH, C-5) $_{66\beta}$, 73.1 (CH, C-5) $_{66\alpha}$, 73.0 (CH, C-6) $_{66\beta}$, 72.9 (CH, C-6) $_{66\alpha}$, 72.0 (CH_2, $PhCH_2$) $_{66\alpha}$, 71.9 (CH_2, $PhCH_2$) $_{66\beta}$, 68.5 (CH, C-4) $_{66\beta}$, 68.3 (CH, C-4) $_{66\alpha}$, 67.1 (CH_2, C-7) $_{66\alpha}$, 67.0 (CH_2, C-7) $_{66\beta}$, 27.0 (CH_3, $(CH_3)_2C$) $_{66\beta}$, 26.9 (CH_3, $(CH_3)_2C$) $_{66\alpha}$, 25.3 (CH_3,$(CH_3)_2C$) $_{66\beta}$, 25.2 (CH_3,$(CH_3)_2C$) $_{66\alpha}$, 20.90 (CH_3, Ac) $_{66\alpha}$, 20.86 (CH_3, Ac) $_{66\beta}$.

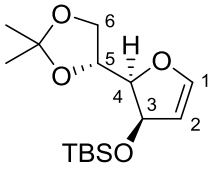
In scale-up reaction ethyl glycoside **159** was isolated along with desired acetate **66**.

Characterisation of (2*S*,3*R*)-3-(benzyloxy)-5-chloro-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-ethoxy-3,6-dihydro-2*H*-pyran (159)



R_f 0.32 (5:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36 –7.29 (complex m, 5H, Bn), 6.24 (d, *J* = 5.8 Hz, 0.16H, H-3), 6.15 (d, *J* = 5.8 Hz, 0.84H, H-3), 5.08 (s, 0.16H, H-1), 4.92 (s, 0.84H, H-1), 4.66 (d, *J* = 4.7 Hz, 2H, $PhCH_2$), 4.40 (m, 1H, H-6), 4.16 (dd, *J* = 8.4, 6.3 Hz, 1H, H-7a), 3.97 (m, 2H, H-5 and H-7b), 3.89 (dd, *J* = 5.6, 2.5 Hz, 1H, H-4), 3.82 (quintet, *J* = 7.0 Hz, 1H, H-8a), 3.60 (quintet, *J* = 7.1 Hz, 1H, H-8b), 1.41 (s, 3H, Ac), 1.40 (s, 3H, Ac), 1.27 (t, *J* = 7.1 Hz, 3H, H-9); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 138.0 (C, Bn), 134.3 (C, C-2), 128.40 (CH, Bn), 128.33 (CH, Bn), 128.23 (CH, Bn), 126.5 (CH, C-3)$_{\mathbf{159\beta}}$, 124.3 (CH, C-3)$_{\mathbf{159\alpha}}$, 109.2 (C, $(CH_3)_2C$), 97.9 (CH, C-1) $_{\mathbf{159\beta}}$, 96.2 (CH, C-1)$_{\mathbf{159\alpha}}$, 73.5 (CH, C-6), 71.9 (CH_2, $PhCH_2$), 71.4 (CH, C-5)$_{\mathbf{159\alpha}}$, 71.1 (CH, C-5)$_{\mathbf{159\beta}}$, 69.1(CH, C-4), 67.2 (CH_2, C-7)$_{\mathbf{159\alpha}}$, 67.0 (CH_2, C-7)$_{\mathbf{159\beta}}$, 64.5 (CH_2, C-8)$_{\mathbf{159\alpha}}$, 62.9 (CH_2, C-8)$_{\mathbf{159\beta}}$, 26.9 (CH_3, $(CH_3)_2C)_{\mathbf{159\beta}}$, 26.8 ($CH_3$, $(CH_3)_2C)_{\mathbf{159\alpha}}$, 25.5 ($CH_3$,$(CH_3)_2C)_{\mathbf{159\alpha}}$, 25.4 ($CH_3$, $(CH_3)_2C)_{\mathbf{159\beta}}$, 15.1 ($CH_3$, C-9)$_{\mathbf{159\beta}}$, 15.0 ($CH_3$, C-9)$_{\mathbf{159\alpha}}$; IR (film from CH_2Cl_2) ν_{max} 2983, 2878, 1756, 1655, 1454, 1370, 1259, 1214, 1108, 1051, 1025, 922, 847, 802, 736, 697 cm^1; HRMS: m/z $C_{19}H_{29}ClO_5N^+$ $[M+NH_4]^+$ calcd 386.1729 found 386.1736.

Preparation of *tert*-butyl(((2*R*,3*R*)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,3-dihydrofuran-3-yl)oxy)dimethylsilane (147)

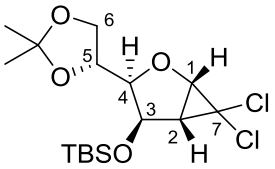


A solution of naphthalene (5.4 g, 42 mmol) in dry tetrahydrofuran (20 mL) was treated with freshly cut sodium (0.51 g, 22 mmol) and stirred at room temperature for two hours to generate the deep–green coloured sodium naphthalenide radical. The mixture was cooled to 0 °C, then treated with cold mannosyl chloride **152** (1.6 g, 5.7 mmol) as a solution in tetrahydrofuran (10 mL) via cannula. The reaction mixture was allowed to stir for ten minutes at 0 °C and 15 minutes at room temperature, then quenched with sat. ammonium chloride solution (20 mL), followed by dilution with water (20 mL). The phases were separated, and then the aqueous layer was extracted with diethyl ether (2x20 mL). The combined organic fractions were washed with brine (20 mL), then dried, filtered and concentrated to provide a mixture of naphthalene and furanoglycal **153** as pale yellow

solid. This mixture was immediately dissolved in a minimum volume of tetrahydrofuran (20 mL), cooled to 0 °C, then treated successively with TBSCl (2.6 g, 23.7 mmol), DMAP (97 mg, 0.8 mmol) and triethyl amine (3.4 mL, 24 mmol). The mixture was allowed to warm to room temperature, then stirred overnight. The reaction was quenched with brine (20 mL) and water (20 mL), then the mixture was extracted with diethyl ether (3x20 mL). The combined organic fractions were washed with brine (20 mL), then dried, filtered and concentrated to provide a mixture of naphthalene and glycal **147** as pale yellow solid. This crude product was dissolved in petroleum ether and flushed through the silica column to get rid of naphthalene then column chromatographed (20:1 petroleum ether: ethyl acetate) to provide glycal **147** as a colourless oil (599 mg, 56%).

R_f 0.38 (20:1 petroleum ether: ethyl acetate); $[\alpha]_D^{24}$ = 82.5 (*c* 0.4, $CHCl_3$); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 6.55 (s, 1H, H-1), 5.09 (apparent s, 1H, H-2), 4.90 (dd, *J* = 6.8, 0.8 Hz, 1H, H-3), 4.48 (m, 1H, H-5), 4.33 (dd, *J* = 6.1, 5.4 Hz, 1H, H-4), 4.08 (dd, *J* = 8.3, 7.1 Hz, 1H, H-6a), 3.95 (dd, *J* = 7.8, 7.1 Hz, 1H, H-6b), 1.45 (s, 3H, $(CH_3)_2C$), 1.36 (s, 3H, $(CH_3)_2C$), 0.91 (s, 9H, TBS), 0.09 (s, 6H, TBS); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 149.4 (CH, C-1), 108.5 (C, $(CH_3)_2C$), 104.5 (CH, C-2), 82.6 (CH, C-4), 73.2 (CH, C-3), 73.1 (CH, C-5), 65.8 (CH_2, C-6), 25.64 (CH_3, $(CH_3)_2C$), 25.62 (CH_3, $(CH_3)_2C$), 18.1 (C, TBS), -3.6 (CH_3, TBS); IR (film from $CDCl_3$) ν_{max} 2985, 2885, 2858, 1642, 1471, 1380, 1254, 1218, 1191, 1128, 1071, 1006, 939, 886, 836, 748, 626 cm^{-1}; HRMS: m/z $C_{15}H_{28}SiO_4Na^+$ $[M+Na]^+$ calcd 323.1649, found 323.1661.

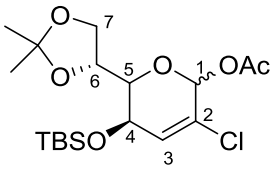
Preparation of *tert*-butyl(((1*S*,3*R*,4*R*,5*S*)-6,6-dichloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxabicyclo[3.1.0]hexan-4-yl)oxy)dimethylsilane (163)



TBS protected glycal **147** (262 mg, 0.67 mmol) was dissolved in chloroform (3 mL), treated with TEBAC (10 mg, 0.04 mmol), then a solution of sodium hydroxide (3.01 g, 75.3 mmol) in water (3.0 mL) and allowed to stir under air at room temperature for 3 hours. The brown colour reaction mixture was dissolved in water (20 mL), and then extracted with diethyl ether (3x20 mL). The ethereal fractions were combined, dried, filtered and concentrated to afford cyclopropane **163** as brown oil (189 mg, 56%). TBS protected cyclopropane **163** used straight after in cyclopropane ring expansion reaction.

R_f 0.55 (20:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 4.54 (d, *J* = 5.9 Hz, 1H, H-4), 4.32 (apparent t, *J* = 6.1 Hz, 1H, H-3), 4.25 (d, *J* = 5.9 Hz, 1H, H-1), 4.20 (m, 1H, H-5), 4.05 (dd, *J* = 8.5, 6.6 Hz, 1H, H-6a), 3.91 (dd, *J* = 8.5, 6.1 Hz, 1H, H-6b), 2.24 (d, *J* = 5.8 Hz, 1H, H-2), 1.40 (s, 3H, $(CH_3)_2C$), 1.31 (s, 3H, $(CH_3)_2C$), 0.92 (s, 9H, TBS), 0.13 (s, 6H, TBS); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 108.8 (C, $(CH_3)_2C$), 88.5 (CH, C-3), 73.5 (CH, C-4), 73.3 (CH, C-5), 67.7 (CH, C-1), 66.4 (CH_2, C-6), 61.1 (C, C-7), 42.2 (C, C-2), 26.5 (CH_3, $(CH_3)_2C$), 25.7 (CH_3, TBS), 25.2 (CH_3, $(CH_3)_2C$), 18.1 (C, TBS), -5.1 (C, TBS), -5.2 (C, TBS).

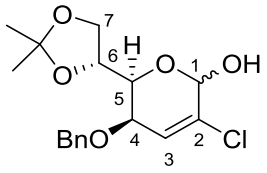
Preparation of (5*R*)-5-((tert-butyldimethylsilyl)oxy)-3-chloro-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-2*H*-pyran-2-yl acetate (148)



A solution of cyclopropane **163** (189 mg, 0.49 mmol) in toluene (3 mL) was treated with silver acetate (246 mg, 1.49 mmol) and sodium acetate (80 mg, 0.98 mmol), then refluxed for one hour. The solution was filtered through a Celite® and eluted with diethyl ether (50 mL). The solution was concentrated to provide a mixture of ring–opened products as yellow oil. This mixture was purified by column chromatography (20:1 petroleum ether: ethyl acetate), providing acetylated glycal **164** and acetyl pyranoside **148** (93 mg, 46 %, (34% over two steps)) as an inseparable yellow oil (1:1:4 ratio of **164: 148$_\beta$: 148$_\alpha$** (anomeric assignment is assumed based on anomeric effect).

R_f 0.51 (20:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz) of major component: ($CDCl_3$) δ_H 6.23 (s, 1H, H-1), 6.22 (d, *J* = 5.4 Hz, 1H, H-3), 4.28 (m, 1H, H-6), 4.23 (dd, *J* = 5.4, 2.1 Hz, 1H, H-4), 4.08 (dd, *J* = 8.6, 6.5 Hz, 1H, H-7a), 3.96 (dd, *J* = 8.6, 3.8 Hz, 1H, H-7b), 3.56 (dd, *J* = 8.6, 2.2 Hz, 1H, H-5), 2.16 (s, 3H, Ac), 1.38 (s, 3H, $(CH_3)_2C$), 1.32 (s, 3H, $(CH_3)_2C$) 0.90 (s, 3H, 3H, TBS), 0.89 (s, 3H, TBS), 0.11 (s, 9H, TBS); ^{13}C-NMR (500 MHz) of major component: ($CDCl_3$) δ_C 169.3 (C, CH_3CO), 132.7 (C, C-2), 129.1 (CH, C-3), 109.3 (C, $(CH_3)_2C$), 89.9 (CH, C-1), 77.6 (CH, C-5), 72.8 (CH, C-6), 67.2 (CH_2, C-7), 63.5 (CH, C-4), 26.9 (CH_3, $(CH_3)_2C$), 25.8 (CH_3, TBS), 25.1 (CH_3,$(CH_3)_2C$), 18.2 (CH_3, Ac), -4.4 (C, TBS), -4.8 (C, TBS);); IR (film from $CDCl_3$) ν_{max} 2931, 2297, 1759, 1659, 1325, 1216, 1069, 973, 907, 837, 729 cm^{-1}; HRMS: m/z $C_{18}H_{35}ClSiO_6N^+$ $[M+NH_4]^+$ calcd 424.1922, found 424.1922.

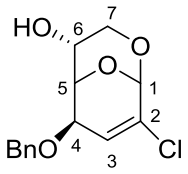
Preparation of (5*R*,6*S*)-5-(benzyloxy)-3-chloro-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-2*H*-pyran-2-ol (67)



A solution of acetates **66** (574 mg, 1.50 mmol) in methanol (15 mL) was treated with a small piece of sodium (3 mg, 0.1 mmol), then stirred at room temperature for one hour. The mixture was concentrated and then passed through a silica plug, which was eluted with dichloromethane (10 mL). The organic solution was concentrated to provide hemiacetal **67** as a viscous yellow oil (517 mg, quantitative), which was used without further purification. The spectral data matched those reported previously.[45]

R_f 0.21 (5:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.30 (complex m, 5H, Bn), 6.17 (d, *J* = 5.7 Hz, 1H, H-3), 5.34 (d, *J* = 4.6 Hz, 1H, H-1), 4.68 (s, 2H, $PhCH_2$), 4.40 (m, 1H, H-6), 4.14 (dd, *J* = 8.4, 6.6 Hz, 1H, H-7a), 4.02 (m, 1H, H-5), 3.99 (m, 1H, H-7b), 3.92 (d, *J* = 5.9 Hz, 1H, H-4), 2.82 (brs, 1H, OH), 1.42 (s, 3H, $(CH_3)_2C$), 1.40 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.9 (C, Bn), 134.6 (C, C-2), 128.4 (CH, Bn), 128.0 (CH, Bn), 127.9 (CH, Bn), 124.6 (CH, C-3), 109.3 (C, $(CH_3)_2C$), 90.9 (CH, C-1), 73.2 (CH, C-6), 72.1 (CH_2, $PhCH_2$), 71.2 (CH, C-5), 68.8 (CH, C-4), 67.2 (CH_2, C-7), 26.9 (CH_3,$(CH_3)_2C$), 25.4 (CH_3, $(CH_3)_2C$).

Preparation of (4*R*,6*R*)-6-(benzyloxy)-8-chloro-2,9-dioxabicyclo[3.3.1]non-7-en-4-ol (182)

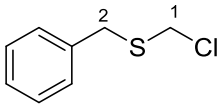


Triphenyl phosphine (0.39 g, 1.50 mmol), carbon tetrabromide (0.49 g, 1.5 mmol) and Zn dust (0.09 1.5 mmol) were stirred at room temperature for one day in 2 mL of tetrahydrofuran. Then it was treated with hemiacetal **67** (0.10 g, 0.3 mmol) at 0 °C. After two hours at room temperature the reaction was quenched with 2 mL of 20% (w/w) $KHSO_4$, followed by water (1 mL). The organic materials were extracted in to dichloromethane (3x5 mL) and dried to obtained brown colour oil. The brown oil was purified with 3:1 petroleum ether: ethyl acetate solution to obtain **182** as colourless oil (27 mg, 31%).

R_f 0.30 (3:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -43 (*c* 0.15, Et_2O); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.38–7.30 (complex m, 5H, Bn), 6.21 (d, *J* = 5.9 Hz, 1H, H-3), 4.97 (s, H, H-1), 4.72 (d, *J* = 11.8 Hz, 2H, $PhCH_2$), 4.66 (d, *J* = 11.7 Hz, 2H, $PhCH_2$), 4.25 (d, *J* = 9.0 Hz, 1H, H-7a), 4.13 (dd, *J* = 9.7, 2.1 Hz, 1H, H-5), 4.06 (ddd, *J* = 9.7, 8.8, 2.0 Hz, 1H, H-6), 4.01 (dd, *J* = 5.8, 2.4 Hz, 1H, H-4), 3.84 (dd, *J* = 9.2, 2.6 Hz, 1H, H-7b) 2.16 (d, *J* = 8.8 Hz, 1H, (OH)H-6)); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.8 (C, Bn), 133.9 (C, C-2), 128.57 (CH, Bn), 128.11 (CH, Bn), 128.07 (CH, Bn), 125.2 (CH, C-3), 95.8 (CH, C-1), 71.8 (CH_2, $PhCH_2$), 68.5 (CH, C-5), 68.3 (CH, C-6), 68.2 (CH, C-4), 66.5 (CH_2, C-7), IR (film from CH_2Cl_2) ν_{max} 3439, 2928, 2868, 1654, 1454, 1374, 1242, 1113, 998, 925, 797, 698 cm^{-1}; HRMS: m/z $C_{14}H_{19}ClO_4N^+$ $[M+NH_4]^+$ calcd 300.0997 found 300.0999.

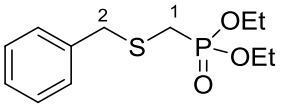
Preparation of Diethyl [(benzylsufonyl)methyl]phosphonate (174)

Step 1: Chloromethyl benzyl sulphide



250 mL three necked round bottom flask fitted with condenser, dropping funnel 3.15 g (0.105 mol) of para formaldehyde was added to the 20 mL of toluene solution. Then, 83.3 mL of conc. HCl was added to the white suspension and heated up to 50 °C. The obtained colourless solution was treated dropwise with benzyl mercaptan (8.55 mL, 0.083 mol) as a solution of toluene (20 mL) over an hour. Then combined solution was stirred for one hour at 50 °C and allowed it to cool down to room temperature. The solution was stirred another three hours at room temperature. The organic layer was extracted and HCl layer was washed with toluene (3x40 mL) and combined organic layers were washed with brine (100 mL) and evaporated on *roto-vap*. Crude product was used without further purification (11.6 g, 81%). ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.37 (complex m, 3H, Bn), 7.36 (m, 2H, Bn), 4.56 (s, 2H, H-1), 3.93 (s, 2H, H-2).

Step 2: Diethyl [(benzylthio)methyl]phosphonate

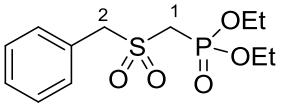


In three necked 100 mL round bottom flask, 26.1 mL of $P(OEt)_3$ was heated up to 130 °C. The flask fitted with the condenser attached to safety bottle charged with ethanol, was filled with 11.6 g (0.067 mol) chloromethyl benzyl suphide. Chloromethyl benzyl sulphide was added dropwise over an hour to the heated solution of $P(OEt)_3$. Then combined solution was stirred overnight at 150 °C. Then reaction mixture was cooled down to room temperature and Diethyl [(Benzylthio)

methyl]phosphonate was obtained as a colourless oil by fractional distillation. (5g, 27% pure 11 g, contaminated with $P(OEt)_3$).

^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.35 (m, 2H, Bn) 7.33 (m, 3H, Bn), 4.17 (apparent quintet, *J* = 7.6 Hz, 4H, Et), 3.91 (s, 2H, H-2), 2.55 (d, $J_{(H-P)}$ = 13.1 Hz, 2H, H-1), 1.35 (t, *J* = 7.1 Hz, 6H, Et). ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.2 (C, Bn), 129.2 (CH, Bn), 128.6 (CH, Bn), 127.3 (CH, Bn), 62.6 (CH_2, J_{C-P} = 6.7 Hz, C-1), 36.9 (CH_2, J_{C-P} = 2.9 Hz, Et), 24.9 (CH_2, J_{C-P} = 40.1 Hz, C-1), 16.5 (CH_3, J_{C-P} = 5.8 Hz, Et); HRMS: m/z $C_{12}H_{20}PSO_3^+$ $[M+H]^+$ calcd 275.0865, found 275.0865.

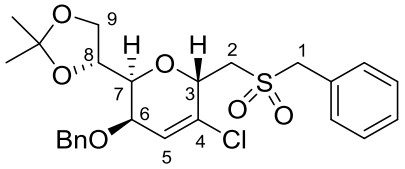
Step 3: Diethyl [(benzylsufonyl)methyl]phosphonate (174)



100 mL three necked round bottom flask connected with thermometer, dropping funnel, and refluxing condenser, 5 g (0.0182 mol) of Diethyl [(benzylthio)methyl]phosphonate and 20 mL of glacial acetic acid were added and heated up to 50 °C. Then 6 mL of 30% H_2O_2 was added drop wise and heated up to 85 °C. After 3 hours reaction mixture was transferred into a beaker with 70 g of ice. Then the solution was treated with 30 mL of 10M NaOH until pH reached 10. Then the organic layer was extracted with dichloromethane (3x50 mL) and dried with dry magnesium sulphate and evaporated on *roto-vap* to obtain a white jelly like material (4.76 g, 85%).

^{1}H-NMR (500 MHz) :($CDCl_3$) δ_H 7.55 (m, 2H, Bn), 7.42 (m, 3H, Bn), 4.62 (s, 2H, H-2), 4.17 (apparent quintet, *J* = 7.2 Hz, 4H, Et), 3.37 (d, $J_{(H-P)}$ = 15.1 Hz, 2H, H-2), 1.35 (t, *J* = 7.1 Hz, 6H, Et); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 131.0 (C, Bn), 129.2 (CH, Bn), 129.1 (CH, Bn), 128.3 (CH, Bn), 63.8 (CH_2, $J_{(C-P)}$ = 6.7 Hz, C-1), 60.2 (CH_2, C-2), 48.4 (CH_2, $J_{(C-P)}$ = 40.1 Hz, Et), 16.4 (CH_3, $J_{(C-P)}$ = 8.3 Hz, Et); HRMS: m/z $C_{12}H_{24}PSO_5N^+$ $[M+NH_4]^+$ calcd 307.0764, found 307.0766.

Preparation of 3-(benzyloxy)-6-((benzylsulfonyl)methyl)-5-chloro-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-3,6-dihydro-2*H*-pyran (175)

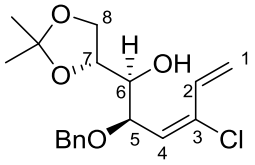


A solution of sulfone **174** (360 mg, 1.18 mmol) in tetrahydrofuran (6 mL) was treated with sodium hydride (50 mg, 1.18 mmol), then stirred at 0 °C for 20 minutes. To this white suspension hemiacetal

67 (249 mg, 0.73 mmol) in tetrahydrofuran (3 mL) was added. Then the mixture was allowed to warm to room temperature and stirred for one day. The reaction mixture was diluted with sat. ammonium chloride solution (20 mL), then extracted with dichloromethane (3x10 mL). The organic fractions were combined, dried, filtered and concentrated to provide crude yellow oil. Upon purification by column chromatography (2:1 petroleum ether: ethyl acetate), pyranosyl sugar sulfone **175** (61 mg, 47%) was obtained as a white crystalline solid.

R_f 0.35 (2:1 petroleum ether: ethyl acetate); m.p. 203.2-204.1 °C; $[\alpha]_D^{22}$ = -40 (*c* 0.05, Et_2O); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.46-7.36 (complex m, 10H, 2Bn), 6.19 (dd, *J* = 5.7, 1.6 Hz, 1H, H-5), 5.00 (dt, *J* = 9.8, 1.7 Hz, 1H, H-3), 4.68 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.64 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.38 (d, *J* = 13.9 Hz, 1H, H-1a), 4.36-4.33 (complex m, 1H, H-8), 4.33 (d, *J* = 13.9 Hz, 1H, H-1b), 4.17 (dd, *J* = 8.8, 5.8 Hz, 1H, H-9a), 4.09 (dd, *J* = 8.8, 6.4 Hz, 1H, H-9b), 3.95 (dd, *J* = 5.8, 2.4 Hz, 1H, H-6), 3.76 (dd, *J* = 6.3, 2.4 Hz, 1H, H-7), 3.43 (dd, *J* = 14.8, 9.9 Hz, 1H, H-2a), 3.27 (dd, *J* = 14.8, 2.1 Hz, 1H, H-2b), 1.35 (s, 3H $(CH_3)_2C$), 1.34 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.7 (C, Bn), 134.5 (C, C-4), 128.5 (CH, Bn), 130.7 (C, Bn (sulfone)), 129.44 (CH, Bn), 129.25 (CH, Bn), 124.13 (CH, Bn), 129.02 (CH, Bn), 128.56 (CH, Bn), 128.49 (CH, Bn), 128.00 (CH, Bn), 124.3 (CH, C-5), 108.7 (C, $(CH_3)_2C$), 74.0 (CH, C-8), 72.0 (CH_2, $PhCH_2$), 71.7 (CH, C-7), 71.6 (CH, C-3), 68.9 (CH, C-6), 66.3 (CH_2, C-9), 61.0 (CH_2, C-1), 50.4 (CH_2, C-2), 26.8 (CH_3, $(CH_3)_2C$), 25.1 (CH_3, $(CH_3)_2C$); IR (film from $CDCl_3$) ν_{max} 2987, 1736, 1652, 1495, 1455, 1372, 1308, 1214, 1120, 1088, 908, 728, 697, 648 cm^{-1}; HRMS: m/z $C_{25}H_{33}ClO_6SN^+$ $[M+NH_4]^+$ cacld 510.1712 found 510.1712. .

Preparation of (1*S*,2*R*,*E*)-2-(benzyloxy)-4-chloro-1-((*R*)-*2*,*2*-dimethyl-1,3-dioxolan-4-yl)hexa-3,5-dien-1-ol (68)

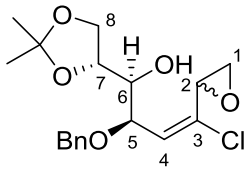


A solution of methyl triphenylphosphonium bromide (4.20 g, 11.75 mmol) in tetrahydrofuran (20 mL) was cooled to −78 °C, then treated with nBuLi (5.87 mL, 11.75 mmol) and stirred at −78 °C for one hour. The mixture was treated with a solution of hemiacetal **67** (1.99 g, 5.87 mmol) in tetrahydrofuran (10 mL), then allowed to warm to room temperature. The reaction was refluxed in tetrahydrofuran for two hours, then diluted with sat. ammonium chloride solution (50 mL) and extracted with diethyl ether (2x20 mL). The organic fractions were combined, dried, filtered and concentrated to provide crude brown oil. Upon purification by column chromatography (5:1

petroleum ether: ethyl acetate), diene **68** (1.07 g, 39%) was obtained as a pale yellow oil. The spectral data matched those reported data.[45]

R_f 0.31 (5:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.37–7.30 (complex m, 5H, Bn), 6.61 (dd, *J* = 16.3, 10.7 Hz, 1H, H-2), 5.99 (dd, *J* = 9.8, 0.8 Hz, 1H, H-4), 5.82 (d, *J* = 16.1 Hz, 1H, H-1a), 5.40 (dd, *J* = 10.8, 1.0 Hz, 1H, H-1b), 4.64 (d, *J* = 11.5 Hz, 1H, $PhCH_2$), 4.49 (dd, *J* = 9.8, 3.0 Hz, H-5), 4.41 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.11 (dt, *J* = 7.5, 5.9 Hz, 1H, H-7), 4.04 (dd, *J* = 8.4, 6.2 Hz, 1H, H-8a), 3.98 (dd, *J* = 8.4, 5.5 Hz, 1H, H-8b), 3.51 (dd, *J* = 7.5,2.7 Hz, 1H, H-6), 2.40 (brs, 1H, OH), 1.38 (s, 3H, $(CH_3)_2C$), 1.34 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.4 (C, Bn), 134.9 (C, C-3), 128.5 (CH, Bn), 128.4 (CH, C-2), 128.2 (CH, C-4), 127.9 (CH, Bn), 120.7 (CH_2, C-1), 109.2 (C, $(CH_3)_2C$), 75.4 (CH, C-7), 75.0 (CH, C-6), 73.3 (CH, C-5), 70.6 (CH_2, $PhCH_2$), 66.7 (CH_2, C-8), 26.8 (CH_3, $(CH_3)_2C$), 25.3 (CH_3, $(CH_3)_2C$).

Preparation of (1*S*,2*R*,*E*)-2-(benzyloxy)-4-chloro-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(oxiran-2-yl)but-3-en-1-ol (69)

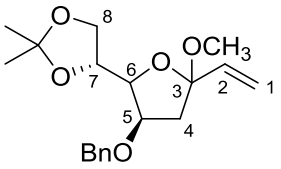


A solution of diene **68** (119 mg, 0.35 mmol) in dichloromethane (5 mL) was treated with *m*-CPBA (173 mg, 0.70 mmol, 77% (w/w)). The mixture was stirred at room temperature for two days, then diluted with sat. sodium bicarbonate solution (20 mL) and water (10 mL), then diethyl ether (30 mL). The mixture was stirred vigorously for few minutes, then the phases were separated. The ethereal fraction was washed with brine (10 mL), dried, filtered and concentrated to provide a colourless oil. Upon purification by column chromatography (3:1 petroleum ether: ethyl acetate), a mixture of epoxides **69** obtained as a colourless oil (1:1 ratio, 58 mg, 47%). The spectral data matched that reported previously.[45]

R_f 0.3 (3:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.41–7.29 (complex m, 5H, Bn), 6.17 (d, *J* = 9.8 Hz, 1H, H-4), 6.14 (d, *J* = 9.8 Hz, 1H, H-4), 4.68 (d, *J* = 11.4 Hz, 1H, $PhCH_2$), 4.59 (dd, *J* = 9.8, 2.7 Hz, 1H, H-5), 4.48 (d, *J* = 11.5 Hz, 1H, $PhCH_2$), 4.14–3.97 (complex m, 3H, H-7, 8a, 8b), 3.72 (m, 1H, H-2), 3.66 (m, 1H, H-2), 3.53–3.48 (complex m, 1H, H-6), 3.05 (dd, *J* = 5.5, 2.3 Hz, 1H, H-1a), 2.99 (dd, *J* = 5.5, 2.4 Hz, 1H, H-1a), 2.92 (dd, *J* = 5.4, 4.2 Hz, 1H, H-1b), 2.86 (dd, *J* = 5.4, 4.1 Hz, 1H, H-1b), 2.46 (brs, 1H, OH), 1.39 (s, 3H, $(CH_3)_2C$), 1.37 (s, 3H, $(CH_3)_2C$), 1.35 (s, 3H, $(CH_3)_2C$), 1.33 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.2 (C, 2xBn), 133.7 (C, C-3), 133.5 (C, C-3), 132.0 (CH,

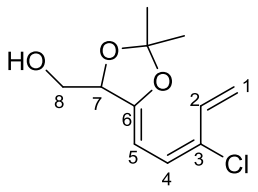
C-4), 131.3 (CH, C-4), 128.5 (CH, Bn), 128.03 (CH, Bn), 128.00 (CH, Bn), 127.96 (CH, Bn), 127.92 (CH, Bn), 109.3 (C, $(CH_3)_2C$), 109.2 (C, $(CH_3)_2C$), 75.5 (CH, 2xC-7), 75.2 (CH, C-6), 75.0 (CH, C-6), 73.3 (CH, C-5), 73.1 (CH, C-5), 70.9 (CH_2, 2x$PhCH_2$), 66.8 (CH_2, C-8), 66.7 (CH_2, C-8), 49.4 (CH, C-2), 48.7 (CH, C-2), 46.6 (CH_2, C-1), 46.5 (CH_2,C-1), 26.8 (CH_3, $(CH_3)_2C$), 26.7 (CH_3, $(CH_3)_2C$), 25.3 (CH_3, $(CH_3)_2C$), 25.2 (CH_3,$(CH_3)_2C$).

Preparation of (4*R*)-4-((3*R*)-3-(benzyloxy)-5-methoxy-5-vinyltetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane (245) and ((*Z*)-5-((*E*)-3-chloropenta-2,4-dien-1-ylidene)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (246)



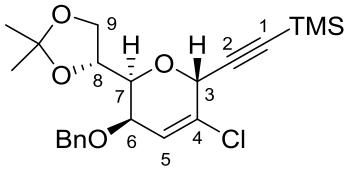
Diene **68** (34 mg, 0.083 mmol) in 1mL of methanol was introduced to solution of 0.016 mg (0.2 mmol) of $PdCl_2(PPh_3)$ and 0.023 mL (0.16 mmol) of triethylamine. Then flask was connected to the condenser attached with CO balloon. CO was purged through the flask for several times and reflux for 18.5 hours under CO atmosphere. Then mixture was diluted up with 5 mL ethyl acetate and filtered through the Celite®. Then reaction mixture was work-up with 5 mL of water and washed with brine (5 mL) and dried over anhy. magnesium sulphate. The crude product was purified with column chromatography to obtain **245** and **246** as pale yellow oils (**245**, 18 mg 18%) and (**246**, 13 mg, 19%, unstable).

(**245**) R_f 0.21 (5:1 petroleum ether: ethyl acetate); $[\alpha]_D^{22}$ = -148 (*c* 0.2, Et_2O); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.35–7.30 (complex m, 5H, Bn), 5.84 (dd, *J* = 17.3, 10.7 Hz, 1H, H-2), 5.49 (dd, *J* = 17.3, 1.7 Hz, 1H, H-1a), 5.27 (dd, *J* = 10.8, 1.7 Hz, 1H, H-1b), 4.53 (d, *J* = 10.9 Hz, 1H, $PhCH_2$), 4.49-4.46 (complex m, 1H, H-7), 4.48 (d, *J* = 12.0 Hz, $PhCH_2$), 4.29 (complex m, 1H, H-5), 4.16-4.12 (complex m, 2H, H-6 and H-8a), 4.04 (dd, *J* = 8.3, 6.4 Hz, 1H, H-8b), 3.15 (s, 3H, OCH_3), 2.36 (dd, *J* = 13.9, 6.6 Hz, 1H, H-4a), 2.05 (dd, *J* = 14.0, 3.4, 1H, H-4b), 1.46 (s, 3H, $(CH_3)_2C$), 1.40 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 138.3 (C, Bn), 136.4 (CH, C-2), 127.51 (CH, Bn), 127.36 (CH, Bn), 127.31 (CH, Bn), 116.9 (CH_2, C-1), 108.7 (C, $(CH_3)_2C$), 107.3 (C, C-3), 81.1 (CH, C-6), 78.6 (CH, C-5), 73.7 (CH, C-7), 71.4 (CH_2, $PhCH_2$), 66.8 (CH_2, C-8), 49.6 (CH_3, OCH_3), 45.6 (CH_2, C-4), 26.6 (CH_3, $(CH_3)_2C$), 25.7 (CH_3, $(CH_3)_2C$); IR (film from Et_2O) ν_{max} 2986, 1725, 1710, 1690, 1659, 1583, 1529, 1482, 1369, 1325, 1211, 1046, 967, 849 cm^{-1}.



(**246**) ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 6.47 (dd, *J* = 17.6, 11.2 Hz, 1H, H-2), 6.34 (d, *J* = 3.2, Hz, 1H, H-4), 6.21 (d, *J* = 3.1 Hz, 1H, H-5), 5.68 (dd, *J* = 17.6, 1.2 Hz, 1H, H-1a), 5.17 (dd, *J* = 11.2, 1.2 Hz, 1H, H-1b), 5.09 (t, *J* = 7.0 Hz, H-7), 4.25 (dd, *J* = 8.3, 6.6 Hz, 1H, H-8a), 4.12 (dd, *J* = 8.3, 7.3 Hz, 1H, H-8b), 1.52 (s, 3H, $(CH_3)_2C$), 1.46 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 153.5 (C, C-3), 151.2 (C, C-6), 124.8 (CH, C-2), 112.7 (CH, C-1), 110.3 (CH, C-4), 108.6 (CH, C-5), 71.4 (CH, C-7), 68.1 (CH_2, C-8), 26.3 (CH_3, $(CH_3)_2C$), 26.0 (CH_3, $(CH_3)_2C$). Unstable-unable to be fully characterised.

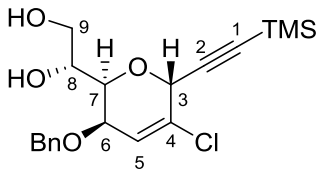
Preparation of (((2*R*,5*R*,6*S*)-5-(benzyloxy)-3-chloro-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-2*H*-pyran-2-yl)ethynyl)trimethylsilane (129) and (*R*)-1-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-chloro-6-((trimethylsilyl)ethynyl)-3,6-dihydro-2*H*-pyran-2-yl)ethane-1,2-diol (194)



Bis(trimethyl)silyl acetylene (0.24 mL, 1.04 mmol) was dissolved in 3 mL of dry dicloromethane and cooled to 0°C. Then acetyl pyranoside **66** (100 mg, 0.26 mmol) was dissolved. Then, 0.26 mL (1M solution in dichloromethane) of $SnCl_4$ was added dropwise to the solution of **66**. Combined solution was stirred for 30 minutes at same temperature to provide sugar acetylenes **129** and **194**. Reaction was quenched with 5 mL of sat. solution of sodium bicarbonate and extracted into dichloromethane (3x10 mL). Crude product was purified by silica gel column chromatograpy to obtain **129** (29.5 mg, 27%) as colourless oil with 20:1 petroleum ether: ethyl acetate. Diol **194** was obtained (9 mg, 9%) as colourless oil with 2:1 petroleum ether: ethyl acetate.

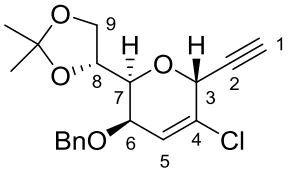
(**129**) R_f 0.33 (20:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -87.5 (*c* 0.4, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.39–7.30 (complex m, 5H, Bn), 6.06 (dd, *J* = 5.7, 1.3 Hz, 1H, H-5), 4.86 (d, *J* = 1.2 Hz, 1H, H-3), 4.69 (s, 2H, $PhCH_2$), 4.40 (ddd, *J* = 8.7, 6.1, 5.3 Hz, 1H, H-8), 4.17 (dd, *J* = 8.6, 6.4 Hz, 1H, H-9a), 3.98 (complex m, 2H, H-6, 9b), 3.88 (dd, *J* = 8.6, 2.1 Hz, 1H, H-7), 1.43 (s, 3H, $(CH_3)_2C$), 1.41 (s, 3H, $(CH_3)_2C$), 0.19 (s, 9H, (CH_3)TMS); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 138.1 (C, Bn), 134.5 (C, C-4), 128.37 (CH, Bn), 128.07 (CH, Bn), 127.80 (CH, Bn), 122.9 (CH, C-5), 109.4 (C, $(CH_3)_2C$), 99.4 (C, C-2), 92.0 (C, C-1), 74.4 (CH, C-7), 72.9 (CH, C-8), 72.1 (CH_2, $PhCH_2$), 69.0 (CH, H-6), 68.0 (CH, C-3), 67.6 (CH_2, C-9),

26.8 (CH_3, $(CH_3)_2C$), 25.5 (CH_3, $(CH_3)_2C$), -0.3 (CH_3, TMS); IR (film from CH_2Cl_2) ν_{max} 3063, 3032, 2986, 2959, 2898, 1650, 1455, 1380, 1371, 1251, 1213, 1085, 1068, 1037, 845, 761, 737, 699 cm^{-1}; HRMS: m/z $C_{22}H_{30}ClO_4Si^+$ $[M+H]^+$ calcd 421.1596, found 421.1623.



(**194**) R_f 0.10 (5:1 petroleum ether: ethyl acetate); $[\alpha]_D^{19}$ = -112 (*c* 0.6, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.38–7.32 (complex m, 5H, Bn), 6.17 (dd, *J* = 5.7, 1.3 Hz, 1H, H-5), 4.90 (d, *J* = 1.2, 1H, H-3), 4.74 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.60 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.08 (dd, *J* = 5.8, 2.3 Hz, 1H, H-6), 4.01 (complex m, 1H, H-8), 3.96 (dd, *J* = 8.8, 2.4 Hz, 1H, H-7), 3.85-3.80 (complex m, 2H, H-9), 2.40 (d, *J* = 5.9 Hz, 1H, OH-8), 1.83 (brs, 1H, OH-9), 0.19 (s, 9H, CH_3 TMS); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.7 (C, Bn), 135.1 (C, C-4), 128.66 (CH, Bn), 128.17 (CH, Bn), 128.05 (CH, Bn), 122.2 (CH, C-5), 99.3 (C, C-2), 92.1 (C, C-1), 72.7 (CH, C-7), 71.2 (CH_2, $PhCH_2$), 69.8 (CH, C-8), 68.4 (CH, C-3 and CH, C-6), 64.1 (CH_2, C-9), -0.4 (CH_3, TMS) ν_{max} 3692, 3637, 2496, 3475, 2531, 2372, 1724, 1455, 1380, 1371, 1251, 1085, 1068, 1037, 845, 761, 737 cm^{-1}; HRMS: m/z $C_{19}H_{25}ClO_4SiNa^+$ $[M+Na]^+$ calcd 403.1103, found 403.1096.

Preparation of (2*S*,3*R*,6*R*)-3-(benzyloxy)-5-chloro-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-ethynyl-3,6-dihydro-2*H*-pyran (190)

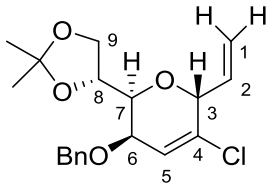


73 mg (0.152 mmol) of compound **129** was dissolved in 4 mL of dichloromethane and treated with 50 mg (0.76 mmol) of K_2CO_3 and 0.8 mL of methanol at room temperature. Then it was stirred for three hours at room temperature. The solution was diluted with another 8 mL of dichloromethane and work up with saturated sodium chloride solution. The combined organic layers were dried over anhy. magnesium sulfate. The terminal alkyne **190** was obtained as colourless oil and purified from silica gel chromatography (48 mg, 79%, highest yield).

R_f 0.27 (9:1 petroleum ether: ethyl acetate); $[\alpha]_D^{20}$ = -140 (*c* 0.8, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.39–7.30 (complex m, 5H, Bn), 6.11 (dd, *J* = 5.8, 1.3 Hz, 1H, H-5), 4.90 (apparent t, *J* = 1.7 Hz, 1H, H-3), 4.70 (s, 2H, $PhCH_2$), 4.41 (ddd, *J* = 8.4, 6.3, 2.2 Hz, 1H, H-8), 4.16 (dd, *J* = 8.7, 6.3 Hz, 1H, H-9a),

4.01 (dd, *J* = 8.6, 5.2 Hz, 1H, H-9b), 3.98 (dd, *J* = 5.8, 2.2 Hz, 1H, H-6), 3.87 (dd, *J* = 8.3, 2.2 Hz, 1H, H-7), 2.52 (d, *J* = 2.1 Hz, H-1) 1.43 (s, 3H,$(CH_3)_2C$), 1.41 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 138.0 (C, Bn), 134.1 (CH, C-4), 128.39 (CH, Bn), 128.06 (CH, Bn), 127.87 (CH, Bn), 123.0 (CH, C-5), 109.4 (C, $(CH_3)_2C$), 78.1 (C, C-2), 74.8 (CH, C-1), 74.5 (CH, C-7), 73.0 (CH, C-8), 72.1 (CH_2, $PhCH_2$), 68.9 (CH, C-6), 67.7 (CH, C-3), 67.4 (CH_2, C-9), 26.9 (CH_3, $(CH_3)_2C$), 25.3 (CH_3, $(CH_3)_2C$); HRMS: m/z $C_{19}H_{25}ClO_4N^+$ $[M+NH_4]^+$ calcd 366.1467, found 366.1481.

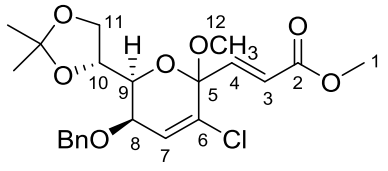
Preparation of (2*S*,3*R*,6*R*)-3-(benzyloxy)-5-chloro-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-vinyl-3,6-dihydro-2*H*-pyran (195)



To a solution of **190** (48 mg, 0,14 mmol) in ethyl acetate (2 mL), Lindlar's catalyst (24 mg) and 2-methyl-2-butene (0.1 mL) were added at room temperature. The mixture was vigorously stirred under hydrogen atmosphere (H_2 bubbling through the solution) for 2.5 hours. The catalyst was removed by filtration through a Celite® pad and the solvent evaporated *in vacuo*. The residue was purified by silica gel chromatography to obtain **195** (36 mg, 73%) as a colourless oil.

R_f 0.37 (14:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -88 (*c* 0.1, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.38–7.26 (complex m, 5H, Bn), 6.14 (dd, *J* = 5.6, 1.1 Hz, 1H, H-5), 5.89 (ddd, *J* = 15.9, 10.6, 5.3 Hz, 1H, H-2), 5.43 (d, *J* = 10.3 Hz, 1H, H-1a), 5.41 (d, *J* = 15.9 Hz, 1H, H-1b), 4.72 (d, *J* = 11.4 Hz, 1H, $PhCH_2$), 4.71 (complex m, 1H, H-3), 4.66 (dd, *J* = 11.6, 1H, $PhCH_2$), 4.38 (m, 1H, H-8), 4.13 (dd, *J* = 8.5, 6.3 Hz, 1H, H-9a), 3.97 (dd, *J* = 8.6, 5.7 Hz, 1H, H-9b), 3.90 (dd, *J* = 5.6, 2.3 Hz, 1H, H-6), 3.67 (dd, *J* = 7.6, 2.2 Hz, 1H, H-7), 1.42 (s, 3H, $(CH_3)_2C$), 1.40 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 138.1 (C, Bn), 136.3 (C, C-4), 131.4 (CH, C-2), 128.4 (CH, Bn), 128.0 (CH, Bn), 127.8 (CH, Bn), 123.0 (CH, C-5), 120.0 (CH_2, C-1), 109.0 (C, $(CH_3)_2C$), 76.5 (CH, C-3), 73.8 (CH, C-8), 72.3 (CH, C-7), 71.8 (CH_2, $PhCH_2$), 69.6 (CH, C-6), 67.0 (CH_2, C-9), 26.8 (CH_3, $(CH_3)_2C$), 25.4 (CH_3, $(CH_3)_2C$); IR (film from $CDCl_3$) ν_{max} 3030, 2990, 2938, 2907, 2360, 1650, 1496, 1401, 1380, 1251, 1211, 1151, 1123, 1077, 987, 933, 910, 846 cm^{-1}; HRMS: m/z $C_{19}H_{24}ClO_4^+$ $[M+H]^+$ calcd 351.1363, found 351.1344.

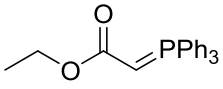
Preparation of methyl (*E*)-3-((5*R*,6*S*)-5-(benzyloxy)-3-chloro-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methoxy-5,6-dihydro-2*H*-pyran-2-yl)acrylate (251)



Acetylene **129** (34 mg, 0.083 mmol) in 1mL of methanol was introduced to solution of 0.016 mg (0.2 mmol) of $PdCl_2(PPh_3)$ and 0.023 mL (0.16 mmol) of triethylamine. Then flask was connected to the condenser attached with CO balloon. CO was purged through the flask for several times and refluxed for 18.5 hours under CO atmosphere. Then mixture was diluted up with ethyl acetate (10 mL) and filtered through the Celite®. Then water (5 mL) and extracted with dichloromethane (3x10 mL). Organic fractions were combined and washed with brine (10 mL) and dried over anhy. magnesium sulfate. The crude product was purified with column chromatography to obtain **251** as colourless oil (11 mg, 30%).

R_f 0.31 (2:1 petroleum ether: ethyl acetate); $[\alpha]_D^{22}$ = -33 (*c* 0.15, Et_2O); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.37–7.30 (complex m, 5H, Bn), 7.01 (d, *J* = 15.9 Hz, 1H, H-4), 6.38 (d, *J* = 15.8 Hz, 1H, H-3), 6.16 (d, *J* = 6.1 Hz, 1H, H-7), 4.66 (d, *J* = 11.7, 1H, $PhCH_2$), 4.59 (d, *J* = 12.0, 1H, $PhCH_2$), 4.43 (m, 1H, H-10), 4.17 (dd, *J* = 8.6, 6.2 Hz, 1H, H-11a), 4.06 (dd, *J* = 8.6, 5.9 Hz, 1H, H-11b), 4.01 (dd, *J* = 6.8, 2.4 Hz, 1H, H-9), 3.91 (dd, *J* = 6.2, 2.2 Hz, 1H, H-8), 3.78 (s, 1H, H-1(OCH_3)), 3.26 (s, 1H, H-12(OCH_3)), 1.42 (s, 3H, $(CH_3)_2C$), 1.40 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.0 (C, C-2), 142.6 (CH, C-4), 138.0 (C, Bn), 136.1 (CH, C-6), 128.42 (CH, Bn), 127.88 (CH, Bn), 127.80 (CH, Bn), 126.2 (CH, C-3), 124.8 (CH, C-7), 109.0 (C, $(CH_3)_2C$), 97.0 (C, C-5), 74.0 (CH, C-10), 72.0 (CH, C-9), 71.4 (CH_2, $PhCH_2$), 68.8 (CH, C-8), 66.7 (CH_2, C-11), 51.9 (CH_3, C-1), 50.4 (CH_3, C-12), 26.7 (CH_3,$(CH_3)_2C$), 25.2 (CH_3,$(CH_3)_2C$); IR (film from Et_2O) ν_{max} 2986, 1725, 1436, 1371, 1303, 1272, 1171, 1110, 1075, 987, 855, 737, 698 cm^{-1}; HRMS: m/z $C_{22}H_{31}ClO_7N^+$ $[M+NH_4]^+$ calcd 456.1784 found 456.1774.

Preparation of ethoxycarbonyl(methylene)triphenylphosphorane



Step 1

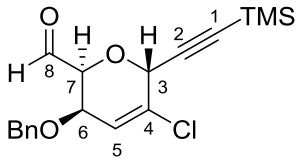
Ethyl-*2*-bromoacetate (5.00 mL, 0.045 mmol) toluene (50 mL) was slowly added to a solution of triphenylphosphine (11.80 g, 0.045 mmol) in toluene (50 mL). The reaction mixture was then stirred

at room temperature for overnight and the white precipitate filtered off, washed with diethyl ether (4×25 mL), and dried under vacuum for 1 hour to obtain (Ethoxycarbonylmethyl)triphenyl-phosphonium Bromide as a white powder (14.96 g, 77.8%).

Step 2

A solution of sodium hydroxide (1.0 M, 150 mL) was added to a solution of Ethoxy carbonyl-methyltriphenylphosphonium bromide (14.96 g, 0.035 mmol) in dichloromethane (150 mL) and the reaction mixture stirred vigorously for 45 minutes. The organic layer was removed and the aqueous layer extracted with dichloromethane (3×25 mL). The combined organic layers were dried over anhy. magnesium sulfate and evaporated under vacuum to obtained Ethoxycarbonyl methylenetriphenylphosphorane as a white solid (4.78 g, 98.3%). The spectral data matched with the reported previously.[111] ^{1}H-NMR: ($CDCl_3$) δ_H 7.75-7.61 (m, 6H, Ph), 7.55 (s, 3H, Ph), 7.46 (s, 6H, Ph), 3.97 (s, 2H, Et), 2.88 (s, 1H), 1.06 (s, 3H, Et).

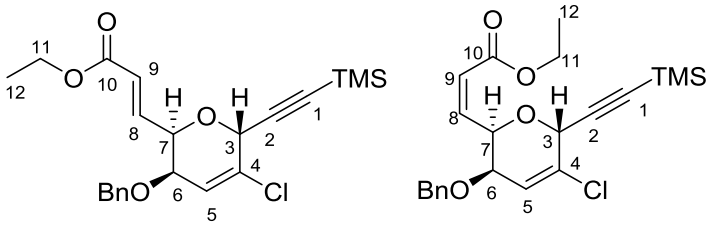
Preparation of (2*S*,3*R*,6*R*)-3-(benzyloxy)-5-chloro-6-((trimethylsilyl)ethynyl)-3,6-dihydro-2*H*-pyran-2-carbaldehyde (224)



A solution of the **194** (92 mg, 0.24 mmol) in tetrahydrofuran (16.6 mL) and pH 7 buffer (3.3 mL) was treated with $NaIO_4$ (427 mg, 1.92 mmol) in one portion. The resulting mixture was stirred for 1 hour, diluted with brine (50 mL), and extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and evaporated to give **224** as colourless oil, which was used without further purification (66 mg, 79%).

^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 9.70 (s, 1H, H-8), 7.36–7.28 (complex m, 5H, Bn), 6.07 (dd, *J* = 5.5, 1.1 Hz, 1H, H-5), 5.07 (d, *J* = 1.2 Hz, 1H, H-3), 4.58 (d, *J* = 11.5 Hz, 1H, $PhCH_2$), 4.52 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.47 (d, *J* = 3.0 Hz, 1H, H-7), 4.17 (dd, *J* = 5.4 Hz, 3.1 Hz, 1H, H-6), 0.18 (s, 9H, (CH_3)TMS); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 199.4 (CH, C-8), 137.0 (C, C-4), 135.3 (C, Bn), 128.52 (CH, Bn), 128.08 (CH, Bn), 128.15 (CH, Bn), 121.1 (CH, C-5), 98.0 (C, C-2), 93.3 (C, C-1), 77.30 (CH, C-7), 71.6 (CH_2, $PhCH_2$), 69.6 (CH, C-6), 68.0 (CH, C-3), -0.37 (CH_3, TMS).

Preparation of ethyl (*E*)-3-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-chloro-6-((trimethylsilyl)ethynyl)-3,6-dihydro-2*H*-pyran-2-yl)acrylate (202) and ethyl (*Z*)-3-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-chloro-6-((trimethylsilyl)ethynyl)-3,6-dihydro-2*H*-pyran-2-yl)acrylate (226)



202 **226**

A) A solution of aldehyde **224** (50 mg, 0.14 mmol in 2 mL of dichloromethane) was treated with Ethoxycarbonyl(methylene)triphenylphosphorane (96 mg, 0.27 mmol) and stirred for 19 hours at room temperature. Then reaction was quenched with sat. solution of sodium bicarbonate (5 mL) and extracted into dichloromethane (2x5 mL). The combined organic layers were dried over anhy. magnesium sulfate and purified with column chromatography (14:1 petroleum ether: ethyl acetate) to provide **202** and **226** as colourless oils (53 mg, 91%, *E:Z* 1:1).

B) A solution of aldehyde **224** (71 mg, 0.20 mmol in 2.5 mL of tetrahydrofuran) was treated with Ethoxycarbonyl(methylene)triphenylphosphorane (140 mg, 0.4 mmol) and stirred for 19 hours at room temperature. Then reaction was quenched with sat. solution of sodium bicarbonate (5 mL) and extracted into dichloromethane (2x5 mL). The combined organic layers were dried over anhy. magnesium sulfate and purified with column chromatography (14:1 petroleum ether: ethyl acetate) to provide **202** and **226** as (80 mg, 96%, *E:Z* 1:1).

C) A solution of aldehyde **224** (28 mg, 0.11 mmol in 2 mL of DMF) was treated with Ethoxycarbonyl(methylene)triphenylphosphorane (76 mg, 0.22 mmol) and stirred for 16 hours at room temperature. Then reaction was quenched with sat. solution of sodium bicarbonate (5 mL) and extracted into dichloromethane (2x5 mL). The combined organic layers were washed with saturated $CuSO_4$ (5x10 mL) and dried over anhy. magnesium sulfate and purified with column chromatography (14:1 petroleum ether: ethyl acetate) to provide **202** and **226** as colourless oils (30 mg, 65%, *E:Z* 2:1).

D) A solution of aldehyde **224** (26 mg, 0.11 mmol in 2 mL of $CHCl_3$) was treated with Ethoxycarbonyl(methylene)triphenylphosphorane (75 mg, 0.22 mmol) and stirred for 19 hours at room temperature. Then reaction was quenched with sat. solution of sodium bicarbonate (5 mL) and

extracted into dichloromethane (2x5 mL). The combined organic layers were dried over anhy. magnesium sulfate and purified with column chromatography (14: petroleum ether: ethyl acetate) to provide **202** and **226** as colourless oils (38 mg, 84%, *E:Z* 1:2).

E) A solution of aldehyde **224** (22 mg, 0.07 mmol in 2 mL of toluene) was treated with Ethoxycarbonyl(methylene)triphenylphosphorane (55 mg, 0.15 mmol) and benzoic acid (1 mg, 0.007 mmol). Then it was stirred for 15 minutes at 80 °C. Then reaction was quenched with sat. solution of sodium bicarbonate (5 mL) and extracted into dichloromethane (2x5 mL). The combined organic layers were dried over anhy. magnesium sulfate and purified with column chromatography (14:1 petroleum ether: ethyl acetate) to provide **202** and **226** as colourless oils (15 mg, 53%, *E:Z* 1:1).

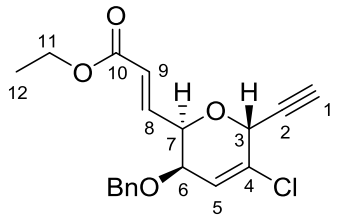
F) A solution of triethyl phosphonoacetate was added to the solvent of tetrahydrofuran (1.5 mL) at -78 °C. Then LiHMDS (0.26 mL, 0.26 mmol) was added drop wise until the solution turned into pale yellow colour. Then combined solution mixture was stirred for 30 minutes at -78 °C. Then aldehyde **224** (50 mg, 0.14 mmol in 2 mL of tetrahydrofuran) was added at -78 °C and stirring was continued for another 15 minutes at same temperature. The temperature of the reaction mixture was slowly increased to room temperature and stirring was continued for another 10 minutes. Then reaction was quenched with sat. solution of sodium bicarbonate (5 mL) and extracted into dichloromethane (2x5 mL). The combined organic layers were dried over anhy. magnesium sulfate and purified with column chromatography (14:1 petroleum ether: ethyl acetate) to provide **202** and **226** as colourless oils (41 mg, 70%, *E:Z* 1:1).

(**202**) R_f 0.20 (14:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -241 (*c* 0.95, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.34–7.28 (complex m, 5H, Bn), 7.05 (dd, *J* = 15.9, 4.0 Hz, 1H, H-9), 6.23 (dd, *J* = 15.9, 1.8 Hz, 1H, H-8), 6.09 (d, *J* = 5.3 Hz, 1H, H-5), 5.00 (s, 1H, H-3), 4.71 (m, 1H, H-7), 4.60 (d, *J* = 11.9 Hz, 1H, $PhCH_2$), 4.52 (d, *J* = 11.9 Hz, 1H, $PhCH_2$), 4.24 (q, *J* = 7.1 Hz, 2H, H-11), 3.97 (dd, *J* = 5.4, 2.8 Hz, 1H, H-6), 1.32 (t, *J* = 7.1 Hz, 3H, H-12), 0.18 (s, 9H, (CH_3)TMS); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.1 (C, C-10), 142.8 (CH, C-9), 137.5 (C, Bn), 135.1 (CH, C-4), 128.37 (C, C-4), 128.46 (CH, Bn), 127.99 (CH, Bn), 127.77 (CH, Bn), 126.6 (CH, C-8), 122.0 (CH, C-5), 98.8 (C, C-2), 92.6 (C, C-1), 72.2 (CH, C-7), 71.0 (CH_2, $PhCH_2$), 70.2 (CH, C-6), 68.2 (CH, C-3), 60.5 (CH_2, C-11), 14.3 (CH_3, C-12), -0.32 (CH_3, TMS); IR ν_{max} (Film from CH_2Cl_2) 2960, 2360, 1717, 1654, 1455, 1303, 1251, 1180, 1089, 1030, 920, 843, 761, 736, 698 cm^{-1}. HRMS: m/z $C_{22}H_{28}ClO_4Si^+$ $[M+H]^+$ calcd 419.1440 found 419.1433

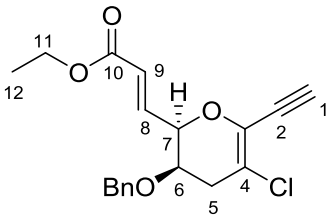
(**226**) R_f 0.33 (14:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -177 (*c* 0.9, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.34–7.28 (complex m, 5H, Bn), 6.38 (dd, *J* = 11.8, 6.9 Hz, 1H, H-8), 6.08 (dd, *J* = 5.5, 1.0 Hz, 1H, H-5), 5.95 (dd, *J* = 11.7, 1.5 Hz, 1H, H-8), 5.58 (ddd, *J* = 6.5, 4.3, 2.5 Hz, 1H, H-7), 4.93 (d, *J* = 1.2,

1H, H-3), 4.58 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.56 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.23 (dd, *J* = 5.5, 2.6 Hz, 1H, H-6), 4.17 (q, *J* = 7.4 Hz, 2H, H-11), 1.29 (t, *J* = 7.2 Hz, 3H, H-12), 0.17 (s, 9H, (CH_3)TMS); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 165.5 (C, C-10), 145.8 (CH, C-9), 137.7 (C, Bn), 134.5 (C, C-4), 128.34 (CH, Bn), 127.98 (CH, Bn), 127.85 (CH, Bn), 122.6 (CH, C-5), 120.6 (CH, C-3), 99.3 (C, C-2), 92.2 (C, C-1), 71.7 (CH_2, $PhCH_2$), 70.9 (CH, C-7), 70.3 (CH, C-8), 68.0 (CH, C-3), 60.4 (CH_2, C-11), 14.2 (CH_3, C-12), -0.37 (CH_3, TMS); IR ν_{max} (film from CH_2Cl_2) 2960, 2337, 2174, 1716, 1653, 1454, 1301, 1251, 1194,, 1087, 1029, 917, 845, 761, 737, 698 cm^{-1}.

Preparation of ethyl (*E*)-3-((2*R*,3*R*,6*R*)-6-acetyl-3-(benzyloxy)-5-chloro-3,6-dihydro-2*H*-pyran-2-yl)acrylate (203) and ethyl (*E*)-3-((2*R*,3*R*)-3-(benzyloxy)-5-chloro-6-ethynyl-3,4-dihydro-2*H*-pyran-2-yl)acrylate (204)



203



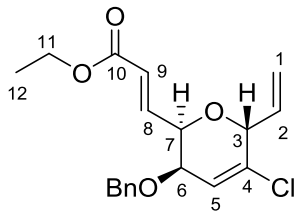
204

73 mg (0.17 mmol) of compound **202** was dissolved in 4 mL of dichloromethane and treated with 120 mg (0.87 mmol) of K_2CO_3 and 0.5 mL of methanol at room temperature. Then it was stirred for three and half hours at room temperature. The solution was diluted with another 8 mL of dichloromethane and work up with saturated sodium chloride solution. The combined organic layers were dried over anhy. magnesium sulfate. The crude material was purified by silica gel chromatography to obtain terminal alkyne as a colourless oil (28 mg, 46% (64 % brsm) 1:3 **204: 203**) and starting material (19 mg, 26%). The terminal alkyne mixture was used in hydrogenation and oxymercuration reactions reported below.

(**203/204**) R_f 0.15 (9:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.34–7.28 (complex m, 5H, Bn), 7.02 (dd, *J* = 15.8, 4.0 Hz, 0.75H, H-8), 6.92 (dd, *J* = 15.9, 4.0 Hz, 0.25H, H-8), 6.21 (dd, *J* = 15.7, 2.0 Hz, 1H, H-9), 6.13 (dd, *J* = 5.6, 1.2 Hz, 1H, H-5), 5.01 (s, 1H, H-3), 4.70 (complex m, 1H, H-7), 4.66 (d, *J* = 12.1 Hz, 0.25H, $PhCH_2$), 4.59 (d, *J* = 12.1 Hz, 0.75H, $PhCH_2$), 4.53 (d, *J* = 12.4 Hz, 0.25H, $PhCH_2$), 4.51 (d, *J* = 11.9 Hz, 0.75H, $PhCH_2$), 4.23 (q, *J* = 7.0 Hz, 2H, H-11), 3.97 (dd, *J* = 5.5, 2.8 Hz, 1H, H-6), 2.64 (dd, *J* = 17.9, 5.3 Hz, 0.25H, H-5a), 2.50 (d, *J* = 2.3 Hz, 0.75H, H-1), 2.48 (dd, *J* = 17.9, 6.0 Hz, 0.25H, H-5b), 1.31 (t, *J* = 7.2 Hz, 3H, H-12); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.0 (C, C-

10), 165.8 (C, C-10)$_{\mathbf{204}}$, 142.4 (CH, C-8), 141.0 (CH, C-8)$_{\mathbf{204}}$, 137.4 (C, Bn), 137.1 (C, Bn)$_{\mathbf{204}}$, 134.6 (CH, C-4), 132.7 (CH, C-4)$_{\mathbf{204}}$, 128.57 (CH, Bn), 128.02 (CH, Bn), 127.98 (CH, Bn), 123.7 (CH, C-9)$_{\mathbf{204}}$, 122.7 (CH, C-9), 122.4 (CH, C-5), 77.9 (C, C-2), 75.08 (C, C-1), 75.06 (CH, C-7), 72.3 (CH_2, $PhCH_2$)$_{\mathbf{204}}$, 71.6 (CH, C-7)$_{\mathbf{204}}$, 71.1 (CH_2, $PhCH_2$), 70.1 (CH, C-6), 67.5 (CH, C-3), 60.6 (CH_2, C-11)$_{\mathbf{204}}$, 60.5 (CH_2, C-11), 33.94 (CH_2, C-5)$_{\mathbf{204}}$ 14.3 (CH_3, C-12); HRMS: m/z $C_{19}H_{23}ClNO_4^+$ $[M+NH_4]^+$ calcd 364.1310 found 364.1328.

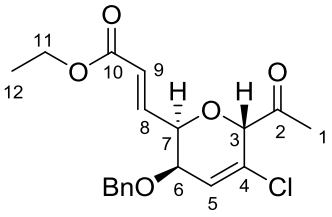
Preaparation of ethyl (*E*)-3-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-chloro-6-vinyl-3,6-dihydro-2*H*-pyran-2-yl)acrylate (207)



To a solution of **203/204** (48 mg, 0,14 mmol) in ethyl acetate (2 mL), Lindlar's catalyst (24 mg) and 2-methyl-2-butene (0.1 mL) were added at room temperature. The mixture was stirred vigorously under hydrogen atmosphere (H_2 bubbling through the solution) for one and half hour. The catalyst was removed by filtration through Celite® pad and the solvent evaporated under *vacuo*. The residue was purified by silica gel chromatography to obtain **207** (18 mg, 47%) as a colourless oil.

R_f 0.27 (14:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.54 – 7.36 (complex m, 5H, Bn), 7.02 (dd, *J* = 15.7, 4.1 Hz, 1H, H-8), 6.22 (dd, *J* = 15.9, 1.9, H, H-9), 6.15 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5), 5.88 (ddd, *J* = 15.4, 10.6, 4.8 Hz, 1H, H-2), 5.38 (m, 2H, H-1), 4.81 (d, *J* = 3.6 Hz, 1H, H-3), 4.62 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.54 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.45 (broad s, 1H, H-7), 4.23 (q, *J* = 7.2 Hz, 2H, H-11), 3.98 (dd, *J* = 5.0, 2.9 Hz, 1H, H-6), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.2 (C, C-10), 143.2 (CH, C-8), 137.7 (C, Bn), 136.3 (C, C-4), 131.2 (CH, C-2), 128.46 (CH, Bn), 127.96 (CH, Bn), 127.93 (CH, Bn), 122.7 (CH, C-5), 122.5 (CH, C-9), 119.3 (CH_2, C-1), 76.3 (CH, C-3), 70.9 (CH, C-7), 70.9 (CH_2, $PhCH_2$), 70.8 (CH, C-6), 60.5 (CH_2, C-11), 14.3 (CH_3, C-12); HRMS: m/z $C_{19}H_{25}ClO_4N^+$ $[M+NH_4]^+$ calcd 366.1467, found 366.1467.

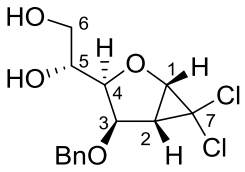
Preparation of ethyl (*E*)-3-((2*R*,3*R*,6*R*)-6-acetyl-3-(benzyloxy)-5-chloro-3,6-dihydro-2*H*-pyran-2-yl)acrylate



To a solution of the compound **203/204** (15 mg, 0.04 mmol) in tetrahydrofuran (0.2 mL) at room temperature was added solution of $HgSO_4$ (2.4 mg, 0.008 mmol, in 0.2 mL of 1M H_2SO_4 solution). This solution was stirred at room temperature until the starting material disappeared (2 hours). The mixture was diluted with diethyl ether (5 mL) and carefully neutralised with powder sodium bicarbonate until pH 7. The aqueous layer was washed with diethyl ether (3x5 mL). The organic layers were combined and dried over magnesium sulfate. The crude obtained was purified by column chromatography with silica gel with 5:1 (petroleum ether: ethyl acetate) to yield the methyl ketone **216** as colourless oil (5 mg, 32%).

R_f 0.23 (9:1 petroleum ether: ethyl acetate); $[\alpha]_D^{19}$ = -110 (*c* 0.2, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.35 – 7.26 (complex m, 5H, Bn), 6.99 (dd, *J* = 15.8, 4.2 Hz, 1H, H-8), 6.25 (d, *J* = 4.9 Hz, 1H, H-5), 6.20 (dd, *J* = 15.8, 1.8, H, H-9), 4.74 (s, 1H, H-3), 4.61 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.53 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.45 (m, 1H, H-7), 4.23 (q, *J* = 7.1 Hz, 2H, H-11), 3.98 (dd, *J* = 4.8, 3.2 Hz, 1H, H-6), 2.33 (s, 3H, H-1), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 202.7 (C, C-2), 165.9 (C, C-10), 142.1 (CH, C-8), 137.3 (C, Bn), 131.8 (C, C-4), 128.53 (CH, Bn), 128.08 (CH, Bn), 127.95 (CH, Bn), 124.3 (CH, C-5), 123.1 (CH, C-9), 80.1 (CH, C-3), 73.1 (CH, C-7), 71.2 (CH_2, $PhCH_2$), 70.4 (CH, C-6), 60.6 (CH_2, C-11), 28.1 (CH_3, C-1), 14.2 (CH_3, C-12); IR (film from $CDCl_3$) ν_{max}, 3660, 3343, 2979, 2961, 1640, 1403, 1266, 1222, 1210, 1163, 1124, 633 cm^{-1}; HRMS: m/z $C_{19}H_{25}ClO_5N^+$ $[M+NH_4]^+$ calcd 382.1412, found 384.1416.

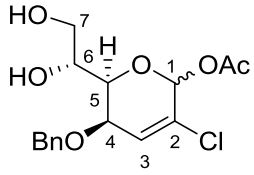
Preparation of (*R*)-1-((1*S*,3*R*,4*R*,5*R*)-4-(benzyloxy)-6,6-dichloro-2-oxabicyclo[3.1.0] hexan-3-yl)ethane-1,2-diol (157)



Cyclopropane **65** (0.197 g, 0.55 mmol) was dissolved in 2 mL of CH_3CN:H_2O (10:1) and cooled to 0 °C. Then it was treated with 0.5 mL of triflouroacetic acid and stirred at room temperature for 10 minutes. Then reaction mixture was diluted with 5 mL of dichloromethane and quenched with sat. solution of sodium bicarbonate. Aqueous layer was extracted with (2x5 mL) of dichloromethane. Combined organic fractions were dried over anhy. magnesium sulfate to obtain **157** as colourless oil. The product was used in cyclopropane ring expansion reaction straight after without any further purification (173 mg, quant.).

R_f 0.5 (1:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -37.5 (*c* 0.4, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.39–7.32 (complex m, 5H, Bn), 4.78 (d, *J* = 11.3 Hz, 1H, $PhCH_2$), 4.57 (d, *J* = 11.3 Hz, 1H, $PhCH_2$), 4.47 (d, *J* = 6.8 Hz, 1H, H-4), 4.31 (dd, *J* = 8.6, 7.0 Hz, 1H, H-3), 4.26 (d, *J* = 6.0 Hz, 1H, H-1), 3.94 (complex m, 1H, H-5), 3.80 (dd, *J* = 11.5, 3.3 Hz, 1H, H-6a), 3.66 (dd, *J* = 11.6, 5.8 Hz, 1H, H-6b), 2.48 (d, *J* = 5.8 Hz, 1H, H-2); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 136.3 (C, Bn), 128.94 (CH, Bn), 128.63 (CH, Bn), 127.92 (CH, Bn), 86.4 (CH, C-3), 81.2 (CH, C-4), 73.3 (CH_2, $PhCH_2$), 69.9 (CH, C-5), 67.9 (CH, C-1), 63.8 (CH_2, C-6), 61.6 (C, C-7), 37.9 (CH, C-2); IR (film from $CDCl_3$) ν_{max} 3660, 3300, 3063, 3031, 1933, 2874, 1496, 1454, 1354, 1193, 1110, 1091, 1045, 910, 857, 810, 737, 698, 649 cm $^{-1}$; HRMS: m/z $C_{14}H_{17}Cl_2O_4^+$ $[M+H]^+$ calcd 319.0498, found 319.0495.

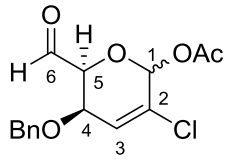
Preparation of (5*R*,6*R*)-5-(benzyloxy)-3-chloro-6-((*R*)-1,2-dihydroxyethyl)-5,6-dihydro-2*H*-pyran-2-yl acetate (158)



Cyclopropane diol **157** (163 mg, 0.51 mmol) was dissolved in 2 mL of glacial acetic acid and treated with silver acetate (150 mg, 0.89 mmol) and stirred at 90 °C for one hour. Then solution was dilute with 5 mL of dichloromethane and quenched with sat. solution of sodium bicarbonate. Aqueous layer was extracted with dichloromethane (2x10 mL) and combined organic fractions were dried over anhy. magnesium sulphate. Excess solvents were evaporated and rude product purified by silica gel column chromatography to obtain **158** as white solid (143 mg, 82%, 4:1 anomeric ratio, 76% over two steps)

R_f 0.16 (1:1 petroleum ether: ethyl acetate); m. p. 117.6 - 118.3 °C; ^{1}H-NMR (500 MHz): ($CDCl_3$); δ_H 7.36–7.33 (complex m, 5H, Bn), 6.36 (d, *J* = 5.8 Hz, 1H, H-3), 6.29 (s, 0.8H, H-1), 6.20 (s, 0.2H, H-1), 4.72 (d, *J* = 11.6 Hz, 1H, $PhCH_2$), 4.58 (d, *J* = 11.6 Hz, 1H, $PhCH_2$), 4.16 (m, 0.2H, H-4), 4.09 (dd, *J* = 5.9, 2.2 Hz, 0.8H, H-4), 4.00 (m, 2H, H-5 and H-6), 3.82 (dd, *J* = 11.3, 0.8Hz, 1H, H-7a), 3.66 (d, *J* = 4.6, 0.2H, H-7a), 3.62 (d, *J* = 4.9, 0.2H, H-7b), 3.67 (dd, *J* = 11.3, 3.9 Hz, 0.8H, H-7b), 2.17 (s, 0.6H, Ac), 2.12 (s, 0.24H, Ac); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 169.6 (C, CH_3CO), 137.5 (C, Bn), 133.1 (C, C-2), 128.72 (CH, Bn), 128.26 (CH, Bn), 127.97 (CH, Bn), 126.6 (CH, C-3)$_{\mathbf{158\beta}}$, 125.4 (CH, C-3), 89.8 (CH, C-1)$_{\mathbf{158\beta}}$, 89.2 (CH, C-1), 74.6 (CH_2, $PhCH_2$)$_{\mathbf{158\beta}}$, 71.3 (CH_2, $PhCH_2$), 71.1 (CH, C-6), 69.6 (CH, C-5)$_{\mathbf{158\beta}}$, 69.4 (CH, C-5), 68.9 (CH, C-4)$_{\mathbf{158\beta}}$,, 68.0 (CH, C-4) 63.5 (CH_2, C-7), 63.4 (CH_2, C-7)$_{\mathbf{158\beta}}$, 20.9 (CH_3, Ac); IR (film from CH_2Cl_2) ν_{max} 3256, 2938, 1745, 1655, 1455, 1371, 1227, 1135, 1056, 1007, 926, 857, 731, 695 cm^{-1}; HRMS: m/z $C_{16}H_{23}ClNO_6^+$ $[M+NH_4]^+$ calcd 360.1208, found 360.1212.

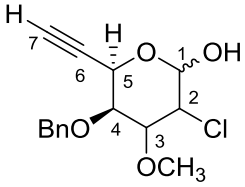
Preparation of (5*R*,6*S*)-5-(benzyloxy)-3-chloro-6-formyl-5,6-dihydro-2*H*-pyran-2-yl acetate (228)



A solution of the diol acetate **158** (91 mg, 0.26 mmol) in tetrahydrofuran (10 mL) and pH 7 buffer (3 mL) was treated with $NaIO_4$ (454 mg, 2.13 mmol) in one portion. The resulting mixture was stirred for 1 h, diluted with dichloromethane (50 mL). Then it was quenched with 0.2 M NaOH 10 mL and organic fractions were dried over Na_2SO_4 and evaporated to give colourless oil, which was used with the Ohira-Bestmann reagent in the following reaction without further purification (40 mg, 48%, 4:1 anomeric ratio).

^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 9.72 (s, 0.2H, H-8), 9.67 (s, 0.8H, H-8), 7.36–7.26 (complex m, 5H, Bn), 6.48 (s, 0.8H, H-1), 6.34 (s, 0.2H, H-1), 6.28 (d, *J* = 5.1 Hz, 0.2H, H-3), 6.26 (d, *J* = 5.8 Hz, 0.8H, H-3), 4.56 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.52 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.39 (apparent d, *J* = 2.9 Hz, 1H, H-5), 4.33 (dd, *J* = 5.2, 2.0 Hz, 0.2H, H-4), 4.26 (dd, *J* = 5.6 Hz, 3.2 Hz, 0.8H, H-4), 2.19 (s, 0.6H, Ac), 2.14 (s, 2.4H, Ac); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 199.1 (CH, C-6), 198.3 (CH, C-6)$_{\mathbf{228\beta}}$, 169.3 (C, Ac), 136.8 (C, Bn), 133.1 (C, C-2), 128.5 (CH, Bn), 128.3 (CH, Bn), 127.1 (CH, Bn), 126.20 (CH, C-3)$_{\mathbf{228\beta}}$, 124.3 (CH, C-3), 89.0 (CH, C-1)$_{\mathbf{228\beta}}$, 88.5 (CH, C-1), 76.1 (CH, C-5), 71.8 (CH_2, $PhCH_2$), 69.6 (CH, C-4)$_{\mathbf{228\beta}}$, 69.2 (CH, C-4), 20.9 (CH_3, Ac), 20.8 (CH_3, Ac)$_{\mathbf{no\beta}}$; IR (film from $CDCl_3$) ν_{max} 1745, 1290, 1215, 1128, 1064, 1024, 933, 910, 729, 693, 648 cm^{-1}.

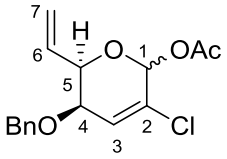
Preparation of (5*S*,6*R*)-5-(benzyloxy)-3-chloro-6-ethynyl-4-methoxytetrahydro-2*H*-pyran-2-ol (230)



A solution of the aldehyde **228** (40 mg, 0.13 mmol) in methanol (2 mL) was treated with K_2CO_3 (53 mg, 0.38 mmol) and Ohira-Bestmann reagent (53 mg, 0.26 mmol). The resulted yellow colour mixture was stirred for 1 h, diluted with diethyl ether (15 mL). Then it was quenched with saturated sodium bicarbonate 10 mL and extracted into diethyl ether (2x10 mL). Organic fractions were combined, dried over Na_2SO_4 and evaporated. Crude product was purified by silica get chromatography (1:1 petroleum ether: ethyl acetate) to give **230** as a colourless oil (10 mg, 27%, 4:1 anomeric mixture).

R_f 0.31 (1:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.38–7.26 (complex m, 5H, Bn), 4.95 (s, 0.2H, H-1), 4.94 (s, 0.8H, H-1), 4.71 (d, *J* = 10.4 Hz, 1H, $PhCH_2$), 4.69 (m, 2H, $PhCH_2$, H-5), 4.36 (apparent t, *J* = 4.2 Hz, 0.2H, H-4), 4.32 (apparent t, *J* = 4.6 Hz, 0.8H, H-4), 4.19 (m, 1H, H-3), 3.95 (m, 1H, H-2), 3.51 (s, 0.6H, OCH_3), 3.42 (s, 2.4H, OCH_3), 2.63 (d, *J* = 2.4 Hz, 0.8H, H-7), 2.60 (d, *J* = 2.5 Hz, 0.2H, H-7); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.4 (C, Bn), 128.51 (CH, Bn), 128.14 (CH, Bn), 128.06 (CH, Bn), 109.9 (CH, C-1), 103.1 (CH, C-1)$_{\mathbf{230\beta}}$, 85.9 (CH, C-5), 85.2 (CH, C-4), 79.5 (CH, C-6), 75.8 (CH, C-6), 72.6 (CH_2, $PhCH_2$), 72.1 (CH_2, $PhCH_2$)$_{\mathbf{230\beta}}$, 55.8 (CH_3, OCH_3)$_{\mathbf{230\beta}}$, 55.3 (CH_3, OCH_3), 47.6 (CH, C-2); IR (film from $CDCl_3$) ν_{max} 3784, 3670, 3643, 3031, 1227, 1135, 1060, 1017, 936, 857, 731 cm^{-1}; HRMS: m/z $C_{15}H_{21}ClO_4N^+$ $[M+NH_4]^+$ calcd 314.1154, found 314.1163.

Preparation of (5*R*,6*R*)-5-(benzyloxy)-3-chloro-6-vinyl-5,6-dihydro-2*H*-pyran-2-yl acetate 196

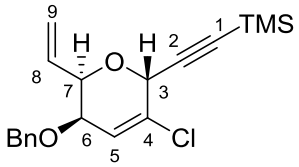


According to the procedure described by Reddy and co-workers,[79] diol acetae **158** (300 mg, 0.87 mmol) and *N,N*-Dimethylformamide dimethyl acetal (1.8 mL, 13.2 mmol) was stirred at 42 °C one day. The mixture was then concentrated in *vacuo*. After concentration, the residue was dissolved in acetic anhydride (1.6 mL) and the mixture was stirred for one day at 107 °C, then reaction diluted with 10 mL of Et_2O and quenched with 10 mL of saturated solution of sat. solution of sodium bicarbonate. Aqueous layer was extracted in to diethyl ether (3x10 mL) and concentrated in *vacuo*. The brown colour residue was purified by flash Chromatography (5:1 petroleum ether: ethyl acetate) to obtain alkene **196** acetate as colourless oil (101 mg, 39%, 4:1 anomeric mixture).

R_f 0.25 (5:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.31 (complex m, 5H, Bn), 6.42 (s, 0.8H, H-1), 6.28 (d, *J* = 5.9 Hz, 0.8H, H-3), 6.24 (s, 0.2H, H-1), 6.22 (d, *J* = 5.9 Hz, 0.2H, H-3), 6.15 (ddd, *J* = 17.0, 10.5, 5.9 Hz, 0.2H, H-6), 6.04 (ddd, *J* = 17.0, 10.5, 5.9 Hz, 0.8H, H-6), 5.45 (d, *J* = 17.3 Hz, 1H, H-7a), 5.34 (d, *J* = 10.5 Hz, 0.8H, H-7b), 5.29 (d, *J* = 10.5 Hz, 0.2H, H-7b), 4.62 (d, *J* = 12.1 Hz, 1H, $PhCH_2$), 4.56 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.51 (m, 0.8H, H-5), 4.40 (m, 0.2H, H-5), 4.15 (m, 0.2H, H-4), 3.88 (dd, *J* = 5.7, 2.8 Hz, 0.8H, H-4), 2.12 (s, 3H, Ac); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 169.5 (C, CH_3CO), 137.8 (C, Bn), 137.5 (C, Bn)$_{\mathbf{196\beta}}$, 133.1 (CH, C-6), 132.9 (CH, C-6)$_{\mathbf{196\beta}}$, 128.46 (CH, Bn), 128.35 (CH, C-3)$_{\mathbf{196\beta}}$, 127.98 (CH, Bn), 127.82 (CH, Bn), 125.7 (CH, C-3), 119.7 (CH_2, C-7)$_{\mathbf{196\beta}}$, 118.1 (CH_2, C-7), 89.1 (CH, C-1), 88.8 (CH, C-1)$_{\mathbf{196\beta}}$, 75.7 (CH, C-5)$_{\mathbf{196\beta}}$, 73.3 (CH, C-5), 71.6 (CH, $PhCH_2$)$_{\mathbf{196\beta}}$, 71.15 (CH, C-4)$_{\mathbf{196\beta}}$, 71.07 (CH, $PhCH_2$), 70.5 (CH, C-4), 21.0 (CH_3, Ac), 20.9 (CH_3, Ac)$_{\mathbf{196\beta}}$; IR (film from

$CDCl_3$) ν_{max} 2922, 2851, 2360, 2341, 1754, 1658, 1453, 1221, 1132, 1065, 1003, 914, 733, 668 cm^{-1}. HRMS: m/z $C_{16}H_{21}ClNO_4^+$ $[M+NH_4]^+$ calcd 326.1154, found 326.1148.

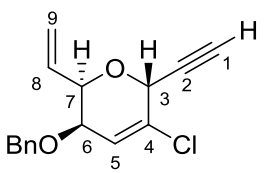
(((2*R*,5*R*,6*R*)-5-(benzyloxy)-3-chloro-6-vinyl-5,6-dihydro-2*H*-pyran-2-yl)ethynyl)trimethylsilane (197)



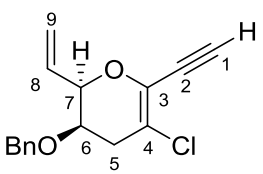
Bis(trimethyl)silyl acetylene (0.73 mL, 1.58 mmol) was dissolved in 5 mL of dry dichloromethane and cooled down to 0°C. Then Acetate **196** (122 mg, 0.39 mmol) was dissolved. $SnCl_4$ (0.39 mL, 0.39 mmol) was added dropwise to the solution. Combined solution was stirred for 20 minutes at same temperature to provide sugar acetylene **197**. Reaction was quenched with 5 mL of sat. solution of sodium bicarbonate and extracted into dichloromethane (3x10 mL). Crude product was purified by column chromatography (20:1 petroleum ether: ethyl acetate) to yield **197** as a colourless oil (126 mg, 92%).

R_f 0.36 (20:1 petroleum ether: ethyl acetate); $[\alpha]_D^{20}$ = -179 (*c* 0.9, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.34–7.28 (complex m, 5H, Bn), 6.08 (ddd, *J* = 17.1, 10.5, 5.8 Hz, 1H, H-8), 6.07 (d, *J* = 5.1 Hz, 1H, H-5), 5.46 (d, *J* = 17.3 Hz, 1H, H-9a), 5.35 (d, *J* = 10.8 Hz, 1H, H-9b), 4.96 (s, 1H, H-3), 4.62 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.56 (d, *J* = 10.8 Hz, 1H, $PhCH_2$), 4.54 (m, 1H, H-7), 3.88 (dd, *J* = 5.3, 2.7 Hz, 1H, H-5), 0.18 (s, 9H, TMS); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.9 (C, Bn), 134.8 (C, C-4), 133.7 (CH, C-5), 128.41 (CH, Bn), 127.88 (CH, Bn), 127.83 (CH, Bn), 122.5 (CH, C-8), 118.0 (CH_2, C-9), 99.5 (C, C-2), 91.9 (C, C-1), 74.0 (CH, C-7), 71.06 (CH, $PhCH_2$), 71.03 (CH, C-6), 68.1 (CH, C-3), -0.3 (CH_3, TMS); IR (film from $CDCl_3$) ν_{max} 2960, 2926, 2866, 1738, 1652, 1454, 1250, 1086, 1039, 930, 917, 842, 733, 697, 624 cm^{-1}; HRMS: m/z $C_{19}H_{27}ClNO_2Si^+$ $[M+NH_4]^+$ calcd 364.1494, found 364.1490.

Preparation of (2*R*,3*R*,6*R*)-3-(benzyloxy)-5-chloro-6-ethynyl-2-vinyl-3,6-dihydro-2*H*-pyran (205) and (2*R*,3*R*)-3-(benzyloxy)-5-chloro-6-ethynyl-2-vinyl-3,4-dihydro-2*H*-pyran (206)



205

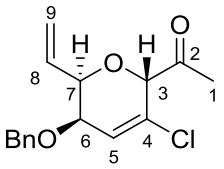


206

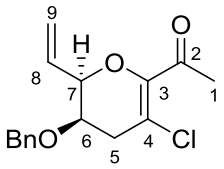
63 mg (0.18 mmol) of sugar acetylene compound **197** was dissolved in 5:1 dichloromethane: methanol and treated with 125 mg (0.91 mmol) of K_2CO_3. Then it was stirred for one and half hours at room temperature. The solution was diluted with another 10 mL of dichloromethane and solid materials were filtered off before the completion of the reaction. Then it was work up with saturated sodium chloride solution followed by extraction into dichloromethane (2x10 mL). The combined organic layers were dried over anhy. magnesium sulfate. The terminal alkyne was obtained in pure as colourless oil after column chromatography (20:1 petroleum ether: ethyl acetate (42 mg, 43% (49 % brsm (4:1 **205: 206**)) and 20 mg, 16% starting material).

(**205/206**) R_f 0.15 (20:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.34–7.29 (complex m, 5H, Bn), 6.12 (d, *J* = 5.4 Hz, 1H, H-5), 6.08 (ddd, *J* = 17.3, 10.8, 4.9 Hz, 0.8H, H-8), 5.98 (ddd, *J* = 17.5, 10.7, 5.5 Hz, 0.2H, H-8), 5.48 (d, *J* = 17.3 Hz, 1H, H-9a), 5.36 (d, *J* = 10.7 Hz, 1H, H-9b), 5.11 (s, 0.2H, H-3), 4.99 (s, 0.8H, H-3), 4.62 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.57 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.54 (complex m, 0.8H, H-7), 4.51 (complex m, 0.2H, H-7), 3.88 (dd, *J* = 5.4, 2.6 Hz, 0.8H, H-5), 3.85 (complex m, 0.2H, H-5), 2.63 (dd, *J* = 17.9, 5.4 Hz, 0.2H, H-5a), 2.52 (dd, *J* = 17.9, 5.7 Hz, 0.2H, H-5b), 2.51 (d, *J* = 1.4 Hz, 1H, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.9 (C, Bn), 137.5 (C, Bn)$_{\mathbf{206}}$, 134.4 (CH, C-8), 133.6 (C, C-4), 133.0 (CH, C-8)$_{\mathbf{206}}$, 132.1 (C, C-4)$_{\mathbf{206}}$, 128.43 (CH, Bn), 128.19 (CH, Bn), 127.97 (CH, Bn), 123.0 (CH, C-5), 118.0 (CH_2, C-9), 117.9 (CH_2, C-9)$_{\mathbf{206}}$, 78.4 (C, C-2), 74.6 (CH, C-1), 74.1 (CH, C-7), 71.13 (CH_2, $PhCH_2$), 71.07 (CH, C-6), 67.5 (CH, C-3), 33.9 (CH_2, C-5)$_{\mathbf{206}}$; IR (film from $CDCl_3$) ν_{max} 3273, 3038, 2891, 2866, 2114, 1655, 1454, 1250, 1336, 1109, 1062, 911, 729, 733, 693 cm^{-1}; HRMS: m/z $C_{16}H_{19}ClNO_2^+$ $[M+NH_4]^+$ calcd 292.1086, found 292.1099.

Preparation of 1-((2*R*,5*R*,6*R*)-5-(benzyloxy)-3-chloro-6-vinyl-5,6-dihydro-2*H*-pyran-2-yl)ethan-1-one (220) and 1-((2*R*,3*R*)-3-(benzyloxy)-5-chloro-2-vinyl-3,4-dihydro-2*H*-pyran-6-yl)ethan-1-one (221)



220



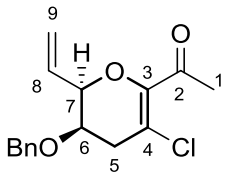
221

To a solution of the compounds **204/205** (42 mg, 0.15 mmol) in tetrahydrofuran (0.6 mL) at room temperature was added $HgSO_4$ (9 mg, 0.03 mmol, in 0.6 mL of 1M H_2SO_4 solution). This solution was stirred at room temperature until the starting material disappeared (2.5 hours). The mixture was diluted with diethyl ether (5 mL) and carefully neutralised with powder sat. solution of sodium bicarbonate until pH reached 7. The aqueous layer was washed with diethyl ether (3x5 mL). The

organic layers were combined and dried over anhy. magnesium sulfate. The crude obtained was purified by column chromatography with silica gel with 9:1 (petroleum ether: ethyl acetate) to yield the methyl ketone **220/221** as colourless oil (34 mg, 76% (4:1 **220:221**)).

(**220/221**)R_f 0.35 (9:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.28 (complex m, 5H, Bn), 6.23 (d, *J* = 4.9 Hz, 0.8H, H-5), 6.11 (d, *J* = 5.8 Hz, 0.2H, H-5), 6.08 (ddd, *J* = 17.4, 10.6, 5.8 Hz, 0.8H, H-8), 5.45 (d, *J* = 17.3 Hz, 1H, H-9a), 5.36 (d, *J* = 10.8 Hz, 1H, H-9b), 4.68 (s, 1H, H-3), 4.62 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.58 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.24 (complex m, 1H, H-7), 3.94 (dd, *J* = 5.4, 2.6 Hz, 0.8H, H-6), 3.83 (complex m, 0.2H, H-6), 2.69 (dd, *J* = 18.2, 5.2 Hz, 0.2H, H-5a), 2.58 (dd, *J* = 18.5, 4.9 Hz, 0.2H, H-5b), 2.36 (s, 0.6H, H-1), 2.32 (s, 2.4H, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 203.3 (C, C-2), 137.7 (C, Bn), 137.4 (C, Bn)**$_{221}$**, 133.0 (CH, C-8), 131.5 (C, C-4), 128.44 (CH, Bn), 128.24 (CH, Bn), 127.84 (CH, Bn), 124.9 (CH, C-5), 118.6 (CH_2, C-9), 80.2 (CH, C-3), 74.9 (CH, C-7), 71.3 (CH, C-6), 71.2 (CH_2, $PhCH_2$), 35.7 (CH2, C-5)**$_{221}$**, 27.7 (CH_3, C-1); IR (film from $CDCl_3$) ν_{max} 3065, 2868, 2360, 2341, 1725, 1708, 1650, 1604, 1454, 1355, 1243, 1101, 911, 733, 647 cm^{-1}; HRMS: m/z $C_{16}H_{21}ClNO_3^+$ $[M+NH_4]^+$ calcd 310.1204, found 310.1205.

1-((2*R*,3*R*)-3-(benzyloxy)-5-chloro-2-vinyl-3,4-dihydro-2*H*-pyran-6-yl)ethan-1-one (221)

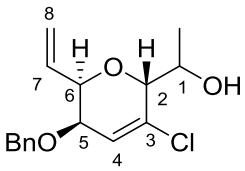


A mixture of methyl ketones **220** and **221** (44 mg, 0.15 mmol) was dissolved in 2 mL of DMF and treated with $Zn(CN)_2$ (44 mg, 0.38 mmol), $Pd_2(dba)_3$ (7 mg, $7.5x10^{-3}$ mmol) and SPhos (12 mg, 0.03 mmol) and heated at 150 °C for 3 hours. Then the solution was quenched with 10 mL of 1M NaOH and extracted into ethyl acetate (3x10 mL). The organic layers were dried over anhy. magnesium sulfate and concentrated on *vacuum*. The crude product was purified by column chromatography (9:1 Petroleum ether: ethyl acetate) to obtain **221** as colourless oil (32 mg, 73%).

R_f 0.35 (9:1 petroleum ether: ethyl acetate); $[\alpha]_D^{19}$ = -158 (*c* 0.3, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.33 (complex m, 5H, Bn), 6.04 (ddd, *J* = 17.2, 10.6, 5.3 Hz, 1H, H-8), 5.41 (d, *J* = 17.7 Hz, 1H, H-9a), 5.36 (d, *J* = 10.8 Hz, 1H, H-9b), 4.68 (d, *J* = 12.2 Hz, 1H, $PhCH_2$), 4.56 (d, *J* = 12.1 Hz, 1H, $PhCH_2$), 4.51 (m, 1H, H-7), 3.83 (m, 1H, H-6), 2.69 (dd, *J* = 18.4, 5.3 Hz, 1H, H-5a), 2.58 (dd, *J* = 18.4, 5.0 Hz, 1H, H-5b), 2.36 (s, 3H, H -1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 193.9 (C, C-2), 144.9 (C, C-3), 137.4 (C, Bn), 132.4 (CH, C-8), 128.51 (CH, Bn), 128.40 (CH, Bn), 127.82 (CH, Bn), 118. 4 (CH_2, C-9), 113.6 (C, C-4), 76.7 (CH, C-7), 71.8 (CH, C-6), 71.5 (CH_2, $PhCH_2$), 35.7 (CH_2, C-5), 28.4 (CH_3, C-1); IR (film from

$CDCl_3$) ν_{max} 3030, 2906, 2362, 1707, 1604, 1650, 1420, 1355, 1242, 1172, 1074, 1027, 927, 734, 698 cm^{-1}; HRMS: m/z $C_{16}H_{21}ClNO_3^+$ $[M+NH_4]^+$ calcd 310.1204, found 310.1197.

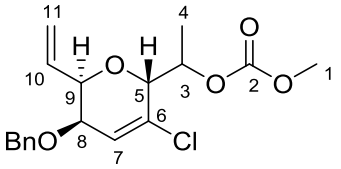
Preparation of (*R*)-1-((2*R*,5*R*,6*R*)-5-(benzyloxy)-3-chloro-6-vinyl-5,6-dihydro-2*H*-pyran-2-yl)ethan-1-ol (222)



Methyl ketone **220** (34 mg, 0.12 mmol) was dissolved in 1.2 mL of methanol and cooled to 0°C using ice-water bath. Then $NaBH_4$ (7 mg, 0.17 mmol) was added and slowly and then warmed up to room temperature. Reaction was quenched with acetone (5 mL) after reaction completed and solvents evaporated on vacuum. Residues were dissolved in 10 mL of dichloromethane and work it up with brine (10 mL). Aqueous layer was extracted with (2x10 mL) of dichloromethane and dried over anhyd. magnesium sulfate. Crude material was introduced to the silica gel column and purified with (9:1 petroleum ether: ethyl acetate) and alcohol **222** was obtained as a colourless oil (21 mg, 61%).

R_f 0.25 (9:1 petroleum ether: ethyl acetate); $[\alpha]_D^{19}$ = -80 (*c* 0.25, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.28 (complex m, 5H, Bn), 6.23 (d, *J* = 4.9 Hz, 1H, H-5), 6.08 (ddd, *J* = 17.4, 10.6, 5.8 Hz, 1H, H-8), 5.45 (d, *J* = 17.3 Hz, 1H, H-9a), 5.36 (d, *J* = 10.8 Hz, 1H, H-9b), 4.68 (complex m, 1H, H-7), 4.62 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.58 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.24 (complex m, 1H, H-2), 4.10 (complex m, 1H, H-6), 3.99 (s, 1H, H-3), 2.32 (d, *J* = 6.5 Hz, 3H, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 203.3 (C, C-2), 137.8 (C, Bn), 133.0 (CH, C-8), 132.8 (C, C-4), 128.45 (CH, Bn), 127.86 (CH, Bn), 127.78 (CH, Bn), 125.8 (CH, C-5), 119.3 (CH_2, C-9), 76.6 (CH, C-3), 74.2 (CH, C-7), 71.9 (CH, C-6), 71.0 (CH, $PhCH_2$), 67.2 (CH, C-2), 19.5 (CH_3, C-1); IR ($CDCl_3$ film) ν_{max} 3784, 3670, 3643, 3031, 2930, 2869, 2342, 1869, 1625, 1496, 1454, 1393, 1374, 1277, 1207, 1074, 1026, 917, 853, 774, 697 cm^{-1}; HRMS: m/z $C_{16}H_{23}ClNO_3^+$ $[M+NH_4]^+$ calcd 312.1361, found 312.1364.

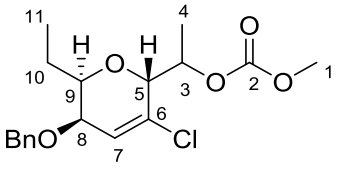
Preparation of (*R*)-1-((2*R*,5*R*,6*R*)-5-(benzyloxy)-3-chloro-6-vinyl-5,6-dihydro-2*H*-pyran-2-yl)ethyl methyl carbonate (270)



Alcohol **222** (21 mg, 0.07 mmol) was dissolved in dichloromethane (1.5 mL) and treated with DMAP (1 mg, 0.007 mmol) and pyridine (0.035 mL). Then reaction mixture was cooled to 0 °C and 0.03 mL (0.28 mmol) of methylchloroformate was added. After one hour, reaction was diluted with 10 mL of dichloromethane quenched with sat. solution of sodium bicarbonate (10 mL). Aqueous layer was extracted into dichloromethane (3x10 mL) and dried over anhy. magnesium sulfate. Crude material was purified with column chromatography (14:1 petroleum ether: ethyl acetate) to obtain **270** as colourless oil (13 mg, 52%).

R_f 0.25 (14:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.35–7.29 (complex m, 5H, Bn), 6.19 (dd, *J* = 4.6, 1.6 Hz, 1H, H-7), 6.08 (ddd, *J* = 17.0, 10.8, 5.8 Hz, 1H, H-10), 5.46 (d, *J* = 17.6 Hz, 1H, H-11a), 5.34 (d, *J* = 10.9 Hz, 1H, H-11b), 5.26 (dq, *J* = 9.1, 6.5 Hz, 1H, H-3), 4.63 (complex m, 1H, H-9), 4.62 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.58 (d, *J* = 9.8 Hz, 1H, $PhCH_2$), 4.19 (complex m, 1H, H-5), 4.01 (dd, *J* = 4.7, 3.5 Hz, 1H, H-8), 3.76 (s, 3H, H-1), 1.42 (d, *J* = 6.5 Hz, 3H, H-4); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 155.0 (C, C-2), 137.9 (C, Bn), 133.6 (CH, C-10), 132.8 (C, C-6), 128.41 (CH, Bn), 127.83 (CH, Bn), 127.74 (CH, Bn), 125.2 (CH, C-7), 118.2 (CH_2, C-11), 76.4 (CH, C-5), 74.5 (CH, C-9), 74.0 (CH, C-3), 71.5 (CH, C-8), 71.0 (CH_2, $PhCH_2$), 54.8 (CH_3, C-1), 16.1 (CH_3, C-4); IR (film from $CDCl_3$) ν_{max} 2987, 2956, 1747, 1653, 1442, 1354, 1259, 1158, 1052, 1027, 941, 914, 856, 789, 734, 698 cm^{-1}; HRMS: m/z $C_{18}H_{25}ClNO_5^+$ $[M+NH_4]^+$ calcd 370.1416, found 370.1415.

(*R*)-1-((2*R*,5*R*,6*R*)-5-(benzyloxy)-3-chloro-6-ethyl-5,6-dihydro-2*H*-pyran-2-yl)ethyl methyl carbonate (272)



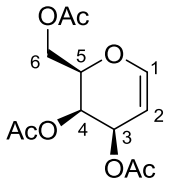
Methyl ester **270** (12 mg, 0.034 mmol) was dissolved in dry toluene (0.3 mL) which is degassed with N_2. Then it was treated with (1 mg, 0.007 mmol) of AIBN and warmed to 50 °C. Then (3x0.027 mL) of Bu_3SnH was added portion wise over one hour. Then solution was refluxed at toluene for one hour

and concentrated in vacuum. Then crude materials were introduced to the silica gel column and purified by 20:1 petroleum ether: ethyl acetate to obtain **272** as colourless oil contaminated with Bu_3SnH (8 mg, 66.4%)

R_f 0.25 (20:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.34–7.27 (complex m, 5H, Bn), 6.26 (d, *J* = 3.7 Hz, 1H, H-7), 5.27 (dq, *J* = 9.0, 6.4 Hz, 1H, H-3), 4.65 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.53 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.13 (complex m, 1H, H-5), 3.90 (complex m, 2H, H-8, H-9), 3.76 (s, 3H, H-1), 1.86 -1.78 (complex m, 1H, H-10a), 1.47-1.44 (complex m, 3H, H-11), 1.32-1.27 (complex m, 1H, H-10b), 0.89-0.82 (complex m, 3H, H-4); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 155.0 (C, C-2), 138.1 (C, C-6), 133.9 (C, Bn), 128.38 (CH, Bn), 127.85 (CH, Bn), 127.78 (CH, Bn), 124.9 (CH, C-7), 76.8 (CH, C-9), 76.7 (CH, C-5), 74.4 (CH, C-3), 70.6 (CH, C-8), 70.2 (CH_2, $PhCH_2$), 54.8 (CH_3, C-1), 29.2 (CH_3, C-11), 27.4 (CH_2, C-10), 16.2 (CH_3, C-4); IR (film from $CDCl_3$) ν_{max} 2955, 2924, 2871, 2853, 1751, 1654, 1442, 1376, 1260, 1157, 1069, 1052, 1027, 944, 909, 861, 789, 733, 696 cm^{-1}.

6.3 Experimental for chapter 3

Preparation of tri-*O*-acetyl-D-galactal (287)

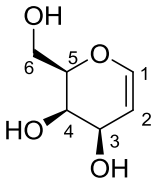


To a magnetically stirred solution of D-galactose (**285**) (62.5 mg, 0.35 mmol) in acetic anhydride (37.5 mL, 402.0 mmol) was treated dropwise with conc. perchloric acid (0.23 mL, 3.4 mmol). Additional D-galactose (9.95 g, 51.3 mmol) was added slowly over 45 minutes, at a rate that maintained a temperature of 40–50 °C. Upon complete addition of D-galactose, the solution was allowed to cool to room temperature, then treated with a 33% (w/w) solution of hydrobromic acid in acetic acid (37.5 mL, 215 mmol). After 90 minutes, the solution was diluted with dichloromethane (180 mL) and washed with ice-cold water (2x50 mL), then cold sat. sodium bicarbonate solution (6x50 mL). The organic phase was dried, filtered and concentrated to afford crude tetra-*O*-acetyl-D-galactcopyranosyl bromide (**286**) as an off-white solid. This was used without further purification. A mechanically stirred dispersion of zinc dust (24 g, 366 mmol) in water (75 mL) was cooled to 0 °C, diluted with acetic acid (75 mL), then treated dropwise with a solution of **286** in diethyl ether (150 mL) over one hour. The reaction was allowed to warm to room temperature and left to proceed

overnight. The solution was filtered, then diluted with dichloromethane (100 mL). The solution was washed successively with water (3x60 mL), sat. sodium bicarbonate solution (4x50 mL), then brine (60 mL). The organic phase was dried, filtered and concentrated to provide **287** as a white solid (8.3 g, 87%). Spectral data matched those which have been previously reported.[45]

^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 6.46 (dd, *J* = 6.1, 1.2 Hz, 1H, H-1), 5.33 (m, 1H, H-3), 5.22 (dd, *J* = 7.5, 5.6 Hz, 1H, H-4), 4.84 (dd, *J* = 6.1, 3.2 Hz, 1H, H-2), 4.39 (dd, *J* = 12.2, 5.9 Hz, 1H, H-6a), 4.25 (m, 1H, H-5), 4.19 (dd, *J* = 12.2, 3.2 Hz, 1H ,H-6b), 2.09 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 170.8 (C, CH_3CO), 170.6 (C, CH_3CO), 169.8 (C, CH_3CO), 145.8 (CH, C-1), 99.1 (CH, C-2), 74.1 (CH, C-5), 67.6 (CH, C-3), 67.3 (CH, C-4), 61.5 (CH_2, C-6), 21.1 (CH_3, CH_3CO), 20.94 (CH_3, CH_3CO), 20.88 (CH_3, CH_3CO).

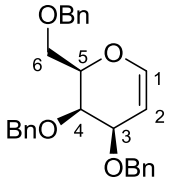
Preparation of D-Galactal (288)



Sodium (24 mg, 1.08 mmol) was reacted with methanol (36 mL) and then treated with a solution of **287** (1 g, 3.6 mmol) in methanol (10 mL). The reaction was stirred at room temperature for 10 minutes and then the solution was concentrated to provide crude D-glucal (**288**). The crude product was treated successively with portions of methanol (15 mL), then successively diluted with acetone (10 mL) and diethyl ether (10 mL), which led to the precipitation of impurities. The solution was filtered and concentrated to afford **288** (508 mg, 96%). Spectral data matched those which have been previously reported.[45]

^{1}H-NMR (500 MHz): (D_2O) δ_H 6.25 (dd, *J* = 6.3, 1.2 Hz, 1H, H-1), 4.77 (dd, *J* = 6.1, 2.4 Hz, 1H, H-2), 4.66 (complex m, 3H, 3xOH) 4.19 (dt, *J* = 7.1, 2.1 Hz, 1H, H-3), 3.84 (complex m, 3H, H-5,H-6), 3.64 (dd, *J* = 9.0, 7.1 Hz, 1H, H-4); ^{13}C-NMR (500 MHz): (D_2O) δ_C 143.8 (CH, C-1), 102.7 (CH, C-2), 78.0 (CH, C-5), 68.7 (CH, C-4), 68.2 (CH, C-3), 59.9 (CH_2, C-6).

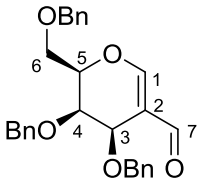
Preparation of tri-*O*-benzyl-D-galactal (81)



A solution of **288** (1.04 g, 7.15 mmol) in DMF (45 mL) was cooled to 0 °C and then treated with sodium hydride (2.14 g, 53.5 mmol). The solution was stirred at 0 °C for 25 minutes, then treated with benzyl bromide (5.6 mL, 46.8 mmol) and allowed to warm to room temperature. After 18 hours, the solution was quenched with water (20 mL) and then extracted with diethyl ether (3x50 mL). The organic fractions were combined, dried, filtered and concentrated to give the crude product as yellow oil. Chromatography of the oil (9:1 Petroleum ether: ethyl acetate) afforded **81** (2.05 g, 68%) as a white crystalline solid. The spectral data matched those reported previously.[45]

R_f 0.3 (9:1 Petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.35 –7.26 (complex m, 15H, Bn), 6.38 (dd, *J* = 6.3, 1.2 Hz, 1H, H-1), 4.89 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.86 (m, 1H, H-2), 4.69–4.61 (complex m, 3H, $PhCH_2$), 4.51 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.43 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.20–4.19 (complex m, 1H, H-3,H-5), 3.96 (m, 1H, H-4), 3.79 (dd, *J* = 10.3, 7.3 Hz, 1H, H-6a), 3.65 (dd, *J* = 10.3, 5.1 Hz, 1H, H-6b); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 144.2 (CH, C-1), 138.5 (C, Bn), 138.3 (C, Bn), 138.0 (C, Bn), 128.4 (CH, Bn), 128.3 (CH, Bn), 128.2 (CH, Bn), 127.9 (CH, Bn), 127.7 (CH, Bn), 127.6 (CH, Bn), 127.4 (CH, Bn), 100.0 (CH, C-2), 75.7 (CH, C-5), 73.4 (CH_2, $PhCH_2$), 73.3 (CH_2, $PhCH_2$), 71.2 (CH, C-4), 70.9 (CH_2, $PhCH_2$), 70.7 (CH, C-3), 68.4 (CH_2, C-6).

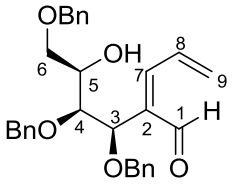
Preparation of 3,4,6-tri-*O*-benzyl-2-formyl-D-galactal (136)



DMF (4 mL) was treated with phosphorous oxycloride (0.675 mL, 7.2 mmol) at room temperature. Then it was cooled until 0 °C and stirred for 30 minutes. Then, the orange colour solution was treated with tribenzylated glycal **81** (1g, 2.4 mmol) and slowly warmed up to room temperature. It was stirred for six hours before quenched with 10 mL of sat. solution of sodium bicarbonate. Organic materials were extracted into diethyl ether (3x15 mL) and dried over anhy. magnesium sulfate. Chromatography of the crude oil (3:1 petroleum ether: ethyl acetate) afforded of 2-*C*-formylated glycal **136** as a yellow oil (0.83 g, 68%). The spectral data matched those reported previously.[44]

R_f 0.31 (3:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 9.36 (s, 1H, H-1), 7.38–7.22 (complex m, 16H, Bn, H-1), 4.75 - 4.54 (complex m, 8H, 3x$PhCH_2$, H-5, H-3), 3.99 (d, *J* = 5.4 Hz, 1H, H-4), 3.83 (apparent t, *J* = 4.9 Hz, 2H, H-6); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 189.4 (CH, C-7), 164.3 (C, C-2), 128.6 (C, Bn), 128.2 (C, Bn), 128.0 (C, Bn), 127.91 (CH, Bn), 127.45 (CH, Bn), 127.69 (CH, Bn), 127.63 (CH, Bn), 127.43 (CH, Bn), 128.11 (CH, Bn), 127.92 (CH, Bn), 127.78 (CH, Bn), 127.67 (CH, Bn), 119.5 (CH, C-1), 78.8 (CH, C-5), 73.7 (CH, C-6), 73.4 (CH_2, $PhCH_2$), 73.0 (CH_2, $PhCH_2$), 71.5 (CH_2, $PhCH_2$), 68.4 (CH, C-4), 64.1 (CH, C-3); HRMS: m/z $C_{28}H_{29}O_5^+$ $[M+H]^+$ calcd 445.2010 found 445.2004.

Preparation of (3*R*,4*S*,5*R*,*Z*)-2-allylidene-3,4,6-tris(benzyloxy)-5-hydroxyhexanal (297)

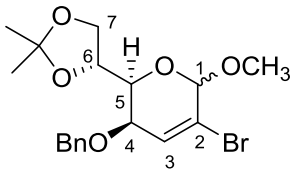


2-*C*-formylated glycal **136** (50 mg, 0.15 mmol) was dissolved in 10 mL of tetrahydrofuran with copper iodide (1.5 mg, 7.83x10 $^{-3}$ mmol). Vinyl magnesium bromide (0.18 mL, 1M sollution) was added to the 2-*C*-formylated glycal solution at -78 °C. Combined solution was slowly warmed up to room temperature and stirred for 3 hours. The black colour reaction mixture was quenched with 5 mL (1M solution) of HCl and extracted into ethyl acetate (3x10 mL). The combined organic fractions were washed with 20 mL of sat. ammonium hydroxide followed by 20 mL of brine. Chromatography of the crude oil (3:1 petroleum ether: ethyl acetate) afforded (36 mg, 51%, unstable compound) of **297** as pale yellow oil.

R_f 2.9 (3:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 9.46 (s, 1H, H-1), 7.38–7.22 (complex m, 15H, Bn), 7.17 (d, *J* = 7.7 Hz, 1H, H-7), 6.95 (d, *J* = 11.4 Hz, 1H, H-8), 5.73 (dd, *J* = 16.7, 9.9 Hz, 2H, H-9), 4.95 (d, *J* = 6.9 Hz, 1H, H-3), 4.50-4.39 (complex m, 6H, $PhCH_2$), 4.04 (dd, *J* = 11.9, 6.3 Hz, 1H, H-5), 3.83 (d, *J* = 6.7 Hz, H = 4), 3.52 (dd, *J* = 6.0, 5.7 Hz, 1H, H-6a), 3.45 (dd, *J* = 6.3, 6.3 Hz, 1H, H-6b), 2.79 (d, *J* = 6.9 Hz, 1H, H-5(OH)); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 194.0 (CH, C-1), 151.8 (CH, C-8), 138.05 (C, Bn), 137.72 (C, C-2), 137.64 (C, Bn), 137.30 (C, Bn), 132.3 (CH, C-7), 129.1 (CH, C-9), 128.50 (CH, Bn), 128.41 (CH, Bn), 128.37 (CH, Bn), 128.29 (CH, Bn), 128.27 (CH, Bn), 128.11 (CH, Bn), 127.92 (CH, Bn), 127.78 (CH, Bn), 127.67 (CH, Bn), 78.8 (CH, C-4), 74.4 (CH, C-3), 73.8 (CH_2, $PhCH_2$), 73.3 (CH_2, $PhCH_2$), 71.6 (CH_2, $PhCH_2$), 71.0 (CH_2, C-6), 69.5 (CH, C-5); IR (film from $CDCl_3$): ν_{max} 3510, 3490, 3025, 2405, 2341, 1626, 1585, 1558, 1496, 1453, 1395, 1331, 1209, 1088, 1073, 937, 860, 731 cm^{-1}.

6.4 Experimental for chapter 4

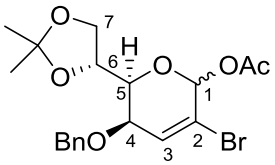
Preparation of (2*S*,3*R*)-3-(benzyloxy)-5-bromo-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-6-methoxy-3,6-dihydro-2*H*-pyran (312)



A solution of glycal **64** (100 mg, 0.36 mmol) in distilled bromoform (1 mL) was treated with K_2CO_3 (149 mg, 1.08 mmol), to make suspension, then MeOH (0.1 mL) and *tert*-butyl ammonium bromide (11 mg, 0.036 mmol) were added. The combined solution was stirred refluxed for one day. The mixture was diluted with water (10 mL), then extracted with ethyl acetate (3x10 mL). The combined organic fractions were dried, filtered and concentrated to provide a dark–brown liquid. This crude product was purified by column chromatography (9:1 petroleum ether: ethyl acetate) to obtained **312** as pale yellow oil (25 mg, 18%, 10:1 anomeric mixture).

R_f 0.31 (9:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.37–7.27 (complex m, 5H, Bn), 6.51 (d, *J* = 6.0 Hz, 0.1H, H-3), 6.39 (d, *J* = 5.7 Hz, 0.9H, H-3), 5.07 (s, 0.1H, H-1), 4.89 (s, 0.9H, H-1), 4.68 (s, 2H, $PhCH_2$), 4.41 (m, 1H, H-6), 4.18 (dd, *J* = 8.4, 6.3 Hz, 1H, H-7a), 4.00 (dd, *J* = 8.4, 5.7 Hz, 1H, H-7b), 3.95 (dd, *J* = 7.9, 1.9 Hz, 1H, H-5), 3.83 (dd, *J* = 5.7, 2.5 Hz, 1H, H-4), 3.47 (s, 3H, OCH_3), 1.42 (s, 3H, $(CH_3)_2C$), 1.41 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.9 (C, Bn), 128.7 (CH, C-3), 128.4 (CH, Bn), 128.0 (CH, Bn), 127.9 (CH, Bn), 124.4 (C, C-2), 109.2 (C, $(CH_3)_2C$), 98.6 (CH, C-1), 73.5 (CH, C-5), 72.0 (CH, C-6), 70.8 (CH_2, $PhCH_2$), 69.7 (CH, C-4), 67.2 (CH_2, C-7), 56.3 (CH_3, OCH_3), 26.8 (CH_3, $(CH_3)_2C$), 25.5 (CH_3,$(CH_3)_2C$), HRMS: m/z $C_{18}H_{27}{}^{79}BrO_5N^+$ $[M+NH_4]^+$ calcd 416.1073, found 416.1084.

Preparation of (2*R*,5*R*,6S)-5-(benzyloxy)-3-bromo-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-2*H*-pyran-2-yl acetate (131), (2S,5R,6S)-5-(benzyloxy)-3-bromo-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-2H-pyran-2-yl acetate (131β),and (4R)-4-((2S,3R)-3,5-bis(benzyloxy)tetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane (313)

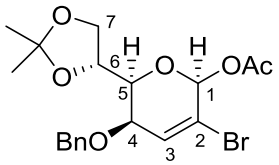


A) glycal **64** (100 mg, 0.36 mmol) was dissolved in a solution of bromoform (1 mL) and tetrahydrofuran (1 mL). It was treated with K_2CO_3 (149 mg, 1.08 mmol) and sodium acetate (60 mg, 0.72 mmol) to make suspension. The combined solution was stirred refluxed for 18 hours after the addition of *tert*-butyl ammonium bromide (11 mg, 0.036 mmol). The crude mixture was filtered and concentrated to provide a dark–brown liquid. This crude product was purified by column chromatography (9:1 petroleum ether: ethyl acetate) to obtain **154** (11 mg, 11%), benzyl glycoside **313** (7 mg, 8%) and acetate **131**(32mg, 21%).

B) A solution of glycal **64** (200 mg, 0.72 mmol) in a solution of bromoform (1.5 mL) and tetrahydrofuran (1.5 mL). It was treated with K_2CO_3 (600 mg, 6.48 mmol), sodium acetate (120 mg, 1.44 mmol) and 18-crown-6 (20 mg) to make suspension. The combined solution was stirred at room temperature for 18 hours after the addition of *tert*-butyl ammonium bromide (11 mg, 0.036 mmol). Then another portion of potassium carbonate (300 mg, 2.16 mmol) and sodium acetate (120 mg, 1.44 mmol) were added and refluxed for one day. The crude mixture was filtered and concentrated to provide a dark–brown liquid. This crude product was purified by column chromatography (9:1 petroleum ether: ethyl acetate) to obtained starting material and acetate **131** (83 mg, 27%).

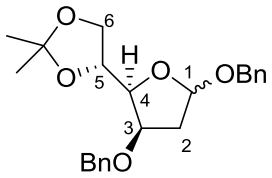
C) A solution of glycal **64** (493 mg, 1.78 mmol) in a solution of bromoform (5 mL) was treated with K_2CO_3 (1.50 g, 10.9 mmol), sodium acetate (540 mg, 6.48 mmol) and 18-crown-6 (20 mg, 0.076 mmol). To the resulting suspension was added *tert*-butyl ammonium bromide (93 mg, 0.304 mmol) and the mixture stirred at room temperature for 24 hours. It was then heated to 82 °C and stirred for two days. The reaction mixture was filtered and concentrated to provide a dark-brown liquid. This crude material was purified by column chromatography (9:1 petroleum ether: ethyl acetate) to obtain the anomeric mixture of acetate **131** as an inseparable as a colourless oil (364 mg, 47%, 4:1 α:β) together with starting material as a yellow oil (69 mg, 14%, contaminated with bromoform).

(**131**) R_f 0.18 (10:1 petroleum ether: ethyl acetate); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.38–7.32 (complex m, 5H, Bn), 6.49 (d, *J* = 5.3, 0.2H, H-3), 6.48 (d, *J* = 6.1 Hz, 0.8H, H-3), 6.35 (s, 0.2H, H-1), 6.25 (s, 0.8H, H-1), 4.71 (s, 1.6H, $PhCH_2$), 4.69 (s, 0.4H, $PhCH_2$), 4.40 (m, 1H, H-6), 4.10 (m, 1H, H-7a), 4.04 (dd, *J* = 8.8, 4.7 Hz, 0.8H, H-7b), 3.94 (apparent d, *J* = 6.1 Hz, 0.8H, H-4), 3.92 (dd, *J* = 5.8, 2.6 Hz, 0.2H, H-4), 3.89 – 3.84 (complex m, 0.4H, H-5, H-7b), 3.70 (dd, *J* = 8.5, 2.0 Hz, 0.8H, H-5), 2.15 (s, 2.4H, Ac), 2.12 (s, 0.6H, Ac), 1.41 (s, 0.6H, $(CH_3)_2C$),1.39 (s, 2.4H, $(CH_3)_2C$), 1.38 (s, 0.6H, $(CH_3)_2C$), 1.36 (s, 2.4H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 169.5 (C, CH_3CO), 169.2 (C, CH_3CO), 138.0 (C, Bn), 137.8 (C, Bn), 131.6 (CH, C-3), 130.2 (CH, C-3)$_{131\beta}$, 128.39 (CH, Bn), 128.24 (CH, Bn), 128.06 (CH, Bn), 127.99 (CH, Bn), 127.90 (CH, Bn), 127.54 (CH, Bn), 124.6 (CH, C-2), 122.6 (CH, C-2) $_{131\beta}$, 109.5 (C, $(CH_3)_2C$), 90.6 (CH, C-1), 90.0 (CH, C-1) $_{131\beta}$, 73.04 (CH, C-6), 73.0 (CH, C-5), 72.1 (CH_2, $PhCH_2$), 71.9 (CH_2, $PhCH_2$) $_{131\beta}$, 69.5 (CH, C-4), 69.1 (CH, C-4) $_{131\beta}$, 67.1 (CH_2, C-7) $_{131\beta}$, 67.0 (CH_2, C-7), 27.01 (CH_3, $(CH_3)_2C$), 26.91 (CH_3, $(CH_3)_2C$) $_{131\beta}$, 25.93 (CH_3, $(CH_3)_2C$), 25.31 (CH_3,$(CH_3)_2C$) $_{131\beta}$, 20.92 (CH_3, Ac), 20.91 (CH_3, Ac) $_{131\beta}$; IR (film from $CHCl_3$) ν_{max} 1812, 1644, 1604, 1496, 1454, 1328, 1308, 1288, 786, 761, 648 cm^{-1}; HRMS: m/z $C_{19}H_{27}{}^{79}BrO_6N^+$ $[M+NH_4]^+$ calcd 444.1016, found 444.1023, m/z $C_{19}H_{27}{}^{81}BrO_6N^+$ $[M+NH_4]^+$ calcd 446.0998, found 446.1007.



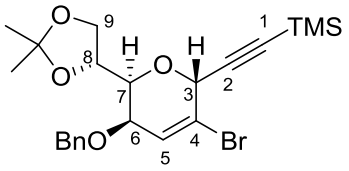
(A portion of the β-anomer of **131** was obtained from an instance of the subsequent reaction that did not proceed to completion. This facilitated analysis of the mixture of **131** described above)

(**131$_\beta$**) R_f 0.18 (10:1 petroleum ether: ethyl acetate); $[\alpha]_D{}^{22}$ = -41 (*c* 0.56, CH_2Cl_2); H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.34 (complex m, 5H, Bn), 6.49 (d, *J* = 5.8 Hz, 1H, H-3), 6.34 (s, 1H, H-1), 4.69 (s, 2H, $PhCH_2$), 4.40 (m, 1H, H-6), 4.11 (dd, *J* = 8.6, 6.4 Hz, 1H, H-7a), 3.92 (dd, *J* = 5.6, 2.4 Hz, 1H, H-4), 3.89-3.84 (complex m, 2H, H-5 and H-7b), 2.14 (s, 3H, Ac), 1.39 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 169.5 (C, CH_3CO), 137.80 (C, Bn), 130.2 (CH, C-3), 128.45 (CH, Bn), 128.34 (CH, Bn), 128.00 (CH, Bn), 122.6 (CH, C-2), 109.5 (C, $(CH_3)_2C$), 90.0 (CH, C-1), 72.96 (CH, C-6) 72.95 (CH, C-5), 72.1 (CH_2, $PhCH_2$), 69.4 (CH, C-4), 67.1 (CH_2, C-7), 26.9 (CH_3, $(CH_3)_2C$), 25.2 (CH_3, $(CH_3)_2C$), 20.9 (CH_3, Ac); IR (film from $CHCl_3$) ν_{max} 2984, 2877, 1648, 1496, 1454, 1341, 1286 cm^{-1}.



(**313**) R_f 0.35 (5:1 petroleum ether: ethyl acetate); $[\alpha]_D^{24}$ = 120 (*c* 0.15, Et_2O); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.26 (complex m, 10H, Bn), 5.37 (dd, *J* = 5.5, 2.9 Hz, 1H, H-1), 4.73 (d, *J* = 11.9 Hz,1H, $PhCH_2$), 4.58 (d, *J* = 11.9 Hz, 1H, $PhCH_2$), 4.53 (d, *J* = 12.1 Hz, 1H, $PhCH_2$), 4.50 (d, *J* = 11.9 Hz, 1H, $PhCH_2$), 4.45 (dd, *J* = 13.0, 6.5 Hz, 1H, H-5), 4.25 (complex m, 1H, H-3), 4.14-4.08 (m, 2H, H-6a, H-4), 3.97 (dd, *J* = 7.7, 6.5 Hz, 1H, H-6b), 2.80 (ddd, *J* = 14.2 5.6, 1.3 Hz, 1H, H-2a), 2.17 (dd, *J* = 14.3, 3.2 Hz, 1H, H-2b), 1.46 (s, 3H, $(CH_3)_2C$), 1.40 (s, 3H, $(CH_3)_2C$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 138.24 (C, Bn), C 137.98 (C, Bn), 128.5 (CH, Bn), 128.40 (CH, Bn), 128.33 (CH, Bn), 128.07 (CH, Bn), 127.93 (CH, Bn), 127.72 (CH, Bn), 108.8 (C, $(CH_3)_2C$), 102.8 (CH, C-1), 81.1 (CH, C-4),78.3 (CH, C-3), 73.3 (CH, C-5), 71.6 (CH_2, $PhCH_2$), 69.7 (CH_2, $PhCH_2$) 67.1 (CH_2, C-6), 40.0 (CH_2, C-2), 26.7 (CH_3, $(CH_3)_2C$), 25.9 (CH_3, $(CH_3)_2C$); IR (film from Et_2O) ν_{max} 3490, 3031, 2983, 2931, 1603, 1496, 1454, 1370, 1255, 1211, 1126, 1066, 1025, 848, 736, 697 cm^{-1}; HRMS: m/z $C_{23}H_{32}O_5N^+$ $[M+NH_4]^+$ calcd 403.2308 , found 403.2298.

Preparation of (((2*R*,5*R*,6*S*)-5-(benzyloxy)-3-bromo-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-2*H*-pyran-2-yl)ethynyl)trimethylsilane (302) and (*R*)-1-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-bromo-6-((trimethylsilyl)ethynyl)-3,6-dihydro-2*H*-pyran-2-yl)ethane-1,2-diol (314)



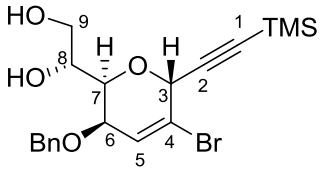
Bis(trimethyl)silylacetylene (1.0 mL, 5.11 mmol) and acetate **131** (546 mg, 1.27 mmol) were dissolved in dry dichloromethane (12 mL) and cooled to -78 °C. Then $SnCl_4$ (1.27 mL, 1M solution in dichloromethane) was added drop wise into the cold solution. The combined solution was stirred for 2 hours at the same temperature and then was quenched with sat. solution of sodium bicarbonate (15 mL) and extracted into dichloromethane (2x10 mL). The crude mixture containing acetonide **302** and diol **314** was purified by gradient column chromatography (20:1 to 2:1 petroleum ether: ethyl acetate) to yield **302** (55 mg, 9%) as a colourless oil and diol **314** (188 mg, 35%) as a colourless oil.

(**302**) R_f 0.45 (5:1 petroleum ether: ethyl acetate); $[\alpha]_D^{22}$ = -45 (*c* 0.32, CH_2Cl_2) ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.37–7.27 (complex m, 5H, Bn), 6.26 (d, *J* = 5.7 Hz, 1H, H-5), 4.92 (s, 1H, H-3), 4.69 (s, 2H, $PhCH_2$), 4.40 (m, 1H, H-8), 4.15 (dd, *J* = 7.4, 6.6 Hz, 1H, H-9a), 3.97 (dd, *J* = 7.8, 5.4, 1H, H-9b), 3.90

(complex m, 2H, H-7, H-6), 1.41 (s, 3H,$(CH_3)_2C$), 1.40 (s, 3H, $(CH_3)_2C$), 0.18 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 138.0 (C, Bn), 128.36 (CH, Bn), 128.08 (CH, Bn), 127.84 (CH, Bn), 126.9 (CH, C-5), 124.9 (C, C-4), 109.4 (C, $(CH_3)_2C$), 99.4 (C, C-2), 92.3 (C, C-1), 74.2 (CH, C-6), 72.9 (CH, C-8), 72.1 (CH_2, $PhCH_2$), 69.9 (CH, C-3), 69.9 (CH, C-7), 67.6 (CH_2, C-9), 26.8 (CH_3, $(CH_3)_2C$), 25.5 (CH_3, $(CH_3)_2C$); IR (film from CH_2Cl_2) ν_{max} 2986, 2959, 2873, 1643, 1455, 1297, 1106, 1079, 1212, 906, 841, 731, 697 cm^{-1}; HRMS: m/z $C_{22}H_{30}{}^{81}BrO_4Si^+$ $[M+H]^+$ calcd 467.1074, found 467.1056.

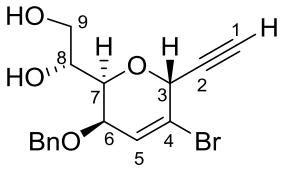
Synthesis of further amounts of compound 314

Acetonide protected alkyne **302** (55 mg, 0.11 mmol) was dissolved in 2 mL of acetonitrile and cooled to 0 °C using an ice-water bath. Then it was treated with trifluoroacetic acid (0.5 mL, 6.5 mmol) and slowly warmed up to room temperature. After stirring for 45 minutes at room temperature, the solution was carefully quenched with powdered sodium bicarbonate and diluted with distilled water. The organic compounds were extracted into dichloromethane (2x10 mL). Diol **314** (46 mg) obtained as colourless oil.



(**314**) R_f 0.38 (2:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -100 (*c* 0.2, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.38–7.31 (complex m, 5H, Bn), 6.37 (d, *J* = 5.4 Hz, 1H, H-5), 4.95 (s, 1H, H-3), 4.73 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.59 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.02-3.96 (complex m, 3H, H-6, H-7 and H-8), 4.01-3.84 (apparent d, *J* = 11.6 Hz, H, H-9a), 3.78 (dd, *J* = 11.6, 4.6 Hz, 1H, H-9b), 0.18 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.6 (C, Bn), 128.69 (CH, Bn), 128.55 (CH, Bn), 128.19 (CH, Bn), 126.4 (CH, C-5), 125.5 (CH, C-4), 99.3 (C, C-2), 92.4 (C, C-1), 72.5 (CH, C-6), 71.2 (CH_2, $PhCH_2$), 69.93 (CH, C-3), 69.76 (CH, C-7 or C-8), 69.38 (CH, C-7 or C-8) 64.0 (CH_2, C-9); IR (film from CH_2Cl_2) ν_{max} 3486, 2985, 2873, 1644, 1454, 1297, 1106, 1079, 912, 843, 732, 698 cm^{-1}; HRMS: m/z $C_{19}H_{25}{}^{81}BrO_4SiNa^+$ $[M+Na]^+$ calcd 449.0580, found 449.0575.

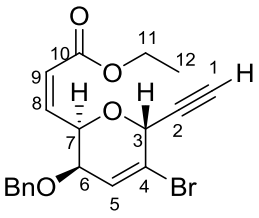
Preparation of the (*R*)-1-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-bromo-6-ethynyl-3,6-dihydro-2*H*-pyran-2-yl)ethane-1,2-diol (315)



Diol **314** (270 mg, 0.63 mmol) was dissolved in dichloromethane (7.5 mL) and treated with methanol 1.5 mL. The reaction mixture became a white suspension and was stirred until the reaction was deemed complete (2 hours). This mixture was diluted with dichloromethane and filtered into a brine solution. The aqueous layer was extracted with dichloromethane (2x10 mL) and the combined organic fractions evaporated at room temperature under reduced pressure to obtain **315** as white solid. The product was used in the next reaction without further purification.

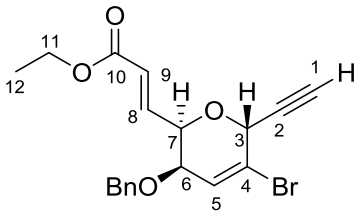
R_f 0.29 (1:1 petroleum ether: ethyl acetate); m.p. 147.9 – 148.8 °C; $[\alpha]_D^{22}$ = -100 (*c* 0.1, CH_2Cl_2); ^{1}H-NMR(500 MHz): ($CDCl_3$) δ_H 7.39–7.31 (complex m, 5H, Bn), 6.42 (d, *J* = 5.4 Hz, 1H, H-5), 5.00 (s, 1H, H-3), 4.74 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.60 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.03 (dd, *J* = 5.6, 2.2 Hz, 1H, H-6), 3.99 – 3.79 (complex m, 2H, H-7, H-8), 3.86-3.84 (apparent d, *J* = 10.6 Hz, 1H, H-9a), 3.78 (dd, *J* = 10.9, 5.2 Hz, 1H, H-9b), 2.53 (d, *J* = 2.2 Hz, 1H, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 137.6 (C, Bn), 128.69 (CH, Bn), 128.22 (CH, Bn), 128.04 (CH, Bn), 126.7 (CH, C-5), 125.1 (CH, C-4), 78.2 (C, C-2), 75.0 (C, C-1), 72.5 (CH, C-7 or C-8), 71.3 (CH_2, $PhCH_2$), 69.8 (CH, C-7 or C-8), 69.4 (CH, C-6), 69.2 (CH, C-3) 63.8 (CH_2, C-9); IR (film from CH_2Cl_2) ν_{max} 3486, 3088, 2981, 1496, 1455, 1369, 1339, 1252, 1214, 1129, 987, 848 cm^{-1}; HRMS: m/z $C_{16}H_{18}{}^{81}BrO_4^+$ $[M+H]^+$ calcd 453.0388, found 453.0367

Preparation of ethyl (*E*/*Z*)-3-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-bromo-6-ethynyl-3,6-dihydro-2*H*-pyran-2-yl)acrylate (*Z*-318) and (*E*-319)



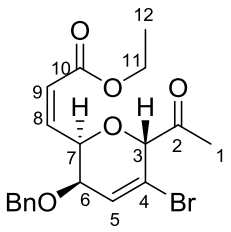
A solution of the crude diol **315** described above (120 mg, 0.34 mmol) in tetrahydrofuran (10 mL) and pH 7 phosphate buffer (3 mL) was treated with $NaIO_4$ (508 mg, 2.38 mmol) in one portion. The resulting mixture was stirred for 1 hour, diluted with brine (50 mL), and extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated to give colourless oil, which was used without further purification. Next the crude aldehyde product was dissolved in tetrahydrofuran (10 mL) and treated with triphenylphosphoranylidene ethyl ester (236 mg, 0.68 mmol). The solution was stirred overnight before concentrating under reduced pressure and purifying with column chromatography (14:1 petroleum ether: ethyl acetate) to yield both (*Z*)-**318** as a colourless oil (94 mg, 38%) and (*E*)-**319** as a colourless oils (25 mg, 10%). Combined yield is 48% over three steps.

(*Z*)-318: R_f 0.33 (14:1 petroleum ether: ethyl acetate); $[\alpha]_D^{20}$ = -188 (c 0.26, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.33–7.26 (complex m, 5H, Bn), 6.35 (d, *J* = 6.4 Hz, 1H, H-5), 6.33 (dd, *J* = 11.3, 6.8 Hz, 1H, H-8), 5.93 (d, *J* = 11.3 Hz, 1H, H-9), 5.55 (broad d, *J* = 6.6 Hz, 1H, H-7), 5.02 (s, 1H, H-3), 4.58 (d, *J* = 11.4 Hz, 1H, $PhCH_2$), 4.50 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.20 (d, *J* = 3.4 Hz, 1H, H-6), 4.14 (q, *J* = 7.2 Hz, 2H, H-11), 2.50 (s, 1H, H-1), 1.28 (t, *J* = 7.2 Hz, 3H, H-12); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 165.6 (C, C-10), 144.8 (CH, C-8), 137.5 (C, Bn), 128.40 (CH, Bn), 128.2 (CH, C-5), 127.98 (CH, Bn), 127.89 (CH, Bn), 120.5 (C, C-9), 78.1 (C, C-2), 75.1 (CH, C-1), 71.8 (CH_2, $PhCH_2$), 71.3 (CH, C-6), 71.0 (CH, C-7), 68.8 (CH, C-3), 60.4 (CH_2, C-11), 14.2 (CH_3, C-12); IR (film from CH_2Cl_2) ν_{max} 3031, 2931, 2872, 2116, 1648, 1539, 1454, 1497, 1388, 1366, 1334, 1031, 911, 846, 735, 698 cm^{-1}; HRMS: m/z $C_{19}H_{21}{}^{81}BrO_4^+$ $[M+H]^+$ calcd 393.0521, found 393.0533.



***(E)*-319**: R_f 0.45 (2:1 petroleum ether: ethyl acetate); $[\alpha]_D^{20}$ = -112 (*c* 0.34, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.37–7.26 (complex m, 5H, Bn), 7.02 (dd, *J* = 15.8, 4.2 Hz, 1H, H-8), 6.34 (d, *J* = 5.5 Hz, 1H, H-5), 6.22 (dd, *J* =15.8, 1.5 Hz, 1H, H-9), 5.09 (s, 1H, H-3), 4.73 (m, 1H, H-7), 4.61 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.53 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.23 (q, *J* = 7.1 Hz, 2H, H-11), 3.92 (dd, *J* = 5.3, 2.8 Hz, 1H, H-6), 2.53 (d, *J* = 2.1 Hz, 1H, H-1), 1.31 (t, *J* = 7.1 Hz, 3H, H-12); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.0 (C, C-10), 142.5 (CH, C-8), 137.4 (C, Bn), 128.13 (CH, Bn), 128.03 (CH, Bn), 127.99 (CH, Bn), 126.6 (CH, C-5), 124.9 (C, C-4), 122.7 (CH, C-9), 77.9 (C, C-2), 75.3 (CH, C-1), 72.2 (CH, C-7), 71.1 (CH_2, $PhCH_2$), 71.0 (CH, C-6), 69.0 (CH, C-3), 60.5 (CH_2, C-11), 14.6 (CH_3, C-12); IR (film from CH_2Cl_2) ν_{max} 2360, 2115, 1664, 1496, 1454, 1392, 1368, 898, 847, 798, 645, 631, 603 cm^{-1}; HRMS: m/z $C_{19}H_{23}{}^{81}BrO_4N^+$ $[M+NH_4]^+$ calcd 408.0805, found 408.0819.

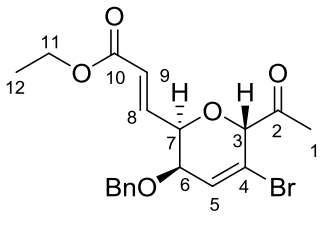
Preparation of ethyl (*Z*)-3-((2*R*,3*R*,6*R*)-6-acetyl-3-(benzyloxy)-5-bromo-3,6-dihydro-2*H*-pyran-2-yl)acrylate (320)



A sample of ethyl ester *(Z)*-**318** (125 mg, 0.32 mmol) was dissolved in tetrahydrofuran (1.5 mL). Then $HgSO_4$ in H_2SO_4 (10% aqueous solution, 1.5 mL, 19 mg, 0.2 equiv) was added to this solution. The reaction mixture was stirred at room temperature for 16 hours. The mixture was diluted with diethyl ether (5 mL) and carefully neutralised with sodium bicarbonate powder until a pH 7 was reached. The aqueous layer was washed with diethyl ether (3x5 mL). The organic layers were combined and dried over magnesium sulfate. The crude product was chromatographed (9:1 petroleum ether: ethyl acetate) to yield the product **320** as a clear oil (95 mg, 72%).

R_f 0.31 (9:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -133 (*c* 0.14, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.34–7.28 (complex m, 5H, Bn), 6.48 (d, *J* = 5.2 Hz, 1H, H-5), 6.36 (dd, *J* = 11.6, 7.2 Hz, 1H, H-8), 5.94 (d, *J* = 11.9 Hz, 1H, H-9), 5.31 (broad d, *J* = 6.9 Hz, 1H, H-7), 4.74 (s, 1H, H-3), 4.59 (d, *J* = 11.9 Hz, 1H, $PhCH_2$), 4.52 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.17 (dd, *J* = 5.0, 3.0 Hz, 1H, H-6), 4.13 (q, *J* = 7.1 Hz, 2H, H-11), 2.32 (s, 3H, H-1), 1.27 (t, *J* = 7.1 Hz, 3H, H-12); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 202.8 (C, C-2), 165.3 (C, C-10), 144.5 (CH, C-8), 137.5 (C, Bn), 128.43 (CH, C-5), 128.40 (CH, Bn), 128.04 (CH, Bn), 127.97 (CH, Bn), 121.50 (C, C-9), 81.2 (CH, C-3), 71.8 (CH_2, $PhCH_2$), 71.4 (CH, C-6), 71.2 (CH, C-7), 60.5 (CH_2, C-11), 28.1 (CH_3, C-1), 14.1 (CH_3, C-12,), IR (film from CH_2Cl_2) ν_{max} 3063, 2872, 1649, 1496, 1454, 1388, 1302, 979, 697 cm^{-1}; HRMS: m/z $C_{19}H_{25}{}^{81}BrO_5N^+$ $[M+NH_4]^+$ calcd 426.0911, found 426.0902.

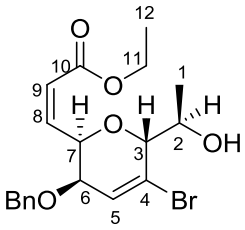
Preparation of ethyl (*E*)-3-((2*R*,3*R*,6*R*)-6-acetyl-3-(benzyloxy)-5-bromo-3,6-dihydro-2*H*-pyran-2-yl)acrylate (321)



A sample of *E*-ethyl ester alkyne **319** (35 mg, 0.09 mmol) was dissolved in tetrahydrofuran (0.7 mL). $HgSO_4$ (5 mg, 0.2 equiv, in 0.7 mL of 10% H_2SO_4 solution) was added to this solution. Then this solution was stirred at room temperature until the starting material disappeared (overnight). The mixture was diluted with Et_2O (5 mL) and carefully neutralised with powder of sodium bicarbonate until pH 7 was reached. The aqueous layer was washed with Et_2O (3x5 mL). The organic layers were combined and dried over magnesium sulfate. The crude product was chromatographed (5:1 petroleum ether: Ethyl acetate) to yield the product **321** as clear oil. (22 mg, 61%)

R_f 0.25 (5:1 petroleum ether: ethyl acetate); $[\alpha]_D^{23}$ = -224 (*c* 0.45, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.29 (complex m, 5H, Bn), 6.98 (dd, *J* = 15.8, 4.2 Hz, 1H, H-9), 6.50 (dd, *J* = 4.1, 0.7 Hz, 1H, H-5), 6.19 (dd, *J* = 15.8, 1.4 Hz, 1H, H-8), 4.81 (s, 1H, H-3), 4.62 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 4.54 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.47 (m, 1H, H-7), 4.24 (q, *J* = 7.2 Hz, 1H, H-11), 3.95 (dd, *J* = 4.3, 3.8 Hz, 1H, H-6), 2.33 (s, 3H, H -1), 1.32 (t, 7.1 Hz, 3H, H-12); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 202.6 (C, C-2), 165.3 (C, C-10), 142.1 (CH, C-9), 137.3 (C, Bn), 128.53 (CH, Bn), 128.52 (CH, Bn), 128.09 (CH, Bn), 127.99 (CH, C-5), 123.1 (CH, C-8), 121.2 (C, C-4), 80.8 (CH, C-3), 72.8 (CH, C-7), 71.2 (CH, C-6 and CH_2, $PhCH_2$), 60.6 (CH_2, C-11), 28.1 (CH_3, C-1), 14.2 (CH_3, C-12); IR (film from Et_2O) ν_{max} 3063, 1664, 1642, 1604, 1496, 1419, 924, 866, 612 cm^{-1}; HRMS: m/z $C_{19}H_{25}{}^{81}BrO_5N^+$ $[M+NH_4]^+$ calcd 426.0911, found 426.0929.

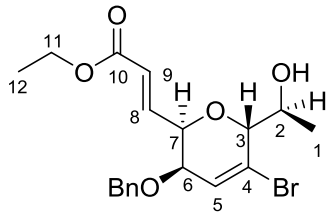
Preparation of ethyl (*Z*)-3-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-bromo-6-((*S*)-1-hydroxyethyl)-3,6-dihydro-2*H*-pyran-2-yl)acrylate (322)



A sample of methyl ketone **320** (95 mg, 0.23 mmol) was dissolved in 2 mL of methanol and cooled to -78 °C using an acetone-dry ice bath and treated with $NaBH_4$ (9 mg, 0.28 mmol). The solution was stirred for 45 minutes at the same temperature to complete the reaction. Unreacted $NaBH_4$ was quenched with acetone (1 mL). The solvent was removed under reduced pressure and the residue re-dissolved in 10 mL dichloromethane. The organic phase was washed with 10 mL water. The extracted organic layer was evaporated and purified by column chromatography (5:1 petroleum ether: ethyl acetate) to yield product **322** as a colourless oil (85 mg, 91%).

R_f 0.24 (5:1 petroleum ether: ethyl acetate); $[\alpha]_D^{20}$ = -65 (*c* 0.2, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.34–7.28 (complex m, 5H, Bn), 6.48 (dd, *J* = 4.8, 1.4 Hz, 1H, H-5), 6.44 (dd, *J* = 11.7, 7.8 Hz, 1H, H-8), 5.99 (d, *J* = 11.8 Hz, 1H, H-9), 5.80 (ddd, *J* = 7.6, 3.2, 1.6 Hz, 1H, H-7), 4.62 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.55 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.36 (m, 1H, H-2), 4.16 (q, *J* = 7.1 Hz, 2H, H-11), 4.12 (partially obscured dd, *J* = 4.2, 3.4 Hz, 1H, H-6), 4.05 (apparent s, 1H, H-3), 1.34 (d, *J* = 6.9 Hz, 3H, H-1), 1.28 (t, *J* = 7.2 Hz, 3H, H-12); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 165.7 (C, C-10), 144.3 (CH, C-8), 137.8 (C, Bn), 129.2 (CH, C-5), 128.39 (CH, Bn), 128.87 (CH, Bn), 127.84 (CH, Bn), 125.2 (C, C-4), 122.5 (CH,C-9), 79.5 (CH, C-3), 71.8 (CH, C-6), 71.4 (CH_2, $PhCH_2$), 69.9 (CH, C-7), 68.0 (CH, C-2), 60.5 (CH_2, C-11), 19.6 (CH_3, C-1), 14.1 (CH_3, C-12); IR (film from CH_2Cl_2) ν_{max} 3467, 3031, 2980, 2930, 1650, 1454, 1232, 1147, 856, 827, 697 cm^{-1}; HRMS: m/z $C_{19}H_{27}{}^{81}BrNO_5^+$ $[M+NH_4]^+$ calcd 428.1067 found 428.1049.

Preparation of ethyl (*E*)-3-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-bromo-6-(1-hydroxyethyl)-3,6-dihydro-2*H*-pyran-2-yl)acrylate (323)

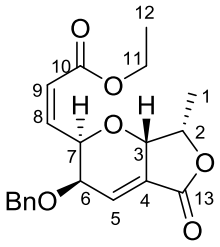


A sample of *E*-ethyl ester methyl ketone **321** (22 mg, 0.05 mmol) was dissolved in 1 mL of methanol and cooled down to -78 ^{0}C using acetone-dry ice bath and treated with $NaBH_4$ (2 mg, 0.06 mmol). The solution was stirred for 15 minutes at same temperature to complete the reaction. Unreacted $NaBH_4$ were quenched with 1 mL of acetone. Solvents removed in reduce pressure and re dissolved in 10 mL of dichloromethane and washed with 10 mL of distilled water. Aqueous layer was extracted with dichloromethane (2x10 mL). Organic fractions were combined, evaporated and purified by column chromatography (5:1 petroleum ether: ethyl acetate) to yield **323** colourless oil (19 mg, 91%).

R_f 0.14 (5:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -137 (*c* 0.15, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$)δ_H 7.37–7.27 (complex m, 5H, Bn), 7.03 (dd, *J* = 15.8, 4.3 Hz, 1H, H-8), 6.46 (dd, *J* = 3.8, 1.6 Hz, 1H, H-5), 6.20 (d, *J* = 15.7 Hz, 1H, H-9), 4.95 (m, 1H, H-7), 4.61 (d, *J* = 12.1 Hz, 2H, $PhCH_2$), 4.56 (d, *J* = 12.0 Hz, 2H, $PhCH_2$), 4.39 (m, 1H, H-3), 4.23 (q, *J* = 7.0 Hz, 2H, H-11), 4.14–4.06 (complex m, 2H, H-2 and H-6), 1.32–1.24 (complex m, 6H, H-1 and H-12); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.2 (C, C-10),

142.8 (CH, C-8), 137.5 (C, Bn), 129.5 (CH, C-5), 128.49 (CH, Bn), 128.08 (CH, Bn), 127.88 (CH, Bn), 124.1 (C, C-4), 123.2 (CH, C-9), 78.5 (CH, C-2), 72.9 (CH, C-7), 72.0 (CH, C-6), 71.1 (CH_2, $PhCH_2$), 68.0 (CH, C-3), 60.7 (CH_2, C-11), 19.3 (CH_3, C-1), 14.1 (CH_3, C-12); IR (film from CH_2Cl_2) ν_{max} 3572, 3458, 2983, 2926, 1650, 1447, 1414, 1331, 1121, 1042, 968, 852, 822, 764, 731 cm^{-1}; HRMS: m/z $C_{19}H_{27}{}^{81}BrNO_5{}^{+}$ $[M+NH_4]^+$ calcd 428.1073 found 428.1078.

Preparation of ethyl (*Z*)-3-((2*R*,3*R*,7*S*,7a*S*)-3-(benzyloxy)-7-methyl-5-oxo-3,5,7,7a-tetrahydro-2*H*-furo[3,4-*b*]pyran-2-yl)acrylate (328)

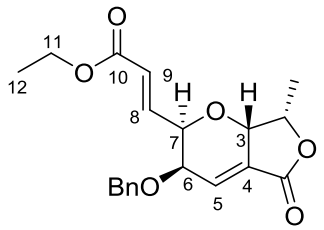


Alcohol **322** (42 mg, 0.11 mmol) was dissolved in 1,4-dioxane (2 mL). Then XantPhos (15 mg, 0.025 mmol, 20 mol%), palladium acetate (6 mg, 0.025 mmol, 20 mol%), sodium carbonate (67 mg, 0.63 mmol), TBAI (9 mg, 0.025 mmol) and triethylamine (0.18 mL, 1.26 mmol) were added sequentially. CO gas was bubbled through the reaction mixture for a few minutes to saturate the solution with CO. Then the flask was connected to a reflux condenser under an atmosphere of CO (balloon) and stirred vigorously at 95 °C overnight. Another portion of XantPhos and palladium acetate (10 mol% each) was added after 16 hours and the mixture stirred vigorously at 95 °C under CO until the reaction was complete (a further 3 hours). The mixture was diluted with 5 mL of dichloromethane and filtered through a silica plug. The crude product was purified by column chromatography (3:1 petroleum ether: ethyl acetate) to yield the lactone **328** as a colourless oil (22 mg, 60%).

R_f 0.37 (5:1 petroleum ether: ethyl acetate); $[\alpha]_D{}^{20}$ = -178 (*c* 0.18, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.35–7.28 (complex m, 5H, Bn), 7.22 (dd, *J* = 5.4, 3.2 Hz, 1H, H-5), 6.49 (dd, *J* = 11.5, 7.7 Hz, 1H, H-8), 5.99 (dd, *J* = 11.5, 1.0 Hz, 1H, H-9), 5.28 (m, 1H, H-7), 5.14 (dd, *J* = 7.5, 3.2 Hz, 1H, H-3), 4.85 (quintet, *J* = 6.8 Hz, 1H, H-2), 4.60 (d, *J* = 11.9 Hz, 1H, $PhCH_2$), 4.51 (d, *J* = 12.2 Hz, 1H, $PhCH_2$), 4.42 (dd, *J* = 5.4, 2.9 Hz, 1H, H-6), 4.15 (q, *J* = 7.2 Hz, 2H, H-11), 1.29-1.26 (apparent m , 6H, H-12, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.4 (C, C-13), 165.6 (C, C-10), 145.5 (CH, C-8), 137.4.0 (C, Bn), 134.9 (CH, C-5), 132.3 (C, C-4), 128.48 (CH, Bn), 128.07 (CH, Bn), 127.80 (CH, Bn), 122.3 (CH, C-9), 78.4 (CH, C-2), 71.8 (CH_2, $PhCH_2$), 71.6 (CH, C-7), 71.2 (CH, C-3), 69.5 (CH, C-6), 60.5 (CH_2, C-11), 15.4 (CH_3, C-12 or C-1), 14.2 (CH_3, C-12 or C-1); IR (film from CH_2Cl_2) ν_{max} 2983, 1650, 1454, 1413, 1386,

1298, 1096, 920, 829, 736, 689, 632 cm^{-1}; HRMS: m/z $C_{23}H_{23}O_6^+$ $[M+H]^+$ calcd 359.1489, found 359.1477.

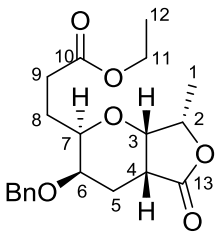
Preparation of ethyl (*E*)-3-((2*R*,3*R*,7*S*,7a*S*)-3-(benzyloxy)-7-methyl-5-oxo-3,5,7,7a-tetrahydro-2*H*-furo[3,4-*b*]pyran-2-yl)acrylate (329)



A sample of *E*-ethyl ester methyl alcohol **323** (20 mg, 0.05 mmol) dissolved in 1 mL of 1,4-dioxane. Then XantPhos (5.6 mg, $9.72x10^{-3}$ mmol, 20%), palladium acetate (2 mg, $9.72x10^{-3}$ mmol, 20%), sodium carbonate (25 mg, 0.24 mmol), TBAI (3 mg, $9.72x10^{-3}$ mmol) triethyl amine (68 µL, 0.49 mmol) were added accordingly. Then this mixture was bubbled with CO for few minutes to saturate the solution with CO. Then the flask was connected to the condenser attaching CO balloon. The whole set-up was evacuated and purged with CO for several time and stirred vigorously at 95 °C for two and half hours. Then the solution was diluted with 5 mL of dichloromethane and filtered through silica plug. Crude product was purified by column chromatography (3:1 petroleum ether: ethyl acetate) to yield lactone **329** as a colourless oil (8 mg, 46%).

R_f 0.24 (3:1 petroleum ether: ethyl acetate); $[\alpha]_D^{20}$ = -234 (c 0.3, $CHCl_3$); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.38–7.29 (complex m, 5H, Bn), 7.13 (dd, *J* = 4.3, 3.7 Hz, 1H, H-5), 7.06 (dd, *J* = 15.8, 5.4 Hz, 1H, H-8), 6.23 (dd, *J* = 15.9, 1.2 Hz, 1H, H-9), 5.08 (m, 1H, H-3), 4.86 (q, *J* = 6.8 Hz, 1H, H-2), 4.65 (d, *J* = 12.2 Hz, 2H, $PhCH_2$), 4.54 (d, *J* = 12.2 Hz, 2H, $PhCH_2$), 4.39 (m, 1H, H-7), 4.28 (apparent t, *J* = 3.6 Hz, 1H, H-6), 4.24 (q, *J* = 7.1 Hz, 2H, H-11), 1.32 (t, *J* = 7.2 Hz, 3H, H-12), 1.24 (d, *J* = 6.6 Hz, 3H, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.0 (C, C-10), 165.8 (C, C-13), 141.9 (CH, C-8), 137.0 (C, Bn), 134.2 (CH, C-5), 132.2 (C, C-4), 128.63 (CH, Bn), 128.27 (CH, Bn), 127.85 (CH, Bn), 124.9 (CH, C-9), 77.9 (CH, C-2), 74.3 (CH, C-7), 71.8 (CH_2, $PhCH_2$), 70.5 (CH, C-3), 69.5 (CH, C-6), 60.7 (CH_2, C-11), 15.3 (CH_3, C-1), 14.2 (CH_3, C-12); IR (film from Et_2O) ν_{max} 2980, 2959, 2926, 1714, 1662, 1447, 1439, 1384, 1302, 1266, 1180, 1039, 977, 915, 825, 726, 694, 666 cm^{-1}; HRMS: m/z $C_{20}H_{26}NO_6^+$ $[M+NH_4]^+$ calcd 376.1760, found 376.1768.

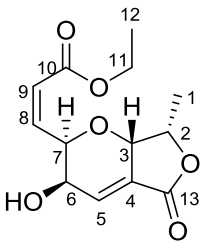
Preparation of Ethyl (*Z*)-3-((2*R*,3*R*,4a*R*,7*S*,7a*S*)-3-(benzyloxy)-7-methyl-5-oxohexahydro-2*H*-furo[3,4-*b*]pyran-2-yl)acrylate (331)



Lactone **328** (10 mg, 0.03 mmol) was dissolved in 1 mL of ethyl acetate and bubbled with hydrogen for few minutes. Then wet Pearlman's catalyst (3.5 mg) was added and bubbled with hydrogen for 10 minutes. Then reaction mixture was filtered through silica plug and concentrated on *roto-vap*. Crude compound was purified by column chromatography to obtain **331** as pale yellow oil (6 mg, 55%).

R_f 0.25 (3:1 petroleum ether: ethyl acetate); $[\alpha]_D^{24}$ = -100 (c 0.05, Et_2O); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.26 (complex m, 5H, Bn), 4.58 (d, *J* = 11.5 Hz, 1H, $PhCH_2$), 4.50 (d, *J* = 11.5 Hz, 1H, $PhCH_2$), 4.46 (dd, *J* = 6.5, 3.1 Hz, 1H, H-2), 4.17 (complex m, 1H, H-3), 4.14 (q, *J* = 7.2 Hz, 2H, H-11), 3.93 (dt, *J* = 11.2, 4.7 Hz, 1H, H-6), 3.65 (dt, *J* = 11.2, 5.2 Hz, 1H, H-7), 2.82 (complex m, 1H, H-4), 2.39 (t, *J* = 7.4 Hz, 2H, H-9), 2.05-2.00 (complex m , 2H, H-5a and H-8a), 1.98-1.91 (complex m ,2H, H-5b and H-8b), 1.37 (d, *J* = 6.9 Hz, 3H, H-1), 1.27 (t, *J* = 7.2 Hz, 3H, H-12); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 176.8 (C, C-13), 173.5 (C, C-10), 138.0 (C, Bn), 128.46 (CH, Bn), 128.07 (CH, Bn), 127.02 (CH, Bn), 78.2 (CH, C-2), 73.7 (CH, C-6), 71.9 (CH, C-7), 71.1 (CH_2, $PhCH_2$), 68.08 (CH, C-3),60.5 (CH_2, C-11), 42.0 (CH, C-4), 30.7 (CH_2, C-9), 22.1 (CH_2, C-8), 19.3 (CH_2, C-5), 14.2 (CH_3, C-12), 13.3 (CH_3, C-1); IR (film from $CDCl_3$) ν_{max} 2917, 1497, 1453, 1386, 1371, 1349, 1303, 1259, 1026, 997, 951, 912, 886, 738, 699 cm^{-1}; HRMS: m/z $C_{20}H_{27}O_6^+$ $[M+H]^+$ calcd 363.1808, found 363.1807.

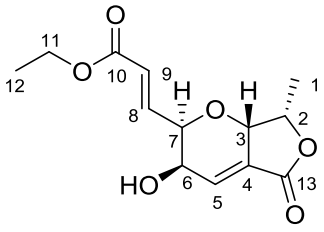
Preparation of ethyl (*Z*)-3-((2*R*,3*R*,7*S*,7a*S*)-3-hydroxy-7-methyl-5-oxo-3,5,7,7a-tetrahydro-2*H*-furo[3,4-*b*]pyran-2-yl)acrylate (140)



To a solution of lactone **328** (30.0 mg, 0.08 mmol) in dichloromethane (1 mL) was added $TiCl_4$ (27 µL, 0.25 mmol) in dichloromethane (0.1 mL) at 0 °C. After stirring at the same temperature for 10 minutes, the reaction was quenched with sat. solution of sodium bicarbonate (5 mL), and the organic layer was separated and extracted with dichloromethane (2x5 mL). The organic layers were combined and dried over anhydrous magnesium sulfate. After filtration and concentration under reduced pressure, the crude product was purified by column chromatography (2:1 petroleum ether: ethyl acetate) to yield (−)-TAN-2483B ethyl ester **140** as a colourless oil (13 mg, 56%).

R_f 0.17 (2:1 petroleum ether: ethyl acetate); $[\alpha]_D^{21}$ = -106 (*c* 0.1, Et_2O); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.16 (dd, *J* = 5.4, 3.4 Hz, 1H, H-5), 6.44 (dd, *J* = 11.7, 7.8 Hz, 1H, H-8), 6.07 (dd, *J* = 11.7, 1.2 Hz, 1H, H-9), 5.32 (ddd, *J* = 7.8, 3.4, 1.4 Hz, 1H, H-7), 5.12 (ddd, *J* = 5.4, 3.2, 1.3 Hz, 1H, H-3), 4.85 (quintet, *J* = 6.8 Hz, 2H, H-2), 4.71 (dd, *J* = 4.8, 3.6 Hz 1H, H-6), 4.19 (q, *J* = 7.2 Hz, 2H, H-11), 1.30 (d, *J* = 6.4 Hz, 3H, H-1), 1.32-1.28 (overlap signal, 3H, H-12); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.4 (C, C-10), 166.1 (C, C-13), 143.7 (CH, C-8), 135.4 (CH, C-5), 130.9 (C, C-4), 123.3 (CH, C-9), 78.0 (CH, C-2), 72.9 (CH, C-3), 70.4 (CH, C-7),64.0 (CH, C-6), 60.9 (CH_2, C-11), 15.2 (CH_3, C-12 or 1), 14.1 (CH_3, C-12 or 1); IR (film from CH_2Cl_2) ν_{max} 3572, 3458, 1650, 1447, 1414, 1386, 1331, 1301, 1121, 1042, 968, 917, 852, 822, 764, 731 cm^{-1}; HRMS: m/z $C_{13}H_{17}O_6^+$ $[M+H]^+$ calcd 269.1025, found 269.1012.

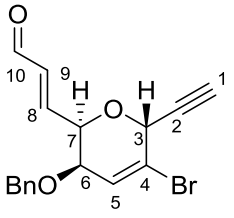
Preparation of ethyl (*E*)-3-((2*R*,3*R*,7*S*,7a*S*)-3-hydroxy-7-methyl-5-oxo-3,5,7,7a-tetrahydro-2*H*-furo[3,4-b]pyran-2-yl)acrylate (141)



To a solution of benzylated lactone **329** (8.0 mg, 0.02 mmol) in dichloromethane (1 mL) was added $TiCl_4$ (7.4 µL, 0.07 mmol) in dichloromethane (0.1 mL) at 0 °C. After stirring at same temperature for 10 minutes, the reaction was quenched with sat. solution of sodium bicarbonate (5 mL), and the organic layer was separated and extracted in to dichloromethane (2x5 mL). The organic layers were combined and dried over anhydrous magnesium sulfate. After filtration and concentration under reduced pressure, the crude product was purified by column chromatography (2:1 petroleum ether: ethyl acetate) to yield pale yellow oil (−)-TAN-2483B ethyl ester **141** (3 mg, 56%).

R_f 0.33 (1:1 petroleum ether: ethyl acetate); $[\alpha]_D^{22}$ = -100 (*c* 0.1, Et_2O); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.17 (dd, *J* = 5.6, 3.3 Hz, 1H, H-5), 7.02 (dd, *J* = 15.7, 5.2 Hz, 1H, H-8), 6.29 (dd, *J* = 15.7, 1.7 Hz, 1H, H-9), 5.13 (dd, *J* = 7.7, 3.1 Hz, 1H, H-3), 4.81 (quintet, *J* = 7.0 Hz, 1H, H-2), 4.56 (m, 1H, H-6), 4.41 (m, 1H, H-7), 4.23 (q, *J* = 7.1 Hz, 2H, H-11), 1.31 (t, *J* = 7.2 Hz, 3H, H-12), 1.28 (d, *J* = 6.6 Hz, 3H, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 165.9 (C, C-13), 165.8 (C, C-10), 141.2 (CH, C-8), 134.8 (CH, C-5), 131.6 (C, C-4), 125.4 (CH, C-9), 77.9 (CH, C-2), 75.1 (CH, C-7), 70.8 (CH, C-3), 63.5 (CH, C-6), 60.8 (CH_2, C-11), 15.3 (CH_3, C-1), 14.2 (CH_3, C-12); IR (film from $CDCl_3$) ν_{max} 3760, 3672, 3644, 3447, 2983, 2929, 1663, 1448, 1370, 1096, 980, 942, 916, 869, 826, 730, 699, 667 cm^{-1}; HRMS: m/z $C_{13}H_{20}O_6N^+$ $[M+NH_4]^+$ calcd 286.1285, found 286.1290.

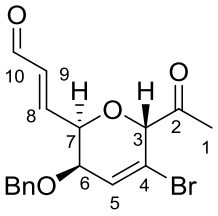
Preparation of (*E*)-3-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-bromo-6-ethynyl-3,6-dihydro-2*H*-pyran-2-yl)acrylaldehyde (332)



Diol **314** (58 mg, 0.14 mmol) was dissolved in a solution of 20% methanol in dichloromethane (1 mL of methanol in 4 mL of Dichloromethane) and treated with potassium carbonate (94 mg, 0.68 mmol). The solution was stirred at room temperature until reaction has completed by TLC analysis. Then reaction mixture was filtered into the 10 mL brine solution and extracted in to dichloromethane (3x5 mL). The organic solution mixture was dried over anhy. magnesium sulfate and evaporated quickly on *roto-vap* (*Note*: water bath temperature of the roto-vap was kept close to room temperature). The crude diol was re-dissolved in 5 mL of tetrahydrofuran and treated with $NaIO_4$ (145 mg, 0.68 mmol) and stirred one hour at room temperature. Reaction was quenched with 5 mL of brine after starting material has been completely consumed. Then it was extracted into diethyl ether (3x5 mL) and organic layer was dried and evaporated on *roto-vap*. The crude aldehyde was re-dissolved in dry tetrahydrofuran (2 mL) and treated with (triphenylphosphoranylidene) acetaldehyde (42 mg, 0.13 mmol) and stirred overnight at room temperature. The excess solvents in crude mixture was evaporated and purified by column chromatography (5:1 petroleum ether: ethyl acetate) to obtain **332** as a colourless oil (20 mg, 42% over three steps).

R_f 0.18 (5:1 petroleum ether : ethyl acetate); $[\alpha]_D^{21}$ = -98 (*c* 1.7, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 9.60 (d, *J* = 7.5 Hz, 1H, H-10), 7.38–7.27 (complex m, 5H, Bn), 6.81 (dd, *J* = 15.9, 4.1 Hz, 1H, H-8), 6.44 (ddd, *J* = 15.8, 7.8, 1.9 Hz, 1H, H-9), 6.39 (dd, *J* = 5.4, 1.2 Hz, 1H, H-5), 5.12 (d, *J* = 1.7 Hz, 1H, H-3), 4.83 (complex m, 1H, H-7), 4.63 (d, *J* = 11.9 Hz, 1H, $PhCH_2$), 4.50 (d, *J* = 11.7 Hz, 1H, $PhCH_2$), 3.99 (dd, *J* = 5.4, 3.0 Hz, 1H, H-6), 2.55 (d, *J* = 2.1 Hz, 1H, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 192.9 (CH, C-10), 151.0 (CH, C-8), 137. 2 (C, Bn), 132.7 (CH, C-9), 128.59 (CH, Bn), 128.21 (CH, Bn), 128.00 (CH, Bn), 126.3 (CH, C-5), 125.1 (C, C-4), 77.7 (CH, C-2), 75.6 (C, C-1), 72.2 (CH, C-7), 70.8 (CH_2, $PhCH_2$ and CH, C-6), 69.1 (CH, C-3); IR (film from $CDCl_3$) ν_{max} 2733, 2217, 2154, 1722, 1646, 1496, 1367, 1301, 1209, 848 cm^{-1}; HRMS: m/z $C_{17}H_{21}{}^{81}BrO_3N^+$ $[M+NH_4]^+$ calcd 364.0543 found 364.0528.

Preparation of (*E*)-3-((2*R*,3*R*,6*R*)-6-acetyl-3-(benzyloxy)-5-bromo-3,6-dihydro-2*H*-pyran-2-yl)acrylaldehyde (333)

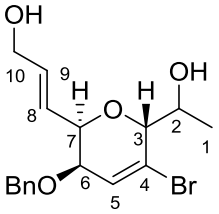


A sample of alkyne **332** (20 mg, 0.06 mmol) was dissolved in tetrahydrofuran (0.5 mL). $HgSO_4$ in H_2SO_4 (10% aqueous solution, 0.5 mL, 3 mg, 0.012 mmol) was added to this solution. The reaction mixture was stirred at room temperature for 4 hours. The mixture was diluted with diethyl ether (5

mL) and carefully neutralised with sodium bicarbonate powder until a pH 7 was reached. The aqueous layer was washed with diethyl ether (3x5 mL). The organic layers were combined and dried over magnesium sulfate. The crude product was chromatographed (3:1 petroleum ether: ethyl acetate) to yield the product **333** as a clear oil (16 mg, 76%).

R_f 0.37 (3:1 petroleum ether: ethyl acetate); $[\alpha]_D^{19}$ = -126.9 (*c* 0.52, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 9.58 (d, *J* = 7.6 Hz, 1H, H-10), 7.37–7.27 (complex m, 5H, Bn), 6.77 (dd, *J* = 15.8, 4.1 Hz, 1H, H-8), 6.53 (dd, *J* = 4.9, 1.4 Hz, 1H, H-5), 6.42 (ddd, *J* = 16.0, 7.8, 2.0 Hz, 1H, H-9), 4.84 (s, H, 1H, H-3), 4.63 (complex m, *J* = 11.9 Hz, 2H, $PhCH_2$ and H-7), 4.52 (d, *J* = 12.0 Hz, 1H, PhCH2), 4.06 (dd, *J* = 4.9, 1.7 Hz, 1H, H-6), 2.34 (s, 3H, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 202.4 (C, C-2), 192.9 (CH, C-10), 150.6 (CH, C-8), 137.1 (C, Bn), 132.9 (CH, C-9), 128.62 (CH, Bn), 128.29 (CH, Bn), 128.0 (CH, Bn), 127.0 (CH, C-5), 121.3 (C, C-4), 80.7 (CH, C-3), 72.8 (CH, C-7), 71.1 (CH, C-6 and CH_2, $PhCH_2$), 28.4 (CH_3, C-1); IR (film from $CDCl_3$) ν_{max} 2958, 2930, 2871, 2733, 2360, 2341, 1881, 1648, 1551, 1496, 1418, 1273, 1208, 1170, 1144, 861, 790, 620 cm^{-1}; HRMS: m/z $C_{17}H_{21}{}^{81}BrO_4N^+$ $[M+NH_4]^+$ calcd 382.0654 found 382.0646.

Preparation of (*E*)-3-((2*R*,3*R*,6*R*)-3-(benzyloxy)-5-bromo-6-(1-hydroxyethyl)-3,6-dihydro-2*H*-pyran-2-yl)prop-2-en-1-ol (334)

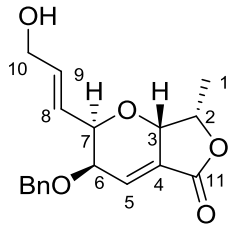


$CeCl_3.7H_2O$ (16 mg, 0.0301 mmol) was added to a solution of aldehyde **333** (16 mg, 0.0301 mmol) in CH_2Cl_2/EtOH (0.6 mL of a 1:1 v/v mixture) maintained at room temperature. This mixture was then cooled to -78 °C, treated with $NaBH_4$ (5.8 mg, 0.15 mmol) in ethanol (0.3 mL) and stirring continued at -78°C for one hour. After this time TLC analysis (1:3 ethyl acetate: petroleum ether) showed the absence of starting material. Then 0.5 mL of acetone was added, concentrated under reduced pressure to give yellow oil. This material was purified by flash chromatography (1:1 petroleum ether: ethyl acetate) to obtain **334** as a colourless oil (14 mg, 93%).

R_f 0.24 (1:1 petroleum ether: ethyl acetate); $[\alpha]_D^{24}$ = -16.6 (*c* 0.15, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.36–7.28 (complex m, 5H, Bn), 6.42 (dd, *J* = 3.4, 1.8 Hz, 1H, H-5), 6.07 (dt, *J* = 15.7, 5.3 Hz, 1H, H-9), 5.93 (dd, *J* = 15.9, 6.4 Hz, 1H, H-8), 4.75 (apparent t, *J* = 5.4 Hz, 1H, H-7), 4.62 (d, *J* = 11.9 Hz, 2H, $PhCH_2$), 4.56 (d, *J* = 11.9 Hz, 2H, $PhCH_2$), 4.36 (complex m, 1H, H-2), 4.21 (d, *J* = 4.9 Hz, 2H, H-10), 4.08 (dd, *J* = 4.8, 1.9 Hz, 1H, H-6), 4.03 (d, *J* = 2.0 Hz, 1H, H-3), 1.32 (d, 3H, *J* = 5.6 Hz, H-1); ^{13}C-

NMR (500 MHz): ($CDCl_3$) δ_C 137.7 (C, Bn), 134.5 (CH, C-9), 130.2 (CH, C-5), 128.48 (CH, Bn), 128.95 (CH, Bn), 127.83 (CH, Bn), 125.8 (CH, C-8), 123.3 (C, C-4), 77.7 (CH, C-3), 73.5 (CH, C-7), 72.9 (CH, C-6), 71.1 (CH_2, $PhCH_2$), 67.7 (CH, C-2), 63.1 (CH_2, C-10), 19.5 (CH_3, C-1); IR (film from $CDCl_3$) ν_{max} 3628, 3381,3033, 2927, 2630, 2339, 1646, 1455, 1345, 1071, 913, 857, 735, 698, 626 cm^{-1}; HRMS: m/z $C_{17}H_{25}{}^{81}BrO_4N^+$ $[M+NH_4]^+$ calcd 386.0961 found 386.0949.

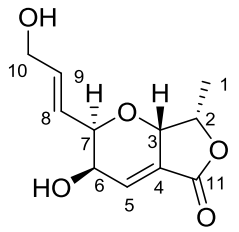
Preparation of (2*R*,3*R*,7*S*,7a*S*)-3-(benzyloxy)-2-((*E*)-3-hydroxyprop-1-en-1-yl)-7-methyl-2,3,7,7a-tetrahydro-5*H*-furo[3,4-*b*]pyran-5-one (335)



A sample of diol **334** (45 mg, 0.12 mmol) dissolved in 1 mL of 1,4-dioxane. Then XantPhos (14 mg, 0.0243 mmol, 20%), palladium acetate (6 mg, 0.0243 mmol, 20%), sodium carbonate (65 mg, 0.61 mmol), TBAI (9 mg, 0.0243 mmol), triethyl amine (303 µL, 1.2 mmol) were added accordingly. Then this mixture was bubbled with CO for few minutes to saturate the solution with CO. Then the flask was connected to the condenser attaching CO balloon. The whole set-up was evacuated and purged with CO for several time and stirred vigorously at 95 °C for one day. Then the solution was diluted with 2 mL of dichloromethane and filtered through silica plug. Crude product was purified by column chromatography (1:1 petroleum ether: ethyl acetate) to yield lactone **335** as a pale yellow oil (20 mg, 52%).

R_f 0.25 (1:1 petroleum ether : ethyl acetate); $[\alpha]_D{}^{21}$ = -60.6 (*c* 0.15, CH_2Cl_2); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.38–7.31 (complex m, 5H, Bn), 7.07 (dd, *J* = 7.8, 3.1 Hz, 1H, H-5), 6.09 (dt, *J* = 15.7, 4.7 Hz, 1H, H-9), 6.03 (dd, *J* = 15.7, 6.9 Hz, 1H, H-8), 5.03 (dd, *J* = 7.9, 3.3 Hz, 1H, H-3), 4.83 (quintet, *J* = 6.8 Hz, 1H, H-2), 4.62 (d, *J* = 11.6 Hz, 2H, $PhCH_2$), 4.56 (d, *J* = 12.1 Hz, 2H, $PhCH_2$), 4.37 (dd, *J* = 6.6, 3.8 Hz, 1H, H-7), 4.25 (dd, *J* = 6.2, 4.2 Hz, 1H, H-6), 4.22 (broad d, *J* = 3.8 Hz, 2H, H-10), 1.24 (d, 3H, *J* = 6.4 Hz, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.2 (C, C-11), 137.3 (C, Bn), 135.7 (CH, C-9), 134.6 (CH, C-5), 131.5 (CH, C-4), 128.57 (CH, Bn), 128.17 (CH, Bn), 127.84 (CH, Bn), 125.6 (C, C-8), 77.8 (CH, C-2), 75.3 (CH, C-7), 71.6 (CH_2, $PhCH_2$), 70.4 (CH, C-6), 70.0 (CH, C-3), 62.9 (CH_2, C-10), 15.3 (CH_3, C-1); IR (film from $CDCl_3$) ν_{max} 3628, 3381,3033, 2927, 1650, 1413, 1386, 1298, 1096, 829, 736, 689, 632 cm^{-1}; HRMS: m/z $C_{18}H_{18}O_5Na^+$ $[M+Na-H_2O]^+$ calcd 321.1097 found 321.1094.

Preparation of (2*R*,3*R*,7*S*,7a*S*)-3-hydroxy-2-((*E*)-3-hydroxyprop-1-en-1-yl)-7-methyl-2,3,7,7a-tetrahydro-5*H*-furo[3,4-*b*]pyran-5-one (145)



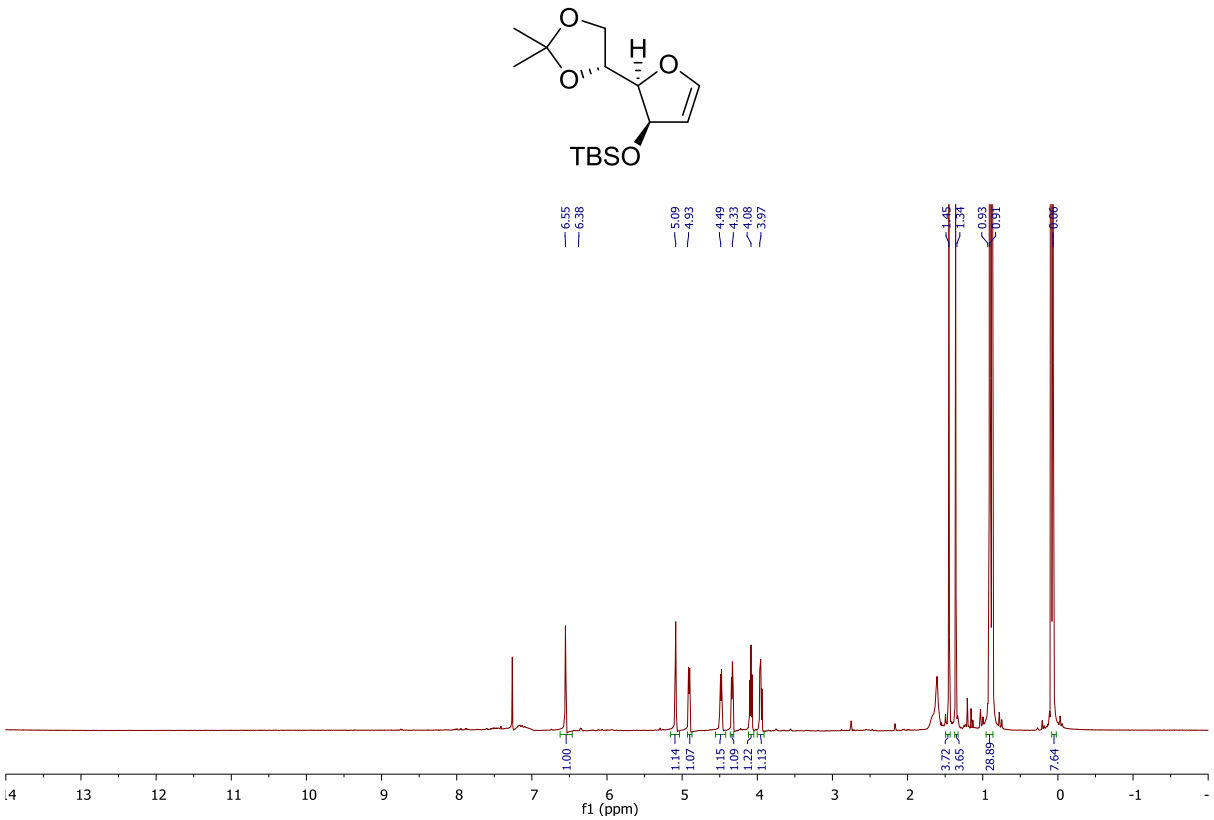
To a solution of lactone **335** (5.0 mg, 0.016 mmol) in dichloromethane (0.5 mL) was added $TiCl_4$ (5.2 µL, 0.047 mmol) in CH_2Cl_2 (0.1 mL) at 0 °C. After stirring at the same temperature for 10 minutes, the reaction was quenched with saturated aqueous sodium bicarbonate (2 mL), and the organic layer was separated and extracted with dichloromethane (2x3 mL). The organic layers were combined and dried over anhydrous magnesium sulfate. After filtration and concentration under reduced pressure, the crude product was purified by column chromatography (ethyl acetate) to yield hydroxy (−)-TAN-2483B **145** as a colourless oil (2.6 mg, 72%).

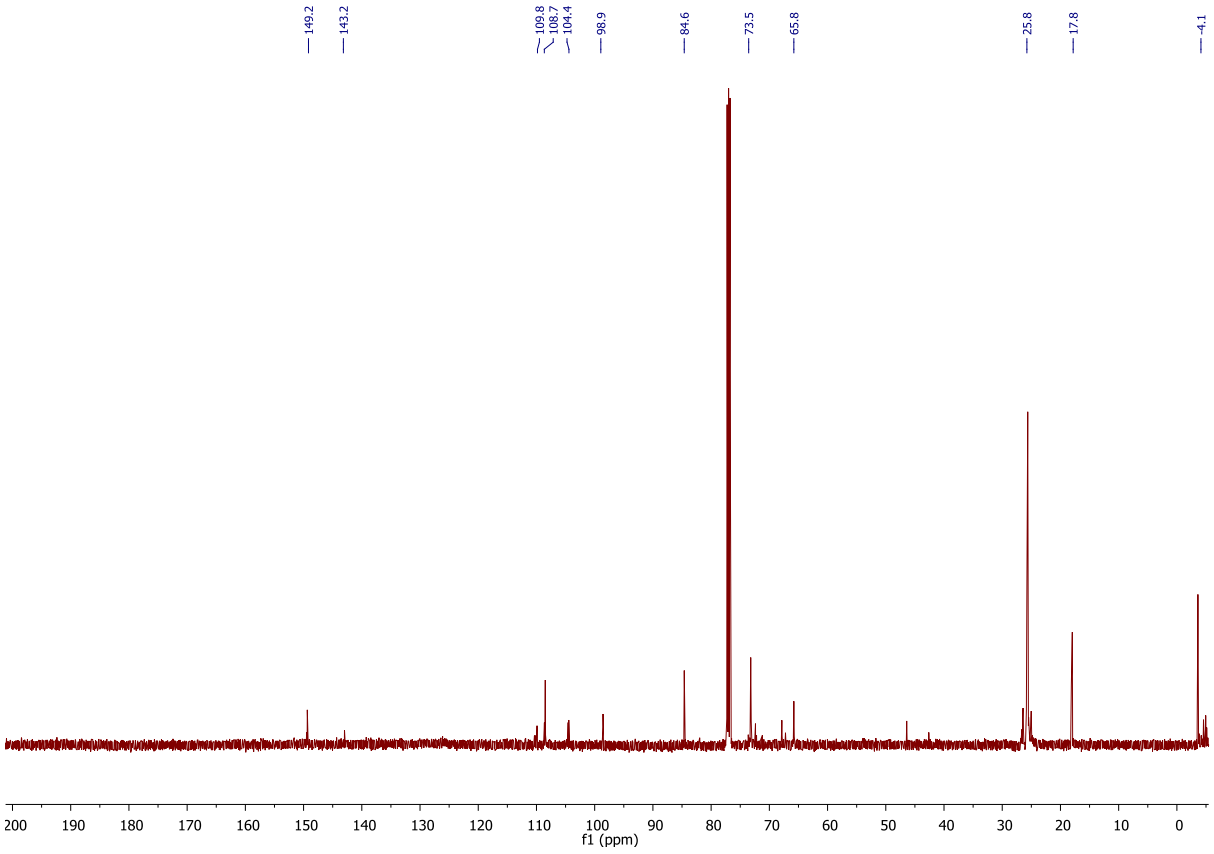
R_f 0.28 (ethyl acetate); $[\alpha]_D^{21}$ = -140 (*c* 0.05, Et_2O); ^{1}H-NMR (500 MHz): ($CDCl_3$) δ_H 7.09 (dd, *J* = 7.5, 3.5 Hz, 1H, H-5), 6.17 (dt, *J* = 15.6, 4.6 Hz, 1H, H-9), 5.98 (dd, *J* = 15.5, 7.0 Hz, 1H, H-8), 5.07 (apparent dt, *J* = 6.4 Hz, 1H, H-3), 4.84 (quintet, *J* = 6.8 Hz, 1H, H-2), 4.49 (m, 1H, H-6), 4.36 (dd, *J* = 6.8, 3.5 Hz, 1H, H-7), 4.26 (broad s, 2H, H-10), 1.27 (d, *J* = 6.6 Hz, 3H, H-1); ^{13}C-NMR (500 MHz): ($CDCl_3$) δ_C 166.3 (C, C-11), 136.5 (CH, C-9), 135.4 (CH, C-5), 131.3 (C, C-4), 124.3 (CH, C-8), 77.8 (CH, C-2), 76.2 (CH, C-7), 70.2 (CH, C-3), 64.2 (CH, C-6), 62.6 (CH_2, C-10), 15.3 (CH_3, C-1); IR (film from Et_2O) ν_{max} 3701, 3379, 2983, 2870, 2362, 2340, 1755, 1691, 1448, 1358, 1332, 1262, 1195, 1141, 1095, 1041, 975, 915, 825, 790, 758, 631, 616 cm $^{-1}$; HRMS: m/z $C_{11}H_{18}O_5N^+$ $[M+NH_4]^+$ calcd 244.1179 found 244.1186.

.

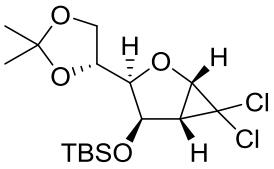
7 Appendix

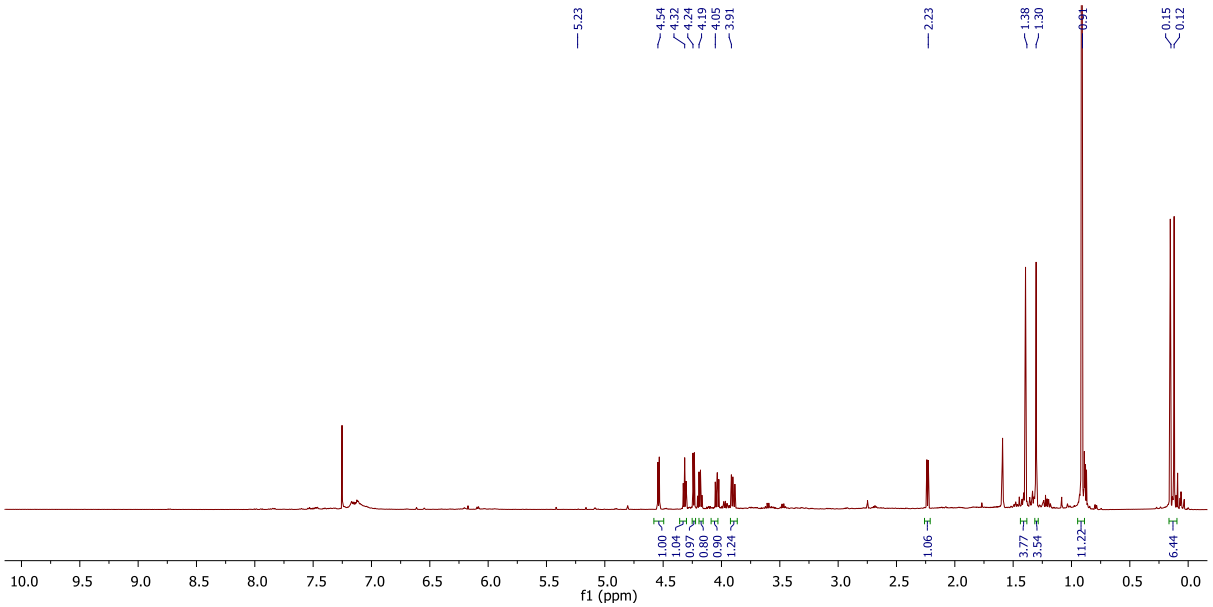
7.1 ^{1}H-NMR and ^{13}C-NMR spectra for selected compounds described in chapter 2

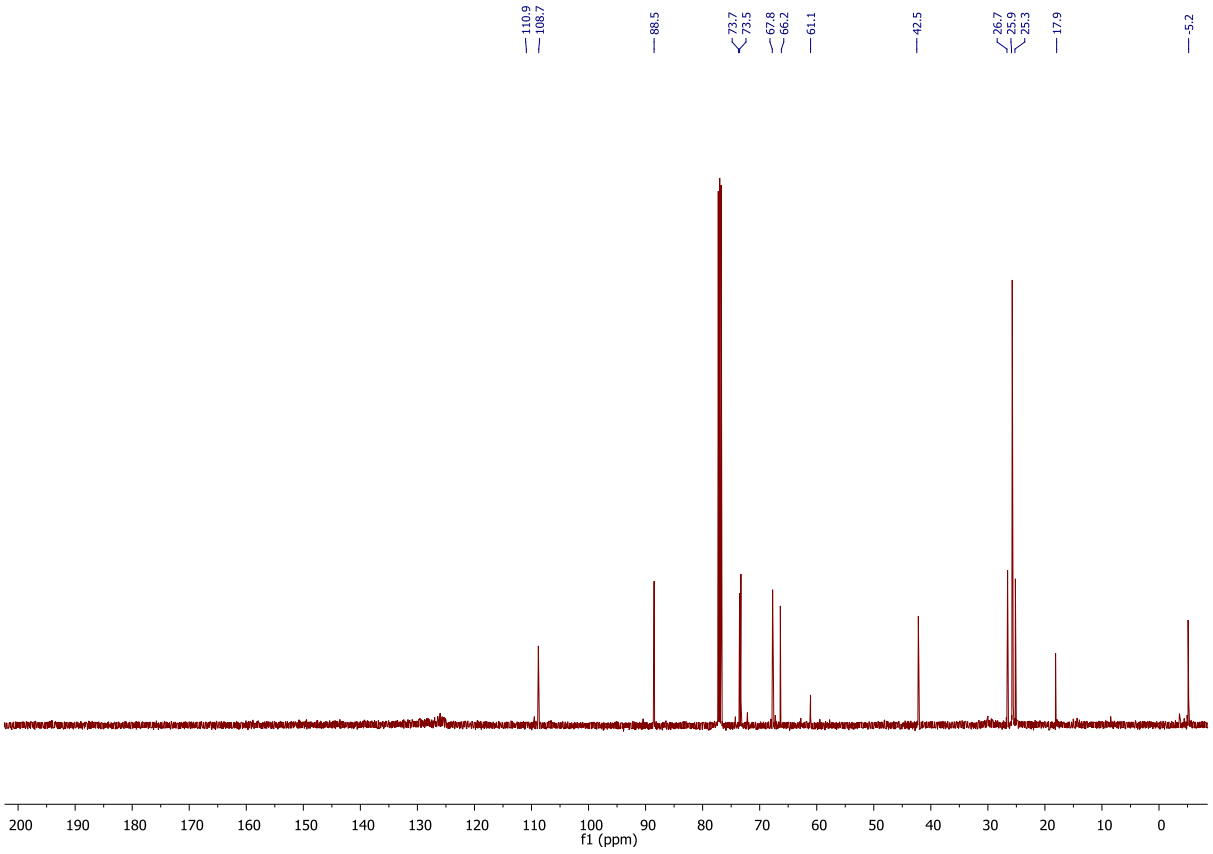




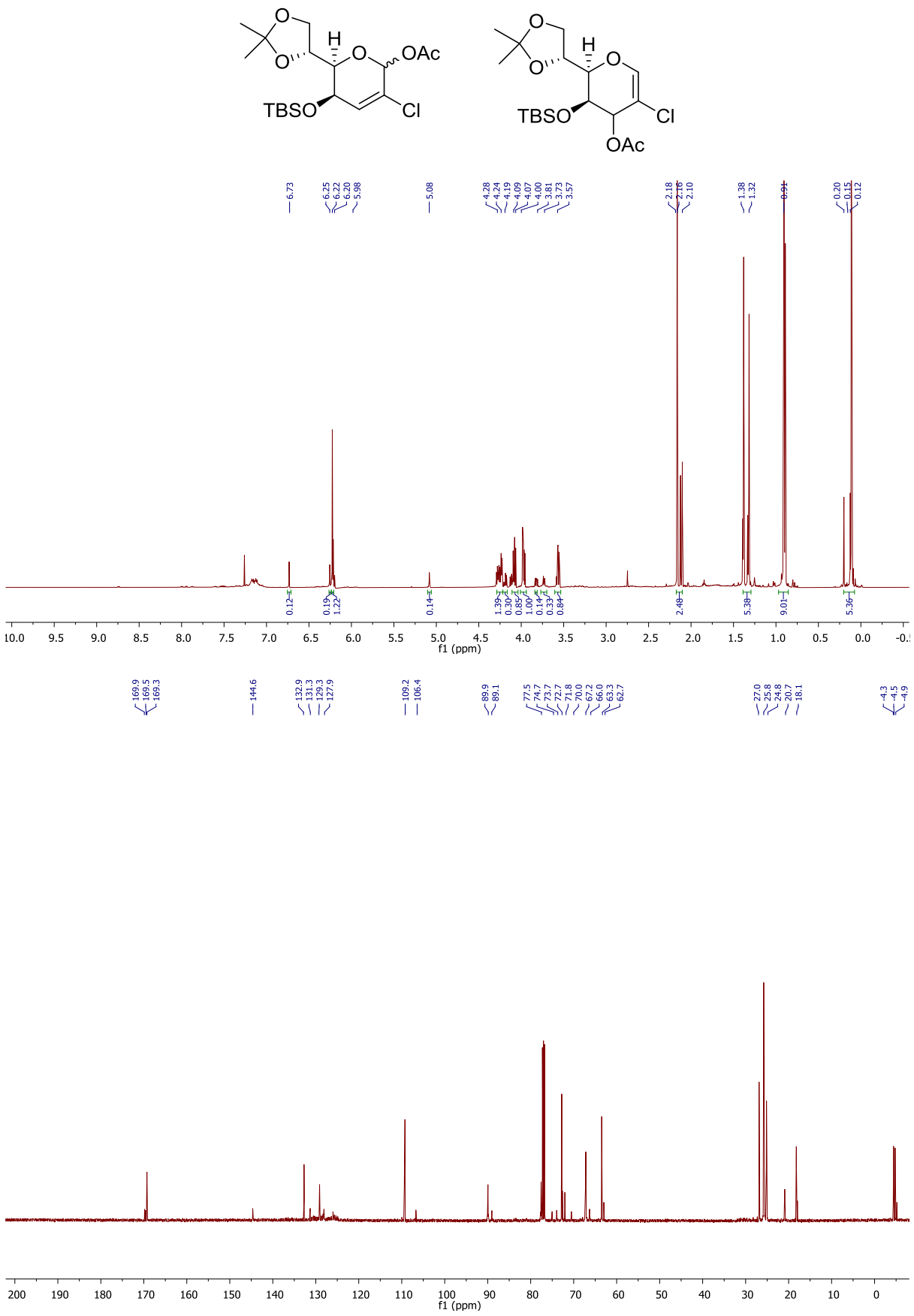
^{1}H-NMR and ^{13}C-NMR spectra of compound **147**



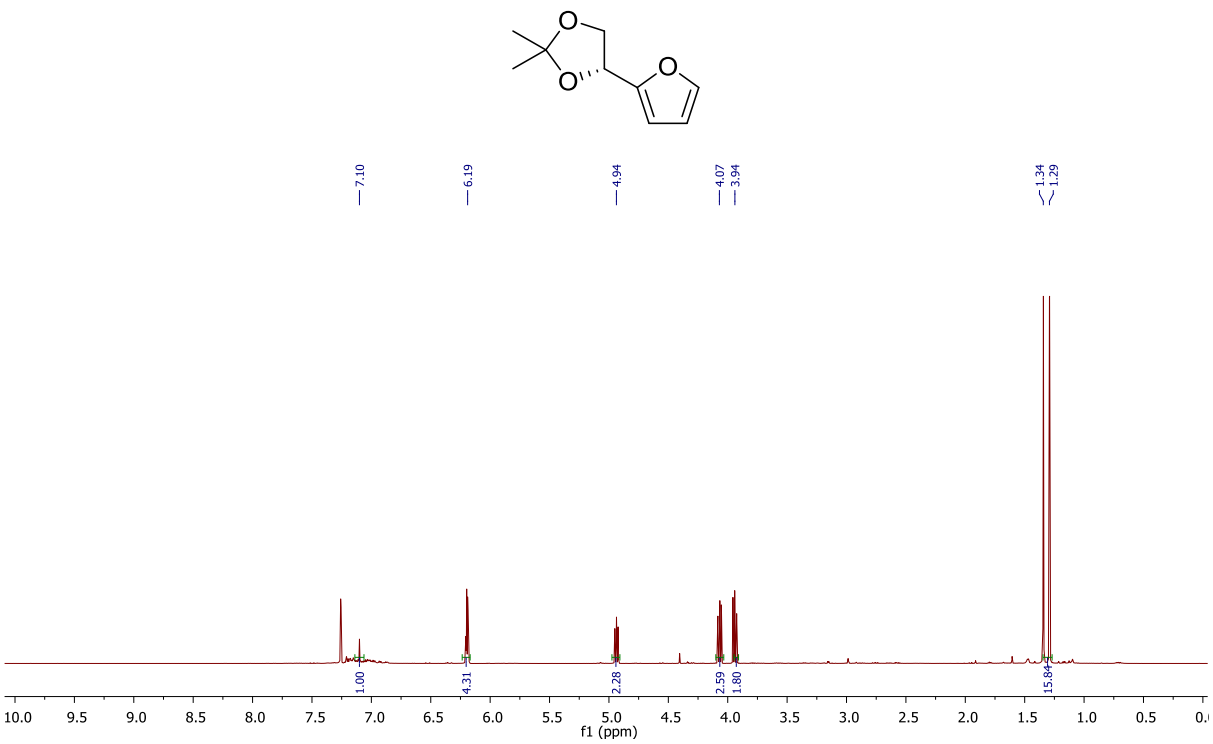


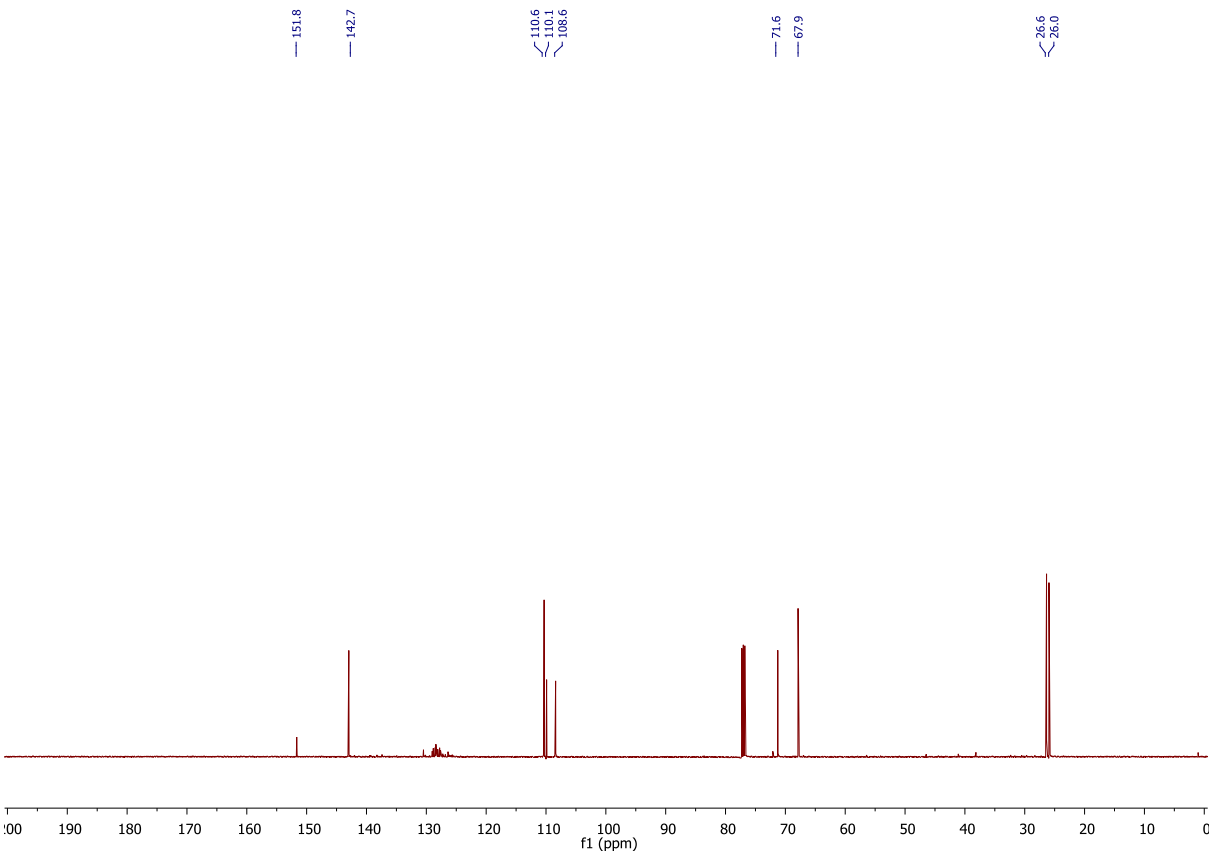


^{1}H-NMR and ^{13}C-NMR spectra of compound **163**

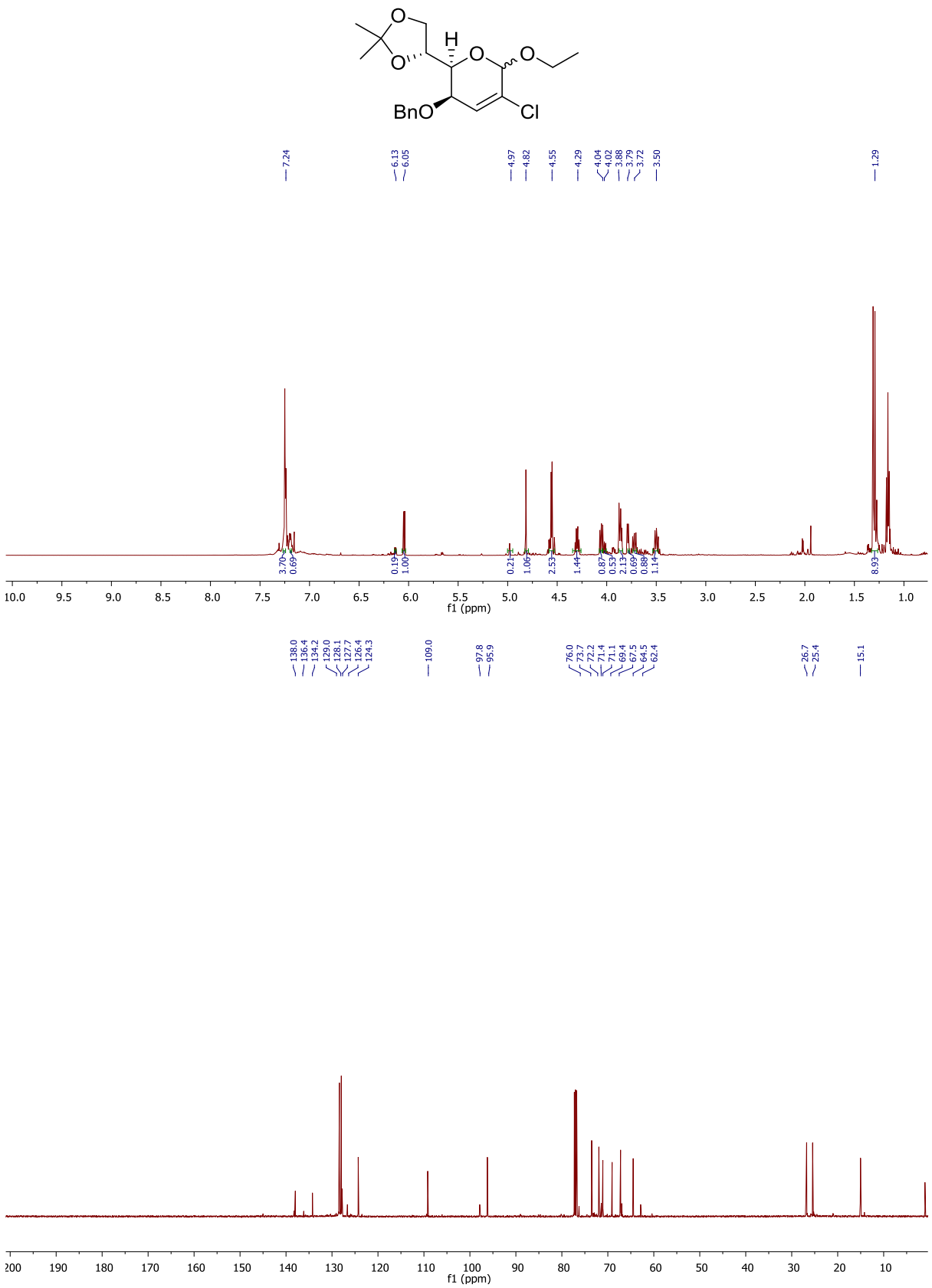


^{1}H-NMR and ^{13}C-NMR spectra of compound mixture **148**

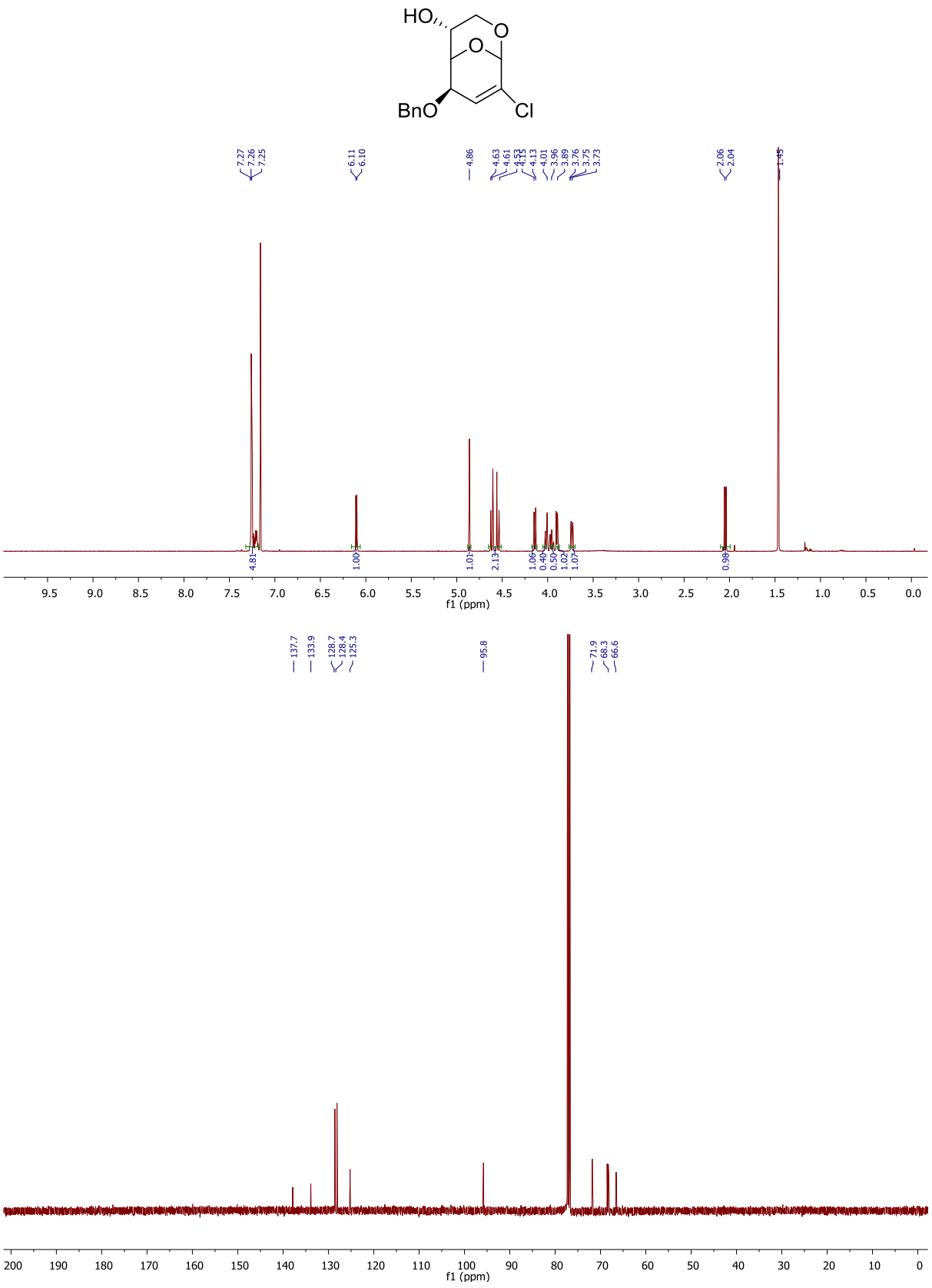




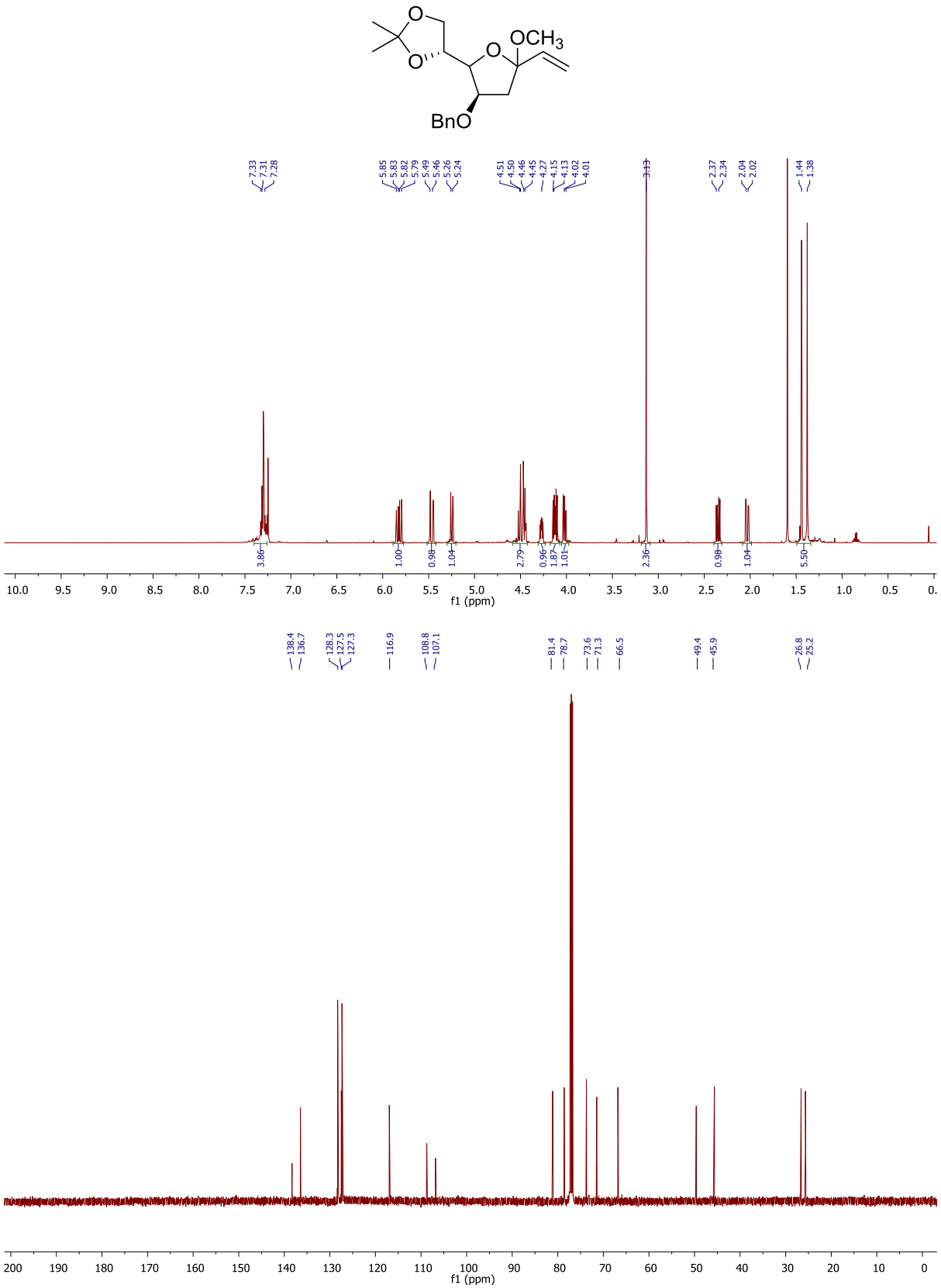
^{1}H-NMR and ^{13}C-NMR spectra of compound **154**



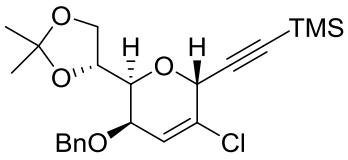
^{1}H-NMR and ^{13}C-NMR spectra of compound **159**

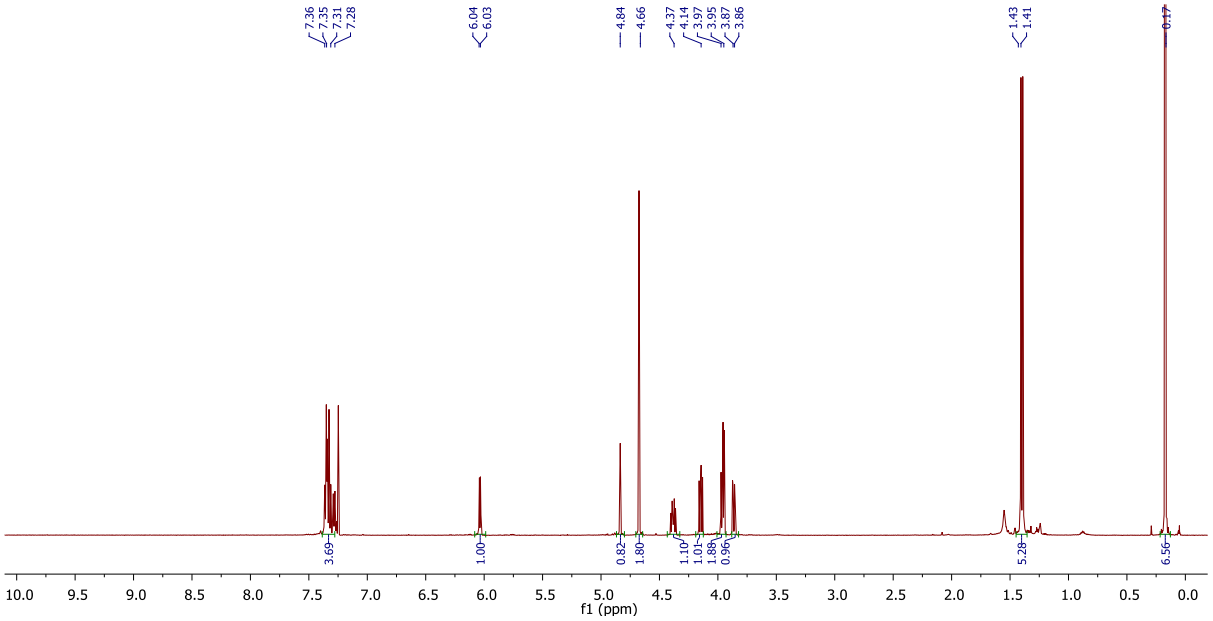


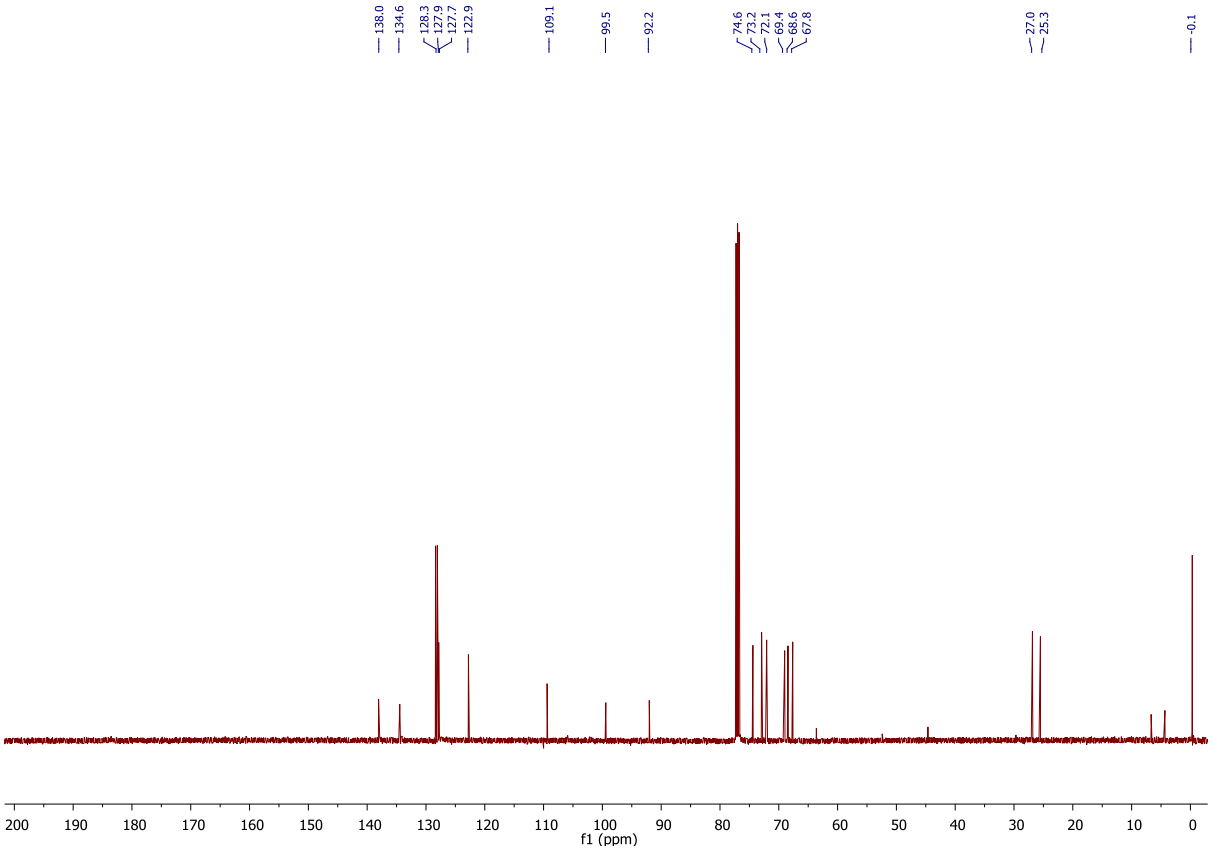
^{1}H-NMR and ^{13}C-NMR spectra of compound **182**



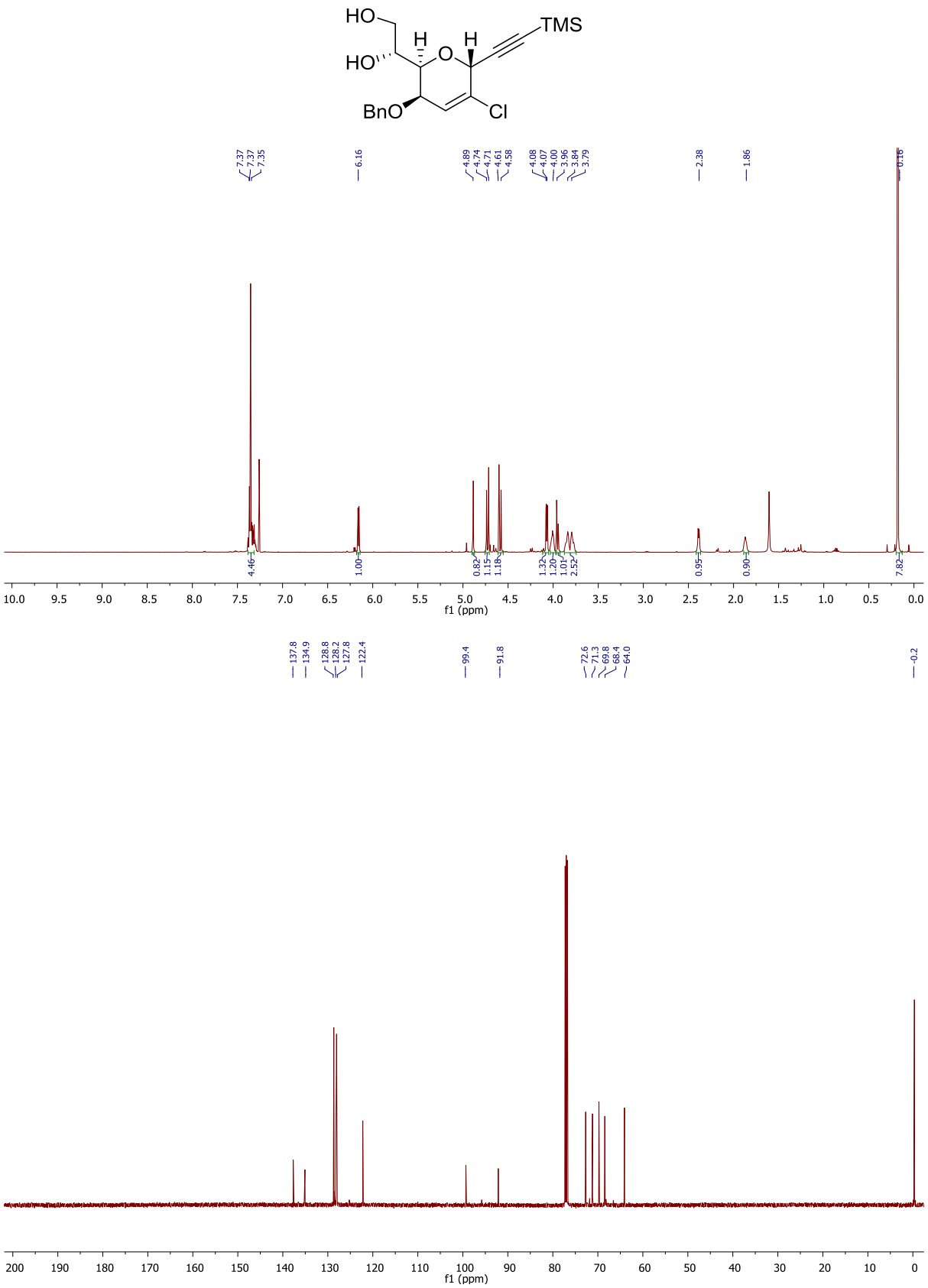
^{1}H-NMR and ^{13}C-NMR spectra of compound **245**



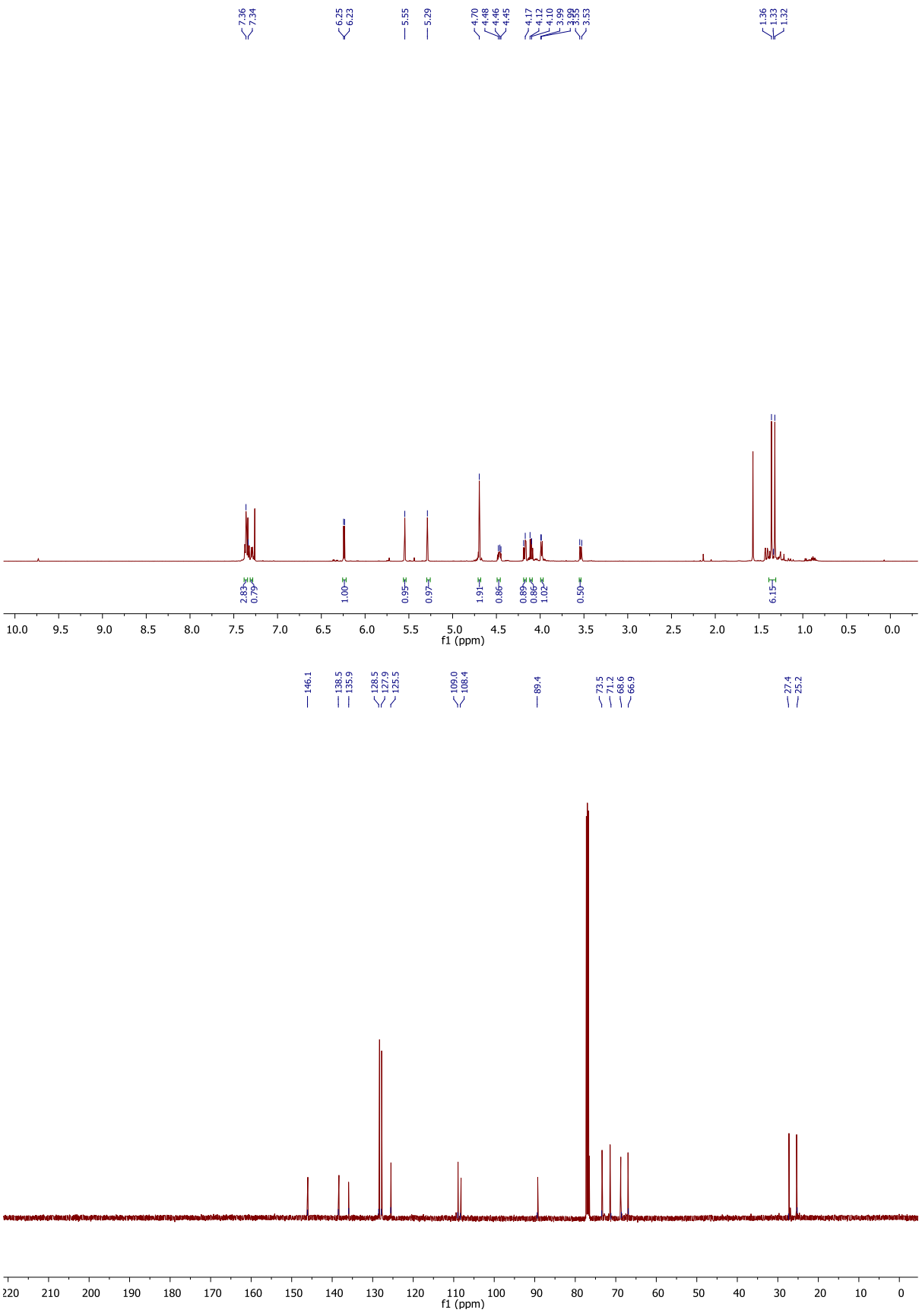




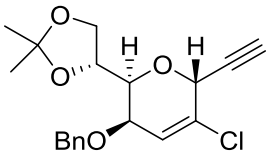
^{1}H-NMR and ^{13}C-NMR spectra of compound **129**

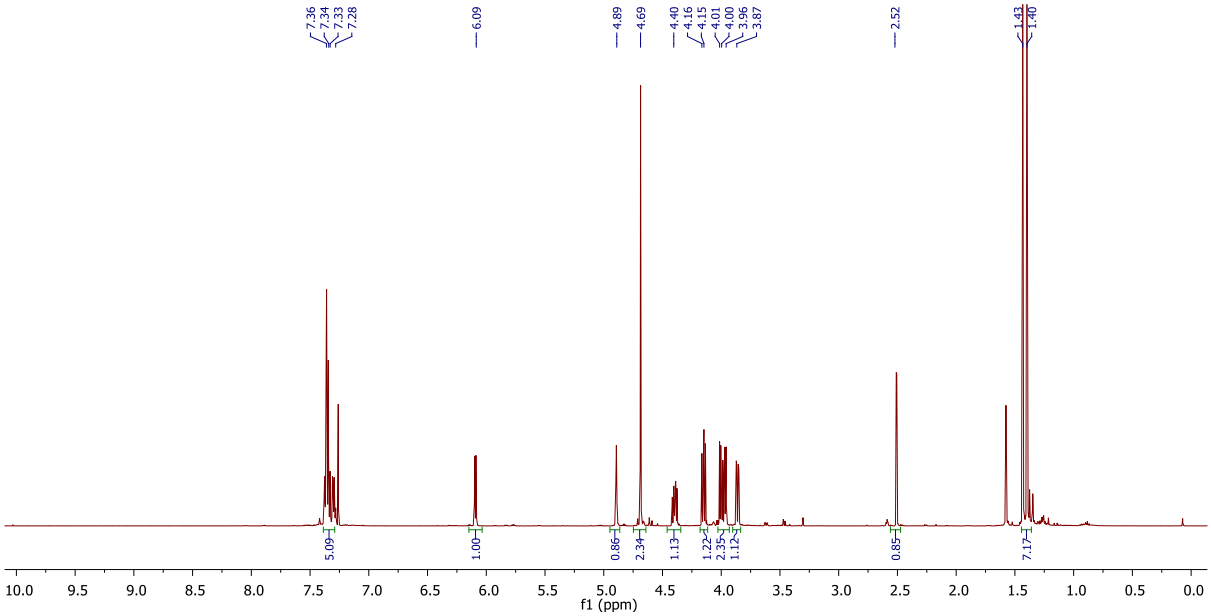


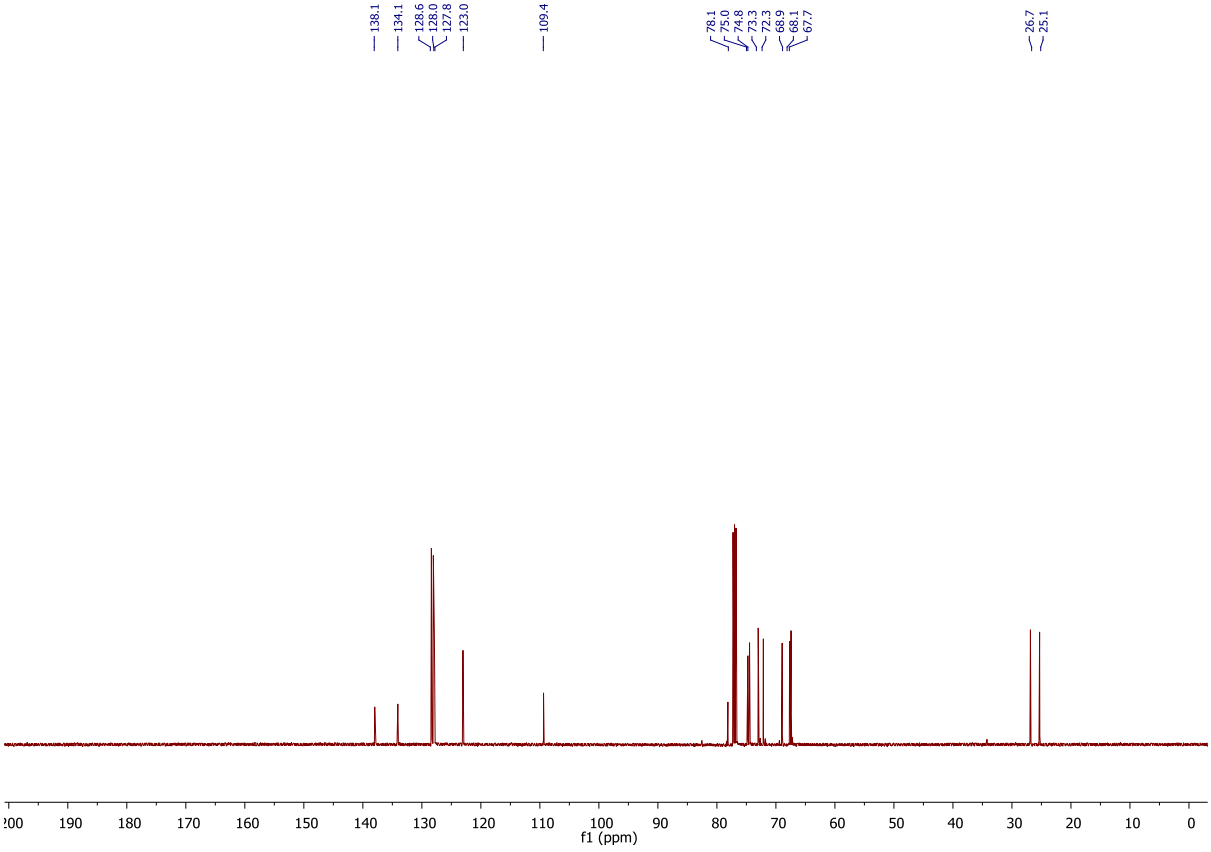
^{1}H-NMR and ^{13}C-NMR spectra of compound **194**



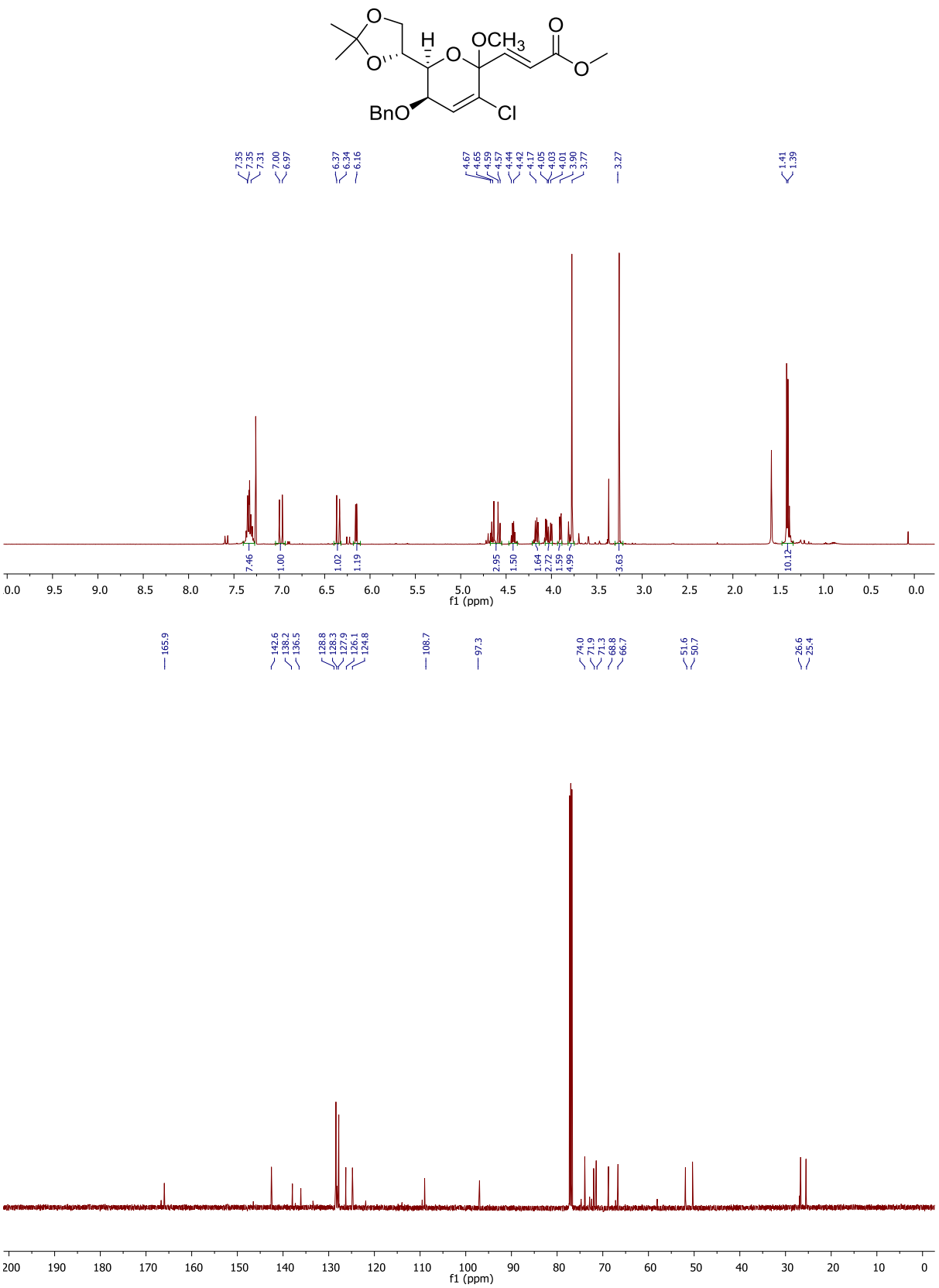
^{1}H-NMR and ^{13}C-NMR spectra of unknown compound **201**



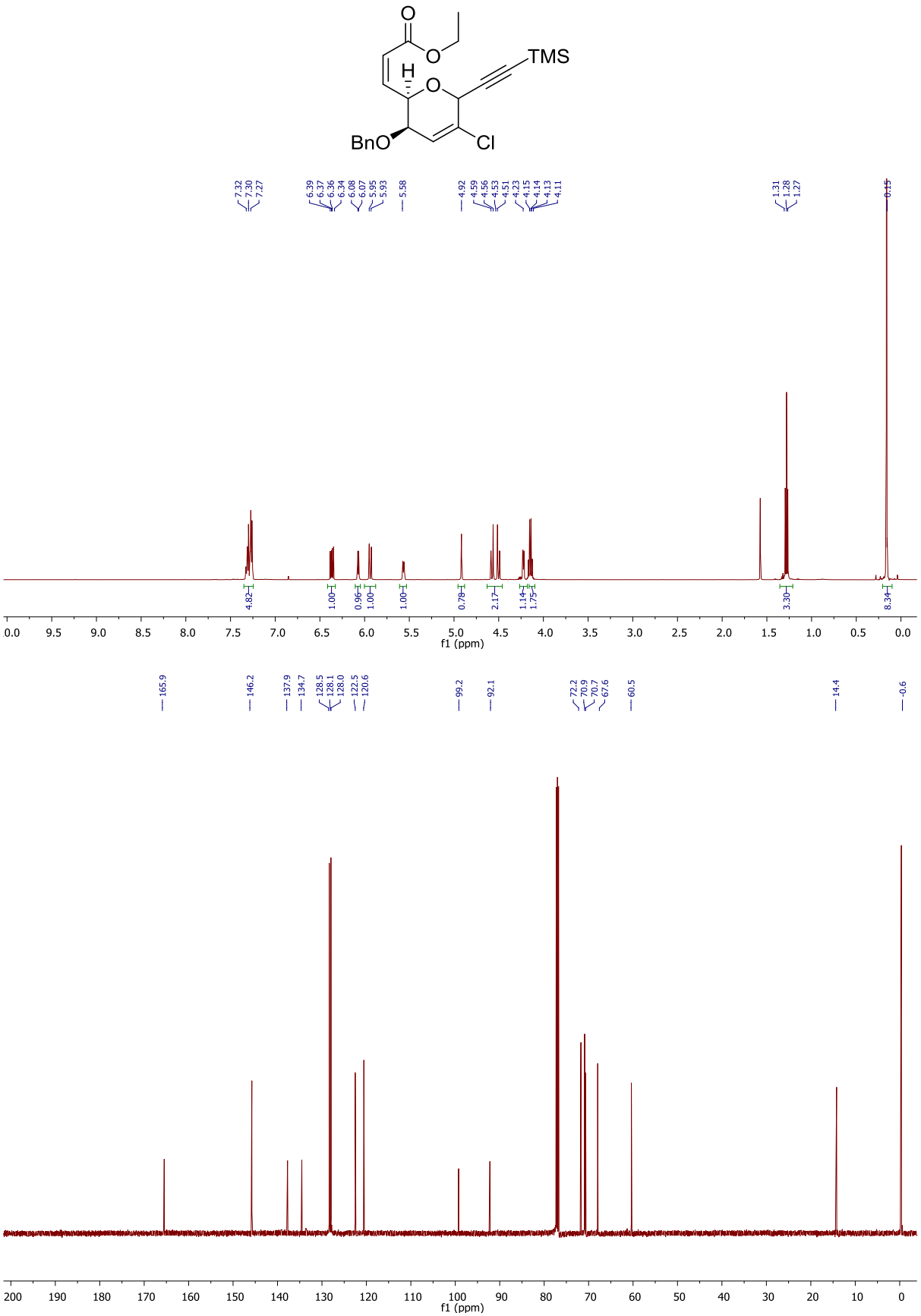




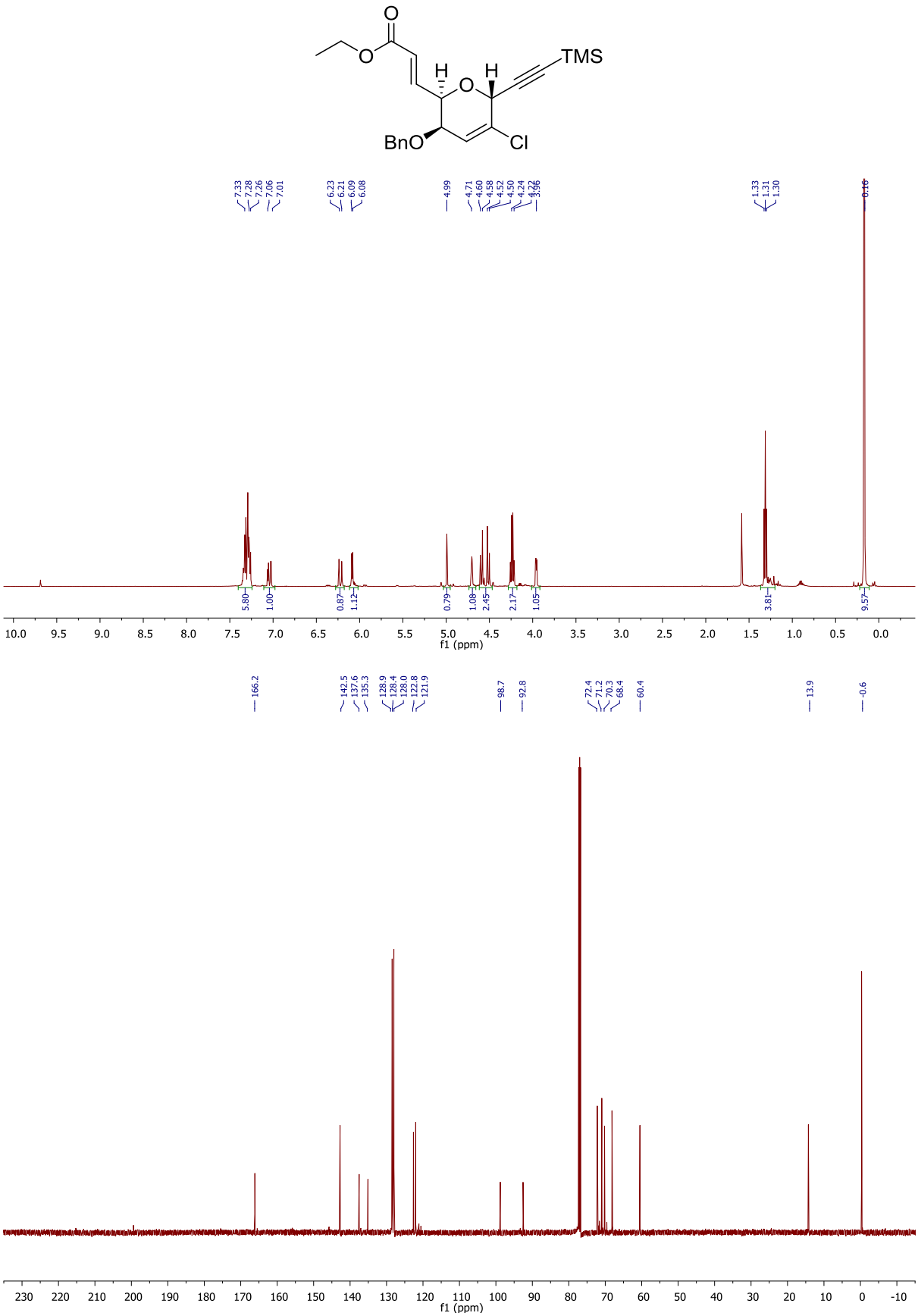
^{1}H-NMR and ^{13}C-NMR spectra of compound **190**



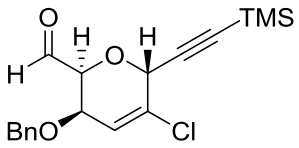
^{1}H-NMR and ^{13}C-NMR spectra of compound **251**

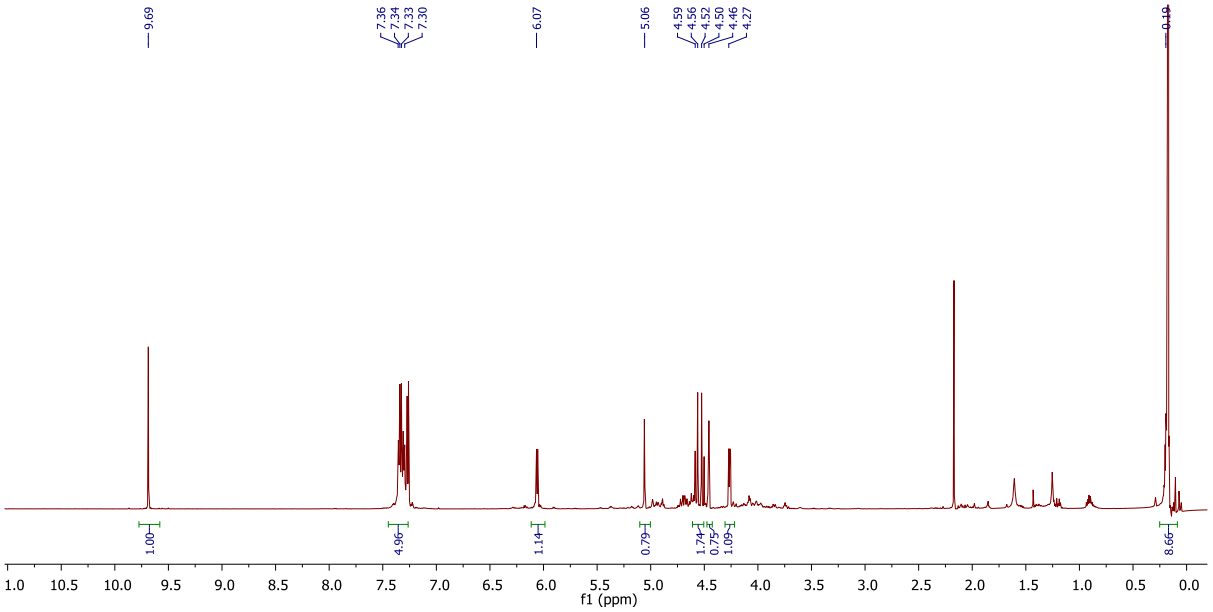


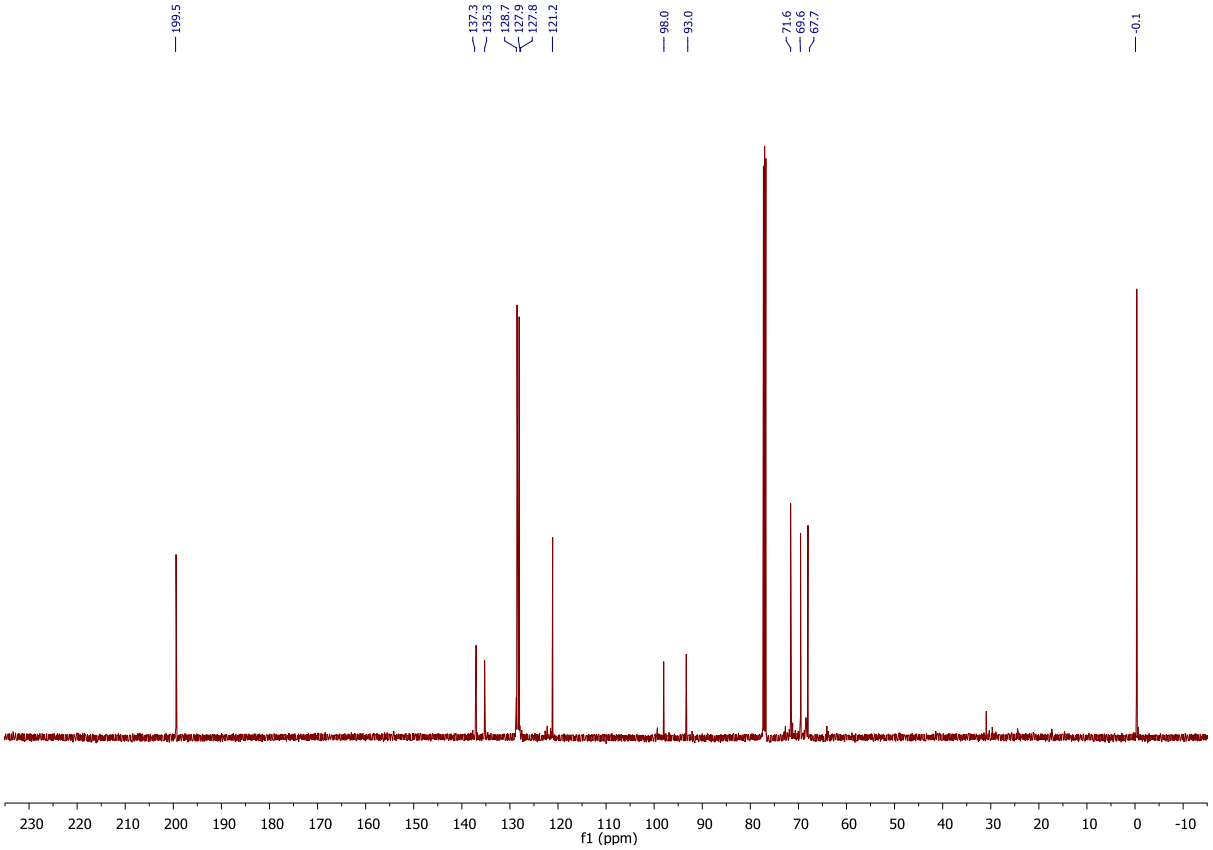
^{1}H-NMR and ^{13}C-NMR spectra of compound **226**



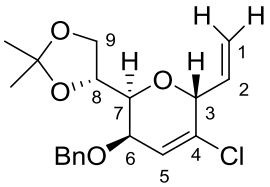
^{1}H-NMR and ^{13}C-NMR spectra of compound **202**

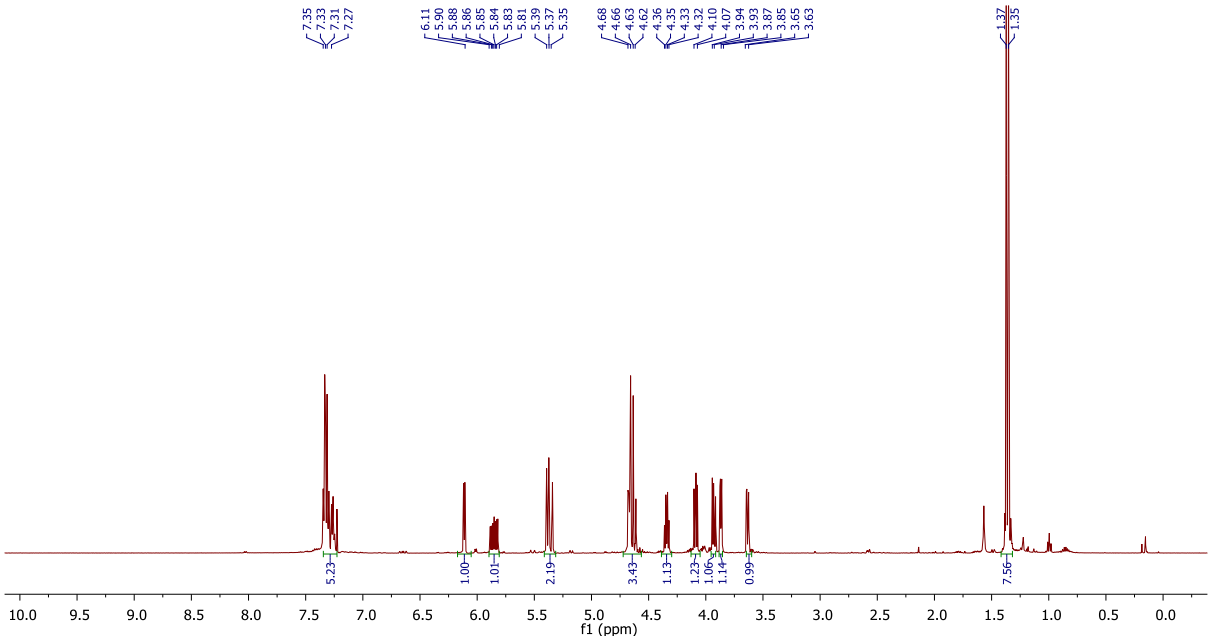


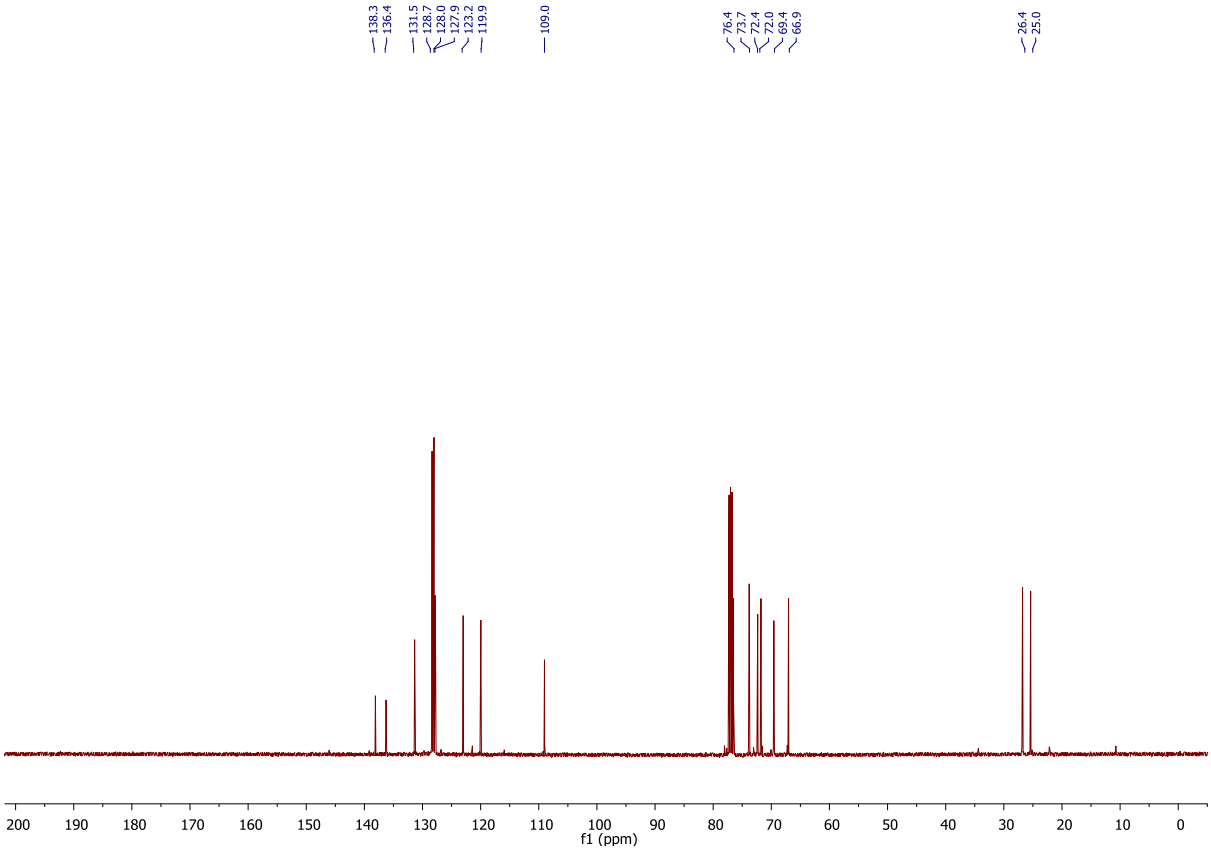




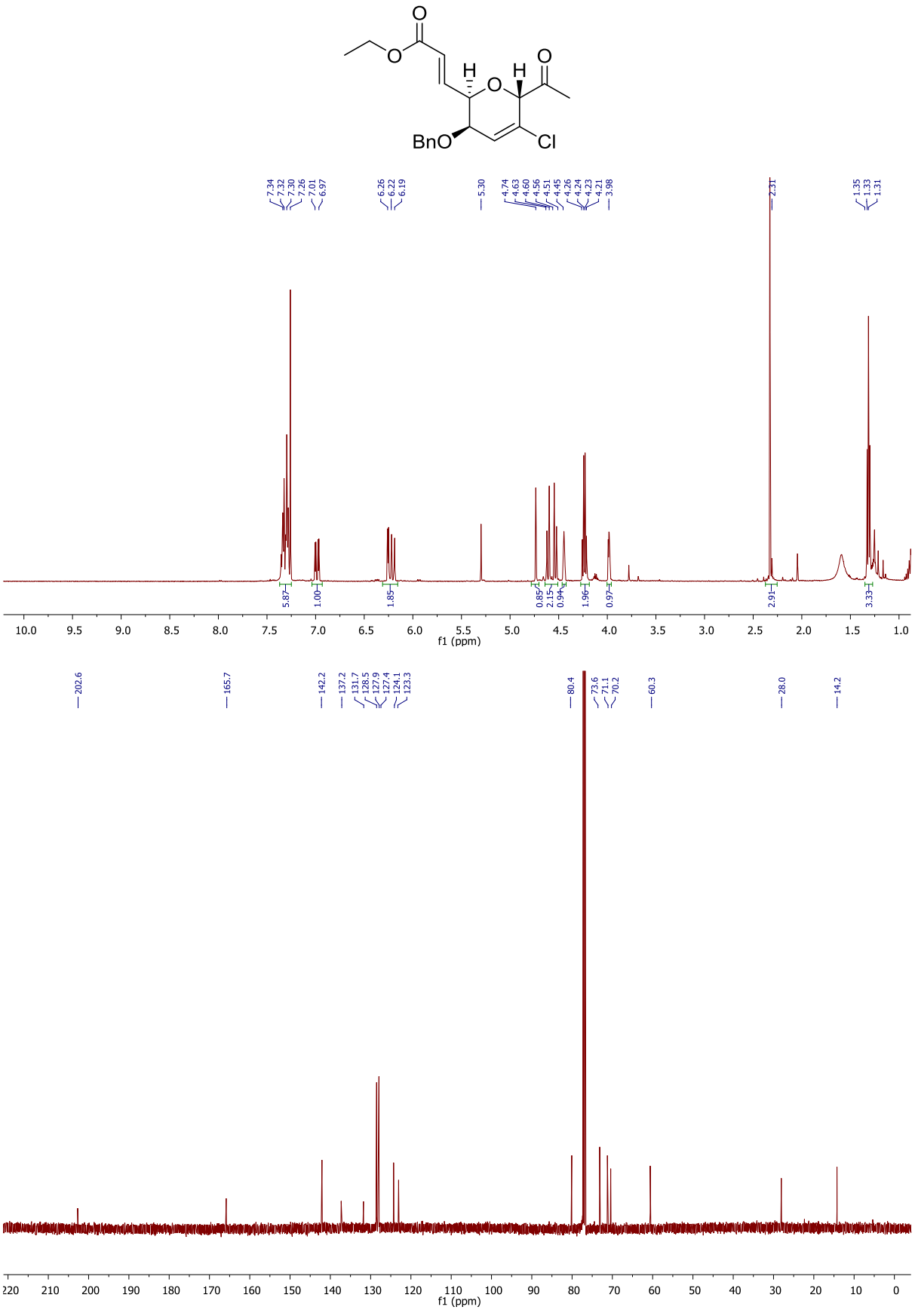
^{1}H-NMR and ^{13}C-NMR spectra of compound **224**



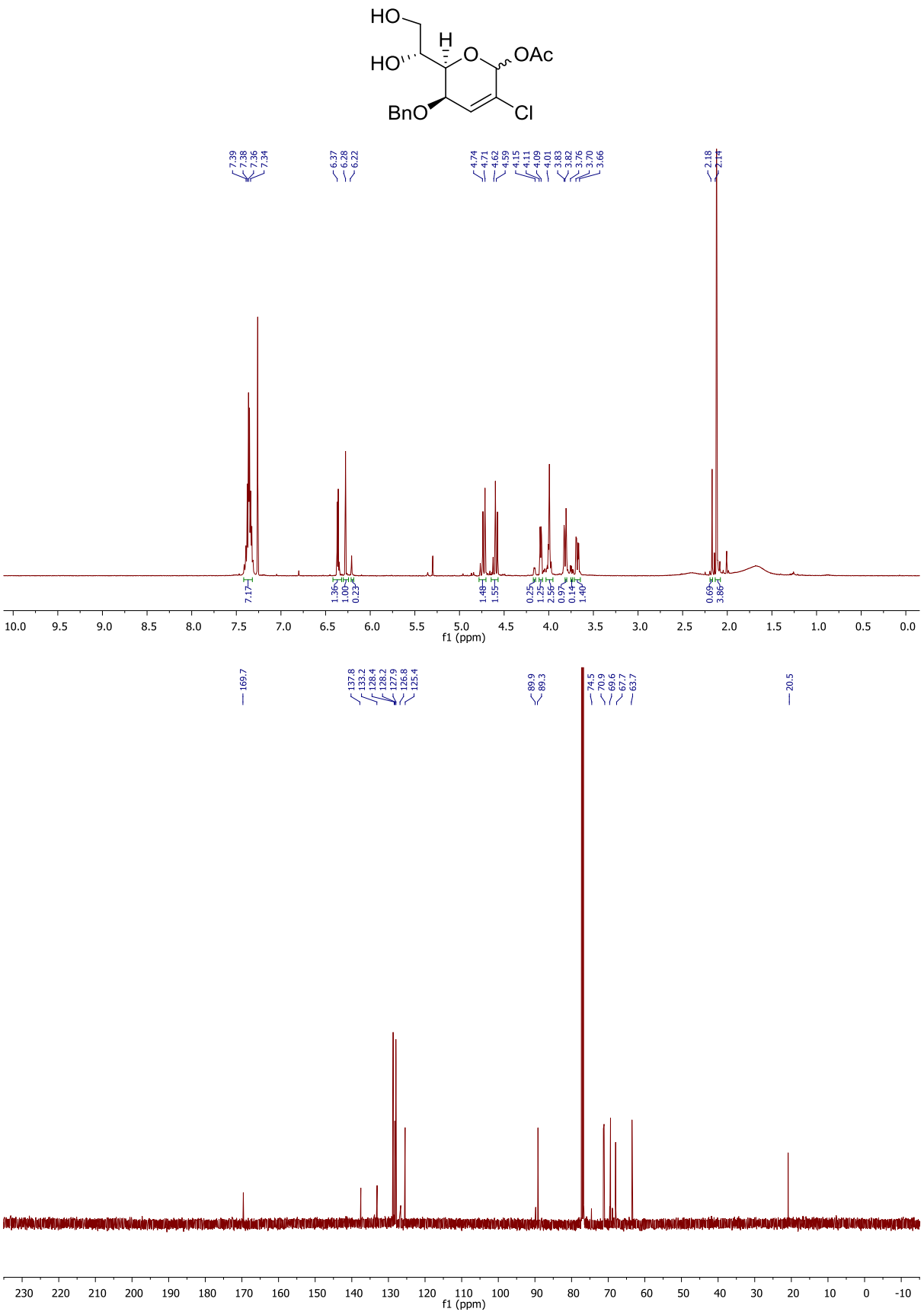




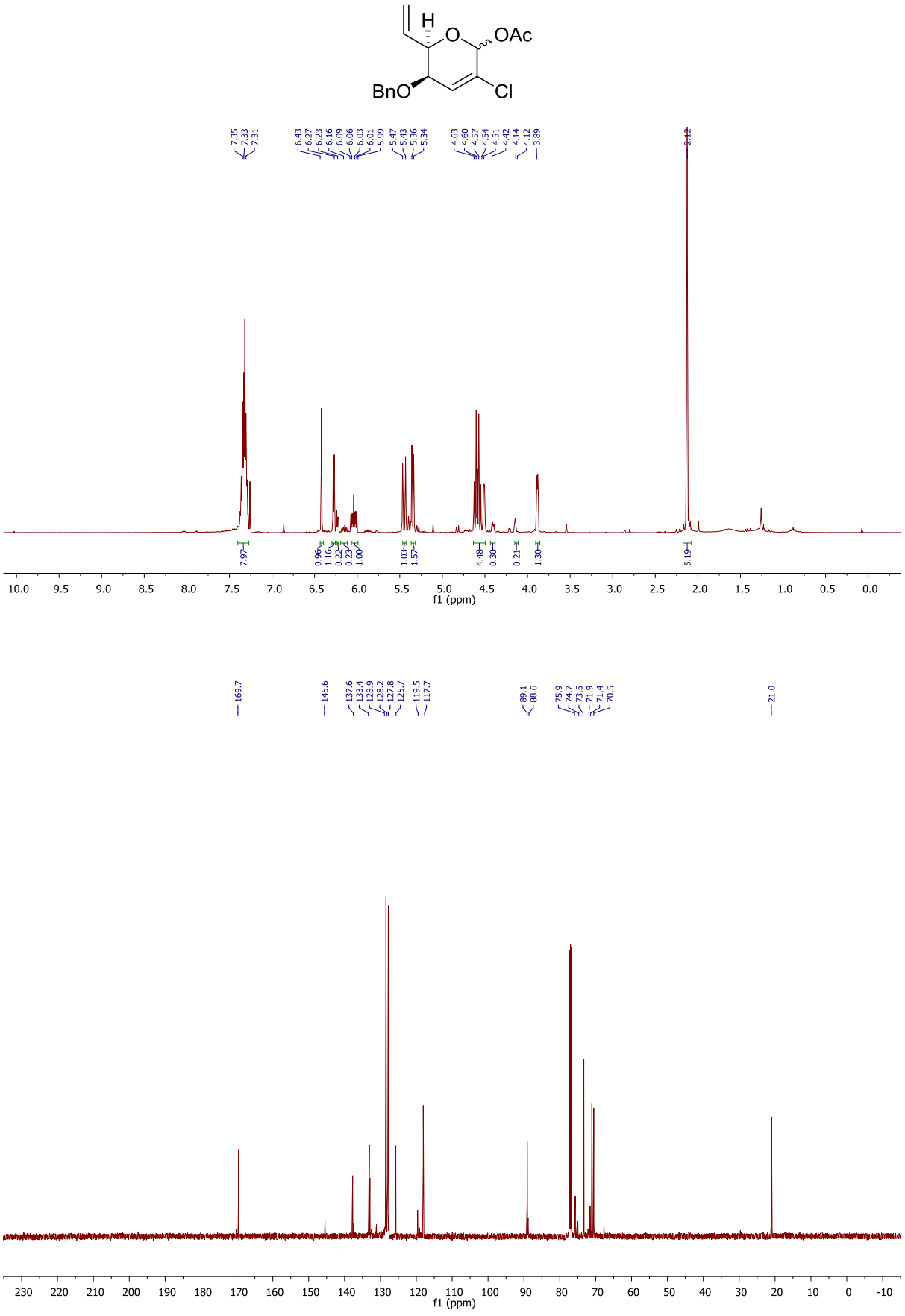
^{1}H-NMR and ^{13}C-NMR spectra of compound **195**



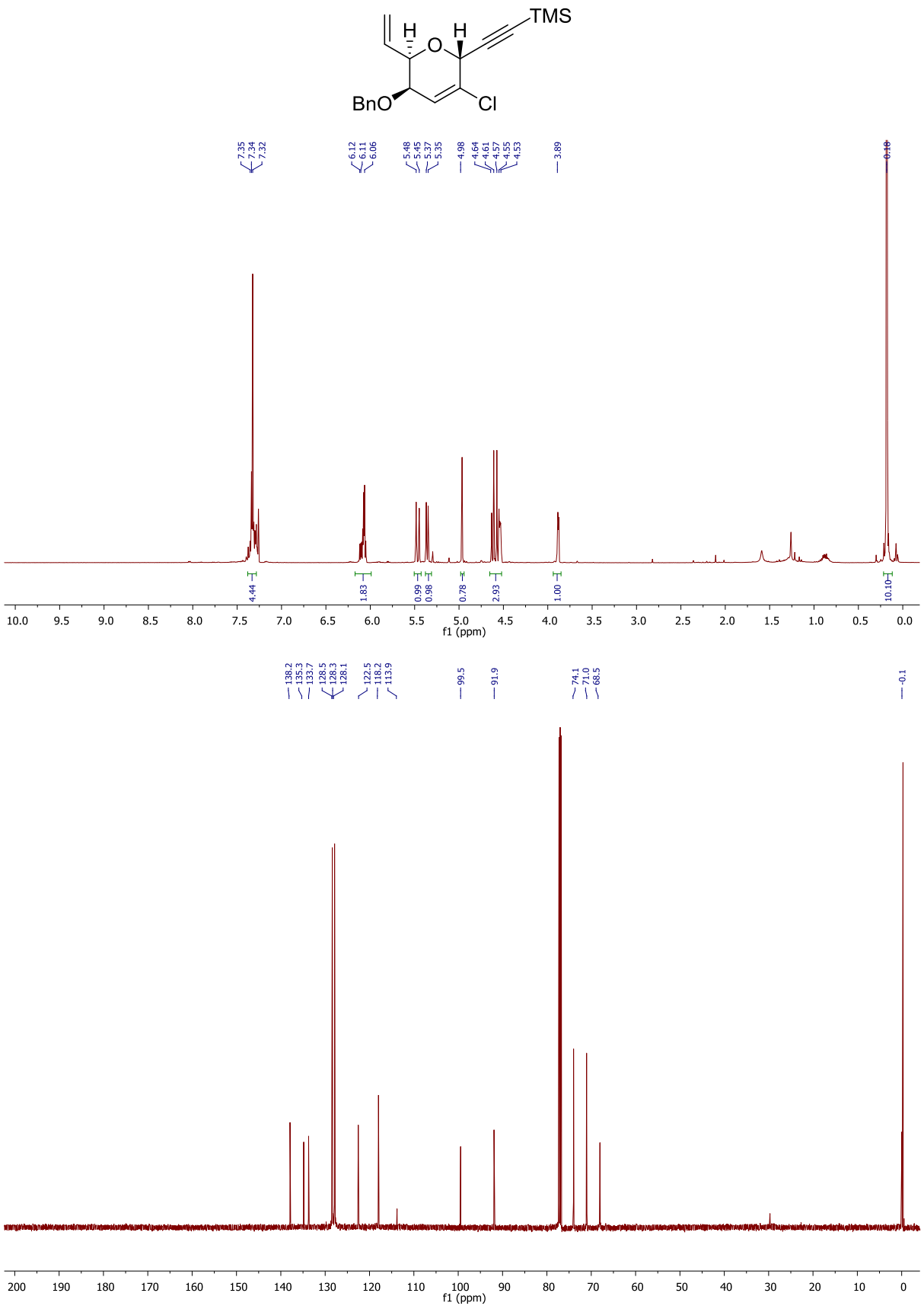
^{1}H-NMR and ^{13}C-NMR spectra of compound **216**



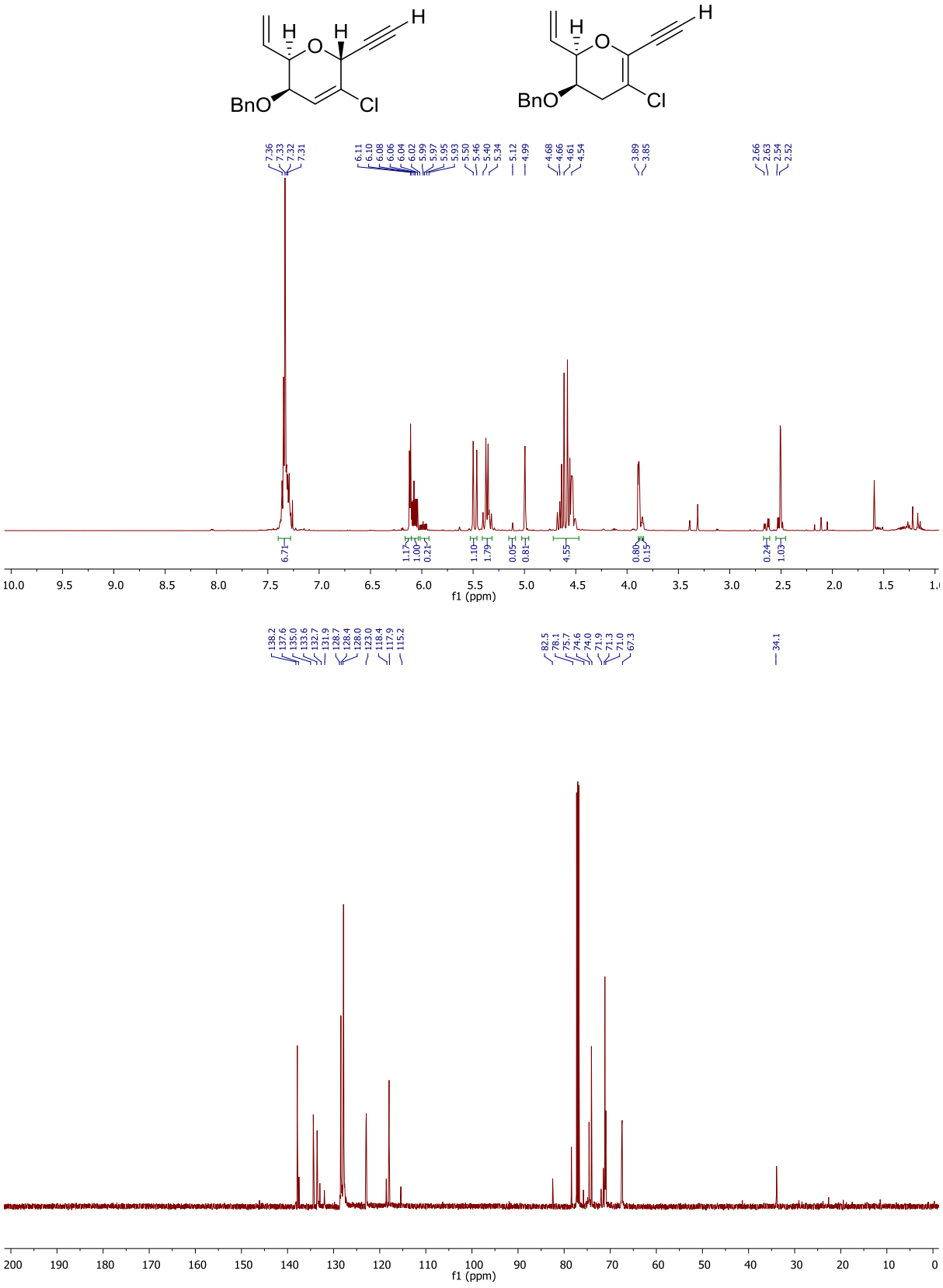
^{1}H-NMR and ^{13}C-NMR spectra of compound **158**



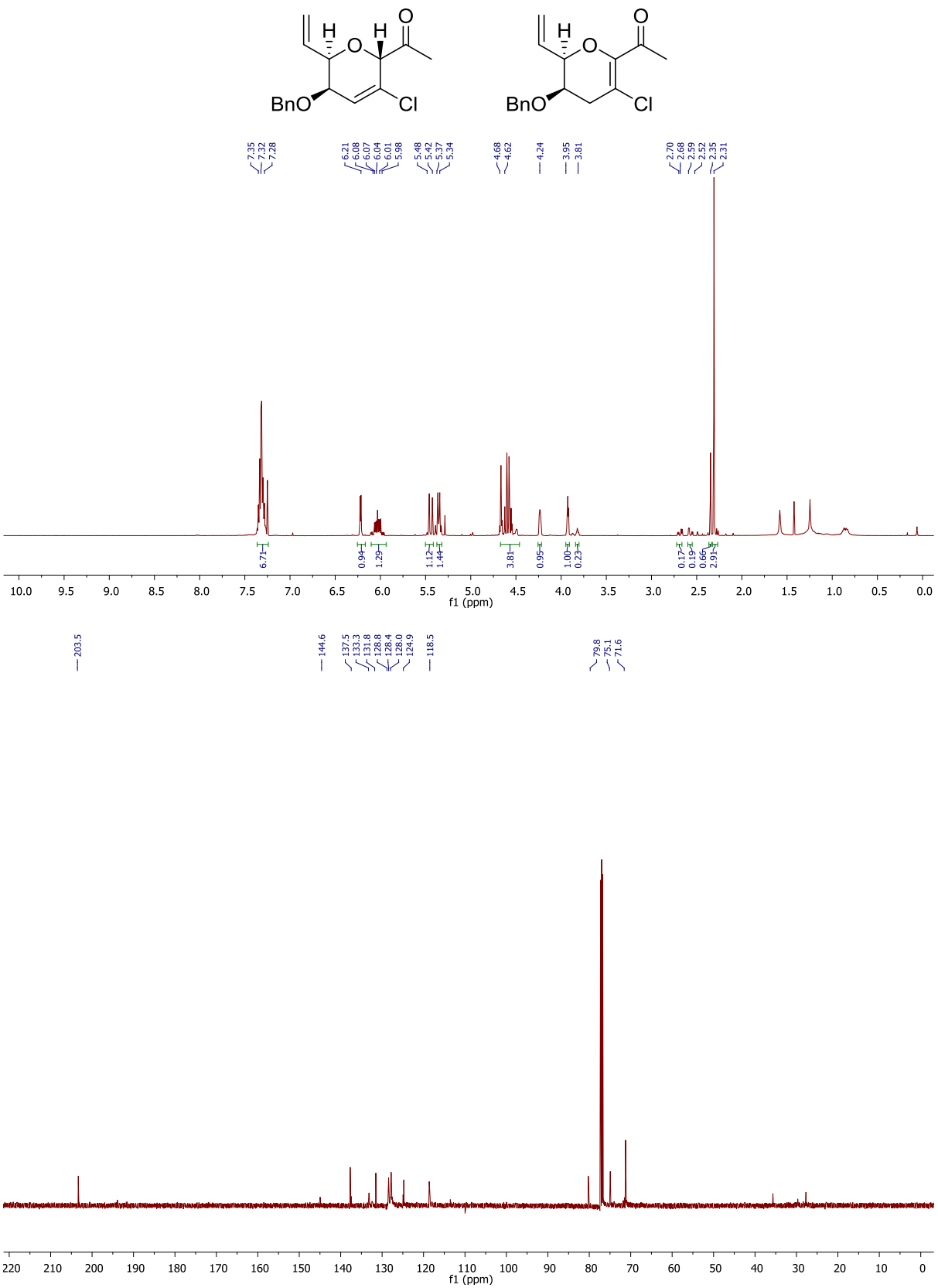
^{1}H-NMR and ^{13}C-NMR spectra of compound **196**



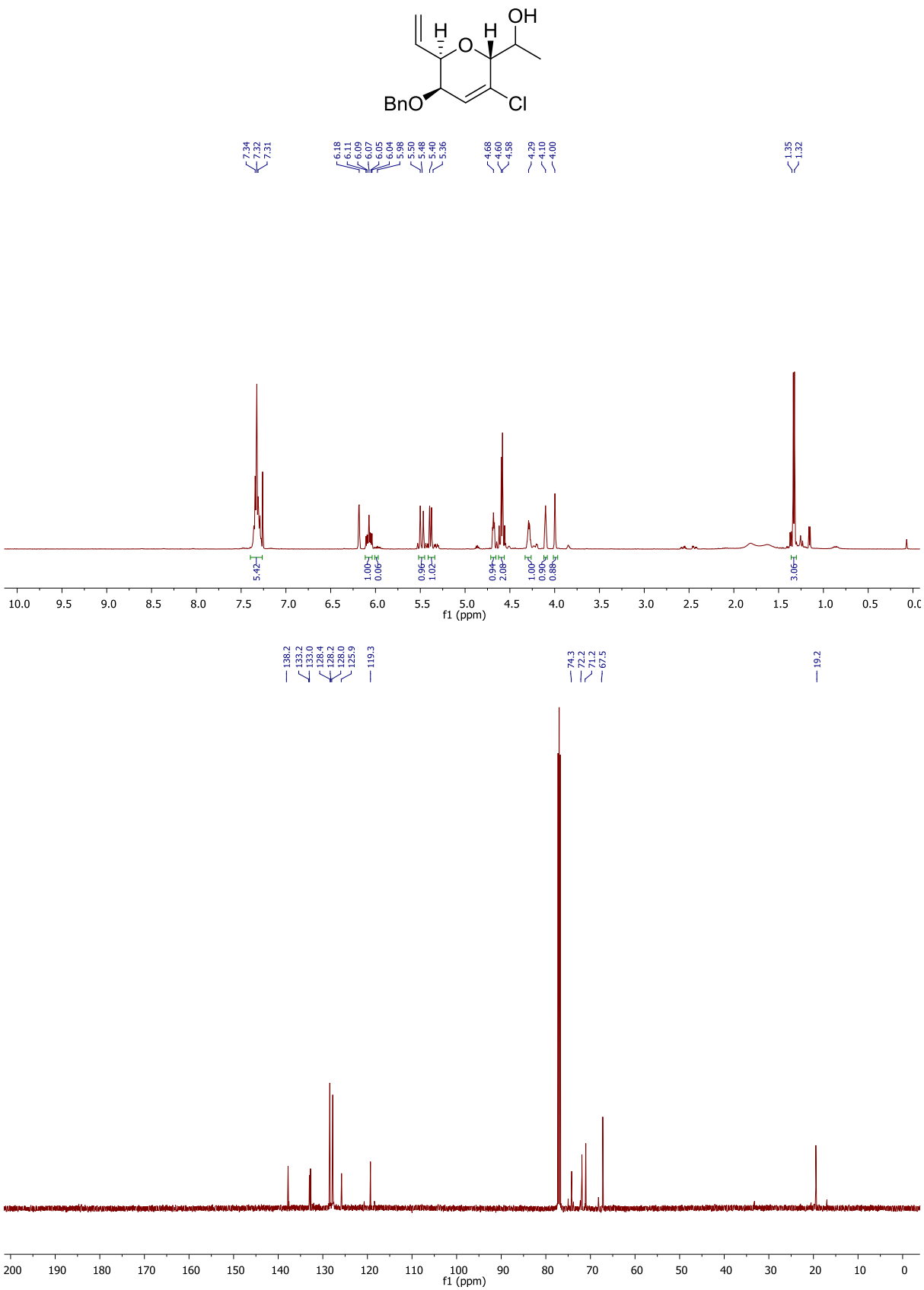
^{1}H-NMR and ^{13}C-NMR spectra of compound **197**



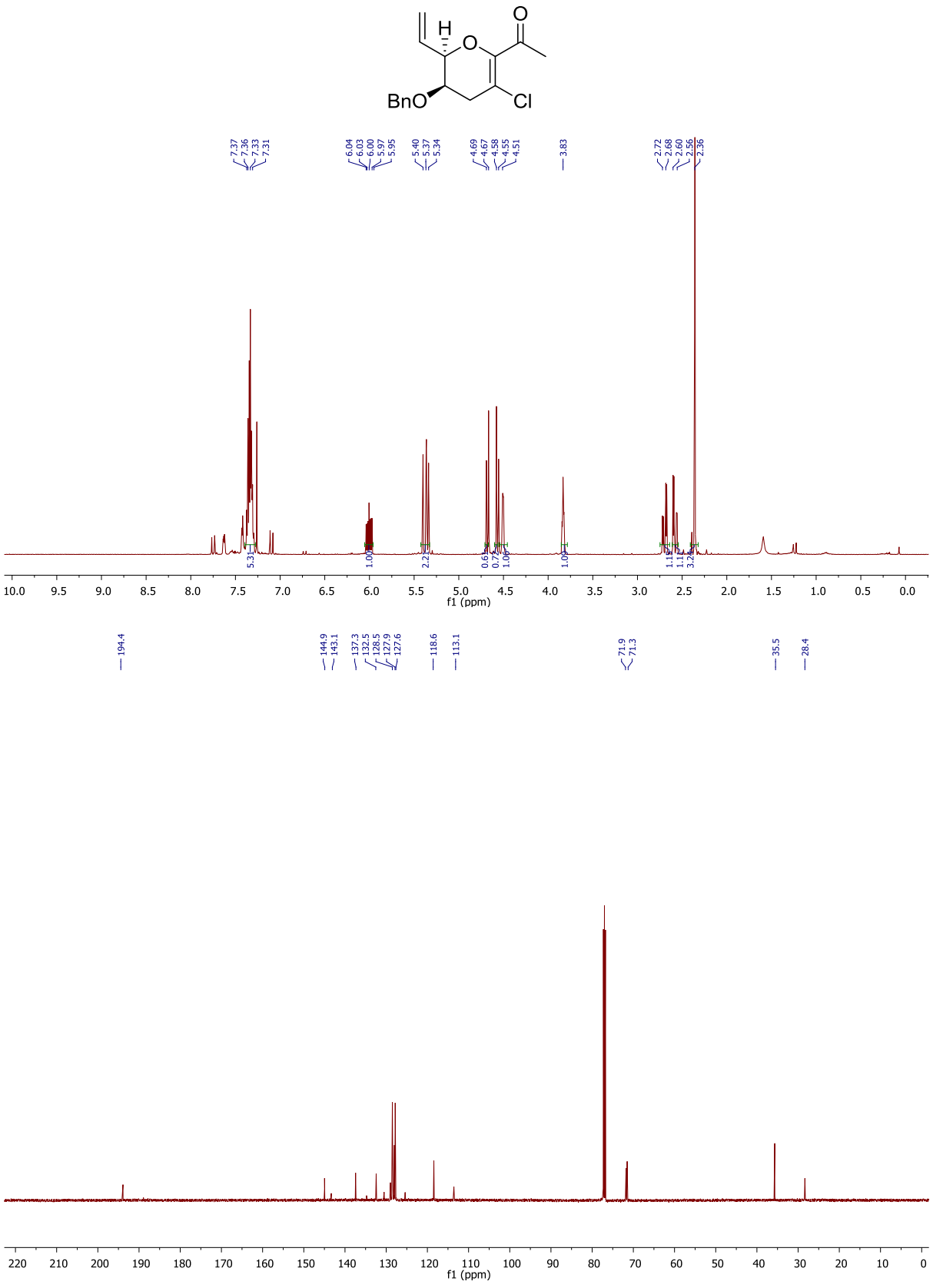
^{1}H-NMR and ^{13}C-NMR spectra of compound **205/206** mixture



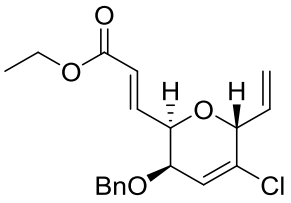
^{1}H-NMR and ^{13}C-NMR spectra of compound **220/221** mixture

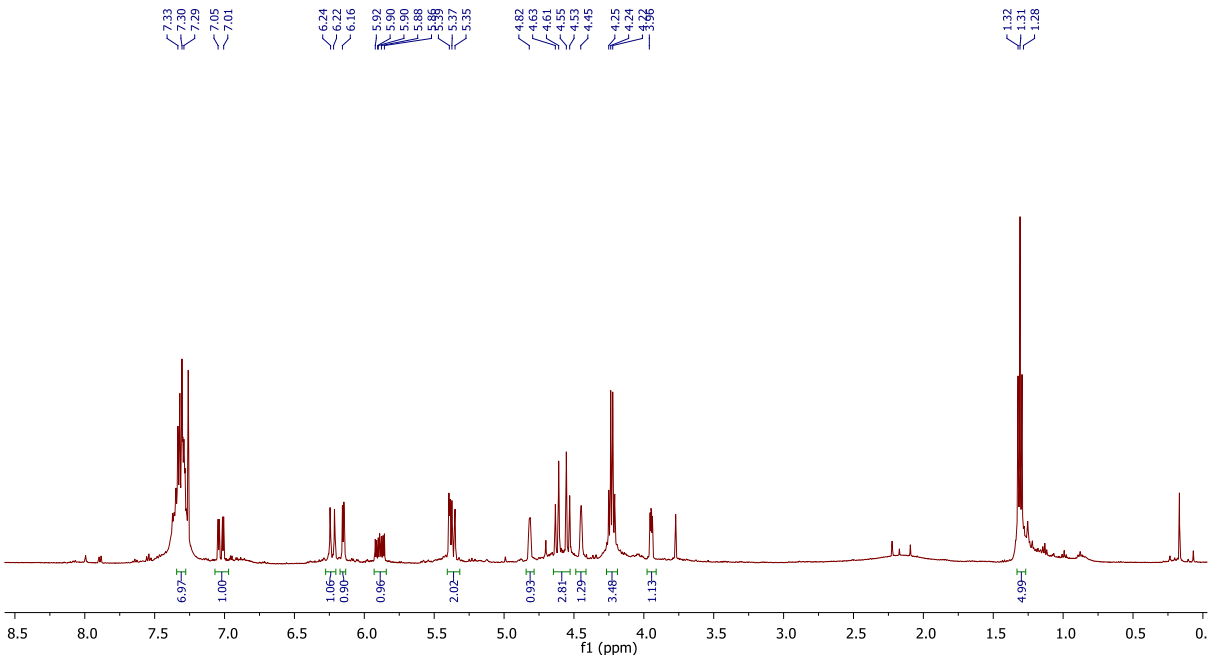


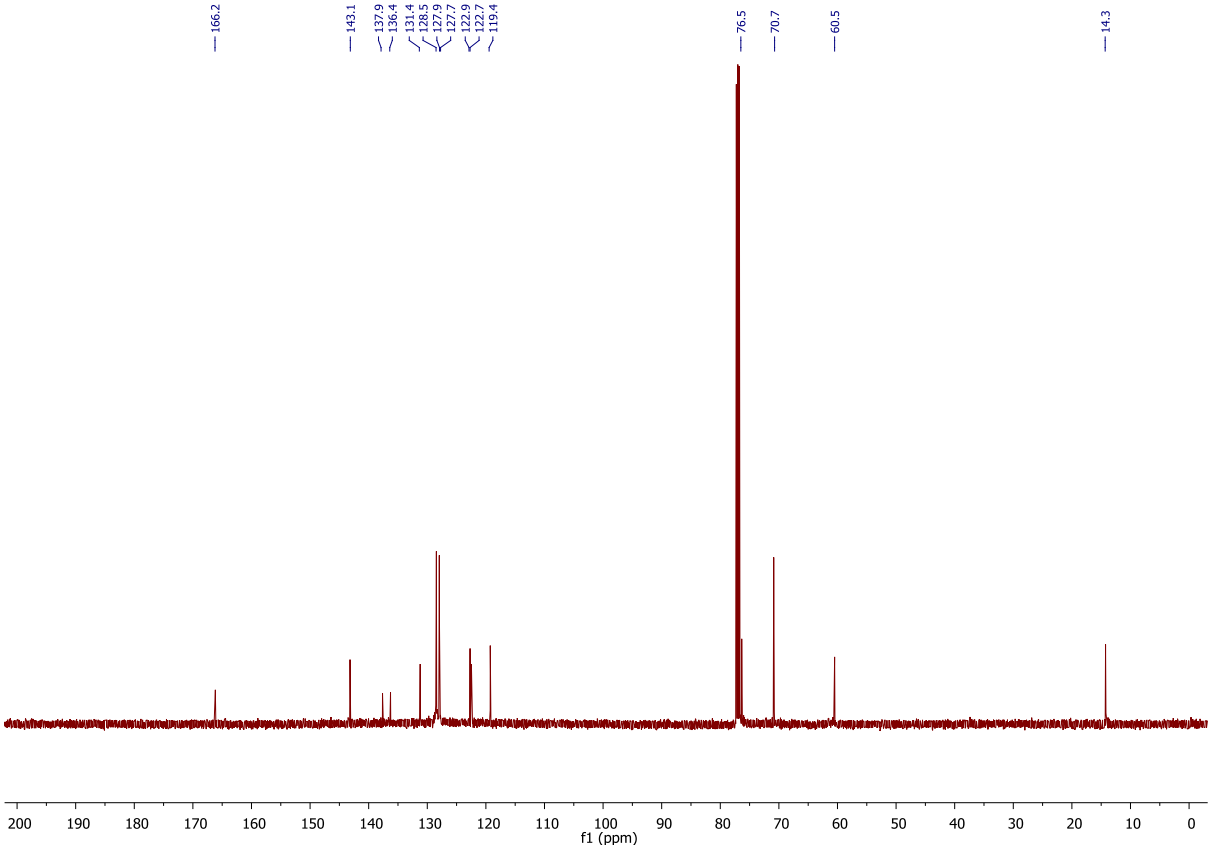
^{1}H-NMR and ^{13}C-NMR spectra of compound **222**



^{1}H-NMR and ^{13}C-NMR spectra of compound **221**

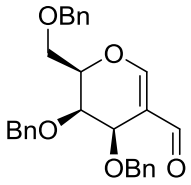


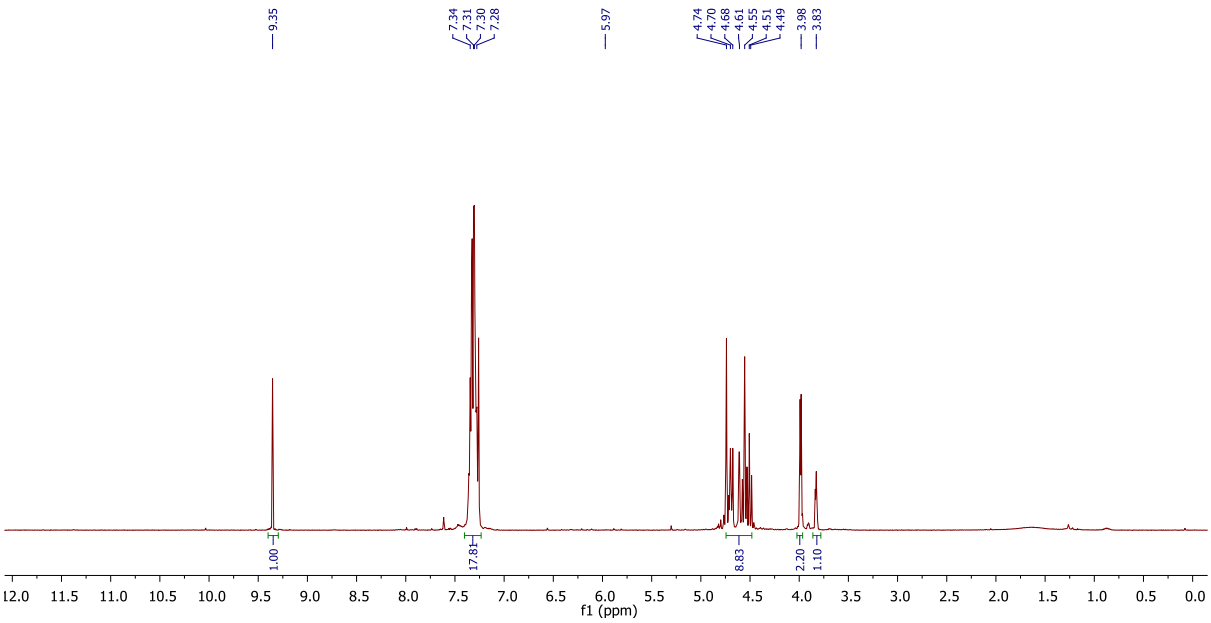


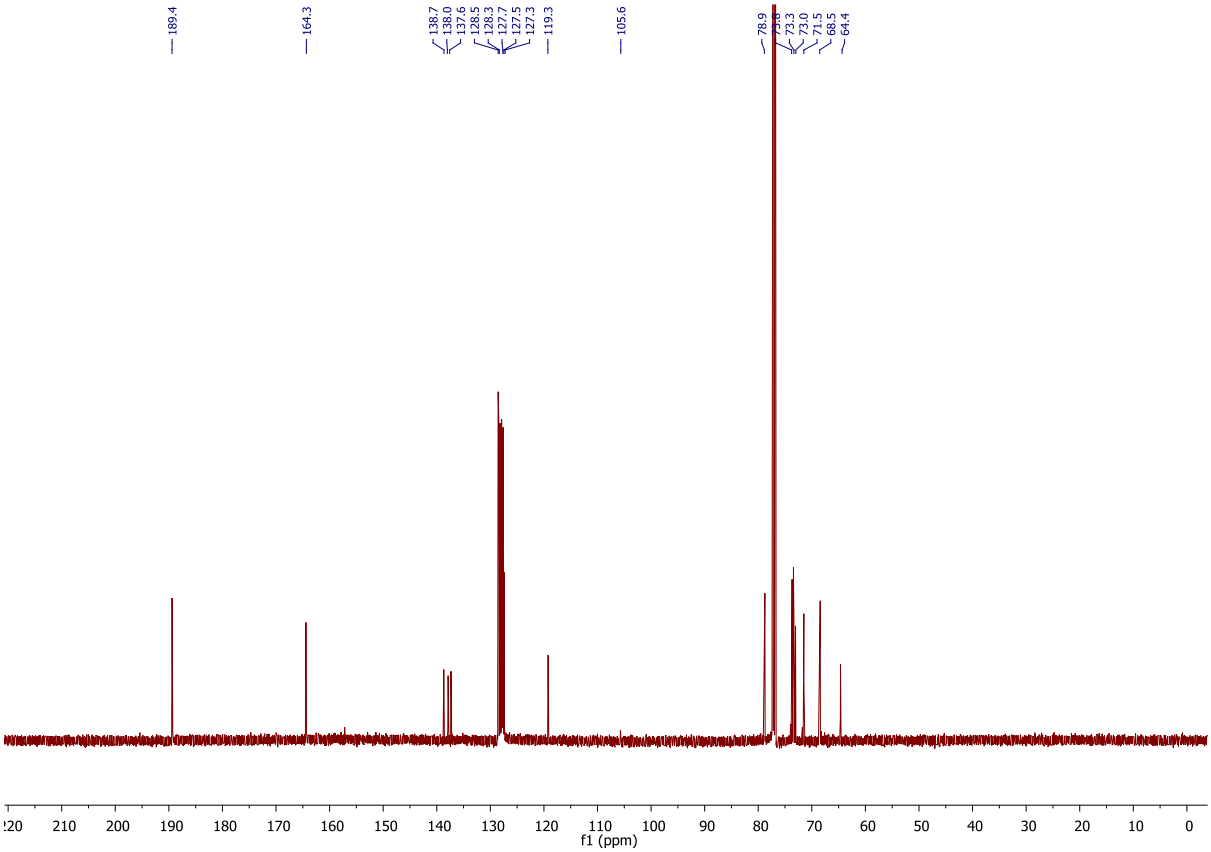


^{1}H-NMR and ^{13}C-NMR spectra of compound **207**

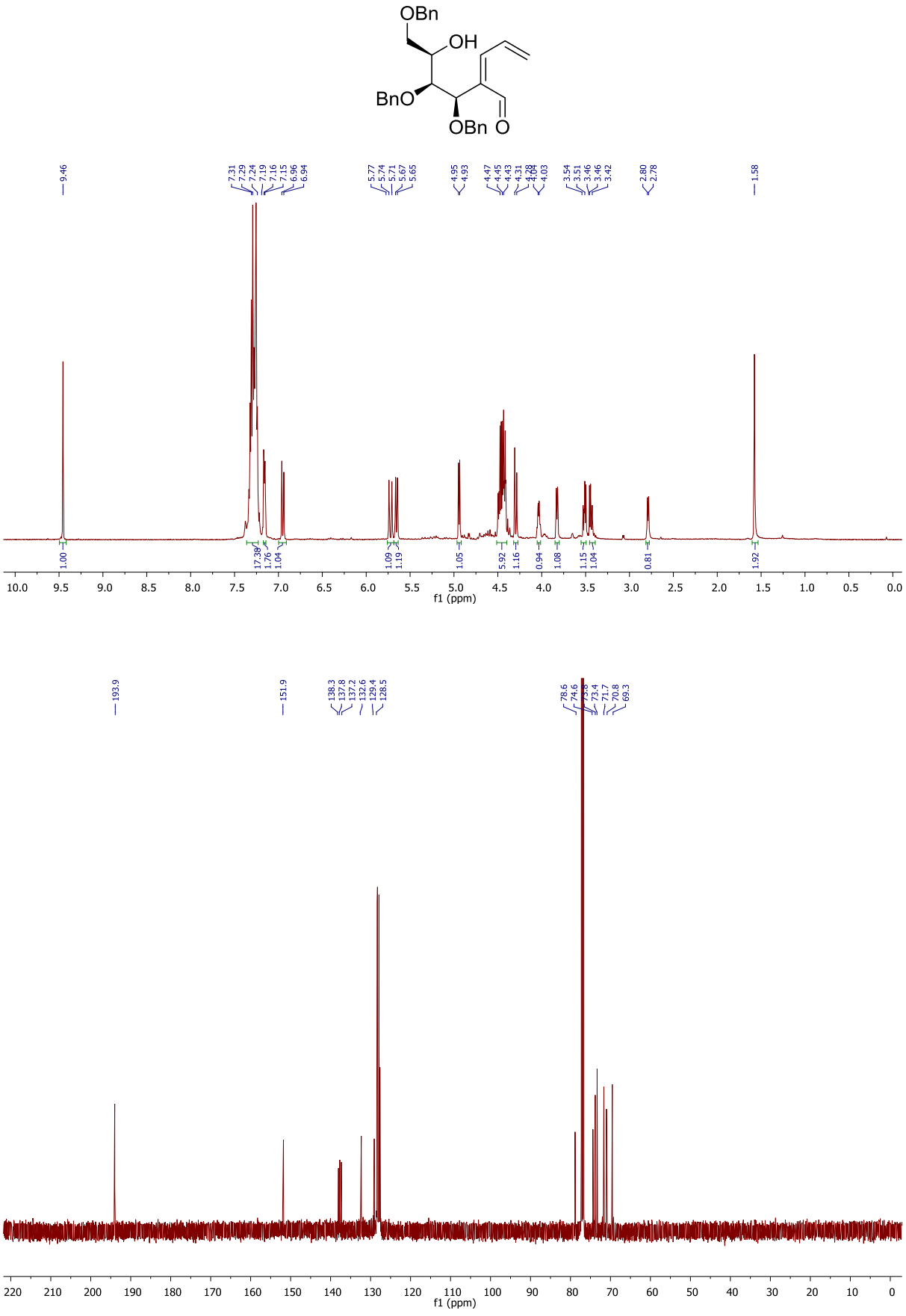
7.2 ^{1}H-NMR and ^{13}C-NMR spectra for selected compounds described in chapter 3





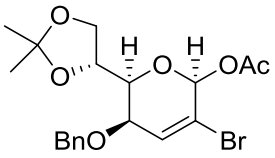


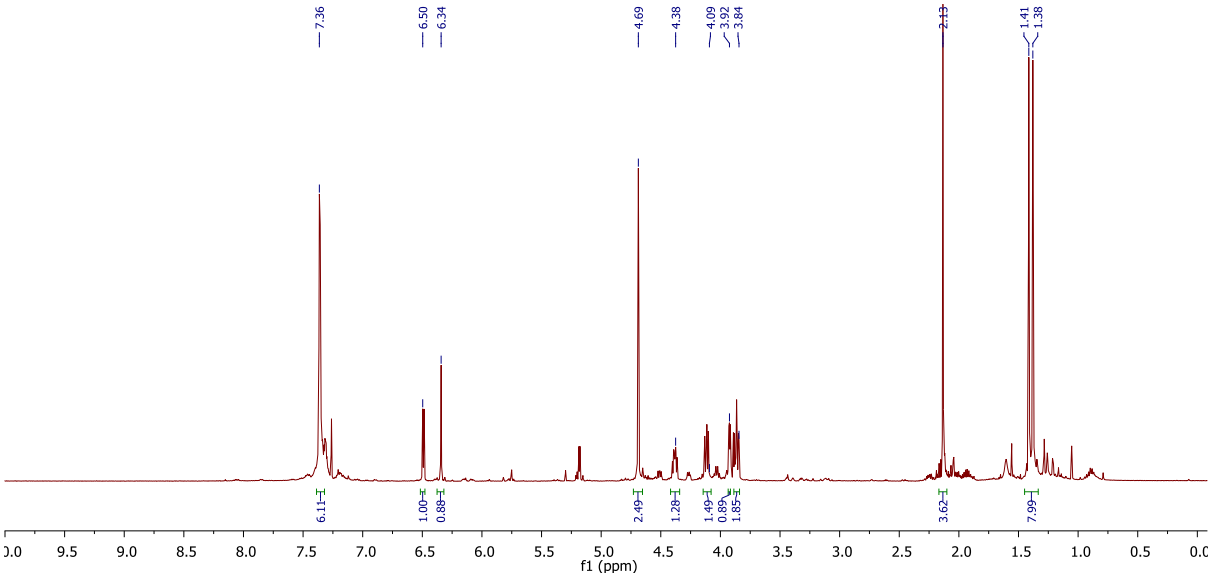
^{1}H-NMR and ^{13}C-NMR spectra of compound **136**

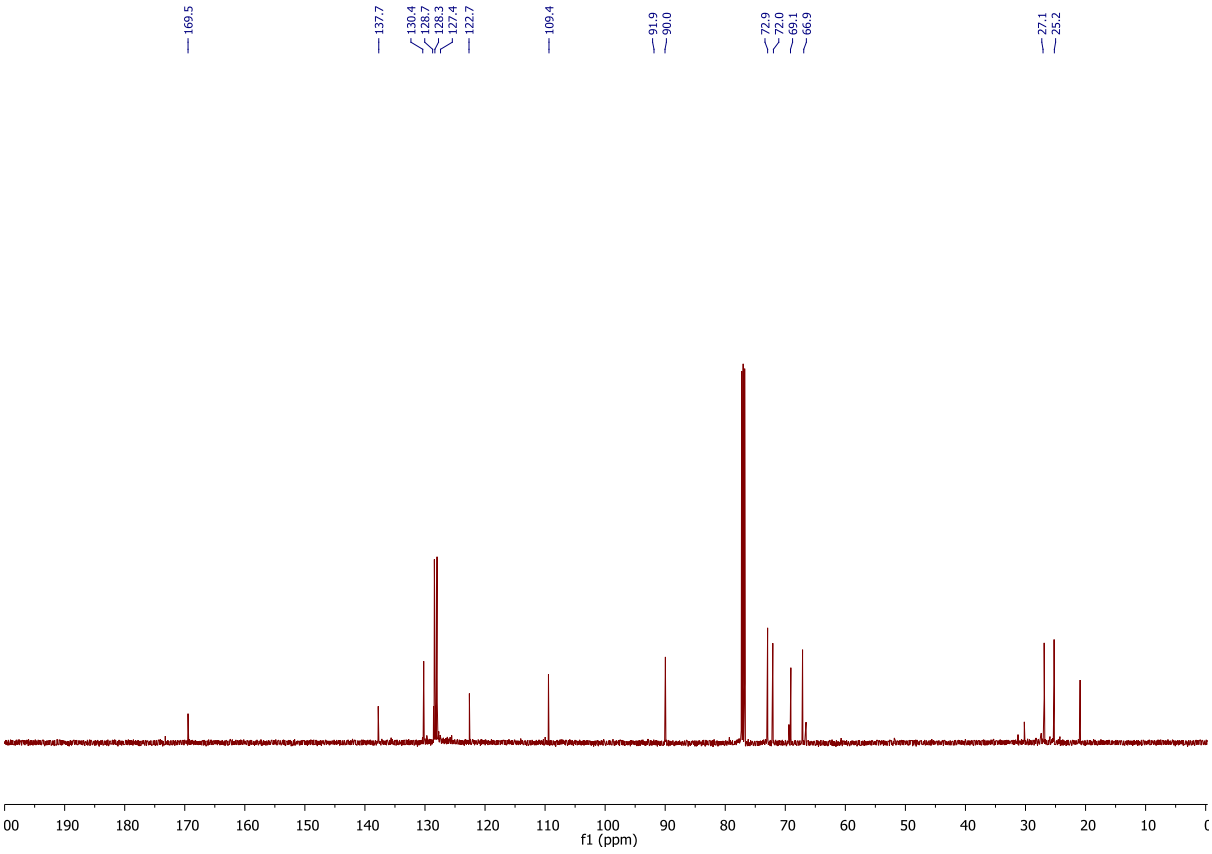


^{1}H-NMR and ^{13}C-NMR spectra of compound **297**

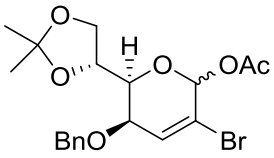
7.3 ^{1}H-NMR and ^{13}C-NMR spectra for selected compounds described in chapter 4

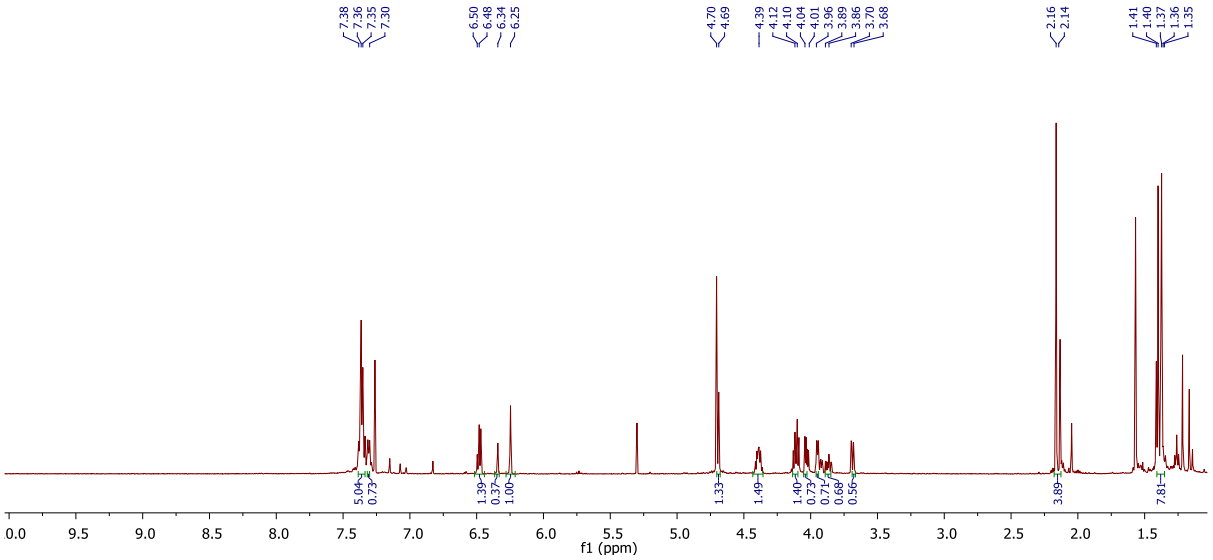


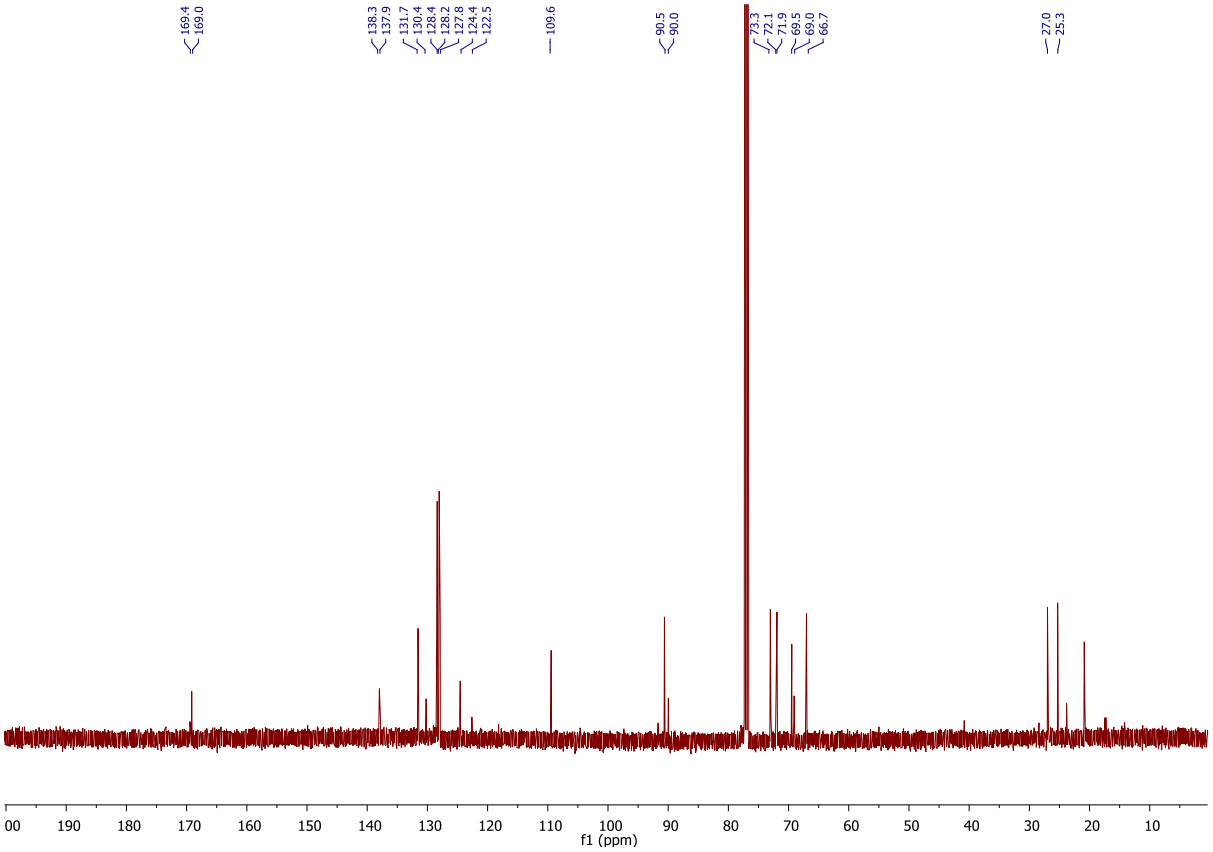




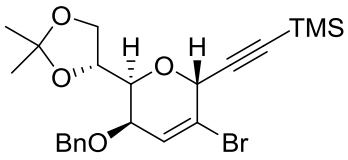
^{1}H-NMR and ^{13}C-NMR spectra of compound **131β**

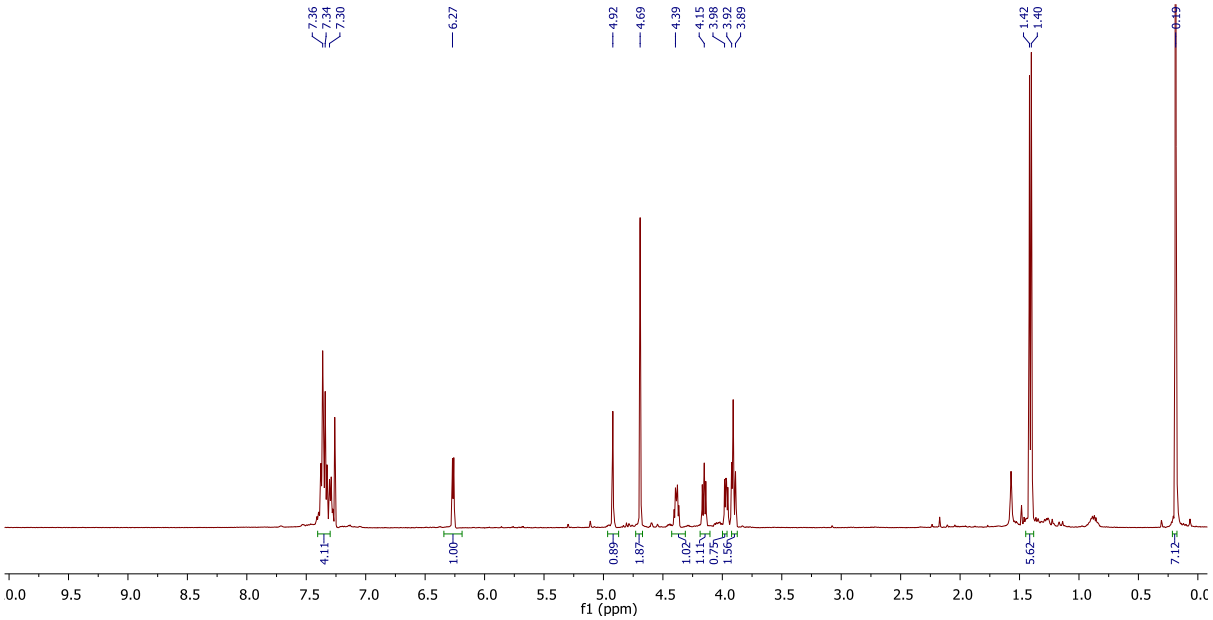


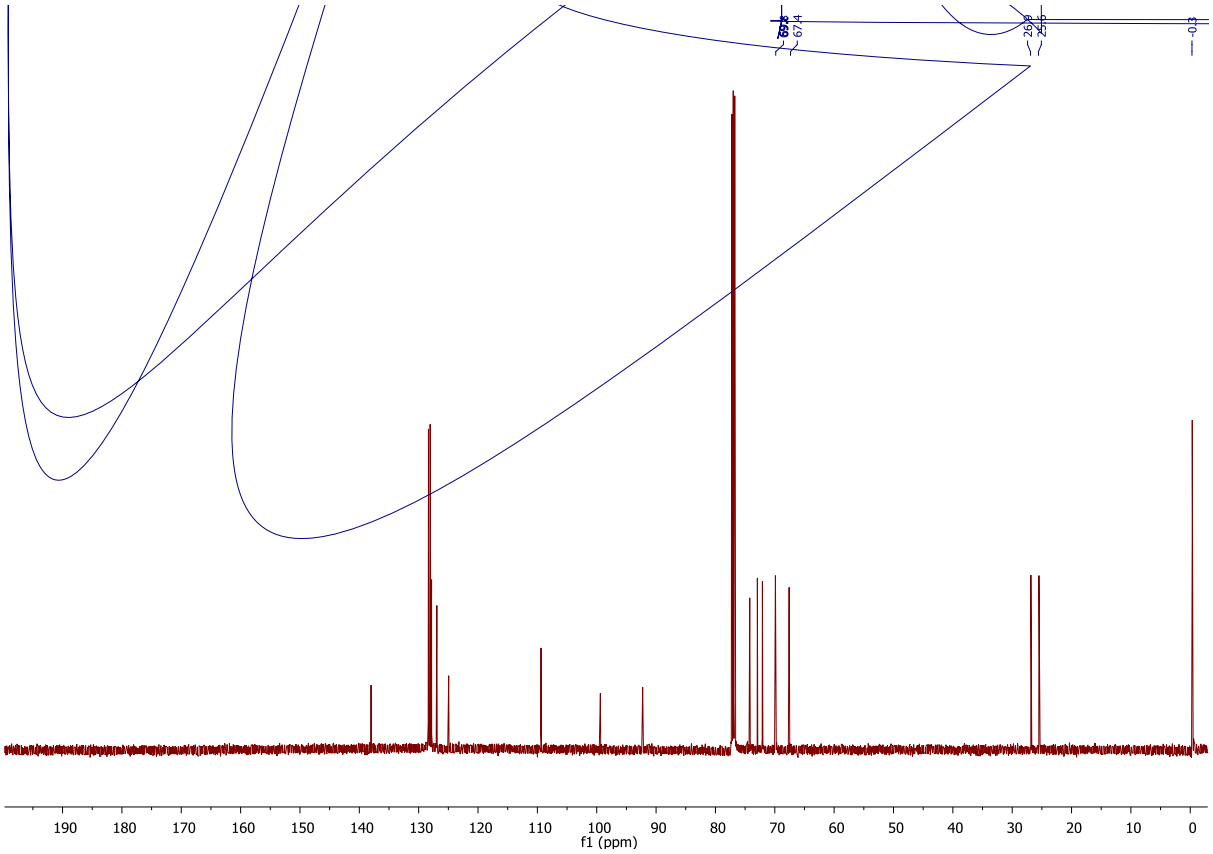




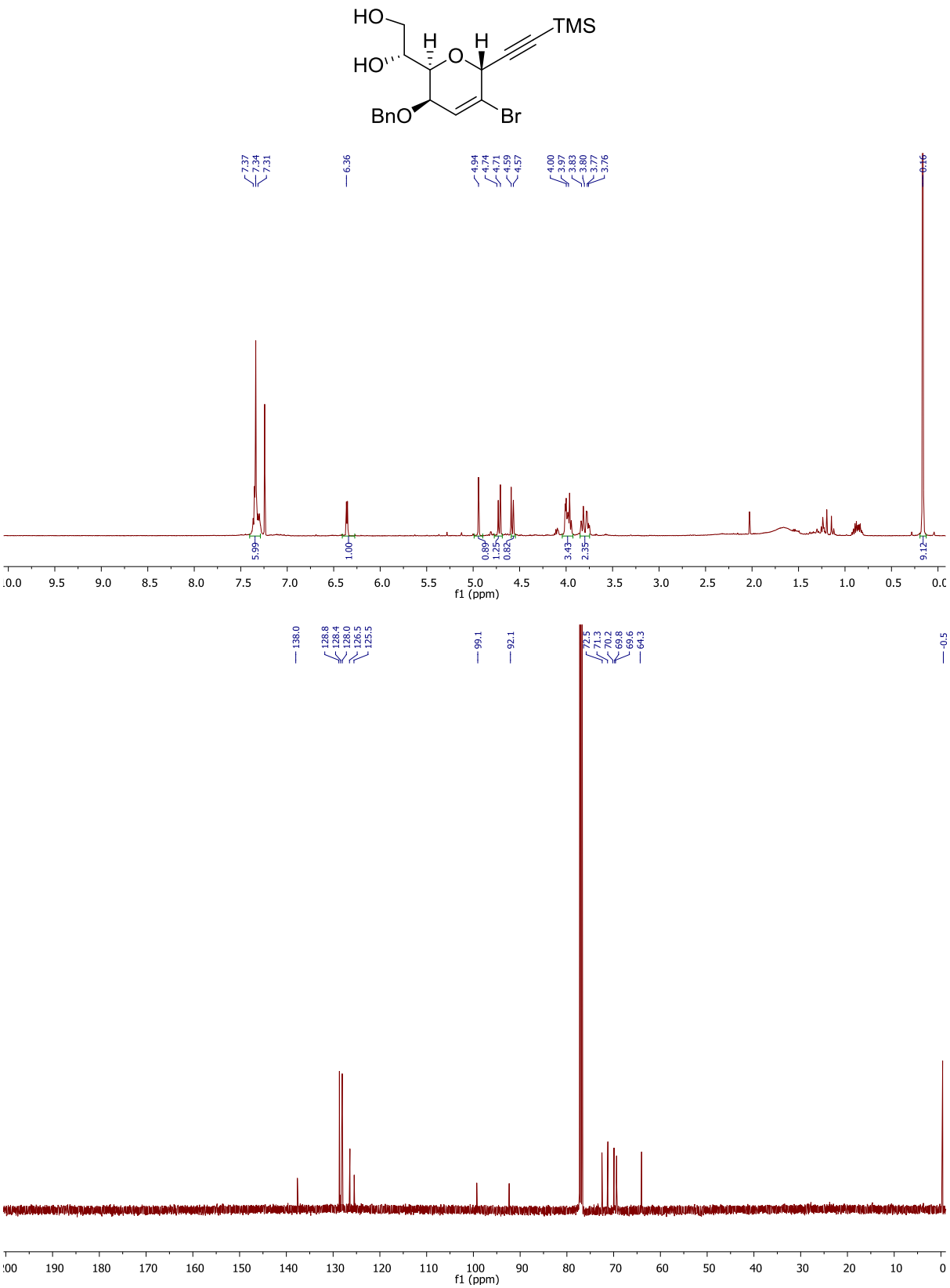
^{1}H-NMR and ^{13}C-NMR spectra of compound **131** (anomeric mixture)



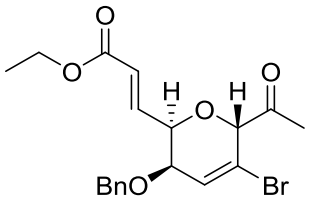


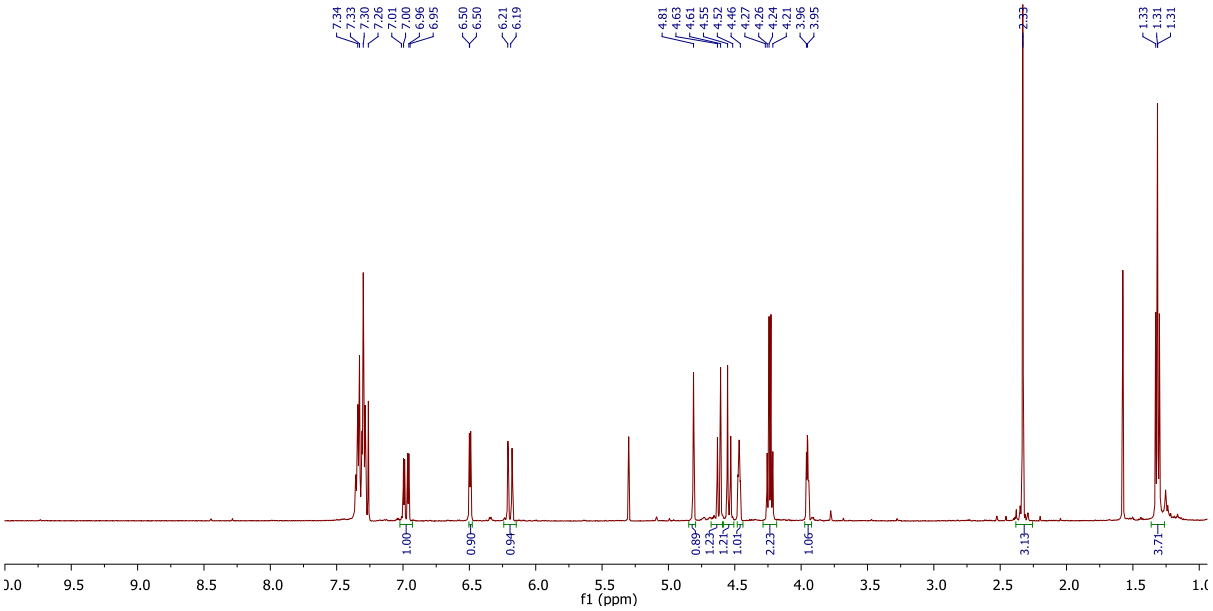


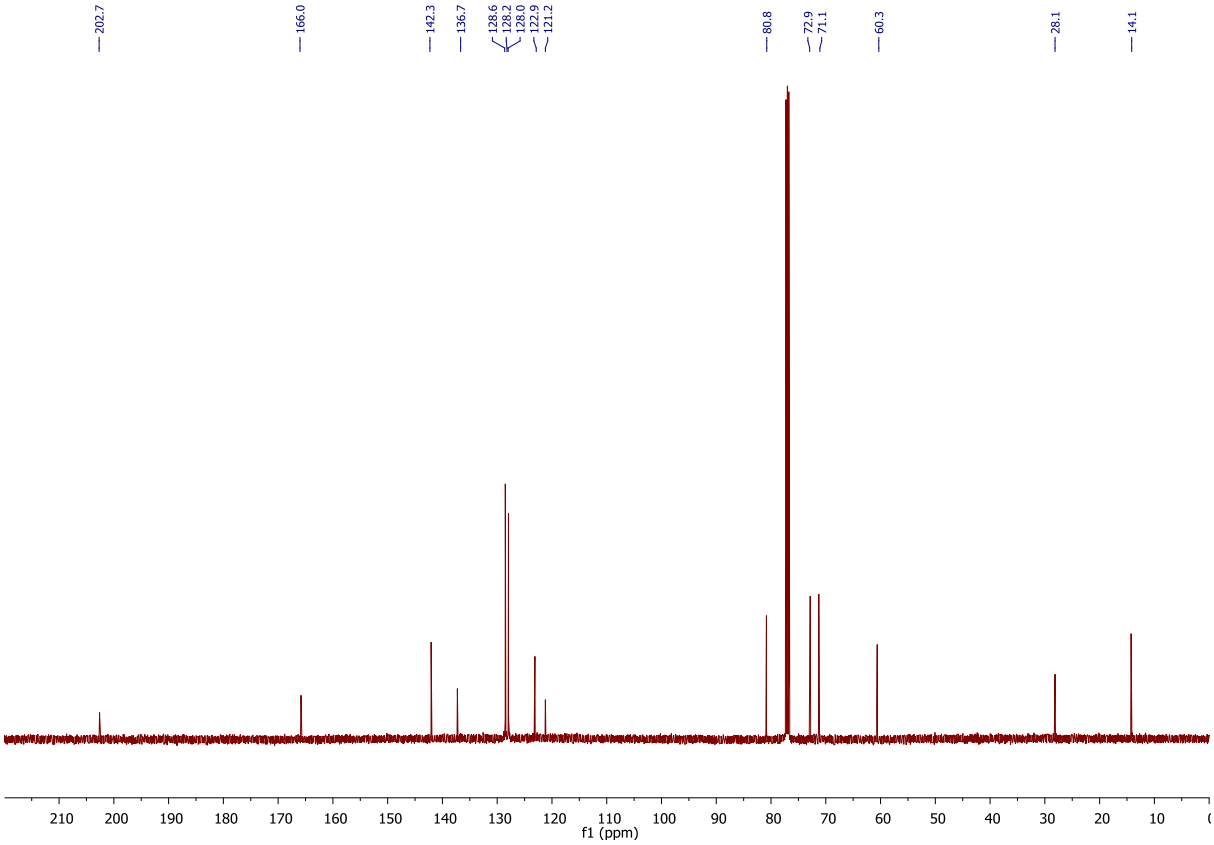
^{1}H-NMR and ^{13}C-NMR spectra of compound **302**



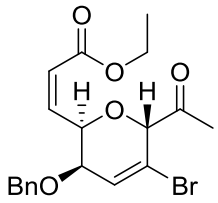
^{1}H-NMR and ^{13}C-NMR spectra of compound **314**

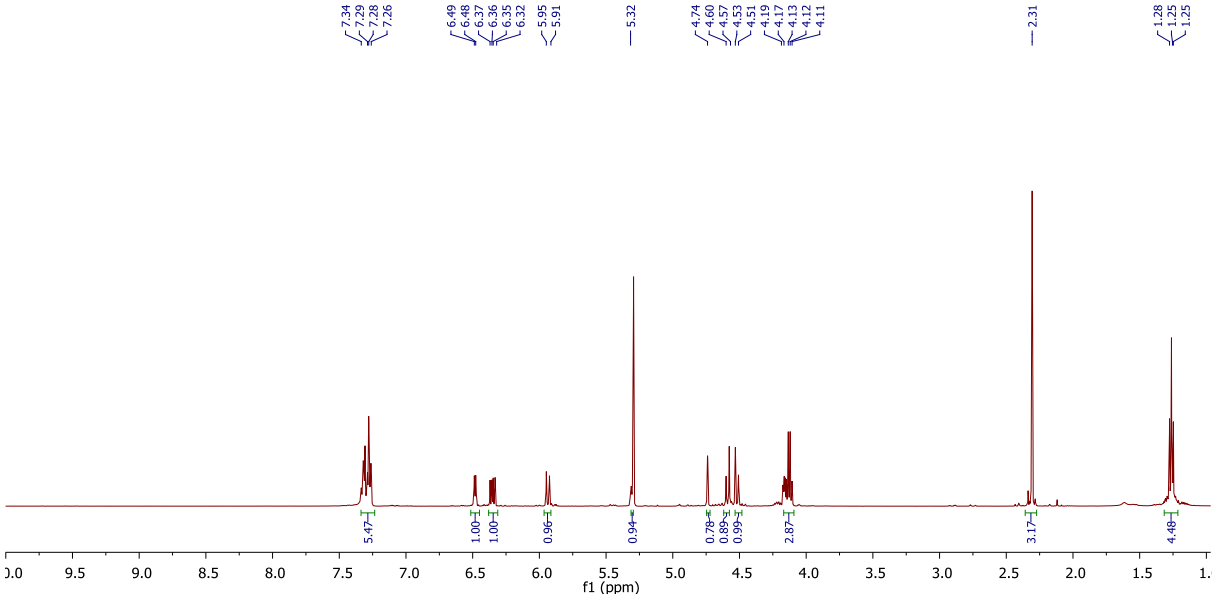


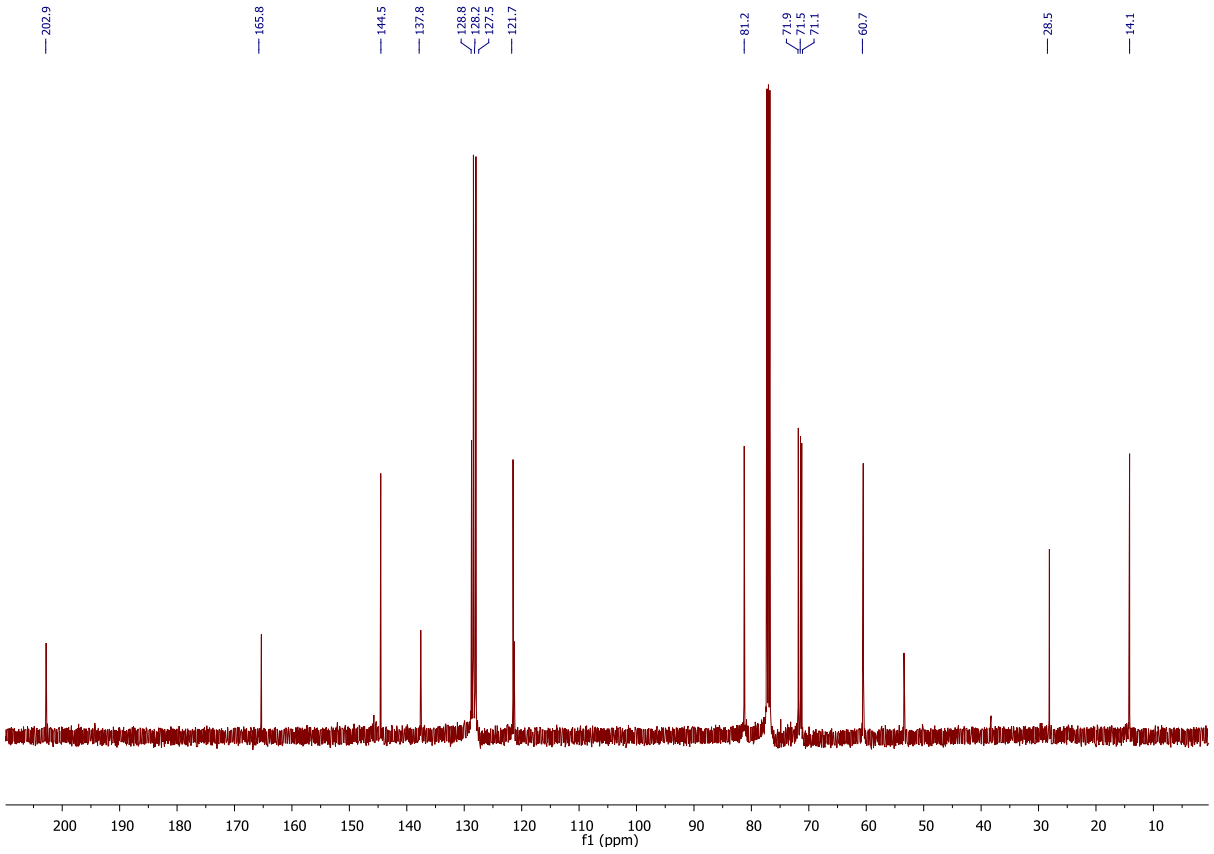




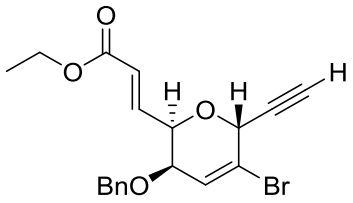
^{1}H-NMR and ^{13}C-NMR spectra of compound **321**

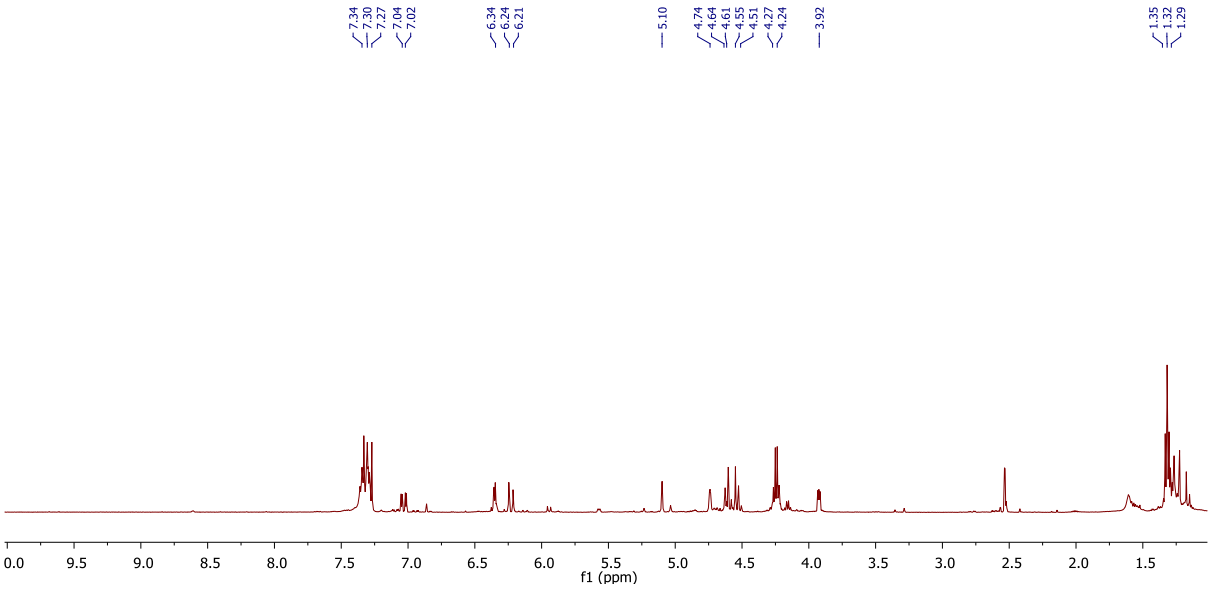


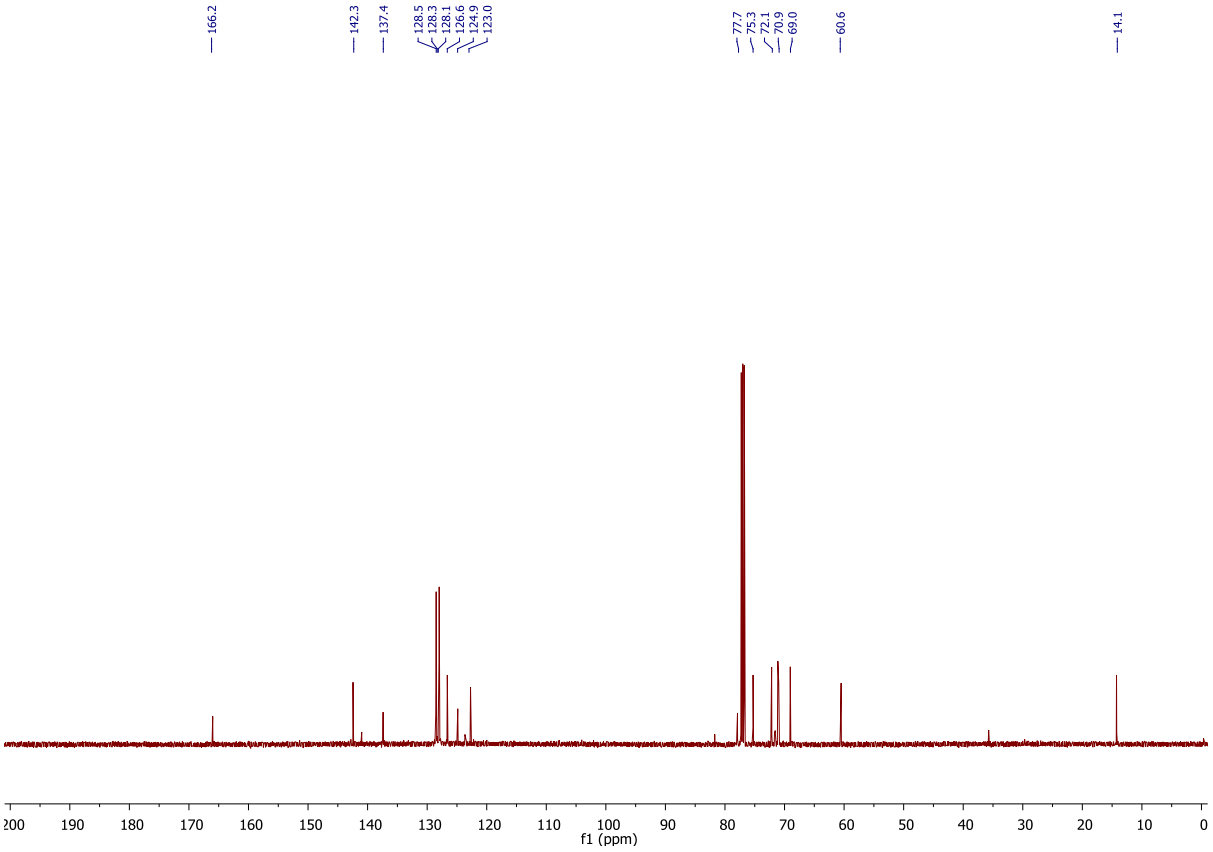




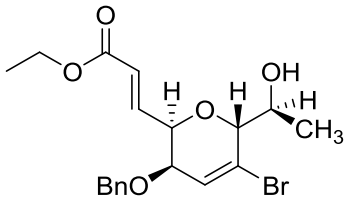
^{1}H-NMR and ^{13}C-NMR spectra of compound **320**

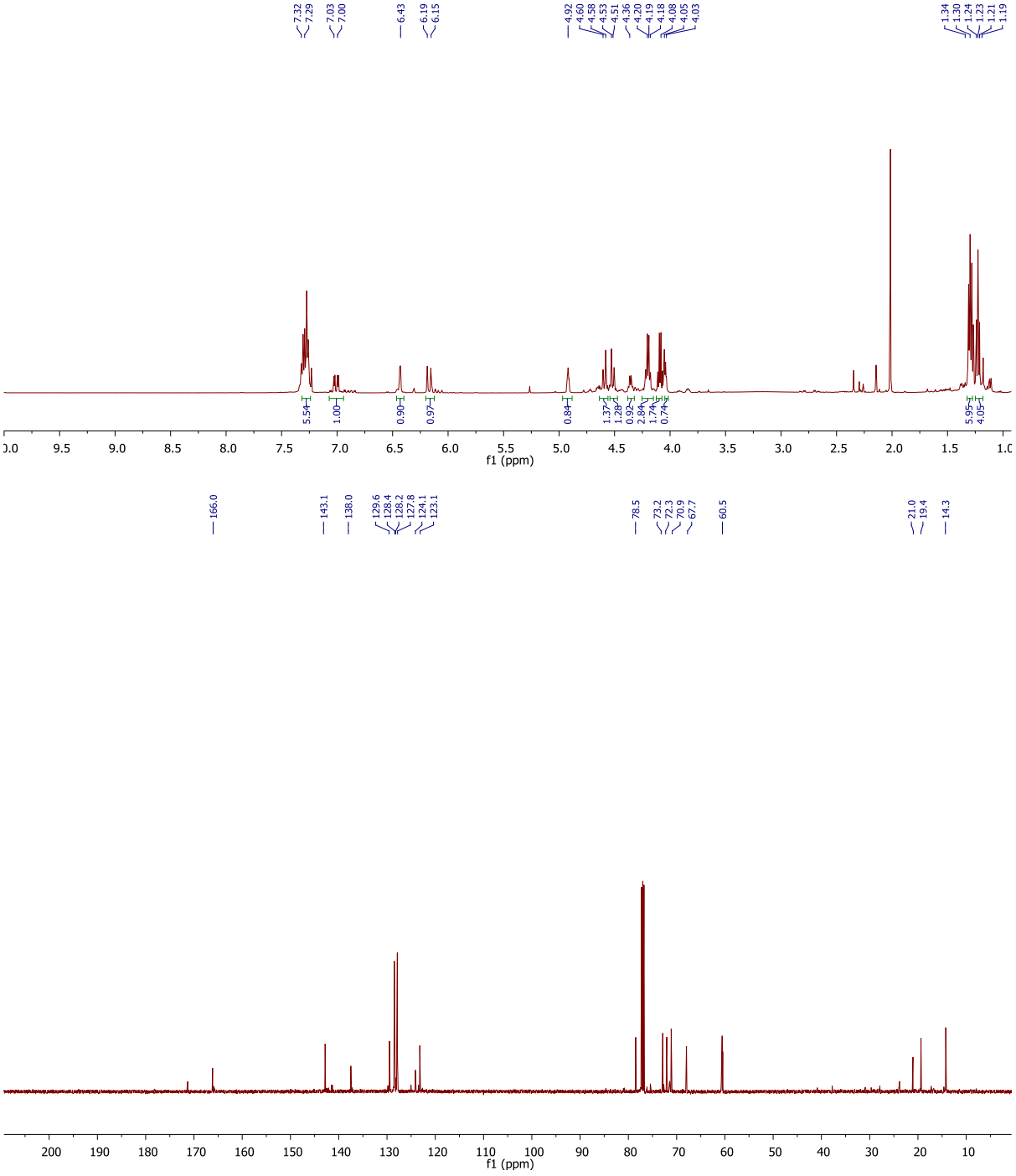




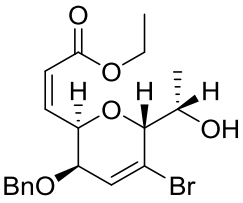


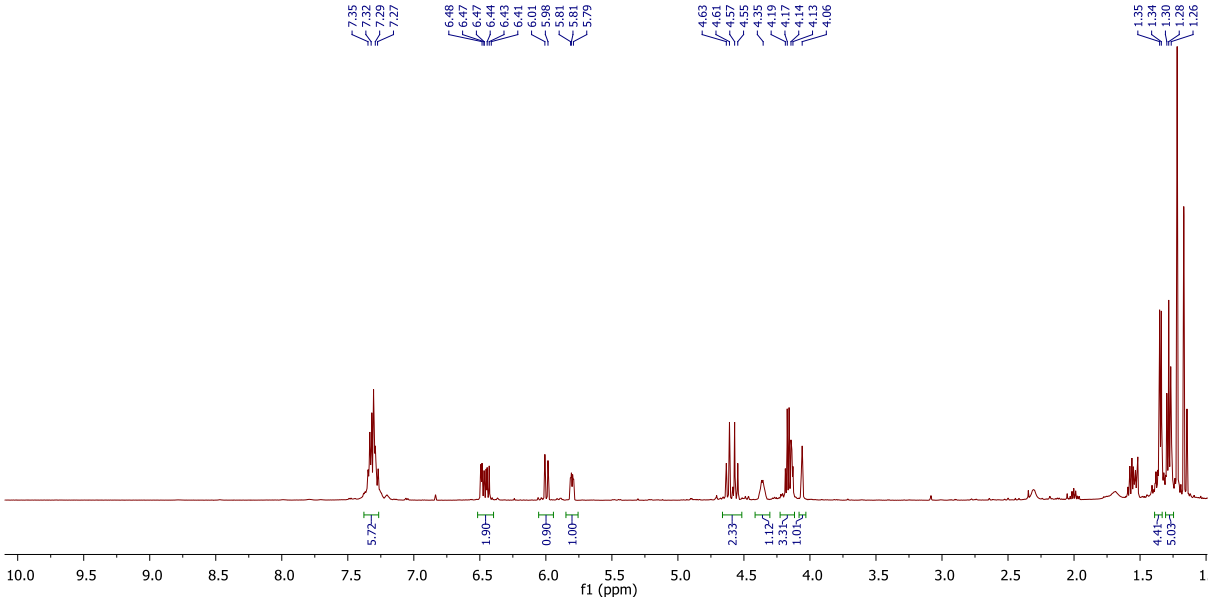
^{1}H-NMR and ^{13}C-NMR spectra of compound **319**

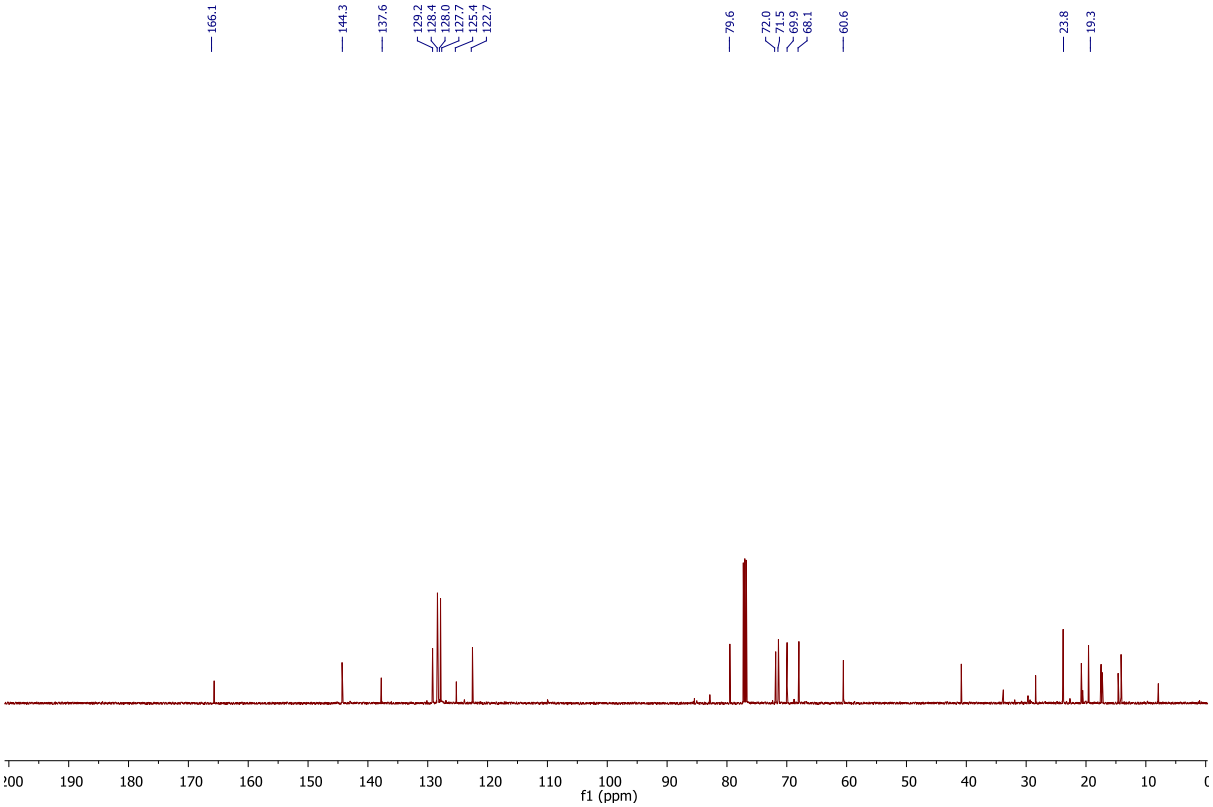




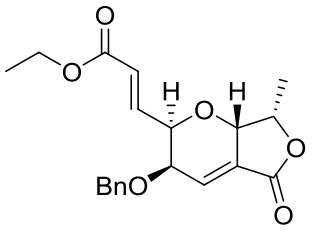
^{1}H-NMR and ^{13}C-NMR spectra of compound **323**

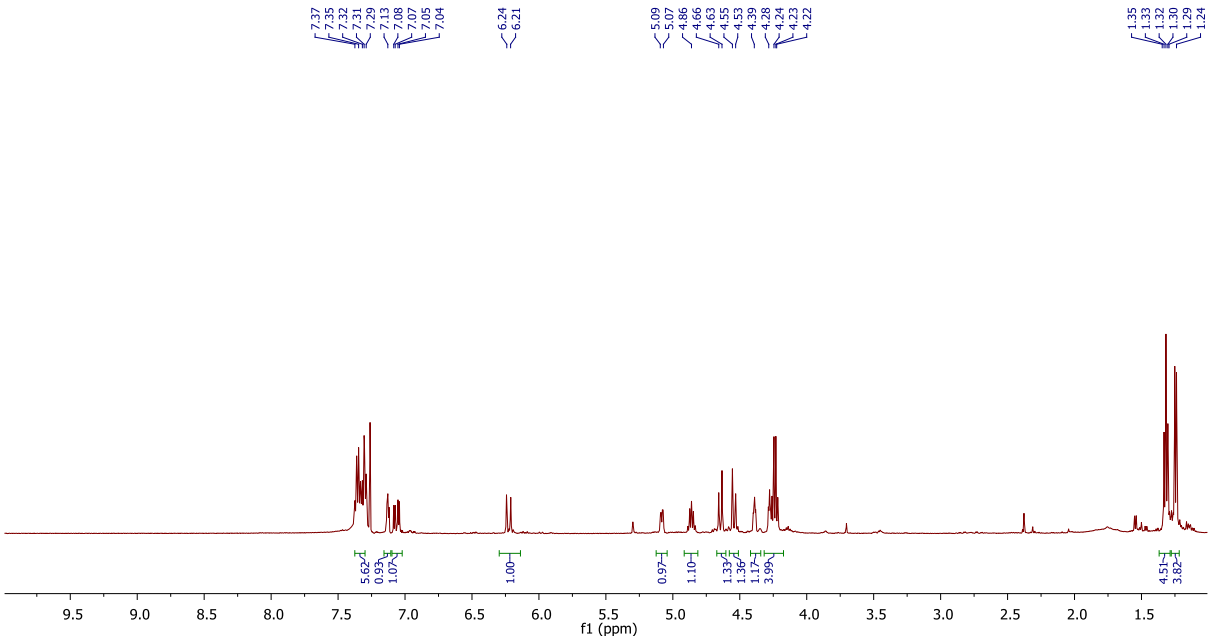


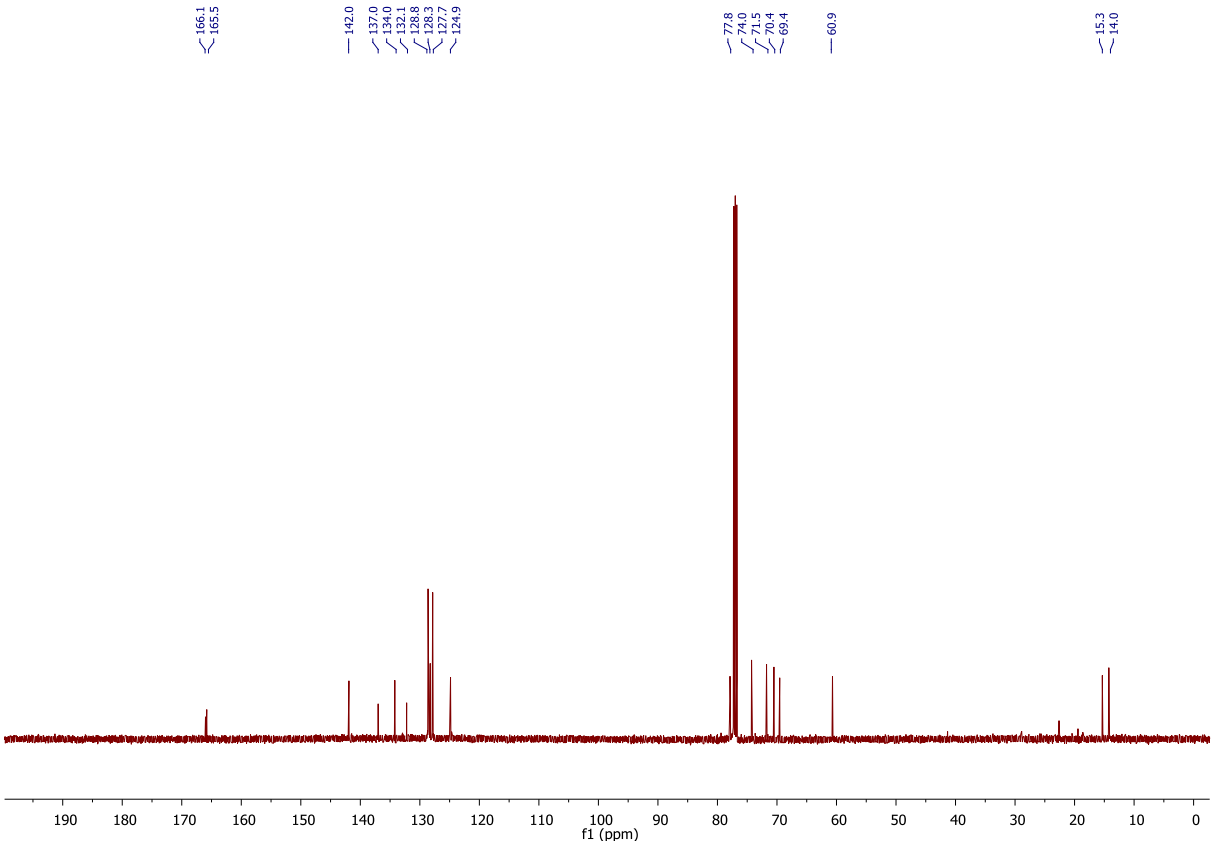




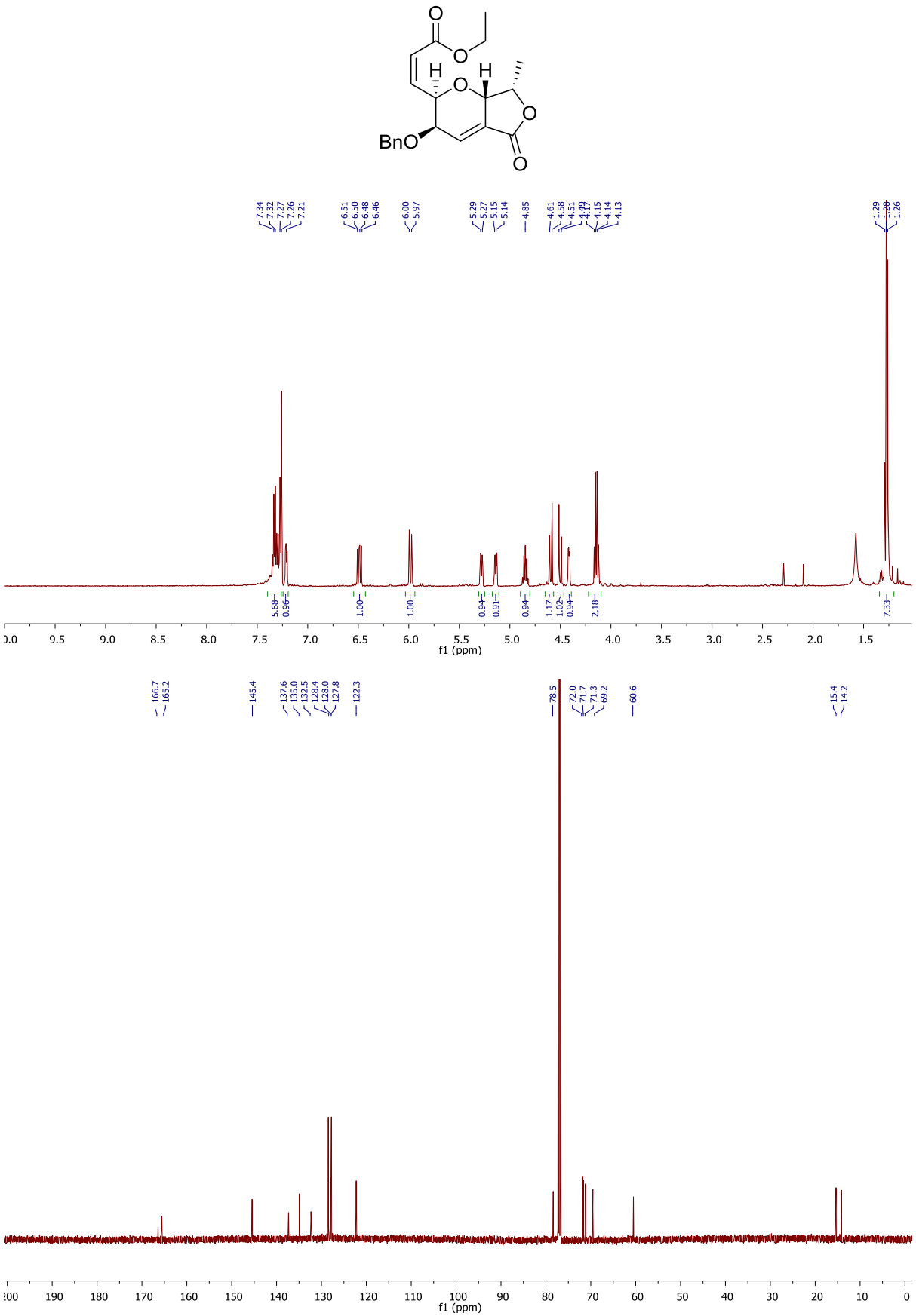
^{1}H-NMR and ^{13}C-NMR spectra of compound **322**



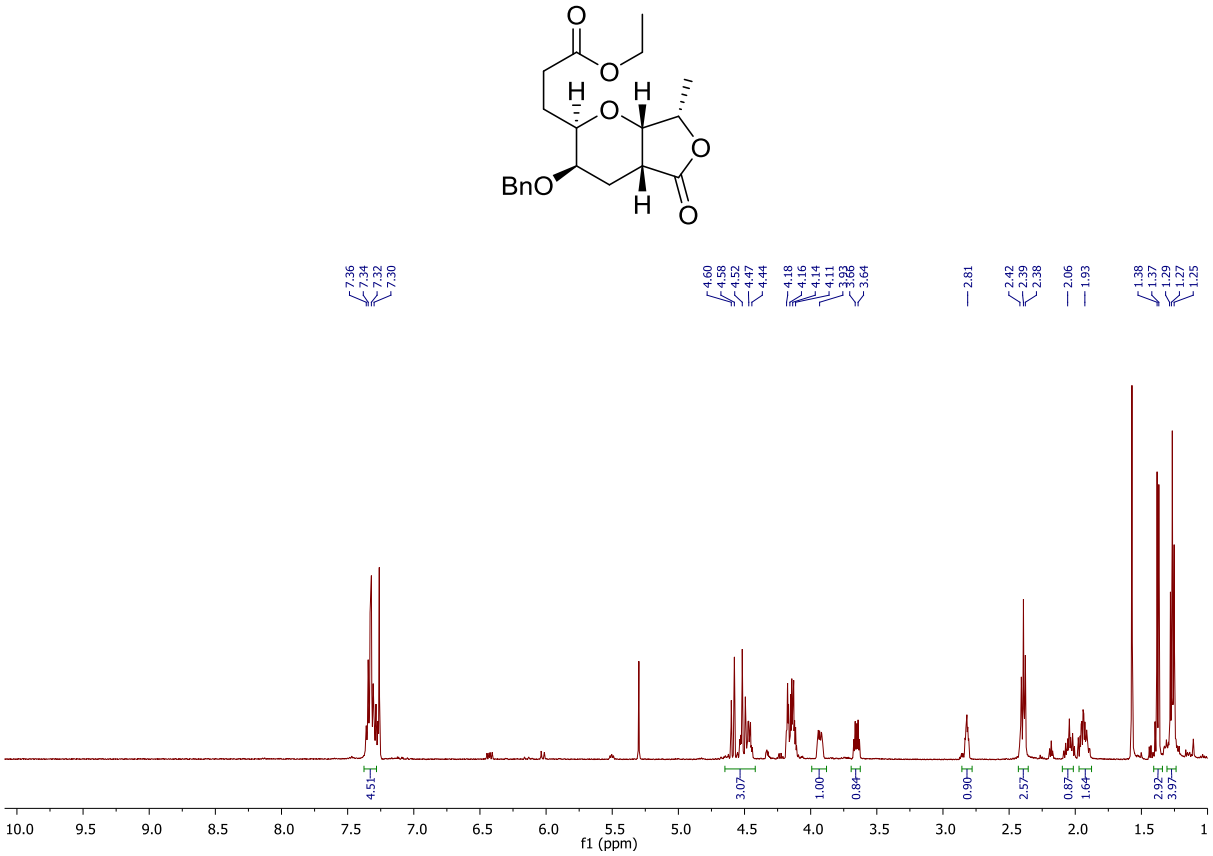




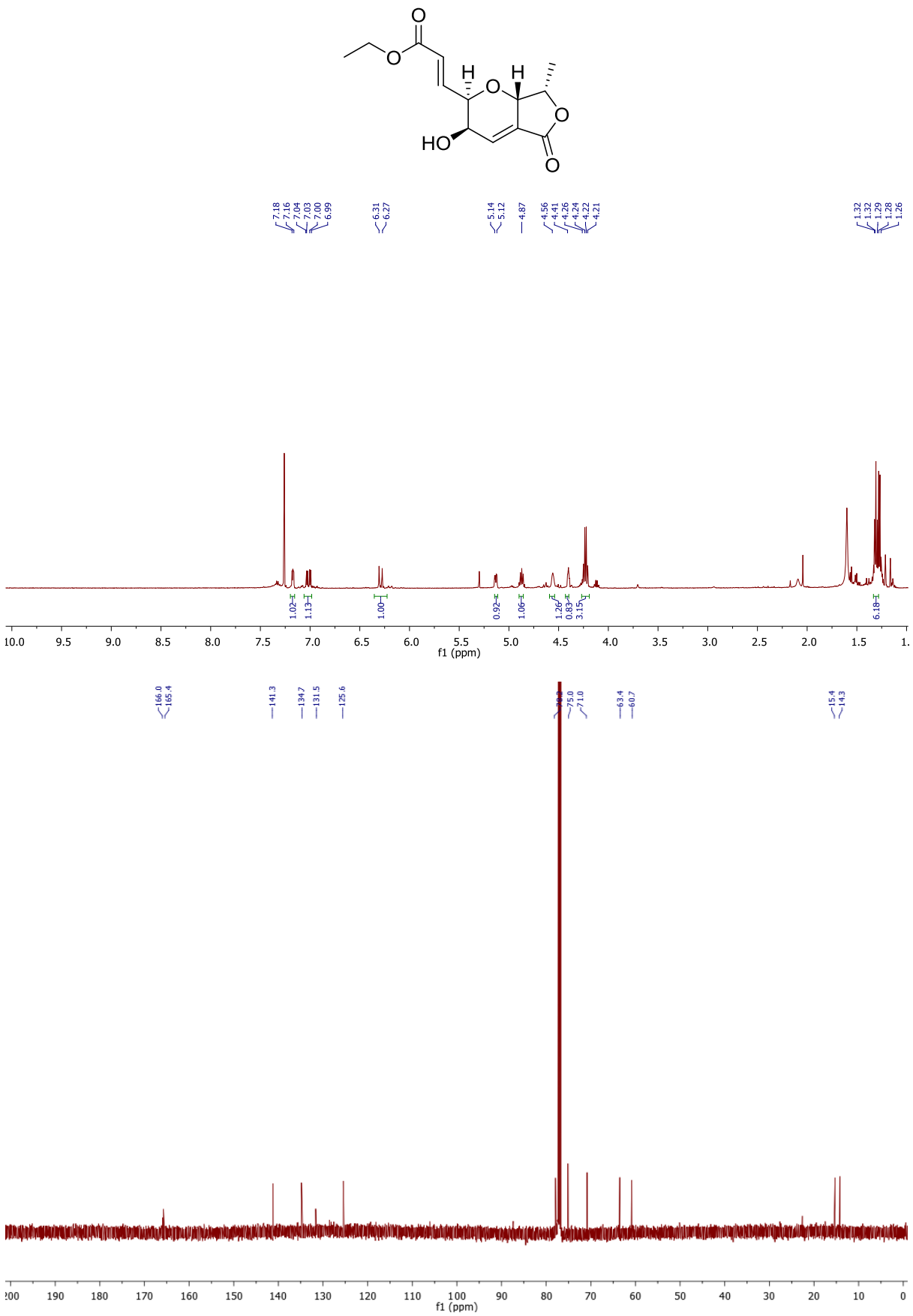
^{1}H-NMR and ^{13}C-NMR spectra of compound **329**



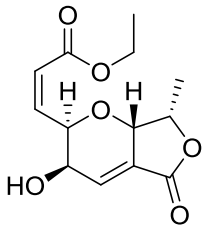
^{1}H-NMR and ^{13}C-NMR spectra of compound **328**

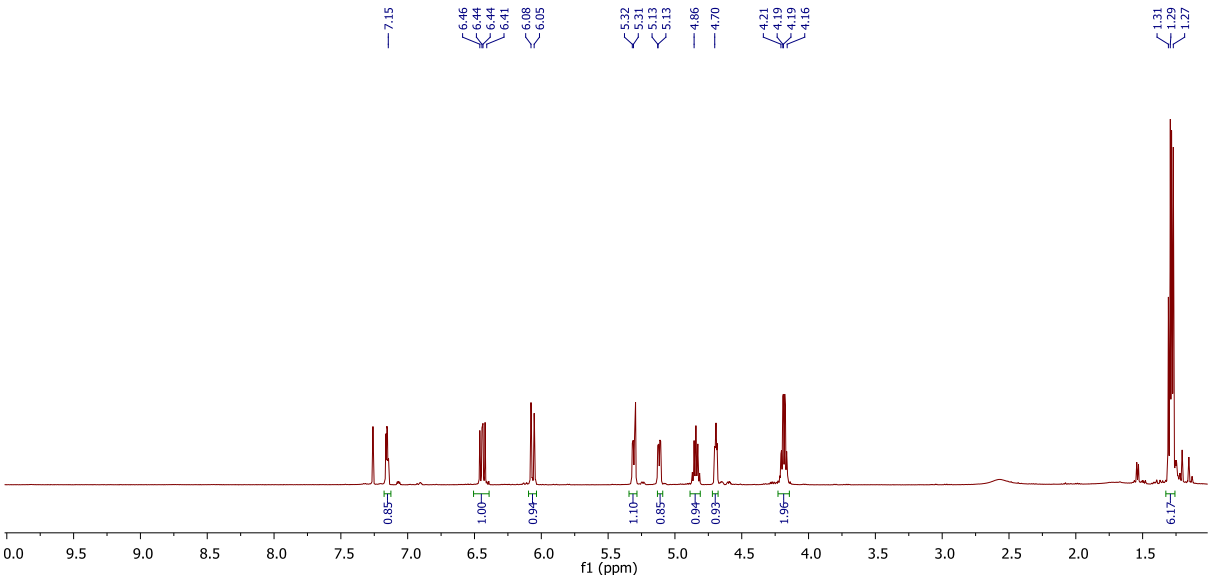


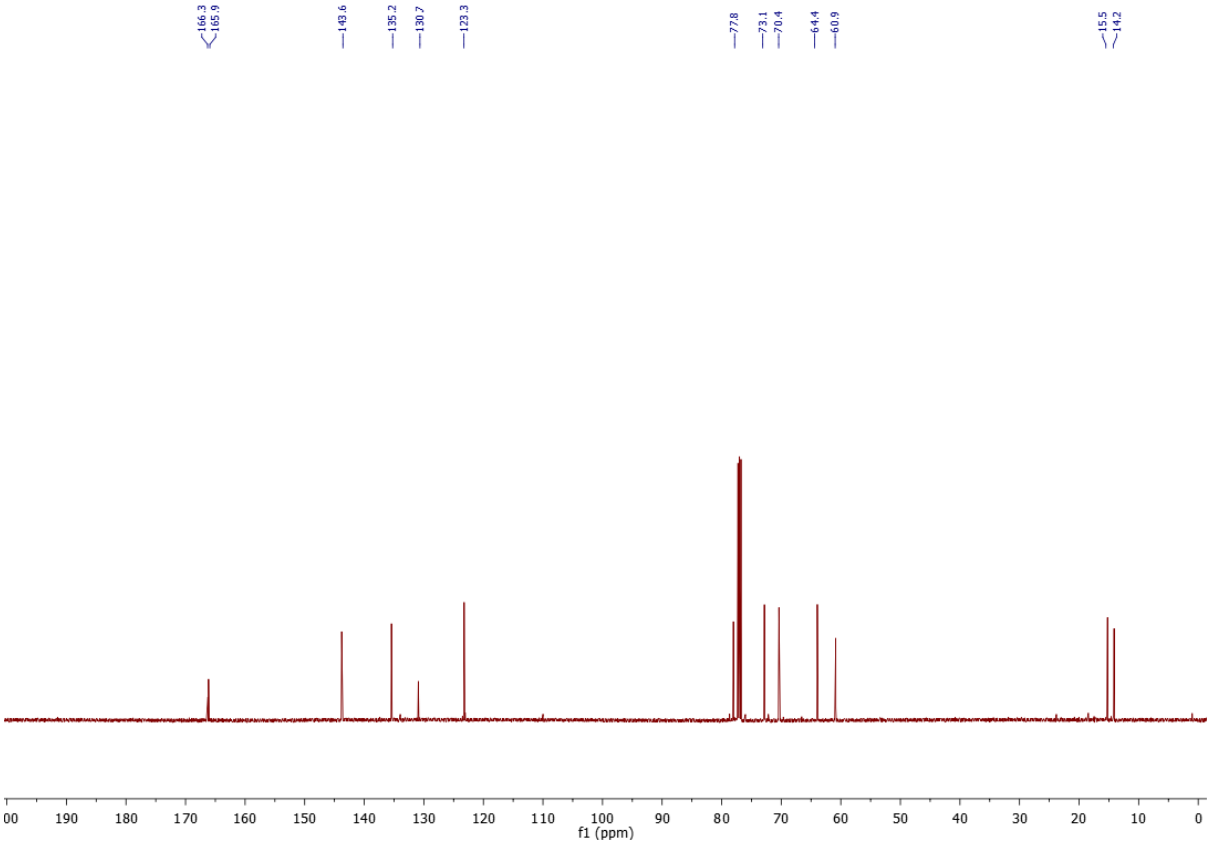
^{1}H-NMR spectrum of compound **331**



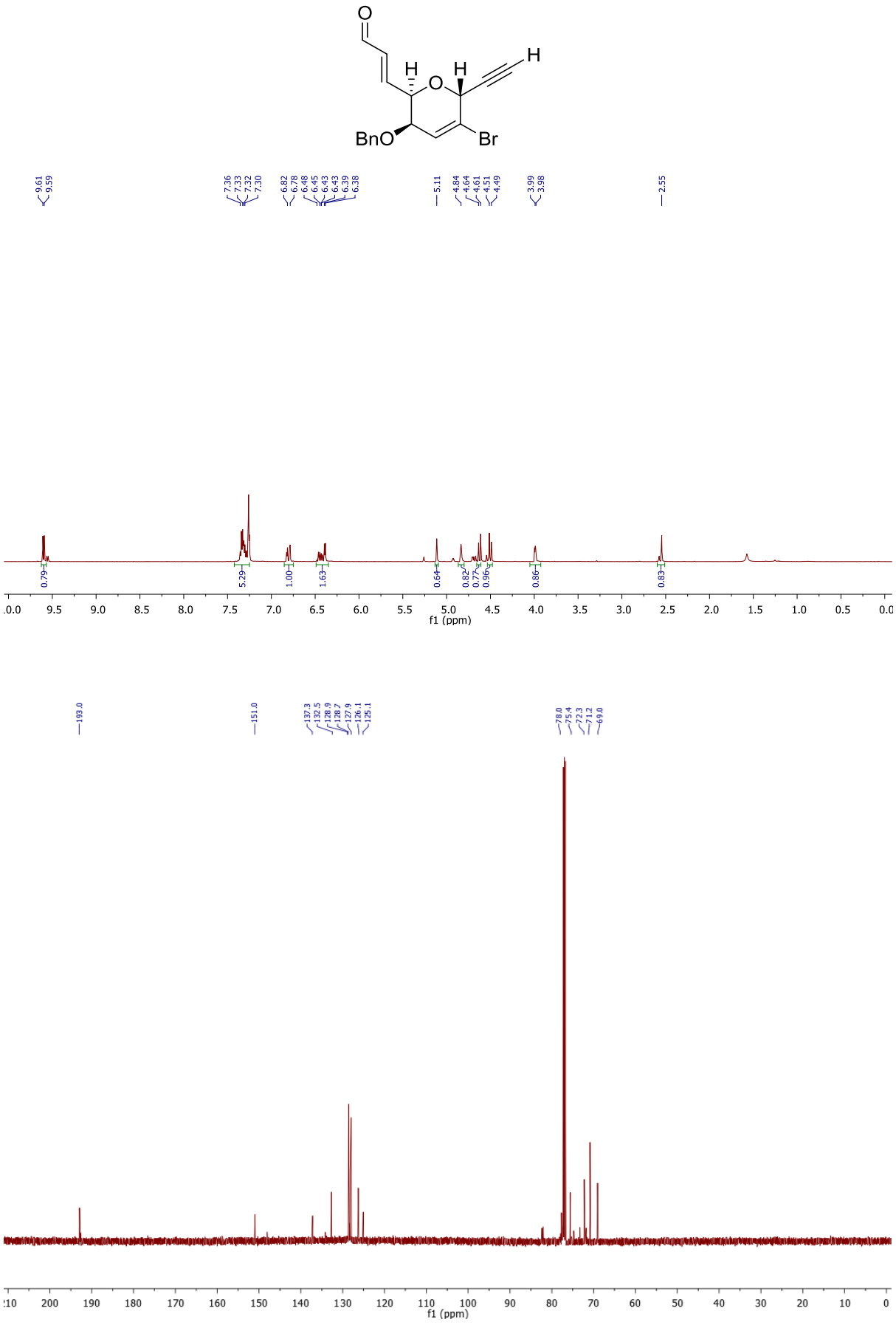
^{1}H-NMR and ^{13}C-NMR spectra of compound **141**



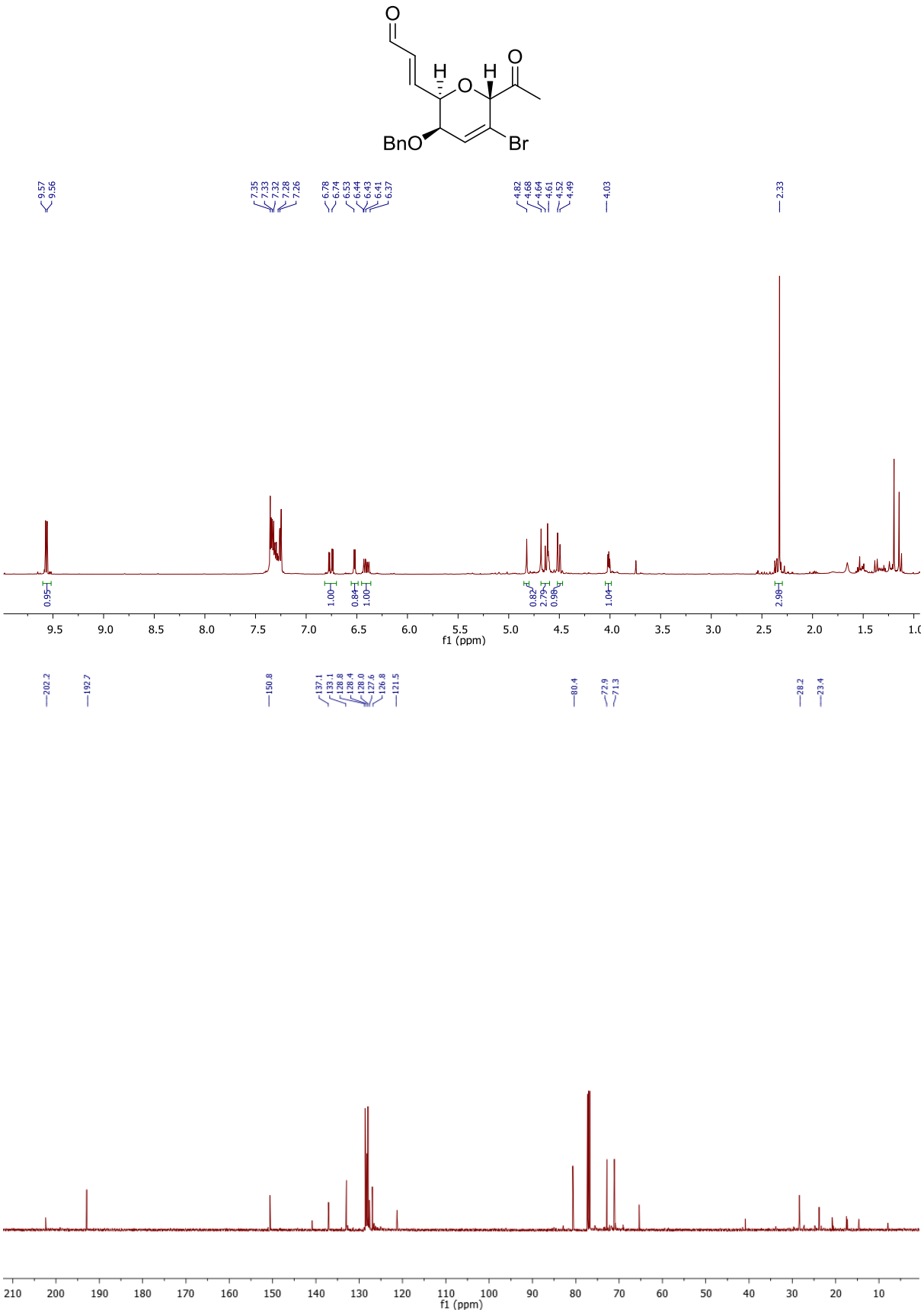




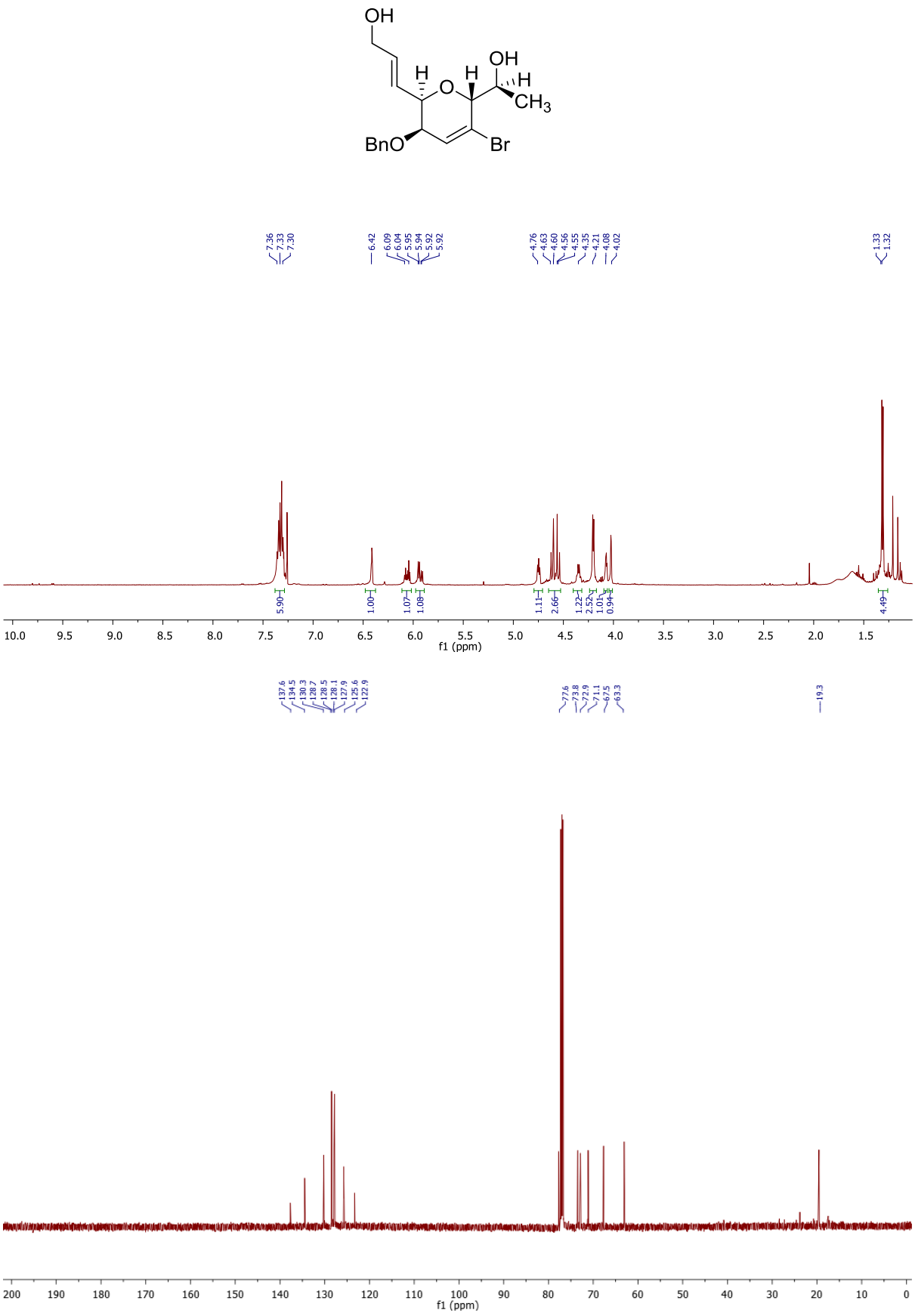
^{1}H-NMR and ^{13}C-NMR spectra of compound **140**



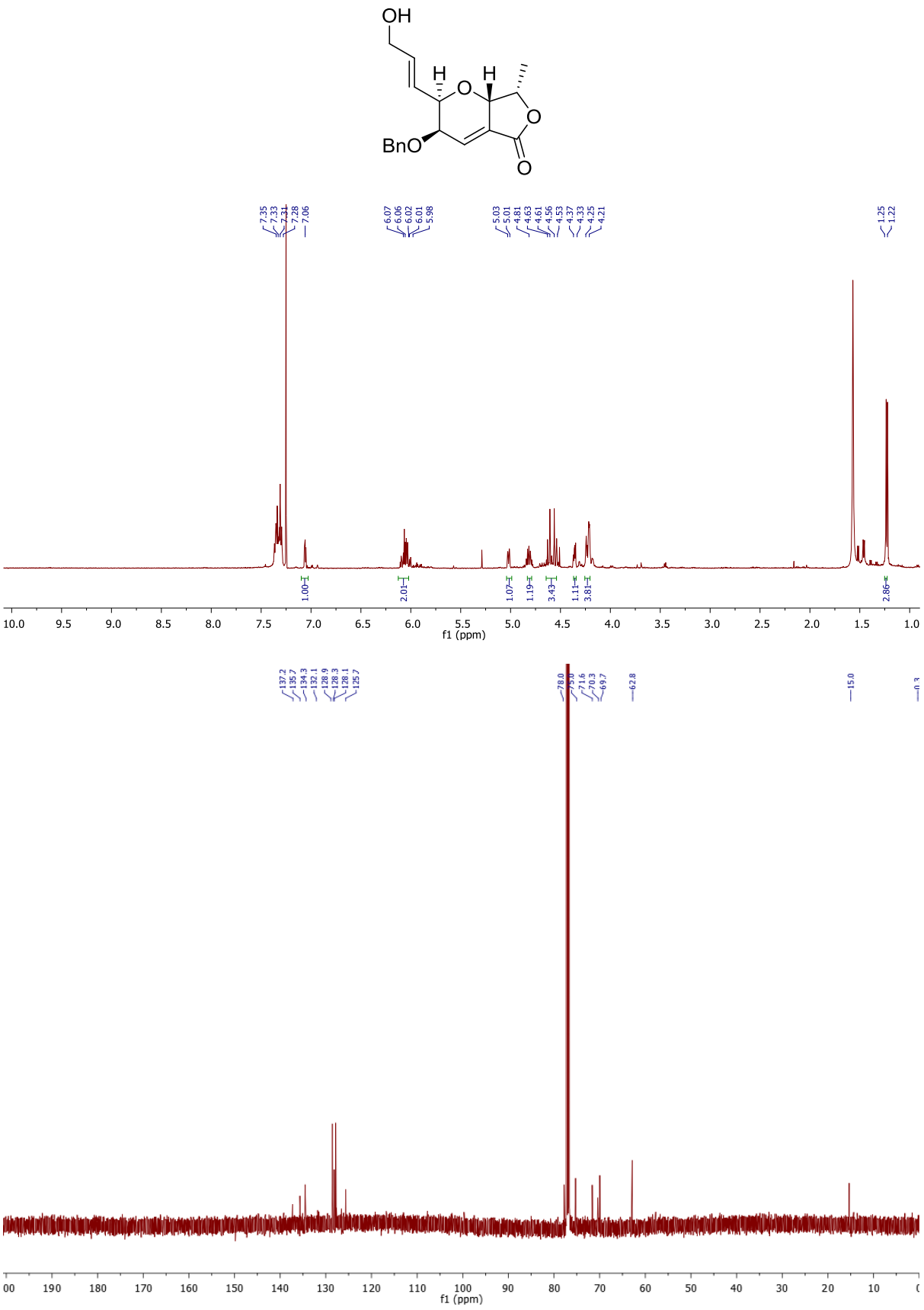
^{1}H-NMR and ^{13}C-NMR spectra of compound **332**



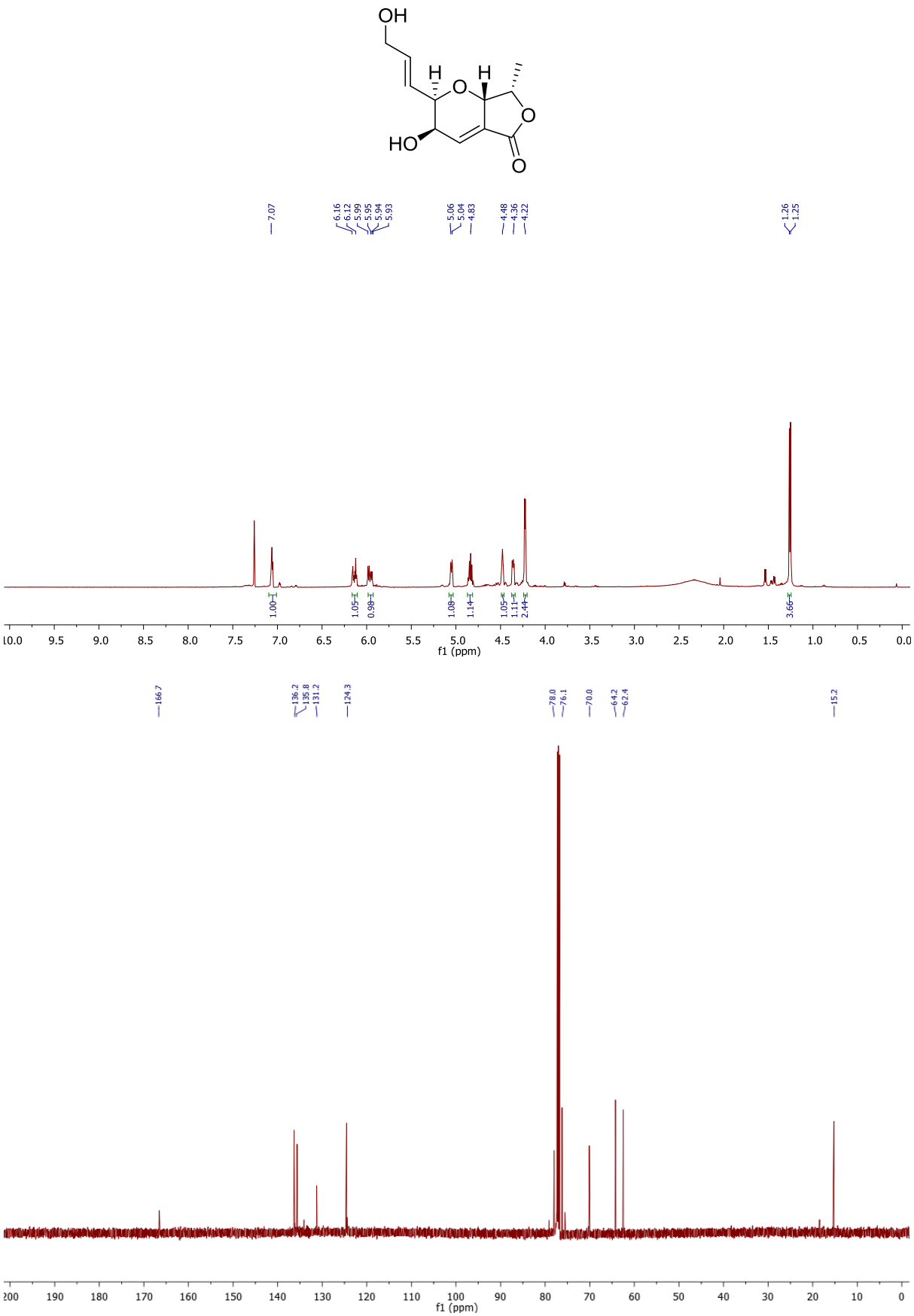
^{1}H-NMR and ^{13}C-NMR spectra of compound **333**



^{1}H-NMR and ^{13}C-NMR spectra of compound **334**



^{1}H-NMR and ^{13}C-NMR spectra of compound **335**



^{1}H-NMR and ^{13}C-NMR spectra of compound **145**

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