ENANTISELECTIVE SYNTHESIS OF NATURAL PRODUCTS

Mariam Azzouz

MARIAM AZZOUZ

ENANTIOSELECTIVE SYNTHESIS OF NATURAL PRODUCTS

DOCTORAL THESIS

Supervised by

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Departament de Química Analítica i Química Orgànica

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Els sotasignants Sergio Castillón Miranda, Catedràtic de Química Orgànica, i Yolanda Díaz Giménez, Professora Titular de Química Orgànica, del Departament de Química Analítica i Química Orgànica de la Universitat Rovira i Virgili.

FEM CONSTAR que aquest treball titulat " Enantioselective Synthesis of Natural Products" presentat per MARIAM AZZOUZ del títol de Doctor, ha estat realitzat sota la nostra supervisió al Departament de Química Analítica i Química Orgànica d'aquesta mateixa universitat.

Tarragona, 14 de Noviembre de 2012

Dr. Sergio Castillón Miranda

Dra. Yolanda Díaz Giménez

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Azzouz, M.; Llaveria, J.; Marcé, P.; Matheu, M. I.; Díaz, Y.; Castillón, S**. Formal Synthesis of Nectrisine.** 16th European Carbohydrate Symposium. Pòster. Sorrento-Nàpols, **2011**.

Azzouz, M.; Llaveria, J.; Marcé, P.; Matheu, M. I.; Díaz, Y.; Castillón, S**. Enantioselective Synthesis of Nectrisine.** X Jornadas de Carbohidratos. Pòster. Granada, **2010**.

Azzouz, M.; Llaveria, J.; Marcé, P.; Matheu, M. I.; Díaz, Y.; Castillón, S**.**
Enantioselective Synthesis of Nectrisine
Manuscript in preparation

Azzouz, M.; Matheu, M. I.; Díaz, Y.; Castillón, S**.**
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ils ne font que traverser l'oreilles des méchants

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ABBREVIATIONS AND ACRONYMS

A

AAA: Asymmetric Allylic Alkylation

Ac_2O: Acetic anhydride

AIDS: Acquired immune deficiency syndrome

AIBN: Azobisisobutyronitrile

ANPs: Acyclic nucleotide phosphonates

AQN: Anthraquinone

B

Boc: *tert*-butoxycarbonyl

Boc_2O : Di-*tert*-butyl dicarbonate

BnBr: Benzyl Bromide

BnCl: Benzyl chloride

BzCl : Benzoyl chloride

C

CM: Cross-metathesis

CLB: *p*-chlorobenzoate

CMV: Cytomegalovirus

CSA: Camphorsulfonic acid

D

DAB: 1,4-dideoxyimino-D-arabinitol

DACH 1,2-diaminocyclohexane

DAST: Diethylaminosulfur trifluoride

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM: Dichloromethane

DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD: Diethyl azodicarboxylate
DEPC: Diethyl phosphorocyanidate
DHPA: 9-(2,3-dihydroxypropyl)adenine
DHQ: Dihydroquinine

DHQD: Dihydroquinidine
DMAP: 4-Dimethylaminopyridine
DMF: *N*,*N*-Dimethylformamide
DNA: Deoxyribonucleic acid
dNTPs : 2'-deoxynucleoside-5'-triphosphates
DPPBA Diphenylphosphinobenzoic acid
DYKAT: Dynamic Kinetic Asymmetric Transformation

F
FIV: Feline immunodeficiency virus

H
HCMV: Human cytomegalovirus
HPMPA: (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine
HPMPC: (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine
HSV: Herpes simplex virus

M
MEQ: 4-Methyl-2-quinolil

N
NBS: *N*-Bromosuccinimide
NCS: *N*-Chlorosuccinimide
NMO: *N*-methyl-morpholine-*N*-oxide
NMR: Nuclear Magnetic Resonance

P
PHAL: Phthalazine
PHN: Phenanthryl ether

PMB: *p*-methoxybenzyl
PFA: Phosphonoformic acid
PMEA: 9-(2-phosphonylmethoxyethyl)adenine
PMPA: (*R*)-9-(2-phosphonylmethoxypropyl) adenine
PK: Protein kinase
Py: Pyridine
Pyr: Pyrimidine

R

RCM: Ring-closing metathesis
RNA : Ribonucleic acid
ROM: Ring-opening metathesis

S

SAH: S-adenosylhomocysteine
SRBC: Sheep Red Blood Cells

T

TBAF: Tetra-*n*-Butylammonium fluoride
TBSOTf: *tert*-Butyldimethylsilyl trifluoromethanesulfonate
TBDPSCl: *tert*-Butyldiphenylsilyl Chloride
TDF: Tenofovir disoproxil fumarate
Teoc *:* 2-trimethylsilylethoxycarbonyl
TFA: Trifluoroacetic acid
THF: Tetrahydrofuran
TIPSCl: Triisopropylsilyl chloride
TLC: Thin Layer Crhomatography
TMEDA: Tetramethylethylenediamine
TMSBr: Trimethylsilyl bromide
TPAP: Tetra-*n*-propylammonium perruthenate
TsOH: *p*-Toluenesulfonic acid
TK: Thymidine kinase

V

VZV: Varicella-Zoster Virus

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RESUMEN

El objetivo general del trabajo presentado es investigar nuevas metodologías para la síntesis de: a) nectrisina, un inhibidor de α-glucosidasas y α-mannosidasas, b) del fragmento oligosacarídico del antibiótico AT2433-A1, un antibiótico utilizado en el tratamiento de numerosos tipos de cánceres y, c) de análogos del cidofovir o HPMPC, nucleósido acíclico que incorpora una unidad de fosfonato, y que se utiliza en el tratamiento del citomegalovirus (CMV) en pacientes con SIDA.

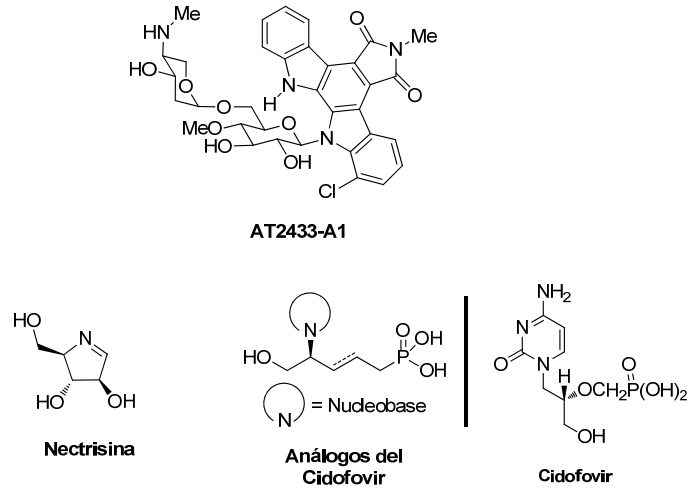
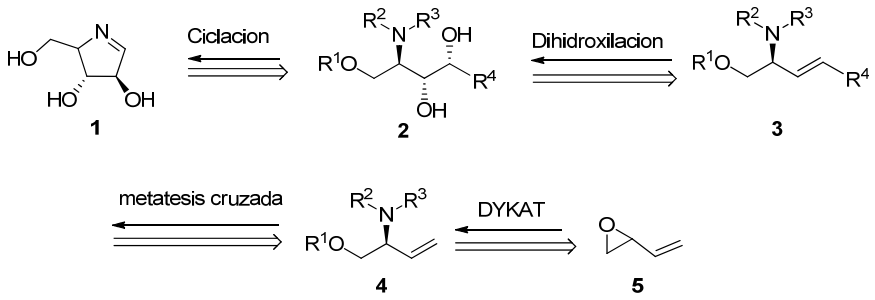


Figura 1. Estructuras del antibiótico AT2433-A1, de la Nectrisina y de análogos del Cidofovir

Síntesis enantioselectiva de nectrisina

Retrosintéticamente la síntesis de la nectrisina puede llevarse a cabo por ciclación del aminoaldehído **2** (R^4=CHO), el cual puede proceder del alqueno *trans* **3** mediante una reacción de dihidroxilación estereoselectiva. La síntesis de **3** puede llevarse a cabo a partir de **4** mediante elongación de la cadena utilizando la reacción de metatesis cruzada catalizada por rutenio. Finalmente, el intermedio clave **4** procede de una aminación alílica asimétrica catalizada por Pd del monepóxido de butadieno racémico **5**, reacción ya descrita por Trost.

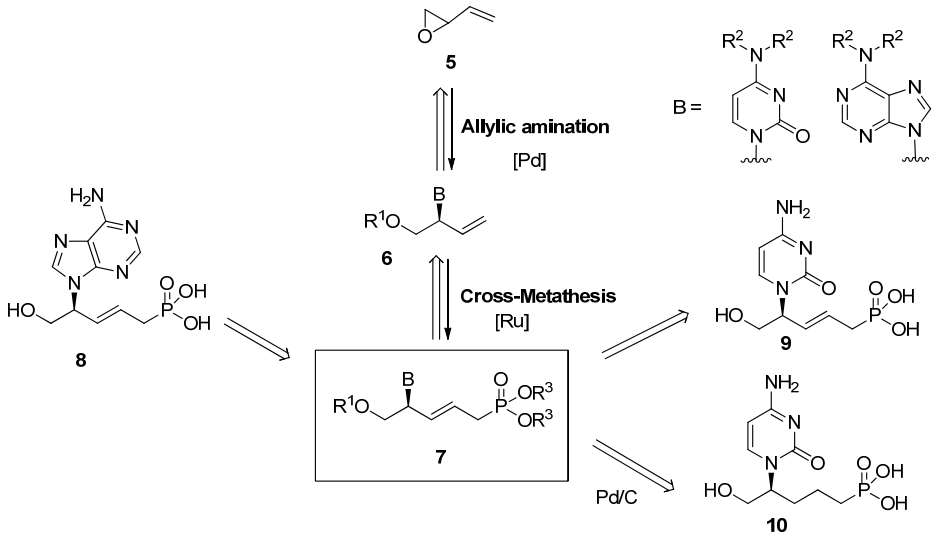


Esquema 1. Retrosíntesis de la nectrisina.

La aminación alílica asimétrica del monepóxido de butadieno racémico catalizada por Pd (η^3-C_3H_5)PdCl/DACH-naftilo transcurrió con elevado rendimiento y enantioselectividad para dar el compuesto **4**. La elongación de la cadena de **4** se realizó mediante una metatesis cruzada catalizada por el catalizador de Grubbs-Hoveyda con diferentes alquenos como acroleína, 2-vinil-1,3-dioxolano, y con acrilato de etilo. Sólo en este último caso se obtuvieron resultados relevantes del compuesto **3** (R^4=COOEt) como para continuar la síntesis. La reacción de dihidroxilación estereoselectiva del alqueno trans **3** (R^4=COOEt) condujo al diol deseado **2** (R^4=COOEt) con buena selectividad utilizando OsO_4/TMEDA. La hidrólisis del benzoato con LiOH y la ciclación *in situ* condujo a la lactama, a partir de la cual se siguió una secuencia sintética descrita en la bibliografía, consistente en la sililación de los grupos hidroxilo, protección del grupo amino en forma de terc-butil carbamato, reducción del carbonilo y eliminación con desprotección concomitante de los grupo sililo para dar la imina, que en nuestras manos no logró llevarse a fin debido a problemas en la última etapa de eliminación para dar la imina.

Síntesis enantioselectiva de análogos de Cidofovir HPMPC

La síntesis de los análogos del cidofovir se planteó siguiendo un esquema sintético similar al de la nectrisina, en el que la síntesis del intermedio **7** se llevó a cabo mediante la aminación alílica asimétrica del monoepóxido del butadieno y posterior reacción de metátesis cruzada como pasos clave.



Esquema 2. Retrosíntesis de **7**

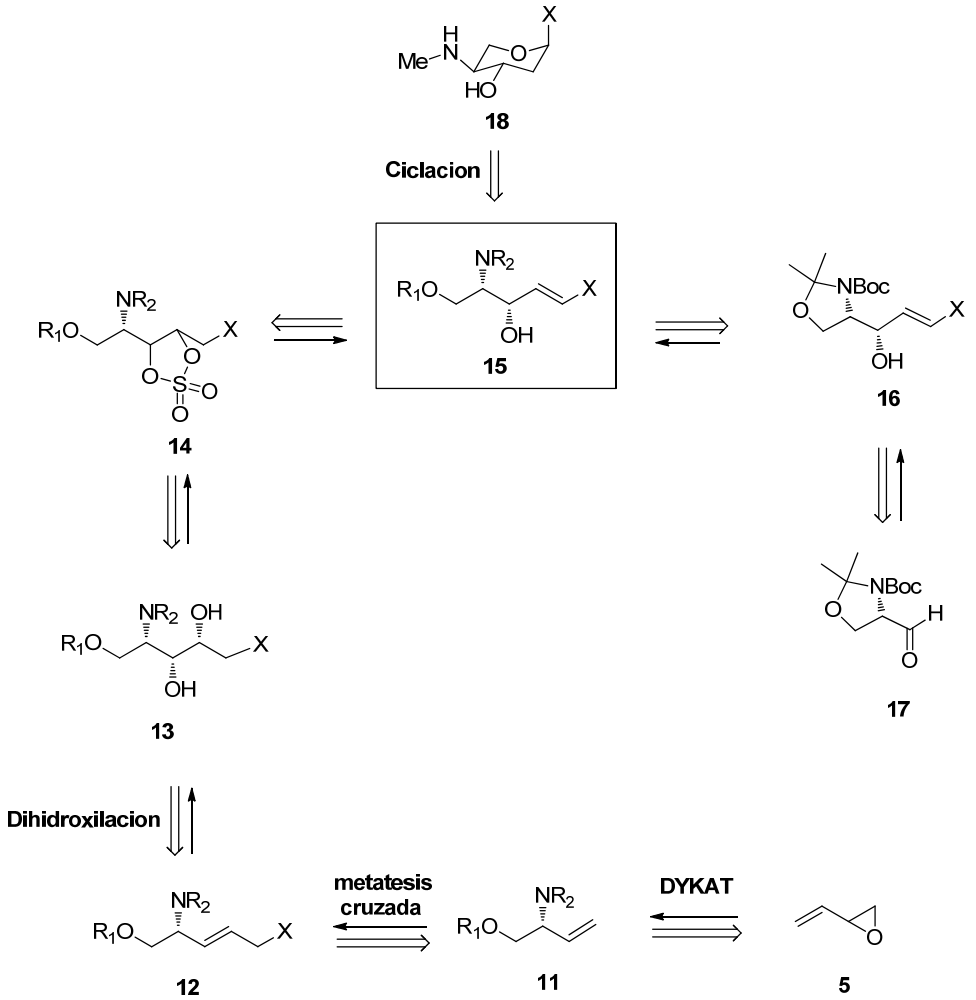
En primer lugar se realizó la aminación alílica asimétrica catalizada por Pd (η^3-C_3H_5)PdCl/DACH-naftil del monepóxido de butadieno racémico, con adenina y citosina la cual se optimizó hasta conseguir rendimientos y excesos enantioméricos superiores al 90%. Seguidamente se optimizó la reacción de metátesis cruzada de los compuestos obtenidos (**6**) con un alil fosfonato convenientemente protegido, obteniendo **7** con buen rendimiento. La síntesis de los análogos de cidofovir insaturados **8** y **9** se completó tras la desprotección de todos los grupos protectores con TMSBr. La síntesis del derivado saturado **10** se realizó mediante la hydrogenación (3 bares de hidrógeno, Pd/C durante 5h) y la eliminación de los grupos protectores.

Síntesis enantioselectiva del fragmento oligosacarídico del antibiótico AT2433-A1

La retrosíntesis de **18** se planteó por ciclación electrófila inducida por yodo de **15**, donde X debiera ser un grupo activador del doble enlace que a su vez se pudiera comportar como grupo saliente en la subsiguiente reacción de glicosilación a partir de **15.** La síntesis del intermedio **15** se planteó por diferentes procedimientos y en particular a partir del sulfato **14**, el cual provendría del diol **13**, que a su vez provendría de la dihidroxilación de **12**. El compuesto **12** debería poder obtenerse a partir de **5** por la secuencia clásica de DYKAT y metatesis cruzada. Así, a partir del compuesto **11** (R=Boc) se realizó la metatesis cruzada con diferentes alquenos y en particular con el alil fenil tioéter. Las limitaciones se encontraron en la reacción de dihidroxilación, ya que en casi todos los casos ensayados se produjo la oxidación del azufre, lo que

conduciría al cambio de la selectividad en posteriores etapas como la ciclación. Se consiguió evitar la oxidación utilizando ligandos quirales en la dihidroxilación, pero con rendimientos muy bajos no compatibles con un esquema de síntesis por etapas.

Alternativamente se exploró otra vía de síntesis a partir del aldehído **17**, pero la síntesis del intermedio **16** tampoco pudo culminarse con éxito.



Esquema 3. Retrosíntesis de **18**.

CHAPTER I

GENERAL INTRODUCTION

1.1. Introduction

The present thesis deals with the development of methodology for the syntheses of several organic molecules that were selected by their interesting biological properties: the antibiotic AT2433-A1, the glycosidase inhibidor nectrisine and analogs of the anti-viral Cidofovir (Figure 1.1) . Although apparently structurally unrelated, they were envisaged to be synthesized through common high-efficient key steps that involve metal-catalyzed process.

On this section, a brief overview on the target molecules will be presented, leaving for the corresponding chapters a more detailed examination. In addition, the key issues of the metal-catalyzed processes involved in the syntheses will be discussed.

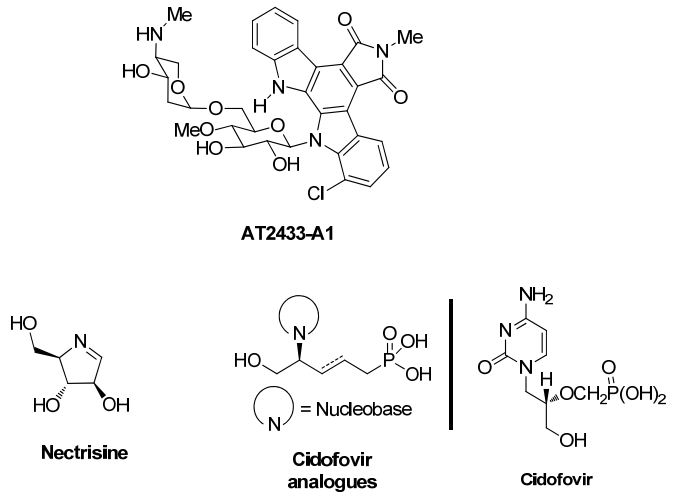


Figure 1.1. Structures of AT2433-A1, nectrisine and cidofovir analogues

1.1.1. Azasugars

Polyhydroxylated nitrogen heterocycle aza-sugars may be considered to be mimics of sugars in which the ring oxygen has been substituted for a nitrogen atom.[1] The often potent inhibitory activity of many of these compounds toward carbohydrate-processing enzymes has suggested their use in a wide range of potential therapeutic

[1] a) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199-210. b) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637-651. c) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645-1680

strategies including the treatment of viral infections,[2] cancer,[3] diabetes,[4] tuberculosis,[5] lysosomal storage diseases,[6] and parasitic protozoa.[7]

Nectrisine is an azasugar isolated from a strain of the fungus *Nectricine lucida* (Figure 1.1) as immunomodulator FR-900483[8] and found to exhibit inhibitory activity on α–glycosidases.Moreover, nectrisine is involved in the prevention of different diseases such as Newcastle disease virus. Due to this important biological activity many organic chemists are focused on the development of new methods to synthesize nectrisine.

1.1.2. Acyclic Nucleoside phosphonates

In the last few years the ever-growing interest in the field of nucleosides and nucleotides has led to renewed efforts in the synthesis of analogues. Nucleosides are fundamental building blocks of biological systems and show a wide range of biological activity. They are sequentially phosphorylated by kinases into their mono-, di- and tri-phosphates and the resultant nucleotides are processed into nucleic acids by polymerases. [9,10] Modifications in the sugar moiety are one of the most important kind

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2 Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci., U.S.A.* **1988**, *85*, 9229-9233.

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7 a) Li, C. M.; Tyler, P. C.; Furneaux, R. H.;. Kicska, G.; Xu, Y. M.; Grubmeyer, C.; Girvin, M. E.; Schramm, V. L. *Nat. Struct. Biol.* **1999**, *6*, 582-587. b) Miles, R. W.; Tyler, P. C.; Evans, G. B.; Furneaux, R. H.; Parkin, D. W.; Schramm, V. L. *Biochemistry* **1999**, *38*, 13147-13154.

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10 Townsend, L. B., Ed., *Chemistry of Nucleosides and Nucleotides*. Plenum Press:New York, **1988**.

of nucleoside derivatives that can lead to promising chemotherapeutic agents.[11] These compounds have attracted much attention as potential antiviral and anticancer agents.[12]

Since the latter part of the 1980s, nucleoside analogs have been investigated with renewed urgency in the search for effective agents against the human immunodeficiency virus (HIV), the causative agent of the AIDS epidemic, in addition to more effective treatment for other viral infections which can prove lethal to AIDS patients and other immuno-compromised individuals.[13,14]

Acyclic nucleosides consist of a familly of nucleosides with a disconnected chain resulting from the omission of bonds from the pentose or cyclopentane rings.

Acyclic nucleoside phosphonates[15] possess a phosphonate group attached to the acyclic nucleoside moiety through a stable P-C bond. In contrast to the phosphate group (which is attached through a P-O-C bond), a phosphonate group (P-C bound) cannot be cleaved off by cellular hydrolases (esterases). Foremost among the acyclic nucleoside phosphonates that have been pursued as antiviral agents are cidofovir (HPMPC) [(*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine], adefovir (PMEA) [9-(2-phosphonylmethoxyethyl)adenine], and tenofovir (PMPA) [(*R*)-9-(2-phosphonylmethoxypropyl) adenine] (Figure 1.2).

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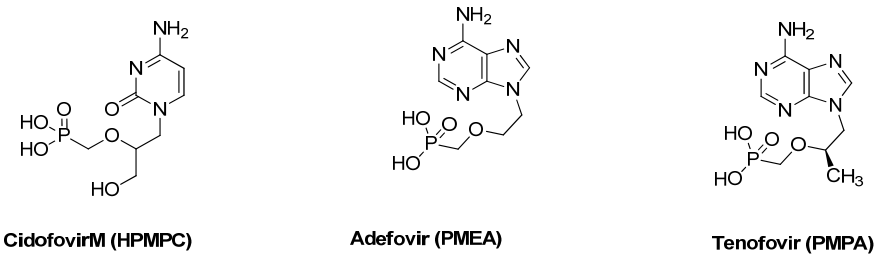

Figure 1.2. Structures of some acyclic nucleoside phosphonates

1.1.3. Deoxyglycosides

Glycoconjugates form a complex group of biomolecules with an unsurpassed structural diversity, performing a variety of biological functions. They play thereby a fundamental role in the development, growth, and functioning of cells and living organisms.[16] Their almost omnipresent occurrence has generated great interest in biology and chemistry. Thus, development of carbohydrate-based therapies has increased the demand for plenty quantities of pure oligosaccharides. However, their isolation from natural sources is very difficult, involving tedious purifications, and it only provides small quantities of material that often lacks the required degree of purity for detailed biochemical studies. Therefore, the synthesis of polysaccharides having defined structures has become an important field of research.[17]

Glycoproteins with *N*-glycans found on cell surfaces and in the blood serum play important roles in many biological events such as cell-cell adhesion, immune system modulation, and signal transduction. Subtle changes of the carbohydrate moieties may result in completely altered functionality of the glycoproteins. Therefore, asparagine linked *N*-glycans have gained intensive investigations.[18]Actually, only a few of these oligosaccharides can be isolated from natural sources due to their microheterogeneity.[19]

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16 Varki, A. Glycobiology, **1993**, *3*, 97–130.

17 a) Weijers, C. A. G. M.; Franssen, M. C. R.; Visser, G. M. *Biotech. Adv.* **2008**, *26*, 436–456. b) Pukin, A. V.; Weijers, C. A. G. M.; van Lagen, B.; Wechselberger, R.; Sun, B.; Gilbert, M.; Karwaski, M. F.; Florack, D. E. A.; Jacobs, B. C.; Tio-Gillen, A. P.; van Belkum, A. F.; Endtz, H. P.; Visser, G. M.; Zuilhof, H. *Carbohydr. Res.* **2008**, *343*, 636–650. (c) Hölemann, A.; Seeberger P. H. *Curr. Opin. Biotechnol.* **2004**, *15*, 615–622. d) Koeller, K. M.; Wong. C. H. *Glycobiology,* **2000**, *10*, 1157–1169.

18 Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Stanley, P.; Bertozzi, C. R.; Hart, G. W.; Etzler, M. E.; Eds. *Essentials of Glycobiology*, 2nd ed.; Cold Spring Harbor Laboratory Press: NY, **2009**.

19 a) Endo, T. *J. Chromatogr. A.* **1996**, *720*, 251–261. b) Rice, K. G. *Anal. Biochem.* **2000**, *283*, 10–16.

These circumstances have stimulated the chemical synthesis of *N*-glycans as a method to provide sufficient quantities for further research.[20]

2-Deoxy- and 2,6-dideoxyglycosides are structural units present in many natural products. Deoxysugars are defined carbohydrates with a substitution of one or more of the hydroxylic groups by another heteroatom or hydrogen. These compounds present varied interesting biological properties, among which we hightlight that as antitumor agents (anthracyclines like Cyclamycine 0, angucyclines like Landomycine A and indolocarbazole glycosides like the antibiotic AT2433-A1 (Figure 1.3).[21] Although the pharmacological effect of these compounds is associated to the aglycone moiety, the oligosaccharidic part is essential for the biological activity because it influences the pharmacokinetic properties, and participates in the molecular recognition. Removing deoxysugars from these clinically important molecules often severely decreases their efficiency and/or specificity.[22] Due to this biological relevance, the development of methods for the efficient, chemo- and stereoselective construction of glycosidic linkages in deoxyglycosides has useful applications in medicinal and bioorganic chemistry by further understanding the biological mechanisms and elaborate new and less toxic drugs.

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20 a) Ogawa, T.; Sugimoto, M.; Kitajima, T.; Sadozai, K. K.; Nukada, T. *Tetrahedron Lett.* **1986**, *27*, 5739–5742. b) Nukada, T.; Kitajima, T.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1992**, *228*, 157–170.

21 Chisholm, J.D.; Van Vranken, D.L. *J. Org. Chem.* **2000**, *65*, 7541–7553.

22 Kren, V.; Martínková, L. *Curr. Med. Chem.* **2001**, *8*, 1313–1338.

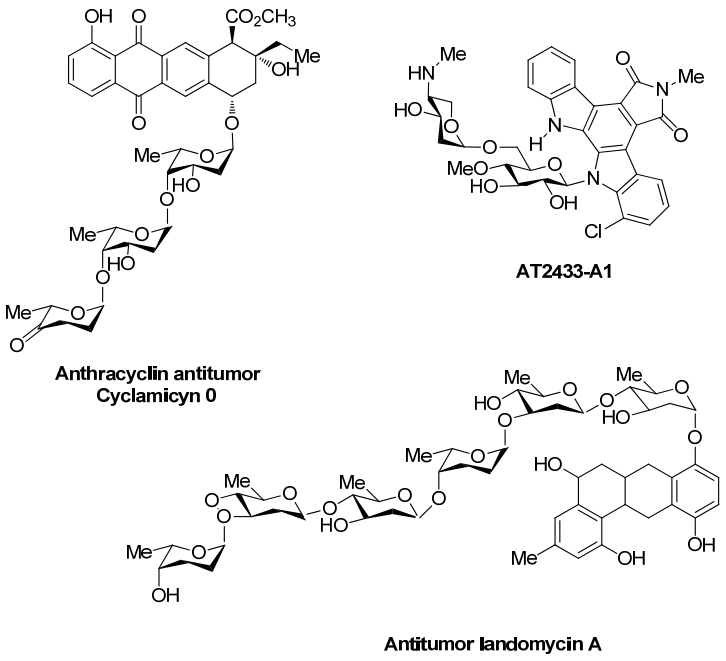

Figure 1.3.. Examples of natural compounds with 2,6-dideoxyoligosaccharide units.

1.2. Background

1.2.1. Synthesis of Allyl Amines by Pd-catalyzed Asymmetric Allylic Alkylation

Transition metal-catalyzed Asymmetric Allylic Alkylation (AAA) reactions have proven to be extremely useful and versatile synthetic transformations. Transition metals such as iron, cobalt, nickel, molybdenum, ruthenium, rhodium, tungsten and platinum have been used for this purpose.[23] However, iridium,[24] palladium[25] and copper[26] have

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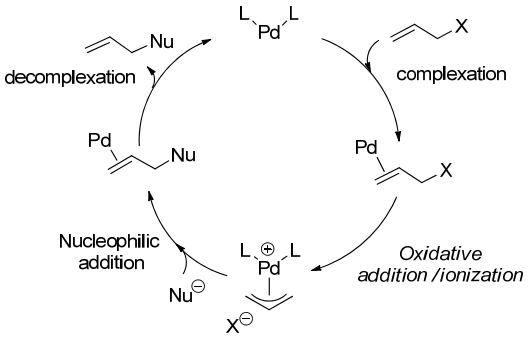
[23] For selected publications see : a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813–5837. b) Mori, M. *Chem. Pharm. Bull.* **2005**, *53*, 457-470. c) Trost, B. M.; Crawley. *Chem. Rev.* **2003**, *103*, 2921-2943. d) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159–167. e) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857-871. f) Trost, B. M. *Pure. Appl. Chem.* **1996**, *68*, 779–784.

[24] For selected publications see: a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164–15165. b) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525–9534. c) Kiener, C. A.; Shu, C. T.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272-14273. d) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025–8026. e) Garcia-Yebra, C.; Janssen, J. P.; Rominger, F.; Helmchen, G. *Organometallics* **2004**, *23*, 5459–5470. f) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595–4597.

[25] For selected publications see: a) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747–760. b). Trost, B. M.; Horne, D. B., Woltering, M. *J. Chem. Eur. J.* **2006**, *12*, 6607–6620. **2006**, *45*, 5246-5248. d) Hirakawa, T.; Ikeda, K.; Ogasa, H.; Kawatsura, M.; Itoh, T. *Synlett* **2010**, *19*, 2887–2890. e) Shi, C.; Chein, C.-W.; Ojima, I. *Chem. Asian J.* **2011**, *6*, 674–680.

[26] For selected publications see: a) Falciola, C. A.; Alxakis, A. *Eur. J. Org. Chem.* **2008**, 3765–3780. b) Geurts, K.; Fletcher, S. P.; Van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008**, *80*, 1025–1037.

been more extensively used. Among them, palladium has so far proven to be the most versatile metal catalyst for these transformations because its easy manipulation, high catalytic activity and high enantioselectivity. Scheme 1.1 shows the catalytic cycle accepted for the Pd-catalyzed allylic alkylation.



Scheme 1.1. Catalytic cycle of the Pd-catalyzed allylic alkylation

Catalytic asymmetric allylic alkylation differs from virtually all other catalytic processes in two important ways. In the first, there are many enantiodiscriminating mechanisms, not just one. As shown in Scheme 1.2, there are at least five such mechanisms.[27] As in most other catalytic asymmetric reactions, differentiating the enantiotopic faces of a π-unsaturation is one mechanism (Scheme 1.2, **A**). A second mechanism is differentiating enantiopic leaving groups (Figure 1.5, **B**). Mechanism **C** involves differentiating enantiotopic termini of a π-allylmetal intermediate. Since this intermediate derives from a chiral racemic precursor in which the chirality of the substrate is lost, this deracemization constitutes a dynamic kinetic asymmetric transformation (DYKAT). Mechanism **D** is a variant of mechanism **A** wherein the π-allylmetal intermediates interconvert faster than they are attacked by a nucleophile and asymmetric induction derives from differential rates of reaction of the two diastereomeric intermediates. This mechanism allows employment of either an achiral precursor or a racemic chiral precursor, the latter then corresponding to a DYKAT. All of the foregoing involves creation of chirality at the π-allyl fragment. Mechanism **E** involves discriminating between the enantiotopic faces of the nucleophile.

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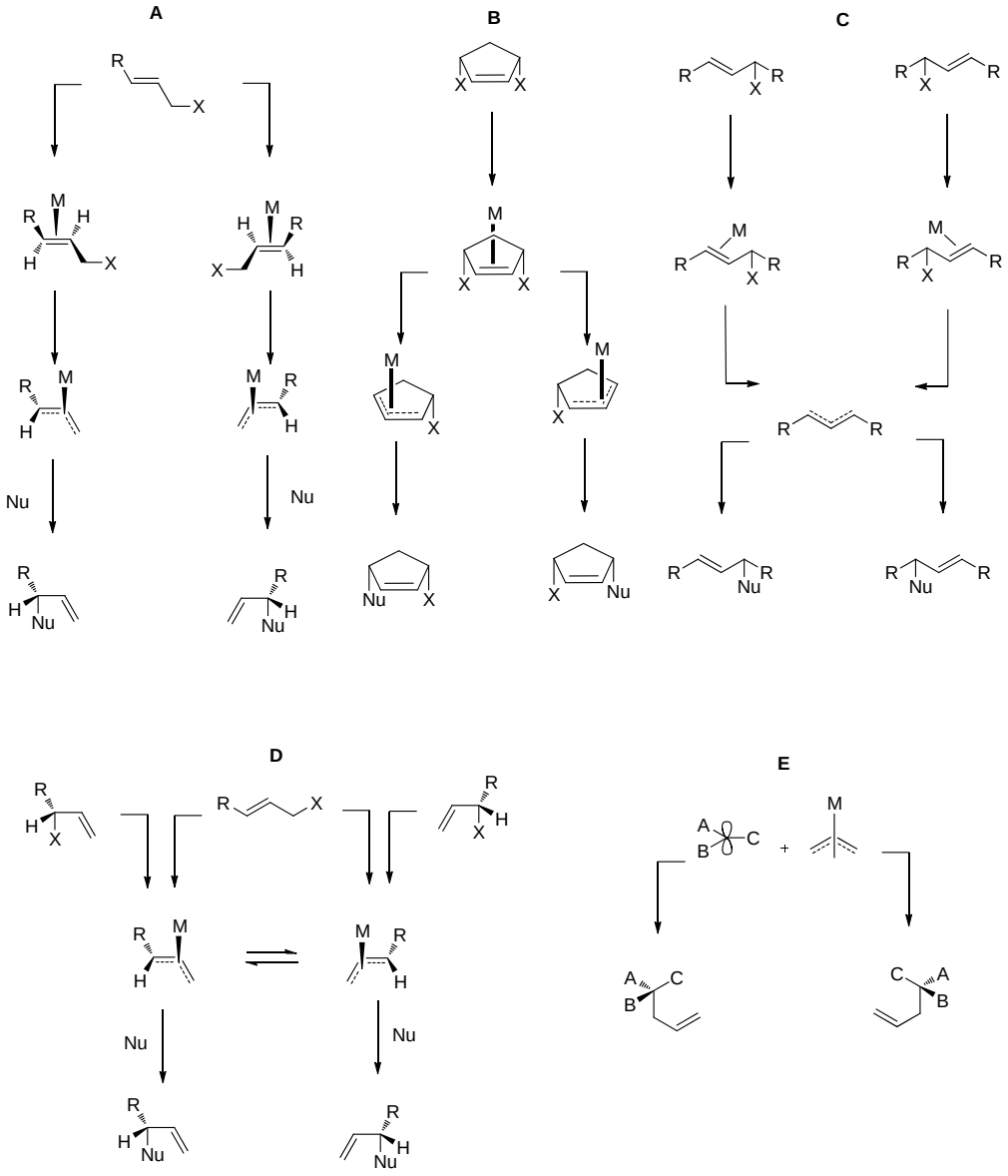
27 Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1–14



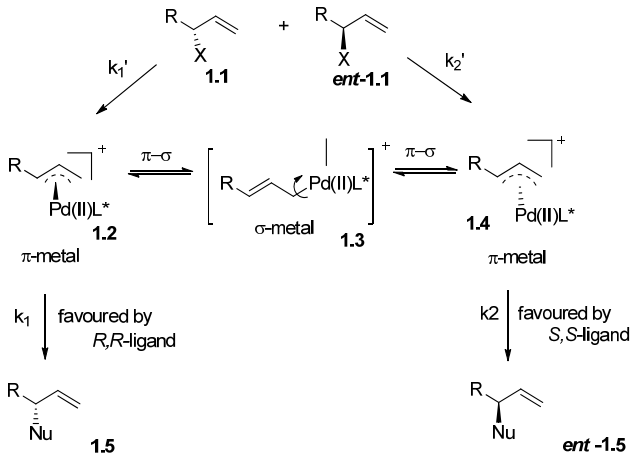
Scheme 1.2. Various Enantiodiscriminating Events in AAA[27]

DYKAT through rapid π–σ–π interconversion of intermediates[28]

This process relies on the rapid interfacial exchange of the allyl ligand through a π–σ–π interconversion. Oxidative addition with inversion of each substrate enantiomer initially forms two diastereomeric π-allyl-Pd(II) intermediates (Scheme 1.3). With a

28 a) Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59–72. b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976. c) Eliel, E. L.; Wilen, S. H. Stereochemistry of organic compounds. Wiley Interscience. **1992**.

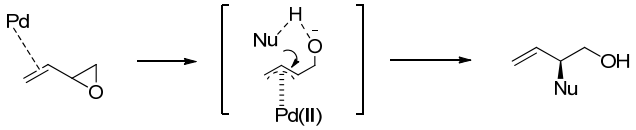
chiral catalyst, a rate difference in the oxidative addition is expected, and a DYKAT occurs with complete comsumption of the mismatched substrate. Asymmetric induction results from the preferential alkylation of one diastereomer intermediate over the other. Accordingly, high enantioselectivity is achieved when, in addition to a selective alkylation (k1>>>k2), a Curtin-Hammett condition is established wherein interconversion is rapid and succesfully competes with nucleophilic addition. Another requirement for this type of DYKAT is the existence of identical geminal substituents on one side of the allyl ligand. If one of the terminus of the allyl ligand is substituted with diferent geminal groups, then the π–σ–π interconversion will result in a geometrical isomerization of the allyl ligand. These π-allylPd(II) intermediates cannot "racemize" through a π–σ–π mechanism. Further complicating the alkylation with unsymmetrical substrates is alkylation at the diferent termini, which leads to regioisomers. Regioselectivity in the AAA has been achieved by both substrate and catalyst control. Although the chiral catalyst provides a significant preference for a regioselective alkylation of one diastereomeric intermediate, optimization of the reaction conditions is often necessary to establish the Curtin-Hammett situation for asymmetric induction.



Scheme 1.3. DYKAT through a π–σ–π-interconversion

A versatil substrate for the palladium-catalyzed dynamic kinetic alkylation AAA is vinyl epoxide, which, due to the ring strain, promotes the oxidative addition and consumption of the mismatched enantiomer required for a DYKAT. Suitable vinyl

epoxides have geminal hydrogens or other identical geminal substituents on the olefin terminus, enabling a Curtin-Hammett condition to be established through a rapid π–σ–π interconversion. In the π–allylPd(II) intermediates, the alcohol or alkoxide can direct the alkylation for the branced products typically through hydrogen bonding or other convalent interaction with the incoming nucleophile (Scheme 1.4).



Scheme 1.4. Regioselectivity of the AAA by substrate control using vinyl epoxide

Vinyl epoxides have shown a broad utility in Pd-catalyzed DYKAT with oxygen[29], carbon[30] and some nitrogen[31] nucleophiles. As far as the reactant is concerned, nitrogen nucleophiles have generally presented challenges in several aspects. First, double alkylation frequently occurs with primary amines since the product, a secondary amine, is more nucleophilic than the starting material, leading to mixtures of products. Second, regioselectivity of the substitution with unsymmetrical allyl systems can be a significant problem and frequently mixtures of products are obtained.

In the palladium-catalyzed process of butadiene monoepoxide, Trost and co-workers studied different nucleophiles that could coordinate to the leaving group in order to improve the regioselectivity. In this sense, sulfonamide and imide nucleophiles have been effectively employed, in particular, phthalimide, an excellent primary amine surrogate, has shown to provide more enantioselection than other imido nucleophiles.

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29 Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702–12703.

30 Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907–12908.

31 A) Trost, B. M.; Bunt, R.C.; Lemoine, R.C.; Calkins, T.L. *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976. b) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett.* **1998**, *39*, 1713–1716.

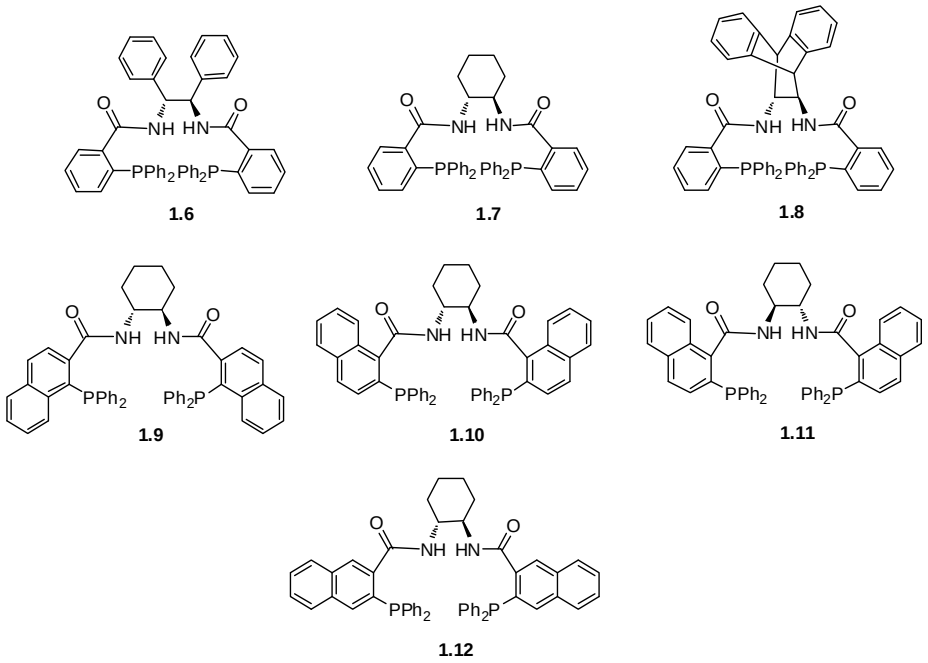

Figure 1.4. Chiral ligands developed by Trost for asymmetric allylic transformations

As for the chiral ligand used in these processes, although BINAP-based ligands have been examined for the DYKAT of vinyl epoxides,[32] high enantioselectivities for the intermolecular addition of nucleophiles to vinyl epoxides typically required the use of diphenylphosphinobenzoic acid (DPPBA) derived ligands. Thus, the ligands studied by Trost and col. (Figure 1.4) in order to effect this transformation were designed taking into account the following issues: i) creating a chiral space with an array of groups whose conformational bais originate from primary stereogenic centers; ii) electronic desymmetrization on the donor atoms of the ligand where different bond lengths on each side of the chiral space promote different reactivity at each terminus. These reactions allowed the use of a broad range of nucleophiles and enabled application of this approach to numerous total syntheses. The AAA of butadiene monoepoxide (**1.13**) with phthalimide **1.14** provided 2-(*S*)-*N*-phthalimido-3-buten-1-ol (**1.15**) (Scheme 1.5) in high regioselectivity, enantioselectivity (>98%) and yield (99%).[33] The obtained

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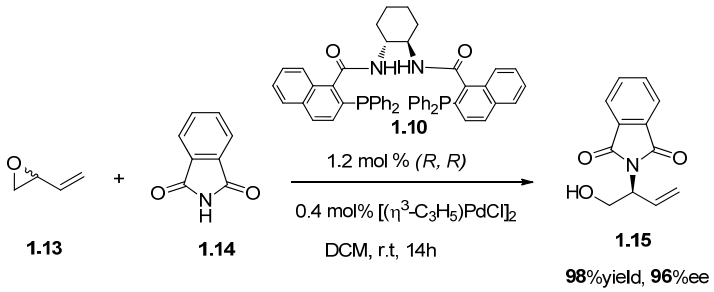
32 a) Hayashi, T.; Yamamoto, a.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99. b) Larksarp, C.; Alper, H. *J. Am. Chem. Soc*. **1997**, *119*, 3709-3715.

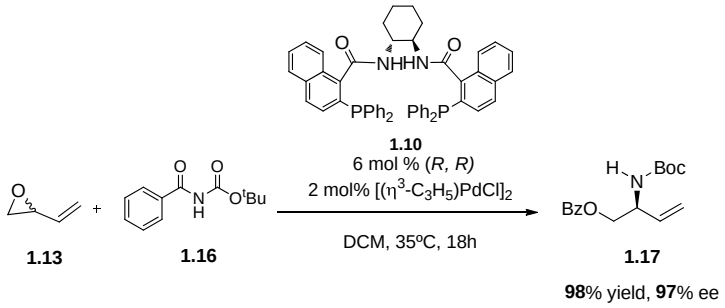
33 a) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5987–5990. b) Harris, M. C. J.; Jackson, M.; Lennon, I. C.; Ramsden, J. A.; Samuel, H. *Tetrahedron Lett.* **2000**, *41*, 3187–3191. c) Trost, B. M.; O'Boyle, B. M. *Org. Lett.* **2008**, *10*, 1369-1372. d) Trost, B. M.; Lemoine, R. C. *Tertrahedron* **1996**, *37*, 9161–9164.

intermediate **1.15** is a useful starting material in the synthesis of different natural products.[27]



Scheme 1.5. Synthesis of 2-(*S*)-*N*-phthalimido-3-buten-1-ol (**1.15)**

Vinylglycinol **1.17** was obtained directly via palladium-catalyzed allylic substitution from butadiene monoepoxide (**1.13**) using 2 mol% of $[(\eta^3\text{-}C_3H_5)PdCl]_2$, 6% of (*R,R*)-DACH-Naphtyl using the corresponding imide **1.16** to afford the desired compound in an 98% yield and 97% ee (Scheme 1.6).[34]



Scheme 1.6. Synthesis of (*S*) –*ter*-butyl-1-benzoyloxybut-3-ene-2-yl-carbamate (**1.19**)

The initial proposal by Trost was that a hydrogen-bonding interaction between the alkoxide of the π-allylPd(II) intermediate and the nucleophile would direct the alkylation. Reactions with triphenylphosphine still favored the branched product with a slightly lower regioselectivity (4:1 branched/linear). Without directing effects, the linear product is favored due to alkylation at the least sterically hindered position. Therefore, both the substrate and catalyst contribute to the high regioselectivity observed in the DYKAT.

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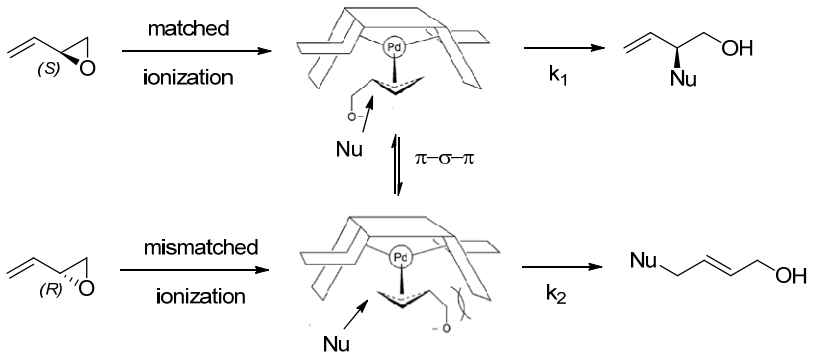
34 Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stilles, D. T. *Angew. Chem. Int. Ed.* **2007**, *46*, 6123–6125.

The asymmetric induction obtained in the allylic alkylations with DPPBA ligands is rationalized by the preferential ionization and alkylation occurring under a flap in the "nun's hat" model (Scheme 1.7).[35] In this model, the walls represent the chiral space created by the propeller-like array of the phenyl rings; the raised flaps represent the phenyls which lie in a plane approximately parallel to the allyl, while the lowered flaps represent the phenyls which are somewhat perpendicular to the allyl. Minimizing any steric interactions between the approaching nucleophile and the chiral ligand also directs it to approach from the front left quadrant. On the other hand, the ligand must afford a chiral environement in which one of the diastereomeric π-allyl complex is favoured, being both diastereomeric species equilibrated faster than nucleophilic attack to achieve a dynamic kinetic asymmetric transformation. The matched alkylation of the mismatched intermediate would favor the linear product, and the matched-intermediate matched alkylation would favor the branched product (Scheme 1.7). Halide additives increase the rate of the necessary interconversion,[36] and improve the regioselectivity by promoting the necessary Curtin-Hammett condition, thus allowing for the prefrerred matched alkylation of the matched intermediate.



Scheme 1.7. Rationalization of the Regioselectivity in the alkylation with DPPBA ligands

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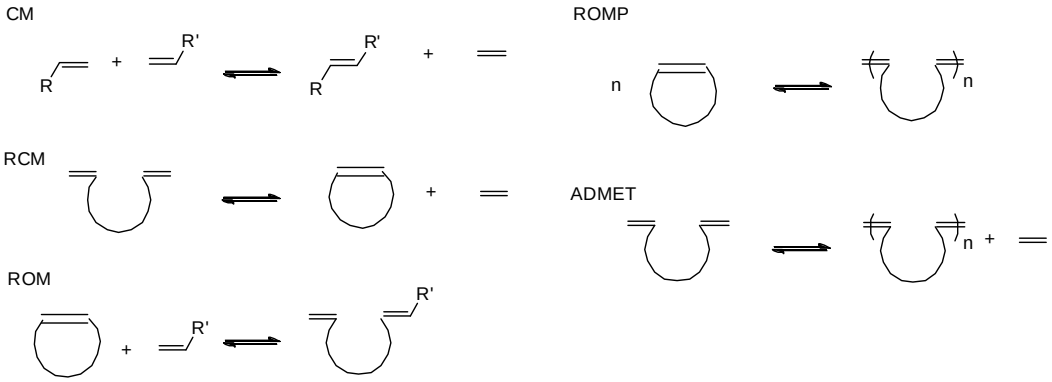
35 a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554. b) Hayashi, T.; Kawatsumura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681–1687.

36 Burckhardt, U.; Baumnann, M.; Togni, A. *Tetrahedron: Asymmet*ry **1997**, *8*, 155-159.

1.2.2. Cross-metathesis reaction

Olefin metathesis transformation entails a redistribution of alkylidene fragments by the scission of carbon-carbon double bonds in two olefin moieties. It can be used in five closely related types of reactions: cross metathesis (CM), ring-opening metathesis polymeration (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMET) and ring-opening metathesis (ROM) (Scheme 1.8).



Scheme 1.8. Types of olefin metathesis

Over the years, olefin cross metathesis (CM) has become a powerful method for the formation of carbon-carbon double bonds[37] while reducing formation of undesired self metathesis product. In comparison with the classical olefination Wittig reaction, cross metathesis reaction is an economical atom reaction since ethylene is the secondary product. Moreover, contrary to other cross-coupling processes, such as Stille or the Miyaura-Suzuki reactions, in cross-metathesis no sophisticated coupling partners need to be prepared.[38]

The first metallic systems used in metathesis reactions consisted on transition metal salts combined with main group alkylating agents or deposited on solid supports. The classic combinations include WCl_6/Bu_4Sn, $WOCl_4/EtAlCl_2$, MoO_3/SiO_2 and Re_2O_7/Al_2O_3, among many others. The utility of these catalysts were limited by the harsh conditions and the strong Lewis acids required. Many mechanistic proposals have

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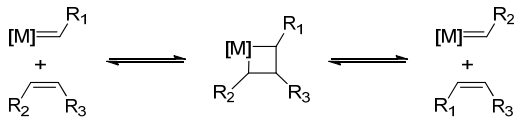
37 Cossy, J.; Arseniyadis, S.; Meyer, C. *Metathesis in Natural Product Synthesis*, **2010**, Willey-VCH, Weinheim.

38 Grubbs, R. H. *Handbook of Metathesis 2*, **2009**, Willey-VCH, Weinheim.

been suggested for this reaction over the years, but the one proposed by Chauvin was found to be the most consistent with the experimental evidences and it remains the generally accepted mechanism. Chauvin proposed that olefin metathesis involves the interconversion of an olefin and a metal alkylidene. This process is believed to occur via a metallacyclobutane intermediate by alternating [2+2] cycloadditions and cycloreversions (Scheme 1.9).[39]



Scheme 1.9. Mechanism of olefin metathesis proposed by Chauvin

The first single-component homogeneous catalyst for olefin metathesis was developed during the late 1970s and early 1980s and involved alkoxide-alkylidene tungsten complexes. These new catalysts included $[(CO)_5W{=}CPh_2]$,[40] bis(cyclopentadienyl)titanocyclobutanes[41] and various dihalo-alkoxide-alkylidene complexes of tungsten.[42,43] As well-defined complexes, these catalysts exhibited better initiation times and higher activity under milder conditions than ever before. The molybdenum and tungsten alkylidenes with the general formula $(NAr)(OR')_2M{=}CHR$ were the first of these catalysts to become widely used, in particular the molybdenum complex **1.18** or the more active **1.19** (Figure 1.6) developed by Schrock and co-workers.[44,45] These catalysts and others based on the early transition metals are highly

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39 Hérrison, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161–176

40 a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737–738. b) Katz, T. J.; Lee, S. J.; Acton, N. *Tetrahedron Lett.* **1976**, *47*, 4247–4250.

41 Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907–915

42 Wallace, K. C.; Liu, A. H.; Dewan, J. C.; Schrock, R. R. *J. Am. Chem. Soc.* **1988**, *110*, 4964–4977.

43 a) Kress, J.; Osborn, J. A.; Greene, R. M. E.; Ivin, K. J.; Rooney, J. J. *J.Am. Chem. Soc*. **1987**, *109*, 899–901. b) Kress, J.; Aguero, A.; Osborn, J. A. *J. Mol. Catal.* **1986**, *36*, 1–12. c) Quignard, F.; Leconte, M.; Basset, J.-M. *J. Chem. Soc., Chem. Commun.* **1985**, 1816–1817.

44 a) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R.R. *J. Am. Chem. Soc.* **1991**, *113*, 6899–6907. b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378–8387. c) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886. d) Schrock, R. R.; Feldman, J.; Cannizzo, L. F.; Grubbs, R. H. *Macromolecules* **1987**, *20*, 1169–1172.

45 For reviews of this area, see: (a) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141-8153. (b) Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158–165.

active, long-lived catalyst systems and do not require Lewis acidic co-catalyst or promoters. However, they show moderate to poor functional group tolerance, high sensibility to air and moisture or even to trace impurities present in solvents, thermal instability on storage and they suffer from expensive preparation.

The ruthenium vinylidene complex $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (**1.20**) (Figure 1.5) has been used extensively in organic chemistry due to its high reactivity with olefinic substrates in the presence of most common functional groups.[46]

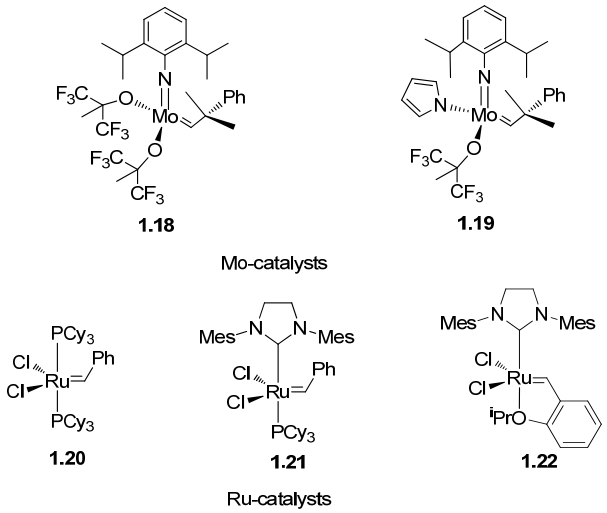


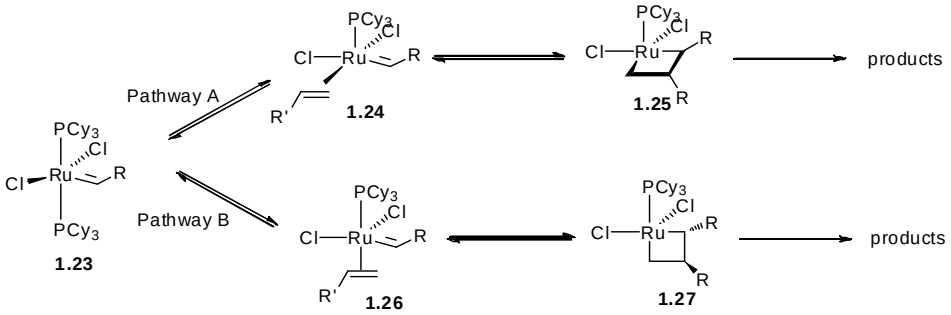
Figure 1.5. Schrock, Grubbs and Hoveyda-Grubbs catalysts

The mechanism of olefin metathesis reactions catalyzed by ruthenium complex **1.24** and its analogues has been the subject of an intense experimental and theoretical investigation, with the ultimate goal of facilitating the rational design of new catalysts displaying higher activity, stability and selectivity.

As illustrated in Scheme 1.10, the first step involves olefin coordination to the metal center, presumably *cis* to the alkylidene and concominant phosphine dissociation. In one possible pathway (Scheme 1.10, A), alkylidene rotation occurs in order to generate the intermediate, in which the olefin remains *cis* to the alkylidene. This intermediate then undergoes metallocyclobutane formation *cis* to the bound phosphine, followed by cleavage to release the metathesis products. An alternative pathway (Scheme 1.10, B) involves phosphine dissociation and rearrangement of the olefin *trans*

[46] Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.

to the remaining phosphine. Then, this intermediate **1.26** undergoes metallacyclobutane formation *trans* to the phosphine **1.27**.



Scheme 1.10. Proposed mechanism of olefin metathesis for $(PCy_3)_2Cl_2Ru{=}CHR$

Early mechanistic studies of the catalyst established that phosphine dissociation is a critical step along the olefin metathesis reaction. Catalysts containing sterically bulky and electron-donating phosphine ligands have been demostrated led to display the highest catalytic activity. This trend was explained on the basis of the increased *trans*-effect of larger and more basic/donating phosphines. One of the contributions of the phosphine ligands is σ-donation to the metal center, which promotes the formation of the mono-(phosphine) olefin complex by facilitating phosphine dissociation and stabilizing the vacant *trans* site. Even more importantly, σ-donation helps to stabilize the 14-electron metallacyclobutane intermediate. The steric bulk of the ligands may also contribute to phosphine dissociation by destabilizing the crowded bis(phosphine) olefin complex.

On the basis of these important studies, a new class of ruthenium alkylidenes containing *N*-heterocyclic carbenes ligands (NHC) (**1.21-1.22**) has been developed (Figure 1.5), which are significantly larger and more electron donating than trialkylphosphines. This second generation of ruthenium olefin metathesis catalysts exhibit dramatically increased reactivity with olefin substrates. The high activity of the *N*-heterocyclic carbene has previously been attributed to its ability to promote phosphine dissociation.[47, 48]

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47 Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749–750.

48 Khan, R. K. M.; O´Brien, R. V.; Li. B.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2012**, 134, 12774–12779.

Olefin metathesis has become a standard synthetic method because of the wide variety of applications. The activity and functional group tolerance of ruthenium catalyst is now sufficiently high for olefin metathesis to compete with more traditional carbon-carbon bond-forming methods. Unfortunately, ruthenium catalysts are limited by incompatibility with basic functional groups, notably nitriles and amines.

In particular, attractive features of ruthenium-catalyzed cross metathesis olefination are: i) high *E*/*Z*-selectivity with good yield in the product, ii) functional group tolerance, iii) high activity providing high yields under mild conditions and iv) reasonable ability in the presence of amino functionality.[49] Minimization of unproductive alkenes from self-metathesis and consequently maximization of productive cross metathesis is a crucial issue to be optimized.

This reaction has recently attracted widespread attention as a versatile and powerful tool for the construction of complex biologically active natural products.[50] In this context, *E*-selective cross-metathesis olefination has been used to synthesize compound **1.29**, which has an *E* double bond in its skeleton (Scheme 1.11). Grubbs and co-workers observed that cross-metathesis between compounds like esters, aldehydes, and ketones and simple terminal olefins in the presence of Ru-catalyst proceeded in good to excellent yields with impressive *E* selectivity. The compound **1.28** afforded the desired product **1.29** under cross-metathesis raction using Ru-catalyst.[51] In spite of impressive advances accomplished during the past two decades, a number of unresolved issues limited the utility of catalytic olefin metathesis reactions,[52] among which a notable shortcoming was the lack of methods that selectively furnish *Z* alkenes.[53] Nearly all ring-opening/ cross-metathesis (ROCM) reactions catalyzed by Mo or Ru complexes afford *E* olefins exclusively or predominantly.[54,55] Only when the cross

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49 Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.

50 Prunet, J. *Curr. Topics Med. Chem.* **2005**, *5*, 1559–1577.

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52 Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251.

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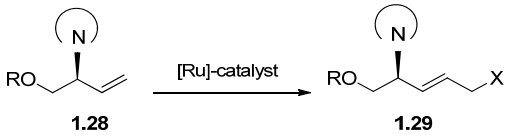
54 Schrader, T. O.; Snapper, M. L. In *Handbook of Metathesis*; Grubbs, R. H., *Ed.; Wiley-VCH: Weinheim, Germany,* **2003**; *2*, 205–245.

55 a) La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767–7778. b) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem.*

partner bears an sp-hybridized substituent (acrylonitrile or an enyne) are Z alkenes, at times, favored.[56] Effective solution to the above critical problem reactions was recently provided in enantioselective ROCM reactions and required the development of structurally distinct catalysts based on an adamantyl-tetrahydroaryloxide-Mo complex,[57] which delivered Z olefins with selectivities that were previously entirely out of reach. These stereogenic-at-Mo monaryloxypyrrolides were also sucesfully used in the more challenging Z-selective olefin cross-metathesis reactions and applied to the syntheses of a variety of natural products.[58]



1.28 **1.29**

Scheme 1.11. Synthesis of compound (**1.29**) by a cross-metathesis reaction

1.2.3. Dihydroxylation reaction

Osmium-mediated dihydroxylation reaction is a widely used method in organic synthesis for the transformation of alkenes to 1,2-diols.[59] The asymmetric version expands this powerful reaction to the synthesis of chiral 1,2-diols.[60] A number of features have turned the osmium-catalyzed asymmetric dihydroxylation process into a powerful method for the asymmetric synthesis: i) the reaction is stereospecific leading to 1,2-*cis*-addition of two OH groups to the olefin, ii) it proceeds with high chemoselectivity, iii) the facial selectivity is readily predicted using a simple mnemonic device and exceptions are very rare, iv) it tolerates the presence of most organic functional groups, v) the diols are always derived from *cis*-addition and, side products,

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[58] Meek, S.J.; O'Brien, B.V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461

[59] a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. b) Français, A.; Bedel, O.; Haudrechy, A. *Tetrahedron* **2008**, *64*, 2495–2524.

[60] Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263–4265.

such as epoxides or *trans*-diols are never observed, and vi) it usually exhibits a high catalytic turnover, allowing low catalyst loading and good yields.[61]

Chiral alkaloid derivatives coordinate to osmium tetraoxide through the nitrogen moiety providing a reaction acceleration and asymmetric induction.[62] In addition, the efficiency of the usually employed stoichiometric reoxidant such as N-methyl-morpholine-N-oxide (NMO),[63] potassium ferricyanide (K_3FeCN_6),[64] or *tert*-butyl hydroperoxide (^tBuOH)[65] favours the metal regeneration. The use of water as a solvent is necessary to facilitate the cleavage of the intermediate osmate esters **1.32**, which is the determining step of the reaction and also $CH_3SO_2NH_2$ leads to shorter reaction times.[66]

Much effort has been made to envision the mechanistic features of this reaction[67] and two distinct reaction pathways were proposed to account for the formation of osmium glycolate **1.32**.[68] i) a concerted reaction mechanism involving a pericyclic [3+2] transition state **1.30** (Scheme 1.12, pathway A) [69] and, ii) a stepwise route involving formation of an osmaoxetane **1.31** from formal [2+2] addition of the alkene to OsO_4 followed by expansion of the metallacycle (Scheme 1.12, pathway B).[70] In this regard, computational studies support the metallaoxetane mechanism because of the minimum energy in that intermediate. [71]

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61 Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, **2004**, Wiley-CVH, 2, Weinheim.Kolb, H. C.; Sharpless, K. B.

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63 VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

64 Minato, M.; Yamamoto, K.; Tsujo, J. *J. Org. Chem.* **1990**, *55*, 766–768.

65 Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986–1987.

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68 a) Ojima, I. Catalytic Asymmetric Synthesis, **2000**, 402-406. Willey-VCH, 2nd edition, Canada.

69 Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319–329.

70 Norrby, P.-O.; Becker, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1996**, *118*, 35–42.

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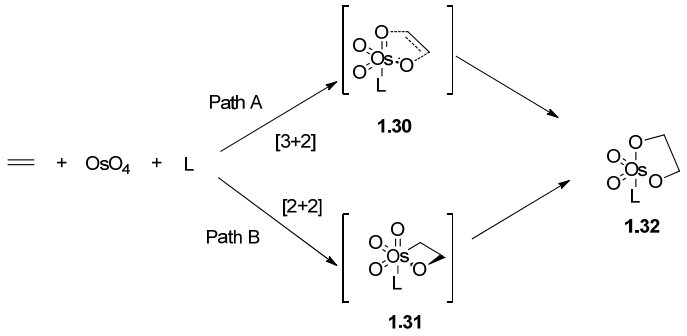

Scheme 1.12. Schematic representation of the concerted [3+2] mechanism (Path A) and the stepwise osmaoxetane mechanism (Path B)

Dihydroquinine and dihydroquinidine, two pseudoenantiomeric alkaloids from cinchona, in combination with different spacers are the ligands of choice for this process.[72] The enantioselectivity is mainly influenced by the nature of the C9 substituent. Initially, CLB (**1.35**) (*p*-chlorobenzoate), MEQ (4-methyl-2-quinolil) (**1.36**) and PHN (phenanthryl ether) (**1.37**) were used as spacers (first generation), however, second generation spacers which are bonded to two chiral ligands such as PHAL (**1.38**) (phthalazine), Pyr (pyrimidine) (**1.39**) and AQN (anthraquinone) (**1.40**) are preferently used (Figure 1.6).

[72] (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H. L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771. (b) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585–4588. (c) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785–3786.

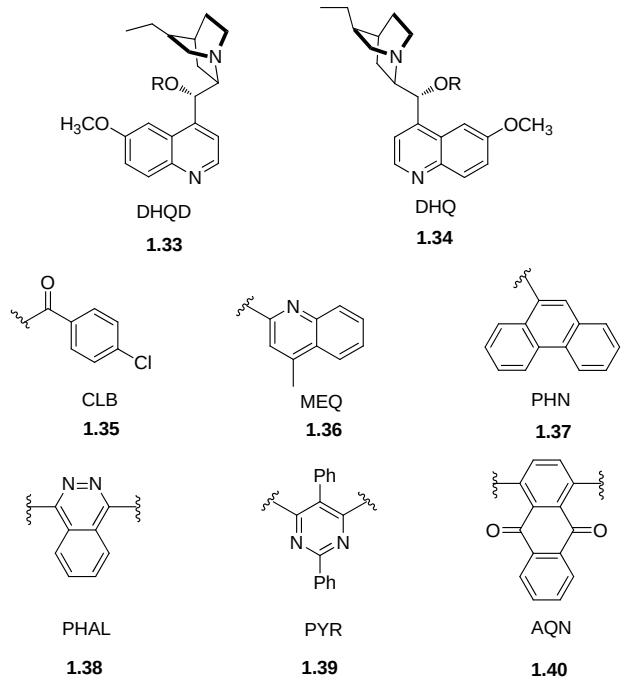

Figure 1.6. Cinchone ligands

Mechanistic studies revealed the presence of a secondary catalytic system as the culprit of the low enantioselectivities found in osmium-catalyzed dihydroxylation. This secondary cycle proceeds with poor-to-no face selectivity, since it does not involve the chiral ligand (Scheme 1.13). The desired path involves the hydrolysis of **1.42** to OsO_4 and the optically active 1,2-diol, whereas the undesired cycle is entered when **1.42** reacts instead with a second molecule of olefin, yielding the osmium (VI) bisglycolate **1.44** and thence 1,2-diol of low enantiopurity.[73] The use of $K_3Fe(CN)_6$ in combination with heterogeneous solvent systems, typically *tert*-butanol/water, allows an olefin osmylation and osmium re-oxidation steps uncoupled, since they occur in different phases. The osmylation takes place in the organic layer, giving rise to the osmium (VI) glycolate **1.42**. This osmium(VI) complex cannot be oxidized to an osmium(VIII) glycolate, because of the absence of the inorganic stoichiometric oxidant $K_3Fe(CN)_6$ in the organic layer. Consequently, the second catalytic cycle cannot occur. This reaction requires hydrolysis of the osmium (VI) glycolate **1.43** to the 1,2-diol and a water soluble inorganic osmium(VI) species, which enters to the basic aqueous layer ready to be oxidized by $K_3Fe(CN)_6$ to OsO_4.

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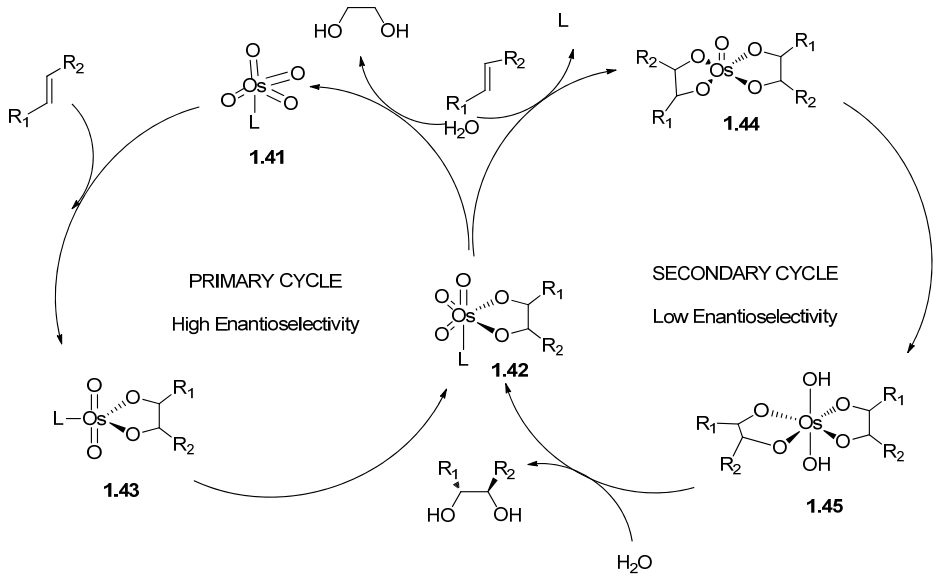
[73] Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123–1125.



Scheme 1.13. Proposed catalytic cycle in osmium-catalyzed dihydroxylation

CHAPTER II

OBJECTIVES

2. Objectives

The research described in this thesis aims to investigate new methods for the stereoselective synthesis of antibiotic AT-2433-A1, Nectrisine and analogues of Cidofovir based on new enantio-, stereo- and diastereoselective methods catalyzed by transition metal complexes (Scheme 2.1).

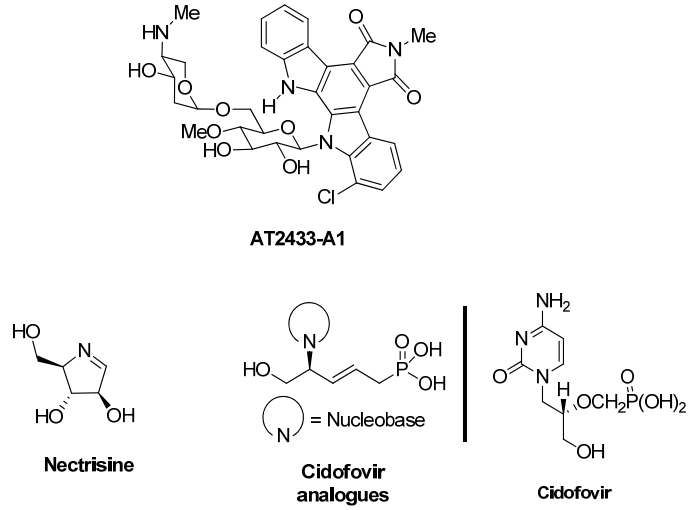


Figure 2.1. Structures of AT2433-A1, nectrisine and cidofovir analogues

In this context, the specific objectives of the present work are the following:

2.1. Enantioselective synthesis of the glycosidic moiety of AT-2433-A1, Nectrisine and analogues of Cidofovir based on the following key reactions:

-Enantioselective synthesis of the key synthon allylamine by asymmetric palladium-catalyzed allylic amination of racemic vinyloxirane with different imido nucleophiles through a Dynamic Kinetic Asymmetric Transformation (DYKAT).

- Study of the ruthenium-catalyzed cross-metathesis reaction of the previously prepared allyl amines with alkenes, in order to obtain different synthetic precursors of target natural products.

- Optimization of the dihydroxylation reaction as one of the key steps in the proposed synthesis of antibiotic AT-2433-A1 and Nectrisine.

In addition, the following issues will be addressed:

2.2. Study of the deprotection and cyclization reaction conditions of the allylic amine intermediate in order to complete the synthesis of the Nectrisine.

2.3. To study hydrogenation reaction for obtaining acyclic nucleoside phosphonates analogues.

CHAPTER III

ENANTIOSELECTIVE SYNTHESIS OF NECTRISINE

UNIVERSITAT ROVIRA I VIRGILI
ENANTISELECTIVE SYNTHESIS OF NATURAL PRODUCTS
Mariam Azzouz

3.1. Introduction

Oligosaccharides have been shown to play important roles in a large number of biological recognition events that range from cell–cell communication, fertilization, and cell differentiation, to pathological processes including cancer metastasis, and inflammation.[74] Iminoanalogues of sugars (also known as azasugars) are known to behave as glycosidase[75] or glycosyltransferase[76] inhibitors by acting as transition state mimics, where the flattened pyrrolidine ring and protonated nitrogen mimic the distorted structure of the glycosyl cation intermediate (Figure 3.1).[77]

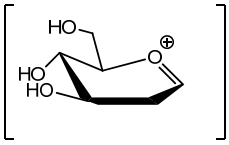


Figure 3.1. Structure of the glycosyl cation intermediate

Hence, this class of sugar mimetics offers therapeutic potential in areas such as inflammatory diseases, lysosomal storage disorders, and cancer.[78] Two of these iminosugars are the pyrrolidine 1,4-dideoxyimino-D-arabinitol (DAB-1) (**3.1**)[79] and the polyhydroxylated dihydropyrrole nectrisine (FR 900483) (**3.2**)[80] (Figure 3.2). These compounds are extremely potent α-glucosidase inhibitors [IC_{50} 1.8×10^{-7} and 4.8×10^{-8} M, respectively (yeast α-glucosidase)] (Figure 3.2).[81 87]

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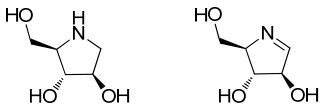

3.1 **3.2**

Figure 3.2. Structures of DAB-1 (**3.1)** and Nectrisine **(3.2)**

Nectrisine (**3.2)** is an azasugar that was isolated from a strain of the fungus *Nectricine lucida* (Figure 3.3) as FR-900483 immunomodulator [80a,81b] and found to exhibit inhibitory activity on α–glycosidases.[82] Moreover, nectrisine is involved in the prevention of different diseases such as Newcastle disease virus.[81b] Due to this important biological activity many organic chemists are focused on the development of new methods to synthesize nectrisine.

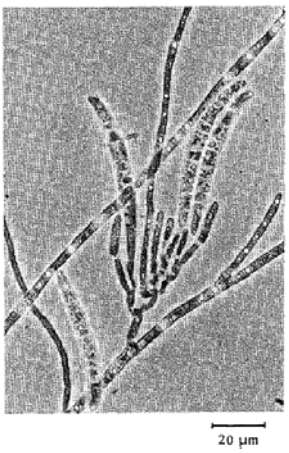

Figure 3.3. Microphotograph of anamorph of strain F-4490[80a]

3.1.1. Physico-chemical Properties[80a]

Nectrisine is a colorless powder (m.p.= 75ºC, $[\alpha]_D^{23}$= +22° (*c* 0.55, H_2O)) soluble in water, slightly soluble in methanol and ethanol and substantially insoluble in acetone, chloroform and ethyl acetate.

3.1.2. Biological activities[80a]

The biological activities of Nectrisine are:

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[82] a) Ganem B., *Acc. Chem. Res*. **1996**, *29*, 340–347. b) Compain, P.; Martin, O.R. *Bioorg. Med. Chem*. **2001**, *9*, 3077–3092. (c) Asano, N. *Glycobiology*. **2003**, *13*, 93R–104R.

- Competitive effect of Nectrisine against immunosuppressive factor obtained from tumor bearing mice serum.[80 a,83]

- Effect of Nectrisine on antibody formation to SRBC (Sheep Red Blood Cells) in the immuno-defecient mice: The administration of FR-900483 reversed the suppressed immuneresponse.[80a,83,84]

- Antimicrobial activity: antimicrobial activity of Nectrisine was determined by a serial broth dilution method in bouillon media for Gram-positive and Gramnegative bacteria and Sabouraud media for fungi and yeast. Nectrisine was devoid of antimicrobial activity when tested versus the following microorganisms at 100 μg/ml; *Escherichia coli*, *Pseudomonas aeruginosa, Bacillus, Staphylococcus aureus*, *Candida albicans*, *Aureobasidium pullulans* and *Aspergillus niger*.[80a]

In addition, Nectrisine exhibited potent inhibitory activity against α-glycoside hydrolase isolated from yeast, gastrointestinal tract of rat or porcine small intestine. Further studies on biological activities of FR-900483 are now in progress.[80a]

3.1.3. Nectrisine as glycosidase inhibitior[81b]

Nectrisine has the structure of 4-amino-4-deoxy-D-arabinose, and previous works have demonstrated its inhibitory activity against α -glucosidase and α -mannosidase as expected from its structure.[80a] To extend this finding, various commercially available glycosidases were tested for their sensitivity to nectrisine. As shown in (Figure 3.4), α-glucosidase was the most sensitive to nectrisine, and the concentration required for the 50% inhibition (IC_{50}) was calculated to be 4.8×10^{-8} M. At higher concentrations, nectrisine inhibited the activities of α-mannosidase, β-mannosidase, β-glucosidase and β-*N*-acetylhexosaminidase, with decreasing sensitivity in that order, and the respective IC_{50} values were 2.0×10^{-6} M, 1.2×10^{-5} M, 4.1×10^{-5} M and $>5.0 \times 10^{-4}$ M.[81b]

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83 Hino, M.; O. Nakayama, Y. Tsurumi, K. Adachi, T. Shibata, H. Terano, M. Kohsaka, H. Aoki.; H. Imanaka. *J. Antibiotics.* **1985**, *38*, 926–935.

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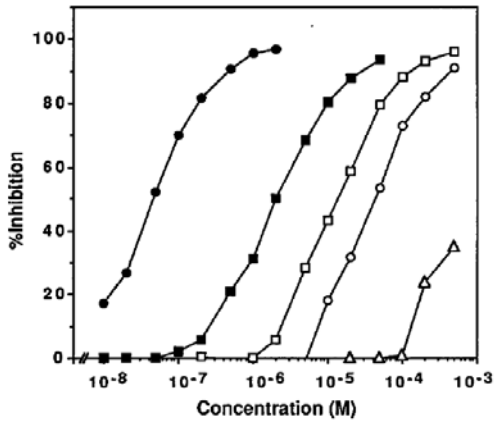
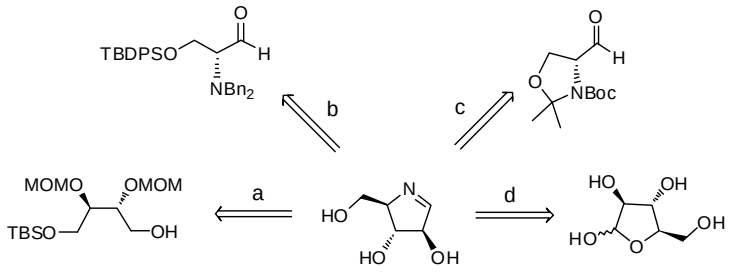


Figure 3.4. Dose dependency of the inhibition of glycosidases by nectrisine. Enzyme solutions were treated with designated concentrations of nectrisine. The amounts of enzymes were as follows: 1 U/ml α-glucosidase (●), 0.5 U/ml, β-glucosidase (○), 0.5 U/ml α-mannosidase (■), 0.1 U/ml β -mannosidase (□), and 0.5 U/ml β -*N*-acetylglucosaminidase (Δ).[81b]

3.1.4. Syntheses of Nectrisine. Background

Nectrisine has been conveniently prepared starting from compounds of the chiral pool like diethyl tartrate (path a),[85,86] aminoacids (path b),[87] Garner aldehyde (path c),[88] and carbohydrates (path d) [89,90] (Scheme 3.1).



3.2

Scheme 3.1. Nectrisine synthesis. Reported procedures

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85 Kim, Y. J.; Takatsuki, A.; Kogoshi, N.; Kitahara, T. *Tetrahedron* **1999**, *55*, 8353–8364.

86 Kim, Y. J.; Kitaraha, T. *Tetrahedron Lett.* **1997**, *38*, 3423–3426.

87 Hulme, A. N.; Montgomery, C.H. *Tetrahedron Lett*. **2003**, *44*, 7649–7653.

88 Ribes, C.; Falomir, E.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2008**, *73*, 7779–7782.

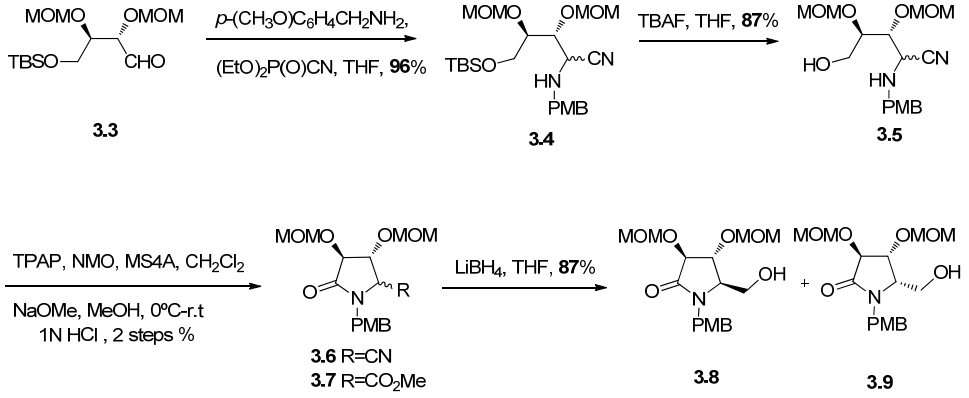
89 Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. Org. Chem.* **2008**, 2929–2947.

90 Bosco, M.; Bisseret, P.; Bouix-Peter C.; Eustache, J. *Tetrahedron Lett.* **2001**, *42*, 7949–7952.

Path a [85,86]

D-(-)-Diethyl tartrate was used as starting material in a synthesis that initially had as objective the preparation of aldehyde intermediate **3.3**. A modified Strecker reaction[91] of the aldehyde **3.3**,[92] with 2.4 eq. of *p*-methoxybenzylamine and 1.2 eq. of diethyl phosphorocyanidate (DEPC) in THF gave aminonitrile **3.4** (2 steps, 96%, Scheme 3.2). The aminonitrile **3.4** was subsequently deprotected with tetra-*n*-butylammonium fluoride (TBAF) in THF to afford the corresponding amino alcohol **3.5** in 87% yield.

The amino alcohol **3.5** was oxidized by reaction with tetra-*n*-propylammonium perruthenate (TPAP)[93] and *N*-methylmorpholine-*N*-oxide (NMO), and cyclized to give the lactam **3.6**. This lactam was treated, without purification, with 3 eq. of sodium methoxide in methanol at room temperature to give the methyl ester **3.7** (2 steps, 71%), which was reduced with $LiBH_4$ (lithium borohydride) in THF to form an alcohol as a chromatographically separable mixture of two diastereomers *trans-lactam* **3.8** *and cis-lactam* **3.9**, in 87% yield, and a ratio of (56:44).



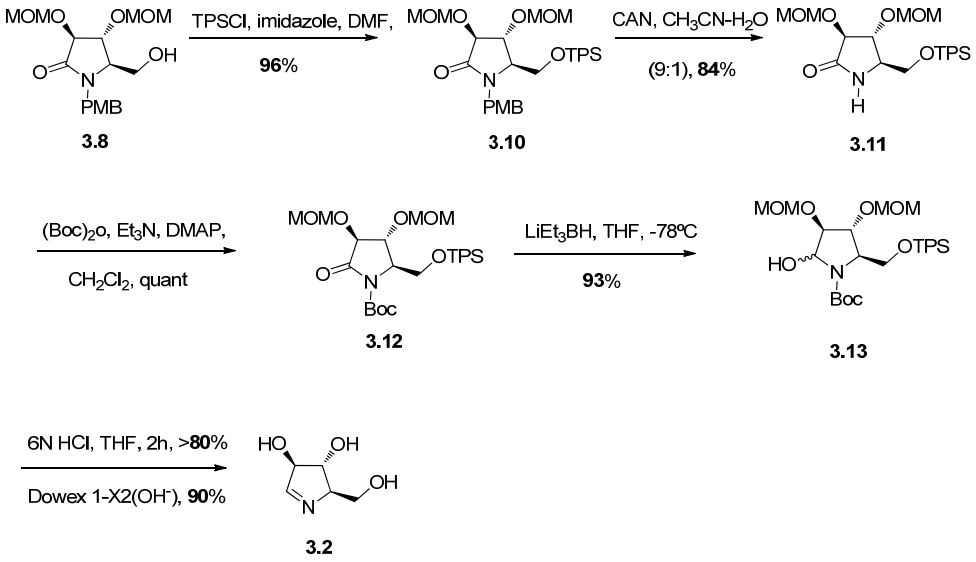
Scheme 3.2. Synthesis of compounds **3.8** and **3.9**

91 Harusawa, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1979**, *20*, 4663–4666.

92 a) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337–3342. b) Kuwahara, S.; Moriguchi, M.; Miyagawa, K.; Konno, M.; Kodama, O. *Tetrahedron* **1995**, *51*, 8809–8814 .

93 Griffith, W.P.; Ley, S.V.; Whitcombe, G.P.; White, A.D.*J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.

Protection of the primary alcohol of *trans-lactam* **3.8** with *t*-butyldiphenylsilyl chloride (TPSCl) and Et_3N gave the silyl ether **3.10** in 96% yield (Scheme 3.3). Treatment of **3.10** with ceric ammonium nitrate (CAN)[94] in CH_3CN-H_2O (9:1) at 0ºC afforded lactam **3.11** in 84% yield. The key step in this synthesis is the reduction of the lactam to the amino alcohol. The reduction of **3.11** with various reducing reagents (DIBAL-H, $LiEt_3BH$, $NaBH_4$ etc) did not afford the desired product. To face this problem, *N*-protecting group, PMB, was replaced with the more electron-withdrawing and easily removable Boc group. Thus lactam **3.11** was treated with di-*t*-butyl dicarbonate $(Boc)_2O$ and Et_3N in CH_2Cl_2 to give an imide **3.12** in quantitative yield. Reduction of the imide **3.12** with $LiEt_3BH$ (Super Hydride ®) in THF at -78ºC cleanly afforded the amino alcohol **3.13** in 93% yield. The final task was the removal of the protecting groups. This was accomplished by treatment of 6N HCI in THF at 50ºC for 2h to give the amino sugar precursor [95] (>80% yield), followed by ion exchange column chromatography (Dowex resin, OH-form) which afforded nectrisine **3.2** in 90% yield.



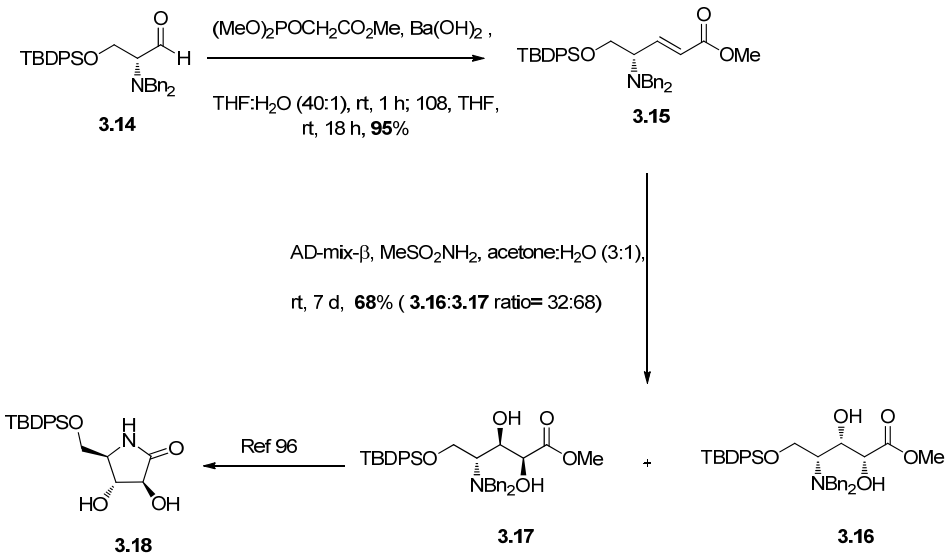
Scheme 3.3. Synthesis of Nectrisine **3.2**

94 Kronenthal, D.R.; Han, C.Y.; Taylor, M.K. *J. Org. Chem.* **1982**, *47*, 2765–2768.

95 Naleway, J.J.; Raetz, C.R.H.; Anderson, L. *Carbohydr. Res*. **1988**, 179, 199–209.

Path b [87]

D-Serine was the starting material in the synthesis of aldehyde intermediate **3.14**, which was achieved in five steps with 88% overall yield using a previously reported procedure.[96, 97] This aldehyde was found to be stable to racemisation on storage at 4°C for up to 48 h. Aldehyde **3.14** was converted to the α,β-unsaturated ester **3.15** in excellent yield (95%) under Horner–Wadsworth–Emmons conditions using the mild base $Ba(OH)_2$ (Scheme 3.4).[98] Osmium tetroxide-catalysed dihydroxylation resulted in a moderate yield (59%) of diols **3.16** and **3.17** in a 65:35 diastereomeric ratio, favouring the undesired all-*syn* diol **3.16**. The use of AD-mix-α resulted in a very sluggish reaction and only a modest improvement in yield (65% based on unrecovered starting material) and no apparent increase in diastereoselectivity. However, the diastereoselectivity could be overturned in favour of the desired *syn* diol **3.17** by use of AD-mix-β, but again the reaction rate was very slow (7 days) and the diastereoselectivity modest (32:68, **3.16**:**3.17**). Separation of the desired *syn* diastereomer **3.17**, conversion to the corresponding Weinreb amide and removal of the *N*-benzyl protecting groups using Pearlman's catalyst $Pd(OH)_2/C$ resulted in conversion *in situ* to the previously reported lactam **3.18**.[96]



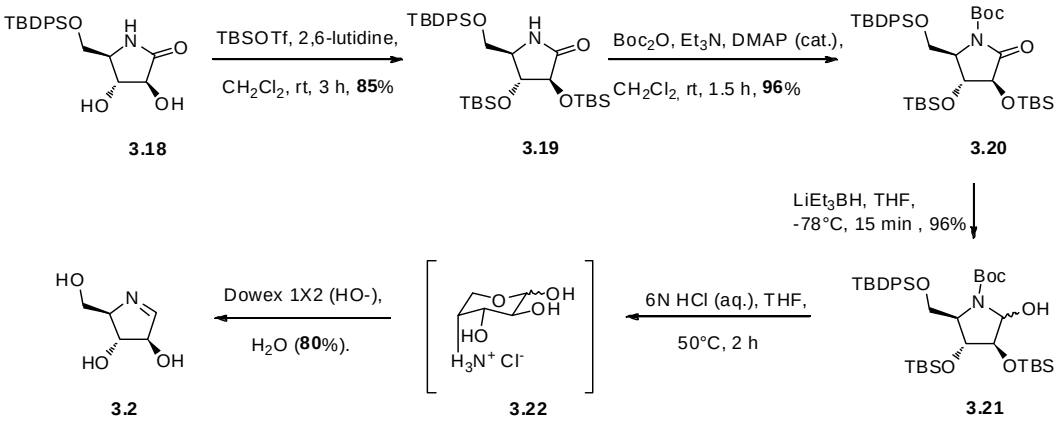
Scheme 3.4. Synthesis of compound **3.18**

96 Hulme, A. N.; Montgomery, C. H.; Henderson, D. K. *J.Chem. Soc., Perkin Trans. 1* **2000**, 1837–1841.

97 Hulme, A. N.; Curley, K. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1083–1091.

98 Paterson, I.; Yeung. K. S.; Smail, J. B. *Synlett* **1993**, 774–776.

Sequential protection in the hydroxyl functions and then in the amino function afforded **3.20** (Scheme 3.5). The increased carbonyl electrophilicity resulting from *N*-Boc protection facilitated the smooth reduction of the lactam with Super Hydride® even at −78°C to give **3.21**. Heating the amino alcohol **3.21** with 6N HCl at 50°C for 2h led to the clean removal of all of the protecting groups and the formation of an intermediate aminosugar **3.22**.[85] Neutralisation and purification by ion-exchange chromatography [Dowex 1X2 (HO−)] provided nectrisine **3.2** in excellent yield.

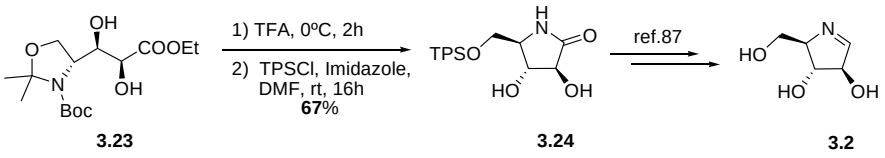


Scheme 3.5. Synthesis of Nectrisine **3.2**

Path c [88]

Dihydroxy ester **3.23** was obtained from Garner's (*R*)-aldehyde [99] via olefination and dihydroxylation. Acid treatment of **3.23** caused cleavage of the Boc and acetonide groups, followed by in situ spontaneous formation of the lactam ring (Scheme 3.6). This gave a crude triol which was then subjected to selective silylation of the primary alcohol group to yield pyrrolidinone **3.24** in 67% yield. Since **3.24** was a late intermediate in Hulme's synthesis of **3.2**[87,96] this constitutes a formal synthesis of this natural compound.

[99] a) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707–1709. b) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136–2157.

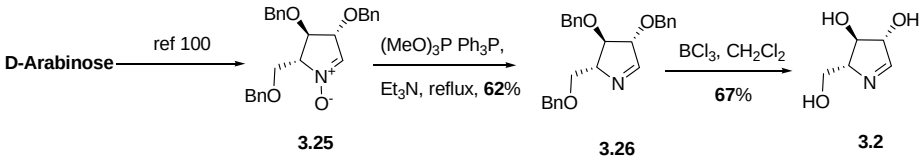


3.23 **3.24** **3.2**

Scheme 3.6. Formal Synthesis of Nectrisine **3.2**

Path d.1 [89]

The starting nitrones **3.25**[100] used for this study were prepared from D-arabinose (Scheme 3.7). Deoxygenation of nitrone **3.25** to provide imine **3.26** was achieved by a modification of a reported procedure.[101] Addition of triphenylphosphine (10 mol-%) and trimethylphosphite in triethylamine allowed **3.26**[90] to be afforded in good yield. Debenzylation of **3.26** with BCl_3,[90] in order to preserve the imine functionality, gave nectrisine **3.2**, which was found to be unstable in D_2O solution,[102] affording hydrated derivatives. On the other hand, ^{13}C NMR spectroscopic data of the crude compound were in agreement with those reported in the literature.[85]



3.25 **3.26** **3.2**

Scheme 3.7. Synthesis of Nectrisine **3.2**

Product **3.25** was prepared from D-arabinose through three steps. D-Arabinose acytalyzation, benzylation of the hydroxyl function using BnCl/KOH and hydrolysis of acetal by acid treatement gave the desired product **3.27** in an 50% yield. The reaction of compound **3.27** with hydroxylamine in pyridine at room temperature and protection of alcohol with TBDPSCl afforded compound **3.28** (100%). Substitution of the OH in **3.28** was then achieved using PPh_3/imidazole/I_2 in hot toluene to furnish the iodo-derivative

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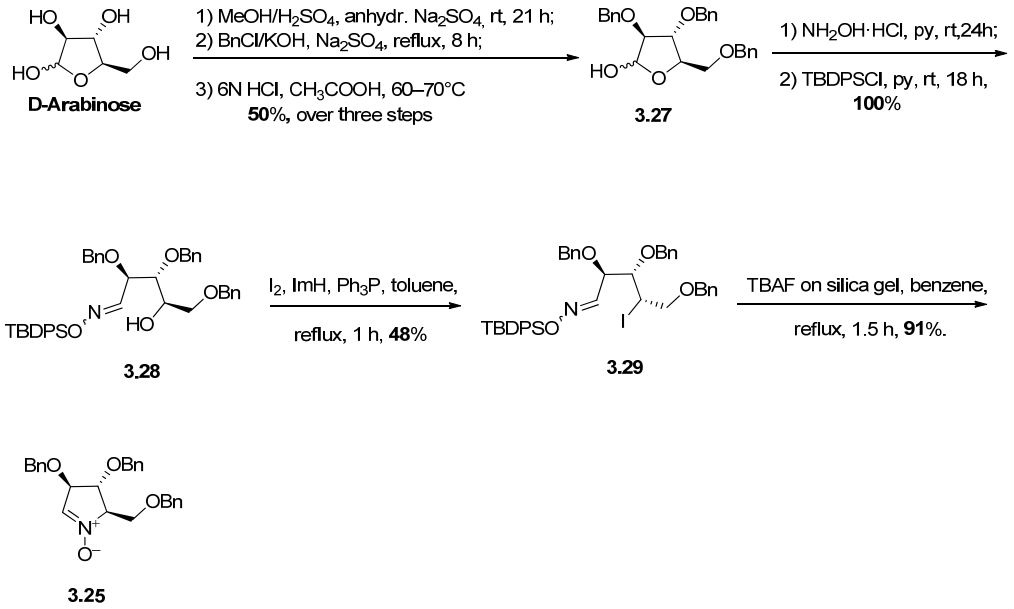
100 Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett*. **2003**, *44*, 2315–2318;

101 Milliet, P.; Lusinchi, X. *Tetrahedron* **1979**, *35*, 43–49.

102 Otero, J. M.; Soengas, R. G.; Estevez, J. C.; Estevez, R. J.; Watkin, D. J.; Evinson, E. L.; Nash, R. J.; Fleet, G. W. *J. Org. Lett*. **2007**, *9*, 623–626.

3.29 in 48 % yield. Deprotection of silyl group was effected by TBAF, which was converted to the desired nitrone **3.25** (91%).



Scheme 3.8. Synthesis of Nitrone **3.25**

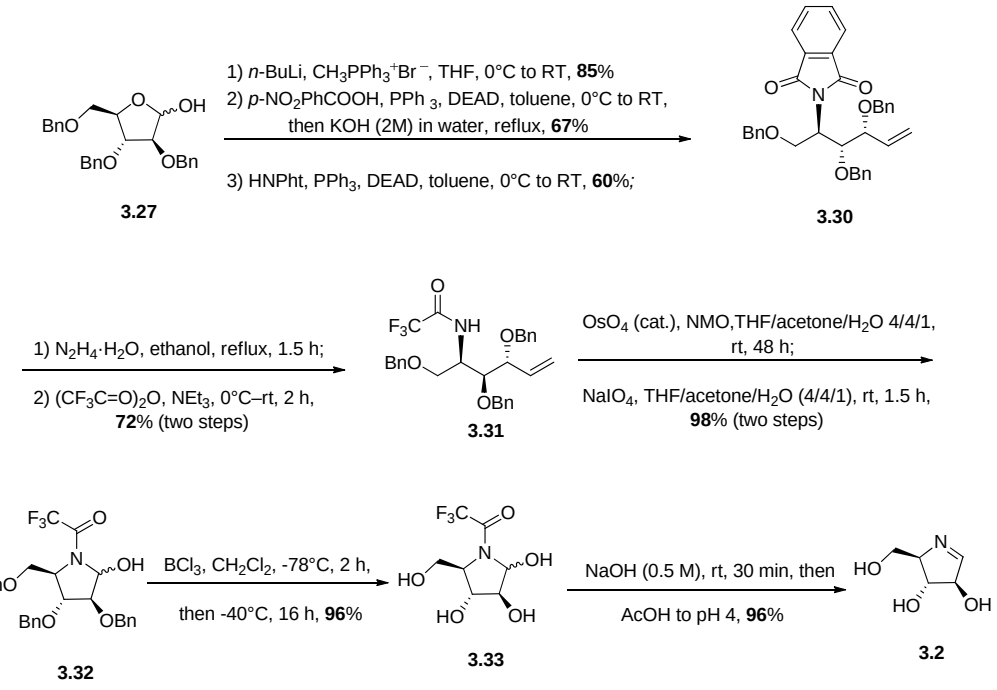
Path d.2 [90]

This synthesis commenced with a Wittig olefination[103] of the commercially available 2,3,5-tri-O-benzyl-D-arabinofuranose **3.27**. Two successive Mitsunobu reactions, first with p-nitrobenzoic acid, then with phthalimide, afforded **3.30**.Hydrazinolysis of phthalimide **3.30**[104] (Scheme 3.9) and treatment of the crude amine thus obtained with trifluoroacetic anhydride provided the trifluoroacetamide **3.31**. Dihydroxylation (OsO_4/NMO) of the olefinic bond and oxidative cleavage ($NaIO_4$) of the resulting diol led to an aldehyde which cyclised to the protected aminal **3.32** upon standing. Initial attempts to remove the benzyl groups in **3.32** by hydrogenolysis, using a variety of conditions, were disappointing as the desired deprotected product **3.33** was obtained only in low yield, always accompanied by substantial amounts of the aminoalcohol arising from reduction of the latent aldehyde function in **3.33.** Hydrolysis of the trifluoroacetamide with dilute NaOH and concomitant dehydration, followed by ion-exchange chromatography (Sephadex® CM-C-25 (NH4+), elution with 2% aqueous

103 Freeman, F.; Robarge, R.D. *Carbohydr. Res.* **1986**, *154*, 270–274.

104 Bouix, C.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **1998**, *39*, 825–828.

ammonia) completed our synthesis of nectrisine, thus obtained in nine steps and 18% overall yield starting from commercially available 2,3,5-tri-*O*-benzyl-(D)-arabinose.[104]

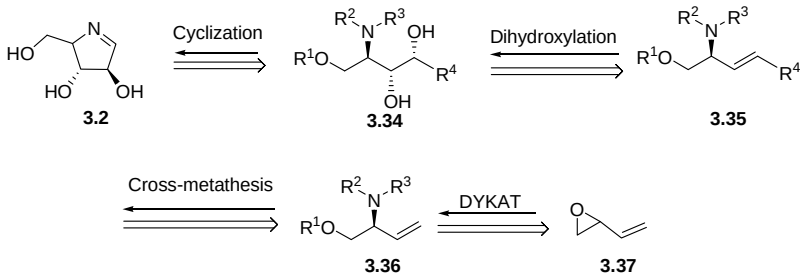


Scheme 3.9. Synthesis of Nectrisine **3.2**

3.2. Retrosynthesis

We recently described that Trost's DYKAT process based on Pd-catalyzed asymmetric allylic amination in combination with cross-metathesis and dihydroxylation reactions is an efficient strategy for accessing important natural products such as sphingosine[105] and Jaspine.[106] Here we explore an enantioselective synthesis of nectrisine based on Pd-catalyzed asymmetric allylic amination, cross-metathesis and dihydroxylation as key steps. Scheme 3.10 shows the retrosynthesis proposed, where the key synthon is the allylamine **3.36** which is obtained in high enantiomeric purity by a deracemization process using Pd/DACH as a catalytic system.[33,34]Cross-metathesis with acrolein will allow increasing the chain length, and at the same time would provide the aldehyde functionality necessary for formation of the cyclic imine moiety in the final nectrisine. The high reactivity of the aldehyde function would, though, pose some problems, which would advise the use of an aldehyde surrogate that might be compatible with the cross metathesis reaction and cyclization process, such as a dioxolane or an ester group.

Besides, configuration of double bond resulting from cross-metathesis must be *E* in order to provide the correct configuration of hydroxyl groups in **3.34** after the dihydroxylation reaction. The stereoselectivity of this reaction will be controlled by the stereocenter in the molecule, which could be also be enhanced by chiral ligands in a matched double stereodifferentiation process.



Scheme 3.10. Retrosynthesis of nectrisine **3.2**

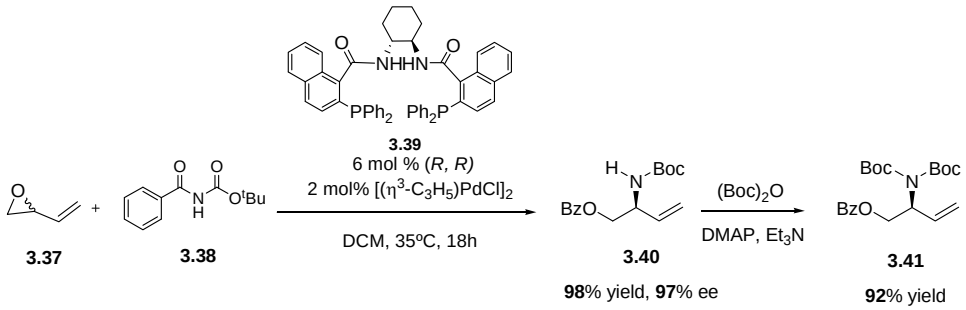
105 Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Lett.* **2009**, *11*, 205–208.

106 Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Eur. J. Org. Chem.* **2011**, 1514–1519.

3.3. Results and discussion

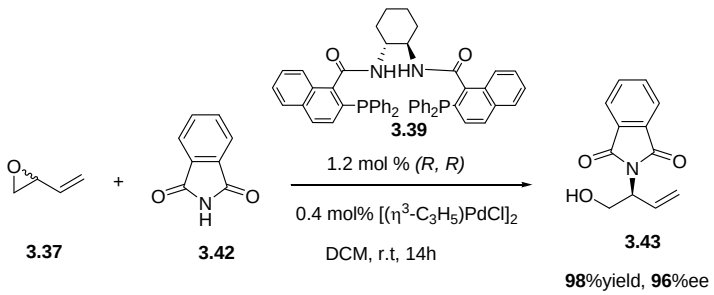
3.3.1. Synthesis of allyl amines by asymmetric Pd-catalyzed allylic amination of butadiene monoepoxide.

For our prupose, we focused on the preparation of enantioenriched 2-amino-3-butenol by means of an asymmetric transformation (DYKAT) consisting in the deracemization of butadiene monoepoxide by means of an asymmetric Pd-catalyzed allylic amination. Thus, reaction of butadiene monoepoxide (**3.37**) with 2 mol% of $[(\eta^{3}\text{-}C_3H_5)PdCl]_2$, 6 mol% of (*R*,*R*)-DACH ligand **3.39** and imide **3.38** afforded allyl amine **3.40** with 98% yield and 97% e.e.[34] Compound **3.40** was subsequently treated with di-*t*-butyl dicarbonate and DMAP to give allyl imide **3.41** in excellent yield (92%) (Scheme 3.11).



Scheme 3.11. Synthesis of compounds **3.40** and **3.40**

2-(*S*)-*N*-phthalimido-3-buten-1-ol **3.43** was prepared under the conditions optimized by Trost.[33]Thus, when **3.37** was treated with phthalimide **3.42** using 0.4 mol% of $[(\eta^{3}\text{-}C_3H_5)PdCl]_2$, 1.2 mol% of (*R*,*R*)-DACH-Naphtyl **3.39**, and Na_2CO_3 in dichloromethane for 14h, allylic amine **3.43** was obtained in an excellent yield (98%) and 96% ee (Scheme 3.12).



Scheme 3.12. Synthesis of compound **3.43**

3.3.2. Synthesis of 1,2-disubstituted allyl amines by Ru-catalyzed cross-metathesis

Among the many types of transition-metal-catalyzed C-C bond forming reactions, olefin methatesis has come to the fore in recent years owing to the wide range of transformations that are possible with commercially available and easily handled catalyst. Consequently, olefin metathesis is now widely considered as one of the most powerful synthetic tools in organic chemistry. Until recently the intermolecular variant of this reaction, cross-metathesis had been neglected despite its potential. With the evolution of new catalysts, the selectivity, efficiency, and functional-group compatibility of this reaction have improved to a level that was unimaginable just a few years ago.

The second generation Grubbs catalyst is compatible with a wide range of functionalities,[107] the generation of olefins with electron-withdrawing functional groups, such as α,β-unsaturated aldehydes, ketones and esters, remains a difficult task in organic synthesis. Other π-conjugated functional groups compatible with alkylidene Schrock catalyst failed to react with first generation of Grubbs catalyst. However, second generation of ruthenium catalyst and, Hoveyda-Grubbs catalyst were found to be very efficient in the reaction with α,β-unsaturated carbonyl compounds.[51]

As mentioned in the retrosynthesis (Scheme 3.10), three different alkenes were considered for the metathesis reaction, acrolein, vinyldioxolane and ethyl acrylate, which were tested in the reaction with allylimides **3.41** and **3.43**. An initial essay with the di-boc derivative **3.41** and acrolein **3.44** did not proceed when the reaction was carried out in toluene at 80ºC for 12h in the presence of catalyst **3.48** (5 mol%) (Table 3.1, Entry 1). When the reaction was performed in dichloromethane at room temperature in the presence of catalysts **3.47** (5 mol%) and **3.48** (5 mol%) the result was also negative (Table 3.1, Entries 2, 6). By contrast, cross-coupling product **3.45** was obtained in the presence of catalyst **3.48** (5 mol%) when the reaction was performed at 55ºC, although conversion was moderate 34% (Table 3.1, Entry 3). The Hoveyda-Grubbs catalyst **3.49** (5 mol%) also provided poor conversion, affording product **3.45**

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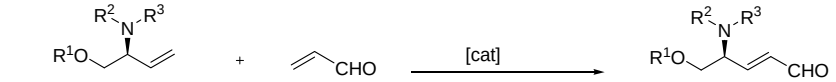
[107] a) Yamamoto, T.; Hasegawa, H.; Hakogi, T.; Katsumura, S. *Org. Lett.* **2006**, *8*, 5569–5572. b) Chaudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Org. Lett.* **2005**, *7*, 5805–5807. c) Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 4502-4504. d) Torsell, S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 1643–1646.

with 13-17% conversion at rt-55ºC (Table 3.1, Entries 4, 5). The best result was obtained by cross-metatesis reaction between phthalimido derivative **3.43** and acrolein **3.44** in the presence of the Hoveyda-Grubbs catalyst **3.49** (5 mol%), under these conditions **3.46** was obtained in 78% yield (Table 3.1, Entry 7).

Table 3.1. Cross-metathesis of allylimides **3.41** and **3.43** with acrolein **3.44**.[a]

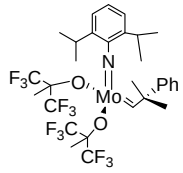


3.41 R^1=Bz, R^2=R^3=Boc
3.43 R^1=H, R^2=R^3=phthalimido

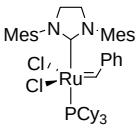
3.44

3.45 R^1=Bz, R^2= R^3=Boc
3.46 R^1=H, R^2=R^3=phthalimido

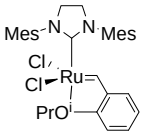
[cat]=



3.47



3.48



4.49

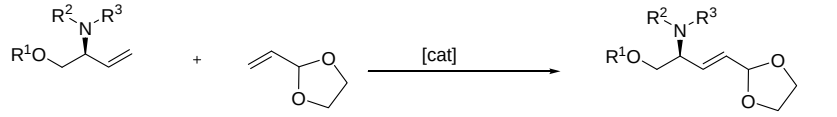
Entry	Allylamine	Cat.	Solvent	Temp. (ºC)	Product	Conv[b] (Yield) [c] (%)
1	**3.41**	**3.48**	Toluene	80	**3.45**	<2
2	**3.41**	**3.48**	CH_2Cl_2	rt	**3.45**	<2
3	**3.41**	**3.48**	CH_2Cl_2	reflux	**3.45**	34
4	**3.41**	**3.49**	CH_2Cl_2	reflux	**3.45**	13
5	**3.41**	**3.49**	CH_2Cl_2	rt	**3.45**	17
6[d]	**3.41**	**3.47**	CH_2Cl_2	rt	**3.45**	<2
7	**3.43**	**3.49**	CH_2Cl_2	reflux	**3.46**	(78)

[a]conditions: mixture of allyl imide (1 equiv) , alkene (5 equiv) and catalyst (5 mol%) were stirred for 12h in 0.5M solution. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Reaction in Dry box.

We studied then the cross-metathesis reaction using vinyldioxolane **3.50** instead of acrolein. In all cases the results obtained were better than with acrolein. When the reaction between the di-boc derivative **3.41** and vinyldioxolane **3.50** was carried out under similar reaction conditions to those optimized previously, dichloromethane as solvent and 55ºC, using the second generation Grubbs **3.48** (5 mol%) or Hoveyda-Grubbs **3.49** (5 mol%) catalysts, product **3.51** was obtained in 55-54% yields, respectively (Table 3.2, entries 1 and 4). The replacement of solvent by toluene and

performing the reaction at 80ºC in the presence of the second generation Grubbs **3.48** (5 mol%) catalyst allowed the product **3.51** to be obtained as the *E*-isomer in 30% yield (Table 3.2, Entry 2). Increasing the number of equivalents of vinyldioxolane **3.50** and working under similar conditions, the yield of compound **3.51** raised to 78% (Table 3.2, Entry 3). Indeed, cross-metathesis reaction of vinyl dioxolane with the phthalimido derivative **3.43** afforded the best results and compound **3.52** was obtained in 81% yield (Table 3.2, Entry 5).

Table 3.2. Cross-metathesis of allylimides **3.41** and **3.43** with vinyldioxolane **3.50**.[a]



3.41 R^1=Bz, R^2=R^3=Boc
3.43 R^1=H, R^2=R^3=phthalimido

3.50

3.51 R^1=Bz, R^2= R^3=Boc
3.52 R^1=H, R^2=R^3=phthalimido

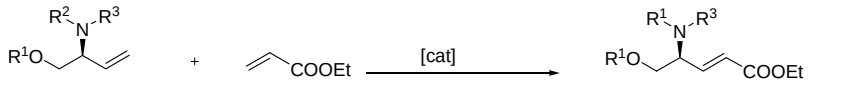
Entry	Allylamine	Cat.	Solvent	Temp. (ºC)	Product	Conv[b] (Yield) [c] (%)
1	**3.41**	**3.48**	CH_2Cl_2	reflux	**3.51**	64(55)
2	**3.41**	**3.48**	Toluene	80	**3.51**	50(30)
3[d]	**3.41**	**3.48**	CH_2Cl_2	reflux	**3.51**	82(78)
4	**3.41**	**3.49**	CH_2Cl_2	reflux	**3.51**	64(54)
5	**3.43**	**3.48**	CH_2Cl_2	reflux	**3.52**	(81)

[a]conditions: mixture of allyl imide (1 equiv), alkene (5 equiv) and catalyst (5 mol%) were stirred for 12h in 0.5M solution. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] (7 equiv) of alkene **3.50** were added.

The cross-metathesis reaction of allylimides **3.40**, **3.41** and **3.43** with ethylacrylate was studied under the conditions optimized previously for acrolein and vinyldioxolane. Yields were moderate to excellent with both allylimides **3.41** and **3.43** when the Grubbs catalyst was used. Thus, cross-metathesis reactions between **3.41** and ethylacrylate **3.53** in the presence of catalyst **3.48** (5 mol%) afforded the cross-product **3.55** with 22% conversion (Table 3.3, Entry 2). Similarly to that reported in Tables 3.1 and 3.2, the reaction with allylimide **3.43** using the same catalyst provides a better yield of 71% (Table 3.3, Entry 4). However, when the reactions of compounds **3.40**, **3.41** and **3.43** were run in the presence of catalyst **3.49**, products **3.54**, **3.55** and **3.56** were obtained in

excellent 96, 98 and 98% yields (Table 3.3, Entries 1, 3 and 5) respectively. Thus, it can be concluded that the cross-metathesis reaction with ethylacrylate affords excellent yields with the allylimides tested and that the Hoveyda-Grubbs catalyst **3.49** (5 mol%) is the catalyst of choice for this reaction.

Table 3.3. Cross-metathesis of allylimides **3.40, 3.41** and **3.43** with ethyl acrylate **3.53**. [a]



3.40 R^1=Bz, R^2=H, R^3=Boc
3.41 R^1=Bz, R^2=R^3=Boc
3.43 R^1=H, R^2=R^3=phthalimido

3.53

3.54 R^1=Bz, R^2=H, R^3=Boc
3.55 R^1=Bz, R^2= R^3=Boc
3.56 R^1=H, R^2=R^3=phthalimido

Entry	Allylamine	Cat.	Solvent	Temp. (ºC)	Product	Conv[b] (Yield) [c] (%)
1 [d]	**3.40**	**3.49**	CH_2Cl_2	reflux	**3.54**	<99(96)
2	**3.41**	**3.48**	CH_2Cl_2	reflux	**3.55**	22
3[d]	**3.41**	**3.49**	CH_2Cl_2	reflux	**3.55**	<99(98)
4	**3.43**	**3.48**	CH_2Cl_2	reflux	**3.56**	(71)
5	**3.43**	**3.49**	CH_2Cl_2	reflux	**3.56**	(98)

[a]conditions: mixture of allyl imide (1 equiv) , alkene (5 equiv) and catalyst (5 mol%) were stirred for 12h in 0.5M solution. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] (10 equiv) of alkene **3.53** were added.

3.3.3. Dihydroxylation of allyl imides

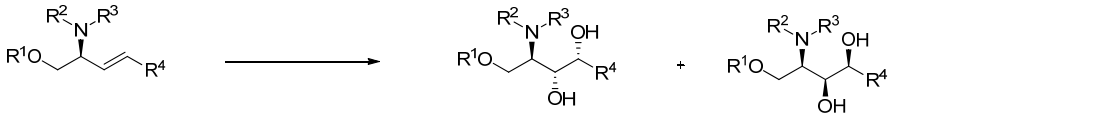
Syn dihydroxylation was the next challenge in our synthetic plan. Dihydroxylation assays of related structurally allyl amides by our group and others[105, 108] had showed that the reaction proceeds under substrate control using achiral catalysts leading to moderate diastereoselectivities, which can be improved if chiral ligands are used in double differentiation process.

Thus, we initially tried the diastereoselective dihydroxylation of di-boc derivative **3.51** bearing a dioxolane ring using AD-mix-β affording a mixture of two products **3.58**

[108] Jeon, J.; Shin, M.; Won Yoo, J.; Seok Oh, J.; Gwang, B. J.; Jung, H. S.; Kim, Y.G. *Tetrahedron Lett.* **2007**, *48*, 1105–1108.

and **3.59** with 33% conversion in a 4:1 ratio (Table 3.4, Entry 1). Unexpectedly, the ethyl carboxylate derivatives bearing *N*-boc protecting group with the alcohol protected **3.54** or unprotected **3.57**, as well as the *N*-di-boc derivative **3.55** afforded no dihydroxylated products in the presence commercial chiral ligands AD-mix-α and AD-mix-β, or even with the catalytic systems prepared *in situ* such as $(DHQD)_2PYR$, $(DHQ)_2PYR$ or $(DHQ)_2AQN$ (Table 3.4, Entries 2-10).

Table 3.4. Catalytic Dihydroxylation assays of alkenes **3.51**, **3.54**, **3.55** and **3.57** using chiral ligands.[105,108,109]



3.51 R^1=Bz, R^2= R^3=Boc, R^4= $CH(OCH_2)_2$
3.54 R^1=Bz, R^2=H, R^3=Boc, R^4= COOEt
3.55 R^1=Bz, R^2= R^3=Boc, R^4= COOEt
3.57 R^1=H, R^2= H, R^3=Boc, R^4= COOEt

3.58 R^1=Bz, R^2= R^3=Boc, R^4= $CH(OCH_2)_2$ **3.59** R^1=Bz, R^2= H, R^3=Boc, R^4= $CH(OCH_2)_2$
3.60 R^1=Bz, R^2=H, R^3=Boc, R^4= COOEt **3.61** R^1=Bz, R^2=H, R^3=Boc, R^4= COOEt
3.62 R^1=Bz, R^2= R^3=Boc, R^4= COOEt **3.63** R^1=Bz, R^2= H, R^3=Boc, R^4= COOEt
3.64 R^1=H, R^2= H, R^3=Boc, R^4= COOEt **3.65** R^1=H, R^2= H, R^3=Boc, R^4= COOEt

Entry	Allyl	Chiral ligand	Tem (ºC)	Time	Product	Ratio[a]	Conversion (%)[a]
1	**3.51**	AD-mix β	rt	30h	**3.58:3.59**	4:1	33
2	**3.54**	AD-mix α	rt	10d	**3.60:3.61**	-	<2
3	**3.54**	AD-mix β	rt	10d	**3.60:3.61**	-	<2
4	**3.55**	AD-mix α	rt	10d	**3.62:3.63**	-	<2
5	**3.55**	AD-mix β	rt	10d	**3.62:3.63**	-	<2
6[b]	**3.55**	AD-mix β	rt	10d	**3.62:3.63**	-	<2
7[c]	**3.55**	$(DHQD)_2PYR$	rt	5d	**3.62:3.63**	-	<2
8[c]	**3.55**	$(DHQ)_2PYR$	rt	5d	**3.62:3.63**	-	<2
9[c]	**3.55**	$(DHQ)_2$ AQN	rt	5d	**3.62:3.63**	-	<2
10	**3.57**	AD-MIX β	rt	24h	**3.64:3.65**	-	<2

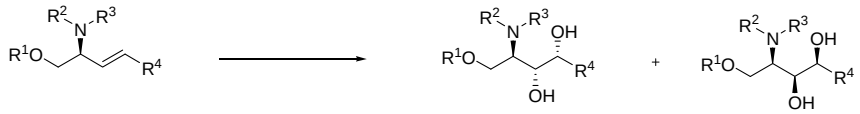
[a] Determined by ^1H NMR. [b] $(DHQD)_2PYR$ ligand was added. [c] Ligand (0.03 equiv), $CH_3SO_2NH_2$ (1.1 equiv), K_2CO_3 (0.3 equiv), $NaHCO_3$ (0.3 equiv), $K_3Fe(CN)_6$ (3equiv), $K_2OsO_2(OH)_4$ (0.02 equiv).

On the other hand, dihydroxylation assays of *N*-di-boc derivatives **3.51** and **3.55**, bearing a dioxolane and a carboxyethyl groups, with OsO_4 and NMO afforded the desired products with total conversion but with unsatisfactory selectivity, 1:1 and 2:1,

[109] Ritsuo, I.; Skurai, O.; Yamashita, T.; Horikawa. H. *Tetrahedron* **1998**, *54*, 10657–10670.

respectively (Table 3.5, Entries 1 and 5). A similar result was obtained from the *N*-Boc protected derivative **3.54**, since a 1:1 diastereomeric mixture was also obtained (Table 3.5, Entry 4). However, when diastereoselective dihydroxylation of compound **3.51** with OsO_4/NMO was tested in water, the desired product **3.58** was isolated in good yield, together with a minor amount of the partially deprotected derivative **3.59** (Table 3.5, Entry 2). Interestingly, in this case the phthalimido derivative **3.52** afforded total conversion and good stereoselectivities under the standard reaction conditions (Table 3.5, Entry 3).

Table 3.5. Dihydroxylation reaction of alkenes **3.51**, **3.52** and **3.54**, **3.55** using OsO_4/NMO.[105,108]



3.51 R^1=Bz, R^2= R^3=Boc, R^4= $CH(OCH_2)_2$
3.52 R^1=H, R^2= R^3=Phth, R^4= $CH(OCH_2)_2$
3.54 R^1=Bz, R^2=H, R^3=Boc, R^4= COOEt
3.55 R^1=Bz, R^2= R^3=Boc, R^4= COOEt

3.58 R^1=Bz, R^2= R^3=Boc, R^4= $CH(OCH_2)_2$ **3.59** R^1=Bz, R^2= H, R^3=Boc, R^4= $CH(OCH_2)_2$
3.66 R^1=H, R^2= R^3=Phth, R^4= $CH(OCH_2)_2$ **3.67** R^1=H, R^2= R^3=Phth, R^4= $CH(OCH_2)_2$
3.60 R^1=Bz, R^2=H, R^3=Boc, R^4= COOEt **3.61** R^1=Bz, R^2=H, R^3=Boc, R^4= COOEt
3.62 R^1=Bz, R^2= R^3=Boc, R^4= COOEt **3.63** R^1=Bz, R^2= H, R^3=Boc, R^4= COOEt

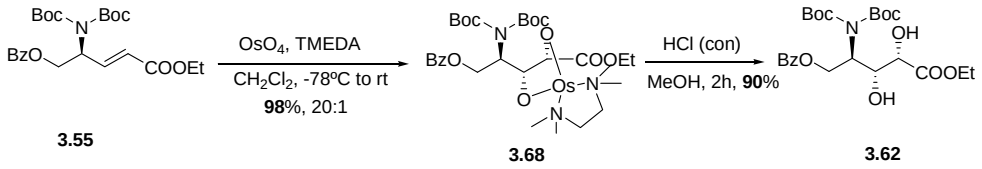
Enty	Substrate	T(ºC)	t(h)	Product	Ratio[b]	Conv (%)[b]	Yield (%)[c]
1	**3.51**	rt	24	**3.58:3.59**	1:1	<99	-
2[c]	**3.51**	rt	24	**3.58:3.59**	5.5:1	<99	70:25
3	**3.52**	rt	24	**3.66:3.67**	5:1	<99	75:20
4	**3.54**	rt	24	**3.60:3.61**	1:1	<99	-
5[c]	**3.55**	rt	24	**3.62:3.63**	2:1	<99	60:36

[a] Conditions: all reaction were stirred in the presence of OsO_4 (0.1 equiv).[and NMO (2.5 equiv).[b] Determined by ^{1}H NMR.[b] Isolated yield. [c] (2.5 mol%) of OsO_4 in water were used .

Stoichiometric dihydroxylation using 1 eq of OsO_4 in the presence of TMEDA at low temperature has been described in many examples to improve diastereoselectivities compared to those of catalytic OsO_4/MNO system.[110] With this prupose, the reaction of **3.55** with stoichiommetric OsO_4 and TMEDA promoted osmylation in excellent yield (98%) and in significantly improved selectivity (20:1) to give, however, the osmate **3.68**, which resulted inert to hydrolysis under the reaction conditions. Subsequent

[110] Donohoe, T . J.; Blades, K..; Helliwell, M.; Moore , P. R.; Winter, J. J. G. *J. Org. Chem.* **1999**, *64*, 2980–2981.

hydrolysis in the presence of HCl and MeOH rendered the desired diol product **3.62** (Scheme 3.13).



Scheme 3.13. Synthesis of compounds **3.68** and **3.62**

3.3.4. Phthalimido and Boc deprotection

- Boc deprotection

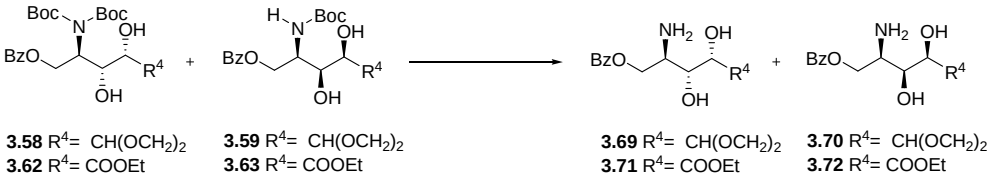
Boc-cleavage in the dihydroxylation products was attempted under acidic conditions. Hydrolysis of ethyl ester **3.62** with HCl/EtOH[111] afforded **3.71** with moderate 50% yield (Table 3.6, Entry 5). The use of trifluoroacetic acid proved more efficient, increasing the yield of **3.71** to an excellent 98% yield (Table 3.6, Entry 4). Hydrolysis starting from the diastereomeric mixture **3.62/3.63** rendered amines **3.71/3.72** in 70% yield (Table 3.6, Entry 3).

Boc-group removal from pure dioxolane derivative **3.58** or the diastereomeric mixture **3.59/3.60** with TFA[88] gave either mixture **3.69/3.70** or **3.69** with 60% and 50% yields (Table 3.6, Entries 1 and 2) respectively. The low efficiency compared to those of the ester derivatives **3.62/3.63** could be attributed to acetalyzation/hydrolysis processes due to the dioxolane moiety, but no aldehyde product was observed in the reaction crude.

It is worth to point out that no lactamization product was observed, as could be expected from reaction of the amino and the ester groups in the molecule in acidic medium.

[111] Bimalendu, R.; Kausikisankar, P.; Balaram, M, *Glycoconj. J* . **2008**, 25, 157–166.

Table 3.6. Boc deprotection.[87,88]

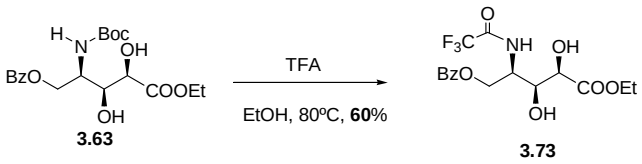


3.58 R^4= $CH(OCH_2)_2$ **3.59** R^4= $CH(OCH_2)_2$ **3.69** R^4= $CH(OCH_2)_2$ **3.70** R^4= $CH(OCH_2)_2$
3.62 R^4= COOEt **3.63** R^4= COOEt **3.71** R^4= COOEt **3.72** R^4= COOEt

Entry	Substrate	Reagents	Solvent	Temp. (ºC)	Product	Yield (%)
1[a]	**3.58/3.59**	TFA	CH_2Cl_2	0	**3.69/3.70**	60
2[b]	**3.58**	TFA	CH_2Cl_2	0	**3.69**	50
3[a]	**3.62/6.63**	TFA	CH_2Cl_2	0	**3.71/3.72**	70
4[b]	**3.62**	TFA	CH_2Cl_2	0	**3.71**	98
5[b]	**3.62**	HCl	EtOH	50	**3.71**	50

[a] mixture yield. [b] Isolated yield.

Treatment of the *N*-Boc derivative **3.63** with TFA in EtOH for 4h at 80ºC rendered product **3.73** in a 60% yield as a result of removal of Boc group and formation of trifluoroacetamide group (Scheme 3.14).

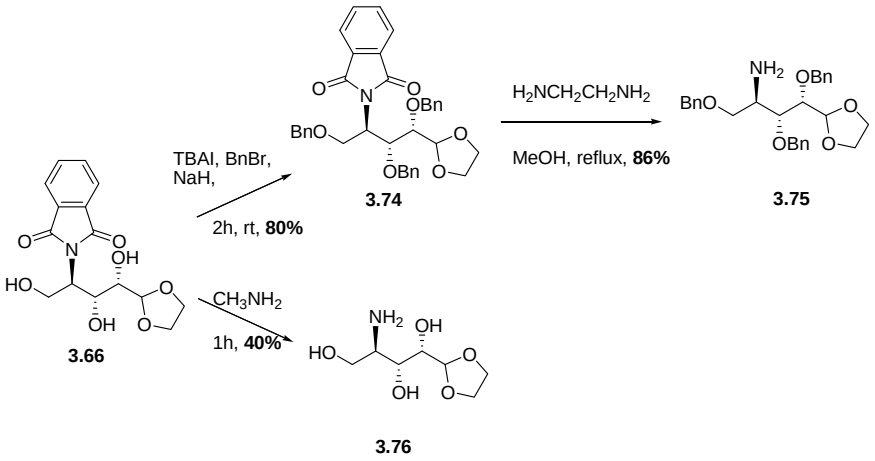


3.63 **3.73**

Scheme 3.14. Synthesis of compound **3.73**

- *Phthalimido deprotection*

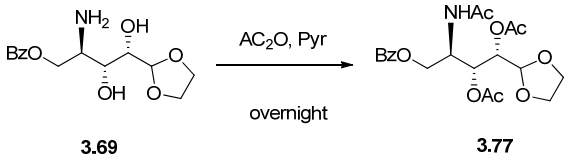
Compound **3.66**, bearing a phthalimido group, resulting from the efficient dihydroxylation of alkene **3.52**, was initially protected by reaction with an excess of BnBr with the previously formed alcoholate in the presence of TBAI, affording product **3.74** in 80% yield. Removal of phthalimido was carried out by treatment with 1,2-ethylenediamine in refluxing methanol to provide compound **3.75** in 86% yield. Deprotection of phthalimido group was also attempted in the unprotected compound **3.66**, by reaction with methyl amine affording **3.76** in 40% yield (Scheme 3.15).



Scheme 3.15. Removal of phthalimido group

3.3.5. Dioxolane deprotection [87, 112]

Acylation of product **3.69** in the presence of acetic anhydride and pyridine afforded the desired product **3.77** (Scheme 3.16).



Scheme 3.16. Synthesis of compound **3.77**

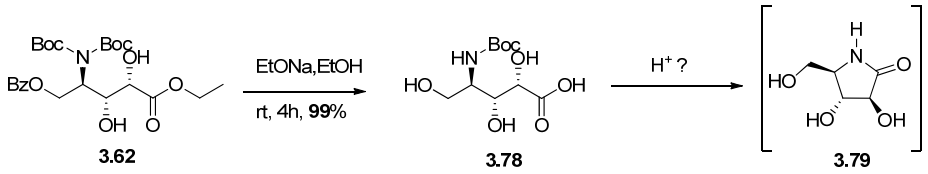
We envisaged that removal of dioxolane protecting group could directly afford monoprotected nectrisine by releasing the aldehyde group and concomitant formation of imine. Any attempt, however, of removing the dioxolane ring to induce the cyclization in **3.69**, **3.75** and acetate **3.77** by treatment with HCl[87] and *p*-TsOH[112] in THF at 50ºC or rt in THF afforded degradation products.

3.3.6. Cyclization and protection reactions

Due to the difficulty of hydrolysis of dioxolane ring we turned our attention to the ester derivative **3.62**. In addition, we considered that benzoate moiety could be the responsible of the failure in cyclization of **3.71**. Thus, we explored the deprotection of

[112] Puls, R.; Al-Haras, A.; Rissig, H. U. *Org. Lett.* **2002**, *4*, 2353–2355.

benzoyl group in **3.62** with NaOEt in EtOH.[113] Unexpectedly, compound **3.78** resulting from the alcoholysis of benzoate group but also from the concomitant deprotection of the acetate group and hydrolysis of the ester group (Scheme 3.17). Formation of this compound, however, should not pose a problem, considering that the subsequent cleavage of the boc group by acid treatment could be followed by spontaneous cyclization to give the lactam **3.79**.

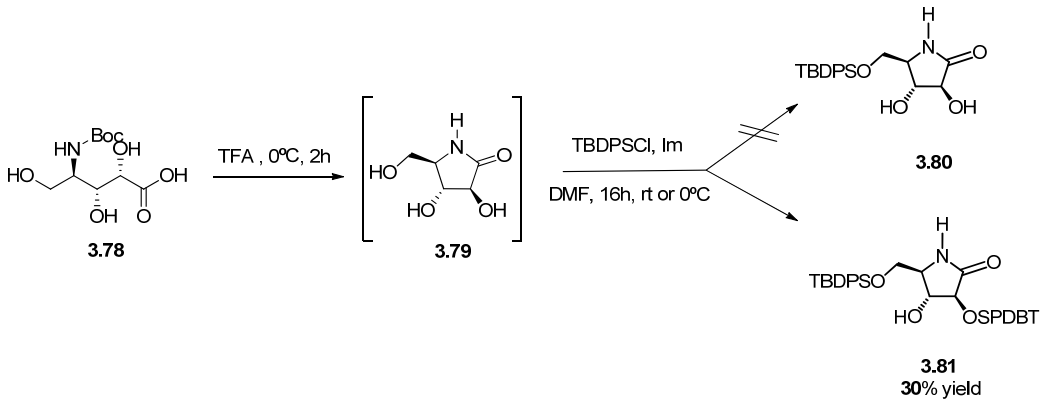


3.62 **3.78** **3.79**

Scheme 3.17. Synthesis of compounds **3.79**

With this purpose, **3.78** was submitted to hydrolysis conditions with TFA at 0ºC for 2h to give a reaction crude that was treated with TBDPSCl, imidazole in DMF at room temperature for 16h. This process sought to monosilylate lactam **3.79**, presumably formed from acid treatement, at position 5 to render lactam **3.80** which had been previously synthesized throught another synthetic strategy.[87] Therefore, synthesis of lactam **3.80** would constitue a formal synthesis of the nectrisine. However, the protection process rendered coumpond **3.81** (14 mg) as a result of disilylation at position 2 and 5.(Scheme 3.18). No change was observed when the protection was carefully monitored at 0ºC, observing that the disilylated product was formed very fast. In fact, the monosilylated product was practically not detected. The fact that the monosilylated product is more soluble in the reaction medium than the starting material can have influence in the outcome of the reaction. Anyway, it was demonstrated that by removing the benzoate at position 5 the cyclization took place

[113] Bimalendu, R.; Kausikisankar, P.; Balaram, M. *Glycoconj. J* . **2008**, *25*, 157–166.

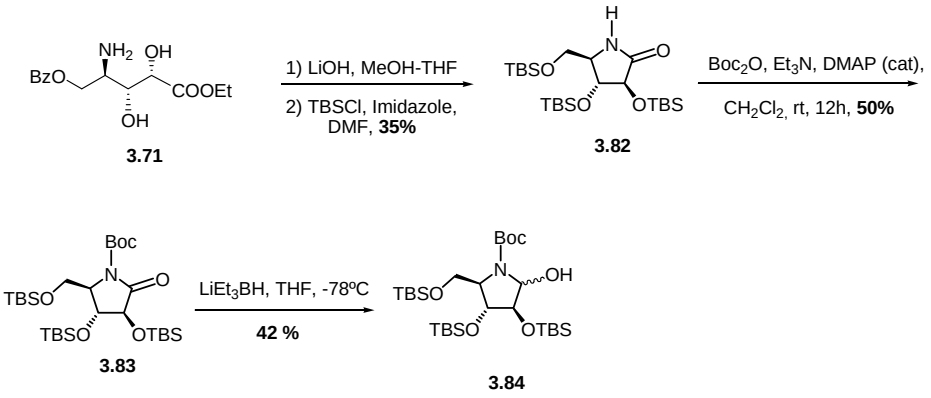


Scheme 3.18. Synthesis and protection of lactam **3.79**

3.3.7. Final steps towards Nectrisine (3.2)[87]

We Next decided to explore the cyclization from compound **3.71** by first removing the benzoate group. Thus, hydrolysis of benzoate in **3.71** with LiOH afforded crude lactam **3.79**, whose hydroxyl functionalities were fully protected by treatment with TBSCl to give **3.82** in 35% yield. Attempting to increase the silylation yield, **3.79** was treated with TBSOTf and lutidine but no protected lactam was recovered after aqueous work-up of the reaction crude. Subsequent protection of **3.82** with di-*t*-butyl dicarbonate $(Boc)_2O$ and Et_3N in CH_2Cl_2 gave imide **3.83** in 50% yield. The increased carbonyl electrophilicity resulting from *N*Boc protection should facilitate the smooth reduction of the lactam **3.83**, which proceeded by reaction with Super Hydride® at −78°C to give **3.84** in (10 mg, 42% yield).

The little amounts of synthetic itermediates **3.81** and **3.84** prevented to move forward in the synthetic route proposed and led the synthesis of nectrisine pending. In our hands, the silylation step has proven troublesome, either by lack of selective protection at the primary position or by unsatisfactory synthetic yield of the fully silylated intermediate, so that in the future a synthetic solution for the silylation step should be provided to assure completion of the synthesis proposed.



Scheme 3.19. Synthesis of Compond **3.84**

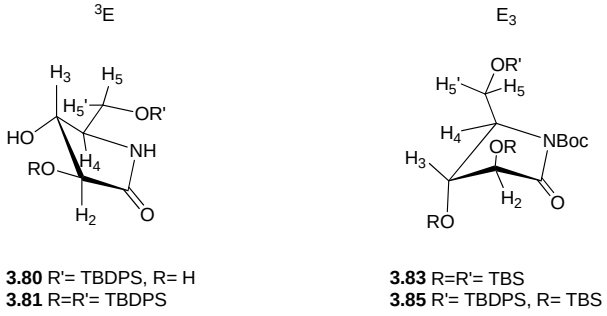
3.3.8. Structural elucidation of compounds

Configuration assignment of acyclic diasteromeric products, like those obtained from dihydroxylation, is usually realised by comparison of the spectroscopical data of further advanced cyclic intermediates, like in this case would have been nectrisine. The impossibility of reaching the end of our synthetic route prevented us from confirming the configuration of the diastereomeric dihydroxylated products. On the other hand, the anomalous disilylation observed in our hands of a process that had been reported to lead to monosilylation, put in us some doubts whether the major dihydroxylated product obtained in our route could be different from that leading to the nectrisine. This fact prompted us to analyze in detail the configuration of the obtained products by NMR techniques. Thus, we compared the spectroscopical data of **3.81** with those of related compounds (Table 3.7). Data of compounds **3.80** and **3.85** correspond to those reported in the bibliography for these compounds. Furthermore, we conducted a NOE experiment of compound **3.81**.

In Table 3.7, NMR data of compounds **3.80** and **3.81**, both without Boc protecting group at nitrogen, and **3.83** and **3.85** which have a protecting group in the nitrogen and are persilylated, are compared. The following observations can be deduced:

- Chemical shift and coupling constants values in **3.80** and **3.81** are very close.
- Chemical shift and coupling constants values in **3.83** and **3.85** are very close, and some differences can be attributed to the fact that spectra of **3.83** were recorded in a 400 MHz equipment while data of **3.85** were obtained in a 250 MHz equipment.

- Coupling constant values of $J_{2,3}$ and $J_{3,4}$ in **3.80** and **3.81** are ca. 7.5 Hz, while the former is around 1.5 Hz for **3.83** and **3.85** and $J_{3,4}$ is not provided, probably due to its low value. This is indicative of a diferent conformational bias of both groups of compounds, so that **3.80** and **3.81** exist in a ^3E conformation whereas **3.83** and **3.85** exist as a E_3 conformation, with the silyloxy groups in a pseudo-trans-diaxial conformation. (Scheme 3.20) This conformational change may be explained by the destabilization of the ^3E conformation in **3.83** and **3.85** due to severe gauche interactions of the bulky neighboring silyl groups altogether with the presence of of N-Boc group.
- The ^{13}C NMR spectra of **3.80** and **3.81** are very similar, and the chemical shifts of C4 and C5 are virtually coincident. ^{13}NMR Chemical shifts for **3.83** and **3.85** are practically identical, except for C_5, which is the position where the protecting groups are different.

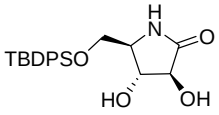
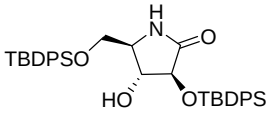
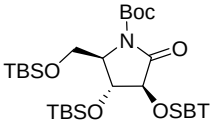
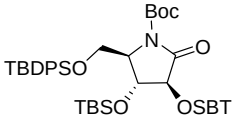


3.80 R'= TBDPS, R= H
3.81 R=R'= TBDPS

3.83 R=R'= TBS
3.85 R'= TBDPS, R= TBS

Scheme **3.20**. Conformations of lactams **3.80**, **3.81**, **3.83** and **3.85**

Table 3.7. Selected ^{1}H and ^{13}C NMR data of compounds **3.80**, **3.81, 3.83** and **3.85** (δ in ppm, *J* in Hz).

(δ in ppm)	 **3.80**	 **3.81**	 **3.83**	 **3.85**
H_2	4.28 (d, 1H) *J* = 7.5 Hz	4.28(d ,1H) *J* = 6.8 Hz	4.13 (t, 1H) *J* = 1.6 Hz	4.31 (t, 1H) *J* = 1.5 Hz
C_2	76.4	78.0	83.2	82.9
H_3	3.99 (t, 1H) *J* = 7.5 Hz	3.94(t, 1H) *J* = 6.8 Hz	3.95 (dd, 1H) *J* = 1.6, 0.8 Hz	4.13-3.96 (m, 2H)
C_3	75.9	77.2	71.8	72.0
H_4	3.52 (td, 1H) *J* = 7.5, 3 Hz	3.32(td, 1H) *J* = 7.2, 3.6 Hz	3.88-3.74 (m, 3H)	4.13-3.96 (m, 2H)
C_4	58.2	57.6	67.0	66.7
H_5	3.89 (dd, 1H) *J* = 10.5, 3 Hz	3.78 (dd, 1H) *J* = 10.8, 3.6 Hz	3.88-3.74 (m, 3H)	3.88-3.74 (m, 2H)
C_5	64.5	65.0	61.6	62.6
$H_{5'}$	3.62 (dd, 1H) *J*=10.5, 7.5 Hz	3.56 (dd, 1H) *J* = 10, 7.8 Hz	3.88-3.74 (m, 3H)	3.88-3.74 (m, 2H)
$C_{5'}$	64.5	65.0	61.6	62.6

The analysis of these data suggest that compounds **3.80** and **3.81** share the same configuration and similar conformation and the same applies to the pair of compounds **3.83** and **3.85**. Between these two groups of compounds, the configuration is identical but the conformation changes.

On the other hand, the results of the NOE study on compound **3.81** are the following:

Table 3.8. Selected NOE contacts in compound **3.81**.

Proton irradiated	NOE effect		
H_2	H_4 (XXX)		
H_3	H_5 (XXX)	H_4 (X)	
H_4	H_2 (XXX)	$H_{5'}$ (XXX)	H_3 (X)
H_5	H_3 (XXX)	H_4 (X)	

XXX= strong, X= weak

Relevant NOE correlsations are H_2-H_4 and H_3-H_5, which indicate that in compound **3.81** H_2 and H_4 are on the same face of the molecule, as well as H_3 and H_5.

These facts together with the conclusions of the previous comparative study, suggest that the configuration for compounds **3.81** and **3.83** is D-arabino, in agreement with that in the natural product nectrisine.

3.4. Experimental Part

3.4.1. General Methods

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLV system-4®). Toluene was purified using standard procedure.

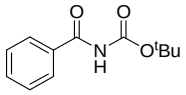
^{1}H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm ^{1}H, 77.23 ppm ^{13}C) or Me4Si as an internal reference (0.00 ppm). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. Elemental analysis (C, H, N, S) were performed on a Carlo Erba® EA 1108 Analyser in the Servei de Recursos Científics (SRCiT-URV). IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Melting points, determined with Reichert apparatus, are uncorrected.

Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F254 glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/H_2SO_4 (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF254 silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

The enantiomeric excess (ee%) determined via chiral HPLC analysis (chiralpack OD column, heptane:^{i}PrOH, flow rate 1 $mlmin^{-1}$).

3.4.2. Compound characterization

_t_-Butyl benzoylimido carboxylate (3.38).

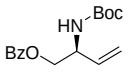


3.38

_t_-butyl alcohol (2.10 ml, 22.4 mmol) was added to a solution of benzoylisocyanate (2.56 ml, 20.4 mmol) in anhydrous dichlorometane 40 ml. The solution was stirred at room temperature for 18h. The evaporation of solvent provided the desired product **3.38** as a white solid in 96% yield (4.3 g).

IR (neat): 3249, 1746, 1675, 1501, 1483, 1370, 1364, 1143, 1128, 1100 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 8.3 (br s, 1H, NH), 7.8 (dd, 2H, *J* = 7.2, 1.2 Hz), 7.5 (tt, 1H, *J* = 14.8, 7.6 Hz), 7.4 (t, 2H, *J* = 7.6 Hz), 1.4 (s, 9H). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ= 165.4, 149.7, 133.5, 132.9, 128.8, 127.6, 82.9, 28.2**.** **ESI-HRMS** $[M+1]^+$ calcd for $C_{12}H_{16}NO_3$: 222.113, Found 222.113.

(2*S*)-2-((*tert*-Butoxycarbonyl)amino)but-3-1-yl benzoate (3.40).

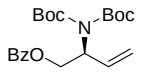


3.40

A 25 mL flamed-dried flask under vacuum, benzoylimido carboxylate **3.38** (0.4 g, 1.88 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.011 g, 0.03 mmol) and *R*,*R* ligand (0.07 g, 0.09 mmol) were added under argon and the flask was purged three times with argon. Then dry dichloromethane (40 mL) was added to the mixture and the solution was stirred 30 min at rt. Butadiene monoepoxide (0.11 ml, 1.57 mmol) was added in one portion and the resulting mixture was stirred at 35 °C for 18h. The resulting mixture was concentrated and purified by flash chromatography using 10:1 hexanes:ethyl acetate as a solvent to afford compound **3.40** as a white solid (0.44 g, 98%). The enantiomeric excess was 97% ee determined by chiral HPLC (chiralpack OD, heptane:^{i}PrOH 95:5, 1 $mlmin^{-1}$, t_R(R) = 6.2 min and t_R(S) = 7 min).

$[\alpha]_D^{25}$ = -41.8 (*c*1, $CHCl_3$). **IR** (neat): 3359, 3069, 2977, 1700, 1516, 1451, 1365, 1269, 1163, 1113, 1069, 709 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 8 .02 (dd, 2H, *J* = 8, 1.6 Hz), 7.54 (tt, 1H, *J* = 7.2 , 1.6 Hz), 7.42 (t, 2H, *J* = 8.4 Hz), 5.88 (ddd, 1H, *J* = 17.2, 10.4, 5.2 Hz) , 5.33 (dd, 1H, *J* =17.2, 2.8, 0.8 Hz), 5.23 (dd, 1H, *J* = 10.4, 2.8, 1.6 Hz), 4.86 (br s, 1H), 4.6 (br s, 1H), 4.35 (d, 2H, *J* = 4.8 Hz), 1.4 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ=166.4, 155.3, 134.8, 133.2, 129.8, 129.7, 128.4, 116.8, 79.8, 66.4, 51.8, 28.4. **ESI-HRMS** [M+23] calcd for $C_{16}H_{21}NaNO_4$: 314.1368, Found: 314.1347**.**

(2*S*)-2-((bis-*tert*-Butoxycarbonyl)amino)but-3-1-yl benzoate (3.41).

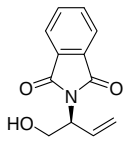


3.41

To a solution of product **3.40** (0.3 g, 1.03 mmol) in 11ml Et_3N were added DMAP (0.25 g, 2.06 mmol) and di-t-butyl dicarbonate (1.17 g, 5.36 mmol) at 0ºC, reaction stirred at 90ºC for 18h. Reaction quenched with NH_4Cl, the aqueous layer was extracted with AcOEt tree times and the combined organic layer was washed with H_2O, brine, dried ($MgSO_4$) and concentred in vacuo. The residue was chromatographed over SiO_2 (Hexane/AcOEt 10:2) to give product **3.41** as yellow liquide in 92% yield (0.37 g).

$[\alpha]_D^{25}$ = +28.2 (*c*0.85, $CHCl_3$). **IR** (neat): 3094, 2979, 2933, 1723, 1700, 1452, 1367, 1347, 1267, 1112, 855, 710 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz**,** δ in ppm): δ= 7.88 (dd, 2H, *J* =8.4, 1.2 Hz), 7.35 (tt, 1H, *J* = 7.6, 1.2 Hz) , 7.24 (t, 2H, *J* = 7.6 Hz), 5.8 (ddd, 1H, *J* = 17.2, 10.4, 6.4 Hz), 5.17 (dd, 1H, *J* =17.6, 1.2 Hz), 5.07 (dd, 1H, *J* =10.4, 1.2 Hz), 5.1 (m, 1H), 4.51(dd, 1H, *J* =10.8, 9.2 Hz), 4.41(dd, 1H, *J* = 11.2, 6 Hz), 1.4(s, 18H). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz, δ in ppm): δ=166.2, 152.8, 133.7, 133.1, 130.1, 129.8, 128.4, 118.4, 82.8, 64.8, 57.2, 28.1. **ESI-HRMS** [M+23] calcd for $C_{21}H_{29}NaNO_6$: 414.1893, Found: 414.1892.

2-(*S*)-3-buten-2-phthalimido-1-ol (3.43).

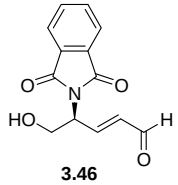


3.43

In a 250 ml flamed-dried flask, Na_2CO_3 (53 mg, 0.05 mmol), phthalimide (**3.42**) (1.47 g, 10 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (14.6 mg, 0.04 mmol) and (*R*,*R*) ligand (**3.39)** (94.6 mg, 0.12 mmol) were added under argon being the flask purged three times with argon. Then dry dichloromethane (80 ml) was added to the mixture and the solution was stirred 15 min at rt. Butadiene monoepoxide (810 μl, 10 mmol) was added in one portion and the resulting mixture was stirred at rt for 14h. The resulting mixture was concentrated and purified by flash chromatography, using 1:1 hexanes:ethyl acetate as a solvent, to afford 2.16 g of compound **3.43** (2.1 g, 98%) as a white solid. An enantiomeric excess of 96% ee was determined by chiral HPLC (chiralpack OD, heptane:^{i}PrOH 90:10, 1 mlmin^{-1}, t_R(S) = 14.1 min and t_R(R) = 16.9 min).

$[\alpha]_D^{25}$ = -65.9 (*c* 1, $CHCl_3$). **Mp** 60-63 ºC. **IR** (neat): 3527, 1763, 1702, 1656, 1609, 1467 and 1388 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz, δ in ppm): δ= 7.73 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.62 (dd, 2H, *J* = 5.6, 3.2 Hz), 6.06 (ddd, 1H, *J* = 17.6, 10.4, 7.2 Hz), 5.19 (ddd, 1H, *J* = 17.6, 1.2, 1.2 Hz), 5.18 (ddd, 1H, *J* = 10.0, 1.2, 1.2 Hz), 4.84 (m, 1H), 4.07 (ddd, 1H, *J* = 11.4, 8.4, 8.0 Hz), 3.86 (ddd, 1H, *J* = 11.4, 7.6, 4.6 Hz), 2.98 (dd, 1H, *J* = 8.0, 4.6). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ= 168.7, 134.3, 132.1, 131.9, 123.5, 119.0, 62.8, 56.1. **ESI-HRMS** [M+1] calcd for $C_{12}H_{12}NO_3$: 218.0817, Found: 218.0813.

(2*E*, 4*S*)-5-hydroxy-4-phthalimido-pent-2-en-1-al (3.46).

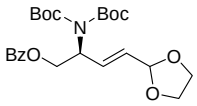


3.46

Compound **3.43** (50 mg, 0.23 mmol) was dissolved in dichloromethane (15 mL) at reflux. Hoveyda-Grubbs catalyst (8 mg, 0.012 mmol, 5%) was added to the solution and then the reaction mixture was stirred under argon. Acrolein (0.05 mL, 0.7 mmol) was added at that temperature over 2h by slowly addition. After 11h the crude was cooled and it was concentrated under vacuum and purified by flash chromatography using hexanes: ethyl acetate (2:1) to give compound **3.46** as an yellow oil (50 mg, 78%).

IR (neat): 3462, 2926, 2706, 1772, 1707, 1467, 1383, 1063, 877, 796, 718 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ = 9.54 (d, 1H, *J* = 8.0 Hz), 7.83 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.72 (dd, 2H, *J* = 5.2, 3.6 Hz), 7.03 (dd, 1H, *J* = 16.0, 4.0 Hz), 6.12 (dd, 1H, *J* = 16.0, 8.0 Hz), 5.17 (m, 1H), 4.18 (m, 1H), 4.09-4.04 (m, 5H). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ = 193.1, 168.2, 149.9, 134.7, 133.8, 131.8, 62.1, 60.6, 54.1, 21.2, 14. 3.

(2*S*,3*E*)-2-{bis[(*tert*-butoxy)carbonyl]amino}-4-(1,3-dioxolan-2-yl)but-3-en-1-yl benzoate (3.51).

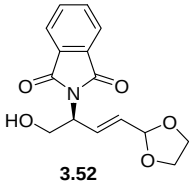


3.51

To a solution of product **3.41** (0.1 g, 0.26 mmol) and (0.011 g, 0.013 mmol) of II generation Grubbs catalyst in dichlorometane (6 ml) was added vinyldioxolane (0.13 ml, 1.3 mmol) at 55ºC. Reaction stirred at 55ºC for 12h, evaporation of solvent and purification by silica chromatography (Hexan:AcOEt, 10:3) provided the desired product **3.51** in 82% conversion and 78% yield (0.094 g).

IR (neat): 2979, 2933, 2888, 1721, 1701, 1367, 1348, 1267, 1147, 1113, 968, 712 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 8.02 (d, 2H, *J* =8.4 Hz), 7.54 (t, 1H, *J* =7.6 Hz), 7.41 (t, 2H, *J* = 7.6 Hz), 6.11 (dd, 1H, *J* = 16, 6.4 Hz), 5.74 (dd, 1H, *J* = 16, 6 Hz), 5.28 (d, 1H, *J* = 6 Hz), 5.26 (m, 1H) , 4.59 (t, 1H, *J* = 10.8 Hz), 4.85 (dd, 1H, *J* = 6, 11.2 Hz), 3.94 (m, 4H), 1.45(s, 18H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz**,** δ in ppm): δ= 166.3, 152.6, 133.3, 131.5, 130.1, 130.0, 128.5, 103.2, 83.1,65.2, 64.7, 55.9, 28.2. **ESI-HRMS** [M+23] calcd for $C_{24}H_{33}NaNO_8$: 486.2104, Found: 486.2109.

(2*S*,3*E*)-4-(1,3-dioxalan-2-yl)-2-phthalimido-but-3-en-1-ol (3.52).

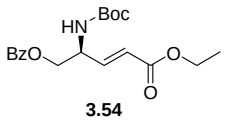


3.52

Compound **3.43** (50 mg, 0.23 mmol) was dissolved in dichloromethane (25 ml) at room temperature. Second generation Grubbs catalyst (5%) was added to the solution and then the reaction mixture was refluxed under argon. Compound **3.50** (0.1 ml, 0.92 mmol) was added at that temperature over 2 h by slowly addition. After 10 h the crude was cooled and it was concentrated under vacuum and purified by flash chromatography using hexanes: ethyl acetate (3:1) to give compound **3.52** as an yellow oil (57 mg, 81%).

$[\alpha]_D^{25}$= +34.0 (*c* 2.7, CH_2Cl_2). **IR** (neat): 3471, 2924, 2854, 1774, 1703, 1466, 1382, 1312, 1273, 1180, 1123, 1029, 719 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ = 7.85-7.81 (m, 2H), 7.77-7.72 (m, 2H), 6.28 (dd, 1H, *J* =16.0, 6.8 Hz), 5.72 (dd, 1H, *J* = 16.0, 5.8 Hz), 5.25 (d, 1H, *J* = 5.8 Hz), 4.95 (m, 1H), 4.12 (m, 1H), 3.67 (m, 2H), 3.87 (m, 1H), 3.74 (m, 1H), 3.6 (m, 1H), 3.01 (brs, 1H, OH). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ = 168.6, 134.4, 131.9, 131.2, 129.9, 123.6, 102.9, 72.5, 65.2, 62.8, 54.6. **ESI-HMRS** [M+1] calcd for $C_{15}H_{46}NO_5$: 290.1028, Found: 290.1009.

Ethyl (2*E*,4*S*)-5-benzoyloxy-4-((*tert*-butoxycarbonyl)amino)-pent-2-enoate (3.54).

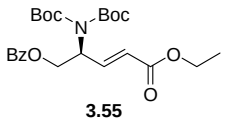


3.54

To a solution of product **3.40** (0.1 g, 0.34 mmol) and (0.011 g, 0.017 mmol) of Hoveyda-Grubbs catalyst in dichlorometane (9 ml) was added ethylacrylate (0.25 ml, 2.38 mmol) at 55ºC. Reaction stirred at 55ºC for 12h, evaporation of solvent and purification by silica chromatography Hexan/AcOEt (15:1) provided the desired product **3.55** in 96% yield (0.12 g).

$[\alpha]_D^{25}$= -1.06 (*c*1.3, $CHCl_3$). **IR** (neat): 3336, 2976, 2935, 1663, 1585, 1452, 1367, 1312, 1072, 1025, 864, 734 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 7.95 (dd, 2H, *J* = 8.4, 1.2 Hz), 7.50 (td, 1H, *J* = 7.2, 1.2 Hz), 7.37 (t, 2H, *J* = 7.2 Hz), 6.92 (dd, 1H, *J* = 15.6, 5.2 Hz), 6.04 (dd, 1H, *J* = 15.6, 1.6 Hz), 5.24 (br d, 1H, *J*= 8.8 Hz), 4.37 (d, 2H, *J* = 4.4 Hz), 4.14(q, 2H, *J* = 7.2 Hz), 1.37 (s, 18H), 1.22 (t, 3H, *J* = 7.6 Hz); **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ= 166.2, 165.8, 155.1, 144.2, 133.3, 129.7, 129.6,129.4, 128.4, 128.3, 122.8, 80, 65.7, 60.7, 50.7, 28.2, 14.1. **ESI-HRMS** [M+23] calcld for $C_{19}H_{25}NaO_6$: 386.1580, Found: 386.1594.

Ethyl (2*E*,4*S*)-5-benzoyloxy-4-((bis-*tert*-butoxycarbonyl)amino)-pent-2-enoate (3.55).

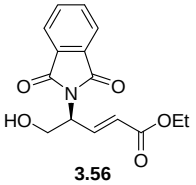


3.55

To a solution of product **3.42** (0.3 g, 0.77 mmol) and (0.024 g, 0.0385 mmol) of Hoveyda-Grubbs catalyst in dichlorometane (20 ml) was added ethylacrylate (0.41 ml, 3.85 mmol) at 55ºC. Reaction stirred at 55ºC for 12h, evaporation of solvent and purification by silica chromatography Hexan/AcOEt (15:1) provided the desired product **3.55** as yellow liquid in 98% yield (0.35 g).

$[\alpha]_D^{25}$= +13.8 (*c*1.1, $CHCl_3$). **IR** (neat) : 2979, 1720, 1452, 1367, 1350, 1265, 1231, 1149, 1112, 975, 854, 710 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 8 (d, 2H, *J* = 8.4 Hz), 7.52 (t, 1H, *J* = 7.6 Hz), 7.4 (t, 2H, *J* = 8 Hz), 7.02 (dd, 1H, *J* = 16, 5.2 Hz), 6.97 (dd, 1H, *J* = 16, 1.6 Hz), 5.3 (m, 1H), 4.56 (dd, 2H, *J* =8.4 4.8 Hz), 4.17(q, 2H, *J* = 7.6 Hz), 1.43 (s, 18H), 1.25 (t, 3H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ= 166.0, 165.8, 152.1, 143.5, 133.6, 133.2, 129.7, 129.6, 128.3, 122.8, 83.3, 64.2, 60.6, 55.3,27.9, 14.2. **ESI-HRMS** [M+23] calcld for $C_{24}H_{33}NNaO_8$: 486.2104, Found: 486.2123.

Ethyl (4*S*,2*E*)- 5-hydroxy-4-phthalimido-pent-2-enoate (3.56).

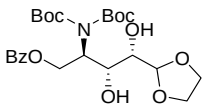


3.56

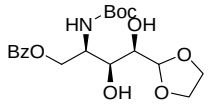
Compound **3.43** (50 mg, 0.23 mmol) and compound **3.54** (0.1 ml, 0.92 mmol) were dissolved in dichloromethane (25 ml) at room temperature. Second generation Grubbs catalyst (5%) was added to the solution and then the reaction mixture was refluxed under argon for 12h. After cooling the reaction mixture it was concentrated under vacuum and purified by flash chromatography using petroleum ether: ethyl acetate (3:2) to give compound **3.56** as a colorless oil (40 mg, 71%).

IR (neat): 3470, 3102, 3083, 2924, 2854, 1774, 1703, 1384, 1314, 1273, 1180, 1027, 719 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 7.92-7.85 (m, 2H), 7.79-7.71 (m, 2H), 7.12 (dd, 1H, *J* = 15.9, 6.0 Hz), 5.92 (d, 1H, *J* = 15.9 Hz) 5.09 (m, 1H), 4.19 (q, 2H, *J* = 6.9 Hz), 4.05 (m, 2H), 3.00 (brs, 1H), 1.27 (t, 3H, *J* = 6.9 Hz). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ = 168.4, 165.7, 141.2, 134.7, 131.7, 124.2, 123.8, 62.6, 61.0, 54.2, 14.4.

(2*R*,3*R*,4*S*)-2-((bis-*tert*-butoxy)carbonyl)amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (3.58).
(2*R*,3*S*,4*R*)-2-((bis-*tert*-butoxy)carbonyl)amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (3.59).



3.58



3.59

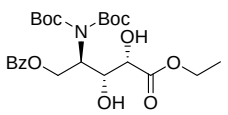
To a solution of product **3.51** (0.28 g, 0.6 mmol) in 25ml dichlorometane were added (0.38 g, 1.5 mmol) NMO and (0.044 ml, 0.015 mmol) OsO_4 in water at 0ºC, reaction stirred at room temperature for 24h. Reaction quenched by $Na_2S_2O_3$ stirred for 15min, the aqueous layer was extracted with AcOEt tree times and the combined organic layer was washed, brine, dried ($MgSO_4$) and concentred in vacuo. Purification

of product (Hexane/AcOEt) provided two products **3.58** (0.2 g, 70%) and **3.59** (0.06 g, 25%)

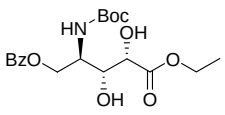
Compound **(3.58). $[\alpha]_D^{25}$**= -3.6 (*c*0.7, $CHCl_3$). **IR** (neat): 3481, 2978, 2924, 1720, 1702, 1367, 1349, 1269, 1148, 1070, 852, 712 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 8.02 (dd, 2H, *J* = 8, 1.2 Hz), 7.54 (tt, 1H, *J* = 7.2, Hz 1.6), 7.42 (t, 2H, *J* = 7.6 Hz), 5.04 (d, 1H, *J* = 4 Hz), 4.8 (dd, 2H, *J* = 6.4, 2 Hz), 4.58 (ddd, 1H, *J* = 8.8, 4.8 Hz), 4.32 (t, 1H, *J* = 8 Hz), 3.98 (m, 4H), 3.67 (t,1H, *J* = 4.8Hz), 3.07 (br s, 1H), 1.64 (brs, 1H), 1.44 (s, 18H). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ= 166.3, 153.9, 133.1, 130.1, 129.9, 128.4, 104.1, 83.5, 70.5, 69.8, 65.6, 65.4, 63.3, 58.1, 28.06. **ESI-HRMS** [M+23] calcld for $C_{24}H_{35}NNaO_{10}$: 520.2159, Found: 520.2128.

Compound **(3.59). $[\alpha]_D^{25}$**= -9 (c0.18,$CHCl_3$). **IR** (neat): 3339, 2972, 2899, 2357, 1717, 1455, 1378, 1271, 1086, 1046, 880, 668 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400MHz**,** δ in ppm): δ= 8.01 (dd, 2H, *J* = 8.8, 1.2 Hz), 7.57 (tt, 1H, *J* = 7.2 1, 6 Hz), 7.44 (t, 2H, *J* = 7.2 Hz), 5.04 (d, 1H, *J* = 5.2 Hz), 4.65 (m, 3H), 4.4 (dd,1H, *J* = 13.2, 3.6 Hz), 3.97 (m, 4H), 3.66 (brs, 1H), 2.60 (brs, 1H), 1.64 (br s, 1H), 1.52 (s, 9H). **^{13}C NMR** ($CDCl_3$**,** 100.6MHz**,** δ in ppm): δ= 166.2, 149.1, 133.6, 129.9, 129.1, 128.7, 102.0, 84.6, 74.6 , 72.6, 65.6, 65.4, 63.6, 55.6, 28.1. **ESI-HRMS** [M+23] calcld for $C_{19}H_{27}NNaO_8$: 420.1634, Found: 420.1582.

Ethyl (2*S*,3*R*,4*R*)-5-(benzoyloxy)-4-((bis-*tert*-butoxycarbonyl)amino)-2,3-dihydroxy-penta noate (3.62) and ethyl (2*S*,3*S*,4*S*)-5-(benzoyloxy)-4-((*tert*-butoxycarbonyl)amino)-2,3-dihydroxy- pentanoate (3.63).



3.62



3.63

Method A

To a solution of product **3.55** (0.7 g, 1.5 mmol) in 50 ml dichlorometane were added (0.44 g, 3.75 mmol) NMO and (0.47 ml, 0.075 mmol) OsO_4 in water at 0ºC,

reaction stirred at room temperature for 24h. Reaction quenched by $Na_2S_2O_3$ stirred for 15 min, the aqueous layer was extracted with AcOEt tree times and the combined organic layer was washed, brine, dried ($MgSO_4$) and concentred in vacuo. Purification of product (Hexane/AcOEt) provided two products **3.62** (0. 447g, 60%) and **3.63** (0.214 g, 36%**)** as yellow liquid**.**

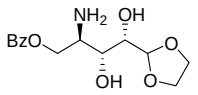
Method B

Compound **3.55** (0.1 g, 0.2 mmol) was dissolved in CH_2Cl_2 (14ml) at -78ºC under dry argon. TMEDA (0.033 ml, 0.22 mmol) was added and the reaction stirred for 5 minutes before the rapid a addition of osmium tetraoxide (0.06 g, 0.22 mmol). The dark coloured solution was stirred for 1 hour at -78ºC before being warmed to room temperature and stirred for 5h . The solvent was removed *in vacuo* and the black solide was resolved in methanol (5ml).Concentrated hydrochloric acid (3drop) was added and the reaction stirred for 2 hours.the solvent was removed *in vacuo* to afford a product **3.63** in 90% yield.

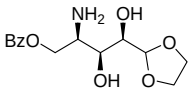
Compound **(3.62). $[\alpha]_D^{25}$** = -6.2 (*c*10, $CHCl_3$). **IR** (cm^{-1}): 3484, 2979, 2931, 1723, 1452, 1367, 1348, 1268, 1227, 1149, 1114, 711. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 8.02 (dd, 2H, *J* = 7.6, 1.2 Hz), 7.5 (tt, 1H, *J* = 7.2, 1.2 Hz), 7.4 (t, 2H, *J* = 7.6 Hz), 4.79 (m ,2H) , 4.66 (m, 1H), 4.48 (t, 1H, *J* = 9.2 Hz), 4.3 (m, 3H), 3.50 (d, 1H, *J* =4.8 Hz), 3.20 (d , 1H, *J* = 9.2 Hz), 1.42 (s, 18H), 1.28 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ= 172.8, 166.3, 154.9, 133.1, 130.1, 129.8, 128.3, 83.5, 71.9, 70.8, 62.3, 63.1, 58.0, 27.9, 14.2. **ESI-HRMS** [M+23] calcd for $C_{24}H_{35}NNaO_{10}$: 520.2159, Found: 520.2156.

Compound (**3.63). $[\alpha]_D^{25}$** = + 23.1 (*c*6, $CHCl_3$). **IR** (neat): 3472, 2981, 2935, 1804, 1722, 1370, 1267, 1208,1154, 1115, 1066, 710 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 8.01 (dd, 2H, *J* = 8, 0.8 Hz), 7.95 (tt, 1H, *J* = 7.6, 1.2Hz), 7.45 (t, 2H, *J* =7.6 Hz), 4.77 (t, 1H, *J* = 2.8 Hz) , 4.63 (m, 2H), 4.52 (dd , 1H, *J* = 10.8, 2 Hz), 4.31 (m, 3H) , 3.31 (d, 1H, *J* = 4.8 Hz), 1.61 (brs, 1H), 1.55 (s, 9H), 1.32 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ= 170.4, 166.1, 148.8, 133.7, 129.9, 129.0, 128.7, 84.8, 75.6, 71.3, 63.7, 63.1, 55.5, 28.0, 14.1. **ESI-HRMS** [M+23] calcd for $C_{19}H_{28}NO_8$: 398.1815, Found: 398.1817.

(2*R*,3*R*,4*S*)-2-amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (3.69) (2*R*,3*S*,4*R*)-2-amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (3.70).



3.69



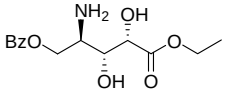
3.70

To a solution of mixture **3.59, 3.60** (0.1 g, 0.2 mmol) in CH_2Cl_2 (1 ml) was treated with triftuoroacetic (1 ml). The mixture was then stirred for 2h at 0ºC. Removal of all volatiles under reduced pressure gave two products one soluble in MeOH (**3.69**, Maj, 0.024 g, 40%) and other soluble in $CDCl_3$ (**3.70**, Min, 0.018 g , 30%).

Compound (3.69). $[\alpha]_D^{25}$ = +8.7 (*c*0.8,CH_3OH). **IR** (neat): 3343, 2922, 1719, 1668, 1540, 1271, 1181, 1131, 1044, 974, 836, 708 cm^{-1}. **^{1}H NMR** (CD_3OD, 400 MHz**,** δ in ppm): δ= 8.13 (d, 2H, *J* = 7.2 Hz), 7.64 (t, 1H, *J* = 6.8 Hz), 7.51 (t, 2H, *J* = 8 Hz), 5.06 (d, 1H, *J* = 4.4 Hz), 4.75 (dd, 1H, *J* = 12, 3.6 Hz), 4.56 (dd, 1H, *J* = 12, 7.2 Hz), 4.11 (dd, 1H, *J* = 6, 3.6 Hz), 3.98 (m, 4H), 3.82 (m, 1H), 3.72 (t, 1H, *J* = 3.6 Hz). **^{13}C NMR (**CD_3OD, 100.6 MHz**,** δ in ppm): δ= 158, 125.1, 121.3, 121.1, 120.1, 94.7, 63.6, 59.4, 56.9, 56.8, 53.7, 45.1. **ESI-HRMS** [M+] calcd for $C_{14}H_{20}NO_6$: 298,1291, Found: 298.1288.

Compound (3.70). $[\alpha]_D^{25}$ = +13.8 (*c*1,$CHCl_3$). **IR** (neat): 3343, 2922, 1750, 1718, 1451, 1394, 1315, 1270, 1114, 1070, 1027, 712 cm^{-}1. **^{1}H NMR** ($CDCl_3$, 400 MHz**,** δ in ppm): δ= 8.01 (d, 2H, *J* = 7.6 Hz), 7.59 (t, 1H, J=6.8Hz), 7.46 (t, 2H, *J* = 7.6 Hz), 5.37(brs, 1H), 5.06 (d, 1H, *J* = 4.8 Hz), 4.64 (dd, 1H, *J* = 4.8, 2.8 Hz), 4.51 (dd, 1H, *J* = 10.8, 3.2 Hz), 4.30 (m, 2H), 3.98 (m, 4H), 3.68 (brs, 1H), 2.60 (brs, 1H). **ESI-HRMS** [M+23] calcd for $C_{14}H_{19}NNaO_6$: 320.111 , Found: 320.2526.

Ethyl (2*S*,3*R*,4*R*)-4-amino-5-(benzoyloxy)-2,3-dihydroxypentanoate (3.71).

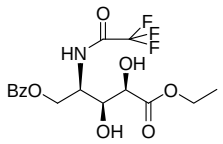


3.71

To a solution of **3.62** (0.8 g, 1.6 mmol) in CH_2Cl_2 (8 ml) was treated with triftuoroacetic (8 ml). The mixture was then stirred for 2h at 0ºC. Removal of all volatiles under reduced pressure gave a product **3.71** in 90% yield (0.42 g).

$[\alpha]_D^{25}$ = + 16.6 (*c*1.1, MeOH). **IR** (neat): 3244, 2968, 1717, 1601, 1451, 1375, 1268, 1098, 1070, 1025, 862, 710 cm^{-1}. **^{1}H NMR** (CD_3OD**,** 400 MHz**,** δ in ppm): δ= 8.04 (d, 2H, *J* = 7.6 Hz), 7.56 (t, 1H, *J* = 7.2 Hz), 7.43 (t, 2H, *J* = 8 Hz), 4.68 (dd, 1H, *J* = 12, 3.6 Hz), 4.51 (dd, 1H, *J* = 12, 6.4 Hz), 4.35 (d, 1H, *J* = 2.4 Hz), 4.25 (dd, 1H, *J* = 2.8, 6 Hz), 4.18 (m, 2H), 3.77 (brs, 1H), 1.22 (t, 3H, *J* = 1.8 Hz). **^{13}C NMR** (CD_3OD, 100.6 MHz, δ in ppm) δ= 171.7, 166.0, 133.2, 129.4, 129.1, 128.2, 71.4, 68.3, 61.7, 61.3, 53.0, 13.0 . **ESI-HRMS** [M+1] calcd for $C_{14}H_{20}NO_6$ m/z $[M+H]^+$: 298.1291, Found: 298.1253

Ethyl (2*R*,3*S*,4*R*)-5-(benzoyloxy)-2-3-dihydroxy-4-(trifluoroacetamido)pentanoate (3.73).

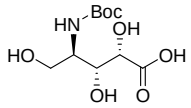


3.73

To a solution of compound **3.63** (0.05 g, 0.12 mmol) in EtOH (0.6 ml) was treated with triftuoroacetic (0.6 ml) at 0ºC. The mixture was then stirred for 4h30 min at8 0ºC. Removal of all volatiles under reduced pressure provided desired product **3.73** in 60% yield (0.028 g).

$[\alpha]_D^{25}$ = +32.3 (*c*1.8,$CHCl_3$). **IR** (neat) : 3343, 2986, 1717, 1451, 1395, 1315, 1369, 1116, 1070, 1025, 862, 711 cm^{-1}. ^{1}H NMR ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 8 (dd, 2H, *J* = 8, 1.2 Hz), 7.57 (tt, 1H, *J* =7.2, 2.8 1.6 Hz), 7.43 (t, 2H, *J* = 8Hz), 6.2 (s, 1H), 4.77 (dd, 1H, *J* = 4.4, 1.6 Hz) , 4.47 (dd, 1H, *J* = 13, 6 Hz), 4.31 (m, 5H), 3.27 (brs, 2H), 1.29 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ= 170.8, 166.3, 158.7, 133.7, 129.9, 129.2, 128.8, 128.7, 79.0, 71.2, 65.4, 62.9, 52.7, 14.2. **ESI-HRMS** [M+] calcd for $C_{16}H_{18}F_3NO_7$: 393.1035, Found: 392.0977.

(2*S*,3*R*,4*R*)-4-((*tert*-butoxycarbonyl)amino)-2,3,5-trihydroxypentanoic acid (3.78).

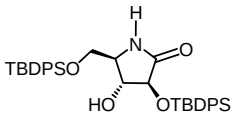


3.78

Product **3.62** (0.1 g, 0.2 mmol) was dissolved in dry ethanol (1 ml), and NaOEt (catalytic amount) was added. The reaction mixture was stirred at room temperature for 4h. Removal of EtOH under reduced pressure provided desired product **3.78** which is soluble in MeOH (0.052 g , 99%)**.**

$[\alpha]_D^{25}$= +19.36 (*c*1.57, CH_3OH). **^{1}H NMR** (CD_3OD**,** 400 MHz**,** δ in ppm): δ= 3.96 (s,1H) , 3.81 (m,1H), 3.65 (m, 3H), 1.4 (s, 9H), **^{13}C NMR** (CD_3OD**,** 100.6 MHz**,** δ in ppm): δ= 177.6, 156.7, 78.5, 70.9, 70.5, 60.7, 53.2, 26.75. **ESI-HRMS** [M+23] calcd. for $C_{10}H_{19}NNaO_7$: 288.1059, Found: 288.1043.

(3*S*,4*R*,5*R*)-3-(*tert*-butyldiphenylsilyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-4-hydroxypyrrolidin-2-one (3.81).



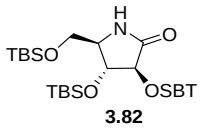
3.81

An ice-cooled solution of dihidroxy ester **3.79** (0.03g, 0.076 mmol) in CH_2Cl_2 (0.4ml) was treated with trifluoroacetic acid (0.4ml).The mixture was than stirred for 2h at 0ºC .Removal of all volatiles under reduced pressure gave residue which was dissolved in dry DMF (1ml) and treated under argon with *tert*-butyldiphenyl chloride (0.022 ml, 0.085 mmol) and imidazole (0.015 g, 0.22 mmol).The mixture was then stirred for 16h at room temperature. Workup (extraction with Et_2O) and column chromatography on silica gel (10:3) Hexan/EtOAC provided **3.81** in 30% yield (0.014 g).

$[\alpha]_D^{25}$ = +6.3 (*c*0.3, $CHCl_3$). **IR** (neat): 2928, 2324, 1698, 1428, 1264, 1111, 896, 820, 702, 607 cm^{-1}. **^{1}H NMR** ($CDCl_3$**,** 400 MHz**,** δ in ppm): δ= 7.86 (d, 2H, *J* = 7.6 Hz),

7.75 (d, 2H, *J* = 7.6 Hz) 7.61 (m, 4H), 7.42 (m, 12H), 5.73 (s, 1H, NH), 4.28 (d, 1H, *J* = 6.8 Hz), 3.94 (td, 1H, 6.8, 3.6 Hz), 3.78 (dd, 1H, *J* = 10.8, 3.6 Hz), 3.56 (dd, 1H, *J* = 7.2, 10, 7.8 Hz), 3.32 (td, 1H, *J* = 7.2, 3.6 Hz), 1.11 (s, 9H), 1.05 (s. 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm)**:** δ= 172.2, 136.3, 135.9, 135.7 (2C), 134.5, 133.0, 132.9, 132.3, 130.4, 130.2 (3C), 128.3, 128.1 (3C), 78.0, 77.2, 65.0, 57.6, 27, 19.4 (2C). **ESI-HRMS** [M+46] calcd for $C_{37}H_{45}Na_2NO_7$: 669.2683, Found: 669.2888.

(3*S*,4*R*,5*R*)-3,4-bis-(*tert*-butyldimethylsilyloxy)-5-((*tert*-butyldimethyldimethylsilyl)oxy Methyl)pyrrolidin-2-one (3.82).

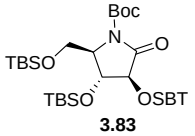


3.82

Lactam **3.79** (0.029 g, 0.2 mmol) was dissolved in dry DMF (1ml) and treated under argon with *tert*-Butyldimethylsilyl chloride (0.12 ml, 0.66 mmol) and imidazole (0.09g, 1.32 mmol).The mixture was then stirred for 16h at room temperature .workup (extraction with Et_2O) and column chromatography on silica gel (30:1) Hexan/EtOAC provided **3.82** as oil (0.034 g, 35%).

^{1}H NMR ($CDCl_3$, 400 MHz**,** δ in ppm): δ= 5.74 (brs, 1H), 4.11 (d, 1H, *J* = 5.6 Hz), 3.88 (t, 1H, *J* = 5.6 Hz), 3.80 (dd, 1H, *J* = 9.6, 4 Hz), 3.48 (dd, 1H, *J* = 10 Hz), 3.38 (td, 1H, *J* = 8.8 Hz, *J* = 4.8 Hz), 0.91 (s, 1H), 0.89 (s, 1H), 0.88 0.19 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 173.4, 77.9, 76.8, 64.4, 60.5, 25.9, 25.7 (2C), 18.3, 17.9, -4.0, -4.1, -4.5, -4.6, -5.3.

***tert*-butyl (3*S*,4*R*,5*R*)-*N*-*tert*-butoxycarbonyl-3,4-bis[(*tert*-butyldimethylsilyl)oxy]-5-((*tert*-butyldimethylsilyloxy)methyl)-2-pyrrolidin-2-one(3.87).**



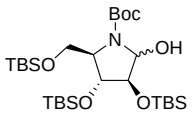
3.83

To stirred solution of **3.82** (0.045g, 0.1 mmol), Et_3N (0.013 ml, 0.13 mmol) and DMAP (catalytic amount) in CH_2Cl_2 (4 ml) was added $(Boc)_2O$ (0.03g, 0.03 mmol) at room temperature. After being stirred for overnight, the solvents were removed under

reduced pressure. The residue was then partitioned with H_2O and EtOAC. The aqueous layer was extracted with EtOAC (3 times) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated in *vacuo*. The residue was chromatographed over SiO_2 (Hexane:EtOAC, 99:1) To give **3.83** as an oil (0.025 g, 50%).

$[\alpha]_D^{25}$ = -19.1 (*c* 0.2, $CHCl_3$), **IR**(neat): 2928, 1791, 1718, 1263, 1110, 835, 781, 735, 703 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 4.13 (t, 1H, *J*=1.6 Hz), 3.95 (d, 1H, *J* = 1.6 Hz), 3.88-3.74 (m, 3H), 1.52 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.10 (s, 6H), 0.053 (s, 3H), 0.042 (s, 3H). **^{13}C NMR** ($CDCl_3$**,** 100.6 MHz**,** δ in ppm): δ= 172.3, 150.3, 83.2, 78.5, 71.8, 67.0, 61.6, 28.2, 26.0, 25.9, 25.8, 18.4, 18.3(2C), 18.1, -4.2, -4.4 (2C), -4.9, -5.2 (2C). **ESI-HRMS** [M+Na] calcd for $C_{28}H_{59}NNaO_6Si_3$: 612.3548, Found: 612.3568.

***tert*-butyl (3*S*,4*R*,5*R*)-*N*-*tert*-butoxycarbonyl-3,4-bis(*tert*-butyldimethylsilyloxy)-5-((*tert*-butyldimethylsilyloxy)methyl)-2-hydroxypyrrolidine (3.84).**



3.84

To a precooled (-78ºC) solution of **3.87** (0.024 g, 0.041 mmol) in THF (1 ml) under argon atmosphere $LiEt_3BH$ (0.06 ml of a 1M THF solution, 0.053 mmol) was slowly added. After being stirred at -78°C for 2h, the solution was quenched at this temperature with methanol (1ml) and subsequently with 2 ml of saturated aqueous $NaHCO_3$ solution. The resulting foamy slurry was allowed to warm to room temperature and then it was vigorously extracted with EtOAc (3 times). The extracts were dried (MgSO4) and concentrated *in vacuo.* The residue was chromatographed over SiO_2 (Hexane/ EtOAc, 50:1) to give (0.010 g, 42%) of **3.88** as an oil.

$[\alpha]_D^{25}$ = -15.2 (*c*0.1, $CHCl_3$). **IR**(neat): 2955, 2928, 1700, 1471, 1390, 1255, 1090, 835, 778, 738 cm^{-1}.**^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm) δ= 5.34 (brs, 0.5H), 5.15 (brs, 0.5H), 4.17 (brs, 1H), 3.86 (t, 1H, *J* = 4 Hz), 3.63 (brs, 2H), 3.49 (brs, 1H), 3.26 (brs, 1H), 1.47 (s, 18H), 0.92 (s, 9H), 0.89 (s, 9H), 0.86 (s, 9H), 0.13 (s, 1H), 0.08 (s, 1H),

0.07 (s, 1H), 0.06 (s, 1H), 0.05 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm) δ= 157.9, 80.3, 76.1, 66.9, 65.8, 62.1, 28.6, 26.1, 26.0, 25.9, 18.4, 18.3, 18.0, -4.4, -4.6 (2C), -4.8, -5.4(2C).

CHAPTER IV

ENANTIOSELECTIVE SYNTHESIS OF CIDOFOVIR ANALOGUES

4.1. Introduction

Over the past 35 years,[114a] antiviral drug discoveries[114b,115] have attracted the interest of both organic and medicinal chemists to propose new potential drugs for the treatment of viral infections, including DNA viruses and retroviruses. Among the various classes of antiviral drugs, acyclic nucleoside and nucleotide derivatives[116,117] have received considerable attention due to their ability to inhibit viral DNA polymerases and reverse transcriptases, which play key roles in the viral cycles. Acyclic nucleoside phosphonates (ANPs) belong to a family of modified nucleotide analogues, in which the sugar moiety has been replaced by a functionalized acyclic chain linking the nucleobase at one end and the phosphonic acid group at the other. Therefore, ANPs are metabolically stable due to the presence of a phosphonate linkage (P–C) instead of a phosphoester (P–O), making these compounds resistant towards phosphatases. Furthermore, they do not require the first intracellular phosphorylation step which is often considered as a limiting-step and essential for the antiviral effect. Indeed, ANPs share their mechanism of action with other nucleoside analogues. Briefly, after two subsequent phosphorylation steps the ANP is converted to its corresponding triphosphate derivative, which can then interfere with nucleic acid biosynthesis as a DNA chain terminator.[118]

Most of the antiviral compounds that are currently used in the treatment of herpesvirus (herpes simplex virus (HSV), varicella-zoster virus (VZV), and cytomegalovirus (CMV) infections[119] can be described as acyclic nucleoside analogues: acyclovir, penciclovir, and ganciclovir (Figure 4.1). To increase their oral bioavailability, acyclovir, ganciclovir, and penciclovir have been converted to their oral prodrug forms (termed valaciclovir, valganciclovir, and famciclovir, respectively). Following their absorption from the gut, these compounds are reconverted to the parent compounds before reaching their target organ(s).[114c]

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114 a) Kasthuri, M.; Chaloin, L;. Perigaud, Christian.; Pyrottes, S. *Tetrahedron : Asymmetry* **2011**, 1505-1511. b) De Clercq, E. *Med. Res. Rev.* **2008,** *28*, 929–953, c) De Clercq, *Clin. Microbiol. Rev*. **2003**, 569-596.

115 De Clercq, E. *Rev. Med. Virol.* **2009**, *19*, 287–299.

116 De Clercq, E. *Biochem. Pharmacol*. **2011**, *82*, 99–109.

117 De Clercq, E. *Biochem. Pharmacol.* **2007**, *73*, 911–922.

118 De Clercq, E.; Holy, A. *Nat. Rev. Drug Disc.* **2005**, *4*, 928–940.

119 De Clercq, E. *Rev. Med. Virol.* **1995**, *5*, 149–164.

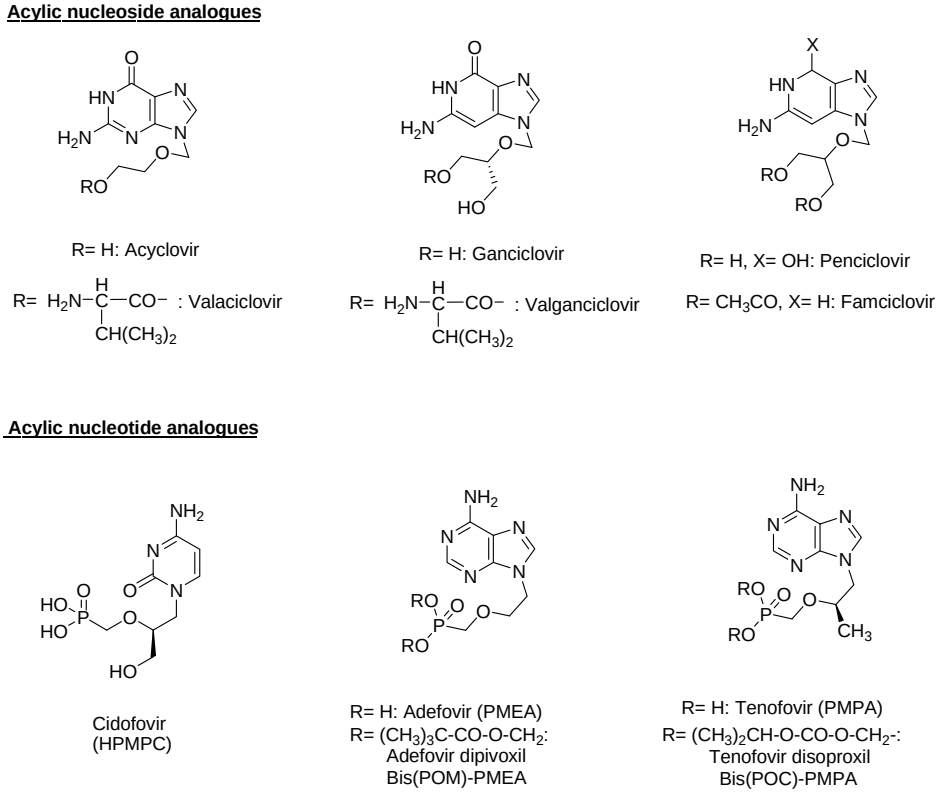

Figure 4.1. Acyclic nucleoside analogues and acyclic nucleotide analogues (acyclic nucleoside phosphonates)[114c]

After the acyclic nucleoside analogues have been taken up by the cells, they have to be phosphorylated through three consecutive phosphorylation steps (Figure 4.2) before they can interact, in their triphosphate form, with their target enzyme, the viral DNA polymerase. Of crucial importance in this phosphorylation process is the first phosphorylation step which is ensured by a specific virus-encoded thymidine kinase (TK) (for HSV and VZV) or a specific virus-encoded (UL97) protein kinase (PK) (for CMV).[120] Once the compounds have been phosphorylated to the monophosphate, cellular kinases (i.e., GMP kinase and NDP kinase) will afford their further phosphorylation to the di- and triphosphate stages.[121] In their triphosphate form, the compounds then interact as competitive inhibitors or alternate substrates with the normal substrates [2'-deoxynucleoside 5'-triphosphates (dNTPs)], and if they are incorporated into the DNA chain, they may act as chain terminators, thus preventing further chain elongation. It should be noted that, as while acyclovir obligatorily acts as a

120 Field, A. K.; Biron. K. K. *Clin. Microbiol. Rev*. **1994**, *7*, 1–13.
121 De Clercq, E. *Biochem. Pharmacol.* **1991**, *42*, 963–972.

chain terminator, ganciclovir and penciclovir may also be incorporated, via an internucleotide linkage, in the interior of the DNA chain.[114c]

Among the acyclic nucleoside phosphonates that have been pursued as antiviral agents are cidofovir (HPMPC) [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine], adefovir (PMEA) [9-(2-phosphonylmethoxyethyl) adenine], and tenofovir (PMPA) [(R)-9-(2-phosphonylmethoxypropyl) adenine]. Because of their limited oral bioavailability, the last two compounds have been converted to their oral prodrug forms, adefovir dipivoxil or bis(pivaloyloxymethyl)- PMEA [bis(POM)-PMEA] and tenofovir disoproxil or bis(isopropyloxycarbonyloxymethyl)- PMPA [bis(POC)-PMPA], respectively (Figure 4.1).[114c]

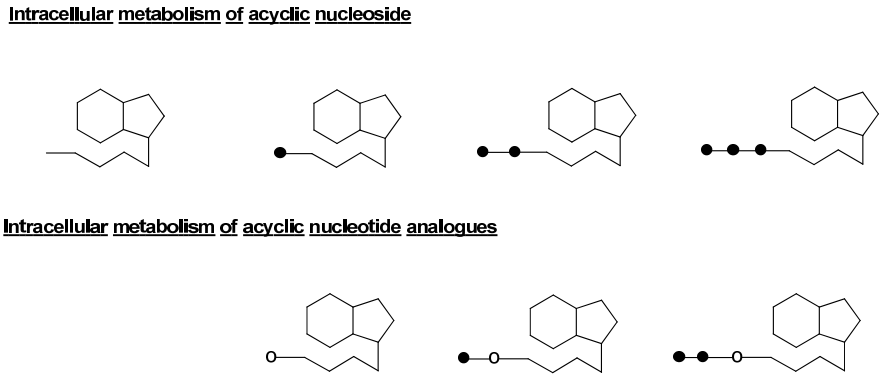

Figure 4.2. Intracellular metabolism of acyclic nucleoside analogues and acyclic nucleotide analogues. The former need three phosphorylation steps whereas the latter only need two to be converted to their active metabolites (the dNTP analogues). Symbols: ●, phosphate; ○, phosphonate.[114c]

The story that would eventually lead to the successful commercialization of the acyclic nucleoside phosphonates as antiviral drugs started some 35 years ago,[117] when Dr. Anthonin Holy decided to collaborate on the exploration of the antiviral activity of new nucleoside analogues, in particular acyclic nucleoside analogues, and the first compound he found active in this series was [9-(2,3-dihydroxypropyl)adenine] (DHPA) (Scheme 4.1).[122]

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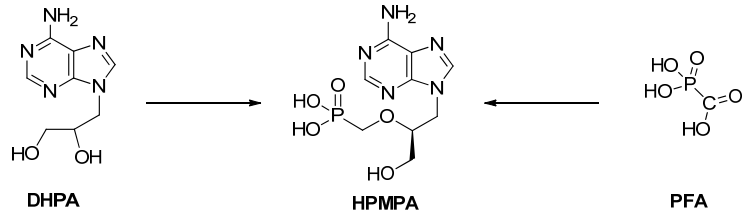
122 De Clercq, E.; Descamps, J.; Somer. P. ; Holy, A. *Science* **1978**, *200*, 563–565.

This publication came just a few months after the acyclic guanosine analogue acyclovir had been described as a selective anti-herpes simplex virus (HSV) agent[123] that owed its selectivity to a specific phosphorylation by the HSV-induced thymidine kinase (TK).[124] Although less potent than acyclovir against HSV, DHPA was active against a broad range of both DNA and RNA viruses, and its antiviral effects, as shown later were due to interference with the S-adenosylhomocysteine (SAH) hydrolase, thus inhibiting viral RNA maturation. In the early eighties, they examined the antiviral potential of various other acyclic nucleoside analogues, i.e. (*R*,*S*)-3-adenin-9-yl-2-hydroxy-propanoic acid (AHPA) derivatives.[125] Their antiviral activity spectrum was essentially similar to that of (*S*)-9-(2,3-dihydroxypropyl)adenine (DHPA) and so was their mechanism of action.[117]

With (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA) a totally new concept was born.[126] This acyclic nucleoside phosphonate, which could be envisaged as hybrid molecule between DHPA and PFA (phosphonoformic acid) (Scheme 4.1) exhibited a remarkable broad-spectrum activity against virtually all DNA viruses, including those that did not induce a specific viral TK, such as human cytomegalovirus (HCMV). Although HPMPA itself was not further developed as an antiviral drug, it served as the prototype compound for a series of acyclic nucleoside phosphonates (cidofovir, adefovir and tenofovir).[117]



Scheme 4.1. (S)-9-(3-Hydroxy-2-phosphonylmethoxypropyl)adenine (**HPMPA**), and its predecessors 9-(2,3-dihydroxypropyl)adenine (**DHPA**) and phosphonoformic acid (**PFA**)[117]

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123 Schaeffer, H. J.; Beauchamp, L.; Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature* **1978**, *272*, 583–585.

124 Elion, G. B.; Furman, P. A.; Fyfe, J. A.; Miranda, P. ; Beauchamp, L. ; Schaeffer, H. J. *Proc. Natl. Acad. Sci. USA.* **1977**, *74*, 5716–5720.

125 De Clercq, E.; Holy, A. *J Med Chem.* **1985**, *28*, 282–287.

126 De Clercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal. P. C. *Nature* **1986**, *323*, 464–467.

4.1.1. Cidofovir[117]

The antiviral properties of (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine (HPMPC, cidofovir), now on the market as Vistide® (Figure 4.3) were first described in 1987.[127] The antiviral activity spectrum of cidofovir (HPMPC) is similar to that of HPMPA. It is active against virtually all DNA viruses, including polyoma-, papilloma-, adeno-, herpes-, and poxviruses. Among the family of herpesviridae, all eight human herpesviruses (HSV-1, HSV-2, VZV, EBV, HCMV, HHV-6, HHV-7 and HHV-8), and, among the poxviruses, vaccinia, variola, cowpox, monkeypox, camelpox, molluscumcontagiosum have proved to be susceptible to the inhibitory effects of cidofovir.

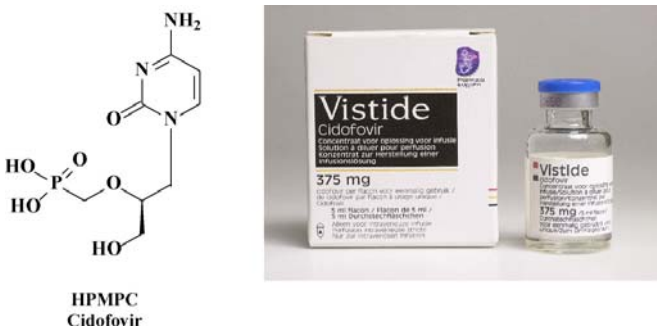

Figure 4.3. (S)-1-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC, cidofovir, Vistide®).[117]

Its mechanism of action, as in the case of human cytomegalovirus (HCMV), has been clearly demonstrated (Scheme 4.2), it is based on DNA chain termination (following the intracellular conversion of cidofovir to its diphosphate and the successive incorporation of two cidofovir units into the growing DNA chain.[128]

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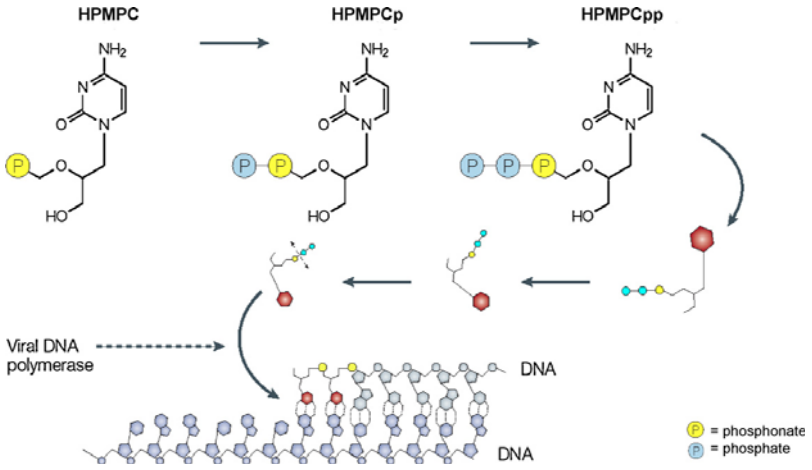
127 De Clercq, E. Sakuma, T.; Baba, M.; Pauwels, R.; Balzarini, J.; Rosenberg, I.; Holy, A. *Antivir. Res.* **1987**, *8*, 261–272.

128 De Clercq, E. *Nature Rev. Microbiol*. **2004**, *2*, 704–720.



Scheme 4.2. Mechanism of action of cidofovir[117]

From a clinical viewpoint, cidofovir has been licensed for use, upon intravenous administration at a dose of 5mg/kg once every other week, in the treatment of HCMV retinitis in AIDS patients[129]. Its future, however, lies in the remarkable, albeit anecdotal, results which have been accumulated with cidofovir when used topically or systemically in the treatment of HPV-associated diseases such as hypopharyngeal papilloma,[130] laryngeal papilloma,[131] recurrent respiratory papillomatosis[132] or plantar warts,[133] or poxvirus-associated diseases, such as molluscum contagiosum in AIDS patients[134] or Orf (ecthyma contagiosum) in immunosuppressed patients.[135] Clearly, cidofovir should be further pursued for its potential in the treatment of those virus infections (i.e. papilloma, pox) for which, at present, there are few, if any, therapeutic alternatives.

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129 De Clercq, E.; Holy, A. *Nat. Rev. Drug Discov.* **2005**, *4*, 928–940.

130 Van Cutsem, E.; Snoeck, R.; Van Ranst, M.; Fiten, P.; Opdenakker , G.; Geboes, K.; Janssens J, Rutgeerts P, Vantrappen G, de Clercq, E. *J. Med. Virol*. **1995**, 4, 230–235.

131 Snoeck, R.; Wellens, W.; Desloovere, C.; Van Ranst, M.; Naesens, L. De Clercq, E. Feenstra, L. *J. Med. Virol*. **1998**, *54*, 219–225.

132 Pransky, S. M.; Magit, A. E.; Kearns, D. B.; Kang, D. R.; Duncan, N.O. *Arch. Otolaryngol. Head Neck. Surg*. **1999**, *125*, 1143–1148.

133 Davis, M. D.; Gostout, B. S.; McGovern, R. M.; Persin, D. H.; Schut, R. L.; Pittelkow, M. R.; *J Am. Acad. Dermatol*. **2000**, *43*, 340–343.

134 Meadows, K. P.; Tyring, S. K.; Pavia, A. T.; Rallis, T. M. *Arch. Dermatol*. **1997**, *133,* 987–990.

135 Geerinck, K.; Lukito, G.; Snoeck, R.; De Vos, R.; De Clercq, E.; Vanrenterghem , Y.; Degreef, H.; Maes, B. *J. Med. Virol* , **2001**, *64*, 543–549.

4.1.2. Adefovir[117]

The antiviral activity spectrum of 9-(2-phosphonylmethoxyethyl)adenine (PMEA, adefovir, now marketed as its oral prodrug form bis(pivaloyloxy methyl) ester of PMEA, adefovir dipivoxil, Hepsera®] (Figure 4.4), is partially overlapping with that of cidofovir in that both are active against herpesviruses (i.e. HSV-1, HSV-2, VZV, EBV, HCMV), but, in addition, adefovir is also active against hepadnaviruses (i.e. human and duck hepatitis B viruses) and retroviruses (HIV-1, HIV-2, SIV, feline immunodeficiency virus (FIV), visna/maedi virus, feline leukemia virus, LP-BM5 (murine AIDS) virus and Moloney (murine) sarcoma virus).

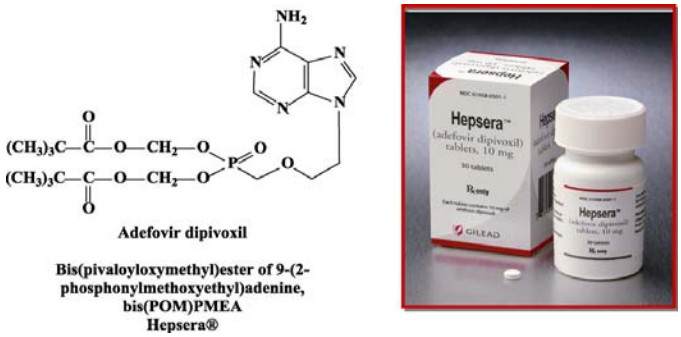
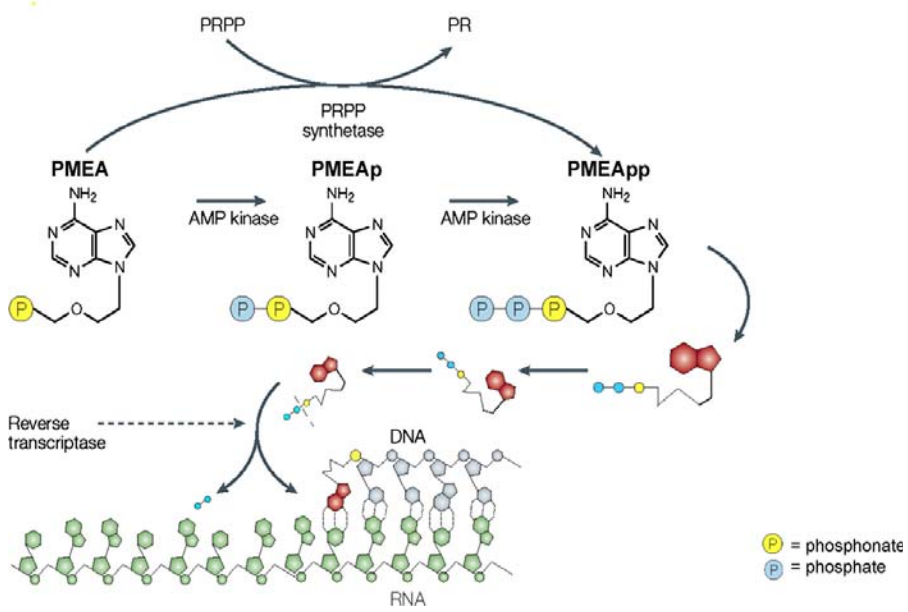


Figure 4.4. Adefovir dipivoxil (Hepsera®).[117]

In its mechanism of action (Scheme. 4.3), adefovir follows a similar strategy as cidofovir. Once adefovir has penetrated into the cell, it needs two subsequent phosphorylations to be converted to its diphosphate, which, after removal of the pyrophosphate moiety, is incorporated into the viral DNA and acts as an obligatory DNA chain terminator.[128]



Scheme 4.3. Mechanism of action of adefovir[117]

From a clinical view point, adefovir was first pursued for its potentiall use in the treatment of HIV infections (AIDS) but was eventually licensed in its prodrug form (adefovir dipivoxil) for the treatment of HBV infections (chronic hepatitis B).[129]

4.1.3. Tenofovir[117]

The antiviral activity of (*R*)-9-(2-phosphonylmethoxypropyl) adenine (PMPA, tenofovir, now marketed as its oral prodrug form [bis(isopropyloxycarbonyloxymethyl) ester of PMPA, tenofovir disoproxil fumarate, TDF, Viread®] (Figure 4.5) was first described in 1993 [136] in a paper also pertaining to the activity of its 2,6-diaminopurine counterpart. The anti-HIV effects of the (R)-enantiomers of PMPA and PMPDAP were demonstrated in several human cell systems, including peripheral blood lymphocytes and freshly isolated monocyte-macrophages.[137] The in vivo anti-HIV efficacy of the prodrug, bis(isopropyloxycarbonyloxymethyl)-(*R*)-9-(2-phosphonylmethoxypro-pyl)-adenine, and its cellular metabolism were reported by Naesens et al.[138] and Robbins et

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136 Balzarini, J.; Holy, A.; Jindrich, J.; Naesens, L.; Snoeck, R.; Schols, D.; De Clercq, E. *Antimicrob. Agents Chemother*. **1993**, *37*, 332–338.

137 Balzarini, J.; Aquaro, S.; Perno, C. F.; Witvrouw , M.; Holy, A.; De Clercq, E. *Biochem. Biophys. Res. Commun.* ***1996***, *219*, 337–341.

138 Naesens, L.; Bischofberger, N.; Augustijns, P.; Annaert, P.; Van den Mooter, G.; Arimilli, M. N.; *Antimicrob. Agents Chemother* **1998**, *42*, 1568–1573.

al.[139] The antiviral activity spectrum of tenofovir is narrower than that of adefovir, in that it no longer extends to herpesviruses but is confined to hepadna- and retroviruses. In its mechanism of action, tenofovir is assumed to follow exactly the same strategy as that of adefovir.[140]

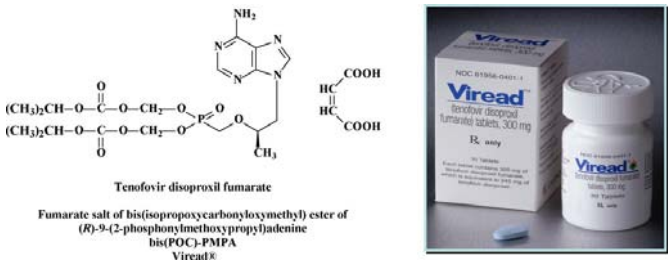

Figure 4.5. Tenofovir disoproxil fumarate (TDF, Viread®)[117]

From a clinical viewpoint, tenofovir disoproxil fumarate (TDF) has been licensed for the treatment of HIV infections (AIDS), as either a single drug (Viread®) (Figure 4.5) once daily.

4.1.4. Synthesis of HPMPC (cidofovir) and HPMPA[143a]

HPMPC (cidofovir) and its cyclic analogue (cHPMPC) exhibit an antiviral activity spectrum that is quite similar to that of HPMPA (and cHPMPA).

Synthesis of (*S*)-HPMP derivatives mostly utilizes basically catalyzed nucleophilic opening of the oxirane ring in (2*S*)-2-[(trityloxy]methyl]oxirane or (*R*)-glycidol butyrate with an appropriate nucleobase like N^4-benzoylcytosine, N^6-benzoyladenine or 2,6-bis(benzoylamino)purine (Scheme 4.4)[141,142] This reaction proceeds regioselectively to N^9 position of the purine or N^1 position of the pyrimidine base. The intermediates 2,3-dihydroxypropyl derivatives formed are subsequently etherified with dialkyl (diethyl or diisopropyl) ester of tosyloxymethanephosphonate in the presence of sodium hydride. After removal of benzoyl and trityl groups, phosphonic

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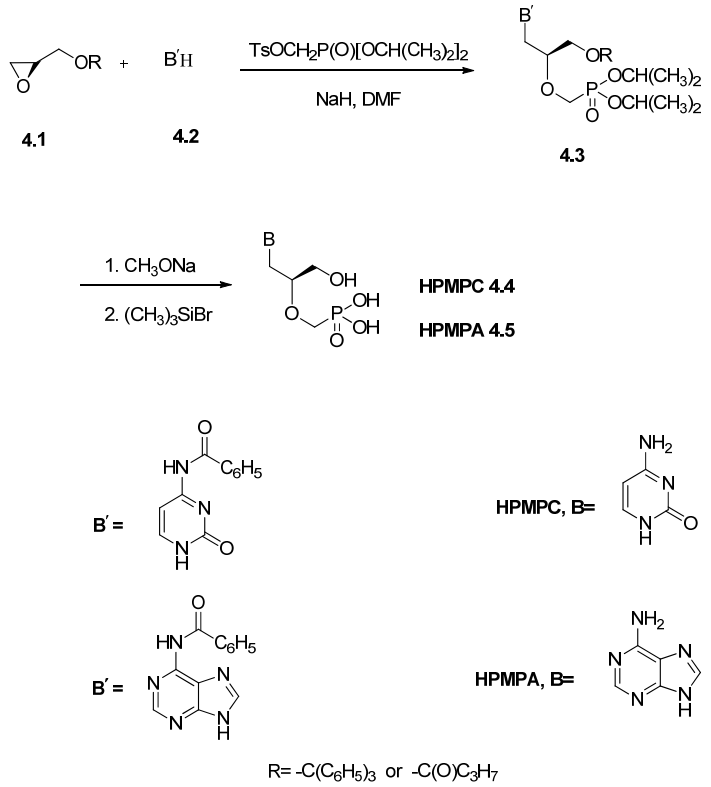
139 Robbins, B. L.; Srinivas, R. V.; Kim, C.; Bischof berger, N.; Fridland, A. *Antimicrob. Agents Chemother* **1998**, *42*, 612–617.

140 De Clercq, E. *Expert Rev. Anti-infect. Ther*. **2003**, *1*, 21–43.

141 Webb, R.R.; Wos, J.A.; Bronson, J.J; Martin, J.C. *Tetrahedron Lett.* **1988**, *29*, 5475–5478,

142 Brodfuehrer, P.R.; Howell, H.G.; Sapino, C.; Vemishetti, P. *Tetrahedron Lett.* **1994**, *35*, 3243–3246.

ester groups were deprotected by the treatment with bromotrimethylsilane followed by hydrolysis.[143b]



Scheme 4.4. Synthesis of (*S*)-[3-hydroxy-2-(phosphonomethoxy)propyl] derivatives of adenine and cytosine (HPMPA and HPMPC) from glycidol[143a]

4.1.5. Synthesis of some unsaturated HPMPC analogues[156]

The key synthetic steps leading to HPMPC analogues, vinyl ANP and allyl ANP, involve the olefin cross-metathesis reaction and the palladium-mediated C5-alkylation of the uracil moiety. Thus, two series of vinyl ANP and their allyl analogues have been obtained from the same N^1- crotyl-5-phenylthiouracil (Figure 4.6).

143 a) Nucleoside and Nucleotide Analogues for the Treatment of Herpesvirus Infections: Current Stage and New Prospects in the Field of Acyclic Nucleoside Phosphonates. b) Holy, A. *Collect.Czech. Chem. Comm.* **1993**, *58*, 649–674.

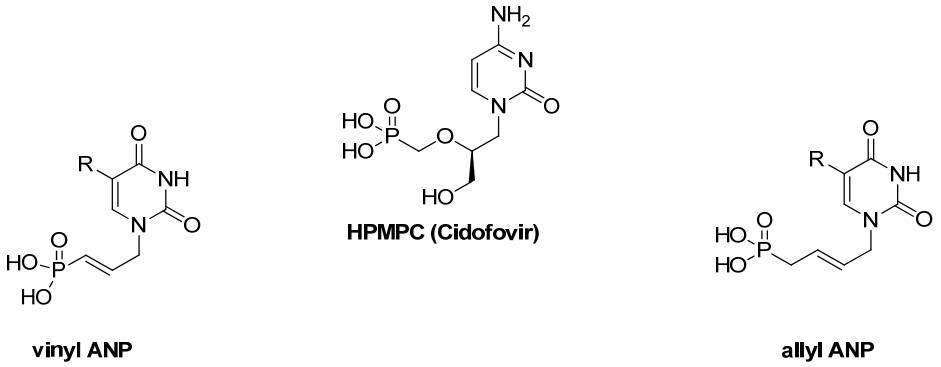
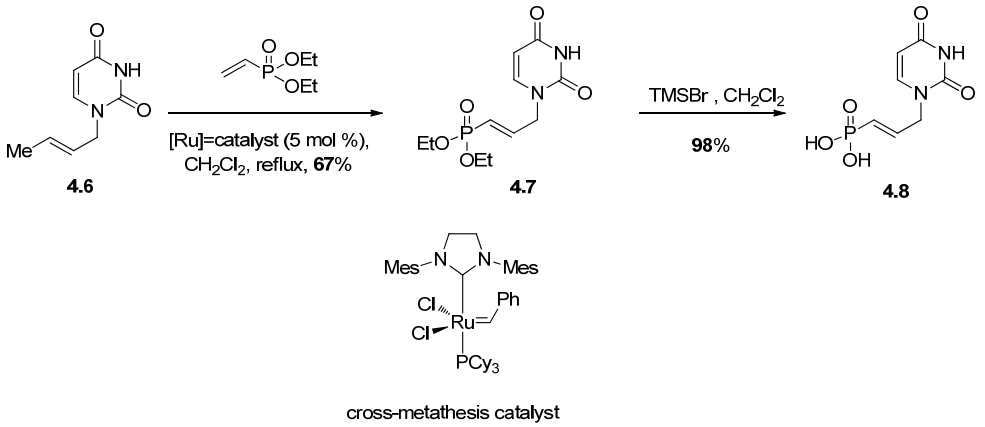


Figure 4.6. Some bioactive acyclic nucleoside phosphonates realted to cidofovir.

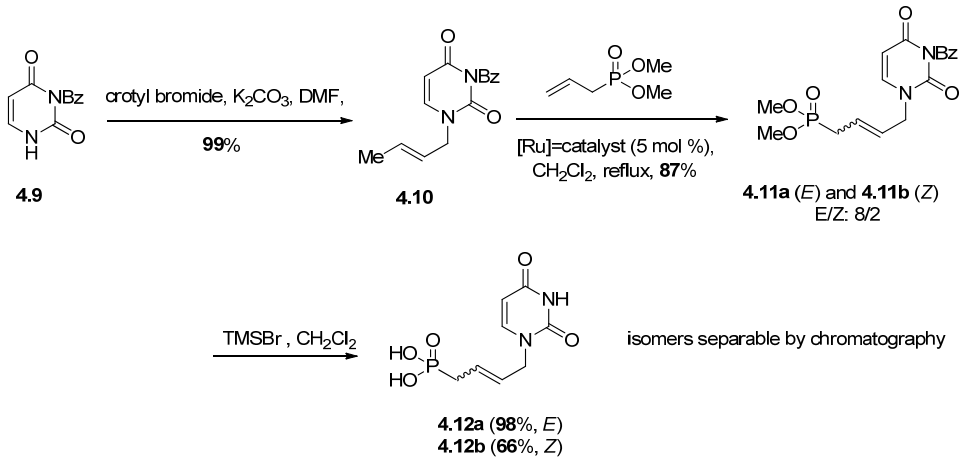
Recently, Grubbs et al.[51] reported on a general model for selectivity in cross-metathesis (CM), by ranking the olefin reactivity in CM by categorizing the olefins in their abilities to undergo homodimerization via CM and by the stability of those homodimers. Based on this model, H. Kumamoto et al began to explore the cross-metathesis reaction of the reactive crotylated uracil **4.6** with vinyl diethylphosphonate, (Scheme 4.5). The desired cross-coupling heterodimer **4.7** was obtained in 67% yield as the *E* isomer. It is important to note that the reaction proceeded without the protection at the N^3-position of the heterocycle. Compound **4.7** was deprotected with TMSBr to afford the desired ANP.



Scheme 4.5. Synthesis of vinyl ANP **4.8**

The same procedure was successfully applied to the cross-metathesis involving dimethylallyl phosphonate. Starting from N^3-benzoylated crotylated uracil **4.10**

prepared from N^3-benzoyluracil **4.9**,[144] the CM reaction gave the desired allyl phosphonate **4.11**, isolated as a mixture of major and thermodynamically stable *E*-isomer (**4.11a**, 72%) with the minor *Z*-isomer present in small amounts (**4.11b**, 15%) (Scheme 4.6). Both isomers can be separated by liquid chromatography on silica gel. Compounds **4.11a** and **4.11b** were deprotected with TMSBr to afford the desired products **4.12a** (98%) and **4.12b** (66%).



Scheme 4.6. Synthesis of allyls ANPs **4.12a** and **4.12b**

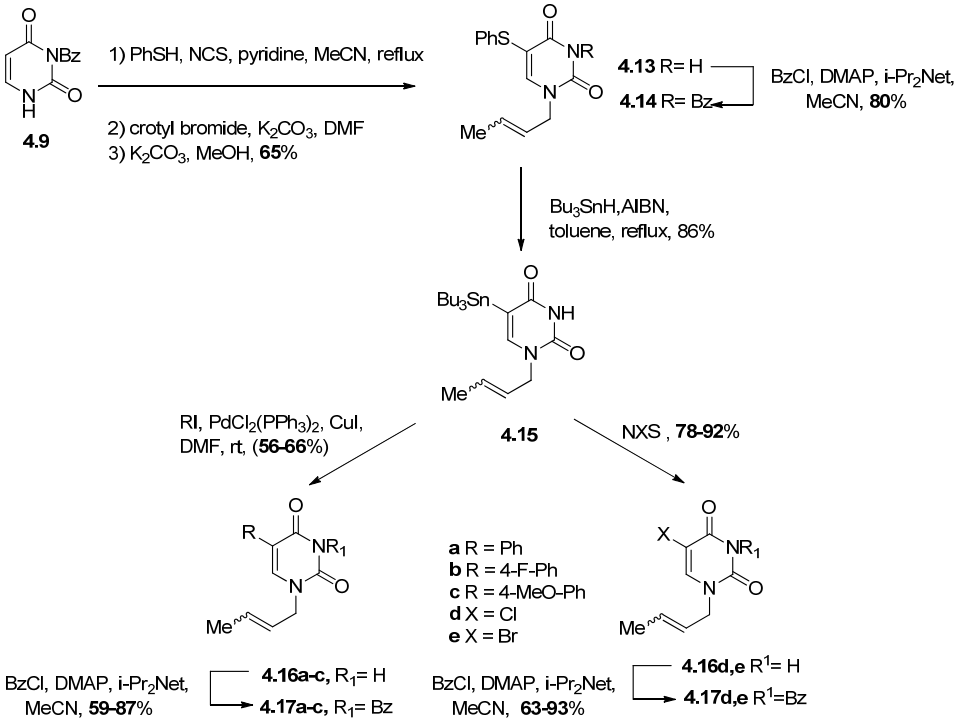
Based on those results, they extended this approach to several 5-substituted uracil derivatives, which were obtained using the 5-phenylsulfonyluracil derivative **4.13** and its 3-*N*-benzoyl derivative **4.14**, as synthetic common intermediates for the construction of either the C5-halogeno- **4.16a-c** or the C5-carbon-substituted **4.16d-f** uracil analogues as well as their N^3-protected analogues **4.17a-f** (Scheme 4.7). Thus, the 5-phenylthio derivative **4.13** was prepared from **4.9** by (i) introduction of phenylthio group at the C5-position, (ii) crotylation of the N^1-position, and (iii) debenzoylation of N^3-position in 65% over three steps. By treating **4.13** with tributyltin hydride, a sulfur-extrusive stannylation[145] occurred and the desired tin derivative **4.15** was obtained in high yields. On the one hand, the Pd(0)-mediated Stille-coupling reaction[146] involving **4.15** allowed the isolation of the desired C5-carbon substituted derivatives **4.16a-c**. On the other hand, compound **4.15** was easily converted into the 5-chloro (**4.16e**), and 5-

144 Cruickshank, K. A.; Jiricny, J.; Reese, C. B. *Tetrahedron Lett.* **1984**, *25*, 681–684.

145 Tanaka, H.; Hayakawa, H.; Obi, K.; Miyasaka, T. *Tetrahedron* **1986**, *42*, 4187–4195.

146 Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev*. **2003**, *103*, 1875–1916.

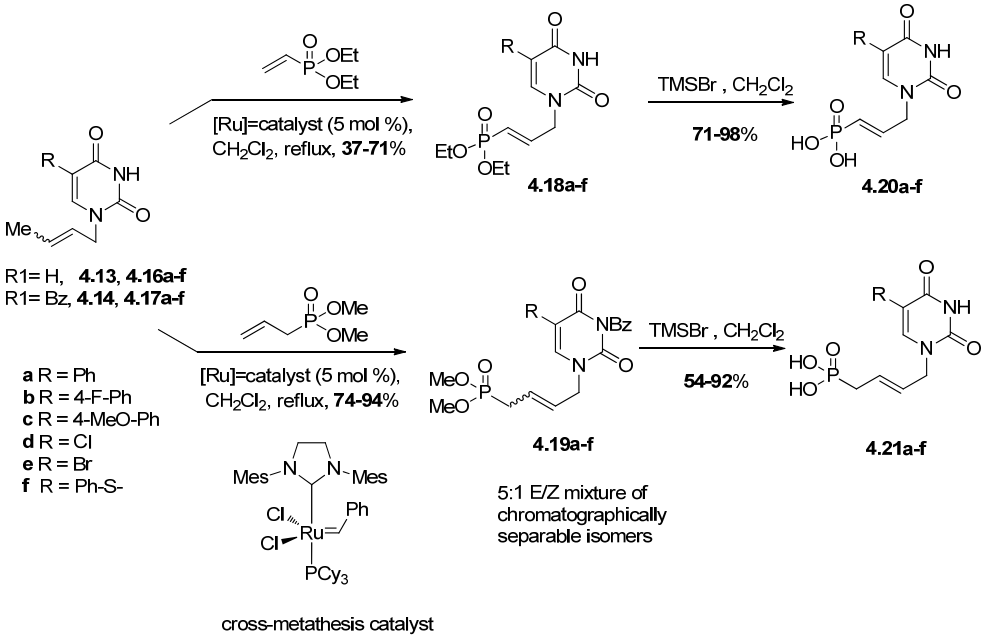
bromo derivatives (**4.16f**) by simple treatment with NCS or NBS, respectively. A final benzoylation of **4.16a-f** afforded the desired protected analogues **4.17a-f**.



Scheme 4.7. Synthesis of vinyls ANPs **4.16a-f** and **4.17a-f**

The C5-substituted N^3-unprotected uracil derivatives **4.13**, **4.16a-e** were engaged in a cross-metathesis reaction with diethyl vinyl phosphonate. The desired cross-metathesis products **4.18a-e** were isolated in moderate to good yield. The stereochemistry of the olefin was confirmed by ^{1}H NMR and ^{31}P NMR spectroscopy. A final deprotection by treatment with TMSBr in CH_2Cl_2 afforded the free phosphonates **4.20a-f** in good yields (Scheme 4.8).

The cross-metathesis of N^3-protected uracil analogues **4.14**, **4.17a-e** with allyl diethylphosphonate was also performed and the cross products **4.19a-f** were isolated as a mixture of *E* and *Z* isomers (average *E/Z* ratio 8:2) separable by chromatography. The final deprotection of N^3-benzoyl and diethylphosphonate was similarly performed by treatment with TMSBr in CH_2Cl_2, and the free phosphonates **4.21a-f** were obtained in good yields, respectively.



Scheme 4.8. Synthesis of allyls ANPs **4.20** and **4.21**

4.2. Retrosynthesis

Spurred by the yet unexplored synthetic possibilities of this family of nucleosides, we became interested in the search for a new enantioselective method for the synthesis of acyclic nucleoside phosphonate analogues, and in particular, Cidofovir (HPMPC) analogues. Figure 4.7 shows the structural modifications proposed in comparison with the structure of Cidofovir and the vinyl ANP and allyl ANP analogues already prepared.

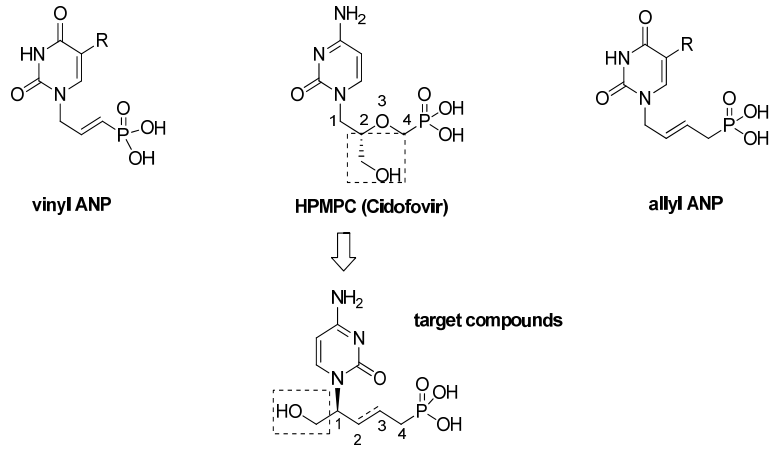
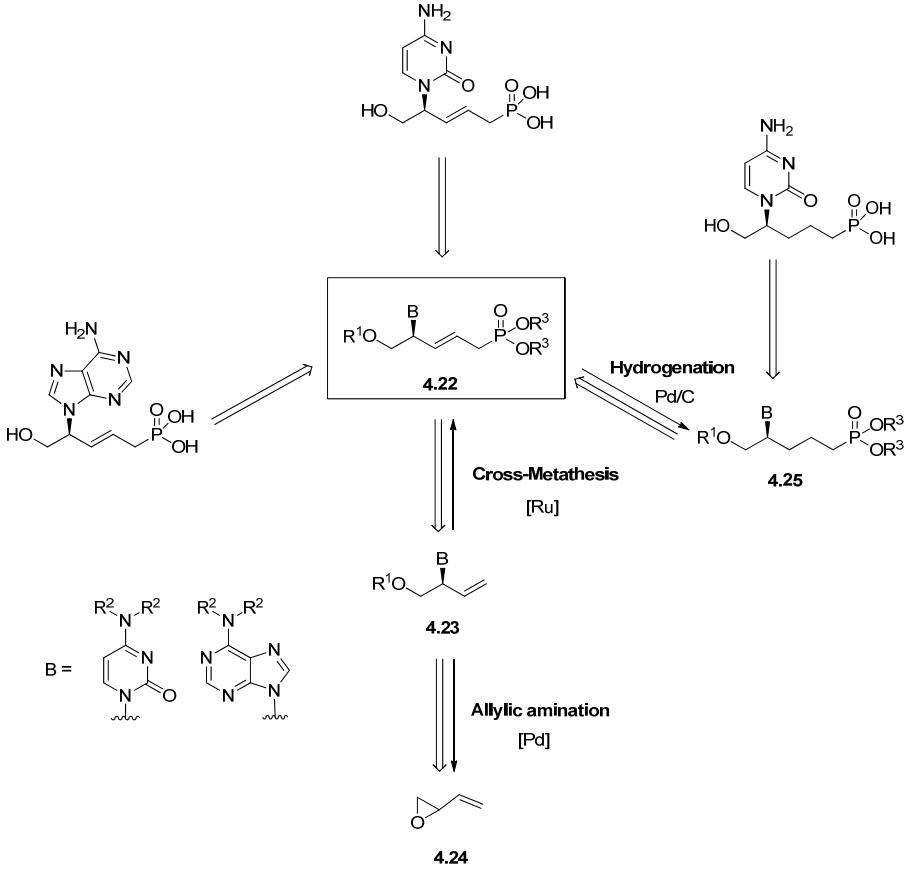


Figure 4.7. Structural relationship between cidofovir and the target compounds

Unlike Cidofovir, where cytosine is bonded to a methylene group, the target compound presents a structure where the nucleic base is directly connected to a sterocenter, whose stereochemistry was chosen according to that of the one present in Cidofovir. We envisaged that the target compounds could be easily accesed using a synthetic scheme similar to that used in the synthesis of the nectrisine, based on palladium catalyzed allylic amination and cross-metathesis. The strategy would afford unsaturated compounds related to that of the allyl ANP analogue (Figure 4.1). A further structural modification to be considered is the reduction of the double bond to afford saturated acyclic nucleotide phosphonate analogs. In comparison to the structure of Cidofovir, those of the saturated compounds proposed would result from formal migration of the hydroxymethyl moiety to the carbon atom directly connected to the nucleic base and replacement of the oxygen atom at position 3 by a methylene group. Besides cytosine, other nucleic bases would be also considered to afford a small library of acyclic nucleotide phosphonates.

In this context, the retrosynthetic proposal is shown in Scheme 4.9. Cidofovir (HPMPC) analogues could be obtained by double bond reduction of product **4.22** followed by protecting group cleavage on compound **4.25**. Compound **4.22** in turn can be synthesized from compound **4.23** via chain elongation mediated by cross-metathesis reaction. Lastly, chiral synthon **4.23** could be obtained by a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) from racemic butadiene monoepoxide (**4.24**).



Scheme 4.9. Retrosynthetic approach for the synthesis of Codofovir (HPMPC) analogues.

4.3. Results and discussion

4.3.1. Synthesis of allyl amines by a Pd-catalyzed allylic amination[33,34,147]

As it was discussed in the introduction and in the previous chapter, Pd-catalyzed asymmetric allylic alkylation (Pd-AAA) has become a powerful tool for the construction of stereocenters and has engendered a number of versatile methods for the total synthesis of natural products and other biologically active targets.

In this regard, we decided to explore the viability of the Pd-catalyzed deracemization of vinyl epoxide with different nucleic bases as nucleophiles using Trost's ligands in order to obtain enantiopure allyl nucleobases that could serve as intermediates for the synthesis of acyclic nucleotide phosphonates.

The use of nucleobases[148,149] as nucleophiles in asymmetric Pd-catalyzed allylic alkylation[150,] is not trivial. They have been shown to behave differently to other simple nucleophiles[151,152,] such as malonates, sulfinates, azides and amines in desymmetrization processes, where the asymmetric induction should in priciple be independent of the nucleophile. Contrarily, they have shown a remarkable effect on the catalytic turnover and the enantioselectivity of desymmetrization reactions, probably as a result of their ability to serve as competitive ligands and thereby disrupt the normal coordination of the palladium.

We initially explored the feasibility of the process with pyrimidine bases such as uracil and thymine. In order to guarantee N^1 alkylation and prevent N^3-alkylation and/or bis-alkylation, the process imposes previous protection of the imino functionality at N^3. Furthermore, protection of the N^3 functionality increases the lipofilicity of the compounds, allowing for the use of common organic solvents in the Pd-catalyzed asymmetric allylic amination. Thus, 3-*N*-benzoyluracil **4.28**[153] was prepared by treating

147 Trost, B. M.; Osipov , M.; Dong. G. *J. Am. Chem. Soc.* **2010**, *132*, 15800–15807.

148 Trost, B. M.; Kuo, G. H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621–622.

149 Trost, B. M.; Madsen, R.; Guile, S, D. *Tetrahedron Lett.* **1997**, *38*, 1707–1710.

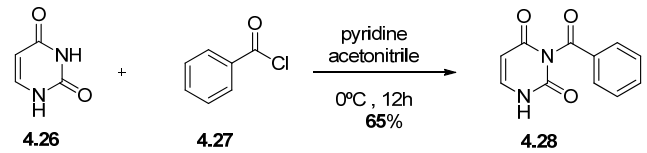
150 Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355–364

151 Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122,* 5947-5956

152 Trost, B.M.; Madsen, R.; Guile, S.G.; Elia, A.E.H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1569-1572

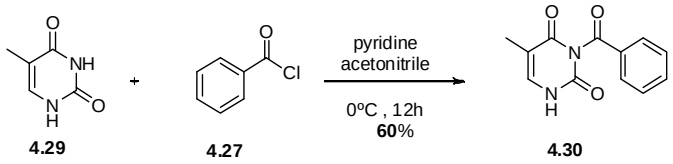
153 Hyunseok, A.; Tae, H, C.; Kathlia, C.; Kyo, C, L.; Byoungsoo, K.; Byung, S, M.; Su Hee, H.; Jong, C,

uracil with an excess of benzoyl chloride (**4.27**), in the presence of pyridine as base to afford the desired product **4.28** [154]with 65% yield (Scheme 4.10).



Scheme 4.10. Synthesis of 3-*N*-benzoyluracil **4.28**

3-*N*-Benzoylthymine **4.30**[154] was similarly prepared from thymine by reaction with an excess benzoyl chloride (Scheme 4.11). The reaction afforded product **4.30** with 60% yield.



Scheme 4.11. Synthesis of 3-*N*-benzoylthymine **4.30**

With the protected uracil and thymine in hand we explored the allylic amination reaction. Thus, when butadiene monoepoxide **4.22** was treated with protected uracil **4.28** in the presence of a 2 mol % $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 6 mol % of ligand **4.35** in dichloromethane (DCM) at room temperature for 18h, the desired product **4.31** was obtained in 81% yield and 82% ee (Table 4.1, Entry 1). Increasing the temperature at 35ºC afforded the desired product **4.31** in 79% yield and 73% ee (Table 4.1, Entry 2). When the reaction was conducted at lower temperature, 0ºC, product **4.31** was obtained in 80% yield and 70% ee (Table 4.1, Entry 3). For high enantioselectivities to be obtained, in addition to a selective alkylation of one diastereomeric intermediate over the other (K1>>>>k2), a Curtin-Hammett condition must be established, wherein interconversion is rapid and successfully competes with nucleophilic addition. In this regard, heating can favor equilibration of the π-allyl intermediates, but at the same time, can also balance the rates of corresponding nucleophilic additions (k1 > k2), leading to

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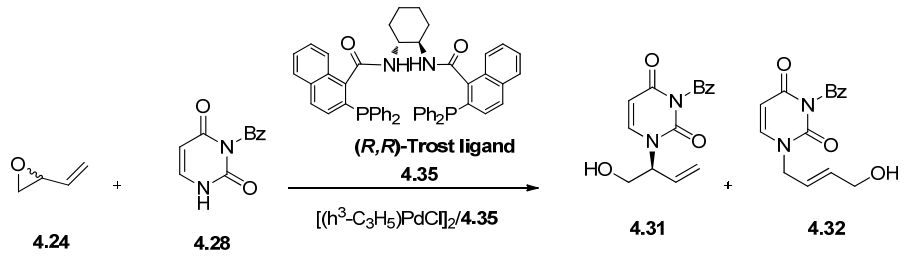
[154] L.; Kwon, S, C.; Gi Jeong, C.; Sang Moo L.; Gwang Il, A.; Hakjune, R. *J. Med. Chem.* **2007**, *50*, 6032–6038. Hyunseok, A.; Tae, H, C.; Kathlia, C.; Kyo, C, L.; Byoungsoo, K.; Byung, S, M.; Su Hee, H.;Jong, C, L.; Kwon, S, C.; Gi Jeong, C.; Sang Moo L.; Gwang Il, A.; Hakjune, R. *J. Med. Chem.* **2007**, *50*, 6032–6038.

decreased enantioselectivities, as it happens to be the case. On the other hand, decreased enantioselectivities when performing the reaction at lower temperatures may be attributed to the rate of π-allyl complex equilibration being slower than the rate of nucleophilic attack.

Shorter reaction times (5h) led to similar results to those obtained in entry 2 (Table 4.1, Entry 4). Additionally, the choice of solvent had a marginal effect on the course of this transformation, with virtually the same values of yield and enantioselectivity (Table 4.1, entries 5 and 6)

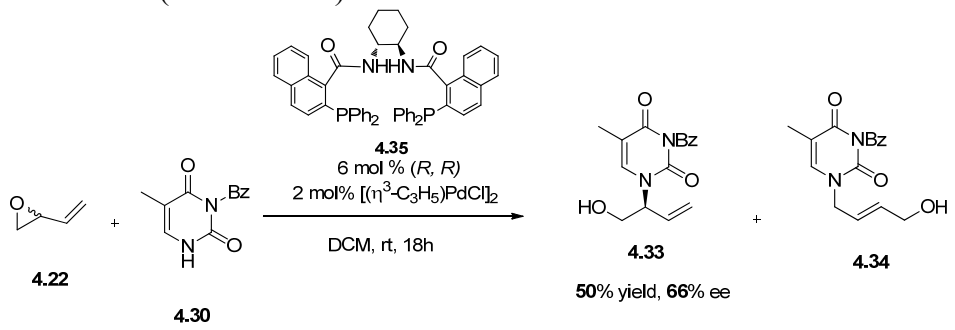
Table 4.1. Allylic amination of butadiene monoepoxide using **4.28** as nucleophile, and $[(\eta^3\text{-}C_3H_5)PdCl]_2$/(*R,R*)-DACH-naphthyl as catalytic system.



Entry	Temp. (ºC)	Solvent	Conv (%)[b]	Regioselec. **4.31:4.32**[c]	Yield of **4.31** (%)[d]	ee (%)[e]
1	rt	CH_2Cl_2	>99	>99:1	81	82
2	35	CH_2Cl_2	>99	>99:1	79	73
3	0	CH_2Cl_2	>99	>99:1	80	70
4[f]	rt	CH_2Cl_2	>99	>99:1	83	84
5	rt	THF	>99	>99:1	80	84
6	rt	CH_3CN	>99	>99:1	85	86

[a] Conditions: $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2 mol%), (*R,R*)-naphtyl Trost ligand (6 mol%), butadiene monoepoxyde (1.1. equiv), nucleic base (1.1 equiv.), time= 18h. [b] Determined by ^{1}H NMR. [c] Determined by ^{1}H NMR as branched:linear ratio. [d] Isolated yield of branched compound. [e] Determined by chiral HPLC Column (hexanes:iPrOH 85:15, 0.4 ml/min, Column OD-H). [f] Reaction stirred for 5h.

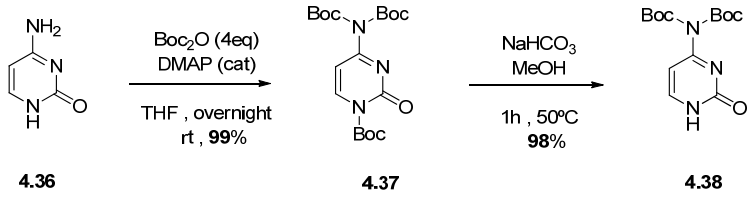
The reaction 3-*N*-benzoylthymine (**4.30**) with butadiene monoepoxide under the optimized conditions afforded the branched *N*-alkylated product **4.33** in lower yield 50% and 66 % ee (Scheme 4.12).



Scheme 4.12. Pd-AAA of butadiene monoepoxide using **4.30** as nucleophile.

Under all the conditions evaluated, the branched. *N*-alkylated product was observed exclusively, demonstrating the profound chemo- and regioselectivity of the transformation.

We next explored the reaction with cytosine, which also required protection in order to avoid selectivity problems. Reaction of cytosine with Boc anhydride in the presence of DMAP and THF at room temperature afforded product **4.37** in 99% yield, which was treated by $NaHCO_3$ and MeOH at 50ºC for 1h to give the desired product **4.38** in 98% yield (Scheme 4.13).[155]



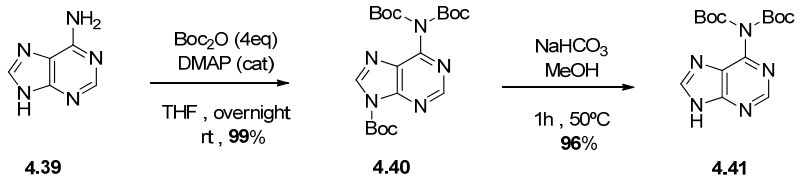
Scheme 4.13. Synthesis of protected cytosine **4.38**

The Pd-catalyzed asymmetric allylic amination of protected cytosine **4.38** and butadiene monepoxide in the presence of 2 mol% Pd/6 mol% DACH naphthyl ligand in dichloromethane at rt for 18 h furnished **4.42** in good yield (82%) and moderate enantioselectivity (67%) (Table 4.2, Entry 1). Working at lower temperatures (0ºC)

155 Andrea, P.; Giampaolo, G.; Ivana, P.; Mariolino, C.; Giammario, N. *Eur. J. Org. Chem.* **2008**, 5786-5797.

rendered the product **4.42** with slightly increased enantioselectivity, whereas gentle heating at 35ºC produced an erosion of the enantioselectivity of the process (36%ee). The temperature effect differs from uracil, where the best enantioselectivitiy was obtained at room temperature. In all cases, conversions are complete and yields do not vary substantially. Furthermore, yield and enantioselectivity remain unaltered regardless the reaction time inverted in the process (5h or 18h).

The study was extended to the use of purine nucleobases. Protected adenine **4.41** was prepared by treatment with an excess of $(BoC)_2O$ to afford fully protected derivative **4.40**, followed by partial hydrolysis with $NaHCO_3$ and MeOH at 50ºC for 1h to give the desired product **4.41** in 96% yield (Scheme 4.14)[155]

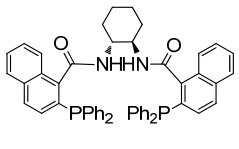


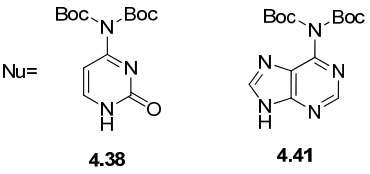
Scheme 4.14. Synthesis of protected adenine **4.41**

All AAA experiments with adenine, butadiene monoepoxide, 2 mol% Pd / 6 mol% DACH naphthyl ligand in dichloromethane led to full conversion, good yield (85-90%) and complete regioselectivity to give compound **4.44**. In general, enantioselectivity values are superior to those obtained for cytosine. The temperature effect over enantioselectivity is similar to that of uracil, with maximum enantioselectivity (91%) at room temperature (Table 4.2, Entries 5, 6 and 9). As already seen in other cases, reaction time does not seem to affect either the yield or the enantioselectivity (Table 4.2, Entries 6, 8), and the same happens to apply to the solvent effect, where replacement of dichloromethane by THF resulted in a marginal erosion in yield and enantioselectivity.

We also studied the reaction of butadiene monoepoxide with acetylcytosine **4.46** in dichloromethane at 35ºC in the presence of 6 mol%(*R*,*R*)-DACH-naphtyl and 2 mol% $[\eta^3(^{-}C_3H_5)PdCl]_2$ as a catalyst precursor obtaining the dialkylated product **4.47** in 40% yield (Scheme 4.15). Since it is clear that both NH present in the compound can react, no further studies were considered.

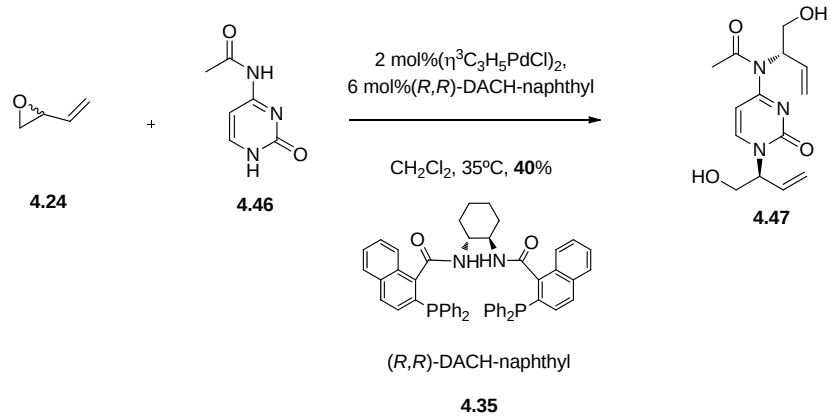
Table 4.2. Allylic amination of butadiene monoepoxide *using* **4.38** and **4.41** as nucleophiles, and Pd/ (*R*,*R*)-DACH- naphthyl Trost ligand as catalytic system.





Entry	Nu	Temp. (ºC)	Solvent	Product	Conversion (%)[b]	Regioselec. Branched/linear[c]	Yield of branched (%)[d]	Ee (%)[e]
1	**4.38**	rt	CH_2Cl_2	**4.42**	>99	>99:1	82	67
2	**4.38**	0	CH_2Cl_2	**4.42**	>99	>99:1	85	72
3	**4.38**	35	CH_2Cl_2	**4.42**	>99	>99:1	81	36
4[f]	**4.38**	rt	CH_2Cl_2	**4.42**	>99	>99:1	80	68
5	**4.41**	35	CH_2Cl_2	**4.44**	>99	>99:1	87	77
6	**4.41**	rt	CH_2Cl_2	**4.44**	>99	>99:1	89	91
7	**4.41**	rt	THF	**4.44**	>99	>99:1	85	87
8[f]	**4.41**	rt	CH_2Cl_2	**4.44**	>99	>99:1	90	92
9	**4.41**	0	CH_2Cl_2	**4.44**	>99	>99:1	85	70

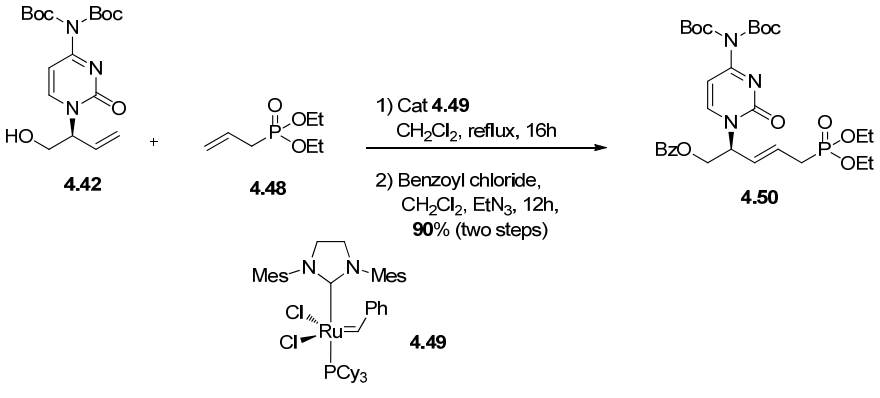
[a] Conditions: catalyst (2 mol%), (R,R)-naphtyl Trost ligand (6 mol%), 1 equiv of butadiene monoepoxide and 1.1 equiv of Nu, all reactions stirred for 18h. [b] Determined by ^{1}H NMR. [c] Determined by ^{1}H NMR as branched:linear ratio. [d] Isolated yield of branched compound. [e] determined by chiral HPLC Column (hexanes:iPrOH 90:10 , 0.5-0.6 ml/min, Column OD-H). [f] Reaction stirred for 5h.



Scheme 4.15. Reaction of butadiene monoepoxide with cytosine **4.47**

4.3.2. Synthesis of 1,2-disubstituted allyl amines by Ru-catalyzed cross-metathesis[156]

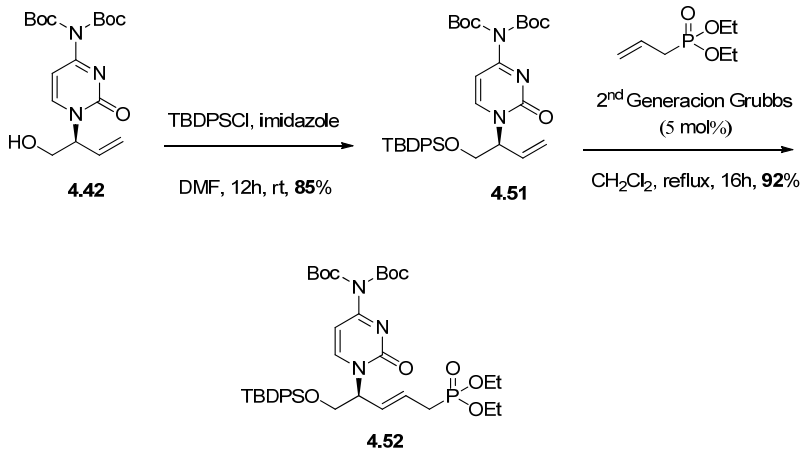
Next synthetic step in our synthetic plan aimed at elongating the hydrocarbon skeleton with an alkyl chain that incorporates the phosphonate moiety while maintaining the unsaturated function. Such a transformation can be carried out by means of a ruthenium-catalyzed cross metathesis. Reaction of the allyl cytosine derivative **4.42** with the reactant of choice, namely diethylallyl phosphonate (**4.48**), in the presence of 5 mol% of 2nd generation Grubbs catalyst in dichloromethane at 55 ºC for 16 h, followed by hydroxyl protection as a benzoate afforded the desired product **4.50** in an excellent 90% yield as the *E* isomer (Scheme 4.16).



Scheme 4.16. Synthesis of compound **4.50**

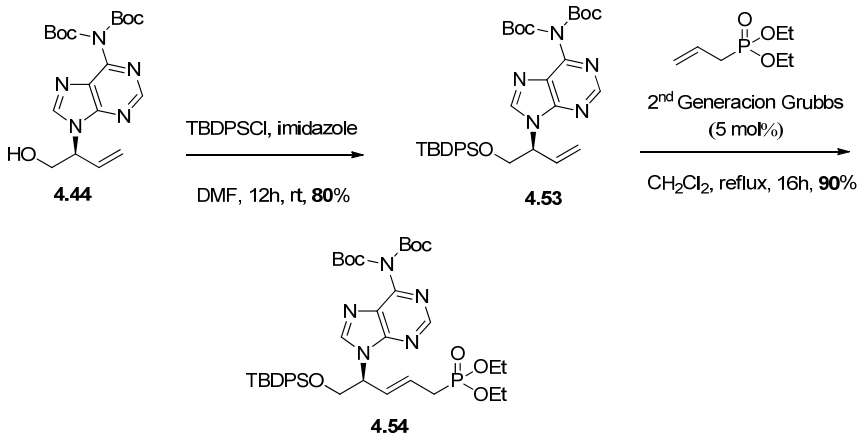
156 Hiroki, k.; Topalis, D.; Broggi, J.; Pradere, U.; Roy, V.; Berteina-Raboin, S.; Nolan, P. S.; Deville-Bonne, D.; Andrei, G.; Snoeck, R.; Garin, D.; Crance, J.M.; Agrofoglio L. A. *Tetrahedron* **2008**, *64*, 3517–3526.

We also attempted the cross-metathesis reaction over the silyl protected derivative **4.51**, which was obtained in 85% yield by reaction of compound **4.42** with TBDPSCl (Scheme 4.17).[88]Cross metathesis reaction of **4.51** with diethylallylphosphonate[156] in presence of 5 mol% 2nd generation Grubbs catalyst and dichloromethane at 55ºC for 16h furnished product **4.52** in 92% yield.



Scheme 4.17. Synthesis of compound **4.52**

The adenine derivatives were also explored. Cross metathesis of compound **4.53**, obtained by silylation of the primary alcohol in compound **4.44** by reaction with TBDPSCl, with diethylallyl phosphonate under the same conditions to those previously tested rendered *E* alkene **4.54** in 90% yield as a green oil (Scheme 4.18).



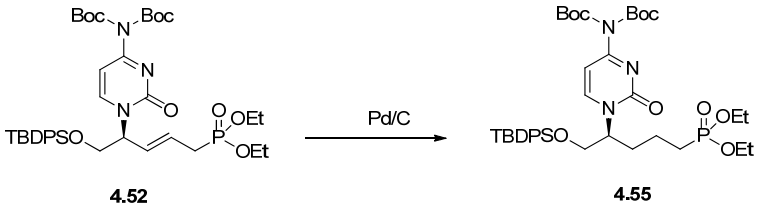
Scheme 4.18. Synthesis of compound **4.54**

4.3.3. Hydrogenation reaction by Pd/C[157]

With the protected forms of the acyclic nucleoside phosphonates in hand, the final steps in the synthetic plan involve on one hand double bond hydrogenation to give access to the saturated nucleoside analogues and on the other hand protecting group cleavage on the saturated and unsaturated derivatives to render the final products.

Attempted hydrogenation reaction of the compound **4.52** with Pd/C in methanol at 1 bar of hydrogen led to no conversion (Table 4.3, Entry 1). At higher hydrogen pressure (10 bar) the presence of two new products was observed by ^{1}H NMR spectroscopy after 12h of reaction. One was assigned to the desired product **4.55** and the second one was attributed to a product in which the hydrogenation of double bonds in cytosine was also produced (Table 4.3, Entry 2).

Table 4.3. Hydrogenation of compound **4.52**



4.52 **4.55**

Entry	Allylamine	solvent	P_{H2} (bar)	Temp. (ºC)	Time (h)	Product	Conversion (%)[b]	Yield (%)[c]
1	**4.52**	MeOH	1	rt	12	**4.52**	**>2**	-
2	**4.52**	MeOH	10	rt	12	**4.55**	**50**	-
3	**4.52**	MeOH	3	rt	3	**4.55**	**73**	51
4	**4.52**	MeOH	3	rt	5	**4.55**	**>99**	87

[a] conditions: All reaction were stirred at room temperature in MeOH in the presence of Pd/C. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

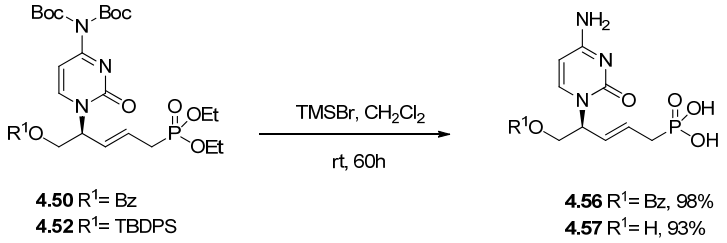
In order to improve the conversion of hydrogenated product **4.55**, we decided to decrease both hydrogen pressure (3 bar) and reaction time (3h). Under these conditions product **4.55** was exclusively obtained although the conversion (73%) was not complete

[157] Tomioka, T.; Yabe,Y.; Takahashi, T.; Simmons, T. K. *J. Org. Chem.* **2011**, *76*, 4669–4674.

(Table 4.3, Entry 3). Full conversion and 87% yield of compound **4.55** were obtained when the reaction time was increased to 5 h (Table 4.3, Entry 4).

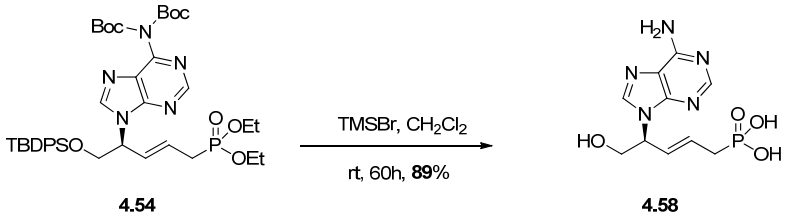
4.3.4. Removal of protecting groups[156]

The unsaturated phosphonate esters derived from cytosine were deprotected by reaction with TMSBr in dichloromethane at room temperature for 60h. Under these conditions the phosphonate alkyl ester, the *N*-Boc groups and the silyl ether in **4.52** were removed affording the fully deprotected target products **4.57** in 93 % yield. Under the same conditions, however, compound **4.50** rendered **4.58** in a 98% yield with the benzoate group unaltered (Scheme 4.19).

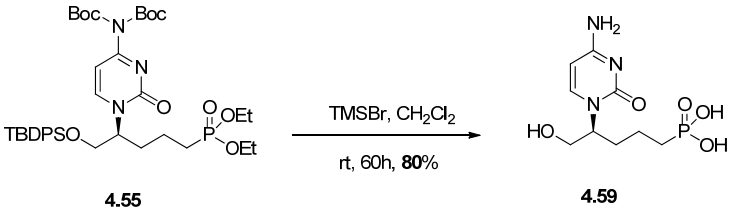


Scheme 4.19. Removal of protecting groups

Analogous deprotection in the unsaturated adenine derivative **4.54** (Scheme 4.20) and the saturated cytosine derivative **4.55** (Scheme 4.21) afforded the fully deprotected target products **4.58** and **4.59** in 89% and 80% yields, respectively



Scheme 4.20. Synthesis of compound **4.58**



Scheme 4.21. Synthesis of compound **4.59**

Biological evaluation of these nucleosides analogues as chemotherapeutic and anti-viral agents is currently in progress in the Laboratory of Virology and Chemotherapy of Prof. Jan Balzarini (University of Leuven, Belgium), and therefore due activity profiles of these compounds will be presented when provided.

4.4. Experimental Part

4.4.1. General Methods

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLVsystem-4®). Toluene was purified using standard procedure.

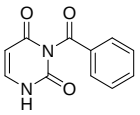
^{1}H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm ^{1}H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Melting points, determined with Reichert apparatus, are uncorrected. Optical rotations were measured at 598 nm on a Jasco DIP-370 digital polarimeter using a 100 mm cell.

Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60F254 glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/H_2SO_4 (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF254 silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and employed a solvent polarity correlated with TLC mobility.

The enantiomeric excess (ee%) determined via chiral HPLC analysis (chiralpack OD column, heptane:^{i}PrOH, flow rate 0.5-1 $mlmin^{-1}$).

4.4.2. Compound characterization

3-*N*-Benzoyluracil (4.28).

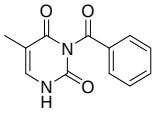


4.28

Benzoyl chloride (1.1 ml, 9 mmol) was added to a uracil solution (0.5 g, 4.5 mmol) in anhydrous pyridine (8 ml) and anhydrous acetonitrile (19 ml). After stirring for 12 h, cold water (12 ml) was added to the reaction mixture. The solvent was removed by rotary-evaporation, and the residue was purified by silica gel column chromatography CH_2Cl_2/MeOH (30:1) (0.63 g, 65%).

^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm) δ= 11.8 (br s, 1H), 7.94 (d, 2H, *J* = 8.4 Hz), 7.77 (t, 1H, *J* = 7.6 Hz), 7.67 (dd, 1H, *J* = 7.6, 1.2 Hz,), 7.60 (t, 1H, *J* = 7.6Hz), 5.63 (dd, 1H, *J* = 8, 1.2 Hz,). **^{13}C NMR** (DMSO-d_6, 100.6 MHz, δ in ppm) δ= 170, 162.9, 150.1, 143.4, 131.3, 130.2, 126.4, 100.1.

3-*N*-Benzoylthymine (4.30).

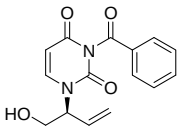


4.30

Benzoyl chloride (1.85 ml, 16 mmol) was added to a thymine solution (1 g, 8 mmol) in anhydrous pyridine (14 ml) and anhydrous acetonitrile (34 ml). After stirring for 12 h, cold water (21 ml) was added to the reaction mixture. The solvent was removed by rotary-evaporation, and the residue was purified by silica gel column chromatography CH_2Cl_2/MeOH (30:1) (1.1 g, 60%).

^{1}H NMR (400 MHz, DMSO-d6, δ in ppm) δ= 7.92 (dd, 1H, *J* = 10, 2 Hz), 7.77 (tt, 1H, *J* = 7.6, 2.8 Hz.), 7.59 (t, 1H, *J* = 8.4 Hz), 7.53 (d, 1H, *J* = 1.2 Hz), 1.6 Z(s, 3H).

3-Benzoyl-1-[(2S)-1-hydroxybut-3-en-2-yl]-1,2,3,4-tetrahydropyrimidine-2,4-dione (4.31).

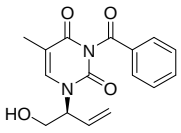


4.31

Compound **4.31** was prepared from butadiene monoepoxide 0.06 ml, 3-*N*-Benzoyluracil (0.1 g, 0.46 mmol), $(\eta^3C_3H_5PdCl)_2$ (0.003 g, 0.0082 mmol) and *(R,R)*-ligand **4.35** (0.02 g, 0.025 mmol) in 10 ml of dichloromethane for 5h. Purification by silica chromatography (1:1 hexane/ACOEt) provided the desired prodauct **4.31** in (0.095 g, 83%) and 84 ee% determined by chiral HPLC (chiralpack OD, hexane:^{i}PrOH 85:15, 0.4 mlmin^{-1}, t_R(R) = 78 min and t_R(S) = 92.2 min).

$[\alpha]_D^{25}$ = -3.7(*c* 1.8, $CHCl_3$). **IR** (neat): 3400, 2921, 2851, 1742, 1698, 1645, 1438, 1361, 1238, 941, 796, 682 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400MHz, δ in ppm): δ= 7.94 (d, 2H, *J* = 7.2 Hz), 7.65 (t, 1H, *J* = 7.2 Hz), 7.50 (t , 2H, *J* = 7.6 Hz), 7.43 (d, 1H, *J* = 8.4 Hz), 5.91 (ddd, 1H, *J* = 17.2, 10.4, 5.2 Hz) , 5.78 (d, 1H, *J* = 7.6 Hz), 5.45(dd, 1H, *J* = 11.6, 1.2 Hz), 5.37 (dd, 1H, *J* = 18, 1.6 Hz), 5.14 (m, 1H), 2.7 (brs, 1H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 169.1, 162.5, 150.5, 142.9, 135.4, 131.8, 131.4, 130.6, 129.4, 121.0, 101.9, 62.7, 59.15. **ESI-HRMS** [M+23] calcld for $C_{15}H_{14}N_2NaO_4$: 309.0851, Found: 309.0833.

3-Benzoyl-1-[(2S)-1-hydroxybut-3-en-2-yl]-5-methyl-1,2,3,4-tetrahydropyrimidine--2,4-dione (4.33).



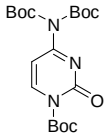
4.33

Compound **4.33** was prepared from butadiene monoepoxide 0.014 ml, product 3-*N*-Benzoylthymine (0.05 g, 0.2 mmol), $(\eta^3C_3H_5PdCl)_2$ (0.0013 g , 0.036 mmol) and *(R,R)*-ligand **4.35** (0.008 g, 0.0108 mmol) in 5 ml of dichloromethane for 18h. Purification by silica chromatography (1:1 hexane/ACOEt) provided the desired

product in (0.021 g, 40%) and 66 ee% determined by chiral HPLC (chiralpack OD, hexane:^{i}PrOH 85:15, 0.4 mlmin^{-1}).

$[\alpha]_D^{25}$ = -4.8 (*c* 0.2, $CHCl_3$). **IR** (neat): 3088, 2921, 2851, 1742, 1698, 1632,1420, 1249, 1221, 962, 763, 683 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400MHz, δ in ppm): δ = 8.10 (dd, 2H, *J* = 8.4, 1.2 Hz), 7.59 (tt, 1H, *J* = 7.6, 2.8 Hz), 7.47 (t, 2H, *J* = 7.2 Hz), 5.94 (ddd, 1H, *J* = 17.2, 10.4, 6 Hz), 5.63 (m, 1H), 5.47 (dt, 1H, *J* = 17.2, 2.8, 1.6 Hz), 5.35 (dt, 1H, *J* =10.8, 2.4, 1.2 Hz), 3.87 (m, 2H), 1.89 (brs, 1H), 1.56 (s, 1H). **ESI-HRMS** [M+1] calcld for $C_{16}H_{17}N_2O_4$ m/z: 301.1188, Found: 301.1214.

1-*tert*-Butoxycarbonylamino-4-((bis(*tert*-butoxycarbonyl)amino)-1,2-dihydropyrimidine-2-one (4.37).

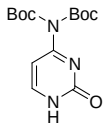


4.37

To a Ar-flushed flask equipped with a magnetic stiring bar and containing cytosine (0.5 g, 4.5 mmol) and DMAP (0.054 g, 0.45 mmol) was added dry THF (30ml). To the stirred suspension was added Boc_2O (4 g, 18 mmol) under Ar atmosphere. The reaction mixture was stirred overnight at room temperature, at which point TLC analysis indicated the presence of single product. The excess amount of THF was removed to give **4.37** (1.83 g, 99%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.95 (d, 1H, *J* = 8 Hz), 7.05 (d, 1H, *J* = 8Hz), 1.57 (s, 9H), 1.52 (s, 18H). **^{13}CNMR** ($CDCl_3$, 100.6MHz, δ in ppm) δ = 162.4, 151.4, 150.3, 149.2, 143.6, 97.0, 86.8, 85.4, 27.8, 27.7.

4-((Bis-(*tert*-butoxycarbonyl)amino)-1,2-dihydropyrimidin-2-one (4.38).[173]

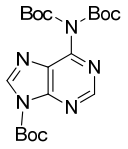


4.38

To a solution of **4.37** (0.27 g, 0.7 mmol) dissolved in MeOH (8 ml) was added saturated $NaHCO_3$aq (4 ml). The turbid solution was stirred at 50ºC for 1h, at which point clear conversion to bis-Boc protected adenine was observed by TLC. After evaporation of MeOH, water (4.5 ml) was added to the suspension, and the layer extracted with CH_2Cl_2 (3×100 ml). The organic layer was dried with Na_2SO_4, filtered and evaporated to give pure **4.38** (0.213 g , 98%) as a white solid.

^{1}H NMR($CDCl_3$, 400MHz, δ in ppm) δ = 13.18 (brs, 1H**),** 7.72 (d, 1H, *J* = 7.2 Hz), 7.04 (d, 1H, *J* = 6.8 Hz), 1.5 (s, 18H).**^{13}C NMR**($CDCl_3$, 100.6MHz, δ in ppm) δ = 163.8, 158.6, 149.6, 146.1, 136.8, 96.8, 85.1, 27.8.

9-*tert*-Butoxycarbonyl-6-bis-(*tert*-butoxycarbonyl)amino-9H-purine (4.40).

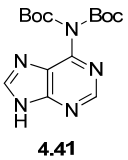


4.40

To a Ar-flushed flask equipped with a magnetic stiring bar and containing adenine (0.5 g, 3.7 mmol) and DMAP (0.045g, 0.37 mmol) was added dry THF (25 ml). To the stirred suspension was added Boc_2O (3.23 g, 14.8 mmol) under Ar atmosphere. The reaction mixture was stirred overnight at room temperature, at which point TLC analysis indicated the presence of single product. The excess amount of THF was removed to give **4.40** (1.6 g, 99%) as yellow oil.

^{1}H NMR ($CDCl_3$, 400MHz, δ in ppm): δ = 8.94 (s, 1H), 8.46 (s, 1H), 1.64(s,9H), 1.35 (s,18H). **^{13}CNMR**($CDCl_3$, 100.6 MHz, δ in ppm): δ = 154, 152.4, 151.2, 150.0, 145.6, 143.2, 129.5, 87.5, 83.9, 27.8. 27.7.

6-Bis-(*tert*-butoxycarbonyl)aminopurine (4.41).

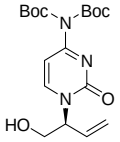


4.41

To a solution of compound **4.40** (1.6 g, 3.7 mmol) dissolved in MeOH (40 ml) was added saturated $NaHCO_3$aq (20 ml). The turbid solution was stirred at 50ºC for 1h, at which point clear conversion to bis-Boc protected adenine was observed by TLC. After evaporation of MeOH, water (23 ml) was added to the suspension, and the layer extracted with CH_2Cl_2 (3×100 ml).The organic layer was dried with Na_2SO_4, filtered and evaporated to give pure **4.41** (1.2 g, 96%) as a white solid.

^{1}H NMR ($CDCl_3$, 400MHz, δ in ppm): δ =12.28 (brs, 1H) , 8.87 (s, 1H), 8.53 (s, 1H), 1.42 (s, 18H). **^{13}CNMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ = 154, 151.8, 150, 150, 145.5, 145, 84.2, 27.7.

4-((Bis(*tert*-butoxycarbonyl)amino)-1-((2S)-1-hydroxybut-3-en-2-yl)-1,2-dihydropyrimidine-2-one(4.42).

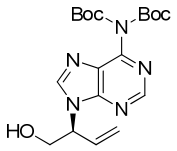


4.42

Compound **4.42** was prepared from butadiene monoepoxide (0.015 ml), product **4.38** (0.06 g, 0.2 mmol), $(\eta^3C_3H_5PdCl)_2$ (0.0013 g, 0.0036 mmol) and *(R,R)*-ligand **4.35** (0.0085 g, 0.0108 mmol) in (5 ml) dichloromethane for 18h at 0ºC. Purification by silica gel chromatography (10:2 hexane/ACOEt) provided the desired product **4.42** in (0.058 g, 85%) and 72 ee% determined by chiral HPLC (chiralpack OD, hexane:^{i}PrOH 90:10, 0.5 mlmin^{-1}, t_R(R) = 16.8 min and t_R(S) = 19.2 min).

$[\alpha]_D^{25}$ = - 7.13 (*c* 1.06, $CHCl_3$). **IR** (neat): 3354, 2980, 2924, 1772, 1742, 1643, 1613, 1312, 1257, 1136, 1112, 787 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400MHz, δ in ppm): δ= 7.68 (d, 1H, *J* = 7.2 Hz), 7.04 (d, 1H, *J* = 7.6 Hz), 5.94 (ddd, 1H, *J* = 17.2, 10.4, 6 Hz), 5.41 (dd, 1H, *J* = 10, 1.2 Hz), 5.32 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.26 (m, 1H), 4.98 (m, 2H), 2.83 (brs, 1H), 1.59 (s, 18H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 161.9, 155.8, 149.7, 147.2, 132.8, 120.5, 96.3, 85.1, 62.7, 61.2, 27.8. **ESI-HRMS** [M+1] calcld for $C_{18}H_{27}N_3O_6$: 382.1978, Found: 382.1985.

6-(Bis-*tert*-butoxycarbonyl)amino)-9-((2S)-1-hydroxybut-3-en-2-yl)-9H-purine (4.44).

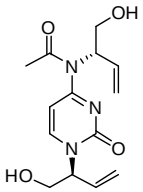


4.44

Compound **4.44** were prepared from butadiene monoepoxide (0.02 ml), product **4.41** (0.1 g, 0.3 mmol), $(\eta^3C_3H_5PdCl)_2$ (0.002 g, 0.0054 mmol) and *(R,R)*-ligand **4.35** (0.013 g, 0.016 mmol) in 6 ml dichloromethane at room temperature for 5h. Purification by silica chromatography (1:1 hexane/ACOEt) provided the desired product in (0.098 g 90%) and 92 ee% determined by chiral HPLC (chiralpack OD, hexane:^{i}PrOH 90:10, 0.6 mlmin^{-1}, t_R(R) = 15.4 min and t_R(S) = 18.2 min).

$[\alpha]_D^{25}$ = -15.80 (*c*0.92,$CHCl_3$). **IR** (neat): 3324, 2978, 2932, 1786, 1750, 1600, 1575, 1369, 1247, 1137, 1104, 848 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 8.83 (s, 1H), 8.18 (s, 1H), 6.20 (ddd, 1H, *J* = 16.8, 10.4, 6 Hz) , 5.38 (d, 1H, *J* = 10.4 Hz), 5.23 (m, 1H), 5.13 (d, 1H, *J* = 17.2 Hz), 5.18 (m, 2H), 3.96 (brs, 1H),1.46 (s, 18H).**^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 153.0, 151.8, 150.7 (2C), 145.2, 132.8, 129.2, 119.7, 84.1, 63.8, 61.2, 28. **ESI-HRMS** [M+1] calcld for $C_{19}H_{28}N_5O_4$: 406.209, Found: 406.2077, **ESI-HRMS** [M+23] calcld for $C_{19}H_{27}N_5NaO_5$: 428.1910, Found: 428.1994.

4-(((2S)-1-hydroxybut-3-en-2-yl)-acetylamino)-1-((2S)-1-hydroxybut-3-en-2-yl)-1,2-dihydropyrimidine-2-one (4.47).

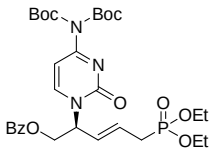


4.47

Compound **4.47** was prepared from butadiene monoepoxide 0.05 ml, Acetylcytosine **4.46** (0.1 g, 0.65 mmol), $(\eta^3C_3H_5PdCl)_2$ (0.0044g, 0.012mmol) and (R,R) ligand (0.03 g, 0.036 mmol) in 12 ml dichloromethane for 18h. Purification by silica chromatography (hexanes/ACOEt) provided (0.07 g, 40%) of product **4.47**.

^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): δ = 7.29 (d, 1H, *J* = 8.4 Hz), 6.19 (ddd, 1H, *J* =18, 10.8, 7.2 Hz), 5.90 (ddd, 1H, *J* = 17.2, 10.4, 5.2Hz), 5.54 (d, 1H, *J* = 8Hz), 5.62 (m, 1H), 5.34 (m,5 H), 4.23 (m, 1H), 3.90 (m, 4H), 2 (s, 3H). **^{13}CNMR** ($CDCl_3$, 100.6 MHz, δ in ppm) 165.6, 164, 151.8, 141.1, 132.5, 132.2, 120.7, 119.1, 101.6, 62.4,59.5, 57.4, 29.9. **ESI-HRMS** [M+1] calcld for $C_{17}H_{26}N_3O_5$ m/z: 294.1454,found: 294.1441.

(2*S*,3*E*)-2-[(4-bis-(*tert*-butoxycarbonyl)amino)-2-oxo-1,2-dihydropyrimidin-1-yl]-5-(diethoxyphosphoryl)pent-3-en-1-yl benzoate (4.50).

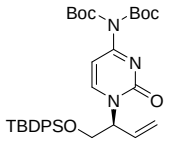


4.50

To a solution of compound **4.42** (0.3 g, 0.8 mmol) and diethylallylphosphonate (0.6 ml, 3.2 mmol) in CH_2Cl_2 (15 ml), II generation Grubbs catalyst (0.03 g, 0.04 mmol) was added. This solution was refluxed for 16h at 55ºC. After evaporation of all volatiles, the residue was dissolved in anhydrous dichloromethane (20 ml) and fresch distilled triethylamine (0.6 ml) was added. The solution was coled at 0ºC and benzoyl chloride (0.21 g, 1.5 mmol) was added dropwise, the resulting mixture was warmed at room temperature for 12h. The mixture was quenched by saturated NH_4Cl aqueous solution and then the organic layer was washed with water and brine. The solvent was removed under vacum and the crude was purified by silica gel chromatography. This procedure provided **4.50** as an oil (0.46 g, 90%).

$[\alpha]_D^{25}$ = - 18.7 (*c* 1.2, $CHCl_3$). **IR** (neat): 3053, 2984, 1725, 1671, 1455, 1371, 1320, 1264, 1138, 1110, 1025, 732 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400MHz, δ in ppm): δ= 7.94 (dd, 2H, *J* = 8.4, 1.2 Hz), 7.66 (d, 1H, *J* = 7.2 Hz), 7.56 (t, 1H, *J* = 7.6 Hz), 7.44 (t, 2H, *J* = 7.2 Hz), 7.06 (d, 1H, *J* = 7.6 Hz), 5.90 (m, 2H), 5.58 (m, 1H), 4.74 (dd, 1H, *J* = 12.4, 5.2 Hz), 4.64 (dd, 1H, *J* = 11.6, 4.8 Hz), 4.06 (m, 4H) , 2.67 (m, 2H), 1.52 (s, 18H), 1.25 (t, 6H, *J*= 6.8 Hz). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 166.0, 162.3, 154.9, 149.6, 146.1, 133.5, 130.2, 129.8, 129.4, 128.8, 128.6, 127.3, 96.5, 85.2, 63.8, 62.4, 62.3, 58.1, 31.4, 30.1, 27.8, 16.6, 16.5. **ESI-HRMS** [M+1] calcld for $C_{30}H_{42}N_3O_{10}P$: 636.2686, Found: 636.2676.

2-[(4-bis-(*tert*-butoxycarbonyl)amino)-1-[(2*S*)-1-(*tert*-butyldiphenylsilyloxy)but-3-en-2-yl]-1,2-dihydropyrimidin-2-one (4.51).

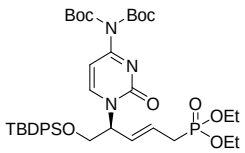


4.51

Compound **4.42** (0.1 g, 0.26 mmol) was dissolved in dry DMF (3 ml) and treated under argon with *tert*-butyldiphenyl chloride (0.08 ml, 0.3 mmol) and imidazole (0.04 g, 0.6 mmol).The mixture was then stirred for 16h at room temperature .workup (extraction with Et_2O) and column chromatography on silica gel (10:2) Hexan/EtOAC provided **4.51** (0.136 g, 85%).

$[\alpha]_D^{25}$ = - 13.5 (*c*1.27,$CHCl_3$). **IR** (neat): 2931, 2857, 1742, 1671, 1524, 1455, 1370, 1319, 1256, 1137, 1110, 784, 701 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400MHz, δ in ppm): δ= 7.75 (d, 1H, *J* = 8 Hz), 7.57 (ddd, 2H, *J* = 6, 3.2, 1.6 Hz), 7.48 (ddd, 2H, *J* = 6.4, 2.8, 1.2 Hz), 7.38 (m**,** 6H), 6.98 (d, 1H, *J* = 7.2 Hz), 6.01 (ddd, 1H, *J* =17.6, 10.4, 6 Hz), 5.38 (dd, 1H, *J* = 10.4, 0.8 Hz), 5.38 (m, 1H), 5.32 (dd, 1H, *J* = 17.6, 0.8 Hz), 3.97 (d, 2H, *J* = 3.6 Hz), 1.57 (s, 18H), 1.02 (s, 9H). **^{13}C NMR** (100.6 MHz,$CDCl_3$): δ= 161.8, 154.9, 149.7, 147.0, 135.6, 135.4, 132.9, 132.5, 130.1, 130.0, 127.9, 120.5, 95.5, 84.8, 63.8, 59.5, 27.8, 26.9, 19.2. **ESI-HRMS** [M+1] calcld for $C_{34}H_{46}N_3O_6Si$: 620.3156, Found: 620.3171.

(2*S*, 3*E*)- 2-[((4-Bis-(*tert*-butoxycarbonyl)amino)-2-oxo-1,2-dihydropyrimidin-1-yl]-1-(*tert*-butyldiphenylsilyloxy)-5-(diethoxyphosphoryl)pent-3-ene (4.52).



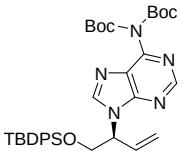
4.52

To a solution of product **4.51** (0.05 g, 0.08 mmol) and (0.004 g, 0.004 mmol) of II generation Grubbs catalyst in dichlorometane (4 ml) was added diethylallylphosphonate (0.06 ml, 0.32 mmol) at 55ºC. Reaction stirred at 55ºC for 16h, evaporation of solvent

and purification by silica chromatography AcOEt /Hexane (2:1) provided the desired product **4.52** as yellow liquid (0.057 g, 92%).

$[\alpha]_D^{25}$ = - 21.4 (*c*1.2,$CHCl_3$). **IR** (neat) 2969, 2931, 1741, 1671, 1455, 1370, 1319, 1255, 1111, 1024, 735, 701 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 7.68 (d, 1H, *J* = 7.6 Hz), 7.56 (dd, 2H, *J* = 7.6, 1.6 Hz), 7.45 (dd, 2H, *J* = 8, 1.6 Hz), 7.38 (m, 6H), 6.97 (d, 1H, *J* = 7.2 Hz), 5.83 (m, 2H), 5.29 (brs, 1H), 4.06 (m, 4H), 3.96 (d, 2H, *J* = 4Hz), 2.62 (d, 1H, *J* = 6.8 Hz), 2.58 (d, 1H, *J* = 6 Hz), 1.56 (s, 18H), 1.27 (t, 6H, *J* = 6.8 Hz), 1.03 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 161.7, 154.6, 149.5, 146.9, 135.5, 135.3, 132.5, 132.4, 130.0, 129.9, 129.5, 129.4, 128.5, 127.8, 126.5, 126.3, 95.4, 84.7, 63.6, 62.0, 61.9, 59.4, 31.3, 29.9, 27.7, 26.8, 19.1, 16.4. **ESI-HRMS** [M+1] calcld for $C_{39}H_{57}N_3O_9PSi$: 770.3602, Found: 770.3797.

6-(Bis-*tert*-butoxycarbonyl)amino)-9-((2S)-1-*tert*-butyldiphenylsilyloxy-but-3-en-2-yl)-9H-purine (4.53).



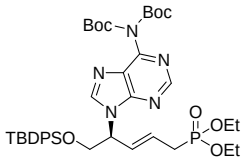
4.53

Compound **4.44** (0.25 g, 0.6 mmol) was dissolved in dry DMF (7 ml) and treated under argon with *tert*-butyldiphenylsilyl chloride (0.18 ml,0.66 mmol) and imidazole (0.09 g, 1.32 mmol). The mixture was then stirred for 16h at room temperature. workup (extraction with Et_2O) and column chromatography on silica gel (10:2) Hexan/EtOAC provided **4.53** (0.3 g, 80%).

$[\alpha]_D^{25}$ = -10.93 (*c* 1.13, $CHCl_3$). IR(neat): 2987, 2362, 1733, 1716, 1558, 1540, 1507, 1456, 1395, 1259, 1066, 749 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 8.79 (s, 1H), 8.26 (s, 1H), 7.48 (td, 4H, *J* = 8, 1.6 Hz), 7.39 (tt**,** 2H, *J* = 9.6, 1.2 Hz), 7.32 (t, 4H, *J* = 7.2 Hz), 6.02 (ddd, 1H, *J* = 17.2, 10.4, 6.4 Hz), 5.34 (dd, 1H, *J* = 11.6, 0.8 Hz,), 5.30 (m, 1H), 5.17 (dd, 1H, *J* = 17.2, 0.8 Hz), 4.16 (dd, 1H, *J* = 11.2, 6.8 Hz), 4.05 (dd, 1H, *J* = 10.8, 4 Hz), 1.43 (s, 18H), 0.94 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 153.3, 151.8, 150.5, 150.3, 144.5, 135.5, 135.4, 132.5, 130.1, 127.9, 127.9, 119.8, 83.7,

64.8, 59.4, 27.9, 26.8, 19.1. **ESI-HRMS** [M+23] calcld for $C_{35}H_{45}N_5NaO_5Si$: 666.3088, Found: 666.3073.

(2*S*,3*E*)-2-[((6-Bis-(*tert*-butoxycarbonyl)amino)-purin-9-yl]-1-(*tert*-butyldiphenylsilyloxy)-5-(diethoxyphosphoryl)pent-3-ene (4.54).

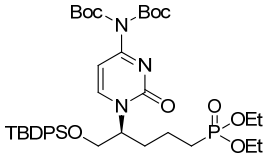


4.54

To a solution of product **4.53** (0.14 g, 0.22 mmol) and (0.009 g, 0.011 mmol) of II generation Grubbs catalyst in dichlorometane (11 ml) was added diethylallylphosphonate (0.16 ml, 0.88 mmol) at 55ºC. Reaction stirred at 55ºC for 16h, evaporation of solvent and purification by silica chromatography AcOEt /Hexan (2:1) provided the desired product **4.54** as green liquide (0.157 g , 90%).

$[\alpha]_D^{25}$ = - 14.6 (*c* 1.36, $CHCl_3$). **IR** (neat) 2929, 2856, 1788, 1599, 1452, 1369, 1252, 1139, 1111, 1026, 704 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 8.77 (s, 1H), 8.20 (s, 1H), 7.42-7.29 (m, 10H), 6.08 (m, 1H), 5.76 (ddd, 1H, *J* = 15.6, 14.4, 7.6 Hz), 5.25 (bsr, 1H), 4.16 (dd, 2H, *J* = 10.4, 6.4 Hz), 4.03 (m, 4H), 3.61 (d, 2H, *J* = 7.2 Hz), 2.56 (d, 1H, *J* = 7.6 Hz), 1.43 (s, 18H), 1.22 (t, 6H, *J* = 6.8 Hz), 0.93 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 153.2, 151.9, 150.6, 150.4, 144.5, 132.5, 135.5, 132.4, 132.4, 130.1, 129.1, 129.0, 128.0, 126.2, 126.1, 83.8, 64.8, 62.2, 62.1, 59.2, 31.3, 29.9, 28.0, 26.9, 19.2, 16.6. **ESI-HRMS** [M+1] calcld for $C_{40}H_{57}N_5O_8$ PSi: 794.3714, Found: 794.3694.

(2*S*)- 2-[((4-Bis-(*tert*-butoxycarbonyl)amino)-2-oxo-1,2-dihydropyrimidin-1-yl]-1-(*tert*-butyldiphenylsilyloxy)-5-(diethoxyphosphoryl)pentane (4.55).

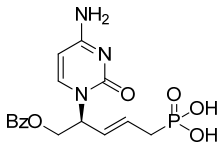


4.55

To a solution of **4.52** (0.15 g, 0.2 mmol) in MeOH (6 mL) was added 5% palladium/carabon. The mixture was stirred under a hydrogen atomosphere (3 atm) at room temperature for 5 h. The reaction mixture was then filtered through Celite with MeOH and concentrated under reduced pressure. The crude product was purified by silicagel column chromatography (EtOAc) to give the compound **4.55** as colorless oil (0.134 g, 87%).

$[\alpha]_D^{25}$ = - 16 (*c* 2, $CHCl_3$). **IR** (neat) 2930, 1743, 1669, 1456, 1320, 1264, 1137, 1113, 733, 702 cm^{-1}.. **^{1}H NMR** ($CDCl_3$, 400MHz, δ in ppm): δ= 7.72 (d, 1H, *J* = 7.2 Hz), 7.55 (dd, 2H, *J* = 8, 1.6 Hz), 7.47 (dd, 2H, *J* = 7.6, 1.6 Hz), 7.40 (m, 6H), 6.99 (d, 1H, *J* = 7.2 Hz), 4.48 (brs, 1H), 4.03 (m, 4H), 3.84 (dd, 1H, *J* = 3.6, 11.2 Hz), 3.80 (dd, 1H, *J* = 3.2, 11.2 Hz), 1.95-1.86 (m, 2H), 1.77-1.63 (m, 4H),1.55 (s, 18H), 1.26 (t, 6H, *J* = 6.8 Hz), 1.01 (s, 9H). **^{13}C NMR** ($CDCl_3$, 400MHz, δ in ppm): δ= 161.8, 155.3, 149.8, 146.2, 135.7, 135.5, 132.7, 132.5, 130.2, 130.1, 128.0, 95.7, 85, 64.4, 61.8, 61.7, 29.8, 27.9, 27, 25.9, 24.5, 19.3, 16.7, 16.6. ESI-HRMS [M+1] calcld for $C_{39}H_{59}N_3O_9PSi$: 772.3758, Found: 772.3730.

(2*S*,3*E*)-2-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-(diethoxyphosphoryl) pent-3-en-1-yl benzoate (4.56).

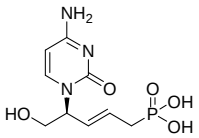


4.56

Compound **4.50** (0.07 g, 0.16 mmol), was solubilized in CH_2Cl_2 (10 mL), and TMSBr (0.12 mL, 0.96 mmol) was added and stirred for 60 h at room temperature under positive pressure of dry Ar. MeOH (3 ml) was added and evaporated with heating (ca. 60 ºC). MeOH (3 mL) was added again, and this procedure was repeated three times more. The residue was extracted with H_2O and CH_2Cl_2, and the inorganic phase was evaporated to dryness to afford the desired compound **4.56** as yellow liquid (0.06 g, 98%).

[α]$_D^{25}$ = +13.97 (*c*1.2, MeOH). **IR** (neat): 2968, 1716, 1670, 1451, 1382, 1268, 1112, 1070, 1024, 973, 926, 713 cm^{-1}. **^{1}H NMR** (D_2O, 400 MHz, δ in ppm): δ= 7.93 (d, 1H, *J* = 8 Hz), 7.85 (d, 2H, *J* = 7.2 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.46 (d, 2H, *J* = 7.6 Hz), 6.16 (d, 1H, *J* = 7.6 Hz), 6 (ddd, 1H, *J* = 15.6, 13.6, 6.8 Hz), 5.88 (dt, 1H, *J* = 15.6, 10.4, 5.6 Hz), 5.47 (m, 1H), 4.64 (m, 2H), 2.76 (d, 1H, *J* = 7.2 Hz), 2.71 (d, 1H, *J* = 7.6 Hz). **^{13}C NMR** (D_2O, 100.6 MHz, δ in ppm): δ= 167.7, 158.8, 148.7, 147.0, 134.1, 129.4, 129.2, 128.8, 128.4, 126.2, 94.92, 63.8, 57.3, 32.4, 31.0. **ESI-HRMS** [M+1] calcld for $C_{16}H_{19}N_3O_6P$:380.1011, Found: 380.1030.

[(2*E*,4*S*)-4-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-hydroxypent-2-en-1-yl]phosphonic acid (4.57).

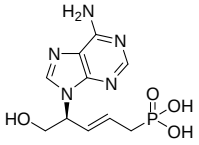


4.57

Compound **4.52** (0.08 g, 0.1 mmol), was solubilized in CH_2Cl_2 (7 mL), and TMSBr (0.08 ml, 0.6 mmol) was added and stirred for 60 h at room temperature under positive pressure of dry Ar. MeOH (3 mL) was added and evaporated with heating (ca. 60 ºC). MeOH (3 mL) was added again, and this procedure was repeated three times more. The residue was extracted with H_2O and CH_2Cl_2, and the inorganic phase was evaporated. The crude product was purified by reverse phase chromatography on Silica C18 using (H_2O, MeOH) as the eluent to give the compound **4.57** as a white solid (0.025 g, 93%).

[α]$_D^{25}$ = - 11.2 (*c* 2.89, MeOH). **IR** (neat): 2969, 1715, 1669, 1540, 1394, 1043, 973, 872, 793, 762, 748, 702 cm^{-1}. **^{1}H NMR** (D_2O, 400 MHz, δ in ppm): δ= 7.85 (d, 1H, *J* = 7.6 Hz), 6.16 (d, 1H, *J* = 8 Hz), 5.77 (m, 2H), 5.16 (brs, 1H), 3.88 (d, 2H, *J* = 6 Hz), 2.65 (d, 1H, *J* = 6 Hz), 2.61 (d, 1H, *J* = 7.2 Hz). **^{13}C NMR** (D_2O, 100.6 MHz, δ in ppm): 158.8, 149.0, 147.0, 127.5, 127.4, 94.6, 60.9, 59.8, 31.8, 30.5. **ESI-HRMS** [M+1] calcld for $C_9H_{14}N_3O_5P$: 298.0569, Found: 298.0582.

[(2*E*,4*S*)-4-(6-amino-9H-purin-9-yl)-5-hydroxypent-2-en-1-yl]phosphonic acid (4.58).

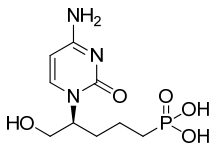


4.58

Compound **4.54** (0.05 g, 0.06 mmol), was solubilized in CH_2Cl_2 (4 ml), and TMSBr (0.64 ml, 0.36mmol) was added and stirred for 60 h at room temperature under positive pressure of dry Ar. MeOH (3 mL) was added and evaporated with heating (ca. 60 ºC). MeOH (3 mL) was added again, and this procedure was repeated three times more. The residue was extracted with H_2O and CH_2Cl_2, and the inorganic phase was evaporated. The crude was purified by reverse phase chromatography on Silica C18 using (H_2O, MeOH) as the eluent to give the compound **4.58** as a white solid (0.015 g, 89%).

$[\alpha]_D^{25}$ = - 12.4 (*c*1.93, MeOH). **IR** (neat): 3070, 2325, 1691, 1609, 1531, 1496, 1425, 1387, 1224, 1107, 937, 770 cm^{-1}. **^{1}H NMR** (D_2O, 400 MHz, δ in ppm): δ= 8.44 (s, 1H), 8.40 (d, 1H), 6.02 (m, 1H), 5.76 (m, 1H), 5.35 (brs, 1H), 4.11 (dd, 1H, *J* = 12.4, 8.4 Hz), 4.05 (dd, 1H, *J* = 11.6, 5.2 Hz), 2.65 (d, 1H, *J* = 7.2 Hz), 2.59 (d, 1H, *J* = 6.8 Hz).**^{13}C NMR** (D_2O, 100.6 MHz, δ in ppm): δ= 149.6, 148.3, 143.9, 143.6, 127.8, 127.6, 127, 126.9, 118.1, 62.3, 59.2, 32, 30.7. **ESI-HRMS** [M+1] calcld for $C_{10}H_{15}N_5O_4P$: 300.0862, Found: 300.0825.

[(4S)-4-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-hydroxypentyl]phosphonic acid (4.59).



4.59

Compound **4.55** (0.12 g, 0.15 mmol), was solubilized in CH_2Cl_2 (12 ml), and TMSBr (0.15 ml, 0.9 mmol) was added and stirred for 60 h at room temperature under positive pressure of dry Ar. MeOH (3 mL) was added and evaporated with heating (ca. 60 ºC). MeOH (3 mL) was added again, and this procedure was repeated three times

more. The residue was extracted with H_2O and CH_2Cl_2, and the inorganic phase was evaporated. The crude product was purified by reverse phase chromatography on Silica C18 using (H_2O, MeOH) as the eluent to give the compound **4.59** as a whit solid (0.033 g, 80%).

$[\alpha]_D^{25}$ = - 12 (*c* 0.2, MeOH). **IR** (neat): 3327, 2918, 1668, 1540, 1456, 1387, 1148, 1050, 920, 785 cm^{-1}. **^{1}H NMR** (D_2O, 400MHz, δ in ppm): δ= 7.87 (d, 1H, *J* = 8 Hz), 6.19 (d, 1H, *J* = 8 Hz), 4.64 (m, 1H), 3.75 (m, 2H), 1.81-1.75 (m, 4H), 1.52(m, 2H). **^{13}C NMR** (D_2O, 100.6 MHz, δ in ppm): δ= 158.7, 149.4, 146.2, 94.2, 61.7, 58.5, 28.8, 26.1, 24.7, 18.3. **ESI-HRMS** [M+24] calcld for $C_9H_{17}N_3NaO_5P$: 301.0804, Found: 301.1373.

CHAPTER V

APPROACHES TO THE ENANTIOSELECTIVE SYNTHESIS OF AT2433-A1

UNIVERSITAT ROVIRA I VIRGILI
ENANTISELECTIVE SYNTHESIS OF NATURAL PRODUCTS
Mariam Azzouz

5.1. Introduction

AT2433-A1, AT2433-A2, AT2433-B1 and AT2433-B2 are antitumor antibiotics which were isolated from the fermentation broth culture of Actinomadura melliaura (ATCC 39691). These compounds are closely related to the antitumor rebeccamycine (**5.1**)[158,159] (Figure 5.1), and were active against Gram-positive bacteria, such as Micrococcus luteus (ATCC 9341), Bacillus subtilus (ATCC 6633), Staphylococcus aureus (A 9537), Streptococus faecalis (A 20688) and Streptococcus faecium (ATCC 9790). Furthermore, AT433-B2 has shown activity against the Gram-negative bacterium Escherichia coli (SS 1431). In addition, AT2433-A1, and AT2433-B1 showed antitumor activity against the transplantable murine P-388 leukemia.

There are two classes of indolocarbazole glycosides,[165] differing both in structure and in mechanism of action. The straurosporine class is characterized by two bonds between the glycoside and indolocarbazole heterocycle. These fused structures exhibit potent inhibition of protein kinases.[160] In contrast, the rebeccamycin[161] class of indolocarbazole glycosides have a single glycosidic linkage and have shown remarkable activity in the poisoning of DNA topoisomerase I.[162,163] The only clinically used antitumor drugs that selectively target topoisomerase I are irinotecan and topotecan, derivatives of camptothecin. Both camptothecin and the indolocarbazole glycosides have been shown to stabilize the intermediate DNA-topoisomerase I complex, leading to cell death.[164] Currently, rebeccamycin derivatives are in phase II clinical trials for the treatment of a wide range of malignancies including refractory pediatric neuroblastoma, advanced renal cell carcinoma, metastatic or locally recurrent colorectal cancer, and stage IIIB or IV breast cancer.[165]

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158 Bush, J. A.; Long, B. H.; Catino, J. J.; Bradner, W. T.; Tomita, K. *J. Antibiotics*. **1987**, *40*, 668–678.

159 Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett*. **1985**, *26*, 4015–4018.

160 Tamaoki, T.; Nomoto, H.; Takahashi, Y.; Kato, M.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun*. **1986**, *135*, 397–402

161 Nettleton, D. E.; Doyle, T. W.; Krishnan, B.; Matsumoto, G. K.; Clardy, J. *Tetrahedron Lett*. **1985**, *26*, 4011–4014.

162 Amashita, Y.; Fujii, N.; Murakata, C.; Ashizawa, T.; Okabe, M.;Nakano, H. *Biochemistry*. **1992**, *31*, 12069–12075.

163 Anizon, F.; Belin, L.; Moreau, P.; Sancelme, M.; Voldoire, A.; Prudhomme, M.; Ollier, M.; Severe, D.; Riou, J. F.; Bailly, C.; Fabbro, D.; Meyer, T. *J. Med. Chem.* **1997**, *40*, 3456–3465.

164 D'Arpa, P.; Liu, L. F. *Biochim. Biophys. Acta.* **1989**, *989*, 163–177.

Interest in the indolo[2,3-a]carbazole glycosides comes from their potent antineoplasic properties. These glycosides are potent antitumor antibiotics currently undergoing clinical trials for the treatment of numerous types of cancer. AT2433-A1 is the most complex member of this family of compounds possessing a unique disaccharide with a sensitive aminodeoxysugar and an unsymmetric aglycon. The synthesis of this natural product requires a method for glycosylation that sets the stereochemistry of the anomeric center and the regiochemistry of the aglycon (Figure 5.2).[165]

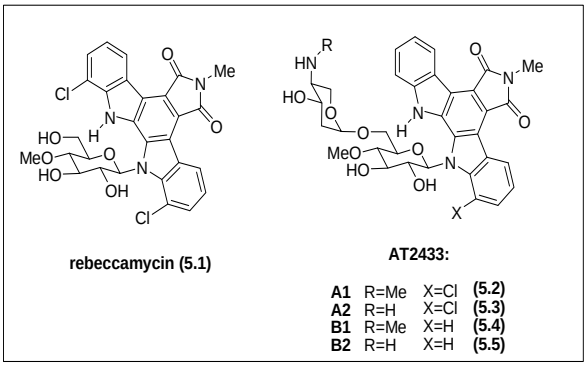

Figure 5.1. Structure of rebecamycine (**5**.**1**), AT2433-A1 (**5.2**), AT2433-A2 (**5.3**), AT2433-B1 (**5.4**) and AT2433-B2 (**5.5**).[165]

The excellent antitumor activity of indolocarbazoleglycosides has led to a significant synthetic effort in this area.[166,167] The greatest challenge in the synthesis of the indolocarbazole glycosides is the formation of the N-glycosidic bond.

Unlike other indolocarbazole natural products, AT2433-A1, AT2433-A2, AT2433-B1, and AT2433-B2 possess a unique disaccharide with a sensitive 2-deoxy aminosugar.[168,169] The complexity of these targets requires an efficient method for regioselective glycosylation in the presence of diverse functionality. While rebeccamycin has chlorine atoms at the 1 and 11 positions of the aromatic sector,

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165 Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem*. **2000,** *65*, 7541–7553.

166 Gribble, G. W.; Berthel, S. J. *Tetrahedron* **1992**, *48*, 8869–8880

167 Prudhomme, M. *Curr. Pharm. Des.* **1997**, *3*, 265–290.

168 Matson, J. A.; Claridge, C.; Bush, J. A.; Titus, J.; Bradner, W.T.; Doyle, T. W.; Horan, A. C.; Patel, M. *J. Antibiot.* **1989**, *42*, 1547–1555.

169 Golik, J.; Doyle, T. W.; Krishnan, B.; Dubay, G.; Matson, J. A. *J. Antibiot.* **1989,** *42*, 1784–1789.

AT2433 A1 and A2 have chlorine atoms only at the 1 position. Thus, the disaccharide must be joined to the more hindered, less nucleophilic nitrogen atom.

The disaccharide of AT2433-A1 consists of a glucose and an aminosugar subunit, 2,4-dideoxy-4-amino-L-xylose (Figure 5.2). Derivatives of this aminosugar are present in the enediyne antitumor antibiotics calicheamicin and esperamicin.[170,171,172]

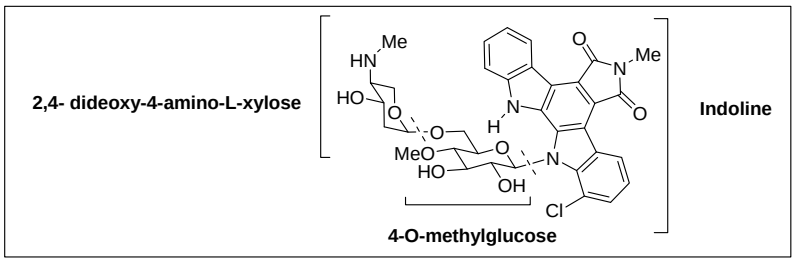

Figure 5.2. General structure of AT2433-A1 **5.2**[165]

5.1.1. Synthesis of AT2433-A1[165]

Following the procedure of Roush and Hunt,[173] homoallyl alcohol **5.6** was prepared from (*R)*-Garner's aldehyde using an allyl dioxaborolane derived from (*R*,*R)*-diisopropyl tartrate. Homoallyl alcohol **5.6** was formed as an 88:12 mixture of diastereomers differing in stereochemistry at the alcohol stereocenter. The mixture of diastereomers was then benzylated, and the latent aldehyde was revealed by dihydroxylation of the double bond with catalytic osmium tetroxide followed by cleavage of the diol with sodium metaperiodate. At the aldehyde stage the undesired diastereomer was separated chromatographically. Selective removal of the acetonide[174] led to the lactol **5.9**, which was then converted to the glycosyl fluoride **5.10** by the action of DAST (Scheme 5.1).

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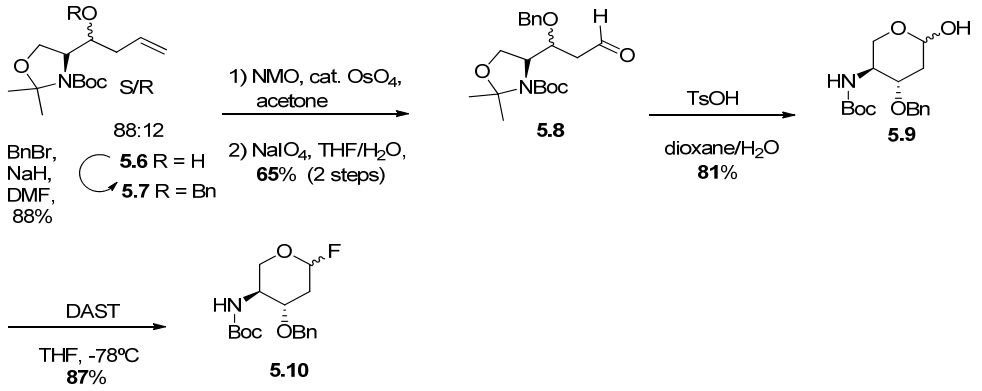
170 Miniker, T. D.; Mukhanov, V. I.; Chkanikov, N. D.; Yartzeva,I. V.; Preobrazhenskaya, M. N. *Carbohydr. Res.* **1978**, *64*, 17–31.

171 Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel,M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464–3466.

172 Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi,H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461–3462.

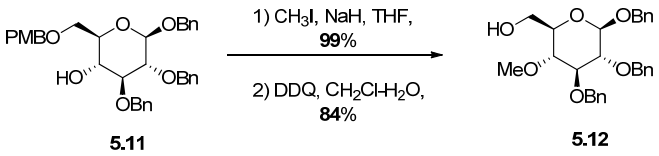
173 Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798–806.

174 Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855–5858.



Scheme 5.1. Synthesis of glycosyl fluoride **5.10**

While 4-*O*-methylglucose had been previously prepared,[175] a strategy was needed for differential protection of the hydroxyl groups at the positions 1-3, 4 and 6. A suitable intermediate was prepared using the method of Samuelsson involving reductive opening of a 4,6-*p*-methoxybenzylidene acetal to give glucoside **5.11**.[176] Methylation of the secondary alcohol using methyl iodide and sodium hydride provided the 4'-*O*-methyl derivative. Selective removal of the 6-PMB protecting group under oxidative conditions led to glucoside **5.12**, ready for glycosylation at the free 6-OH (Scheme 5.2).



Scheme 5.2. Synthesis of compound partially protected **5.12**

Coupling of the primary alcohol **5.12** with glycosyl fluoride **5.10** was performed under Mukaiyama-Nicolaou[177] conditions (Scheme 5.3). Within 15 min, the equatorial (β) and axial (α) glycosides were formed in a 2:1 ratio, consistent with results of Deslongshamps[178] and Woerpel.[179]

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175 Bouveng, H. O.; Lindberg, B.; Theander, O. *Acta Chem. Scand.* **1957,** *11*, 1788–1789.

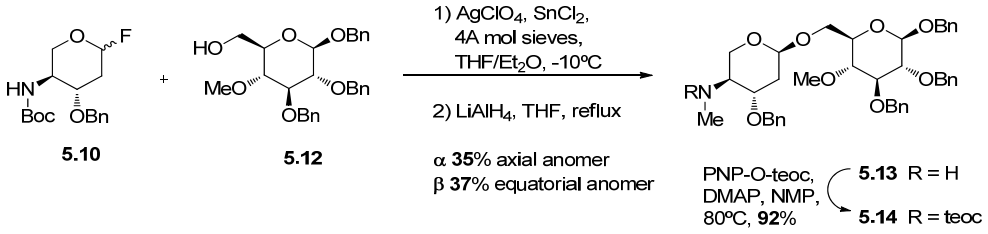
176 Johansson, R.; Samuelsson, B.*J. Chem. Soc. Perkin1* **1984**, 2371–2373.

177 Mukaiyama, T.; Murai, Y.; Shoda, S. I. *Chem. Lett.* **1981**, *10*, 431–432.

178 Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597–7602.

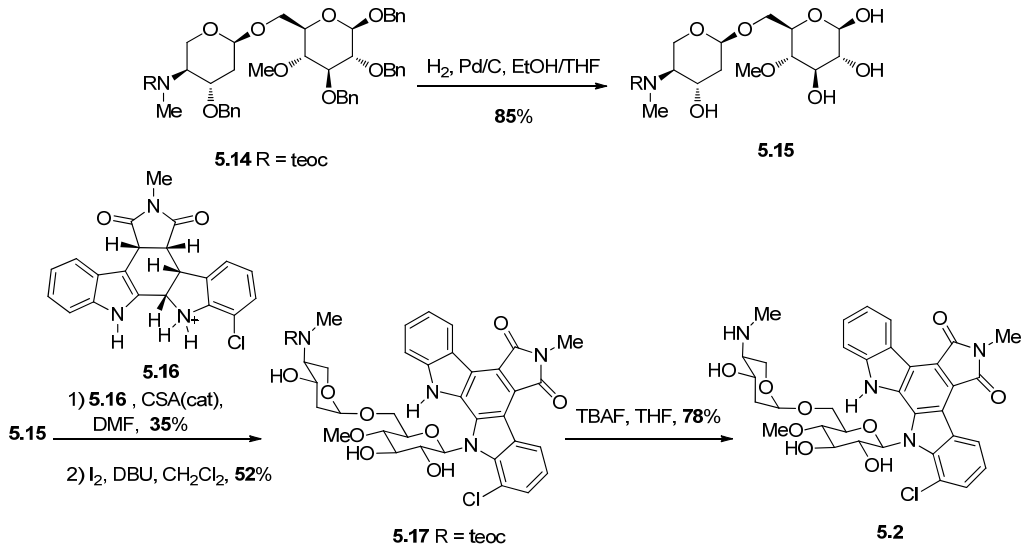
179 Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168–169.

The equatorial and axial anomers were inseparable until the *N*-Boc group was reduced to the corresponding methylamino group. Reprotection of the methylamino group as the Boc derivative led to problems during deprotection due to the sensitivity of the 2-deoxypyranoside linkage.[180] Instead, the methylamino group of disaccharide **5.13** was then protected as the *N*-trimethylsilylethyl carbamate (Teoc) derivative.



Scheme 5.3. Coupling of the glycosyl fluoride **5.10** with primary alcohol **5.12**

Debenzylation with palladium and hydrogen provided the deprotected disaccharide **5.15**, which was used in the synthesis of AT2433-A1 by condensation with 3 equiv of aglycon **5.16** in 35% yield. The dehydrohalogenation could be accomplished with DBU and iodine in methylene chloride in 52% yield to furnish the aromatic core of the aglycone. Finally, deprotection of the teoc group with TBAF provided material that matched AT2433-A1 (Scheme 5.4).

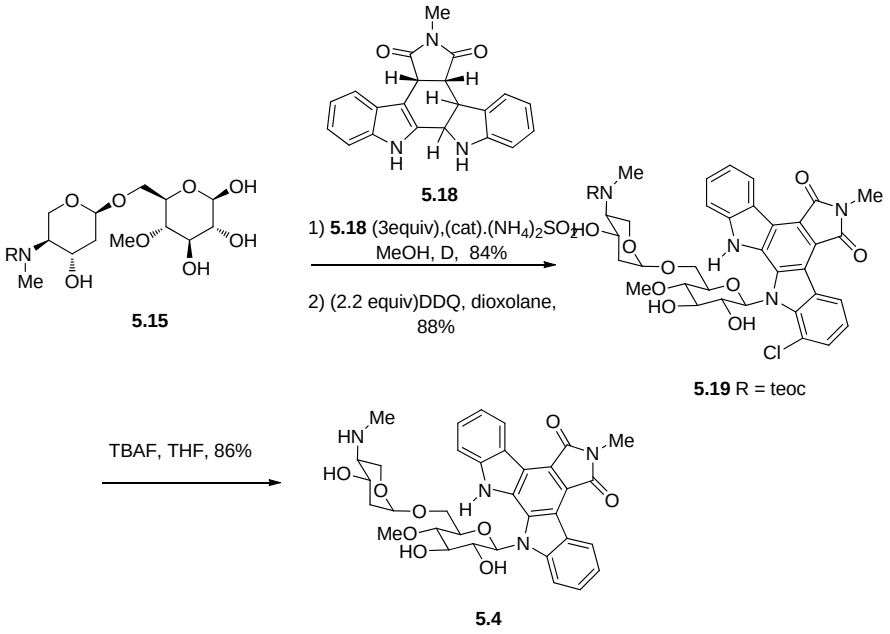


Scheme 5.4. Synthesis of AT2433-A1 (**5.2)**

[180] Chisholm, J. D.; Golik, J.; Krishnan, B.; Matson, J. A.; VanVranken, D. L. *J. Am. Chem. Soc*. **1999**, *121*, 3801–3802.

5.1.2. Synthesis of AT2433-B1[165]

The disaccharide of AT2433-B1 **5.4** consists of disaccharide **5.15** linked to aglycone **5.18**, similar to **5.7**, but lacking the chlorine atom. Refluxing of lactol **5.15** with 3 equiv of **5.18** in methanol for 72 h gave 84% yield of glycosylated product. Oxidative aromatization of the mixture of diastereomers with DDQ led to the protected natural product **5.19** in 80% yield. Finally, deprotection of the Teoc carbamate with TBAF provided AT2433-B1 **5.4** in good yield 86% (Scheme 5.5).



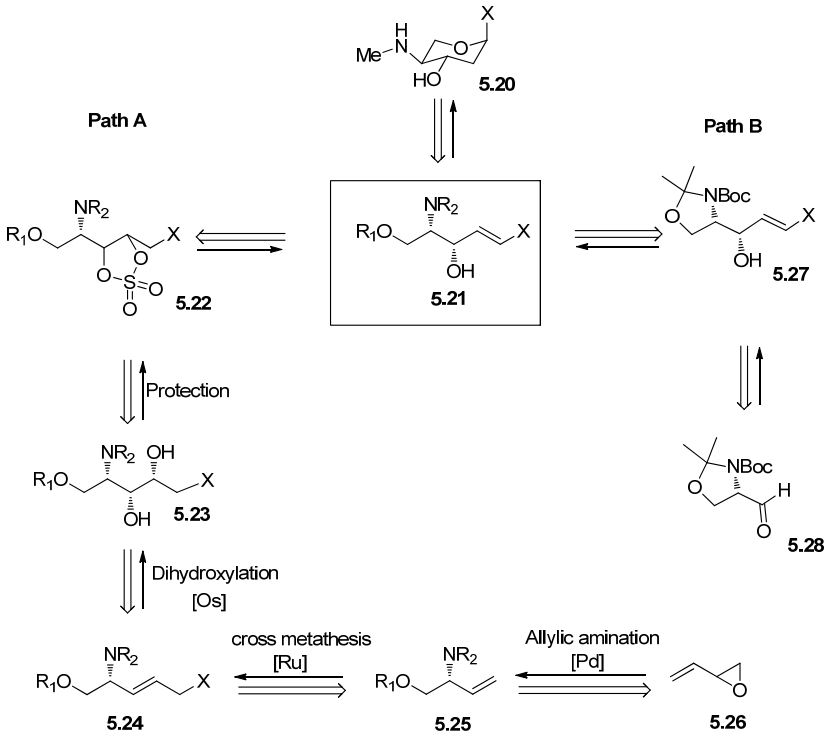
Scheme 5.5. Synthesis of AT2433-B1 **5.4**

5.2. Retrosynthesis

The objective of this work was to explore a new enantioselective method to obtain AT2433-A1 with special focus on the synthesis of the 2,4-dideoxy-4-amino-xyloside moiety. The retrosynthetic proposal is shown in Scheme 5.6. The aminodeoxysugar (**5.20**) could be obtained from **5.21** by eletrophile-induced cyclization. A key point is the selection of group X, since it must control the regioselectivity of the cyclization to an *endo*-mode and eventually must behave as a leaving group in a future glycosylation reaction.

Amino alcohol **5.21** could be prepared from allylic amine **5.24** by dihydroxylation, sulphate formation and elimination. Compound **5.24** can be synthesized from allyl amine **5.25** via chain elongation mediated by cross-metathesis reaction. Lastly, chiral allyl amine **5.25** could be obtained, similarly to the previous chapters, by a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) from the racemic butadiene monoepoxide **5.26**.

On the other hand, the intermediate **5.21** could be also obtained by addition to the Garner aldehyde (**5.28**) followed by deprotection of the protecting groups in **5.27**.



Scheme 5.6. Retrosynthetic approach for the synthesis of aminodeoxysugar **5.20**

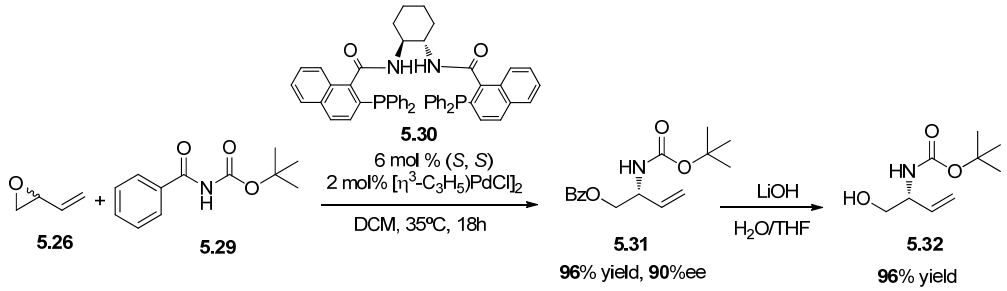
The main steps of this approach will be the palladium-catalyzed asymmetric allylic amination of racemic butadiene monoepoxide (**5.26**),[33,34] followed by chain elongation mediated by a ruthenium-catalyzed cross-metathesis reaction and a dihydroxylation reaction of the *E*-alkene intermediate. The stereoselectivity of the dihydroxylation reaction should be expected to be controlled by the stereocenter present in the molecule but if necessary, it could be enhanced by using the asymmetric method. Thus, the proposed approach relies on three metal-catalyzed reactions: i) palladium-catalyzed Dynamic Kinetic Asymmetric Transformation, ii) ruthenium-catalyzed cross-metathesis and iii) osmium-catalyzed dihydroxylation.

5.3. Results and discussion

5.3.1. Synthesis of the 2-deoxy-aminosugar from racemic monoepoxide butadiene

5.3.1.1. Synthesis of allyl imides by DYKAT

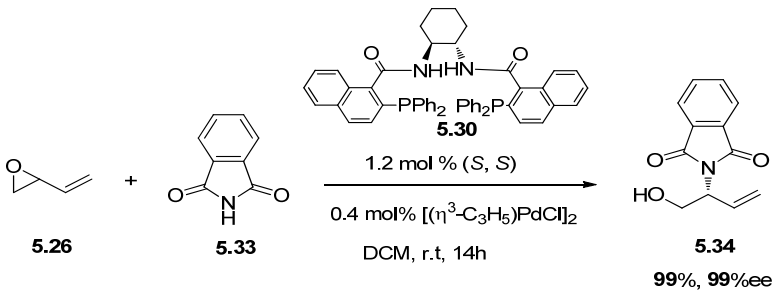
Based on our previous experience, compound **5.31** was obtained directly via palladium-catalyzed allylic substitution from butadiene monoepoxide (**5.26**) using 2 mol% of $[(\eta^{3}\text{-}C_3H_5)PdCl]_2$, 6 mol% of (*S*,*S*)-DACH-Naphtyl (**5.30**)[34] and imide **5.29** to afford the desired compound in a 96% yield and 90% e.e. (Scheme 5.7). Deprotection of benzoyl group in **5.31** using LiOH in THF[181] afforded the desired compound **5.32** in 96% yield.



Scheme 5.7. Synthesis of compounds **5.31** and **5.32**

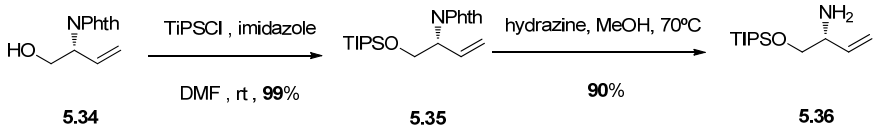
The synthesis of compound 2-(*R*)-*N*-phthalimido-3-buten-1-ol (**5.34**) was carried out, as reported in the previous chapters, under the conditions optimized by Trost. Thus, using 0.4 mol% of $[(\eta^{3}\text{-}C_3H_5)PdCl]_2$, 1.2 mol% of (*S*,*S*)-DACH-Naphtyl (**5.30**), and Na_2CO_3 in dichloromethane for 14h, allylic amine **5.34** was obtained in an excellent yield (99%) and 99% e.e. after recrystallization (Scheme 5.8).[33]

[181] Julian, L.D.; Wang, Z.; Bostick, T.; Caille, S.; Choi, R. *J. Med. Chem.* **2008**, *51*, 3953–3960.



Scheme 5.8. Synthesis of compound **5.34**

Reaction of **5.34** with TIPSCl and imidazole in DMF in order to selectively protect the primary hydroxyl group rendered silylether **5.35** in a 99% yield, which was subsequently treated with hydrazine to remove the pthalimido group to furnish allyl amine **5.36** in 90% yield (Scheme 5.9).



Scheme 5.9. Synthesis of compounds **5.35** and **5.36**

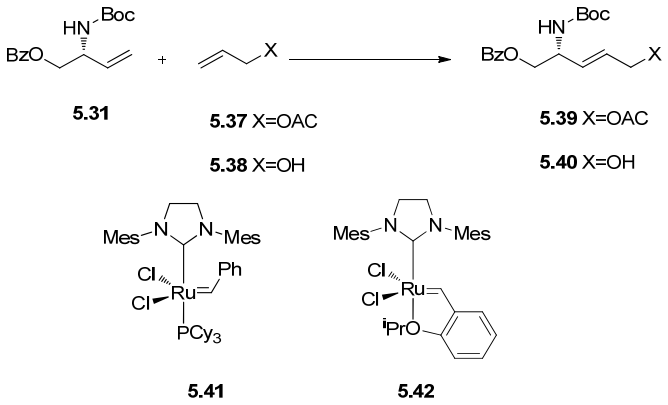
5.3.1.2. Cross metathesis reaction of allyl amines and C3-allyl derivatives

Elongation of the hydrocarbon skeleton was next explored via a cross metathesis reaction. As already pointed out, the group X at the reacting alkene partner in the cross metathesis should first enable such a process, but should be also an electrodonating group to direct the electrophilic-promoted cyclization to an endo-mode to give the pyranose derivative. Furthermore, it should be able to act as a leaving group in the glycosylation step, or at least, should be an easily derivatizable group to be converted into such a group. The X groups initially chosen for that purpose were the hydroxyl and the acetate group.

Thus, we studied the cross metathesis reaction of compound **5.31** with allyl acetate **5.37** and allyl alcohol **5.38**. The metathesis reaction with compound **5.31** and allyl acetate **5.37** in presence of the second generation Grubbs **5.41** and Hoveyda-Grubbs **5.42** catalysts in refluxing dichloromethane led to no conversion, as observed by TLC and ^{1}H NMR after 12h of reaction (Table 5.1, Entries 1 and 2). No product was

observed either by TLC and ^{1}H NMR after 12h of reaction when cross metathesis between compound **5.31** and allyl acohol **5.38** was carried out in the presence of the second generation Grubbs catalyst **5.41** (Table 5.1, Entry 4). A possible reason for these results could be the partial deactivation of the catalyst. For that reason the reaction was conducted using 10 mol/% of catalyst loading, but again no product was observed (Table 5.1, Entries 3, 5).

Table 5.1. Ru-catalyzed cross-methatesis of compound **5.31** with alkenes **5.37**, **5.38**.

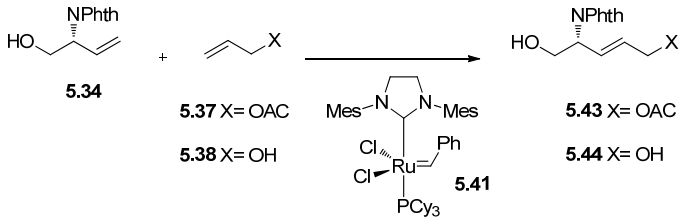


Entry	Reactant	Catalyst	Solvent	Temp. (ºC)	Product	Conversion (%)[b]	Yield (%)[c]
1	**3.37**	**5.42**	CH_2Cl_2	reflux	**5.39**	< 2	-
2	**3.37**	**5.41**	CH_2Cl_2	reflux	**5.39**	< 2	-
3[d]	**3.37**	**5.41**	CH_2Cl_2	reflux	**5.39**	< 2	-
4	**3.38**	**5.41**	CH_2Cl_2	reflux	**5.40**	< 2	-
5[d]	**3.38**	**5.41**	CH_2Cl_2	reflux	**5.40**	< 2	-

[a] Reactions were stirred for 12h, 5 mol% catalyst loading, 0.5M in solvent. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Reactions were stirred for 12h, 10 mol% catalyst loading, 0.5M in solvent.

The cross metathesis reaction was then performed by reaction of compound **5.34** and allyl acetate **5.37** in presence of the second generation Grubbs catalyst **5.41** in refluxing dichloromethane to afford **5.43** in a 43% yield (Table 5.2, Entry 1). When allyl acohol **5.38** was made to react with **5.34** in the presence of the second generation Grubbs catalyst **5.42** in refluxing dichloromethane, no crossed-product was obtained (Table 5.2, Entry 2).

5.2. Ru-catalyzed cross-methatesis betwen compound **5.34**, allyl acetate **5.37** and allyl alcohol **5.38**.



Entry	Reactant	Catalyst	Solvent	Temp T(ºC)	Product	Yield (%)[b]
1	**5.37**	**5.41**	CH_2Cl_2	reflux	**5.43**	43
2	**5.38**	**5.41**	CH_2Cl_2	reflux	**5.44**	-

[a] All reactions were stirred for 12h, 5 mol% catalyst loading, (3equiv) of substrate **5.38** and **5.39**, 0.5M in solvent. [b] Isolated yield.

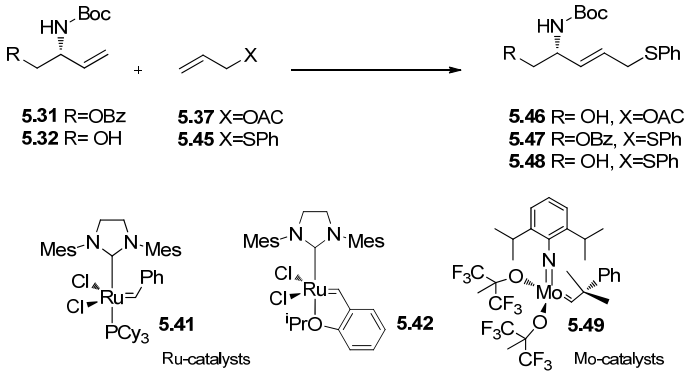
Since the results of cross-metathesis starting from alkene **5.34** were somewhat disappointing, we decided to explore analogous reactions using as starting material alkenes **5.31** and **5.32**, with a carbamoyl group at the nitrogen atom and with the hydroxyl group protected and unprotected, respectively. Moreover, together with alkene **5.37**, which had provided the more promising results, we also explored other alkenes such allyl phenyl sulphide **5.45**, which also fulfilled the requirements of the retrosynthesis. Indeed, the phenylsulphanyl group can control the regioselectivity of the cyclization reaction as well as being a good leaving group in glycosylation reactions. Besides, we also decided to perform these reactions in the presence of Ru- and Mo-catalyst.

Thus, when cross-metathesis reaction was performed between allyl acetate **5.37** and compound **5.32** in the presence of second generation Grubbs catalyst **5.41** in refluxing dichloromethane, the desired product **5.46** was obtained in moderate 50% yield (Table 5.3, Entry 2), which decreased to 22% when the reaction was performed in toluene at 80ºC (Table 5.3, Entry 1).

We then tried the reaction with allyl phenyl sulphide **5.45**, which was initially treated with compound **5.31** in the presence of the second generation Grubbs catalyst **5.41** in refluxing dichloromethane to afford compound **5.47** in low yield (17%) (Table 5.3, Entry 3). The reaction with compound **5.32** under similar reaction conditions

afforded **5.48** in an improved 50% yield (Table 5.3, Entry 4). Slow addition of substrate **5.32** over 10h maintaining the other reaction conditions did not allow to improve the yield and compound **5.48** was obtained in 28% yield (Table 5.3, Entry 5).

Table 5.3. Ru-catalyzed cross-methatesis betwen allyl amines **5.31**, **5.32** and alkenes **5.37** and **5.45**.



Entry	Allyl amine	Reactant	Catalyst	Solvent	Temp (ºC)	Product	Yield (%)[b]
1	**5.32**	**5.37**	**5.41**	Toluene	80	**5.46**	22
2	**5.32**	**5.37**	**5.41**	reflux	55	**5.46**	50
3	**5.31**	**5.45**	**5.41**	reflux	55	**5.47**	17
4	**5.32**	**5.45**	**5.41**	reflux	55	**5.48**	50
5[c]	**5.32**	**5.45**	**5.41**	reflux	55	**5.48**	28
6	**5.32**	**5.45**	**5.42**	reflux	55	**5.48**	80
7[c]	**5.32**	**5.45**	**5.42**	reflux	55	**5.48**	25
8	**5.32**	**5.45**	**5.42**	Toluene	80	**5.48**	< 2
9	**5.31**	**5.45**	**5.49**	reflux	55	**5.47**	< 2

[a] All reactions were stirred for 12h, 5 mol% catalyst loading, 0.5M in solvent. [b] Isolated yield. [c] 5.46 was added dropwise for 10h.

Yields significantly improved when the reaction between allyl phenyl sulphide **5.45** and allyl amine **5.32** was carried out in the presence of Hoveyda–Grubbs catalyst **5.42** in refluxing dichloromethane. In this case an excellent 80% yield of compound **5.48** was obtained (Table 5.3, Entry 6). The slow addition of substrate **5.32** (Entry 7), or

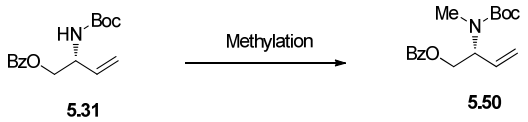
the increase of temperature to 80ºC using toluene as the solvent (Table 5.3, Entry 8) did not improve the results.

Unexpectedly, the reaction of phenyl sulphide **5.45** in the presence of Shrock catalyst **5.49** at refluxing dichloromethane did not give the expected cross-product (Table 5.3, Entry 9).

Since the structure of the aminodeoxysugar **(5.20)** has a *N*-methyl substituent at position 4, we considered convenient to introduce this group in the initial steps, and in particular by methylation of compound **5.31** to afford compound **5.50**. An initial test of methylation of **5.31** using dimethyl sulfate $(CH_3)_2SO_4$ in THF/water as the solvent gave negative results (Table 5.4, Entry 1), although when the reaction was carried out in anhydrous THF the desired product **5.50** was obtained in 43% yield (Table 5.4, Entry 2). When the reaction was heated to reflux no product was observed (Table 5.4, Entry 3). Increasing dimethyl sulphate $(CH_3)_2SO_4$ and sodium hydride (NaH) equivalents in THF at room temperature did not improve the results, and product **5.50** was obtained in 30% yield (Table 5.4, Entry 4).

Replacement of other agent dimethyl sulfate by MeOTf was not efficient (Table 5.4, Entry 5). When methyl iodide (CH_3I) was used as a methylating agent in the presence of pyridine as a base, the reaction did not evolve (Table 5.4, Entry 6). Reaction of **5.31** with CH_3I and sodium hydride led to the formation of **5.50** in 44% yield (Table 5.4, Entry 7).

Table 5.4. Methylation of compound **5.31** to give compound **5.50**. Optimization of reaction conditions.[182]



5.31 **5.50**

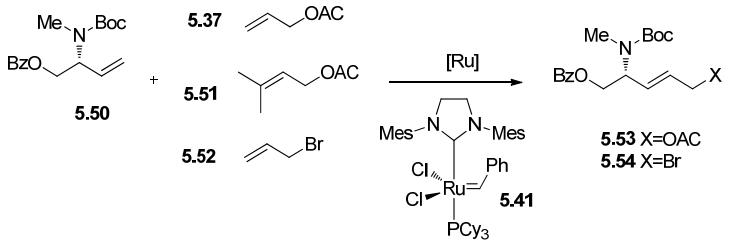
Entry	Reagents	Solvent	Temp (ºC)	Time (h)	Yield (%)[b]
1	$(CH_3)_2SO_4$, NaH	THF, H_2O	rt	7	-
2	$(CH_3)_2SO_4$, NaH	THF	rt	6	43
3	$(CH_3)_2SO_4$, NaH	THF	reflux	-	-
4[c]	$(CH_3)_2SO_4$, NaH	THF	6	rt	30
5	TfOMe, py	CH_2Cl_2	rt	-	-
6	CH_3I, Py	THF	rt	-	-
7	CH_3I, NaH	THF	rt	6	44

[a] 1.8 equiv of $(CH_3)_2SO_4$ loading and 2 equiv of NaH , [b] Isolated yield. [c] 3.6 equiv of $(CH_3)_2SO_4$ loading and 4 equiv of NaH.

In spite of the yield obtained in the methylation reaction being moderate, we decided to go on with the synthesis, and we tried the cross-metathesis reaction between **5.50** and different alkene partners such as **5.37**, **5.51** and **5.52**. The reaction of **5.50** with allylacetates **5.37** and **5.51** in the presence of 5 mol% of the second generation of Grubbs catalyst **5.41** in refluxing dichloromethane did not afford the desired product **5.53** (Table 5.5, Entries 1, 2). Cross experiment of **5.50** with **5.52** under the same reaction conditions led to the cross-product **5.54** in a 28% yield **(**Table 5.5, Entry 3).

[182] Mahavir, P.; Denis,H.; Bin,H.; Hong-Yong, K.; Oljan, R.;Thomas J, B. *Org. Lett*. **2003**, *5*, 125–128.

Table 5.5. Ru-catalyzed cross-methatesis between of allyl amine **5.50** and alkenes **5.37**, **5.51** and **5.52**.



Entry	Reactant	Catalyst	Solvent	Temp (ºC)	Product	Conversion (%)[b]	Yield (%)[c]
1	**5.37**	**5.41**	CH_2Cl_2	reflux	**5.53**	< 2	-
2	**5.51**	**5.41**	CH_2Cl_2	reflux	**5.53**	< 2	-
3	**5.52**	**5.41**	CH_2Cl_2	reflux	**5.54**	30	28

[a] All reactions were stirred for 12h, 5 mol% catalyst loading, 0.5M in solvent, [b] Determined by ^{1}H NMR spectroscopy, [c] Isolated yield.

To conclude, cross metathesis reaction allowed us to obtain the *E*-alkene necessary for the synthesis of a target molecule with complete control of the stereoselectivity. Although in general yields were between low and moderate, reasonably good synthetic yields (80%) were obtained by reaction of allyl carbamate **5.32** and allyl phenyl sulphide.

5.3.1.3. Dihydroxylation of allyl amines[105,183,184]

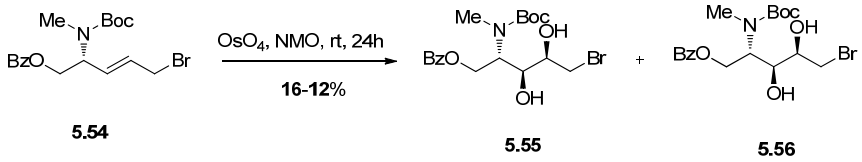
Dihydroxylation reaction is one of the key steps in the synthesis of the target compound. From the two hydroxyl functions to be installed, the one adjacent to the amino moiety is that where control of the stereoselectivty is crucial, whereas the other one is of minor interest, considering that a subsequent elimination process will destroy the chirality of that center and generate a double bond. Among the numerous processes for installing a diol moiety, osmium-catalyzed dihydroxylation with catalytic OsO_4 and NMO as a terminal oxidant is probably one of the most efficient methods, and a priori

183 a) Sammakia,T.; Hurley,T.B.; Sammond, D.M.; Smith, R. S. *Tetrahedron Lett*. **1996**, *37*, 4427–4430.
b) Walsh, P. J.; Tong Ho, P.; King, S. B.; Sharples, K, B. *Tetrahedron Lett.* **1994**, *35*, 5129–5132.

184 Ritsuo, I.; Skurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657–10670.

may well fit our purpose, producing *syn*-dihydroxylation of the *E*-alkene in a diastereoselective process controlled by the chirality of the substrate, that is, *anti* to the adjacent amino moiety. Furthermore, this method offers further possibilities for the transformation of chiral substrates when diastereoselectivities with achiral catalysts are not optimal, by using the asymmetric version, the so-called Sharpless dihydroxylation, in double stereodifferentiation processes, where usually the chiral catalyst can even override the inherent stereoselectivity bias of the substrate in mismatched processes.

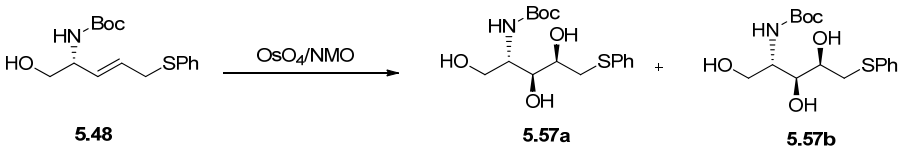
Compound **5.54**, which was obtained with a low yield, was initially reacted at room temperature with 5 mol % of OsO_4 and stoichometric amounts of oxidant NMO. Dihydroxylation products were obtained as a diastereomeric mixture of compounds **5.55** and **5.56** in 16% and 12 % yields, respectively.



Scheme 5.10. Dihydroxylation of alkene **5.54** to afford diols **5.55** and **5.56**

Given the low yield obtained in all the process involving methylation and reactivity of *N*-methylated compounds, we decided to explore other possibilities. Compound **5.48**, which was obtained with the best yield and stereoselectivity in the Ru-catalyzed cross-metathesis, was initially reacted at room temperature with 5 mol % of OsO_4 and stoichometric amounts of NMO for 20h. The expected dihydroxylation products were not observed but instead products of sulfur oxidation were obtained[183b] (Table 5.6, Entry 1). Applying the reactions conditions described in the literature for the dihydroxylation of substrates containing sulphur moieties, that is, 5 mol % of OsO_4, K_2CO_3 (3eq) and $K_3Fe(CN)_6$ (3eq) instead of NMO (Table 5.6, Entry 2) led to no conversion. The uses of other conventional methods of dihydroxylation using different oxidation agents for regenerating OsO_4 afforded almost exclusively the oxidation of sulfur.[183 a]

Table 5.6. Dihydroxylation of alkene **5.48**.



5.48 **5.57a** **5.57b**

Entry	Reagents	Tem (ºC)	Time	Products	Conversion (%)[a]
1	OsO_4/NMO	rt	20h	**5.57a:5.57b**	>2:<2
2[b]	OsO_4	rt	10d	**5.57a:5.57b**	>2:<2

[a] Determined by ^{1}H NMR, [b] K_2CO_3 (3eq), $K_3Fe(CN)_6$ (3eq).

Intending to search for systems able to produce synthetic yields of dihydroxylation products without oxidising the sulphur atom, asymmetric dihydroxylation reaction using commercially available AD-mix-α and β was also explored. Indeed, when compound **5.48** was treated with commercial AD-mix-α and β for 20-48h the selective formation dihydroxylation products was observed although in low conversions (28-37%) and low ratio a/b (Table 5.7, Entries 1-3). In order to improve the conversion, 1 equivalent of $K_3Fe(CN)_6$ was added to the reaction between compound **5.48** and AD-mix-β, which was stirred for 10 days. This modification gave the diastereomeric compounds **5.57a/b** with moderate conversion 45% and unsatisfactory selectivity, 1.4:1, and sulfur oxidation was also observed (Table 5.7, Entry 5). Attempted dihydroxylation of compound **5.48** using the Sharpless procedure[185] resulted in low to moderate yields of the desired products. The catalytic system OsO_4/AD-mix gave poor results in this case, probably because the bulky osmium-ligand complex is sterically demanding and reacts slowly with the sterically hindered alkene.[186]

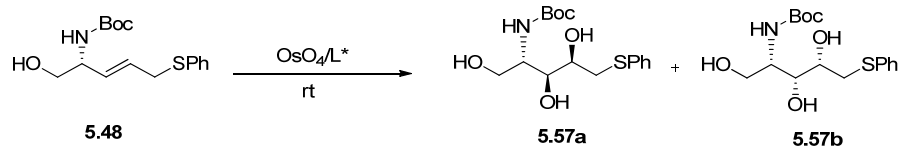
These results indicate that there is a fine balance between olefin dihydroxylation and sulfur oxidation, and the factors influencing the rate of either reaction depend on the structure of the substrate. Moreover, the separation of diastereomeric compounds

185 Sharpless, K. B.; Amberg,W. Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.S.; Morikawa, K.; Wang, Z. M.; Xu ,D. Zhang, X. L. *J. Org. Chem.* **1992**, *54*, 2768–2771.

186 Annuziata, R.; Cinquini, M.; Cozzi, F. *Tetrahedron* **1988**, *44*, 6897–6902.

5.57a/b proved unsuccessful, which prompted us to discard this approach towards AT-2433-A1.

Table 5.7. Dihydroxylation of alkene **5.48** using different conditions

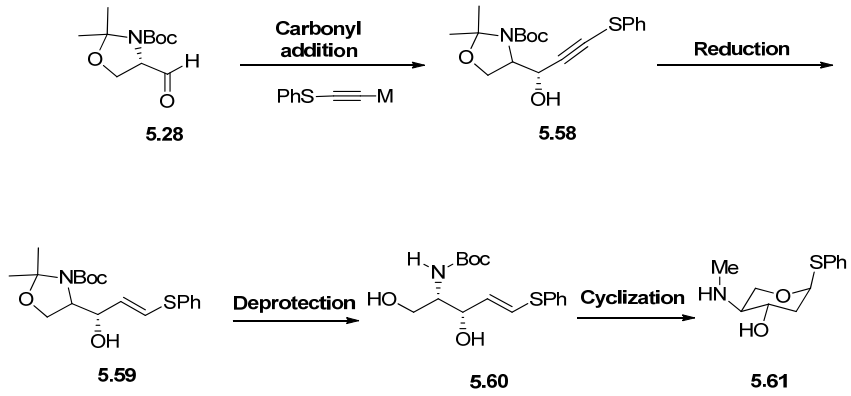


Entry	Chiral ligand	Time	Products	Conversion (%)[a]	Ratio **5.57a/5.57b**
1	AD-MIX β	20h	**5.57a-5.57b**	28	1.1:1
2	AD-MIX α	20h	**5.57a-5.57b**	30	1:1.2
3	AD-MIX β	48h	**5.57a-5.57b**	37	1.1:1
5[b]	AD-MIX β	10d	**5.57a-5.57b**	45	1.4:1

[a] Determined by 1H NMR , [b]Ligand (0.03 eq), $K_3Fe(CN)_6$ (1eq).

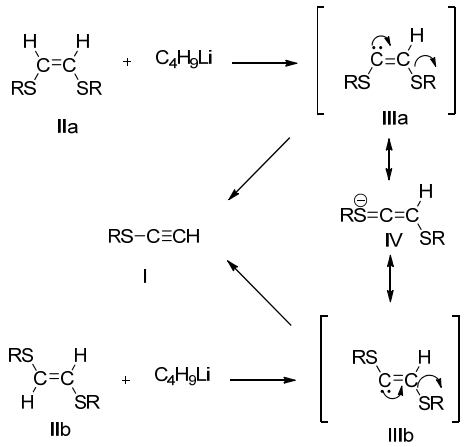
5.3.2. Attempts of synthesis of the 2-deoxyaminosugar from Garner aldehyde

We decided to explore an alternative procedure based on the use of Garner aldehyde as starting material. This approach maintains the electrophilic cyclization from an acyclic precursor as a final step to produce the pyranose derivative, but avoids the dihydroxylation reaction which led to such disappointing results. Scheme 5.1 shows the synthetic scheme proposed. We expect that reaction of Garner aldehyde **5.28** with a metal phenylthioacetylide, followed by triple bond reduction will afford compound **5.59**. Deprotection and protection steps will give access to **5.60**, from which 2-deoxyaminosugar **5.61** can be obtained by a electrophile induced cyclization reaction (Scheme 5.11).



Scheme 5.11. Synthetic approach for the synthesis of 2-deoxyaminosugar **5.61** from Garner aldehyde

The first objective was the synthesis of phenylthioacetylene. Parhan and Stright[187] described a synthesis of phenylthioacetylene (I) by reaction of *cis*- or *trans*-1,1-bis-(phenylthio)ethylene (IIa) with buthyllithium. The reaction is quite general for the synthesis of alkyl or arylmercaptoacetylenes, with little preference in elimination of normal alkyl or aromatic mercaptide. The reaction is, however, subject to steric and electronic effects and the product of reaction is consistent with β-elimination mechanism (Scheme 5.12).

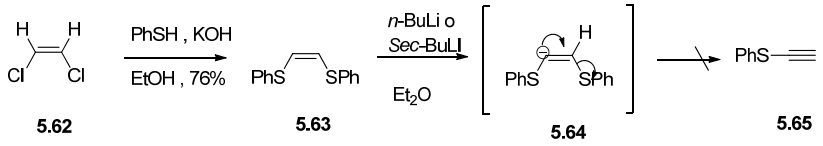


Scheme 5.12. Synthesis of phenylthioacetylene and mechanism

Synthesis of *bis*(tiophenil)ethene **5.63** was carried out from *cis*-1,2-dichloroethylene **5.62** in 76% yield in the presence of thiophenol and KOH in

187 Parham,W. E. P.; Stright, P. L. *J. Am. Chem. Soc*, **1956**, *78*, 4783–4787.

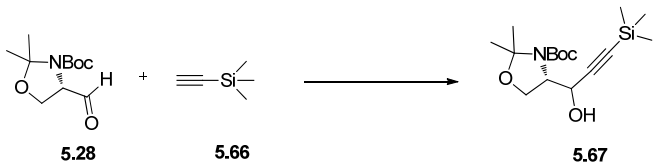
Ethanol[188,189] (Scheme 5.13). Treatment of compound **5.63** with *n*-BuLi or *Sec*-BuLi in ether did not afford the desired product **5.65**.



Scheme 5.13. Synthesis of *cis*-1,2-bis (tiophenol) ethyl **5.63**

Proven the difficulties for obtaining the phenylthioacetilene, we decided to attempt the addition of an acetylide donor to the Garner aldehyde and leave for subsequent steps the installation of the sulphide moiety. Thus, we attempted the addition of lithium silylacetylide **5.66** to the the Garner aldehyde **5.28** under chelating conditions ($ZnBr_2$) (Table 5.8, Entry 1). However, the formation of the desired product **5.67** was not observed. The same result was observed in the absence of $ZnBr_2$ (Table 5.8, Entry 2).

Table 5.8. Synthesis of compound **5.67** [190]



Entry	Substrate	Reagents	Solvent	Temp(ºC)	Product
1	**5.66**	n-BuLi, $ZnBr_2$	Et_2O	-78- rt	-
2	**5.66**	n-BuLi	Et_2O	-78- rt	-

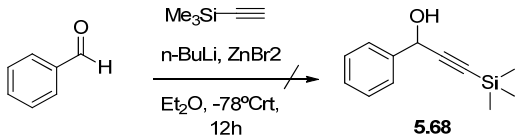
[a] All reactions were stirred for 12h

188 Parham,W. E. P.; Heberling, P. *J. Am. Chem. Soc, **1955***, 77, 1175–1177.

189 a) Truce, W. E.; Simms, J. A.; Boudakian, M. M. *J. Am. Chem. Soc.* **1956** , 78 ,695–696. b) Parham,W. E. P.; Motter, R. F.; Mayo, G. L. O. *J. Am. Chem. Soc*, **1959**, *81*, 3386–3391.

190 Hillaert, U.; Boldin-Adamsky, S.; Rozenski, J.; Busson, R.; Futermanand, A. H.; Van Calenbergh, Serge. *Bioog. Med. Chem.* **2006**, *14*, 5273–5284.

To check wheter the absence of results was due to the particular reactivity of the substrate we treated benzaldehyde under similar conditions observing that compound **5.68** was not formed either (Scheme 5.14).



Scheme 5.14. Synthesis of compound **5.68**

In the light of the unsuccessful results obtained either in dihydroxylation reaction or in the addition of acetylide synthons to the Garner aldehyde we decided to abandon this synthesis.

5.4. Experimental Part:

5.4.1. General Methods

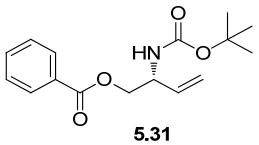
All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLV system-4®). Toluene was purified using standard procedure.

^{1}H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm ^{1}H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. Elemental analysis (C, H, N, S) were performed on a Carlo Erba® EA 1108 Analyser in the Servei de Recursos Científics (SRCiT-URV). IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Melting points, determined with Reichert apparatus, are uncorrected.

Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F_{254} glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/H_2SO_4 (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility. The enantiomeric excess (ee%) determined via chiral HPLC analysis (chiralpack OD column, heptane:^{i}PrOH, flow rate 1 $mlmin^{-1}$).

5.4.2.Compound characterization

(*R*)-*tert*-Butyl-1-benzoyloxybut-3-ene-2-ylcarbamate (5.31).

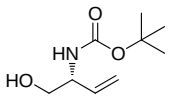


5.31

In a 25 mL flamed-dried flask under vacuum, *t*-butyl benzoyl imido carboxylate **5.30** (0.4 g, 1.88 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.011 g, 0.03 mmol) and (S,S)-ligand **5.30** (0.07 g, 0.09 mmol) were added under argon and the flask was purged three times with argon. Then dry dichloromethane (40 mL) was added to the mixture and the solution was stirred 30 min at rt. Butadiene monoepoxide (0.11 ml, 1.57 mmol) was added in one portion and the resulting mixture was stirred at 35 °C for 18h. The resulting mixture was concentrated and purified by flash chromatography using 10:1 hexanes:ethyl acetate as a solvent to afford compound **5.31** as a white solid in (0.483 g. 96%) and 90% ee.

$[\alpha]_D^{25}$ = +37.2 (*c* 1, $CHCl_3$). **IR** (neat): 3359, 3069, 2977,1700, 1516, 1451, 1365, 1269, 1163, 1113, 1069, 709 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 8 .02 (dd, 2H, *J* = 8, 1.2Hz), 7.54 (tt, 1H, *J* = 7.6 , 1.2 Hz), 7.42 (t, 2H, J = 8 Hz), 5.88 (ddd, 1H, *J* = 17.2, 10.4, 5.2 Hz) , 5.33 (ddd, 1H, *J* =17.2, 1.6, 0.8 Hz), 5.23 (ddd, 1H, *J* = 10.4, 1.6, 0.8 Hz), 4.86 (br s, 1H), 4.6 (br s, 1H), 4.35 (d, 2H, *J* = 5.2 Hz), 1.4 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ=166.4, 155.3, 134.8, 133.2, 129.8, 129.7, 128.4, 116.8, 79.8, 66.4, 51.8, 28.4. **ESI-HRMS** [M+23] calcd for $C_{16}H_{21}NaNO_4$: 314.1368, Found: 314.1347**.**

(2*R*)-*tert*-Butyl-1-hydroxybut-3-en-2-ylcarbamate (5.32).



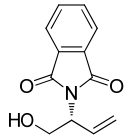
5.32

To a solution of product **5.31** (0.05 g, 0.17 mmol) in 1:1 THF/MeOH (2 ml) was added LiOH (0.0048g, 0.204 mmol). After being stirred for 3h, After being stirred for 3h the reaction mixture was diluted with water, extracted with 10% MeOH/CH_2Cl_2 (x5), dried with Na_2SO_4 and concentrated in vacuo. Purification by silica gel chromatography

using (10:4 hexane/ACOEt) as solvent afforded **5.32** product as colorless oil (0.03 g, 96%).

$[\alpha]_D^{25}$ = +21.6 (*c* 1, $CHCl_3$). **IR** (neat): 3329, 2978, 2931, 1687, 1456, 1392, 1367, 1167, 1071, 1051, 922 cm^{-1} . **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 5.79 (ddd, 1H, *J* = 16.4, 10.4, 5.6 Hz), 5.25-5.17 (m, 2H), 5.06 (brs, 1H), 4.19 (brs, 1H), 3.66 (dd, 1H, *J* = 11.2, 4.4 Hz), 3.58 (dd, 1H, *J* = 11.2, 5.6 Hz), 2.96 (brs, 1H), 1.42 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 156.3, 135.8, 116.5, 80.0, 65.2, 54.8, 28.5. **ESI-HRMS** [M+1] calcd for $C_9H_{18}NO_3$: 388.1287, Found: 388.1821.

(2*R*)-Phthalimido-3-buten-1-ol (5.34).



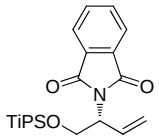
5.34

In a 250 mL flamed-dried flask, Na_2CO_3 (53 mg, 0.05 mmol), phthalimide **5.33** (1.47 g, 10 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (14.6 mg, 0.04 mmol) and *S*,*S*-ligand **5.30** (94.6 mg, 0.12 mmol) were added under argon being the flask purged three times with argon. Then dry dichloromethane (80 mL) was added to the mixture and the solution was stirred 15 min at rt. Butadiene monoepoxide (810 μl, 10 mmol) was added in one portion and the resulting mixture was stirred at rt for 14h. The resulting mixture was concentrated and purified by flash chromatography, using 1:1 hexanes:ethyl acetate as a solvent, to afford 2.16 g of compound **5.34** (99%) as a white solid. An enantiomeric excess of 99% ee was determined by chiral HPLC (chiralpack OD, heptane:^{i}PrOH 90:10, 1 $mlmin^{-1}$, t_R(R) = 14.1 min and t_R(S) = 16.9 min).

$[\alpha]_D^{25}$ = +65.9 (*c* 1, $CHCl_3$). **Mp** 60-63 ºC. **IR** (neat): 3527, 1763, 1702, 1656, 1609, 1467 and 1388 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ 7.73 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.62 (dd, 2H, *J* = 5.6, 3.2 Hz), 6.06 (ddd, 1H, *J* = 17.6, 10.4, 7.2 Hz), 5.19 (ddd, 1H, *J* = 17.6, 1.2, 1.2 Hz), 5.18 (ddd, 1H, *J* = 10.0, 1.2, 1.2 Hz), 4.84 (m, 1H), 4.07 (ddd, 1H, *J* = 11.4, 8.4, 8.0 Hz), 3.86 (ddd, 1H, *J* = 11.4, 7.6, 4.6 Hz), 2.98 (dd, 1H, *J* = 8.0, 4.6). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ 168.7, 134.3, 132.1, 131.9,

123.5, 119.0, 62.8, 56.1. **ESI-HRMS** [M+1] calcd for $C_{12}H_{12}NO_3$: 218.0817, Found: 218.0813.

(2*R*)-1-*tri*-Isopropylsilyloxy-2-phthalimido-3-butene (5.35).

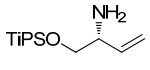


5.35

To a solution of product **5.34** (0.1 g, 0.465 mmol) and imidazole (0.93ml, 0.93mmol) in 1.5 ml of DMF was added TiPSCl at 0ºC. The mixture was stirred for 3h at room temperature, evaporation of solvent and purification by silica gel chromatography hexane: ethyl acetate (3:1) provided the desired compound **5.35** as a white solid (0.149 g , 99%).

$[\alpha]_D^{25}$ = +9.4 (*c* 1.2, $CHCl_3$). **IR (neat)** 3110, 2942, 2865, 1767, 1704, 1466, 1385, 1361, 1109, 1083 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 7.79 (dd, 1H, *J* = 5.2, 3.2 Hz), 7.68 (dd, 2H, *J* = 5.6, 3.2 Hz), 6.32 (ddd, 1H, *J* = 17.2, 10, 7.6 Hz), 5.26 (ddd, 1H, *J* = 17.6, 1.2, 1.2 Hz) , 5.22 (ddd, 1H, *J* = 10.4, 1.2, 1.2 Hz), 4.92(m, 1H), 4.23(dd, 1H, *J* = 10 Hz) , 3.94 (dd , 1H, *J* = 10, 6 Hz), 1.04(s, 3H), 0.96 (s, 18H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 168.1, 133.8, 132.4, 132.02, 123.07, 118.9, 62.6, 55.9, 17.8, 11.8 . **ESI-HRMS** [M+1] calcd for $C_{21}H_{32}NO_3Si$: 374.2151, Found: 374.2138.

(2*R*)-1-*tri*-Isopropylsilyloxy-2-phthalimido-3-butene (5.36).

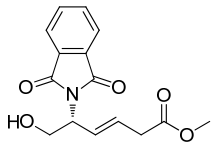


5.36

To a solution of product **5.35** (0.17g , 0.46 mmol) in MeOH (2 ml) was added hydrazine (0.024 ml, 0.68 mmol) the mixture stirred at 70ºC for 18hThe reaction crude was concentrated, dissolved in $CHCl_3$, and was filtered over Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography hexane: ethyl acetate (3:1) to afford the desired compound **5.36** as a yellow liquid (0.09 g, 90%).

^{1}H NMR ($CDCl_3$, 400MHz, δ in ppm): δ= 5.83 (ddd , 1H, *J*= 17.2, 10, 6 Hz), 5.22 (ddd, 1H , *J* = 17.2, 1.2, 1.2 Hz) , 5.08 (ddd, 1H , *J* = 10.4, 1.6, 0.8 Hz), 3.71 (m , 1H) , 3.48(m, 2H), 1.64 (brs, 2H), 1.26 (s, 3H), 1.08 (s, 18H).

Methyl (2*R*,2*E*)-5-phthalimido-6-hydroxyhex-3-enoate (5.43).

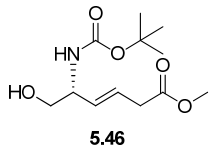


5.43

To a solution of product **5.34** (0.02 g, 0.09 mmol) and (0.0038 g, 0.0045 mmol) of 2nd generation Grubbs catalyst in dichlorometane (1 ml) was added dropwise allyl acetate (0.027 ml, 0.27 mmol) at 55ºC. Reaction was stirred at 55ºC for 12h, evaporation of solvent and purification by silicagel chromatography using hexanes/AcOEt (3:2) provided the desired product **5.43** as a colorless oil (0.011 g 43%).

IR (neat): 3405, 2926, 1772, 1705, 1386, 1058, 721 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400MHz, δ in ppm): δ = 7.80 (dd, 2H, *J* = 5.6, 2.8 Hz), 7.70 (dd, 2H, *J* = 5.2, 3.2 Hz), 6.1 (ddt, 1H, *J* = 15.6, 7.4, 1.8), 5.82 (dtd, 1H, *J* = 16.8, 5.6, 1.2 Hz), 4.96 (m, 1H), 4.56 (dd, 2H, *J* = 6, 0.8 Hz), 4.11(ddd, 1H, *J* = 11.6, 6 Hz), 3.95(ddd, 1H, *J* = 11.6, 4Hz), 2.69 (dd, 1H, *J* = 8.4, 4Hz), 2.04(s, 1H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 171.8, 168.8, 134.4, 131.9, 128.9, 127.9, 123.6, 64.1, 63.1, 60.6, 55.3, 21.2.

Methyl (3*E*,5*R*)-5-*tert*-butoxycarbonylamino-6-hydroxy-hex-3-enoate (5.46).

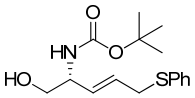


5.46

To a solution of product **5.32** (0.07 g, 0.37 mmol) and 2nd generation Grubbs catalyst (0.016 g, 0.013 mmol) in dichlorometane (5 ml) was added allyl phenyl acetate (0.11 ml, 1.29 mmol). Reaction stirred at 55ºC for 12h, evaporation of solvent and purification by silica chromatography using hexanes/AcOEt (1:1) solvent provided 0.048 g of the desired product **5.48** as yellow liquid (50%).

$[\alpha]_D^{25}$ = -4.2 (*c* 1, $CHCl_3$). **IR** (neat): 3271, 1734, 1674, 1506, 1367, 1265, 1168, 966, 732, 701 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 5.77 (m, 2H) , 4.91(brs, 1H), 4.75 (brs, 1H), 4.56 (dd, 2H, *J*= 4.4, 1.2 Hz), 4.26 (brs, 1H), 3.68 (m, 2H), 2.301 (brs, 1H), 2.06 (s,3H) 1.4 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 155.7, 135.2, 131.1, 130.5, 128.9, 127.7, 126.7, .79.6, 65.4, 53.6, 36.4, 28.2. **ESI-HRMS** [M+23] calcd for $C_{12}H_{21}NNaO_5$: 282.1317, Found: 282.1325

(2*R*,3*E*)-2-(*tert*-Butoxycarbonyl)amino-1-hydroxy-5-(phenylsulfanyl)pent-3-ene (5.48).

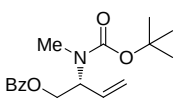


5.48

To a solution of product **5.32** (0.04 g, 0.21mmol) and (0.007 g, 0.011 mmol) of Grubbs-Hoveyda catalyst in dichlorometane (3 ml) allyl phenyl sulphide (0.16 ml, 1.05 mmol) was added. Reaction was stirred at 55ºC for 12h. Evaporation of solvent and purification by silica gel chromatography using hexan/AcOEt (3:2) as eluent provided the desired product **5.47** as yellow liquid (0.052 g, 80%) .

$[\alpha]_D^{25}$ = +11.4 (*c* 2, $CHCl_3$). **IR** (neat): 3433, 3053, 2359, 1684, 1506, 1366, 1165, 898, 877, 734, 701 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 7.32-7.7.28 (m, 4H), 7.2 (tt, 1H, *J* = 7.2, 1.2 Hz), 5.69 (dtd, 1H , *J* = 15.6, 7.2, 1.6 Hz) , 5.35 (ddt, 1H, *J* = 15.2, 5.6, 1.2 Hz), 4.75 (brs, 1H), 4.12 (brs, 1H), 3.52 (m, 2H), 3.42 (m, 2H), 1.82 (brs,1H) 1.39 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 155.7, 135.2, 131.1, 130.5, 128.9, 127.7, 126.7, .79.6, 65.4, 53.6, 36.4, 28.2. **ESI-HRMS** [M+23] calcd for $C_{16}H_{23}NNaO_3S$: 332.1296, Found: 332.1266.

(2*R*)-2-(*tert*-butoxycarbonyl-methyl)-amine-but-3-en-1-yl benzoate (5.50).

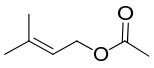


5.50

To a solution of NaH (0.008 g, 0.34 mmol) in THF (1ml) was added product **5.31** drop wise (0.05g, 0.17 mmol) in THF, the mixture was stirred for 10 min at room temperature, after was added dimethylsulphate (0.029 ml, 0.306 mmol). The mixture was stirred at this temperature until the starting material was not observed by TLC.then the reaction was quenched with NH_3, stirred for 1h, and after toluene and water was added. The aqueous layer was extracted with water, the combined organic layer was dried by $MgSO_4$ and concentred in vacuo. Purification by silica gel chromatography using 10:1 hexanes:ethylacetate provided the desired product **5.50** as a yellow liquid (0.024 g, 43%).

$[\alpha]_D^{25}$ = -7.5 (*c*1.1, $CHCl_3$). **IR** (neat) 3400, 2926, 2853, 2600, 1638, 1648, 1100, 1150, 1030, 1230 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400MHz, δ in ppm): δ= 8.01 (dd , 2H , *J* = 8.4, 1.6 Hz), 7.55 (t, 1H, *J* = 7.6Hz), 7.42 (t , 2H, 7.6 Hz), 5.82 (ddd, 1H, *J* = 17.2, 10.4, 4.8 Hz), 5.29 (dd, 1H, *J* = 10.8, 1.2 Hz), 5.23 (dd, 1H, *J* = 17.6, 1.2 Hz), 4.9(brs, 1H) , 4.44(m, 2H), 2.8 (brs, 3H), 1.4 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 166.4, 133.6, 133.2, 130.0 129.9, 128.5, 118.1, 80, 63.6, 29.9, 28.6. **ESI-HRMS** [M+1] calcd for $C_{17}H_{24}NO_4$:306.1705, Found: 306.1766.

3-Methylbut-2-en-1-yl acetate(5.51).

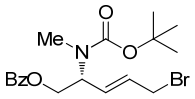


5.51

A solution of 3-methyl-2-buten-1-ol (3 ml, 29.98 mmol) and pyridine (24.12 ml, 299.8 mmol) was stirred for 5 min at room temperature, and after acetic anhydride was added. The mixture was stirred for 20h. The organic layer was extracted with HCl, diluted with ethylacetate, neutralized with bicarbonate and wached with water and brine. The resulting solution was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum to afford (3 g , 93%) of compound **5.51** as a colorless oil.

IR (neat): 1734, 1434, 1375, 1228, 1046, 1021, 962, 819, 773 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400MHz, δ in ppm): δ= 5.4 (t, 1H), 4.6 (d, 2H), 2 (s, 3H), 1.76 (s, 3H), 1.7 (s, 3H). **ESI-HRMS** [M+23] calcd for $C_7H_{13}NNaO_3$: 151.0724, Found: 151.0735.

(2*R*,3*E*)-5-bromo-2-(*tert*-butoxycarbonyl-methyl)-amino-pent-3-en-2-yl benzoate (5.54).

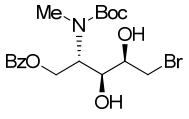


5.54

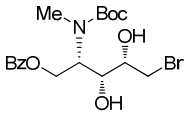
To a solution of product **5.50** (0.058 g, 0.19 mmol) and (0.016g, 0.019 mmol) of 2nd generation Grubbs catalyst in dichloromethane (2 ml), allyl bromide (0.054 ml, 0.501 mmol) was added. The Reaction was stirred at 55ºC for 12h. Evaporation of solvent and purification by silica gel chromatography hexanes/AcOEt (10:1) provided 0.021 g (28%) of product **5.54** as a yellow liquid .

^{1}H NMR ($CDCl_3$, 400MHz, δ in ppm): δ= 8 (dd, 2H, *J* =6.8, 1.6 Hz), 7.55 (t, 1H, *J* = 14.8, 7.6 Hz), 7.4 (t, 2H, *J* = 14.8, 7.6 Hz), 5.9 (dt, 1H, *J* = 15.2, 7.2 Hz) , 5.76 (dd, 1H, *J* = 15.2, 5.2 Hz), 5 (m, 1H), 4.2 (m, 2H), 4(d, 2H, *J* = 7.2 Hz), 2.8 (s, 3H), 1.4 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 133.3, 133.2, 129.94, 129.9,128.5, 63.4, 31.4, 30.2, 29.8, 28.52.

(2*S*,3*S*,4*R*)-5-bromo-2-(bis-*tert*-butoxycarbonyl)amino-3,4-dihydroxypent-3-en-2-yl benzoate (5.55), and (2*S*,3*R*,4*S*)-5-bromo-2-(bis-*tert*-butoxycarbonyl)amino-3,4-dihydroxypent-3-en-2-yl benzoate (5.56).



5.55



5.56

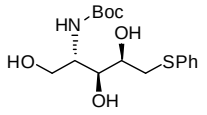
In a 10 ml round bottomed flask NMO (0.006 g, 0.053 mmol) was dissolved in water (1 ml), OsO_4, acetone (1 ml) and ^{t}BuOH (1 ml) were added. The mixture was stirred for 5 minutes at 0 ºC and then, a solution of compound **5.54** (0.0177 g, 0.044 mmols) in acetone (1 ml) was added in one portion. The mixture was stirred for 20 hours at room temperature. When the reaction had finished a solution of Na_2SO_3 was added and the resulting clear mixture was stirred for 15 minutes. The reaction mixture was diluted with ethyl acetate and the organic layer was washed with brine, dried over MgSO4 and concentrated. The reaction mixture was purified by column

chromatography with hexane:ethyl acetate (5:2) to obtain **5.55** (0.003 g, 16%) and **5.56** (0.002 g, 12%) **.**

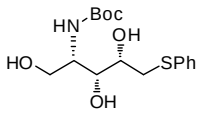
Compound **5.56**: $[\alpha]_D^{25}$ = +4.2 (*c* 0.2, $CHCl_3$). **IR** (neat): 3413, 2359, 1720, 1451, 1276, 1153, 900, 873, 755, 710 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 8.01 (d, 2H, *J* = 7.2 Hz), 7.57 (t, 1H, *J* = 7.2 Hz), 7.44 (t, 1H, *J* = 7.6 Hz), 4.74 (m, 2H), 4.39 (m, 2H), 3.91 (m, 2H), 3.76 (brs, 1H), 3.52 (d, 2H, *J* = 5.6 Hz), 2.84 (s, 3H), 2.57 (brs, 1H), 1.45 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 166.3, 163.5, 133.1, 131.1, 129.6, 128.4, 75.76, 74.0, 71.7, 62.6, 54.1, 36.4, 28.2. **ESI-HRMS** [M+1] calcd for $C_{18}H_{27}BrNO_6$: 432.1022, Found: 432.0912.

Compound **5.56**: $[\alpha]_D^{25}$ = -13 (*c* 0.27, $CHCl_3$). **IR** (neat): 3431, 2359, 1720, 1684, 1366, 1272, 1151, 864, 739, 710 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 8.01 (d, 2H, *J* = 7.2 Hz), 7.57 (t, 1H, *J* = 8 Hz), 7.44 (t, 1H, *J* = 7.6 Hz), 4.65 (m, 2H), 4.30 (brs, 1H), 3.82 (m, 2H), 3.66 (dt, 1H, *J* = 16.4, 4.8 Hz), 3.54 (dd, 1H, *J* = 10.4, 6.4 Hz), 2.97(s, 3H), 2.80 (brs, 1H), 1.45 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 166.4, 163.0, 133.4, 131.1, 129,8, 128.6, 71.7, 70.9, 69.5, 62.5, 53.3, 35.2, 28.4. **ESI-HRMS** [M+23] calcd for $C_{18}H_{26}BrNNaO_6$: 454.0821, Found: 454.0708.

(2*R*,3*R*,4*R*)-2-(*tert*-Butoxycarbonyl)amino-1,3,4-tri-hydroxy-5-(phenylsulfanyl)pentane (5.57a) and (2*R*,3*S*,4*S*)-2-(*tert*-Butoxycarbonyl)amino-1,3,4-trihydroxy-5-(phenylsulfanyl) pentane (5.57b).



5.57a



5.57b

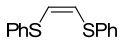
In a 10 ml flask were weighted 0.45 g AD-mix-β and (0.011 g, 0.32 mmol) of methansulfanamide. Over this mixture, 4 ml of a solution of ^{t}BuoH/H_2O were injected and the orange red solution was coled at 0ºC. This mixture was added in one portion at the corresponding olefine **5.48** (0.1 g, 0.32 mmol). The mixture was stirred for 48h at room temperature. A solution of $Na_2S_2O_3$ was added over the yellow suspension and the resulting claear solution was stirred for additional 15 min. The reaction mixture was extracted with EtOAC, and the combined organic layer were washed with 1N KOH,

H_2O and brine, the organic phase was dried over $MgSO_4$, filtration and evaporation of solvent provided (37%, 31 mg) products **5.57a/b** as a yellow paste.

Compound (5.57a) : ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): δ = 7.39 (dd, 2H, *J* = 8, 1.6 Hz), 7.29 (t, 2H, *J* = 6.8), 7.20 (t, 1H, *J* = 7.2 Hz), 5.18 (brs, 1H), 4.05 (brs, 2H), 3.74 (m, 4H), 3.52 (brs, 1H), 3.14 (m, 2H), 2.39 (brs,1H), 1.38 (s, 9H).

Compound (5.57b) : ^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): δ = 7.39 (dd, 2H, *J* = 8, 1.6 Hz), 7.28 (t, 2H, *J* = 7.2), 7.20 (t, 1H, *J* = 7.6Hz), 5.28 (brs, 1H), 3.84-3.68 (m, 6H), 3.24 (brs, 2H), 3.04 (dd, 1H, *J* = 14, 4.6 Hz), 2.88 (brs,1H), 1.42 (s, 9H).

***(Z)*-1,2-bis-(phenilthio)ethene (5.63).**



5.63

Compounds KOH (1.907 g, 33.99 mmol) and thiophenol (2.108 ml, 20.6 mmol) were dissolved in ethanol (27 ml) and after *cis*-1,2-dichloroethylene (1g, 10.3 mmol) was added dropwise. The resulting solution was refluxed for 5 hours, evaporated and then water was added. The aqueous layer was extracted with ether 3 times, the combined organic layer were wached with NaOH, water, and was dried over anhydrous $MgSO_4$. Removal of solvent provided 1.9 g (76%) of compound **5.63** as yellow-orange liquid product.

IR (neat): 3058, 1581, 1539, 1437, 1293, 1091, 1070, 1023 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ in ppm): δ= 7.54 (dd, 2H, *J* =7.2 , 1.6 Hz), 7.44 (dddd, 4H, *J* =14.8, 7.6, 2.4, 0.8 Hz), 7.36 (dddd, 2H, *J* =14.4, 6, 2.4, 1.2 Hz), 6.65(s, 2H). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ in ppm): δ= 135.3, 129.6, 129.2, 127.0, 125.1. **ESI-HRMS** [M+1] calcd for $C_{14}H_{13}S_2$: 245.0459, Found: 245.0420.

CHAPTER VI

CONCLUSIONS

UNIVERSITAT ROVIRA I VIRGILI
ENANTISELECTIVE SYNTHESIS OF NATURAL PRODUCTS
Mariam Azzouz

CONCLUSIONS

Chapter 3: Enantioselective synthesis of nectrisine

The asymmetric allylic amination from racemic butadiene monoepoxide using (η^3-C_3H_5)PdCl/DACH-naphtyl system and *t*-Butyl-benzoyl-imido carboxylate as a *N*-nucleophile proceeded with excellent yield (98%) and enantioselectivity (97%) to obtain the chiral allylic amine synthon.

Elongation of the chain of the key chiral allylic imides **3.40**, **3.41** and **3.43** with ethyl acrylate through cross metathesis using Hoveyda-Grubbs catalyst (5 mol%), proceeded quatitatively to obtain the trans alkene intermediates **3.54**, **3.55** and **3.56**, respectively.

The installation of the *syn* diol moiety via dihydroxylation of the alkene proceeded with high yield and moderately good diastereoselectivity with OsO_4/TMEDA.

Hydrolysis of benzoate group in **3.71** with LiOH and in situ cyclization led to the lactam **3.79.**

Chapter 4: Enantioselective synthesis of Cidofovir analogues

The asymmetric allylic amination of racemic butadiene monoepoxide with cytosine **4.38** as *N*-nucleophile was carried out with (η^3-C_3H_5)PdCl/DACH-naphtyl system to obtain chiral allylic cytosine **4.42** in 85% yield and 72% ee. The reaction was successfully expanded to other pyrimidine and purine bases, among which adenine **4.41** afforded chiral allyl adenine **4.44** in 90% yield and 92% ee.

Chain elongation via Ru-cross metathesis of key allylic nucleobases **4.51, 4.53** and diethyl allylphosphonate with second generation Grubbs catalyst (5 mol%), produced **4.52** and **4.54** in 92% and 90% yield, respectively.

Deprotection of all protecting groups with TMSBr afforded the desired unsaturated acyclic nucleosides **4.57** and **4.58** in good yields.

Hydrogenation with (H_2, /Pd/C) at 3 bar rendered the saturated Cidifovir analogues **4.59**.

Chapter 5: Approaches to the Enantioselective Synthesis of AT2433-A1

The asymmetric allylic amination from racemic butadiene monoepoxide using (η^3-C_3H_5)PdCl/DACH-naphtyl system and imide **5.29** as a nitrogen nucleophile proceeded with good yield (96%) and enantioselectivity (90%).

Chain elongation of key chiral allylic amine **5.32** was carried out by cross metathesis with allyl phenyl sulphide with Hoveyda-Grubbs catalyst (5 mol%) to obtain the corresponding trans alkene **5.48** in 80% yield.

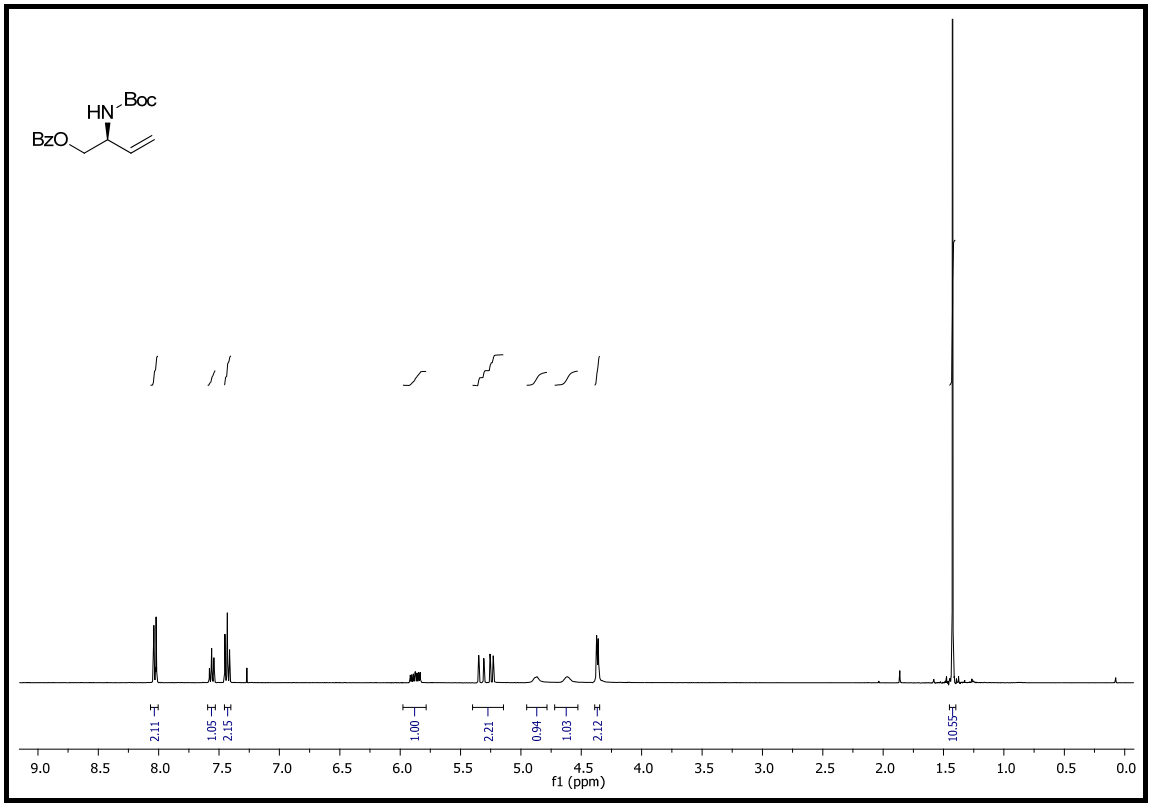
The installation of the diol moiety with OsO_4 was unsuccesful, due to the competitive oxidation of sulfur, preventing the completion of the synthesis.

CHAPTER VII

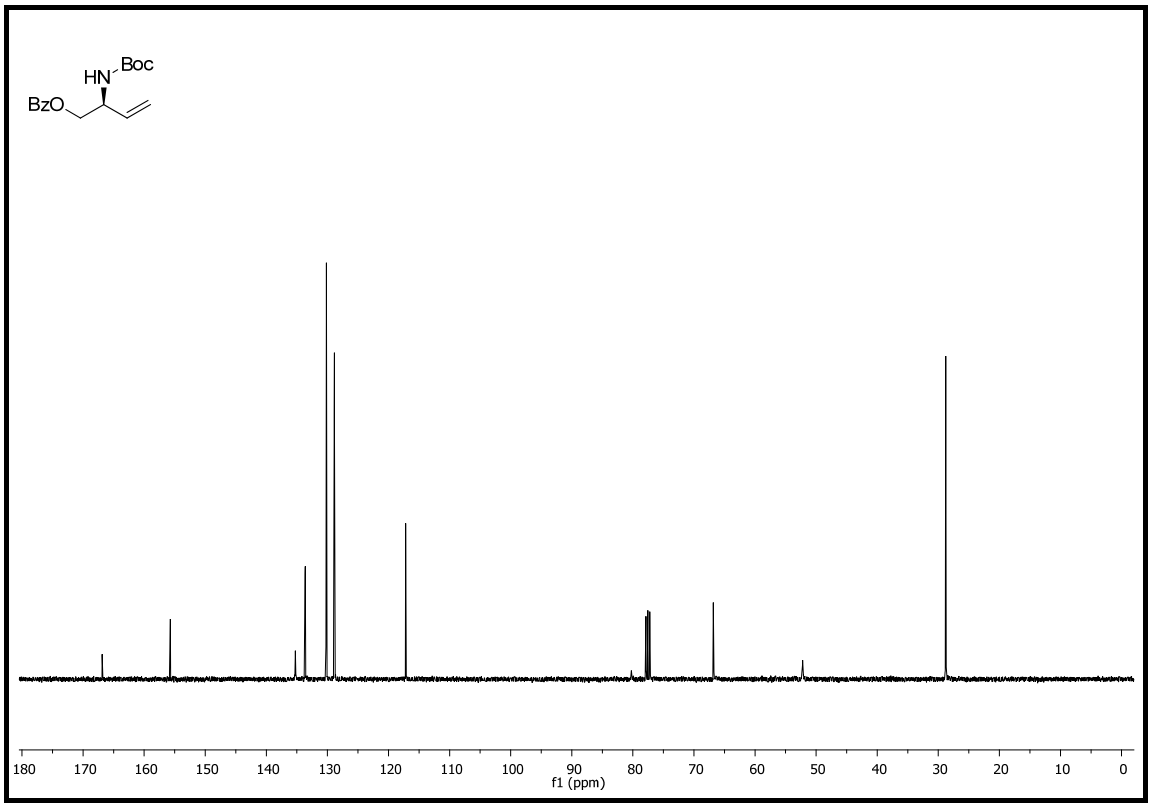
ANNEX

UNIVERSITAT ROVIRA I VIRGILI
ENANTISELECTIVE SYNTHESIS OF NATURAL PRODUCTS
Mariam Azzouz

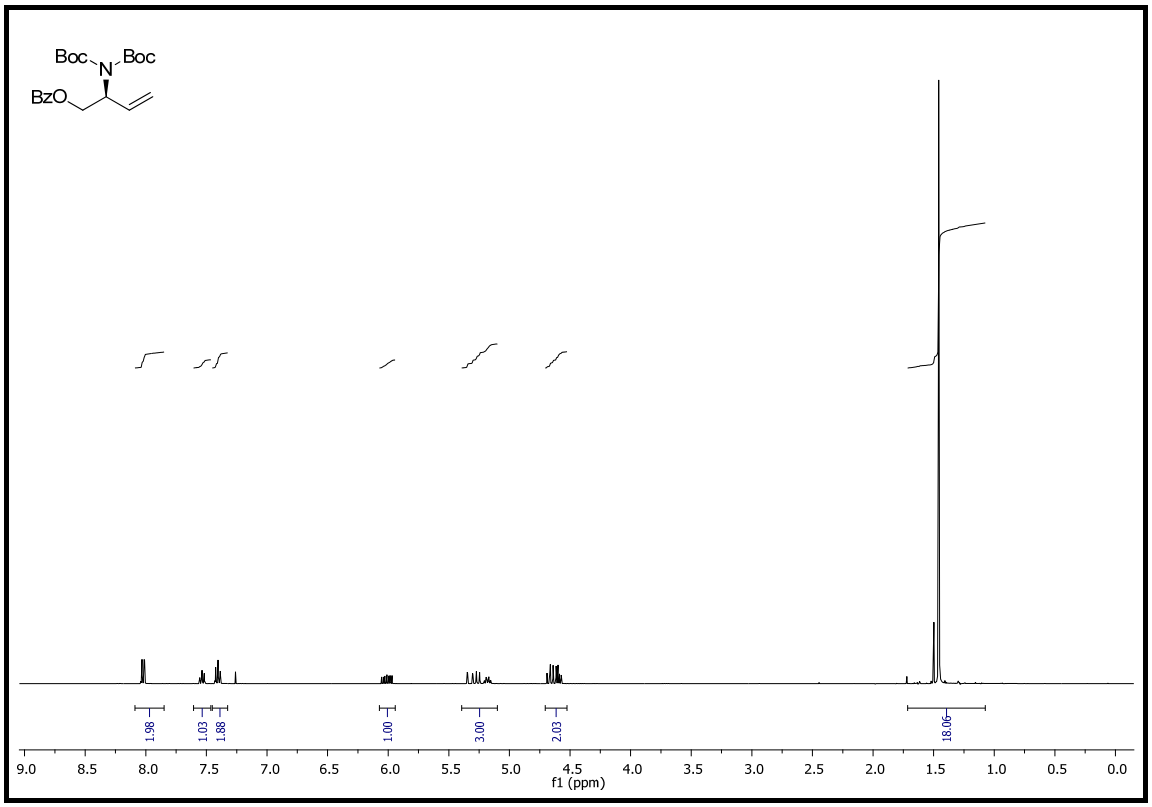
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*S*)-2-((*tert*-Butoxycarbonyl)amino)but-3-1-yl benzoate (3.40).



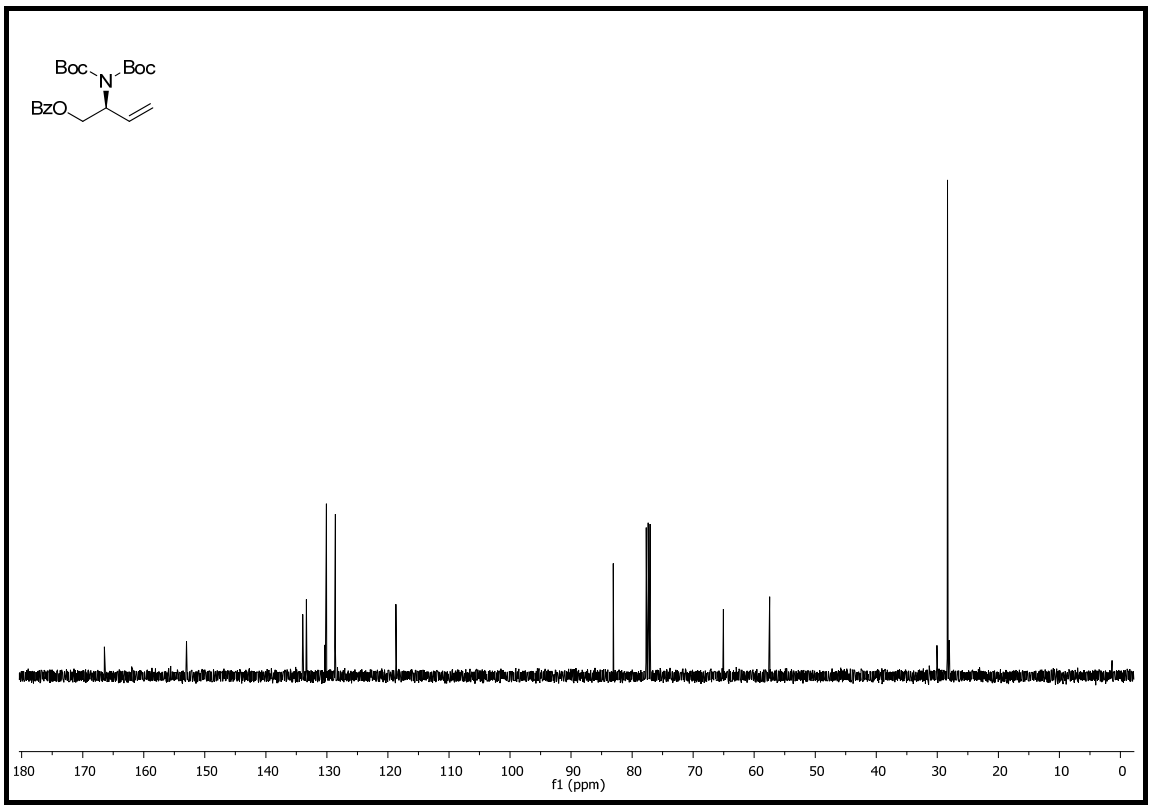
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*S*)-2-((*tert*-Butoxycarbonyl)amino)but-3-1-yl benzoate (3.40).



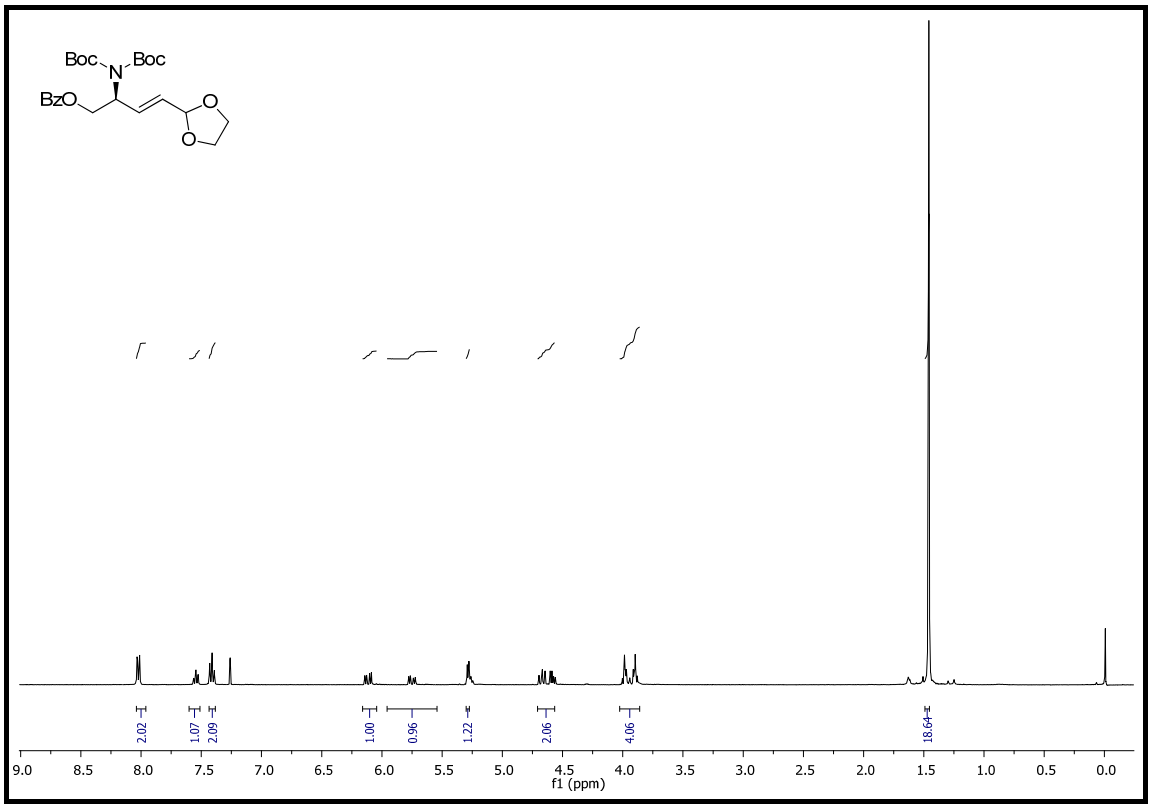
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*S*)-2-((bis-*tert*-Butoxycarbonyl)amino)but-3-1-yl benzoate (3.41).



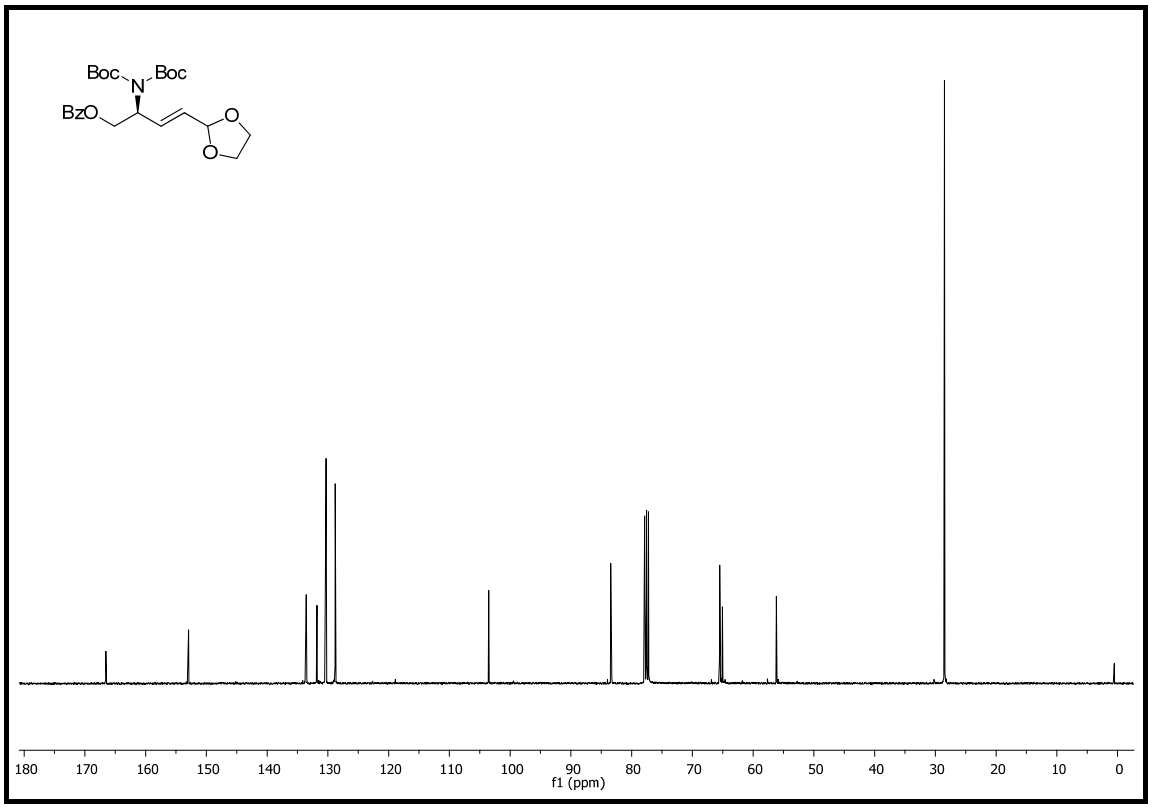
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*S*)-2-((bis-*tert*-Butoxycarbonyl)amino)but-3-1-yl benzoate (3.41).



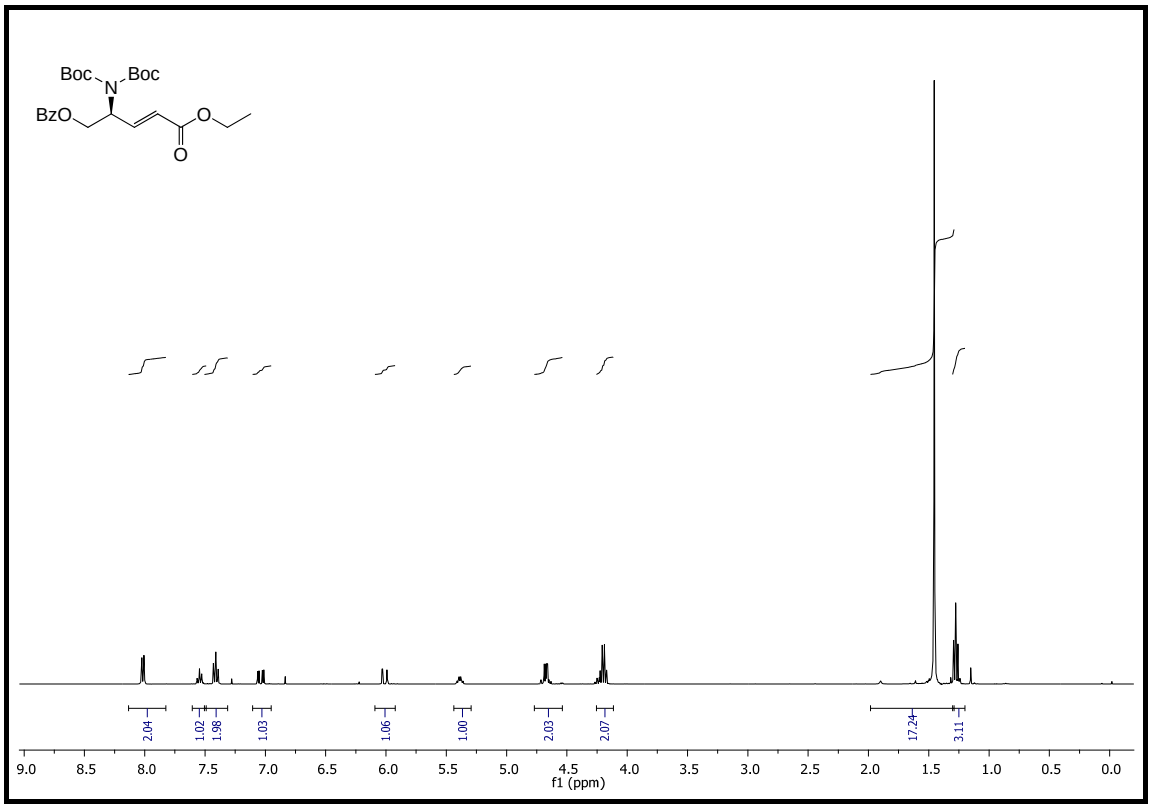
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*S*,3*E*)-2-{bis[(*tert*-butoxy)carbonyl]amino}-4-(1,3-dioxolan-2-yl)but-3-en-1-yl benzoate (3.51).



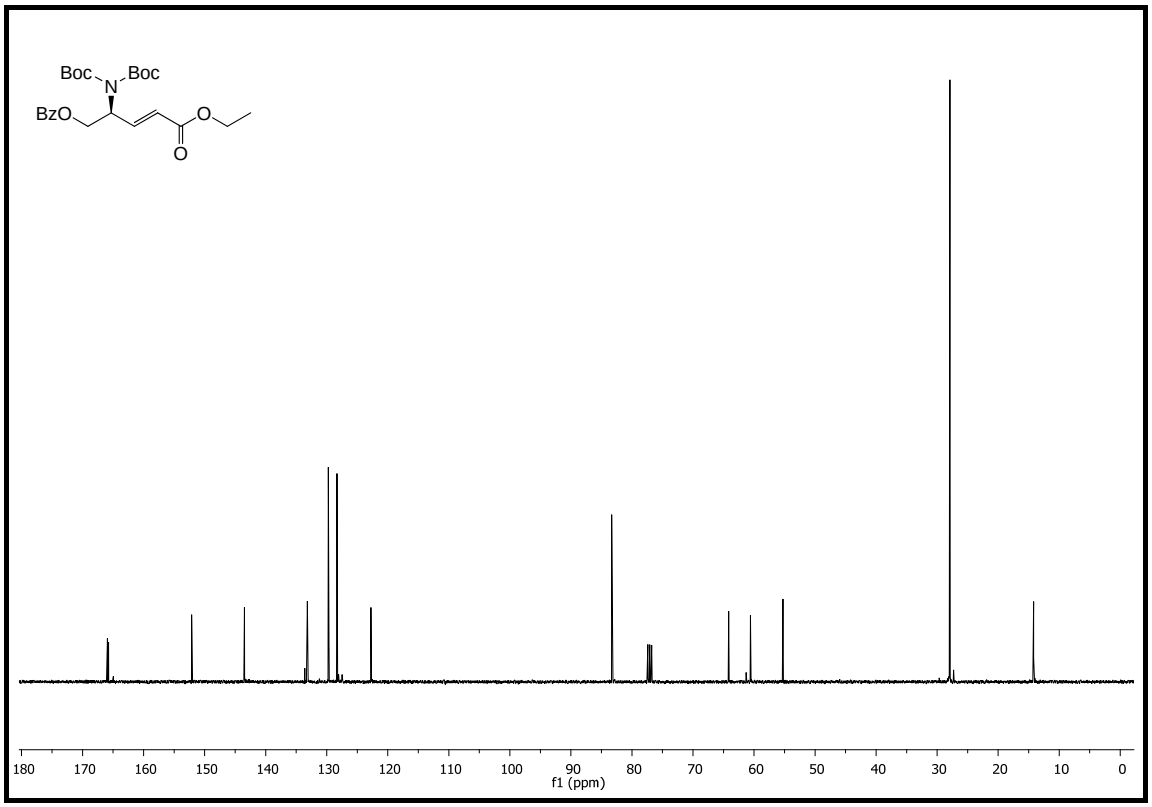
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*S*,3*E*)-2-{bis[(*tert*-butoxy)carbonyl]amino}-4-(1,3-dioxolan-2-yl)but-3-en-1-yl benzoate (3.51).



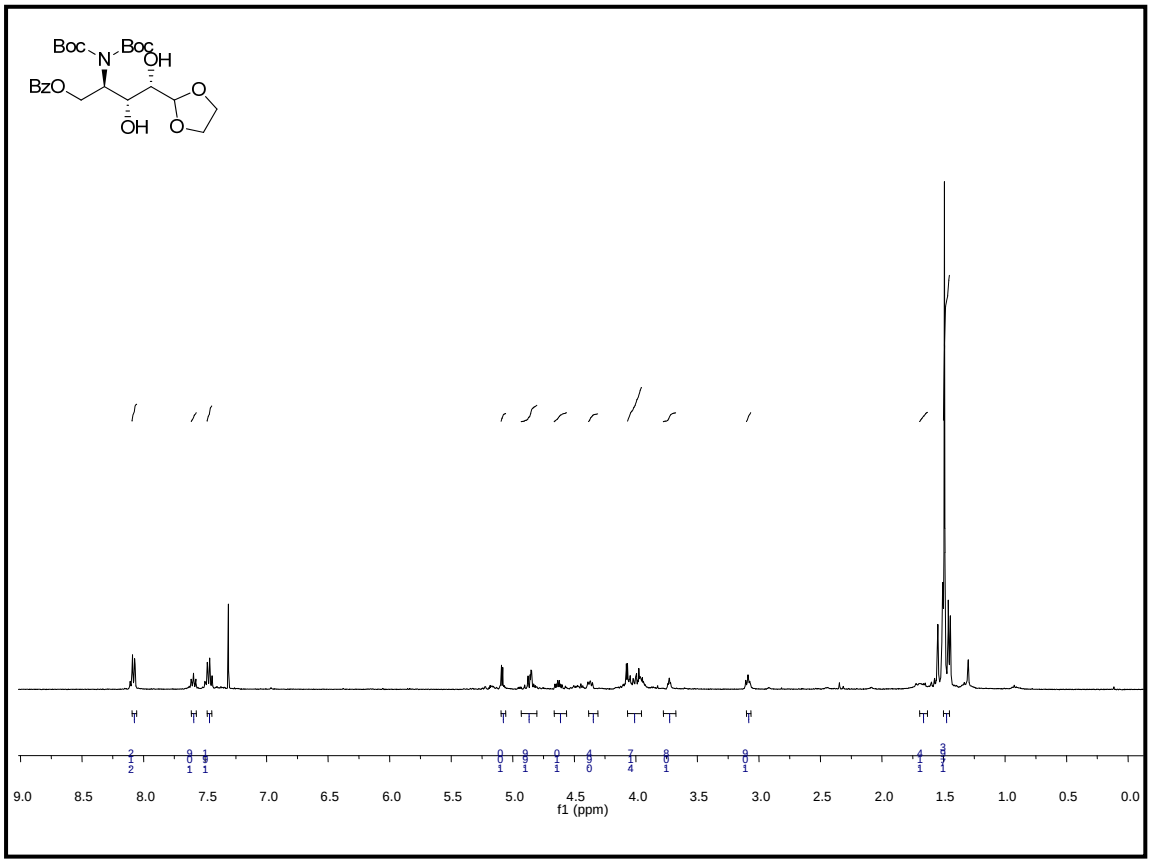
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of Ethyl (2*E*,4*S*)-5-benzoyloxy-4-((bis-*tert*-butoxycarbonyl)amino)-pent-2-enoate (3.55).



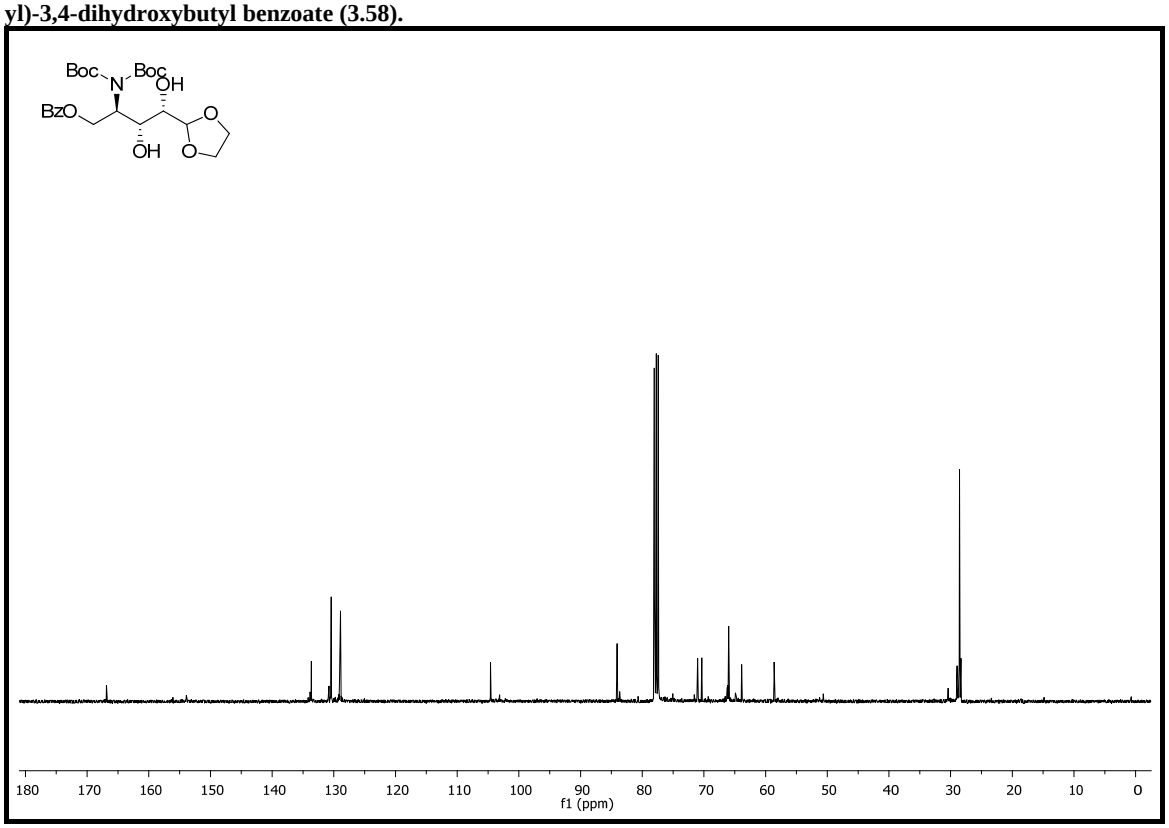
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of Ethyl (2*E*,4*S*)-5-benzoyloxy-4-((bis-*tert*-butoxycarbonyl)amino)-pent-2-enoate (3.55).



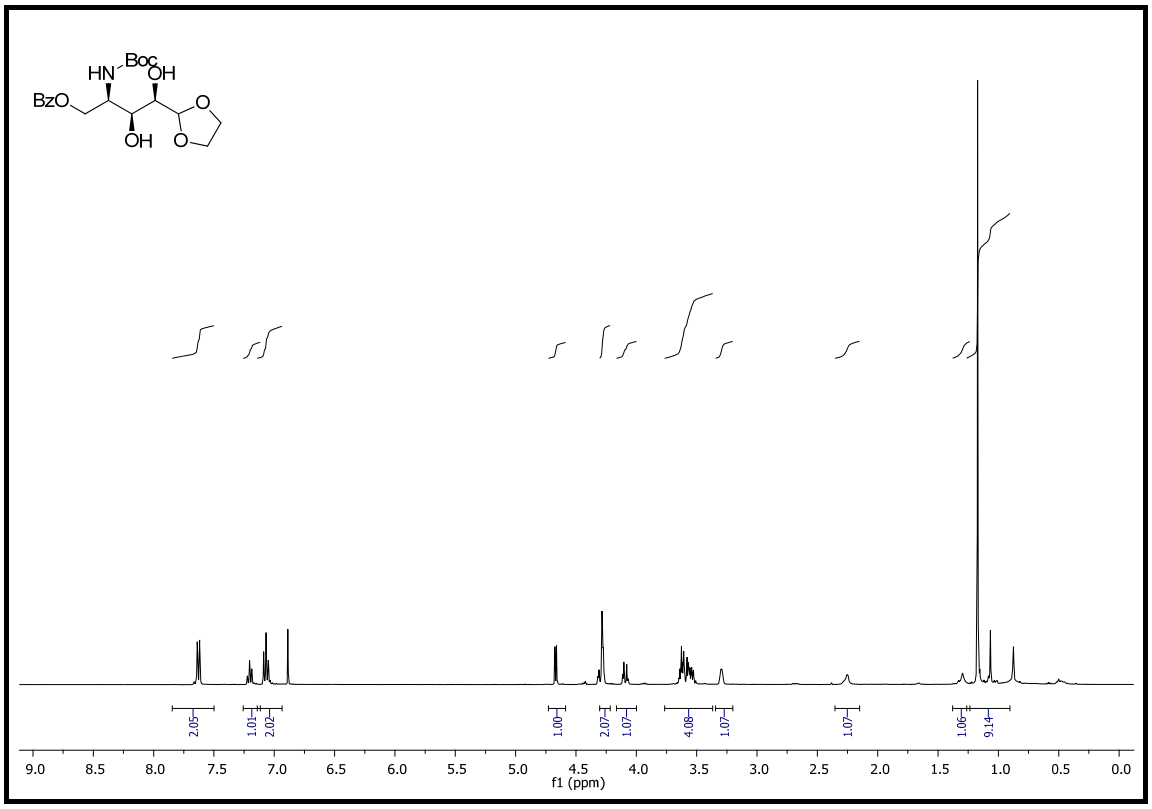
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*R*,3*R*,4*S*)-2-((bis-*tert*-butoxy)carbonyl)amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (3.58).



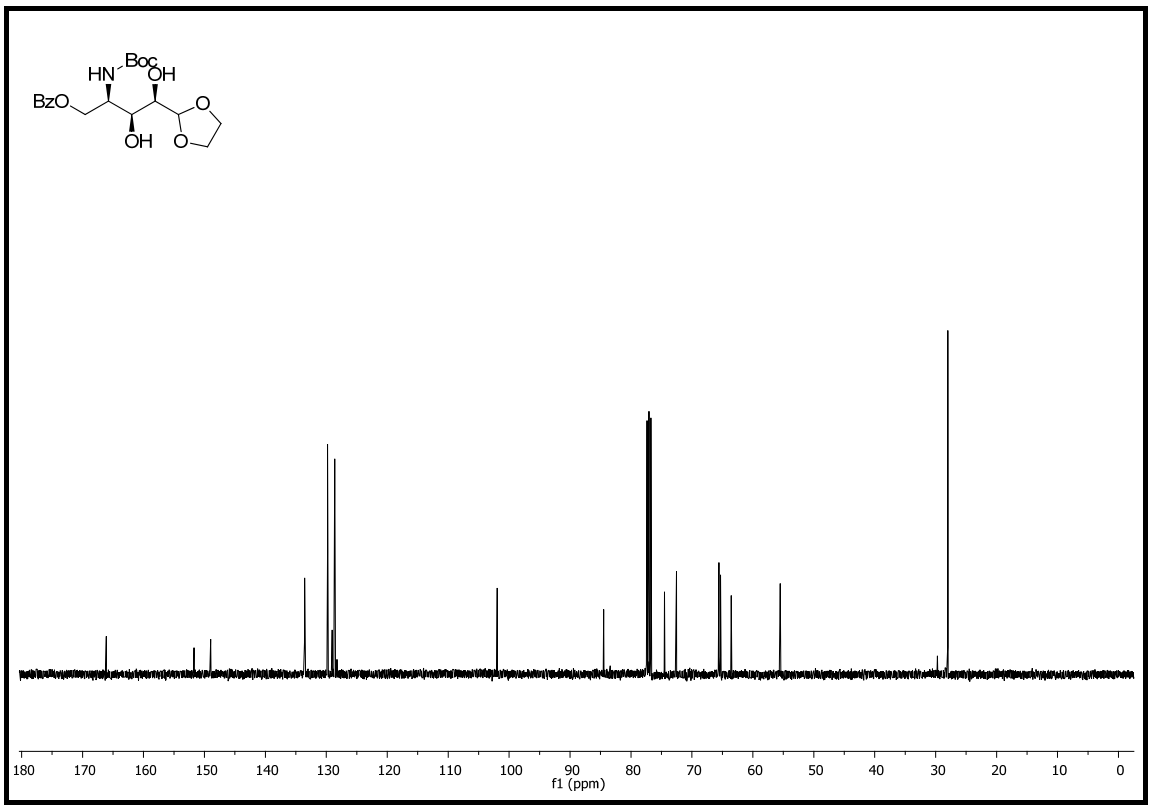
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*R*,3*R*,4*S*)-2-((bis-*tert*-butoxy)carbonyl)amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (3.58).



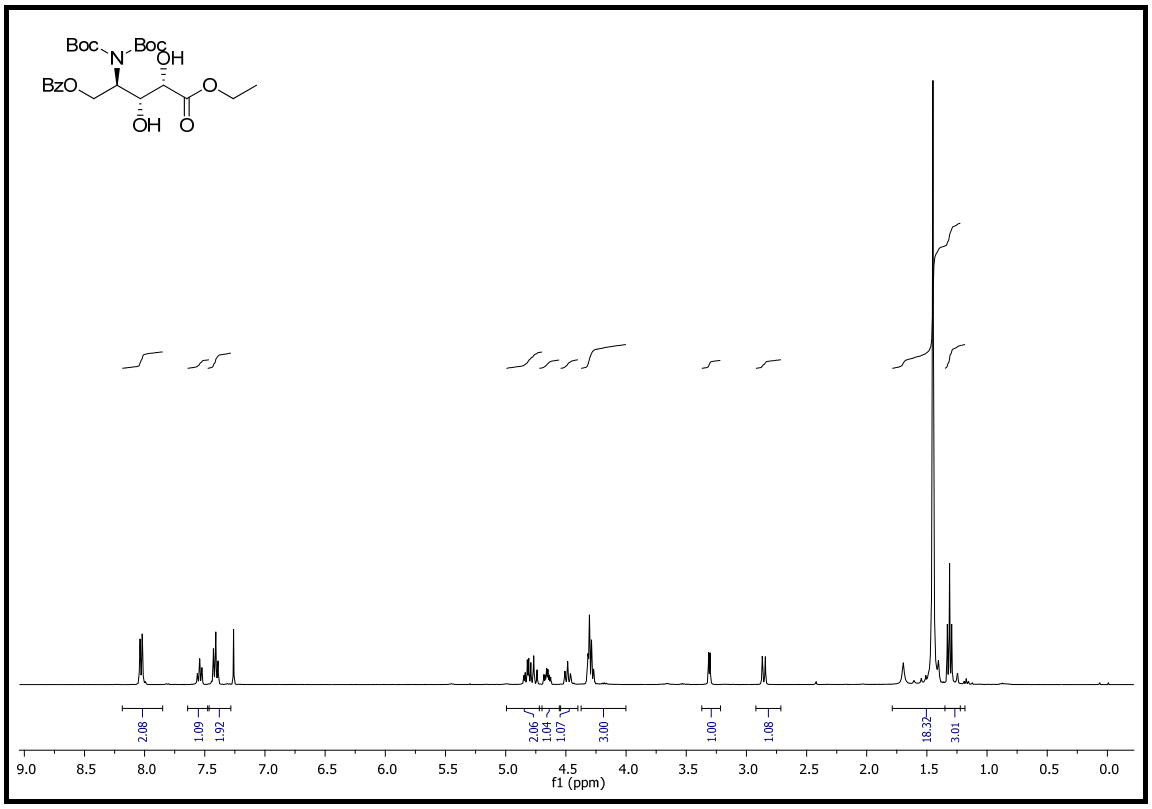
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*R*,3*S*,4*R*)-2-((bis-*tert*-butoxy)carbonyl)amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (3.59).



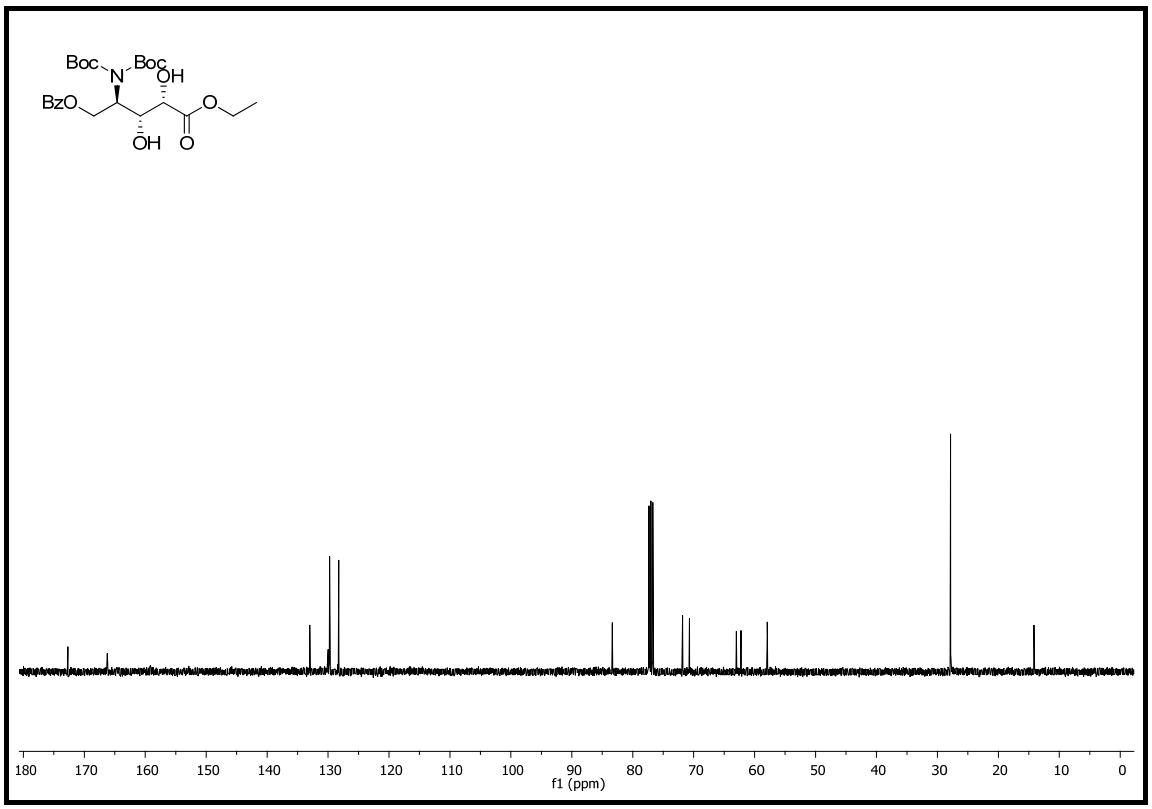
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*R*,3*S*,4*R*)-2-((bis-*tert*-butoxy)carbonyl)amino-4-(1,3-dioxolan-2-yl)-3,4-dihydroxybutyl benzoate (3.59).



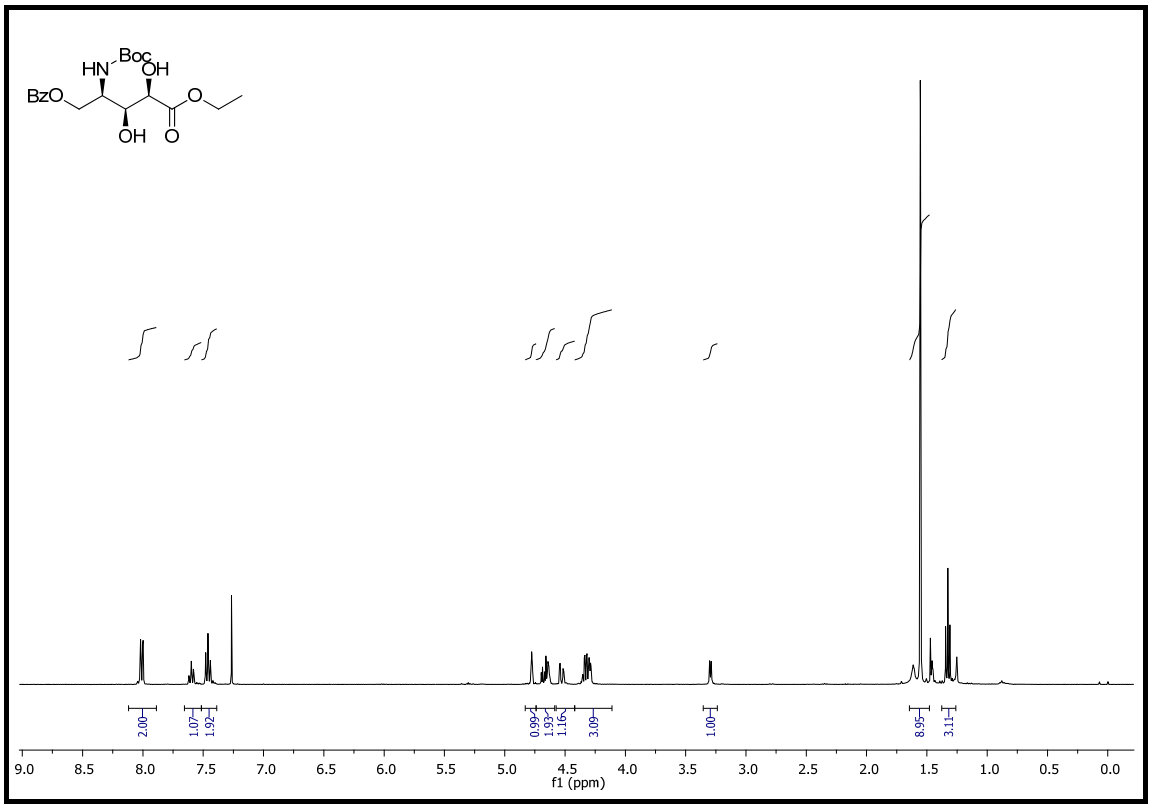
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of Ethy (2*S*,3*R*,4*R*)-5-(benzoyloxy)-4-((bis-*tert*-butoxycarbonyl)amino)-2,3-dihydroxypentanoate (3.62).



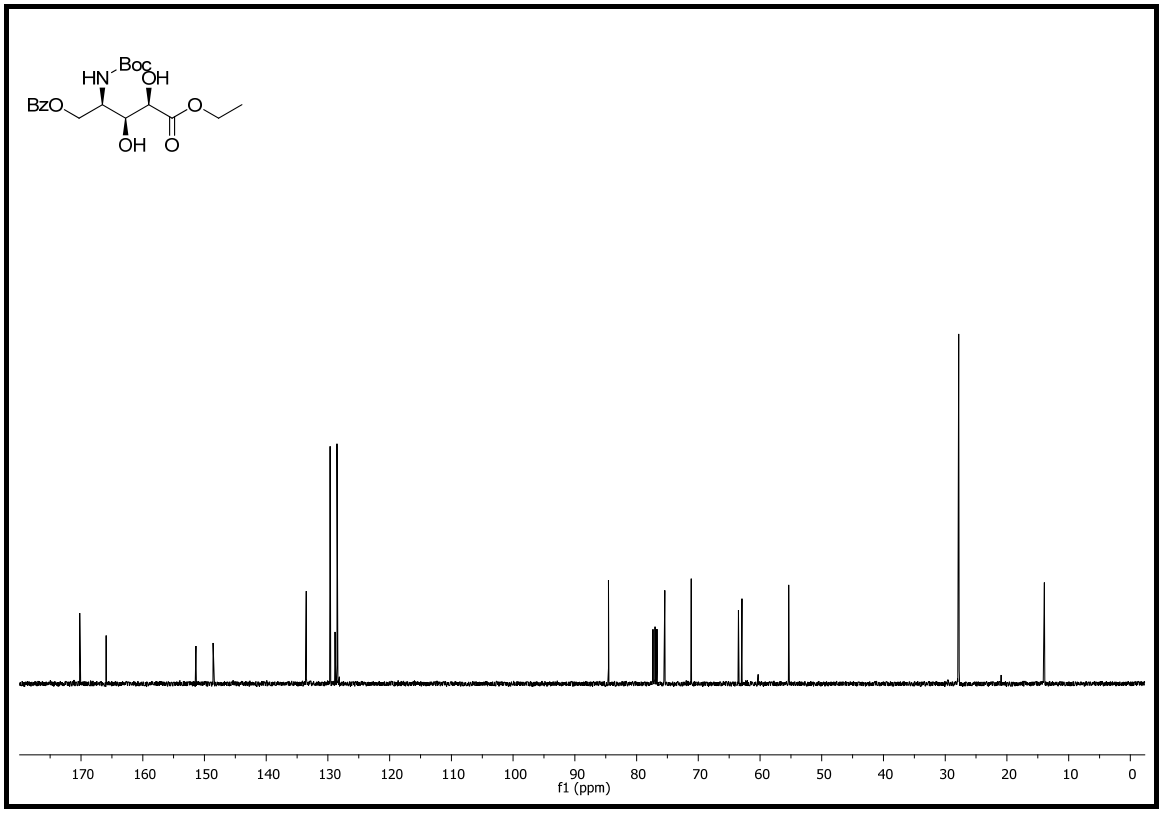
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm)of Ethy (2*S*,3*R*,4*R*)-5-(benzoyloxy)-4-((bis-*tert*-butoxycarbonyl)amino)-2,3-dihydroxypentanoate (3.62).



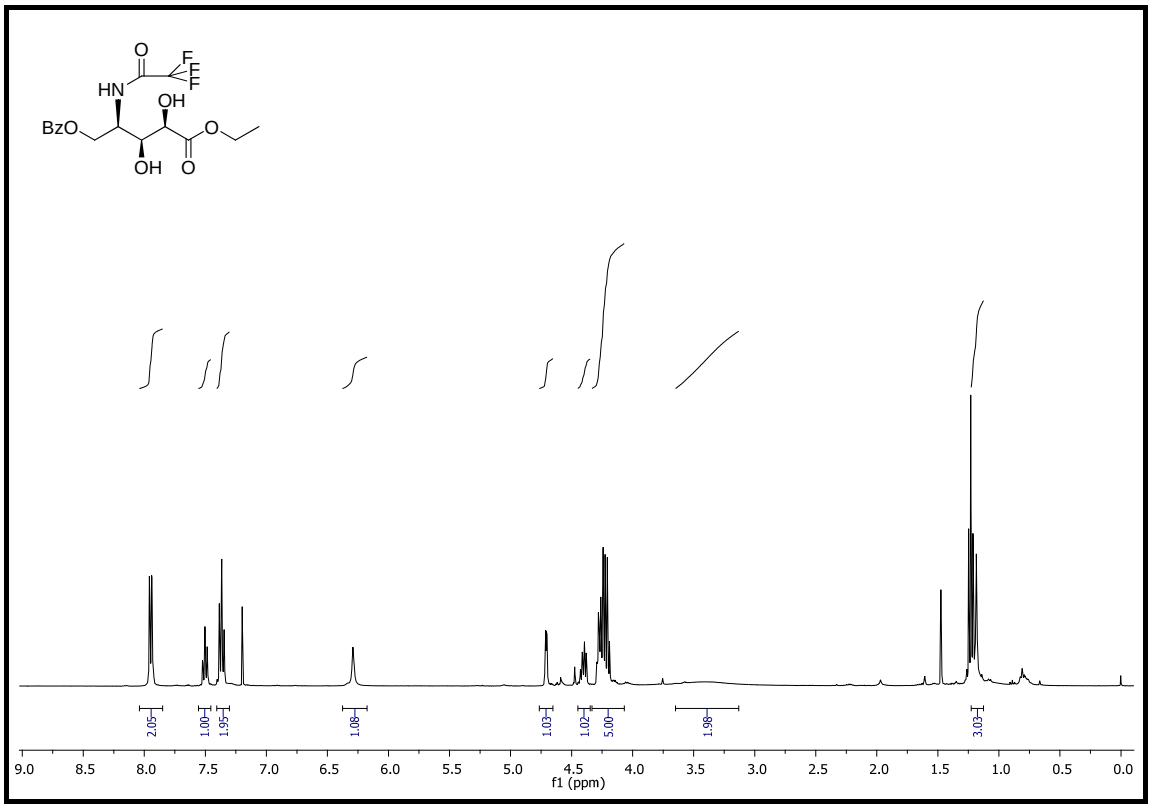
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of Ethyl (2*S*,3*S*,4*S*)-5-(benzoyloxy)-4-((*tert*-butoxycarbonyl)amino)-2,3-dihydroxypentanoate (3.63).



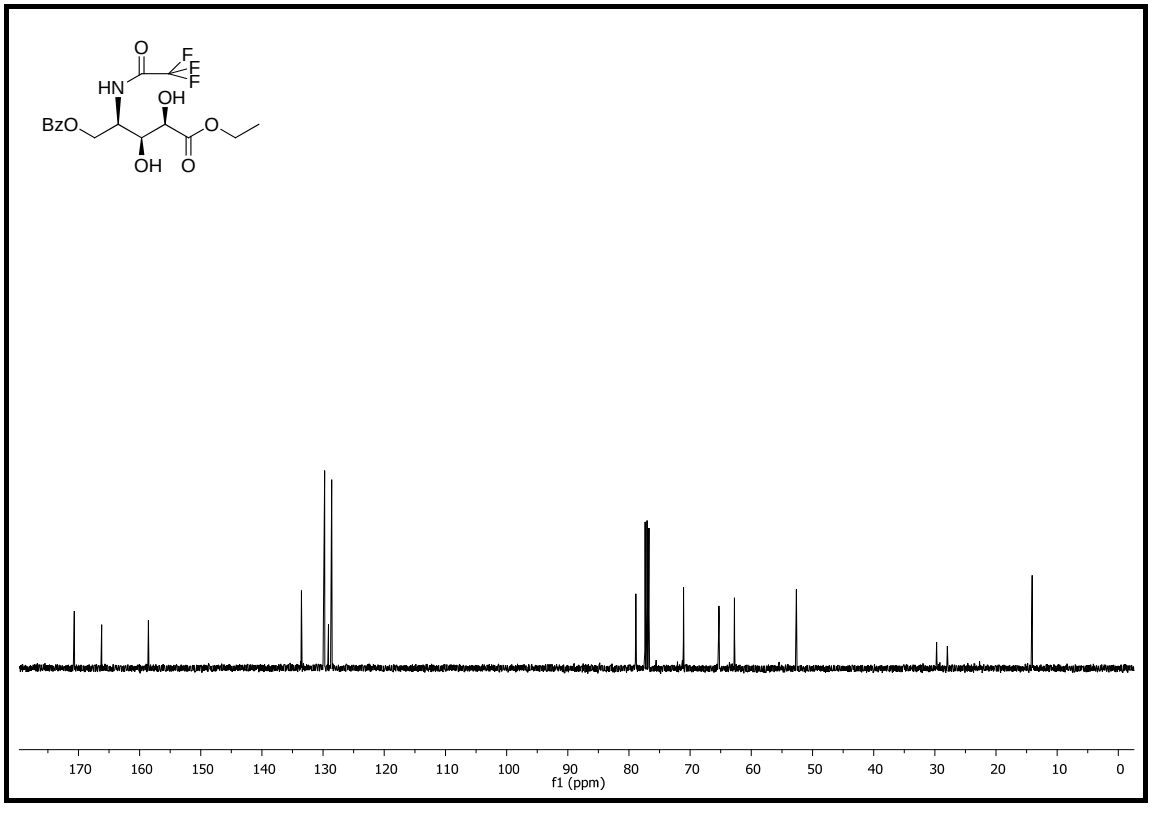
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of Ethyl (2*S*,3*S*,4*S*)-5-(benzoyloxy)-4-((*tert*-butoxycarbonyl)amino)-2,3-dihydroxypentanoate (3.63).



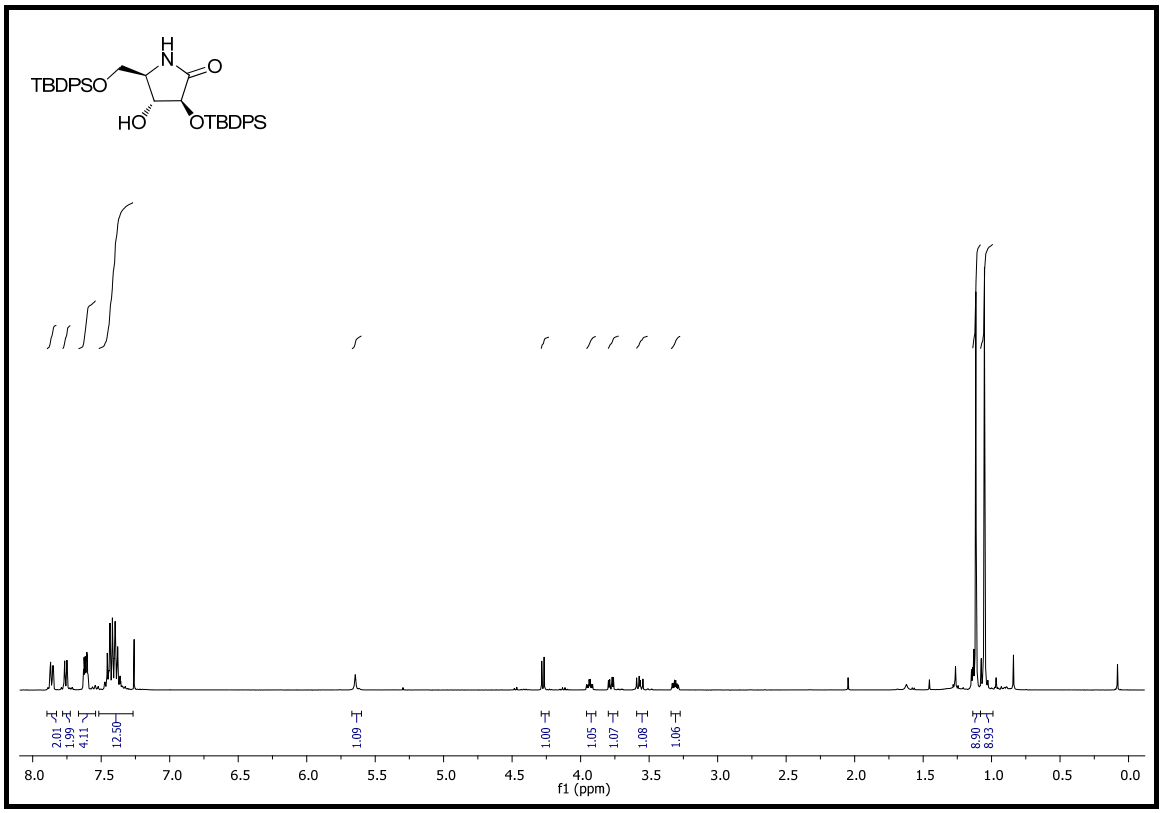
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of Ethyl (2*R*,3*S*,4*R*)-5-(benzoyloxy)-2-3-dihydroxy-4-(trifluoroacetamido)pentanoate (3.73).



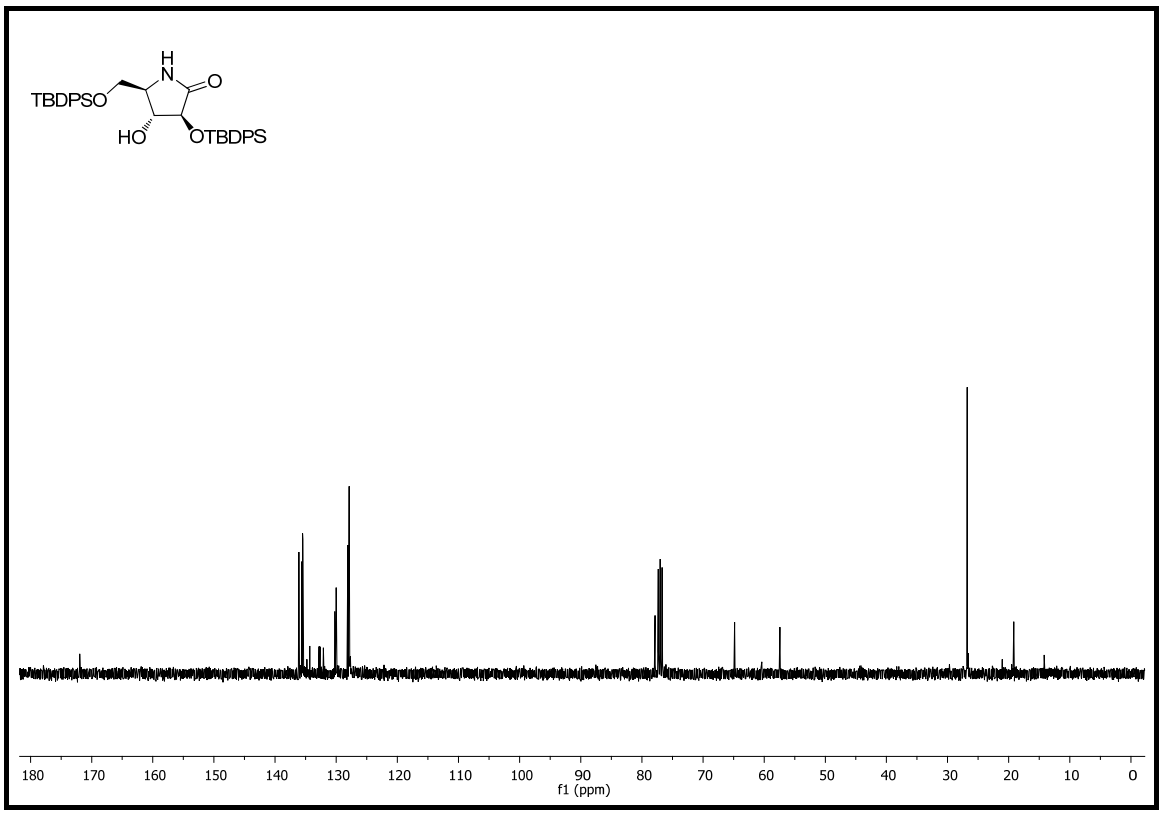
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of Ethyl (2*R*,3*S*,4*R*)-5-(benzoyloxy)-2-3-dihydroxy-4-(trifluoroacetamido)pentanoate (3.73).



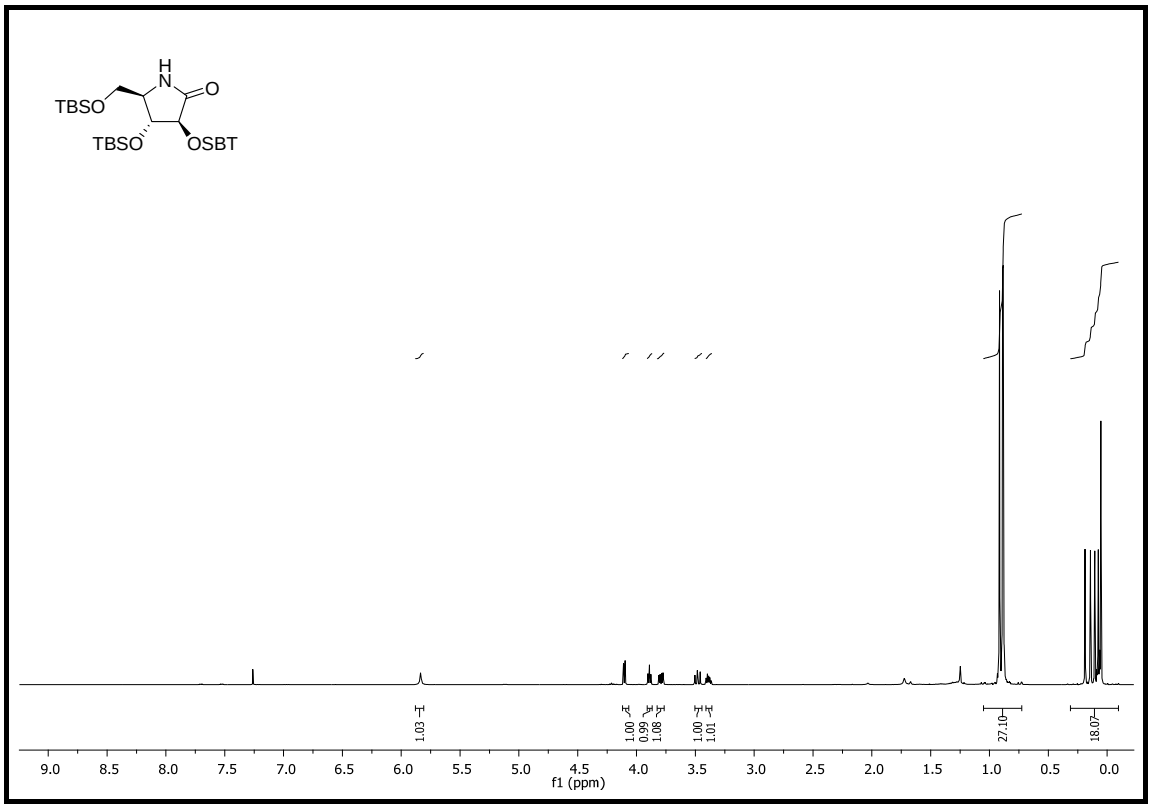
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (3*S*,4*R*,5*R*)-3-(*tert*-butyldiphenylsilyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-4-hydroxypyrrolidin-2-one (3.81).



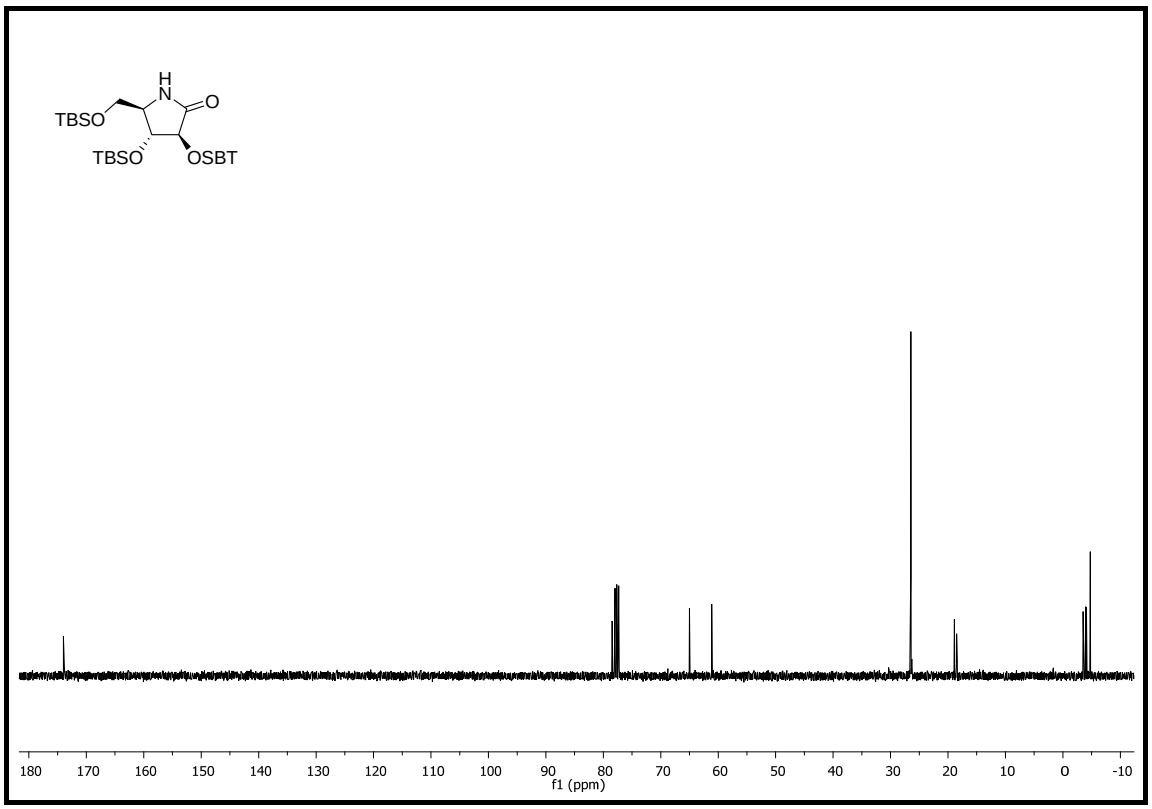
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (3*S*,4*R*,5*R*)-3-(*tert*-butyldiphenylsilyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-4-hydroxypyrrolidin-2-one (3.81).



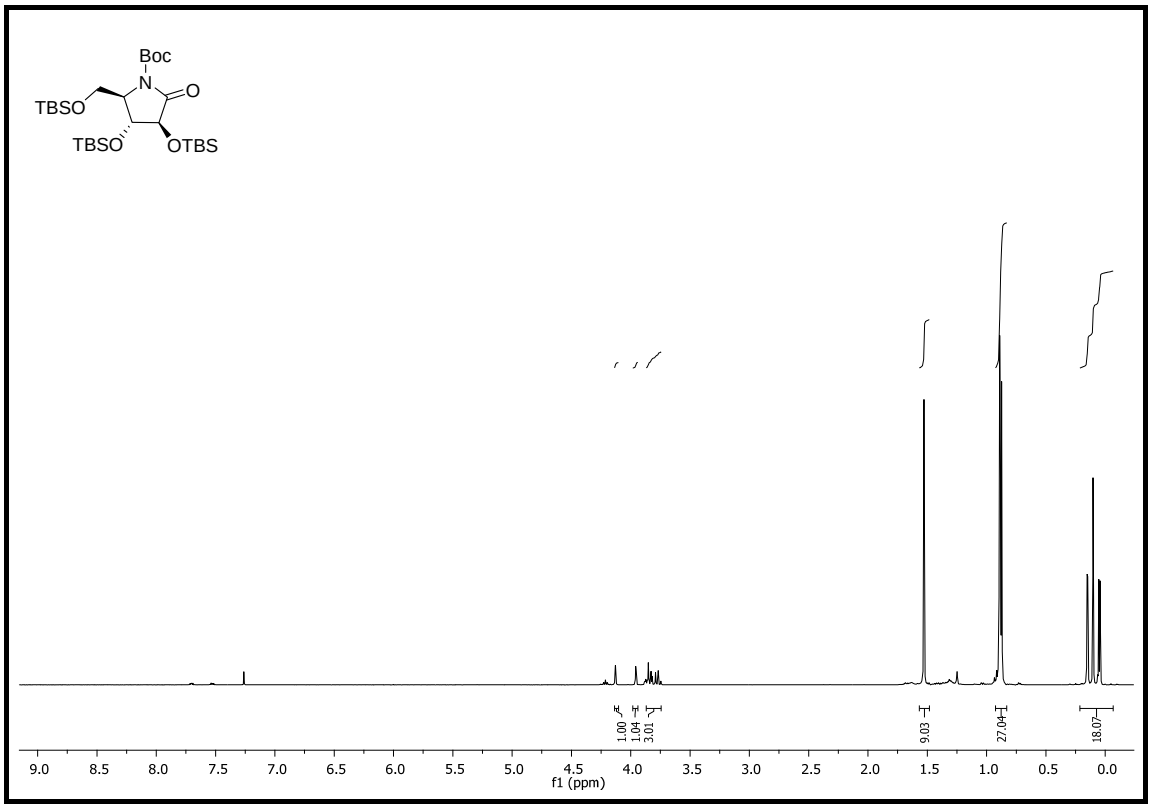
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (3*S*,4*R*,5*R*)-3,4-bis-(*tert*-butyldimethylsilyloxy)-5-((*tert*-butyldimethyldimethylsilyl)oxyMethyl)pyrrolidin-2-one (3.82).



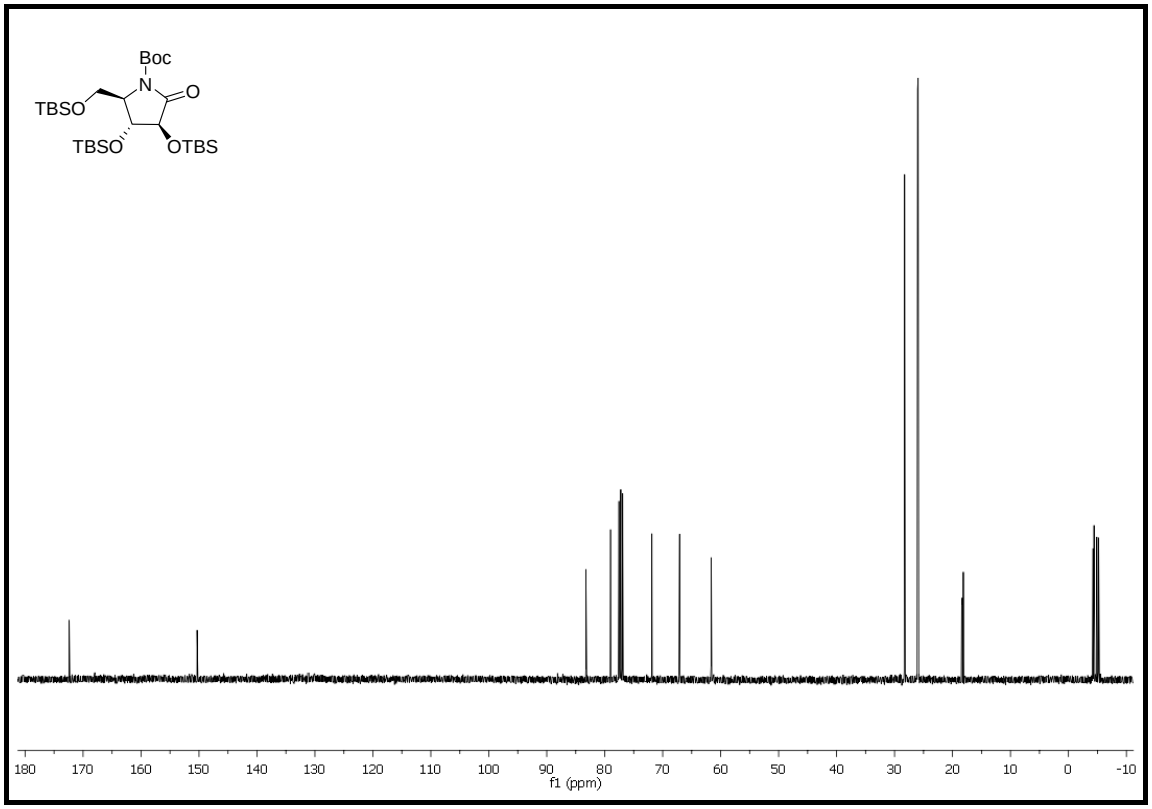
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (3*S*,4*R*,5*R*)-3,4-bis-(*tert*-butyldimethylsilyloxy)-5-((*tert*-butyldimethyldimethylsilyl)oxyMethyl)pyrrolidin-2-one (3.82).



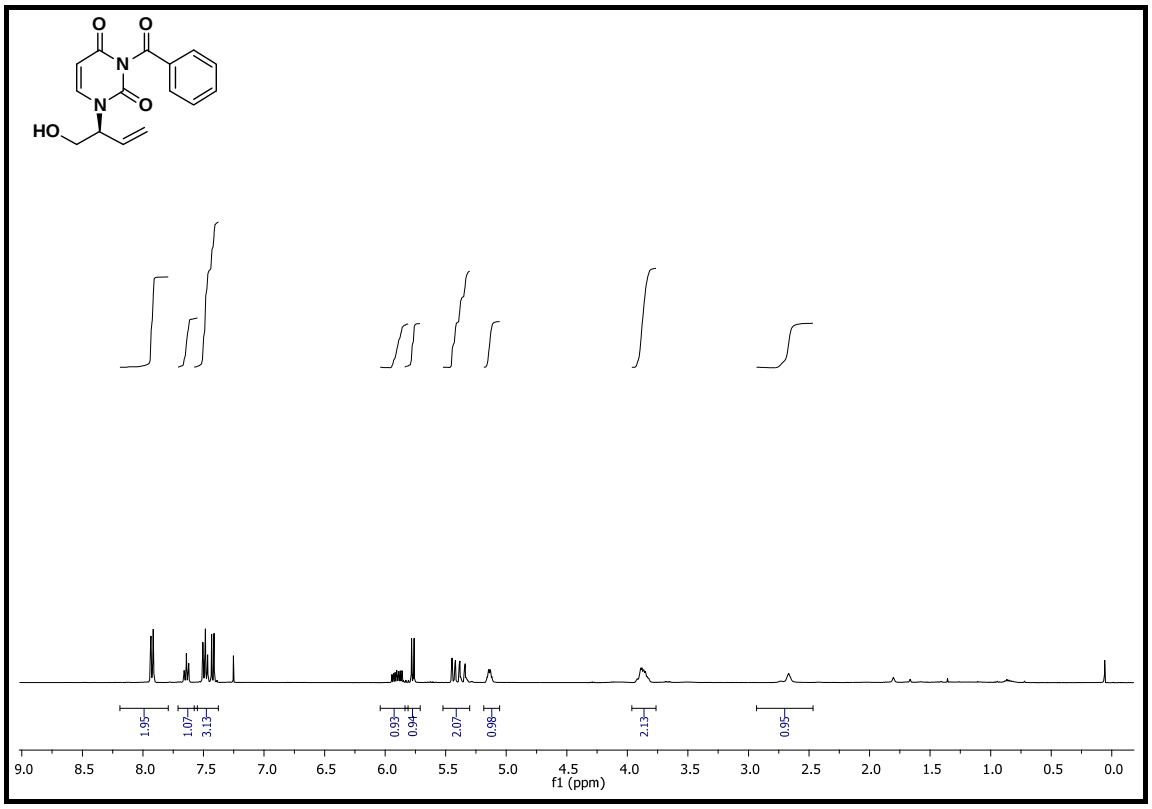
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of *tert*-butyl (3*S*,4*R*,5*R*)-*N*-*tert*-butoxycarbonyl-3,4-bis[(*tert*-butyldimethylsilyl)oxy]-5-((*tert*-butyldimethylsilyloxy)methyl)-2-pyrrolidin-2-one (3.83).



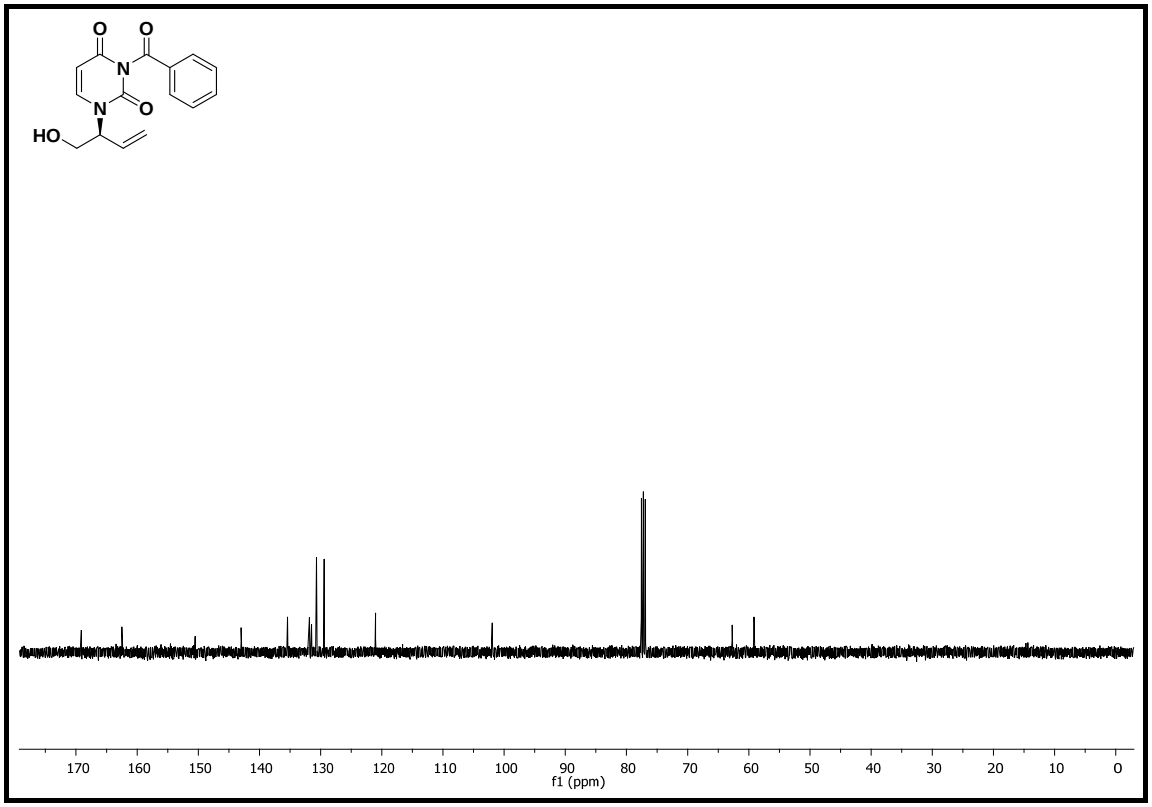
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of *tert*-butyl (3*S*,4*R*,5*R*)-*N*-*tert*-butoxycarbonyl-3,4-bis[(*tert*-butyldimethylsilyl)oxy]-5-((*tert*-butyldimethylsilyloxy)methyl)-2-pyrrolidin-2-one (3.83).



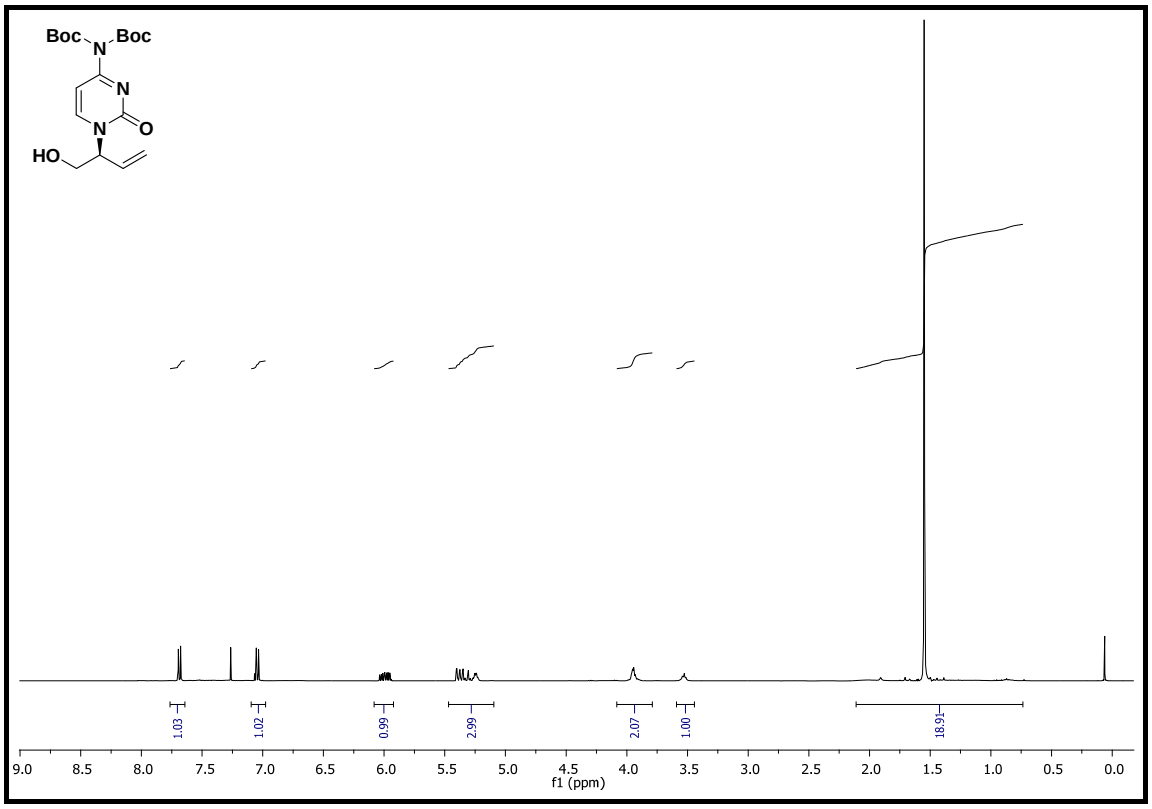
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of 3-Benzoyl-1-[(2S)-1-hydroxybut-3-en-2-yl]-1,2,3,4-tetrahydropyrimidine-2,4-dione (4.31).



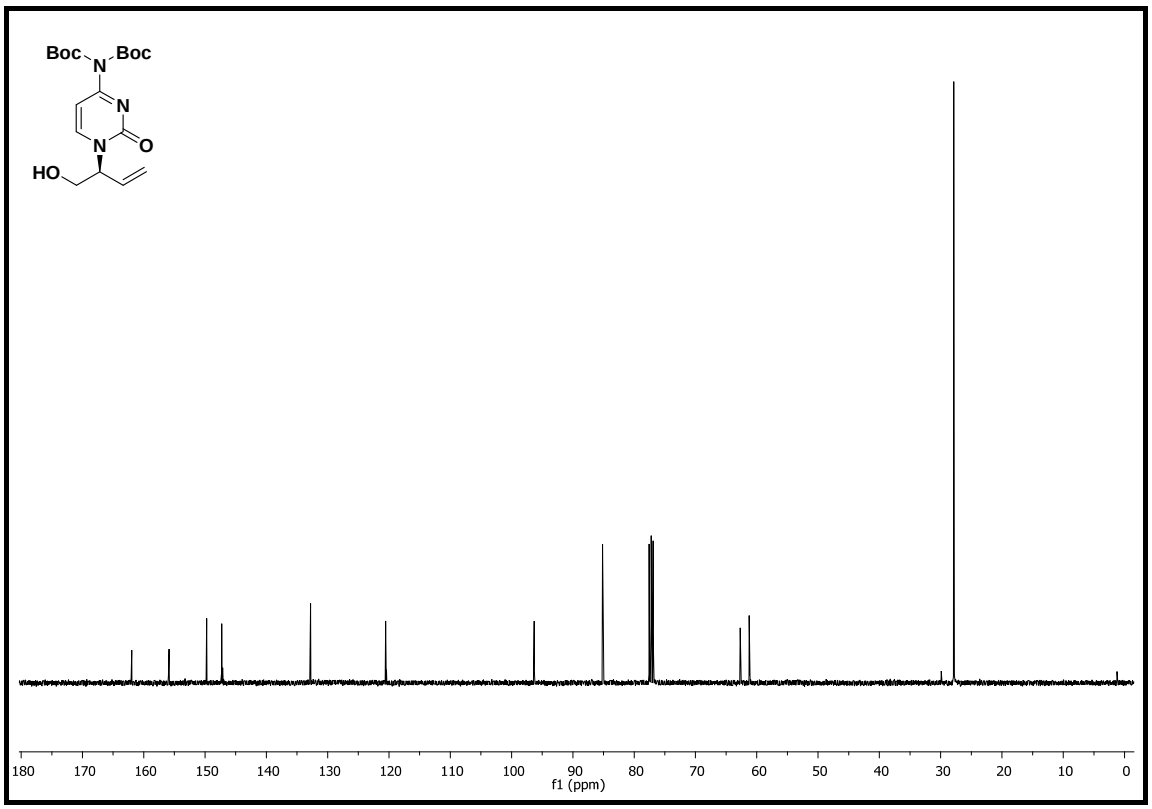
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of 3-Benzoyl-1-[(2S)-1-hydroxybut-3-en-2-yl]-1,2,3,4-tetrahydropyrimidine-2,4-dione (4.31).



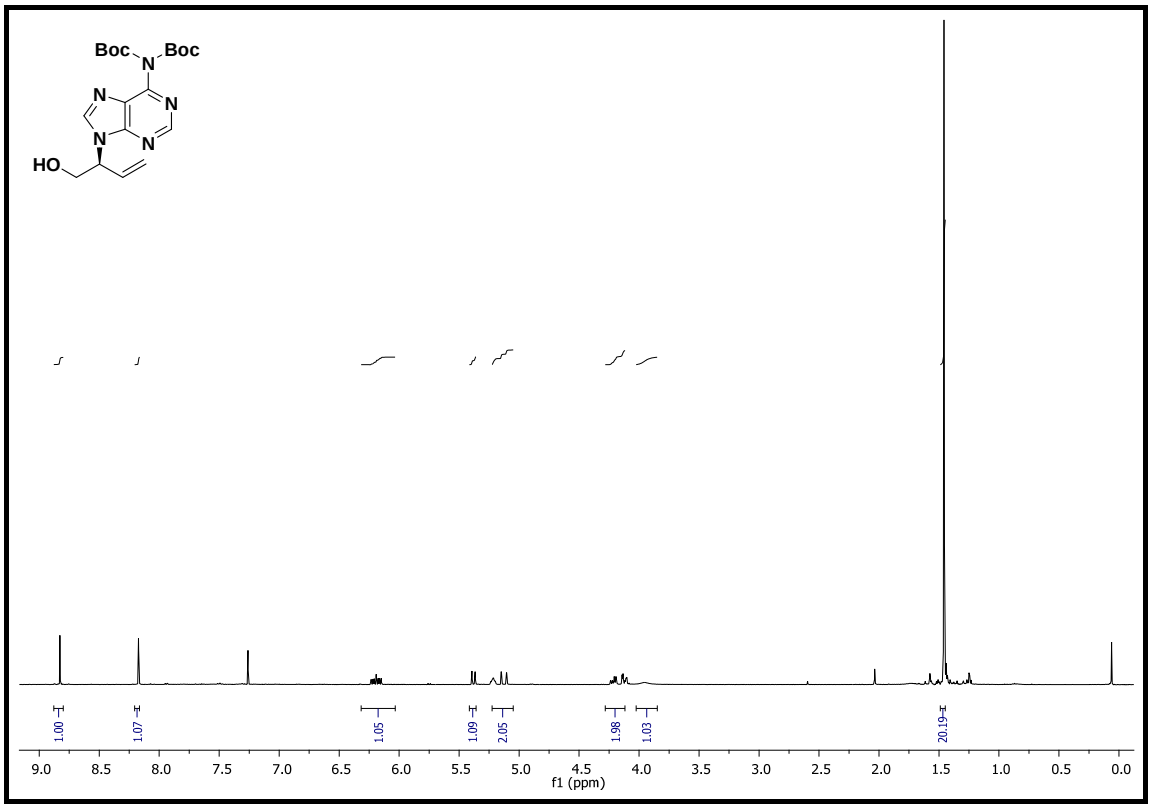
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of 4-((Bis(*tert*-butoxycarbonyl)amino)-1-((2S)-1-hydroxybut-3-en-2-yl)-1,2-dihydropyrimidine-2-one(4.42).



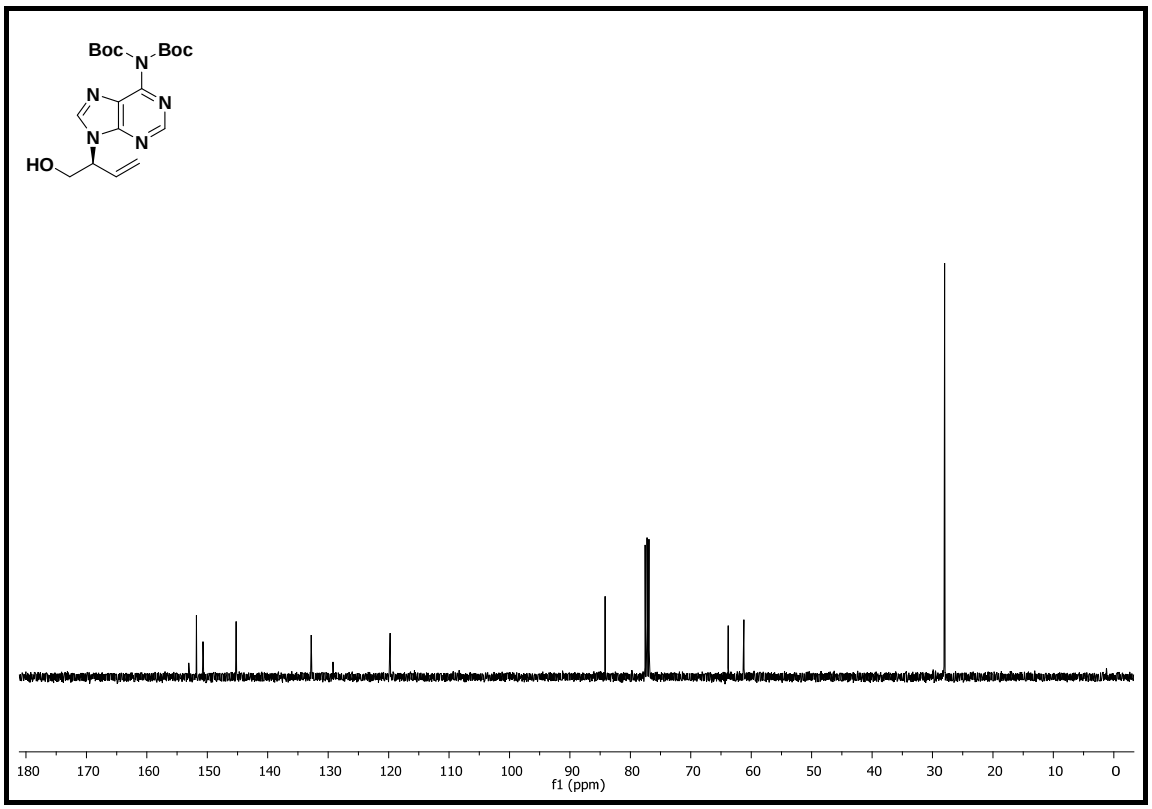
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of of 4-((Bis(*tert*-butoxycarbonyl)amino)-1-((2S)-1-hydroxybut-3-en-2-yl)-1,2-dihydropyrimidine-2-one(4.42).



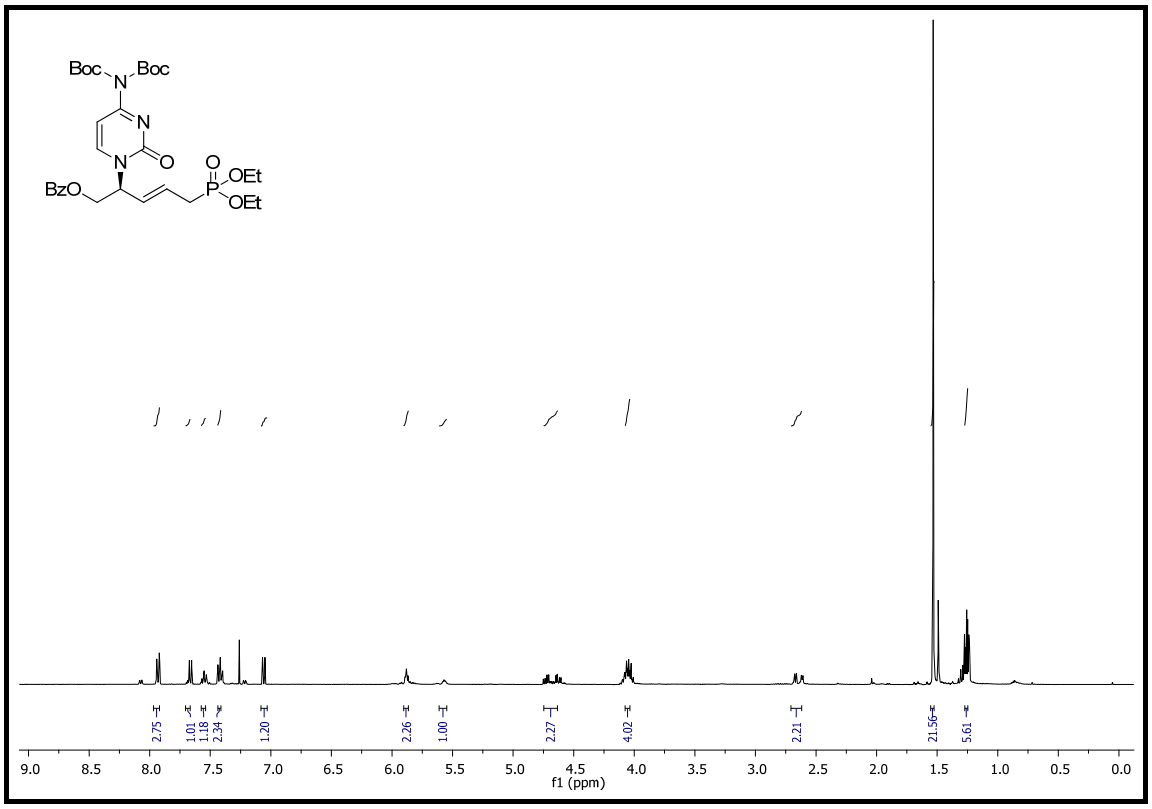
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of 6-(Bis-*tert*-butoxycarbonyl)amino)-9-((2S)-1-hydroxybut-3-en-2-yl)-9H-purine (4.44).



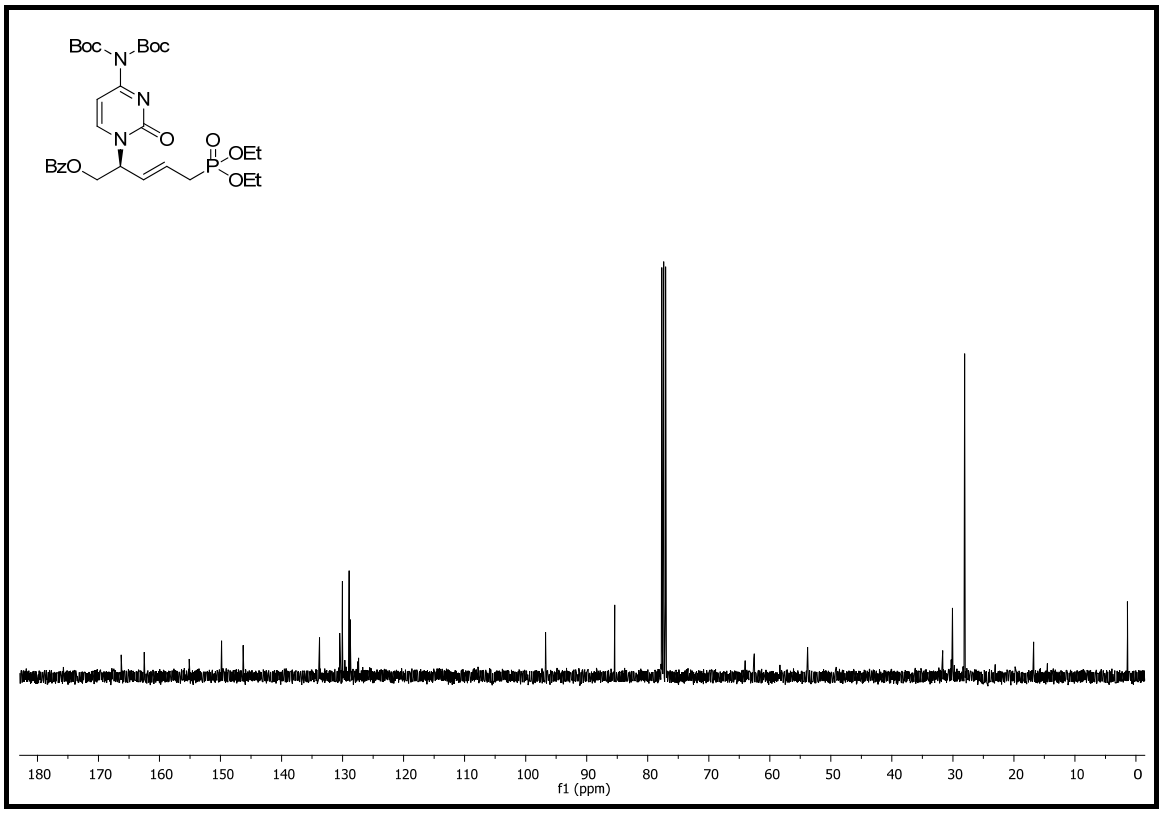
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of 6-(Bis-*tert*-butoxycarbonyl)amino)-9-((2S)-1-hydroxybut-3-en-2-yl)-9H-purine (4.44).



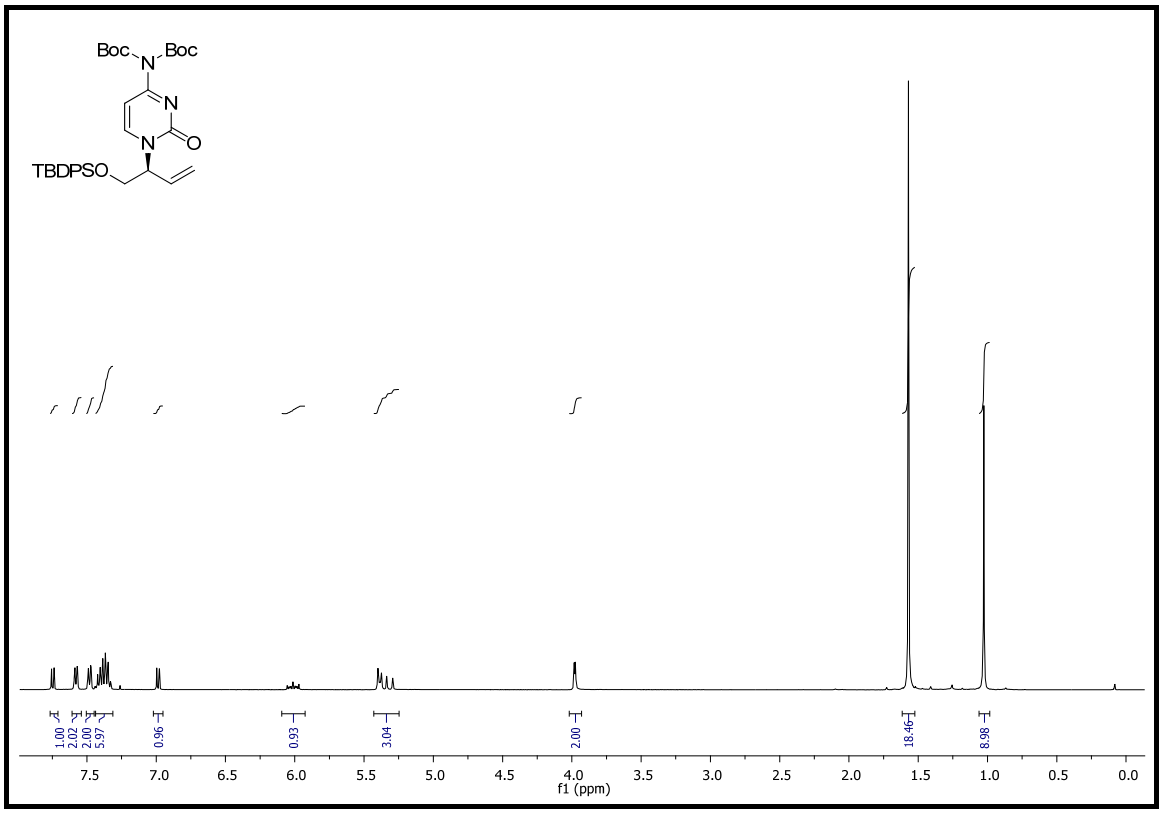
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*S*,3*E*)-2-[(4-bis-(*tert*-butoxycarbonyl)amino)-2-oxo-1,2-dihydropyrimidin-1-yl]-5-(diethoxyphosphoryl)pent-3-en-1-yl benzoate (4.50).



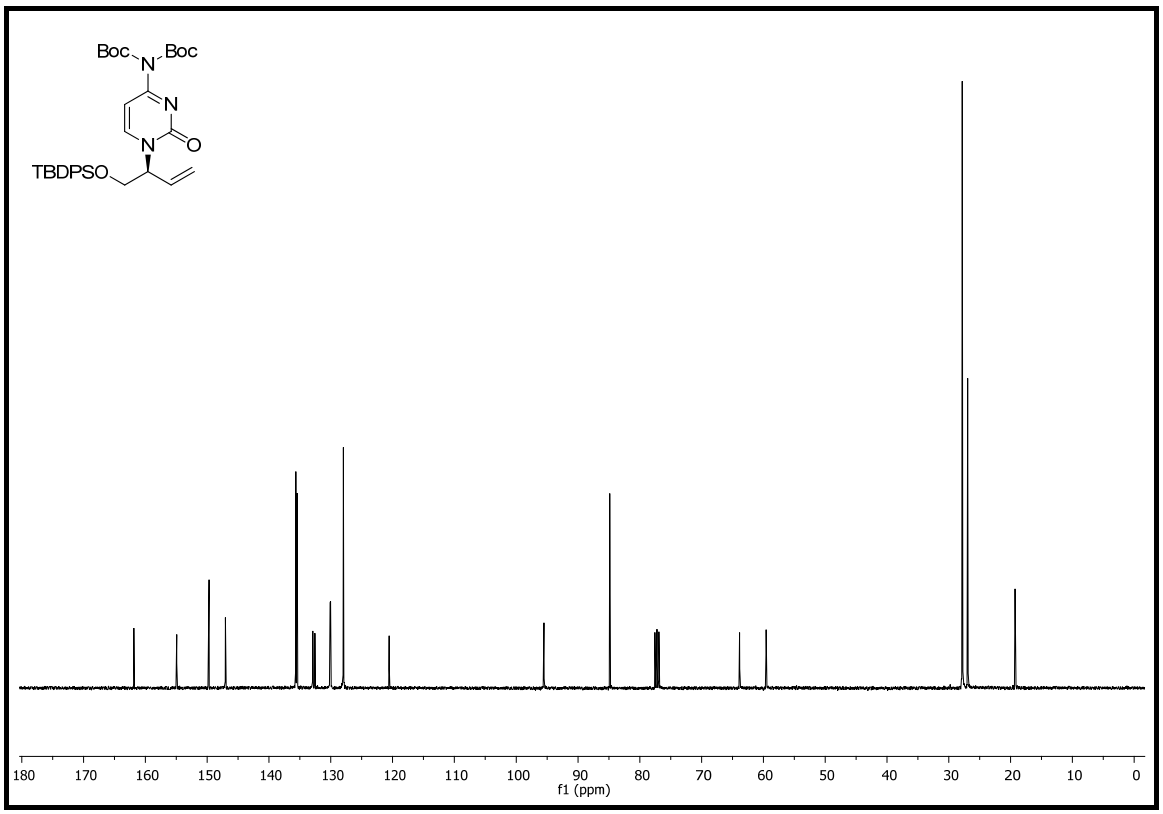
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*S*,3*E*)-2-[(4-bis-(*tert*-butoxycarbonyl)amino)-2-oxo-1,2-dihydropyrimidin-1-yl]-5-(diethoxyphosphoryl)pent-3-en-1-yl benzoate (4.50).



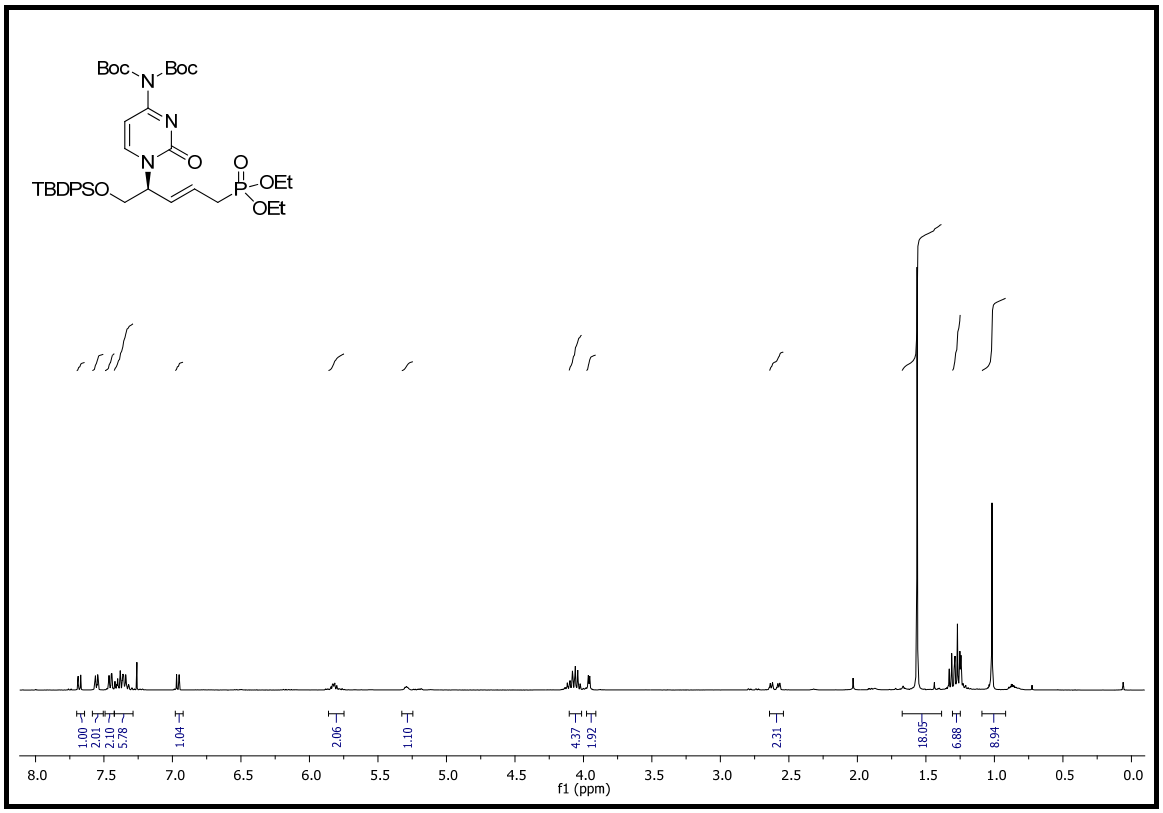
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of 2-[(4-bis-(*tert*-butoxycarbonyl)amino)-1-[(2*S*)-1-(*tert*-butyldiphenylsilyloxy)but-3-en-2-yl]-1,2-dihydropyrimidin-2-one (4.51).



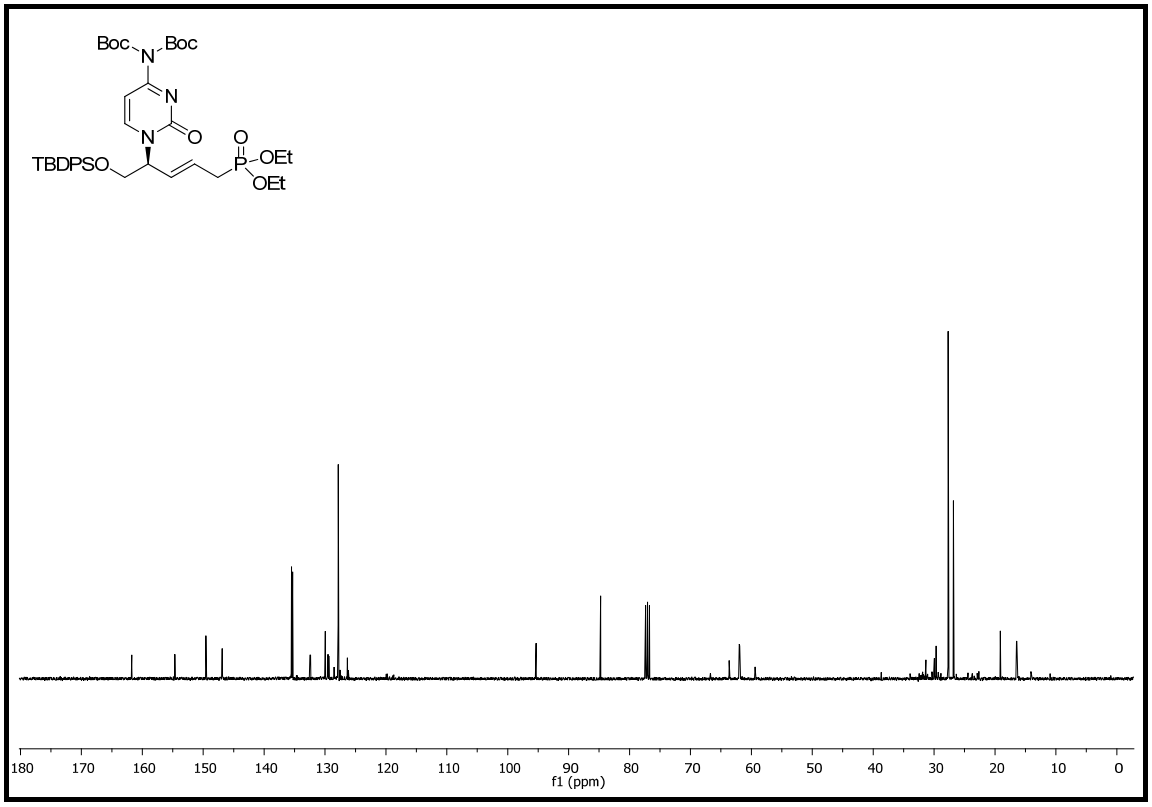
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of 2-[(4-bis-(*tert*-butoxycarbonyl)amino)-1-[(2*S*)-1-(*tert*-butyldiphenylsilyloxy)but-3-en-2-yl]-1,2-dihydropyrimidin-2-one (4.51).



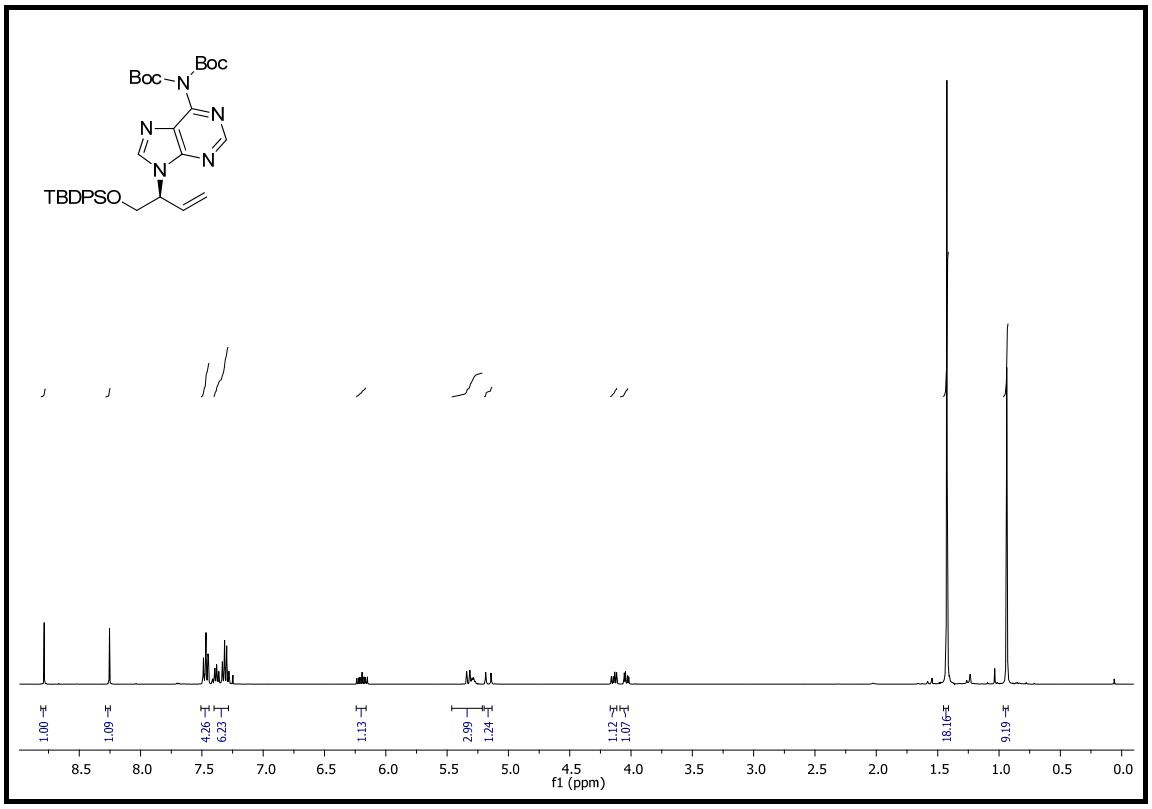
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*S*, 3*E*)- 2-[((4-Bis-(*tert*-butoxycarbonyl)amino)-2-oxo-1,2-dihydropyrimidin-1-yl]-1-(*tert*-butyldiphenylsilyloxy)-5-(diethoxyphosphoryl)pent-3-ene (4.52).



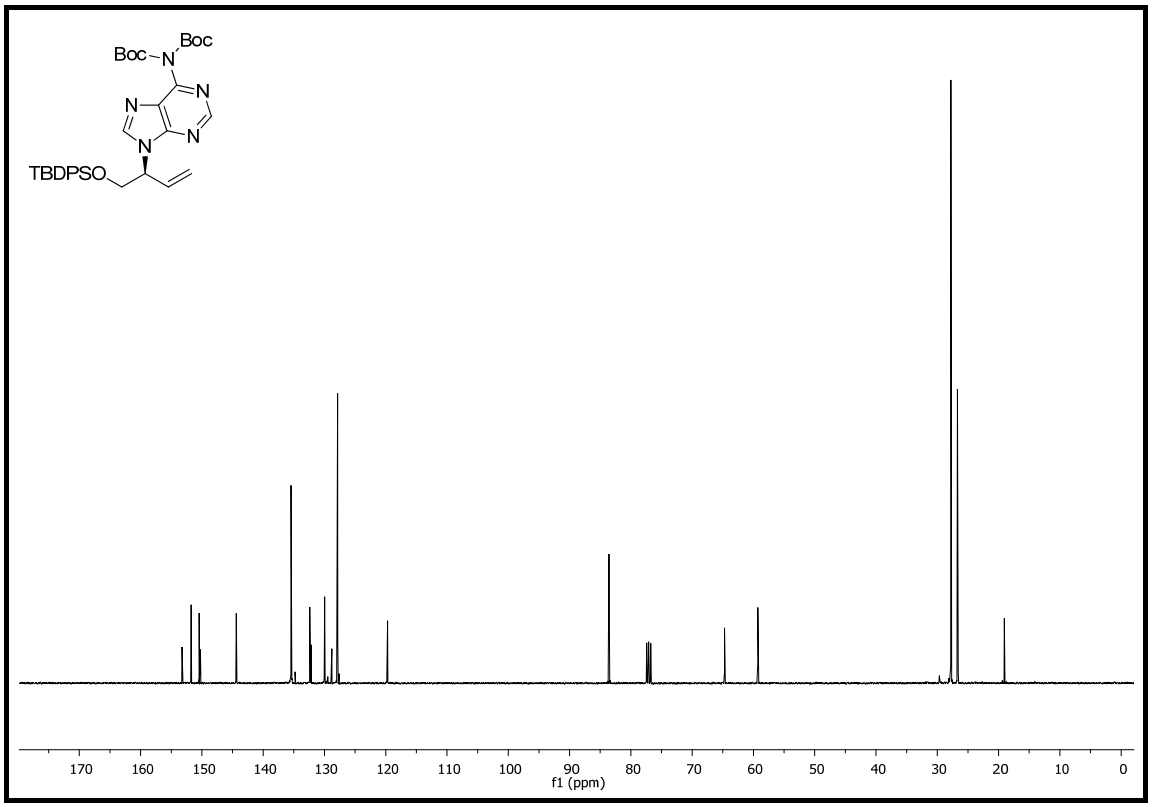
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*S*, 3*E*)- 2-[((4-Bis-(*tert*-butoxycarbonyl)amino)-2-oxo-1,2-dihydropyrimidin-1-yl]-1-(*tert*-butyldiphenylsilyloxy)-5-(diethoxyphosphoryl)pent-3-ene (4.52).



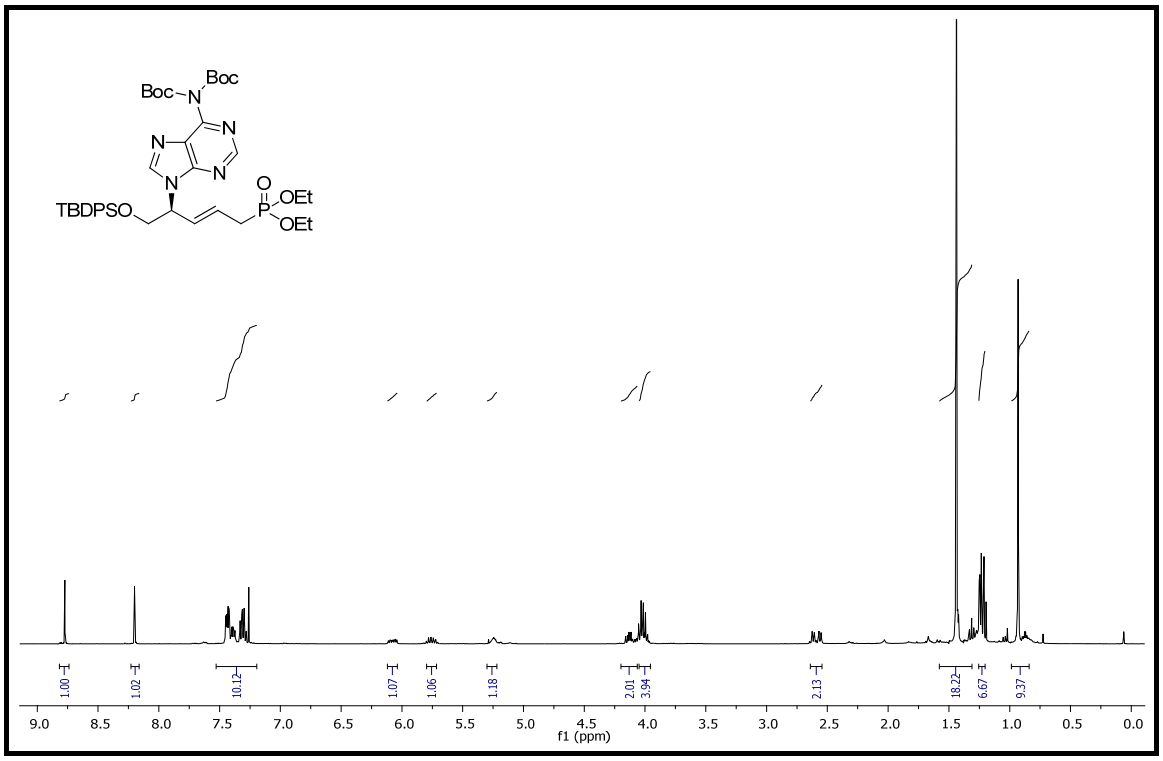
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of 6-(Bis-*tert*-butoxycarbonyl)amino)-9-((2S)-1-*tert*-butyldiphenylsilyloxy-but-3-en-2-yl)-9H-purine (4.53).



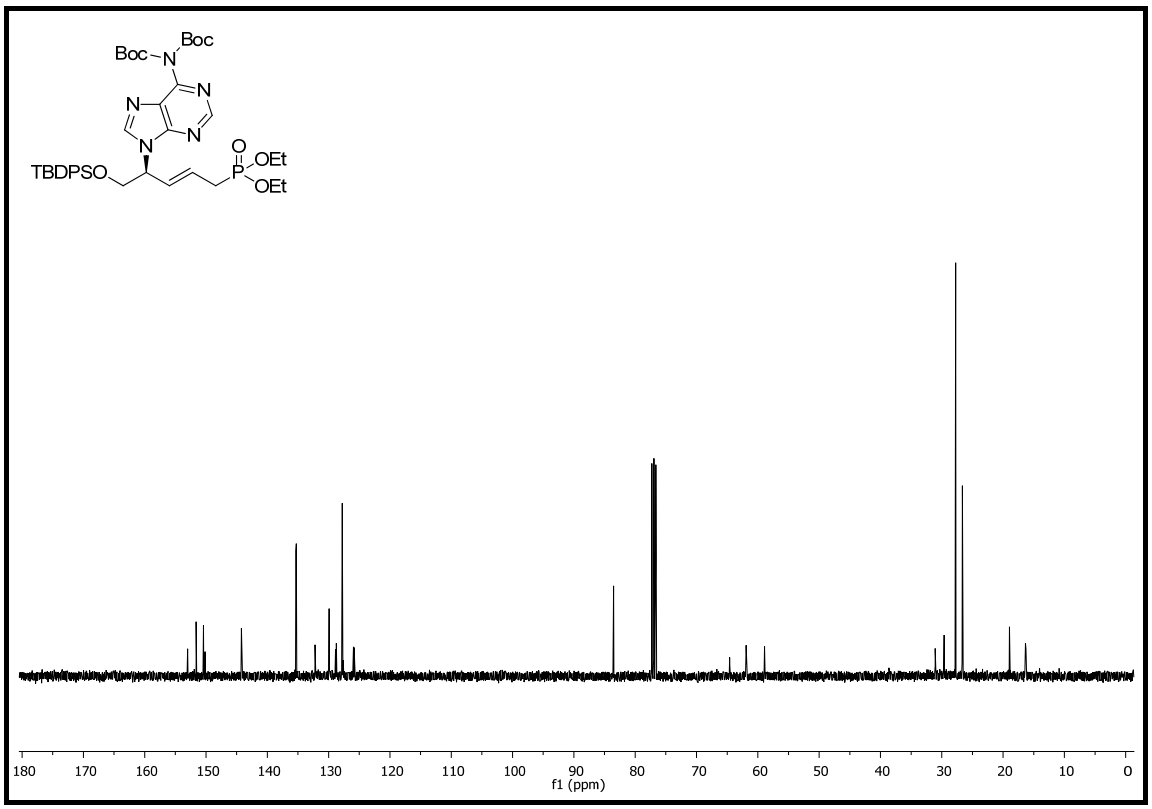
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of 6-(Bis-*tert*-butoxycarbonyl)amino)-9-((2S)-1-*tert*-butyldiphenylsilyloxy-but-3-en-2-yl)-9H-purine (4.53).



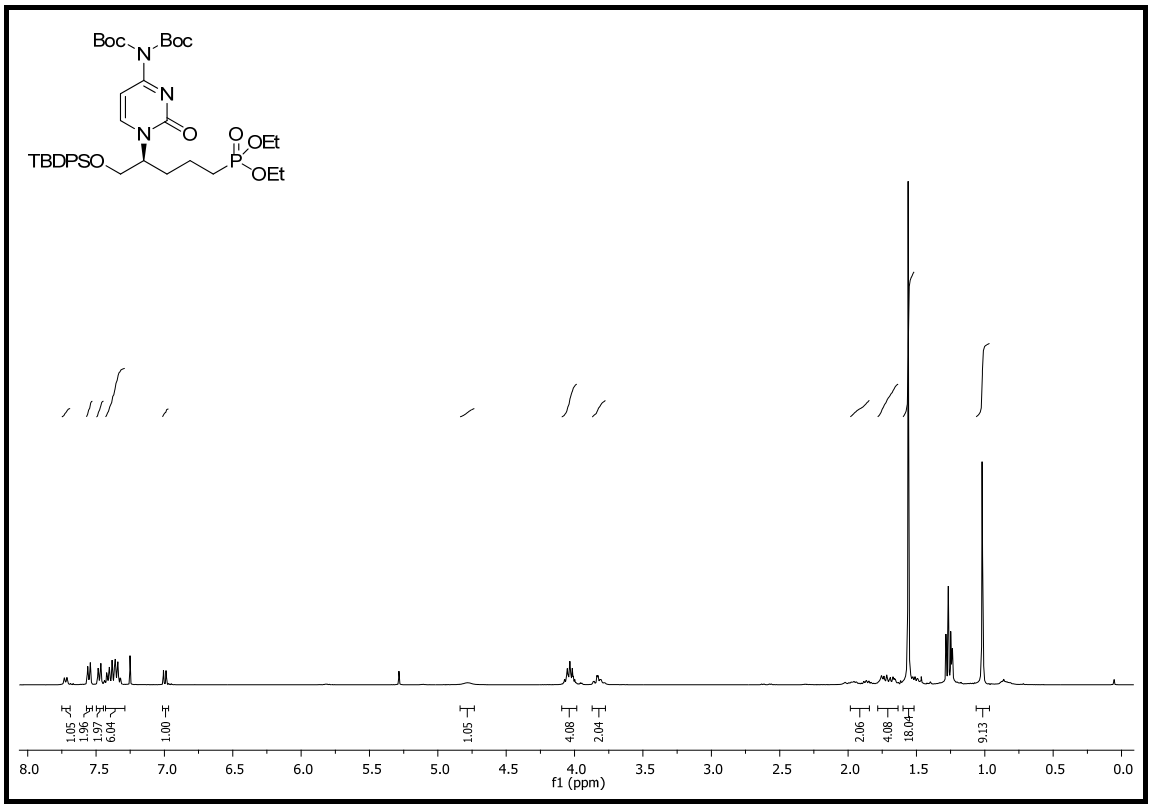
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*S*,3*E*)-2-[((6-Bis-(*tert*-butoxycarbonyl)amino)-purin-9-yl]-1-(*tert*-butyldiphenylsilyloxy)-5-(diethoxyphosphoryl)pent-3-ene (4.54).



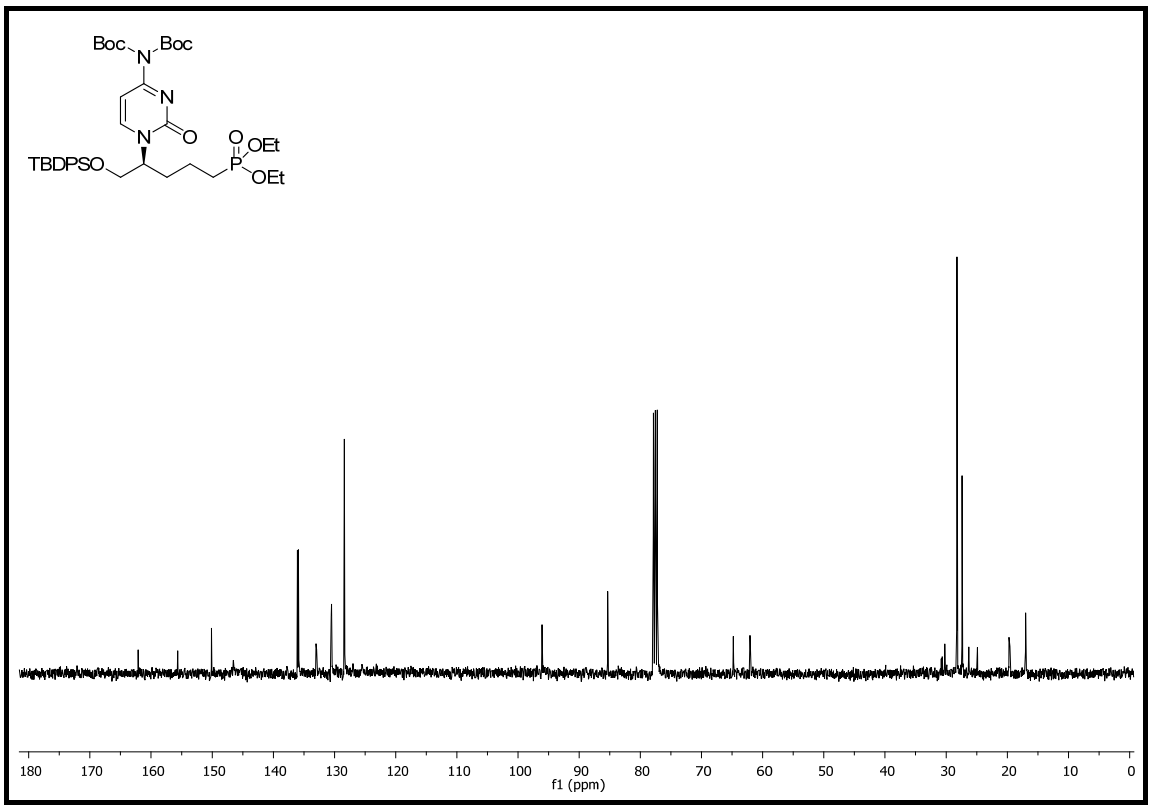
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*S*,3*E*)-2-[((6-Bis-(*tert*-butoxycarbonyl)amino)-purin-9-yl]-1-(*tert*-butyldiphenylsilyloxy)-5-(diethoxyphosphoryl)pent-3-ene (4.54).



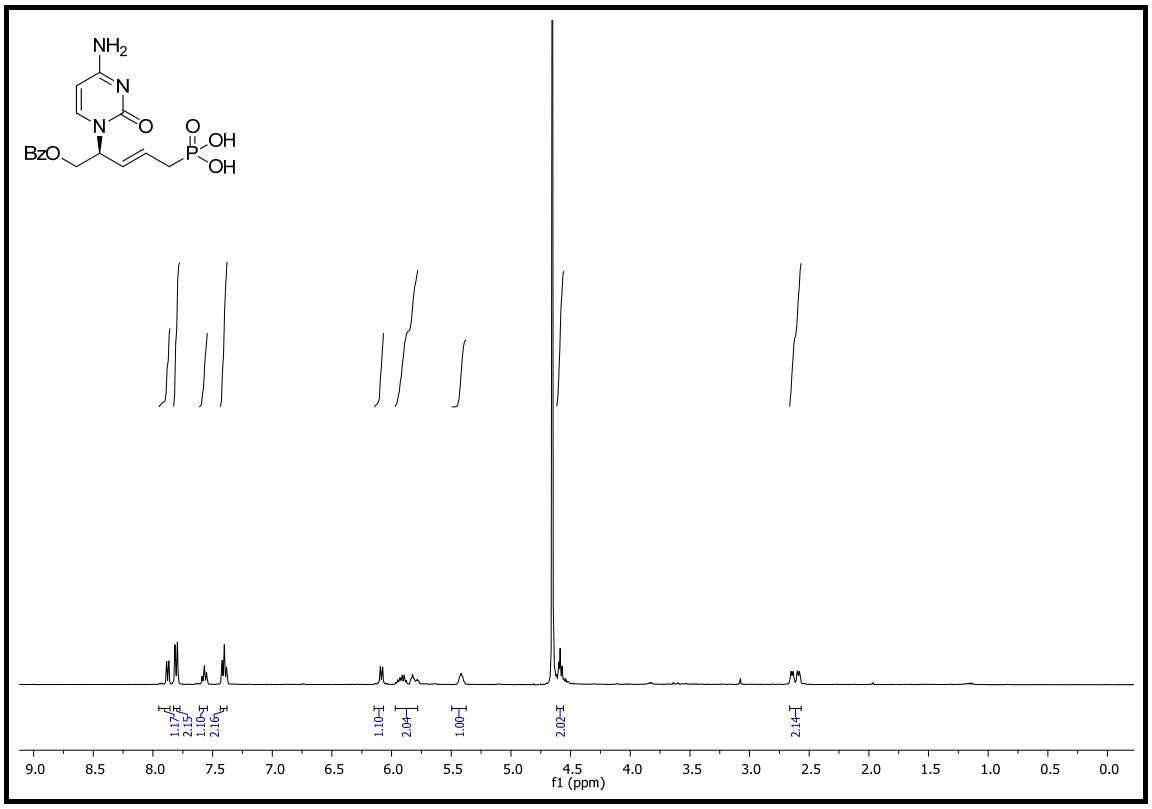
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*S*)- 2-[((4-Bis-(*tert*-butoxycarbonyl)amino)-2-oxo-1,2-dihydropyrimidin-1-yl]-1-(*tert*-butyldiphenylsilyloxy)-5-(diethoxyphosphoryl)pentane (4.55).



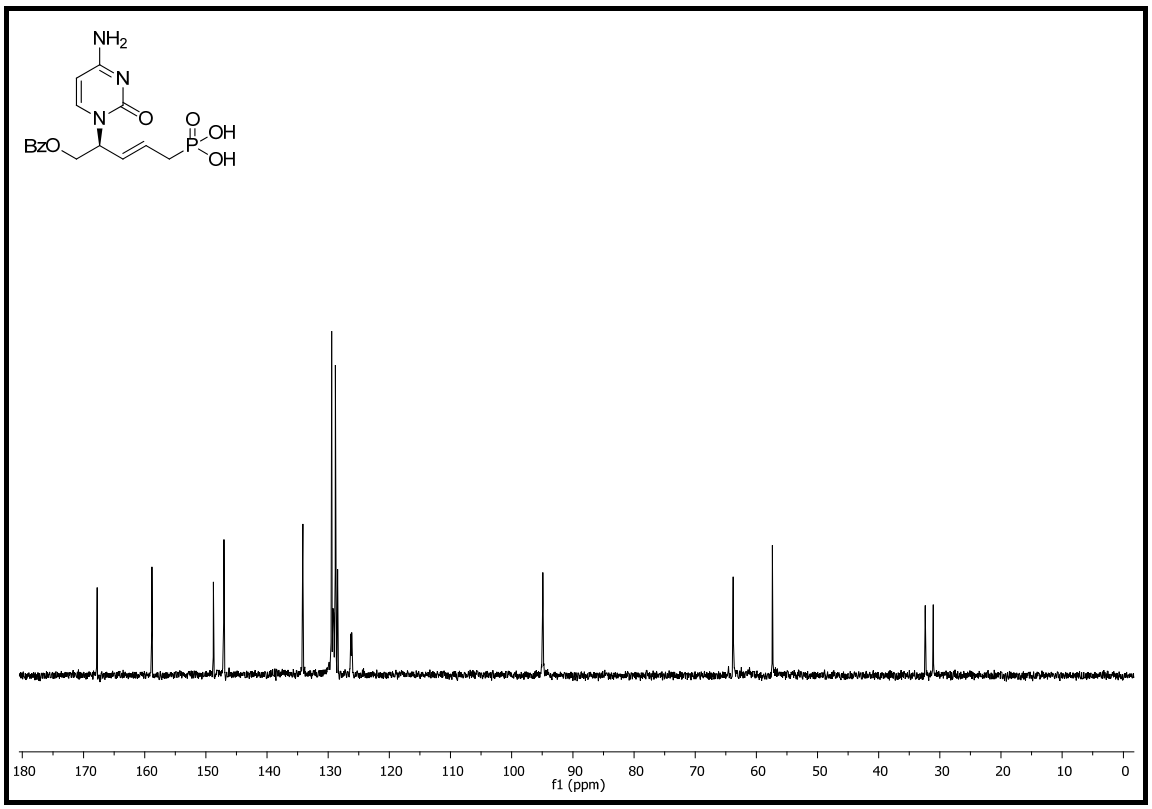
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of of (2*S*)- 2-[((4-Bis-(*tert*-butoxycarbonyl)amino)-2-oxo-1,2-dihydropyrimidin-1-yl]-1-(*tert*-butyldiphenylsilyloxy)-5-(diethoxyphosphoryl)pentane (4.55).



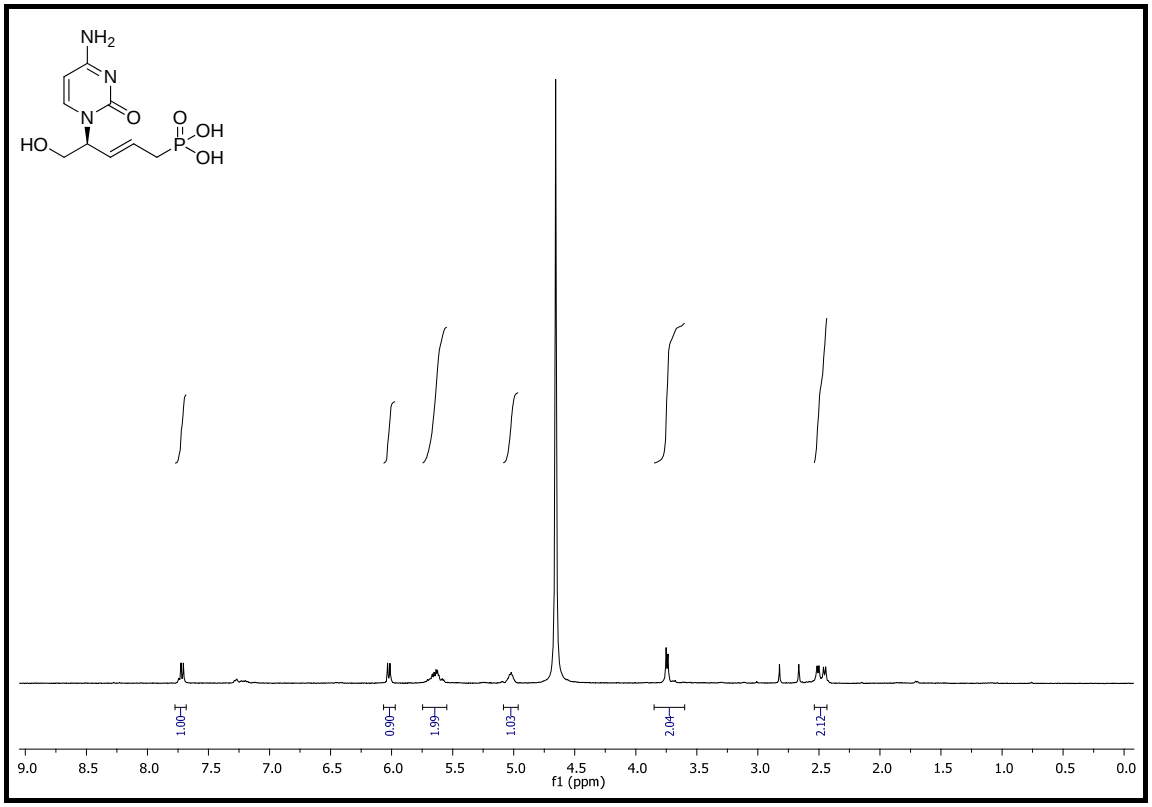
^{1}H NMR (D_2O, 400 MHz, δ in ppm) of (2*S*,3*E*)-2-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-(diethoxyphosphoryl) pent-3-en-1-yl benzoate (4.56).



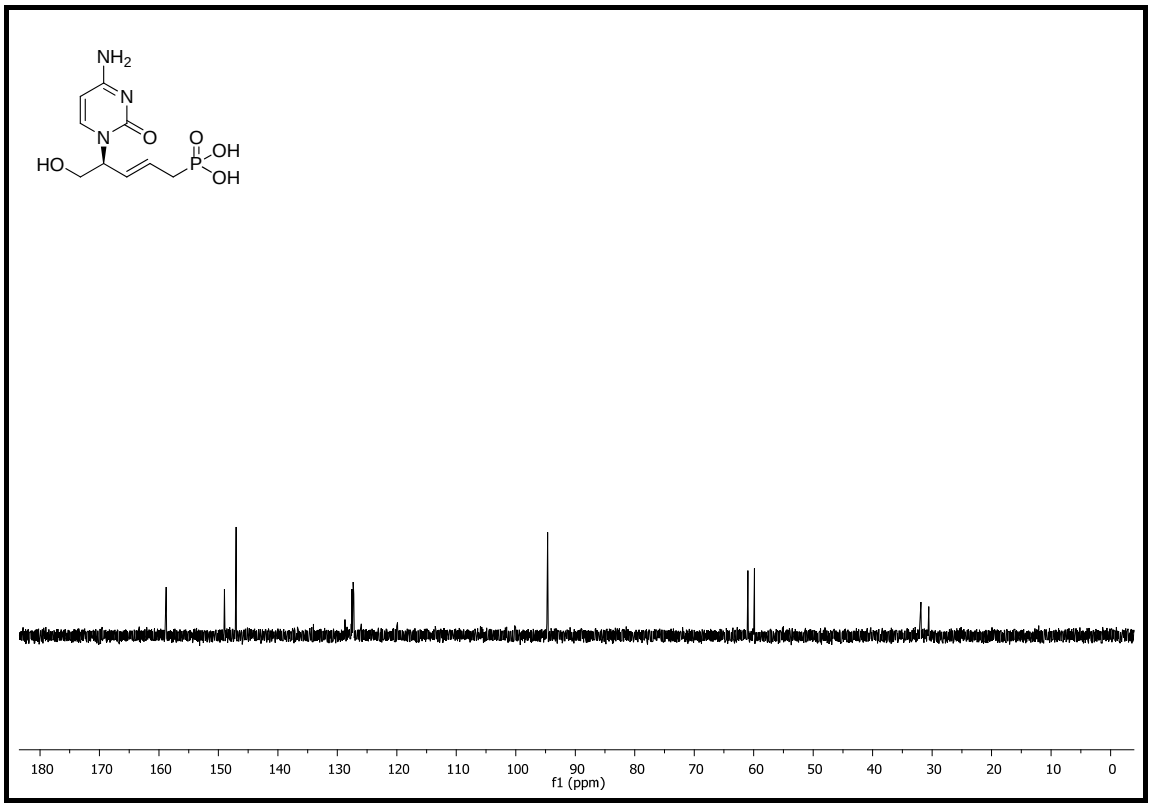
^{13}C NMR (D_2O, 100.6 MHz, δ in ppm) of (2*S*,3*E*)-2-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-(diethoxyphosphoryl) pent-3-en-1-yl benzoate (4.56).



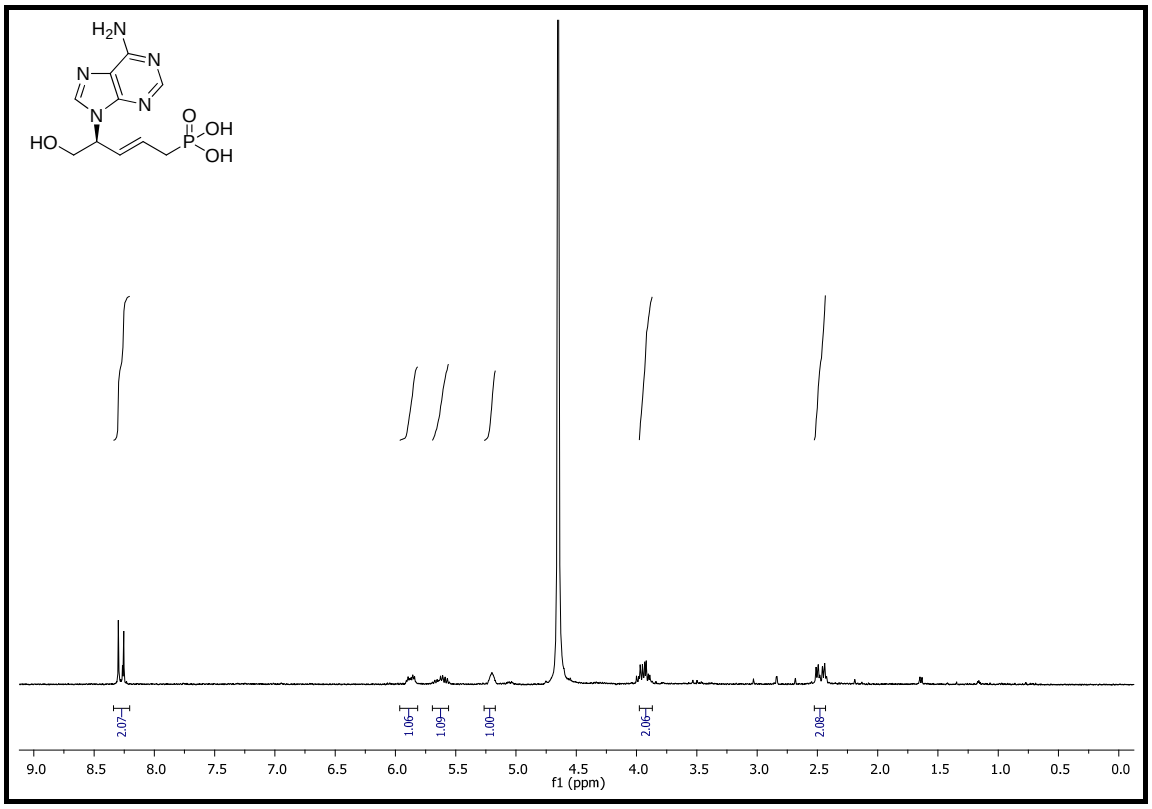
^{1}H NMR (D_2O, 400 MHz, δ in ppm) of [(2*E*,4*S*)-4-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-hydroxypent-2-en-1-yl]phosphonic acid (4.57).



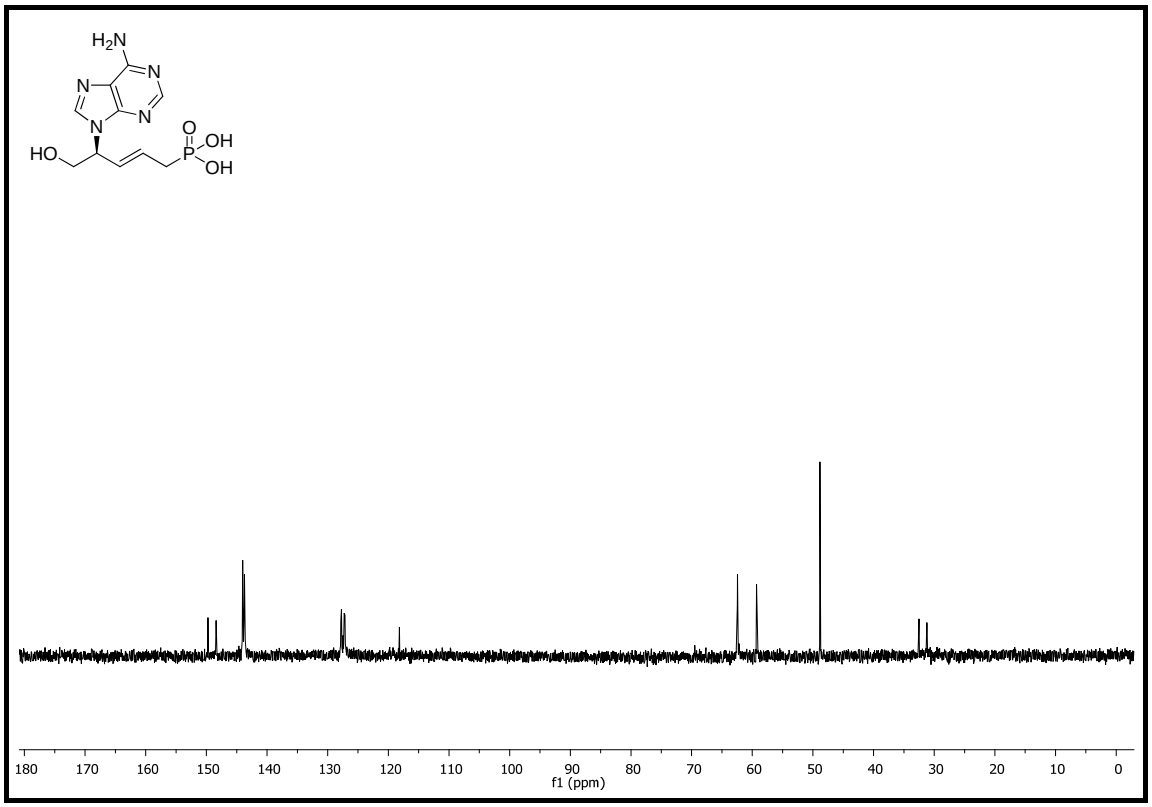
^{13}C NMR (D_2O, 100.6 MHz, δ in ppm) of [(2*E*,4*S*)-4-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-hydroxypent-2-en-1-yl]phosphonic acid (4.57).



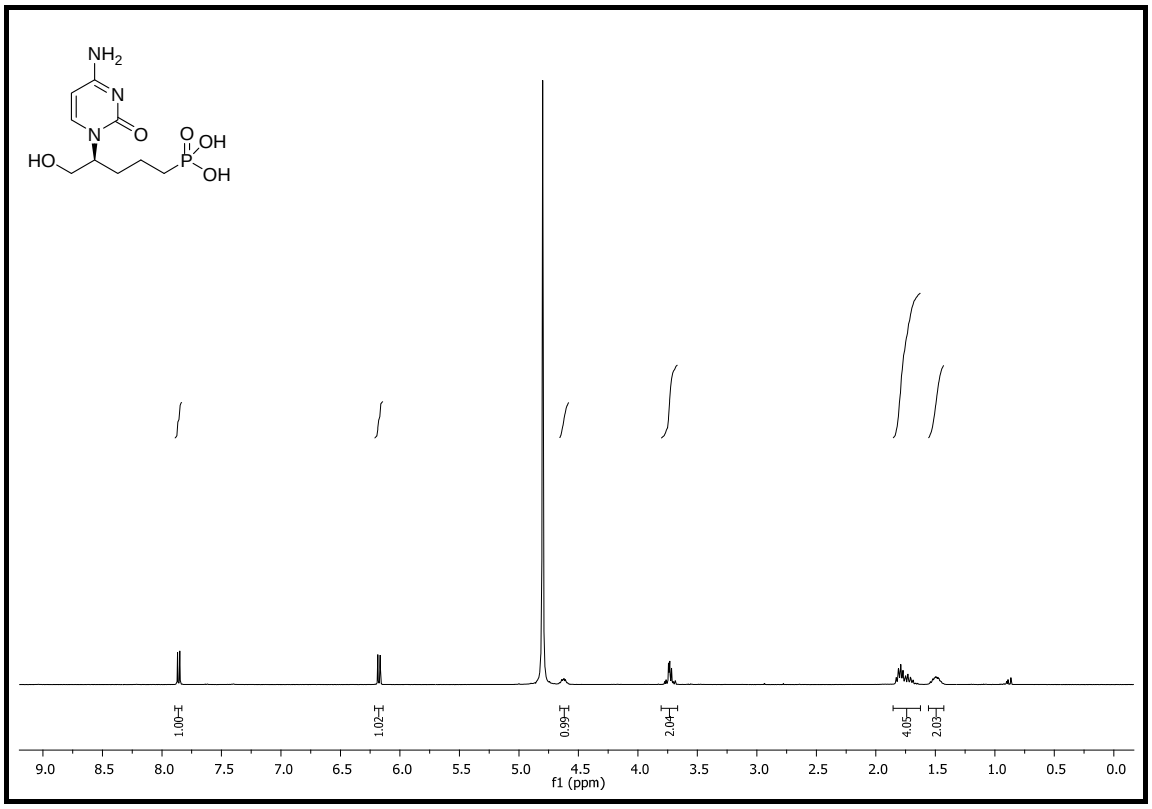
^{1}H NMR (D_2O, 400 MHz, δ in ppm) of [(2*E*,4*S*)-4-(6-amino-9H-purin-9-yl)-5-hydroxypent-2-en-1-yl]phosphonic acid (4.58).



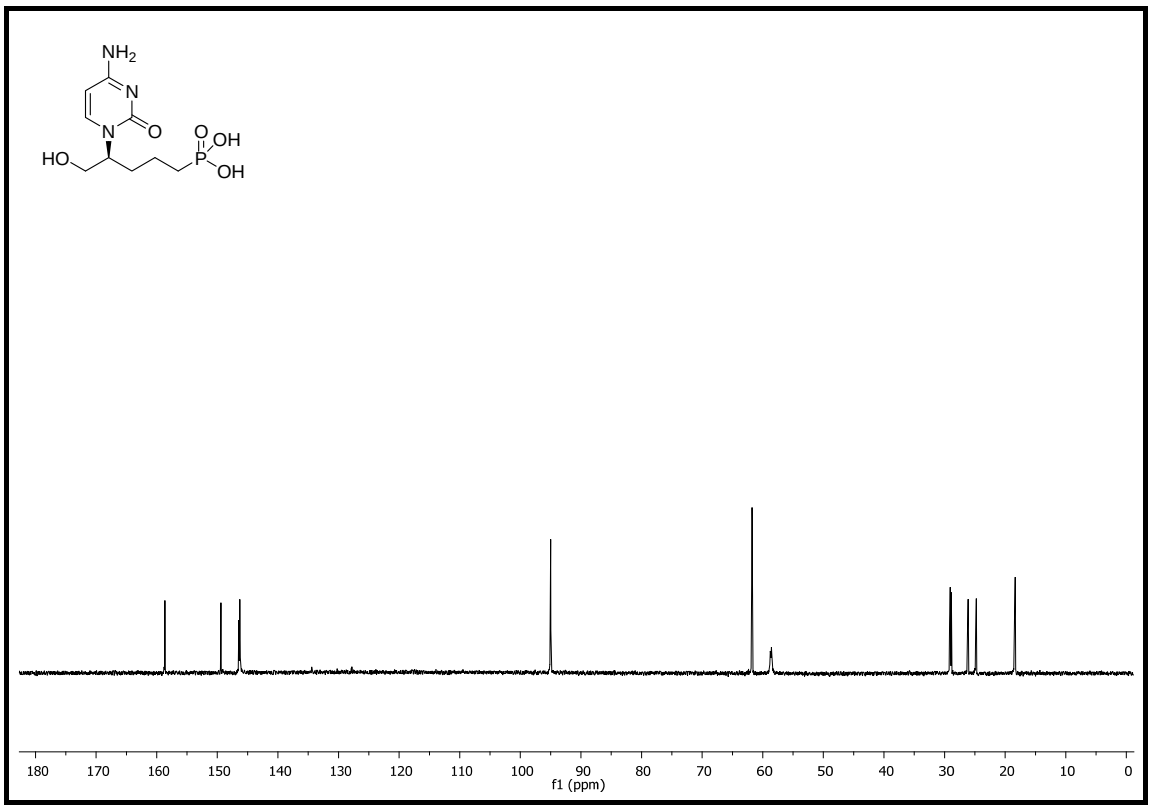
^{13}C NMR (D_2O, 100.6 MHz, δ in ppm) of [(2*E*,4*S*)-4-(6-amino-9H-purin-9-yl)-5-hydroxypent-2-en-1-yl]phosphonic acid (4.58).



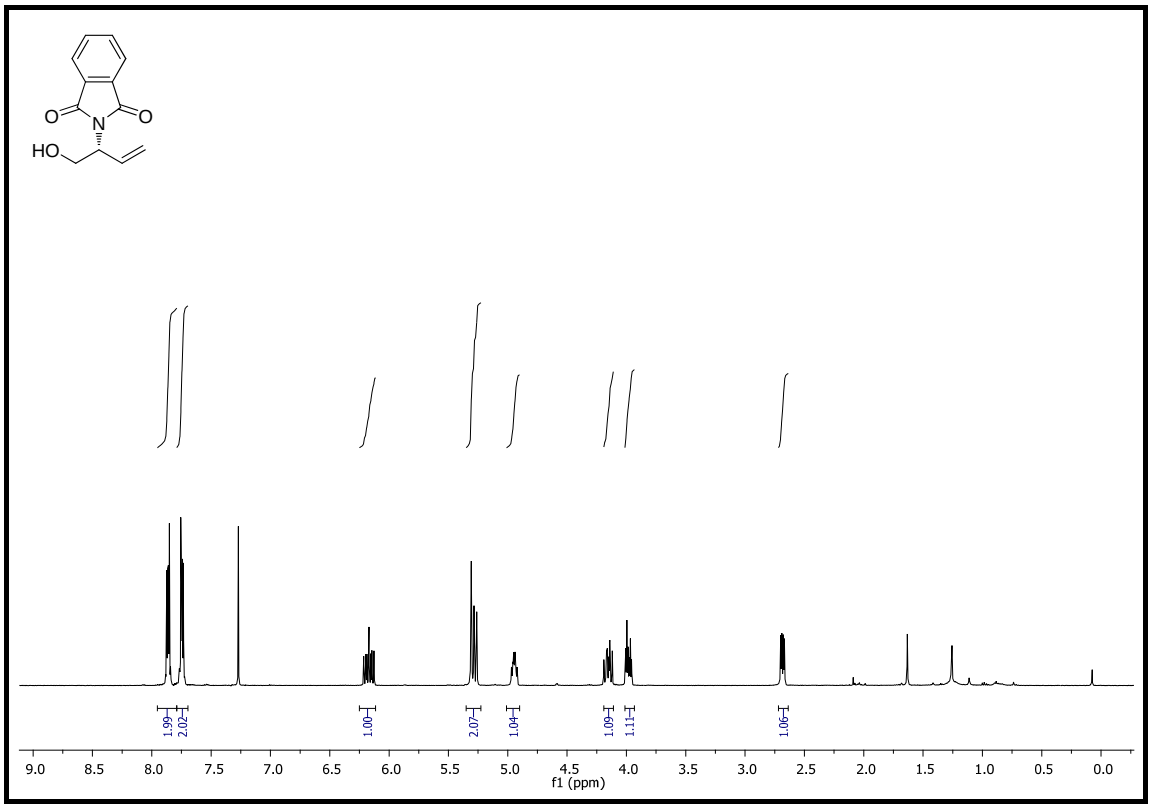
^{1}H NMR (D_2O, 400 MHz, δ in ppm) of [(4S)-4-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-hydroxypentyl]phosphonic acid (4.59).



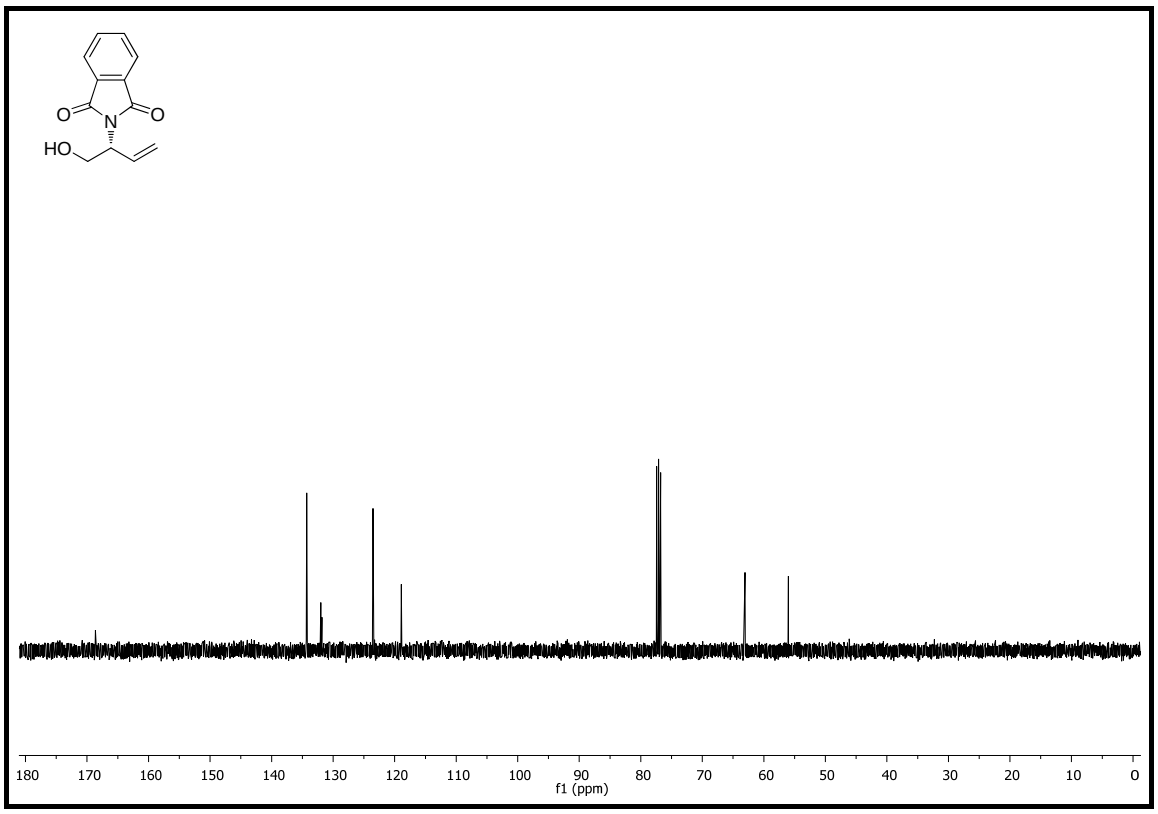
^{13}C NMR (D_2O, 100.6 MHz, δ in ppm) of [(4S)-4-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-5-hydroxypentyl]phosphonic acid (4.59).



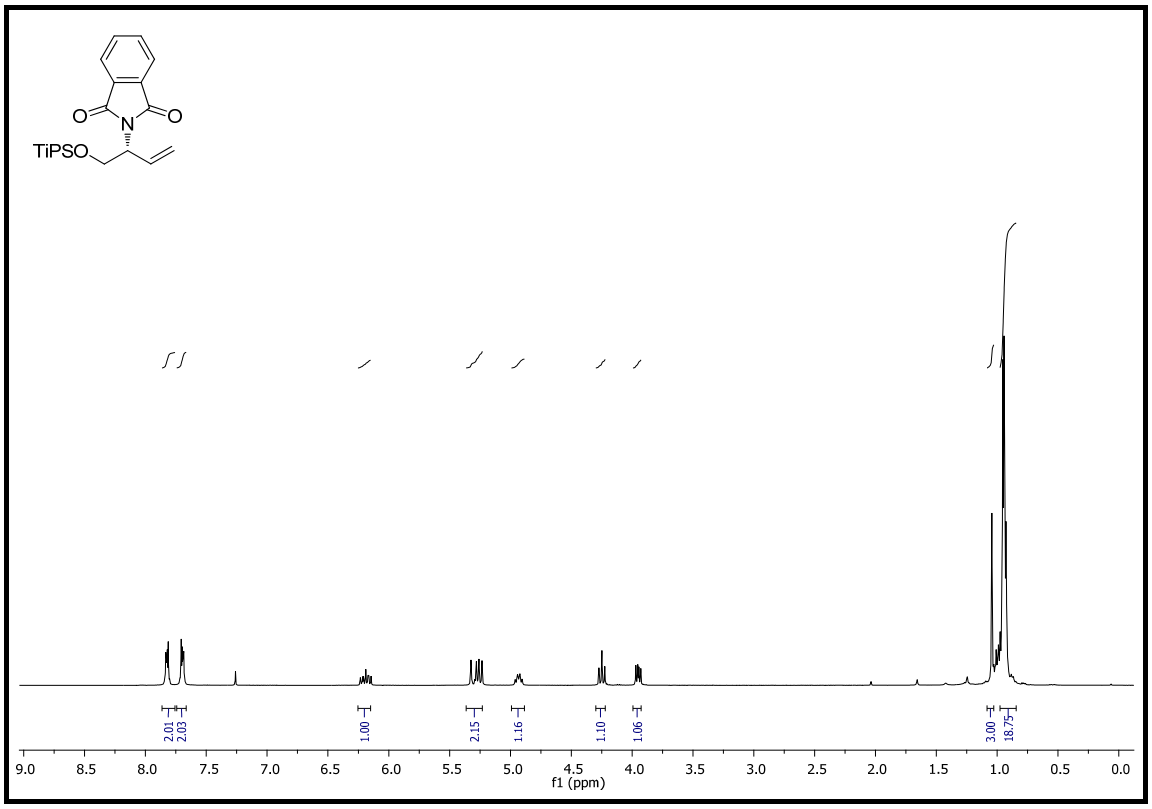
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*R*)-Phthalimido-3-buten-1-ol (5.34)



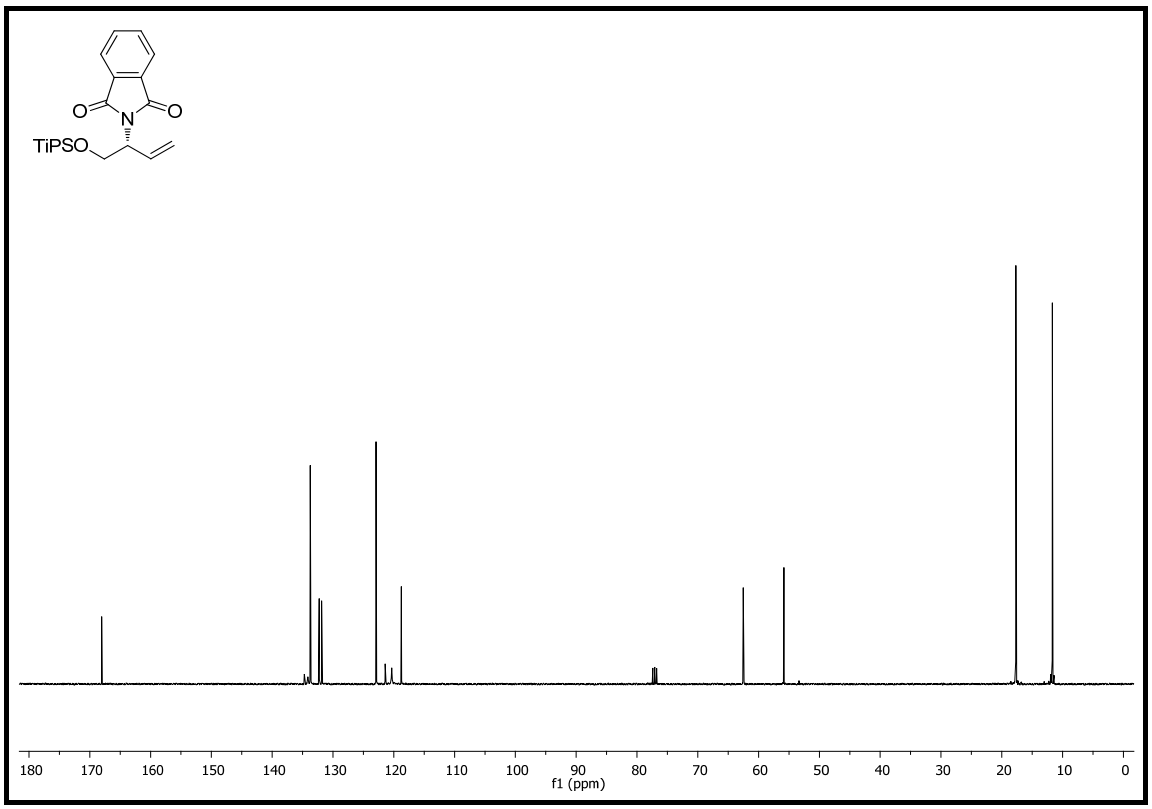
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*R*)-Phthalimido-3-buten-1-ol (5.34)



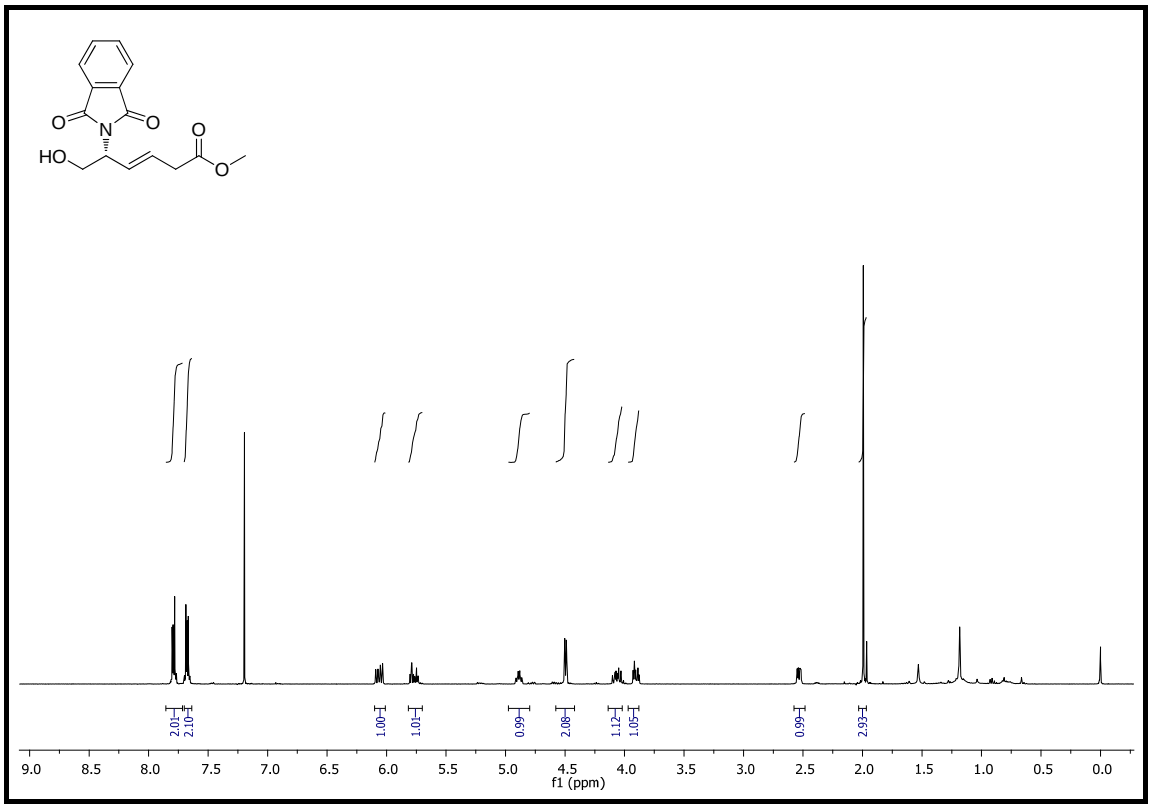
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*R*)-1-*tri*-Isopropylsilyloxy-2-phthalimido-3-butene (5.35).



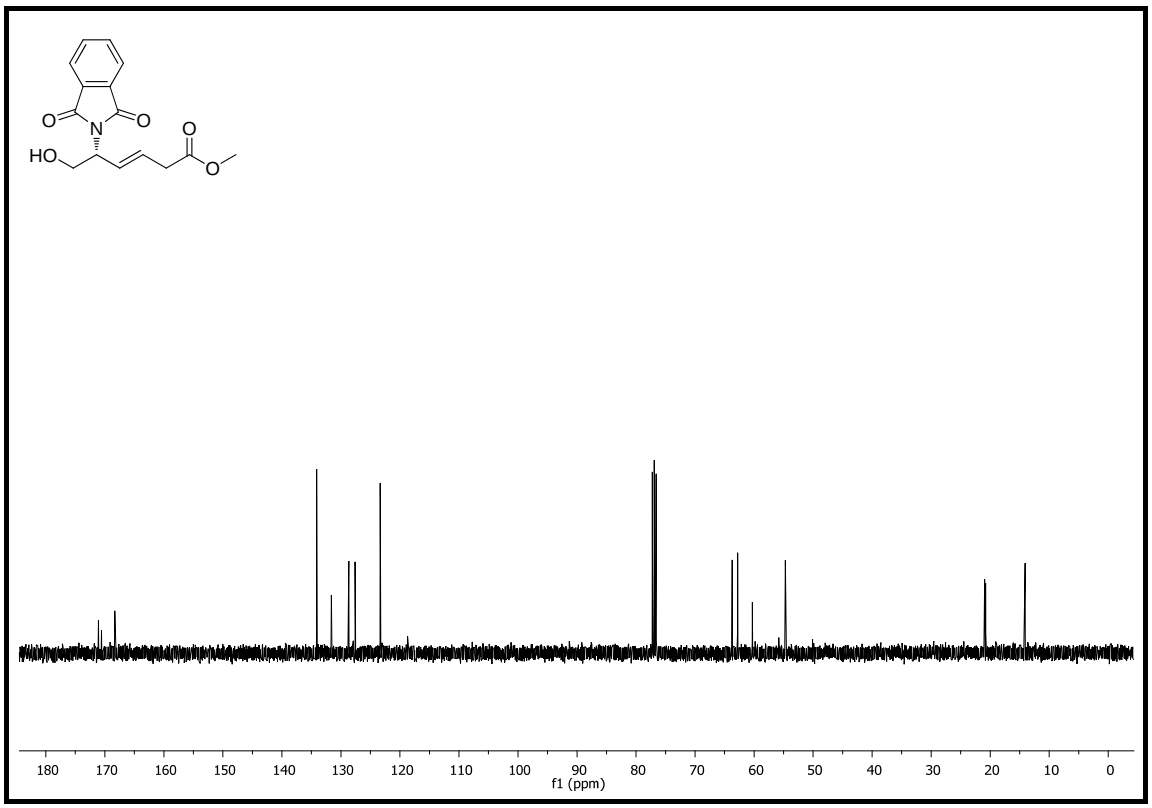
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of (2*R*)-1-*tri*-Isopropylsilyloxy-2-phthalimido-3-butene (5.35).



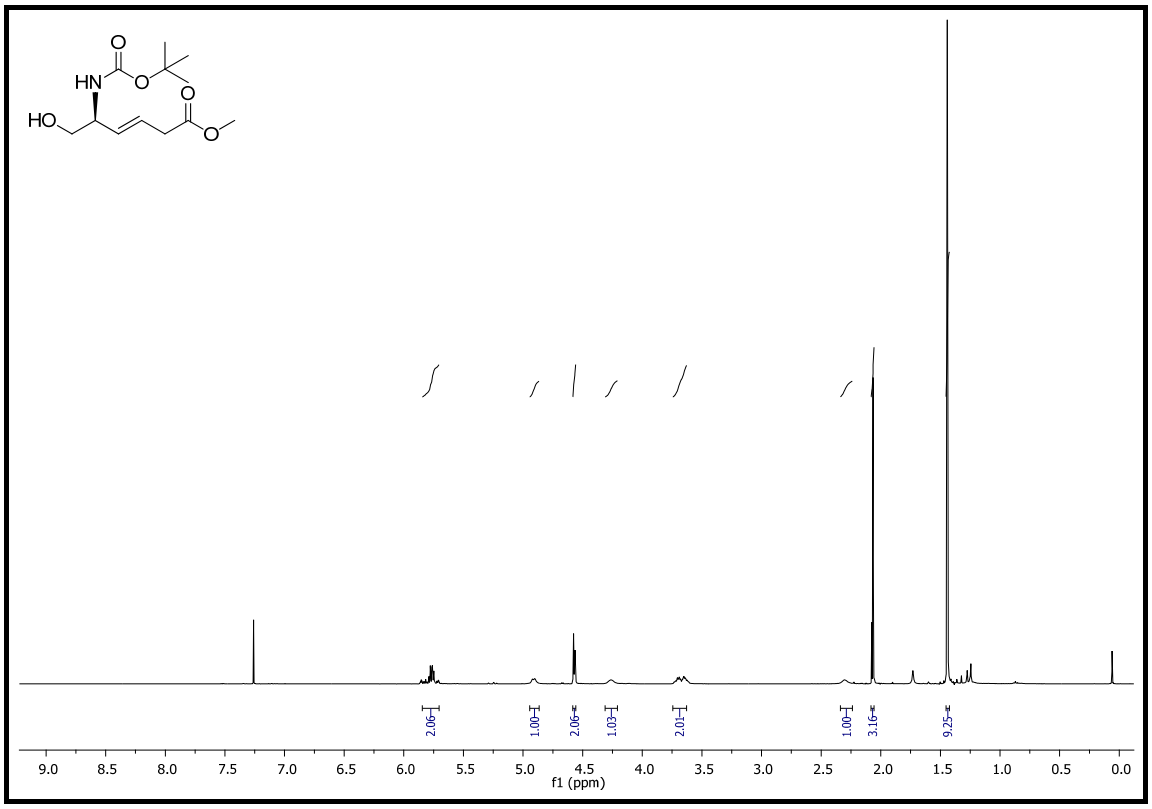
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of Methyl (2*R*,2*E*)-5-phthalimido-6-hydroxyhex-3-enoate (5.43).



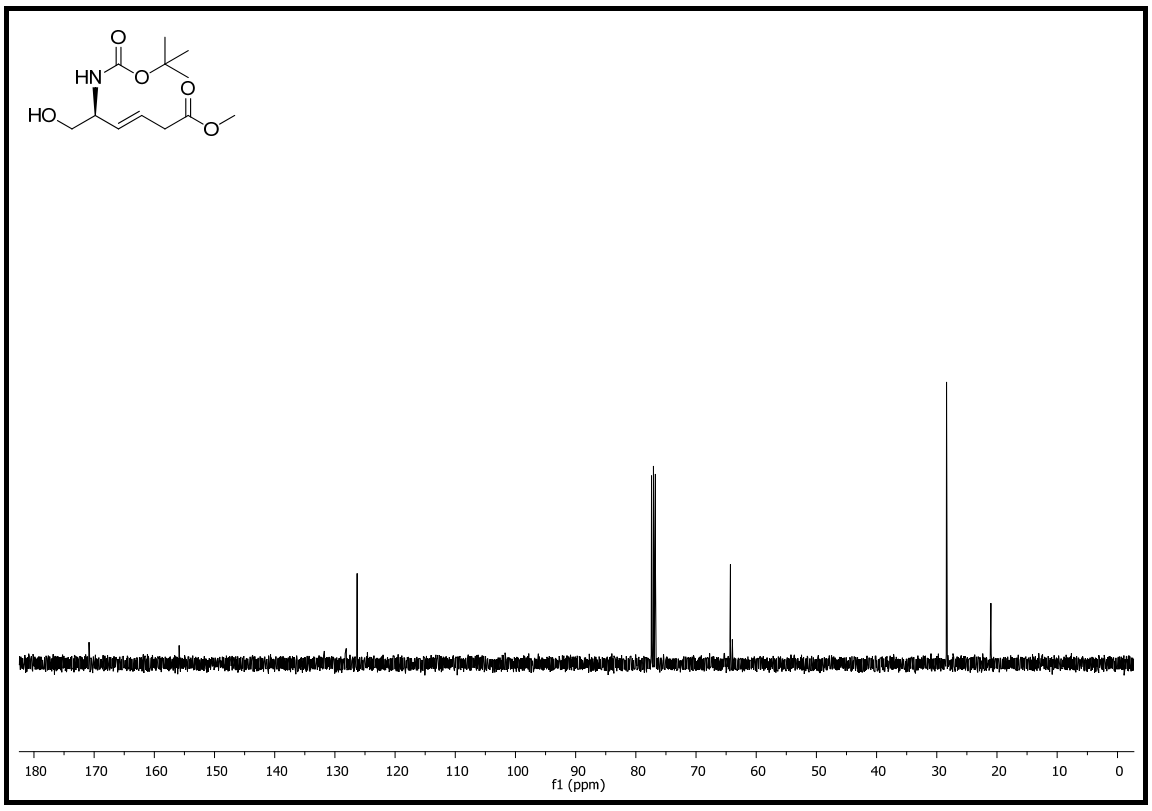
^{13}C NMR ($CDCl_3$, 100.6 MHz, δ in ppm) of Methyl (2*R*,2*E*)-5-phthalimido-6-hydroxyhex-3-enoate (5.43).



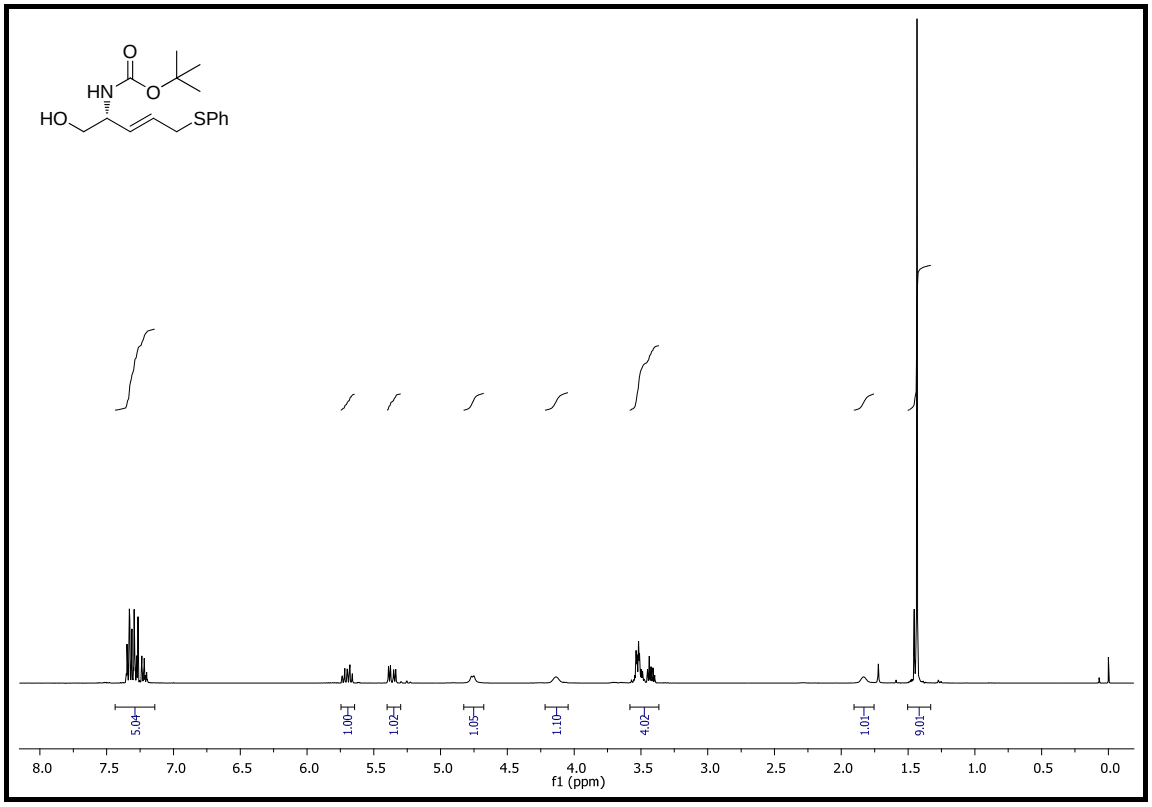
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of Methyl (3*E*,5*R*)-5-*tert*-butoxycarbonylamino-6-hydroxy-hex-3-enoate (5.46).



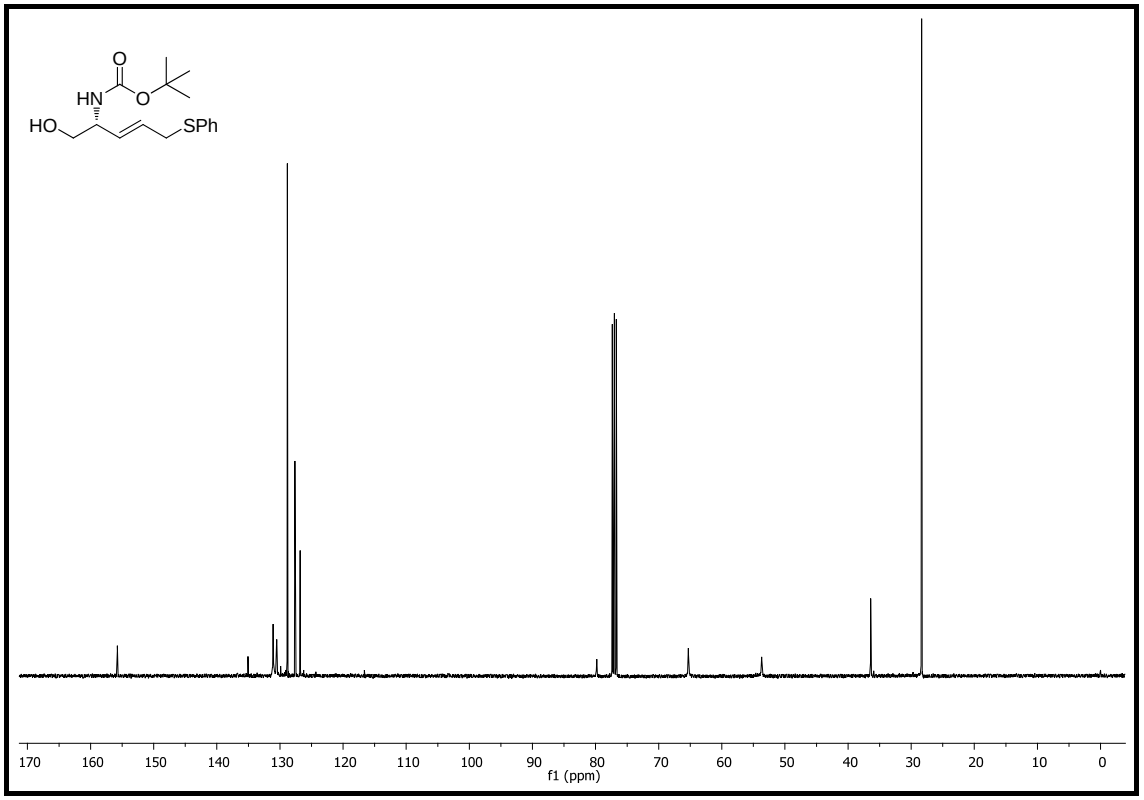
^{13}C NMR ($CDCl_3$, 400 MHz, δ in ppm) of Methyl (3*E*,5*R*)-5-*tert*-butoxycarbonylamino-6-hydroxy-hex-3-enoate (5.46).



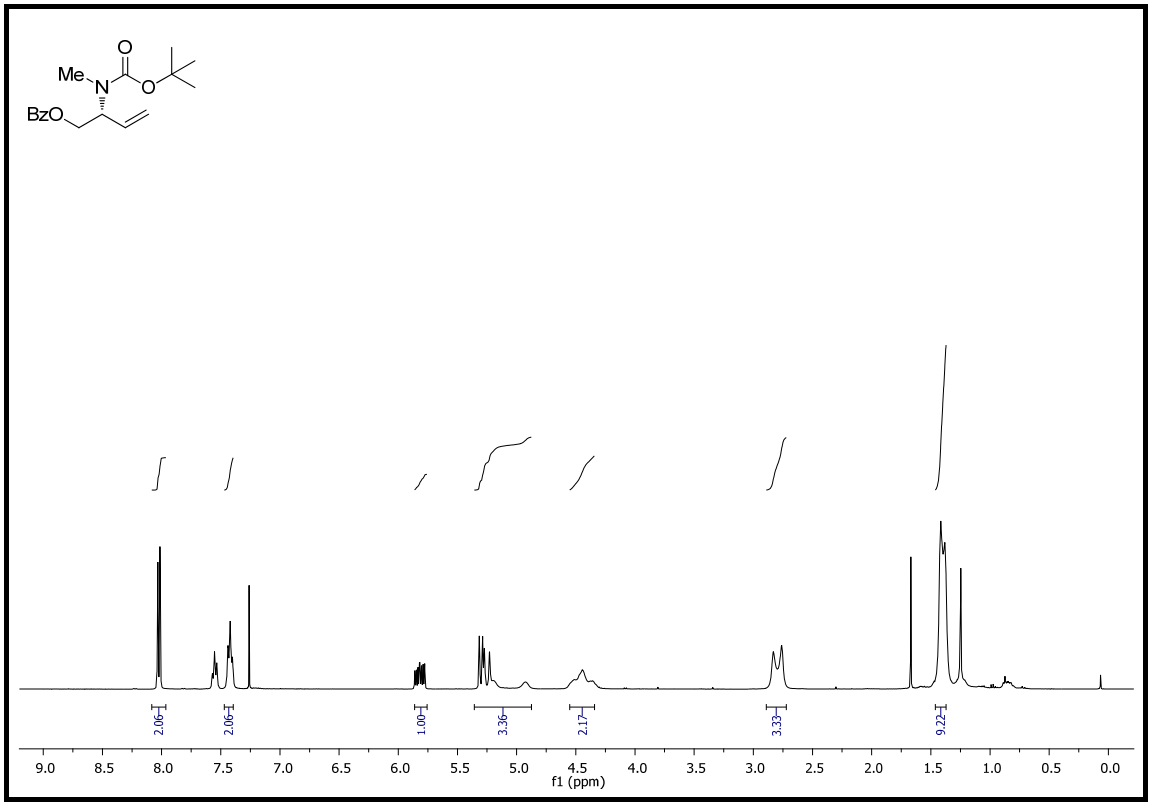
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*R*,3*E*)-2-(*tert*-Butoxycarbonyl)amino-1-hydroxy-5-(phenylsulfanyl)pent-3-ene (5.48).



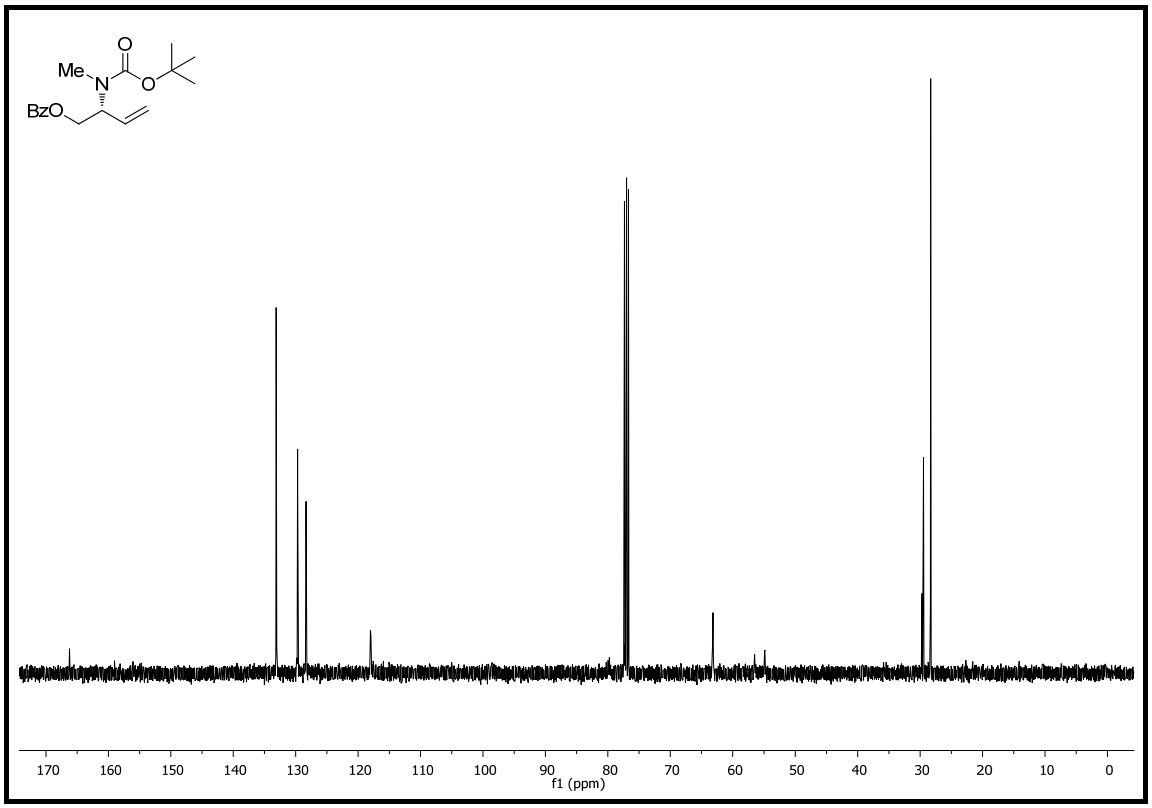
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*R*,3*E*)-2-(*tert*-Butoxycarbonyl)amino-1-hydroxy-5-(phenylsulfanyl)pent-3-ene (5.48)



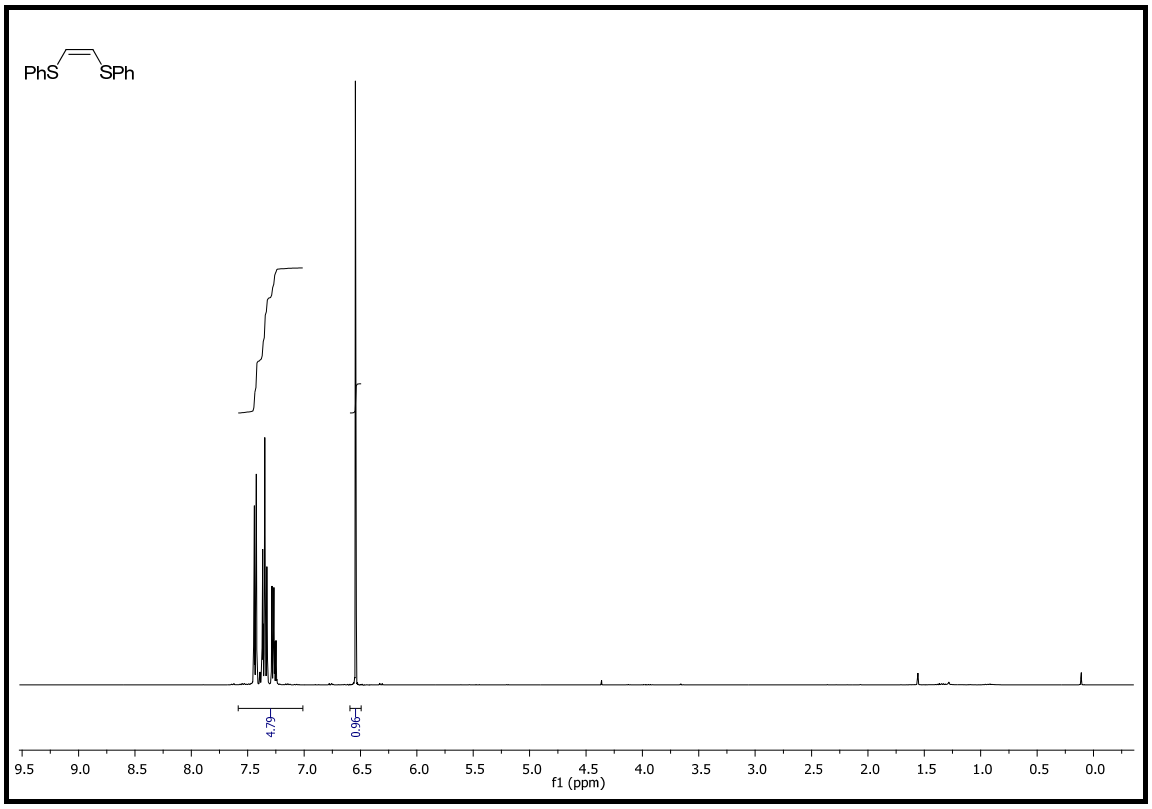
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*R*)-2-(*tert*-butoxycarbonyl-methyl)-amine-but-3-en-1-yl benzoate (5.50).



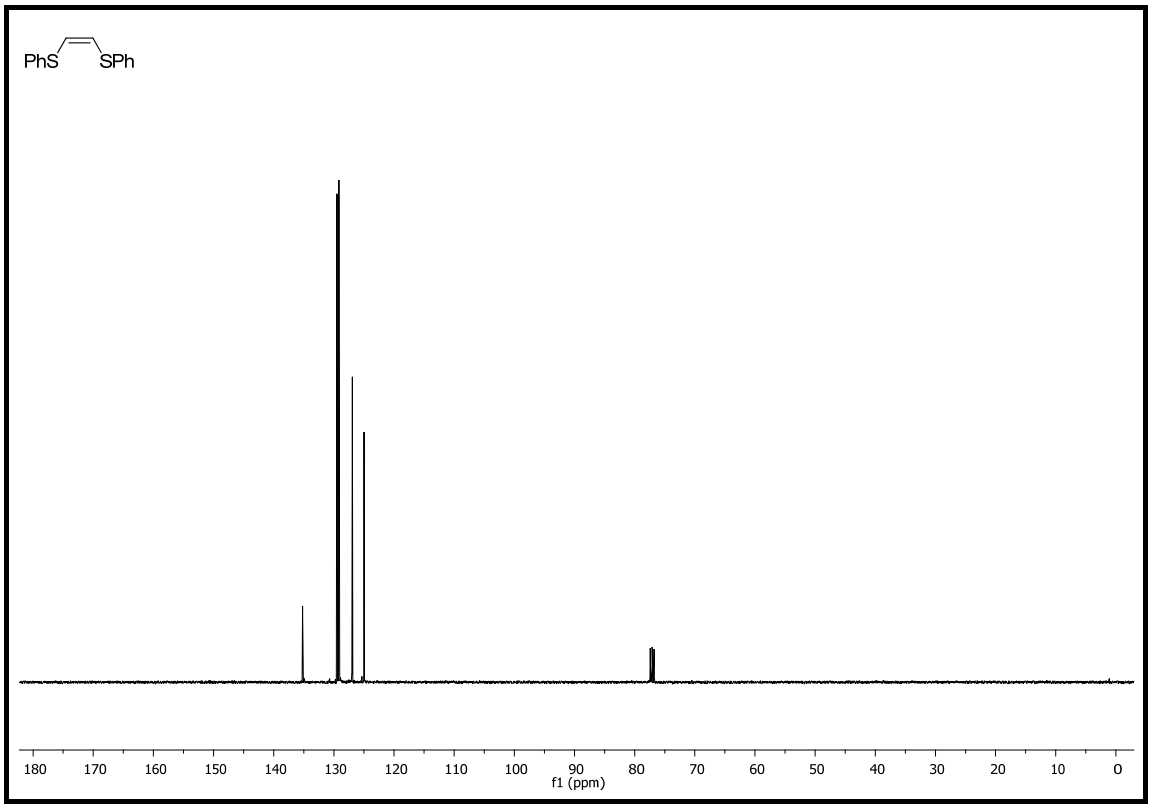
^{13}C NMR ($CDCl_3$, 400 MHz, δ in ppm) of (2*R*)-2-(*tert*-butoxycarbonyl-methyl)-amine-but-3-en-1-yl benzoate (5.50).



^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm) of *(Z)*-1,2-bis-(phenilthio)ethene (5.63).



^{13}C NMR ($CDCl_3$, 400 MHz, δ in ppm) of *(Z)*-1,2-bis-(phenilthio)ethene (5.63).



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