Rien ne se perd, rien ne se crée, tout se transforme.

- Antoine Lavoisier

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GHENT UNIVERSITY

FACULTY OF BIOSCIENCE ENGINEERING

Synthesis and reactivity study of allenylphosphonates and aminoallenylphosphonates

ir. Jan Berton

Thesis submitted in fulfilment of the requirements for the degree of doctor (PhD) of Applied Biological Sciences: Chemistry and Bioprocess Technology

Dutch translation of the title:

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Antoine Laurent Lavoisier (1743–1794) and His Wife (Marie Anne Pierrette Paulze, 1758–1836) by Jacques Louis David (1748-1825), 1788, Metropolitan Museum of Art, New York.

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The author,

ir. Jan Berton

The promoter,

Prof. dr. ir. Christian Stevens

Woord vooraf

Het woord vooraf. De laatste paragrafen die de auteur schrijft, de enige die van menig lezer de aandacht weten te trekken. Ook wel de leukste om te schrijven aangezien het een moment van terugblikken is en dat terugblikken gebeurt met een glimlach op het gezicht dankzij de collega's, vrienden en familie die van de voorbije zes jaar een zeer aangename periode hebben gemaakt.

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pour rejoindre votre équipe et travailler sur un nouveau sujet. C'est dommage que ça se soit passé aussi vite, mais j'ai beaucoup appris de cette expérience internationale. Merci beaucoup pour votre excellent encadrement! Prof. Kristof Van Hecke wil ik graag bedanken om ons de mogelijkheid te geven X-ray analyses te laten uitvoeren, terwijl het labo van Prof. Lieve Naesens het mogelijk maakte enkele van mijn verbindingen te screenen in antivirale testen. De samenwerking was stukken vlotter dan het obligate papierwerk tussen twee verschillende instituten en nogmaals hartelijk bedankt om spoed te steken achter de laatste testen, zodat ik die ook nog in mijn manuscript kon inpassen.

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Jan

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List of Abbreviations

A^3 coupling	aldehyde-amine-alkyne coupling
ACE	angiotensin converting enzyme
ATP	adenosine triphosphate
Alk	alkyl
aq.	aqueous
BINOL	1,1'-bi-2-naphtol
Boc	*tert*-butyloxycarbonyl
BPO	benzoyl peroxide
calcd	calculated
CAN	ceric ammonium nitrate
cat.	catalytic
Cbz	carboxybenzyl
CM	complex mixture
Cp	cyclopentadienyl
dba	dibenzylideneacetone
dppb	1,4-bis(diphenylphosphino) butane
DBP	dibenzylphosphite
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEP	diethyl phosphite
DNA	deoxyribonucleic acid
DMI	1,3-dimethyl-2-imidazolidinone
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMTMSP	dimethyl trimethylsilyl phosphite
dr	diastereomeric ratio
e.g.	exempli gratia
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EDG	electron donating group
equiv	equivalent
ESI	electrospray ionization
EWG	electron withdrawing group
f.i.	for instance
FDA	Food and Drug Administration
GC-MS	gas chromatography mass spectrometry
Gly	Glycine
HBV	Hepatis B Virus
HCMV	Human cytomegalovirus

HIV/AIDS	human immunodeficiency virus/acquired immunodeficiency syndrome
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMF	hydroxymethylfurfural
HSV	Herpes Simplex Virus
HSQC	heteronuclear single-quantum correlation spectroscopy
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
IC_{50}	half maximal inhibitory concentration
IR	infrared
kt	kamertemperatuur
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LPDE	lithium perchlorate diethyl ether
*m*CPBA	3-chloroperbenzoic acid
MS	mass spectrometry *or* molecular sieves
Ms	methanesulfonyl
MW	microwave
n-BuLi	*n*-butyllithium
NBS	*N*-bromosuccinimide
ND	not determined
NFM	*N*-formyl morpholine
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile
NuH	protic nucleophile
on	overnight *or* overnacht (*ca*. 16h)
phen	phenantroline
Phth	phthaloyl
PMB	*para*-methoxybenzyl
PTC	phase transfer catalyst
pTLC	preparative thin layer chromatography
*p*TsOH	*para*-toluenesulfonic acid
Py	pyridine
quant.	quantitative
RCM	ring-closing metathesis
RNA	ribonucleic acid
RP	reversed phase
rt	room temperature
SM	starting material
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

T	temperature
t	time
TSAO-T	[2',5'-bis-*O*-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]-3'-spiro-5"-(4-amino-1",2"-oxathiole-2",2"-dioxide) thymine
TEBAC	benzyltriethylammonium chloride
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TLC	thin layer chromatography
Ts	*para*-toluenesulfonyl
UV	ultraviolet
WHO	World Health Organization
wt%	weight-weight percentage
X_2	molecular halogen
Δ	reflux temperature

Introduction and Goals

Chemistry is all around us. Protons, neutrons and electrons make up elements, elements combine to molecules and monomeric molecules form the polymers of which our plastic bags, house insulation, or even our delicious French fries are made of. Life also equals chemistry. Other than that carbohydrate (starch) in potatoes, molecules combine to make peptides and lipids. Peptides, originating from information embedded in each species' DNA code, assemble to bigger units: proteins. Proteins make up enzymes which regulate numerous critical processes such as digestion in the human body, providing it with the required energy we ingest from the food we consume. Phospholipids on the other hand make up the cell membrane, holding the cell and its constituents together.

But what are these macromolecules chemically made of? Almost 99% of human body mass consists of six elements: carbon, hydrogen, oxygen, nitrogen, calcium and phosphorus. While water (H and O), proteins (C, H, O and N), carbohydrates and lipids (C, H, O) mainly consist of just four elements, other constituents of the human body contain calcium (mainly in hydroxyapatite, a mineral in the bone matrix) and phosphorus (again in hydroxyapatite, but also in DNA, RNA and phospholipids) atoms (Figure 1).[1]

Figure 1: Elemental composition of the human body by mass (left), 'The Alchemist Discovering Phosphorus' by Joseph Wright of Derby (right).

Phosphorus was the unlucky 13th element to be discovered, more than a hundred years before oxygen, and first synthesized in 1669 by the German alchemist Brandt. In his unsurprisingly unsuccessful quest for the philosopher's stone, a substance that would turn inexpensive metals such as copper or zinc into gold, *Herr Doktor* Brandt - as he wished to be called - found one night in Hamburg that upon intensively heating copious amounts of urine, a glow-in-the-dark material was obtained (Figure 1). Unknowingly, he had prepared elemental phosphorus, from the phosphate excreted in urine. The glowing properties did not originate from phosphorescence, the phenomenon where certain materials emit light at a reduced intensity

after they have been charged with intense light, but from a chemiluminescent reaction. White phosphorus, one of the allotropes of elemental phosphorus, reacts with oxygen, simultaneously emitting light. Other researchers later correctly observed that phosphorus can be made from several other living – plant or animal – materials, such as mammals, fish, birds, plants and trees. The association of phosphorus with life had been demonstrated for the first time.[2]

Phosphorus is indeed involved in important biological processes. Phosphorylation of sugars is the first step in their catabolism, eventually providing the cell with energy in the form of ATP.[3] ATP, adenosine triphosphate, is known as the energy carrier of the cell, as it is constantly being used and replenished in numerous transformations that require energy in living beings. The creation and scission of phosphorus-oxygen bonds in phosphates illustrates that the P-O bond is a highly energetic bond, which is easily hydrolysable. In organophosphorus compounds, at least one of those P-O bonds has been replaced by a bond between phosphorus and carbon, which is resistant to hydrolysis. This important feature has led to the development of several phosphonate-containing drugs. Twelve of the twenty-four FDA-approved phosphorus-containing drugs belong to the family of phosphonates and phosphonic acids.[4]

What makes organophosphorus compounds such interesting targets? First of all, organophosphorus natural products have been a rich source for agricultural and medicinal applications. Ciliatine **1**, 2-aminoethyl phosphonic acid, was the first phosphonate natural product to be isolated (Figure 2). Between its discovery in 1959 and 2013, twenty-two more naturally occurring phosphonate (containing one P-C bond) and phosphinate (containing two P-C bonds) small molecules were isolated, every single one of them displaying biological activities. Bioassays showed that they inhibit bacterial and fungal growth or prevent seed germination. Three of those natural products – fosfomycin **2**, bialaphos **3** and phosphinotricin **4** – have been commercialized as a drug or a biotechnological product. In addition to that, fosmidomycin **5** and its *N*-acetylated analogue FR900098 **6** have been tested in clinical trials against *Plasmodium*, for the treatment of malaria.[5] Very recently, an intensive genome mining program, allowed the isolation and identification of nineteen more phosphonate natural products.[6]

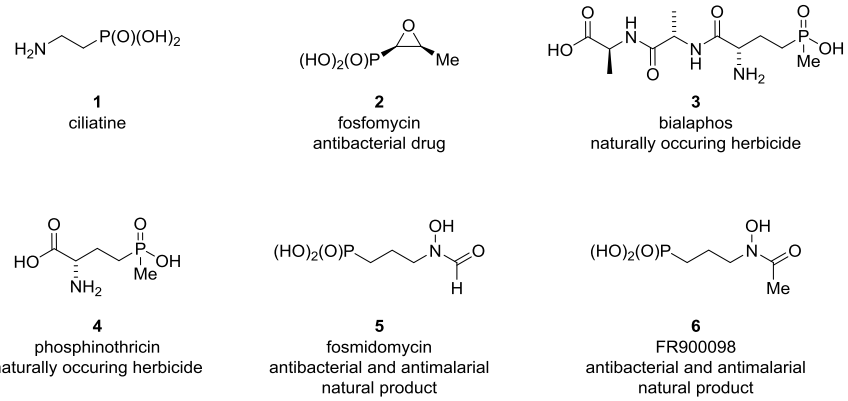
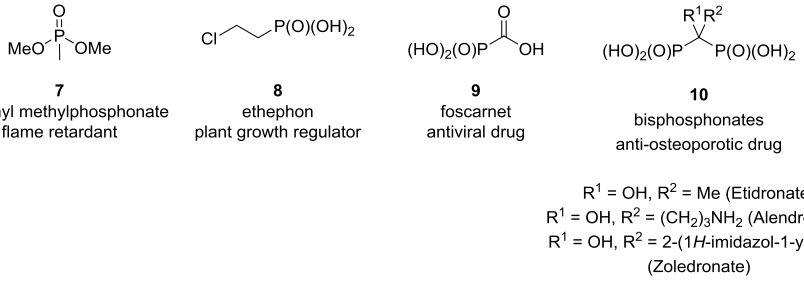


Figure 2: Examples of phosphonic and phosphinic acid natural products.

Apart from phosphonate natural products, a great deal of synthetic phosphonates have been prepared. Because of their chelating properties, phosphonates are used as water-softening and anti-scaling agents in cooling water systems, preventing iron or steel corrosion.[7, 8] These chelating properties also make them peroxide bleach stabilizers in the pulp and paper manufacturing industry, by complexing the metals that would otherwise inactivate the peroxide.[9] These three features are the reason why they are widely used in detergents as well.[10] One of the most simple phosphonates is dimethyl methylphosphonate **7** and is used commercially as a flame retardant (Figure 3).[11] Bayer Crops Science's ethephon **8** is the most widely used plant growth regulator and has greatly facilitated the production of cotton. It releases ethylene upon plant metabolism, which regulates plant growth and ripeness.[12] Importantly, phosphonates are characterized by low aquatic toxicities and are readily biodegraded, as certain soil bacteria have evolved to metabolize phosphonates, probably because of the presence of phosphonate natural products in the environment.[13]

Another very small phosphonate is foscarnet **9**, an antiviral medication approved in 1991 for the treatment of herpes (HSV-1 and HSV-2) and human cytomegalovirus (HCMV) retinitis and is particularly of interest in infections where resistance against other antiviral agents has developed.[14-16] Bisphosphonates **10**, developed in the 19th century and initially used to soften water in irrigation systems, were investigated in the 60s for the treatment of bone diseases such as osteoporosis.[17] In the 90s, their mechanism of action was demonstrated, preventing osteoclasts from destroying bone, a process that inevitably occurs in the body upon aging. Currently, ten bisphosphonate drugs are marketed worldwide.[18]



7
dimethyl methylphosphonate
flame retardant

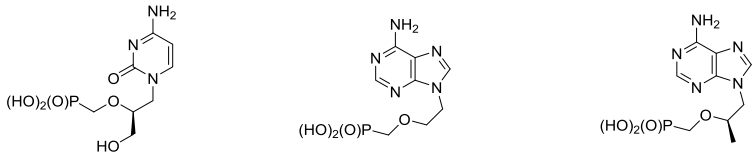
8
ethephon
plant growth regulator

9
foscarnet
antiviral drug

10
bisphosphonates
anti-osteoporotic drug

Figure 3: Examples of marketed phosphonate and phosphonic acid compounds.

Cidofovir **11**, adefovir **12** and tenofovir **13** are three acyclic nucleoside phosphonates that have acquired a prominent position in the treatment of antiviral diseases (Figure 4). Cidofovir **11** has been licensed for the treatment of HCMV retinitis in AIDS patients by terminating viral DNA chain elongation. Adefovir **12** was eventually approved by the FDA as treatment for HBV infections (chronic hepatitis B). Since 2001, tenofovir **13** has been licensed for the treatment of HIV infections and is marketed as a single drug (Viread®) or in combinatorial therapies (Truvada® or Atripla™). These one pill daily drugs are considered a real breakthrough in the management of HIV infections, being much more effective than the twenty something pills, HIV-cocktails used to consist of.[19] Tenofovir has also been approved for prophylactic use, effectively protecting individuals from contracting HIV.[20]



11
cidofovir
HPMPC, Vistide®

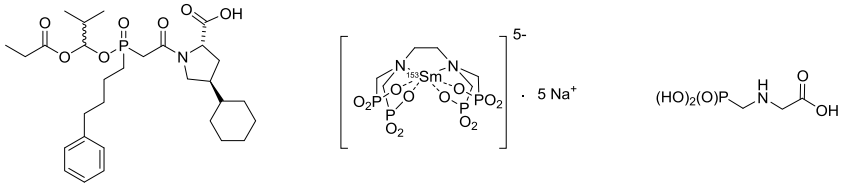
12
adefovir
PMEA, Hepsera®

13
tenofovir
PMPA, Viread®

Figure 4: Structures of nucleoside phosphonic acids marketed as antiviral drugs.

Aminophosphonates are the phosphonic acid analogues of amino acids, although they differ in terms of acidity (more acidic than the corresponding amino acids), size (bigger steric hindrance) and shape (carboxylates are planar whereas phosphonates are tetrahedral). The phosphonate moiety successfully mimics the tetrahedral intermediate that is formed when the amide bond in peptides is being hydrolyzed. Aminophosphonates can thus act as inhibitors of these enzymes, a phenomenon that is well described for metalloproteases. This strategy has resulted in the development of fosinopril **14** (Figure 5), a phosphinate antihypertensive drug, which inhibits angiotensin I converting enzyme (ACE). The chelated complex samarium (^{153}Sm) lexidronam **15** (trade name Quadramet) contains several phosphonate groups, which

effectively chelate a samarium radioisotope, used for pain relief when cancer has spread to the bone. It is preferentially absorbed where the bone has been invaded by cancer, killing nearby cells through emission of β-particles.[21, 22] Glyphosate **16** (commercialized by Monsanto as Roundup in the 70s) also belongs to the class of aminophosphonates, and has been used on an enormous scale as a herbicide.[23] Although glyphosate and its formulations have been approved by regulatory bodies all over the world, it is still met with criticism regarding toxicity to mammals and environmental risks.[24] At present there is no consensus about its toxicity as the WHO concluded in 2015 that glyphosate is "probably carcinogenic in humans",[25] while the EFSA's assessment in the same year said that "the substance is unlikely to be genotoxic (i.e. damaging DNA) or to pose a carcinogenic threat to humans."[26] June 2017, the EFSA and ECHA again came to the conclusion that "there is no reason to doubt the toxicity studies stating that glyphosate is not carcinogenic."[27]



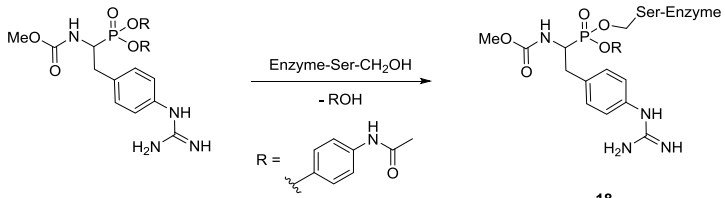
14
fosinopril
antihypertensive drug

15
samarium (^{153}Sm) lexidronam
pain killer in cancer treatment

16
glyphosate
(trade name Roundup)

Figure 5: Examples of marketed aminophosphinates and aminophosphonic acids.

Aminophosphonates can also irreversibly bind enzymes, as has been showcased for proteases with a serine residue in the catalytic center. P-Terminal amino acids and peptide diaryl phosphonates can transesterify the serine residue, effectively preventing the enzyme to interact with its normal substrate through its covalent bonding mode. This approach has resulted in the synthesis of inhibitors of proteases, involved in several diseases such as hypertension, type 2 diabetes and cancer. Diaryl aminophosphonate **17**, for instance, successfully inhibits uPa (Urokinase-type plasminogen activator), a key serine protease involved in tumor cell invasion and metastasis (Scheme 1).[28]



17
IC_{50} = 3.4 nM

18

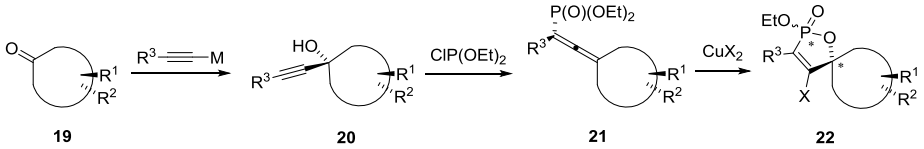
Scheme 1: Inhibition of uPa (urokinase-type plasminogen activator) by irreversible enzyme inhibition.

For almost two decades, the development of new methodologies for the synthesis of phosphonylated azaheterocycles and aminophosphonates has been one of the major research topics of the SynBioC Research Group of the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering at Ghent University.[29-33] This has resulted in the synthesis of a variety of phosphonylated compounds, such as aziridines,[34, 35] pyrrolidines,[36] benzazepines,[37] phosphonopyrroles,[38-40] bicyclic[41] and tricyclic[42] aminophosphonates, benzazocines,[43] oxazolidinones and imidazolidinones,[44] β-lactams,[45-47] γ-lactams,[48] benzocarbacephems,[49] isoindoles[50] and tetrahydroquinolines.[51]

Accordingly, the aim of this work was to synthesize an innovative type of highly functionalized building blocks, aminoallenylphosphonates, and to explore their potential as precursors to innovative aminophosphonates. Allenes are highly interesting building blocks, displaying a broad range of reactivities owing to their unique molecular structure of cumulated double bonds.[52, 53] They are excellent substrates for transition-metal-catalyzed cycloisomerizations and readily participate in cycloadditions.[54] They are, however, often underused because of their supposed low stability. Heteroatom substituents can bring about important changes in the electron density on the allene. Allenes bearing an *O*- or *N*-substituent are donor-substituted allenes, while allenes conjugated to a carbonyl group are classified as acceptor-substituted allenes. Moreover, heteroatoms such as *N* and *P* are present in important natural products and synthetic drugs. Hence, the synthesis of an allene, decorated with both a *N* and *P* substituent, would be highly interesting. Would this densily functionalized small molecule **25** (Scheme 4) behave as an acceptor- or donor-substited allene and what kind of reactivities would be possible? Amino-substituted allenes react with alcohols, thiols, and secondary amines to give 1,2-adducts[55] and react in [2 + 2] or [2 + 4] cycloadditions.[56] Amidoallenes, being less electron-rich, are hydroaminated through Lewis acid activation of the proximal double bond[57] or undergo alkoxylation at the α- or γ-position, but usually not at the β-position.[58] On the other hand, nucleophilic addition to acceptor substituted allenes usually takes place at the β-position. This is the case if the well-documented allenylphosphonates are reacted with nucleophiles, while they cyclize upon addition of electrophiles.

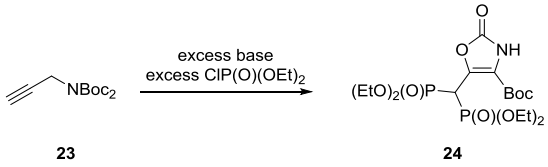
In a first chapter, cyclization of these allenylphosphonates – lacking a *N*-substituent – with electrophiles will be evaluated in the design of chiral spirocyclic oxaphospholenes **22**. Although achiral versions of these compounds have been prepared in the past, chiral spirocyclic oxaphospholenes have never been reported. These compounds could be of interest as novel chiral inducers in asymmetric synthesis, given their resemblance to BINOL phosphate catalysts and the configurational rigidity, produced by the spirocyclic backbone. The designed approach passes through allenylphosphonates **21**, which would be prepared from acetylide

addition to chiral pool ketoterpenes **19**, followed by treatment with $ClP(OEt)_2$ (Scheme 2). Upon addition of a Lewis acid, cyclization should occur, producing spirocycles **22**.



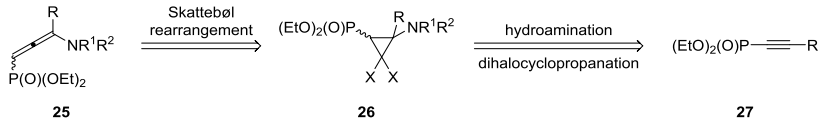
Scheme 2: Strategy towards chiral spirocyclic oxaphospholenes.

Secondly, a one-pot procedure for the preparation of bisphosphonomethyl oxazol-2-ones **24** will be investigated (Scheme 3). This transformation was discovered in preliminary research and was thought to pass through an aminoallenylbisphosphonate intermediate. The original procedure, however, suffered from low isolated yields. Nonetheless, these bisphosphonomethyl oxazol-2-ones **24** are of interest as they are unprecedented compounds that combine two interesting structural features. The hydrogenated counterparts, oxazolidin-2-ones, are known for their use as chiral auxiliaries and is also the pharmacophore in a variety of marketed drugs, while the bisphosphonomethyl motif is of huge importance in bisphosphonate drugs.



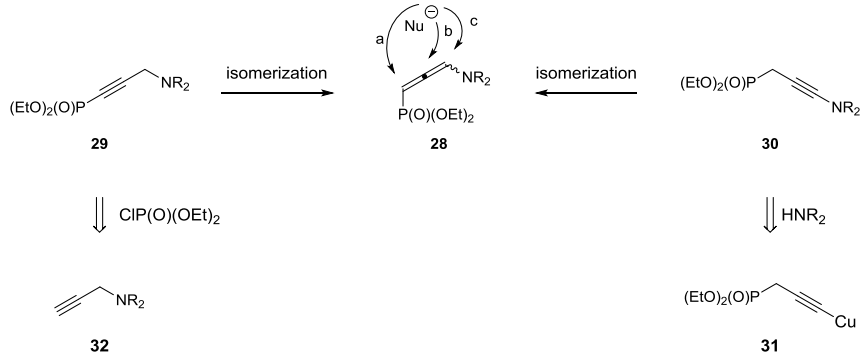
Scheme 3: One-pot synthesis of 5-bisphosphonomethyl oxazol-2-ones.

The third and fourth chapter of this research focuses on the preparation of 3- aminoallenylphosphonates **25** (Scheme 4). As not a single synthesis of these compounds had been reported at the start of this research, it was to be investigated if they could be prepared at all. A first strategy relied on the Skattebøl rearrangement, in which dihalocyclopropanes are transformed into allenes upon treatment with an organolithium reagent. The required dihalocyclopropyl aminophosphonates **26** will be prepared through dihalocarbene addition to enaminophosphonates. These precursors will be obtained through a copper-catalyzed hydroamination of alkynylphosphonates **27**.[59]



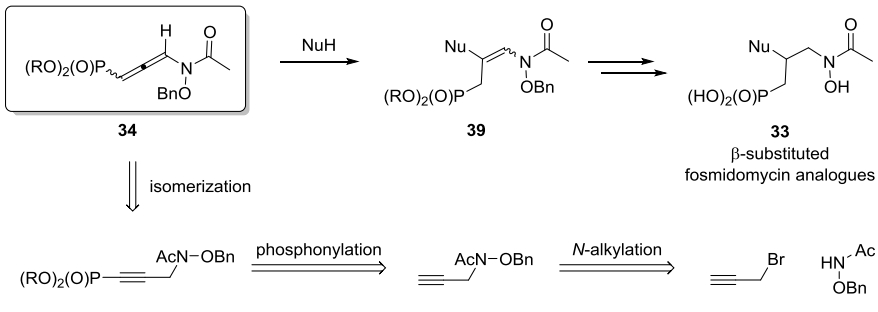
Scheme 4: Retrosynthetic approach towards 3-aminoallenylphosphonates *via* the Skattebøl rearrangement.

A second synthetic approach targets 3-aminoallenylphosphonates **28** through isomerization of 3-aminoprop-1-yn-1-yl phosphonates **29** or 3-aminoprop-2-yn-1-yl phosphonates **30** (Scheme 5). 3-Aminoprop-2-yn-1-yl phosphonates **30** should be accessible through a copper-catalyzed cross coupling reaction of copper acetylide **31** with a nitrogen nucleophile.[60] 3-Aminoprop-1-yn-1-yl phosphonates **29** will be prepared by phosphonylation of protected propargylamines **32** with diethyl chlorophosphate. In case these aminoallenylphosphonates **28** could be prepared, their reactivity will be evaluated. Since allenylphosphonates are known to undergo nucleophilic addition at the central β-carbon, while non-phosphonylated *N*-containing allenes react as nucleophiles themselves, it is not straightforward to predict the reactivity of this densily functionalized small molecule.



Scheme 5: Strategies towards 3-aminoallenylphosphonates starting from protected propargylamines or copper acetylides.

In a last, more exploratory part of this work, the synthesis of fosmidomycin-inspired antimalarial analogues **33** will be investigated (Scheme 6). As the 3-carbon linker between the phosphonate and the amino functionalities in aminoallenylphosphonates **28** corresponds to the motif found in fosmidomycin **5**, it was reasoned that aptly substituted aminoallenylphosphonates **34** could serve as a precursor to substituted fosmidomycin and FR900098 derivatives. This is of huge interest, given the developing resistance against currently available antimalarial drugs. In a retrosynthetic approach, it was anticipated that alkynylphosphonate precursor **35** could be prepared through phosphonylation of *N*-propargyl hydroxamate **36**, which in turn should be accessible from *O*-benzyl hydroxamic acid **37** and propargylbromide. Isomerization of alkynylphosphonate precursor **35** should then yield aminoallenylphosphonate **34**, which can ultimately be derivatized.



34 **39** **33**

β-substituted fosmidomycin analogues

35 **36** **38** **37**

Scheme 6: Retrosynthetic approach towards new fosmidomycin analogues *via* an aminoallenylphosphonate intermediate.

Literature Overview

Fifty years of (benz)oxaphospholene chemistry

As delineated in the Introduction and Goals, this work focuses on the preparation and reactivity of allenylphosphonates and aminoallenylphosphonates. Since the synthesis of the latter is still in its infancy, a short overview of the available literature will be given at the beginning of chapter 3 in the Results and Discussion. Since the huge number of existing reports on allenylphosphonates in literature and since these allenylphosphonates will be used to produce oxaphospholenes in chapter 1 of the Results and Discussion, the part Literature Overview of this work will be devoted to the existing synthetic entries into benzoxaphospholenes and oxaphospholenes.

1. Introduction

Organophosphorus compounds have attracted since long the attention of chemists because of their interesting biological properties.[61, 62] Aminophosphonates can serve as amino acid mimetics,[63] several bisphosphonates are marketed for the treatment of bone diseases[64] and phosphonate nucleoside analogues are important antiviral drugs. Tenofovir **13**, for instance, is used in the treatment of Hepatitis B and HIV/AIDS (Figure 6).[19] Phosphorus heterocycles, more specifically, are no longer laboratory oddities, but are of interest as ligands and as molecular components in electronic devices.[65] Ifosfamide and cyclophosphamide **40**, two phosphorus-containing heterocycles, were introduced on the market more than thirty years ago and are still used to date in the treatment of cancer.[4, 66] Oxaphospholenes **41**-**42**, five-membered heterocycles containing one double bond, one oxygen and one phosphorus atom, could be useful precursors for furanose carbohydrate mimics,[67] while the saturated oxaphospholanes **43** are bioisosteres of γ-butyrolactones. α-Methylene-γ-butyrolactones are structural motifs often found in natural products, which are associated with numerous biological activities.[68] Parthenolide **44** is an example of an α-methylene-γ-butyrolactone being evaluated as a potential anticancer treatment.[69] On the other hand, bactericidal,[70] insecticidal,[70] pesticidal,[70] herbicidal[71] and fungistatic[72] properties have been attributed to several benzoxaphospholes and phospholene oxides.

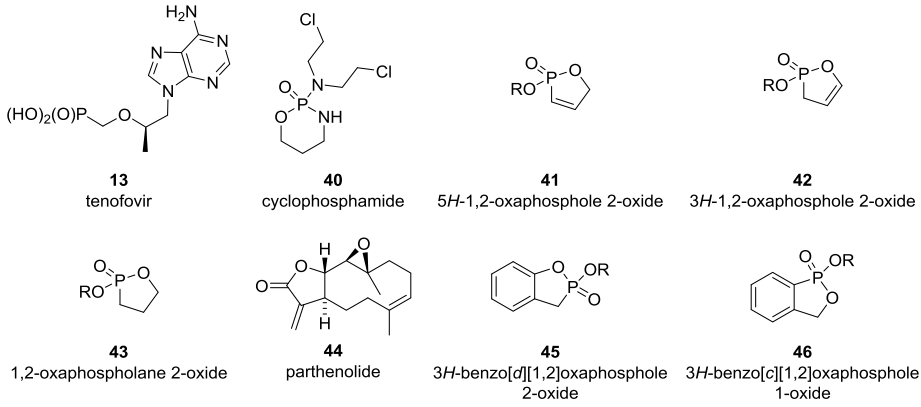


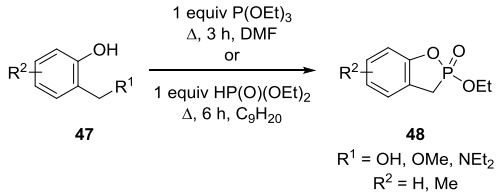
Figure 6: Structures of tenofovir, cyclophosphamide, different (benz)oxaphospholene isomers, an oxaphospholane and parthenolide.

This literature review will focus on oxaphospholenes with structures **41** and **42** and benzoxaphospholenes with structures **45** and **46**. Publications in which (benz)oxaphospholenes are formed as an intermediate and were not isolated, are not considered within the scope of this review. References dealing with the corresponding oxaphospholenic acids are not included either. The focus of this review is on the synthetic routes towards these oxaphospholenes and benzoxaphospholenes.

2. Synthetic routes towards oxaphospholenes and benzoxaphospholenes

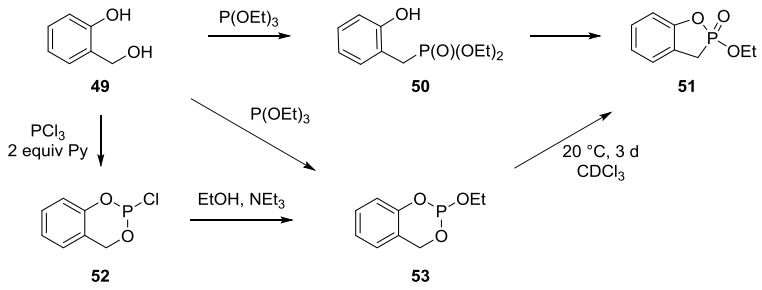
2.1. Transesterification reactions at P

The first type of oxaphospholenes ever mentioned in literature were benzoxaphosphole oxides **48**, reported exactly fifty years ago (Scheme 7).[73-76] These were prepared from salicyl alcohol **47**, or from the corresponding ether or amine.



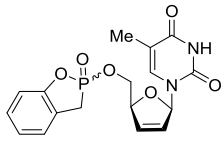
Scheme 7: Preparation of benzoxaphospholenes from salicyl alcohols and phosphites.

It was proposed that, under these harsh conditions, substitution of the poor leaving group by the phosphite took place, followed by cyclization/transesterification at the phosphorus atom of benzylphosphonate **50** (Scheme 8). According to the authors, in the case of salicyl alcohol, kinetic experiments and spectral data ruled out a mechanism involving the mixed phosphite **53**. Later however, when the mixed phosphite **53** was prepared by ethanolysis from the cyclic chlorophosphite **52**, the mixed phosphite **53** was found to contract spontaneously to the corresponding benzoxaphosphole oxide **51**.[77]



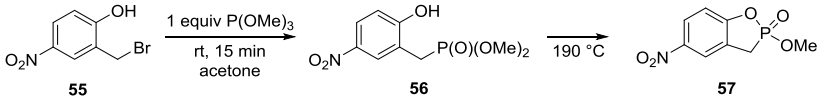
Scheme 8: Plausible mechanisms for the formation of benzoxaphospholenes from salicyl alcohol and $P(OEt)_3$.

The same authors were also able to couple Stavudine (d4T), a nucleoside derivative used in the treatment of HIV/AIDS, to a cyclic chlorophosphite, yielding a benzoxaphosphole oxide **54**, carrying a nucleoside containing ester moiety at the phosphonate in 10% yield (Figure 7).[77] Later, Wakselman reported on the Arbuzov reaction of trimethyl phosphite with 2-(bromomethyl)phenol **55**, giving the acyclic phosphonate **56**. Heating to 190 °C resulted in cyclization, yielding the benzoxaphosphole oxide **57** (Scheme 9).[78]



54
dr 1/1

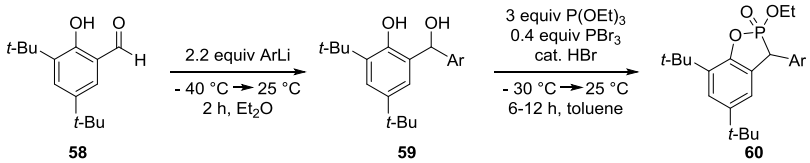
Figure 7: Stavudine-containing benzoxaphosphole oxide.



55
56
90%
57
75%

Scheme 9: Arbuzov reaction of trimethyl phosphite with 2-(bromomethyl)phenol.

Benzoxaphosphole oxides **60** were prepared through addition of an aryllithium reagent to aldehyde **58**, followed by treatment with PBr_3 and triethyl phosphite (Scheme 10).[79] Benzoxaphosphole oxides were next investigated for their reactivity towards oxygen: a low reactivity is an essential property of a potential antioxidant. This is usually not the case for *C*-centered radicals, although lactone HP-136 **61** (Figure 8) has been patented and commercialized as an antioxidant.[80, 81] Because of the structural resemblance, a similar kind of behavior was expected for benzoxaphosphole oxide **60**. Transient absorption spectroscopy experiments, following excitation of the synthesized compounds in the presence of di-*tert*-butyl peroxide, did indeed show a low reactivity towards oxygen. In follow-up experiments, it was demonstrated that acyclic benzylphosphonates were not reactive towards hydrogen abstraction.[82]



Scheme 10: Preparation of sterically hindered benzoxaphosphole oxides.

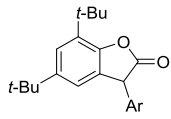
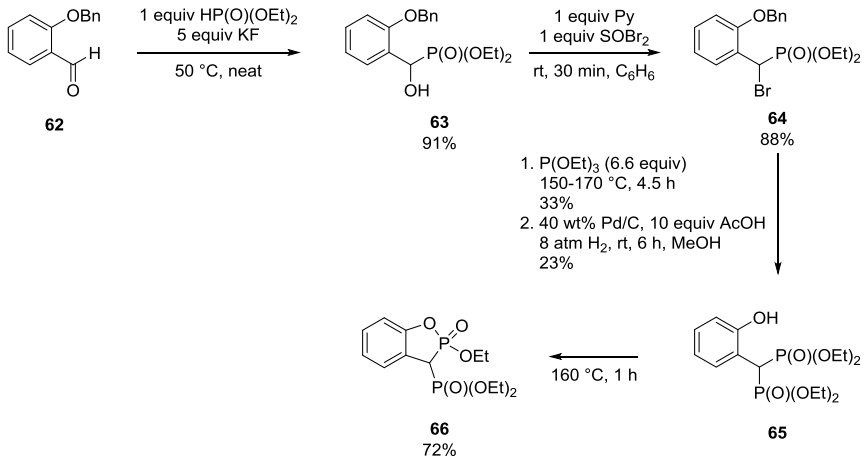


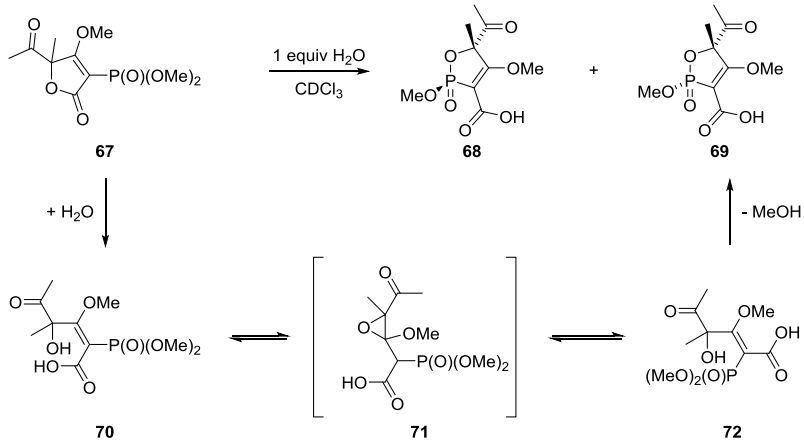
Figure 8: Structure of lactone HP-136.

During the 90's, Gross prepared the phenolic bisphosphonate **65** from protected salicylaldehyde **62** and diethyl phosphite (Scheme 11).[83] After reaction with thionyl bromide, an Arbuzov reaction and deprotection of the benzyl protective group, the phenolic bisphosphonate **65** was obtained. Upon heating, transesterification occurred to give the phosphonylated benzoxaphospholene **66** in good yield.



Scheme 11: Preparation of phosphono-substituted benzoxaphosphole oxides.

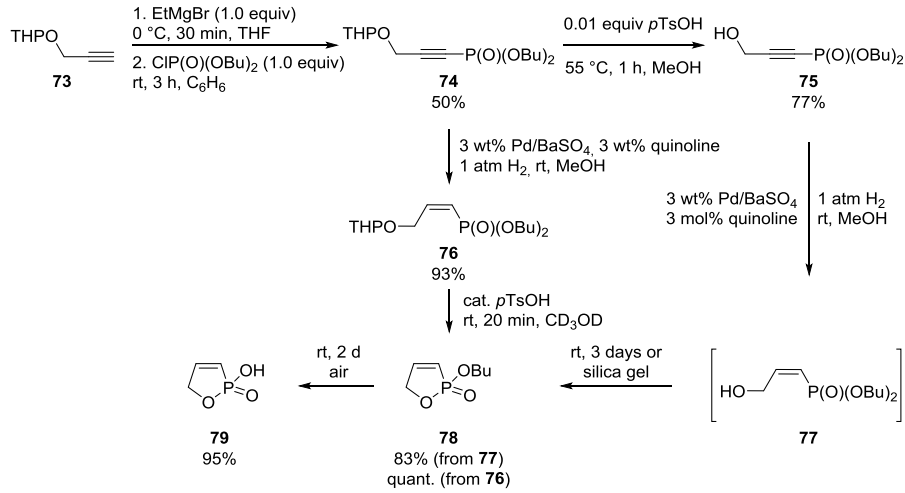
Amongst the first oxaphospholenes to be reported were compounds **68** and **69,** resulting from the hydrolysis of lactone **67** and subsequent transesterification at the phosphorus atom (Scheme 12).[84] Two diastereomers, epimers at the phosphorus atom, were obtained through a probable epoxide intermediate **71**, which allowed the *Z*/*E* interconversion of the alkene moiety. Butenolides **67** were obtained from biacetyl and trimethyl phosphite in a first step, followed by reaction with carbon suboxide (C_3O_2).



Scheme 12: Synthesis of oxaphospholenes out of lactones.

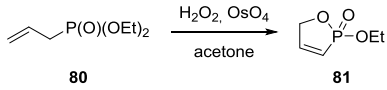
At the end of the seventies, Saito found that 1,2-oxaphosphole-3-ene-2-oxide **78** was spontaneously formed out of hydroxyphosphonate **77**, during column chromatography or upon three days of standing at room temperature (Scheme 13).[85] Hydroxyphosphonate **77** was

prepared through partial hydrogenation of alkynylphosphonate **75**, which was obtained after Grignard addition of the terminal alkyne **73** to dibutyl chlorophosphate followed by THP deprotection. 1,2-Oxaphosphole-3-ene-2-oxide **78** spontaneously hydrolyzed to the corresponding phosphonic monoacid **79** upon two days of standing under air at room temperature. When stored under nitrogen however, no such conversion took place. Alternatively, oxaphospholene **78** could also be obtained by partial hydrogenation of **74**, followed by THP deprotection and simultaneous cyclization with *p*TsOH.



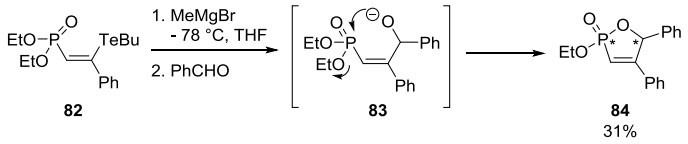
Scheme 13: Synthesis of oxaphospholene out of protected propagyl alcohols.

Sturtz showed in 1987 that diol phosphonates, prepared through dihydroxylation of alkenylphosphonates **80**, could perform an intramolecular cyclization (Scheme 14).[86]



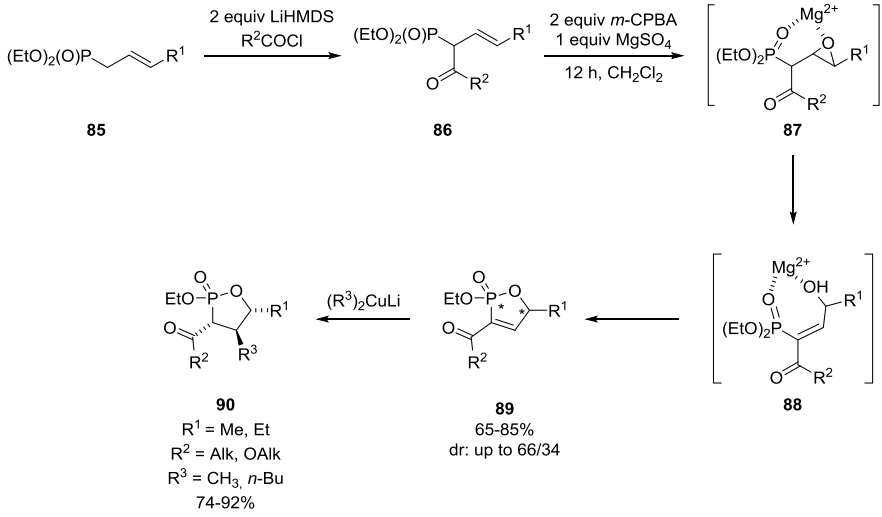
Scheme 14: Dihydroxylation of allylphosphonates producing unsubstituted oxaphospholenes.

When studying the hydrotelluration of internal alkynes, Lee found in 2000 that the produced telluroalkenylphosphonate **82** yielded an oxaphospholene in low yield upon treatment with MeMgBr and benzaldehyde (Scheme 15).[87] After transmetallation of the telluroalkenylphosphonate **82**, the intermediate allylic alcohol **83** could not be isolated and spontaneously cyclized to the oxaphospholene **84**.



Scheme 15: Preparation of disubstituted oxaphospholenes from telluroalkenylphosphonates.

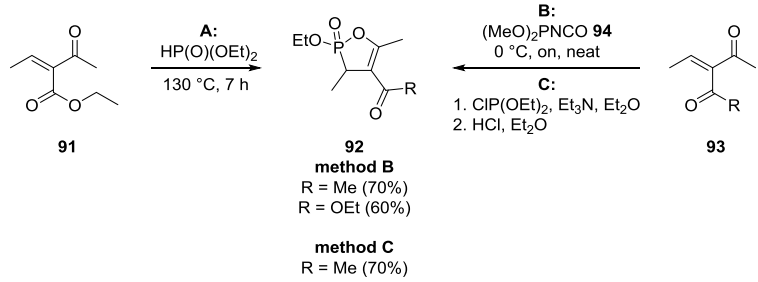
This was the incentive to investigate the synthesis of oxaphospholenes **89** with an electron withdrawing group in the 3-position, which could be of interest as precursors for 1,2-oxaphospholane-2-oxides **90** (Scheme 16). To that end, an acyl group was installed in allylic phosphonates **85**, which were subsequently treated with *m*-CPBA.[67] The expected epoxide **87** could not be isolated and instead the oxaphospholene **89** was obtained, in a low 25% yield. However, this product was only recovered if $MgSO_4$ was used during work-up. The authors reasoned that the formed epoxide **87** was not stable enough to be isolated, but was stabilized through coordination by Mg^{2+} in the form of the allylic alcohol **88**, which then rapidly cyclized at the phosphorus atom. Next, a series of substituted oxaphospholenes **89** were prepared in good yields, without a very pronounced diastereoselectivity. The isolated oxaphospholene diastereomers **89** finally underwent entirely stereoselective 1,4-addition with cuprates to yield 1,2-oxaphospholane-2-oxides **90**, which are of interest as carboyhydrate mimics.



Scheme 16: Synthesis of 1,2-oxaphospholane-2-oxides *via* epoxidation of allylphosphonates.

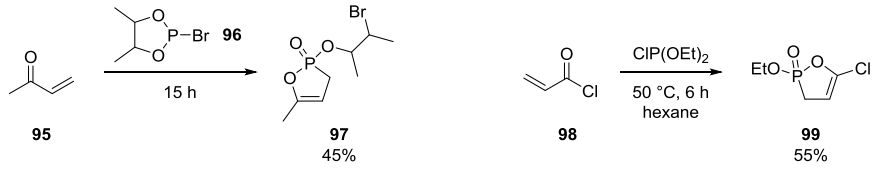
2.2. Addition of phosphorus nucleophiles to carbonyl compounds

Activated alkenes have provided an entry to oxaphospholenes since the end of the 60s. In 1967, Arbuzov reported on the Michael addition of diethyl phosphite to acetyl alkenoate **91**, which after cyclization yielded a 3*H*-1,2-oxaphosphole 2-oxide **92** for the first time (Scheme 17, method A).[88] The isolated yield was not reported, but later on, this product was also isolated as the result of a competing cyclization reaction in the acetylation of hydroxyallylphosphonates.[89] Later, 3-ethylidene acetylacetone **93** was found to react with dimethyl phosphorisocyanatidite **94** to give product **92** again (Scheme 17, method B).[90, 91] 3-Ethylidene acetylacetone **93** also gave rise to oxaphospholenes after reaction of its enolate with diethyl chlorophosphite, followed by a cyclization step (Scheme 17, method C).[92] In this way, oxaphospholenes with a fluorine-containing ester chain could be prepared as well when fluorinated dialkyl phosphite was used.[93]



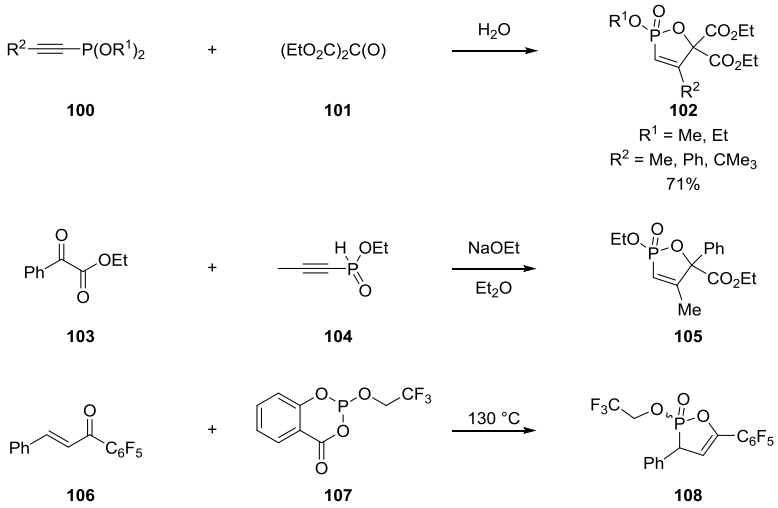
Scheme 17: Preparation of oxaphospholenes from acetyl alkenoates or acetyl enones.

Simple enones[94] **95** or acryloyl chlorides[95] **98** were shown to produce respectively methyl substituted or chlorinated oxaphospholenes **97** or **99** when treated with dialkyl halophosphites (Scheme 18). In almost the same way, thiocarbonyl compounds gave rise to oxaphospholenes in a reaction with trimethylsilyl dimethyl phosphite.[96]



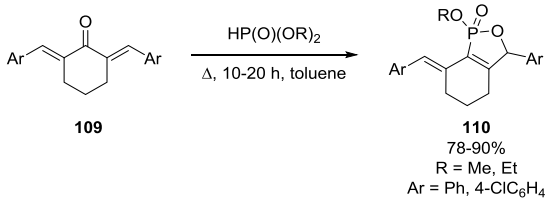
Scheme 18: Synthesis of oxaphospholenes via reaction of unsaturated carbonyl compounds with halo dialkylphosphites.

Addition of phosphonite **100** to diethyl mesoxolate **101** yields dicarboxyl-substituted oxaphospholenes **102**[97] as does the addition of *H*-phosphinates **104** to α-ketoesters **103**[98] (Scheme 19). Using dioxaphosphorinone **107** as a nucleophile allowed the synthesis of a 3,5-disubstituted oxaphospholene **108** (Scheme 19).[99]



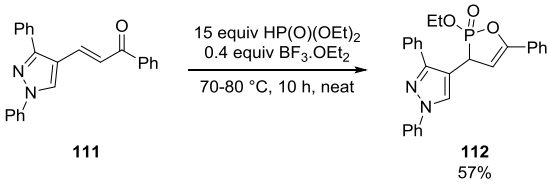
Scheme 19: Preparation of oxaphospholenes through addition of alkynyl phosphites or phosphonites to carbonyl compounds.

1,2-Addition of dialkyl phosphites to 2,6-dibenzylidene cyclohexanone **109** afforded the disubstituted hexahydrobenzoxaphosphole oxides **110** in good yields upon refluxing in toluene (Scheme 20).[100]



Scheme 20: Addition of dialkyl phosphites to dibenzylidene cyclohexanone.

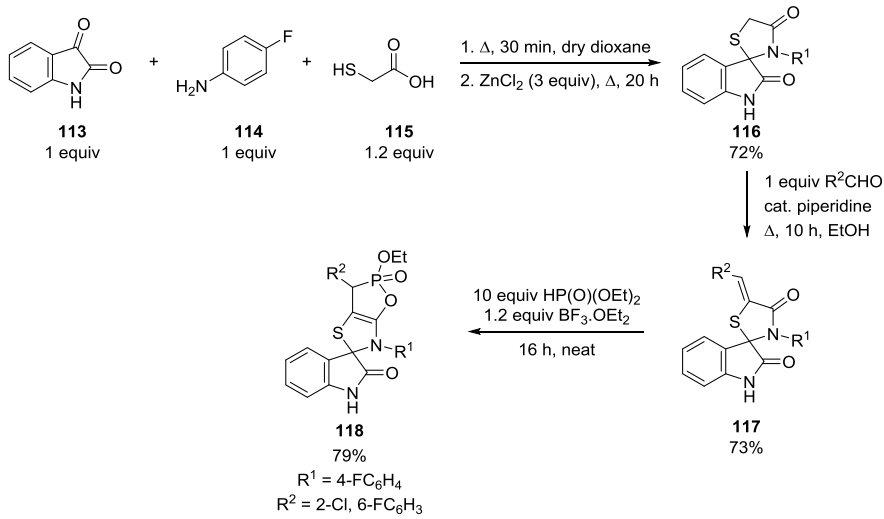
Quite recently, an example of an oxaphospholene carrying a 4-pyrazolyl substituent was reported, resulting from the 1,4-addition of diethyl phosphite to enone **111** (Scheme 21).[101]



111 **112** 57%

Scheme 21: Preparation of an oxaphospholene bearing a 4-pyrazolyl substituent.

As part of a screening on antioxidant activity of *S*- and *N*-containing spirocycles, one tetracyclic structure **118** containing an oxaphospholene moiety was obtained in a three-step sequence (Scheme 22).[102] Spirocyclic tricycle **116**, which was obtained by condensation of indoline-2,3-dione **113** with *p*-fluoro aniline **114** and 2-mercaptoacetic acid **115**, was transformed into enone **117** *via* a Knoevenagel-type condensation. Treatment of **117** with diethyl phosphite and $BF_3 \cdot OEt_2$ eventually gave tetracycle **118** after 1,4-addition and subsequent transesterification/cyclization at the phosphorus center.



113 1 equiv; **114** 1 equiv; **115** 1.2 equiv; **116** 72%; **117** 73%; **118** 79%

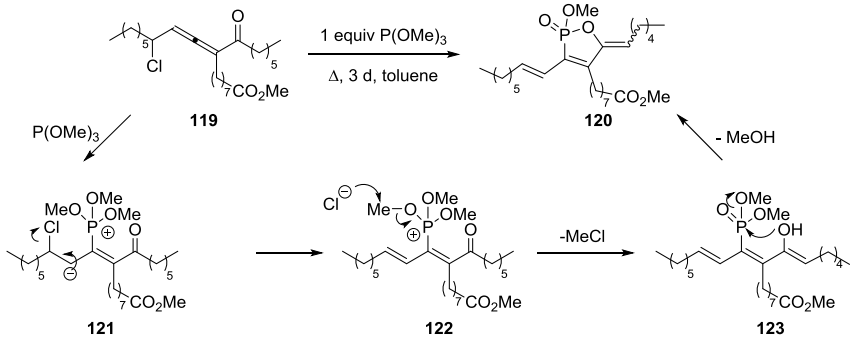
R^1 = 4-FC_6H_4

R^2 = 2-Cl, 6-FC_6H_3

Scheme 22: Preparation of tetracyclic oxaphospholenes.

Only one example of an oxaphospholene substituted with long alkyl chains, is described. Fürmeier reported the addition of trimethyl phosphite to allenylketone halides under reflux conditions in toluene (Scheme 23).[103] In the case of a chlorine substituent in the 4-position with respect to the ketone, addition of the phosphite to the central allene carbon atom results in the formation of a vinylogous enolate **121** according to the proposed mechanism. After elimination of the chloride, it dealkylates one of the methoxy groups, producing a phosphonylated enone. The corresponding enol **123** finally transesterifies at the phosphorus atom, yielding the

oxaphospholene **120**. Alternatively, an S_N2' reaction can also account for the formation of intermediate **122**.

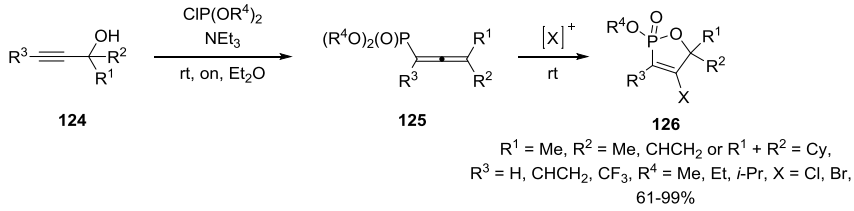


Scheme 23: Halo allenylketones as precursors for the synthesis of oxaphospholenes.

2.3. Through cyclization of allenylphosphonates promoted by electrophiles

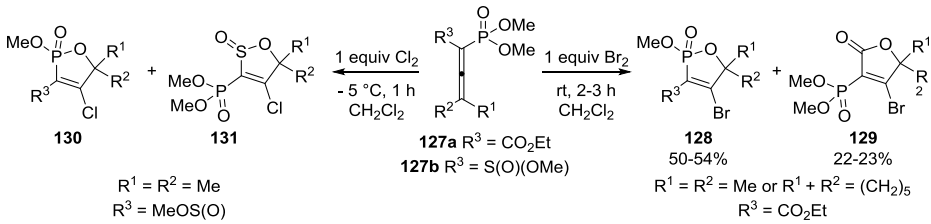
When the cyclization of allenic carboxylic acid esters to halogenated lactones by addition of bromine was discovered in the mid-seventies,[104, 105] it was demonstrated soon after that oxaphospholenes could be synthesized from the corresponding allenylphosphonates.[106] Thanks to the discovery by Mark and Boisselle in 1962 of the [2,3]-sigmatropic rearrangement which occurs after treatment of propargylic alcohols **124** with diethyl chlorophosphites,[107, 108] a very convenient synthesis of allenylphosphonate precursors **125** was available. Indeed, allenylphosphonates cyclized just as easily as allenic carboxylic acid esters upon addition of electrophiles such as chlorine,[109] sulfurylchloride,[110-112] bromine,[113, 114] iodine,[115] iodine monohalogenides[116] or $KICl_2$[117, 118] (Scheme 24). The distal, more electron-rich, double bond first forms a halonium intermediate, which is then attacked intramolecularly by the phosphoryl group. Dealkylation of one of the alkoxy groups by the corresponding halide yields the oxaphospholenes **126**.[113] When unsubstituted 1,2-propadienylphosphonates were treated with bromine, electrophilic addition of the dihalogen took place instead of cyclization, probably because of the lack of stabilization of the halonium intermediate. Under the same conditions, 3-monosubstituted allenylphosphonates predominantly gave the oxaphospholene cyclization products.[113] Vinyl, allyl, benzyl and propargyl substituents were well tolerated in this electrophilic addition/cyclization step,[114, 119, 120] while allenylphosphonates carrying a cyclohexyl group produced spirocyclic oxaphospholenes.[121] Soon, this two-step strategy became the method of choice to prepare oxaphospholenes **126**.[122-125] Later, when other synthetic entries to allenylphosphonates were found, the cyclization reaction of these allenylphosphonates with

dihalogens remained an attractive strategy to afford oxaphospholenes.[126] Oxaphospholenes with a 3-phenylthio-,[114] 3-phenylseleno,[114] 3-hydroxymethyl,[127] 3-fluoromethyl,[128] or an extra 3-halo-substituent[129] could be synthesized from the appropriately functionalized allenylphosphonates.



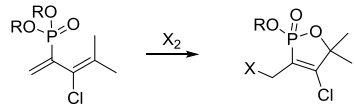
Scheme 24: Traditional strategy for the synthesis of oxaphospholenes through preparation of allenylphosphonates and cyclization with an electrophile.

In a competition experiment, 2-phosphoryl-2,3-alkadienoate **127a** was treated with bromine and a mixture of two cyclization products was obtained (Scheme 25). Both the oxaphospholene **128**, which was formed as the major product, and the lactone **129** were isolated.[130] Competitive reactions also occurred when the phosphonyl group is in γ-position with respect to the carboxyl function.[131] Treatment of 1-phosphoryl-1-sulfinate-2,3-butadiene **127b** similarly yielded a mixture of two heterocycles, which could each be isolated separately.[132]



Scheme 25: Competition experiment of substituted allenylphosphonates yielding oxaphospholenes, lactones and 5*H*-1,2-oxathiole 2-oxides.

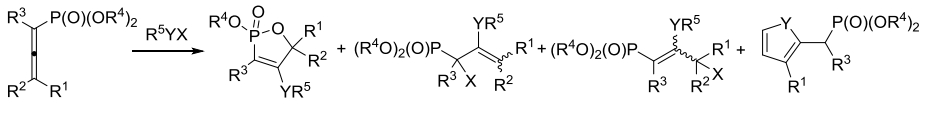
Alternatively, phosphono pentadienes can serve as precursors for the electrophile-induced synthesis of oxaphospholenes as well. The terminal alkene in the 2-phosphonopentadiene **132** is activated by the electrophile, which is followed by ring closure through intramolecular attack of the phosphoryl group onto the internal double bond (Scheme 26).[133, 134]



132 **133**
R = Me, Et
X = Cl, Br
78-80%

Scheme 26: Phosphono pentadienes as precursors for the preparation of oxaphospholenes.

Not only halogen sources could initiate cyclization of allenylphosphonates **125**. Sulfenyl-,[135-139] selenyl-[110, 140-145] or tellurylhalides[146, 147] efficiently gave rise to 4-chalcogeno oxaphospholenes **134** (Scheme 27). In reaction with sulfenylhalides, 1,3,3-trisubstituted and 1,3-disubstituted allenylphosphonates exclusively yielded the oxaphospholene cyclization products **134**,[138, 139] while 3,3-disubstitued allenylphosphonates also gave small amounts of 1,2-adducts **135** of the sulfenylchloride in some cases.[136, 137, 139, 142, 143] Unsubstituted allenylphosphonates did not produce oxaphospholenic cyclization products and only yielded 1,2-adducts **135** or 2,3-adducts **136**.[138, 148-152] 3-Monosubstituted allenylphosphonates gave mixtures of oxaphospholenes and 1,2- and 2,3-adducts **135** and **136**.[148-150] 1-Vinylsubstituted and 3-vinylsubstituted allenylphosphonates gave mixtures of phosphonylated thiophenes **137** and 4-thio oxaphospholenes **134**.[135, 153] With sulfur dichloride the produced oxaphospholenyl sulfenylchlorides could further be transformed into the corresponding thioethers when reacting these with alkenes.[154, 155]



125

134
X = Cl, Br
Y = S, Se, Te
R^4, R^1, R^2 = Alk
R^3, R^4 = Ar, Alk

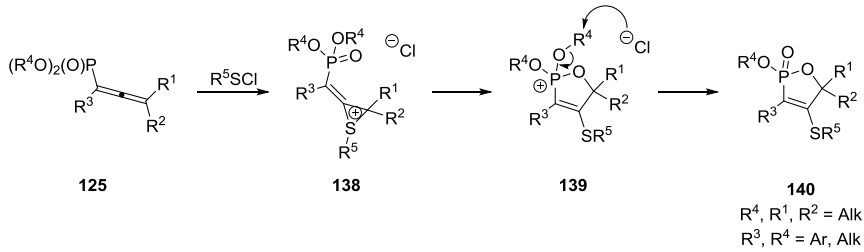
135
X = Cl, Br
Y = S, Se
R^4, R^1, R^2 = Alk
R^3, R^5 = Ar, Alk

136
X = Cl, Br
Y = S, Se
R^4, R^1, R^2 = Alk
R^3, R^5 = Ar, Alk

137
X = Cl, Br
Y = S, Se
R^4, R^1= Alk
R^2 = vinyl
R^3, R^5 = Ar, Alk

Scheme 27: Variety of electrophiles capable of inducing cyclization to oxaphospholenes.

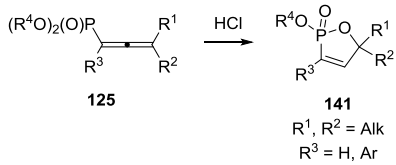
From a mechanistic point of view, a thiiranium intermediate **138** is first formed in these cyclization reactions, through the reaction of the sulfenylchloride with the distal double bond of allenylphosphonate **125** (Scheme 28). Intramolecular attack of the phosphoryl group yields a phosphonium intermediate **139**, which usually undergoes dealkylation swiftly. When bis(methylthio)sulfonium hexachloroantimonate (MDTSAN) was used as the electrophile, the phosphonium intermediate could be isolated and converted to the oxaphospholene upon heating.[156]



Scheme 28: Mechanism of the sulfenylchloride-promoted cyclization of allenylphosphonates.

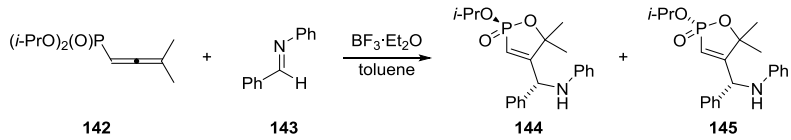
Selenylhalides, in contrast to sulfenylchlorides, selectively yielded oxaphospholenes in some cases,[140-145] but the formation of 1,2- and 2,3-adducts could not always be avoided in non-extensively substituted allenylphosphonates.[157, 158] Phosphonylated selenophenes and selenium-containing bicyclic oxaphospholenes were formed as well.[153, 159] Alternatively, phenylselenylamides could also be used as electrophiles when activated with sulfur trioxide pyridine complex.[160] Alternatively, oxaphospholenes with a thiophosphate substituent installed in the 4-position were prepared through reaction of allenylphosphonates with the phosphorus containing pseudohalogens of structure $(RO)_2(O)PSCl$.[161] Not only allenylphosphonates, but also 1,3-pentadienylphosphonates could lead to oxaphospholenes when reacted with phenylsulfenylchloride.[162]

In 1980 Mikhailova reported on the acid-promoted cyclization of allenylphosphonates to produce oxaphospholenes withouth a substituent in the 4-position (Scheme 29).[163] Oxaphospholenes **141** were obtained selectively when the allenylphosphonate **125** contained a tertiary γ-carbon and when the reaction was run in a polar solvent.



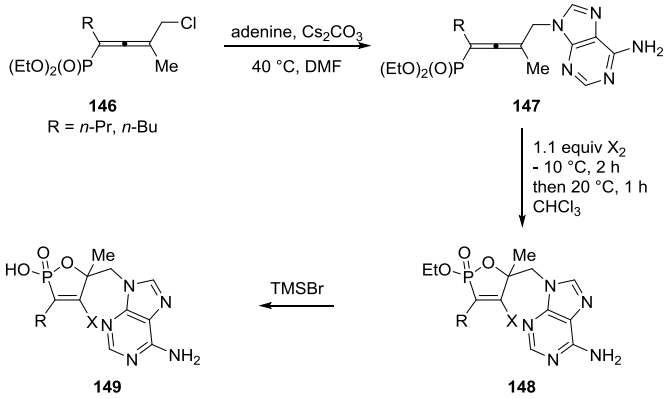
Scheme 29: HCl-promoted cyclization of allenylphosphonates.

In 1985 Trifonov found that allenylphosphonate **142** could be transformed into aminomethyl oxaphospholenes **144**-**145** through electrophilic addition of imine **143**, activated by $BF_3 \cdot OEt_2$ (Scheme 30).[164]



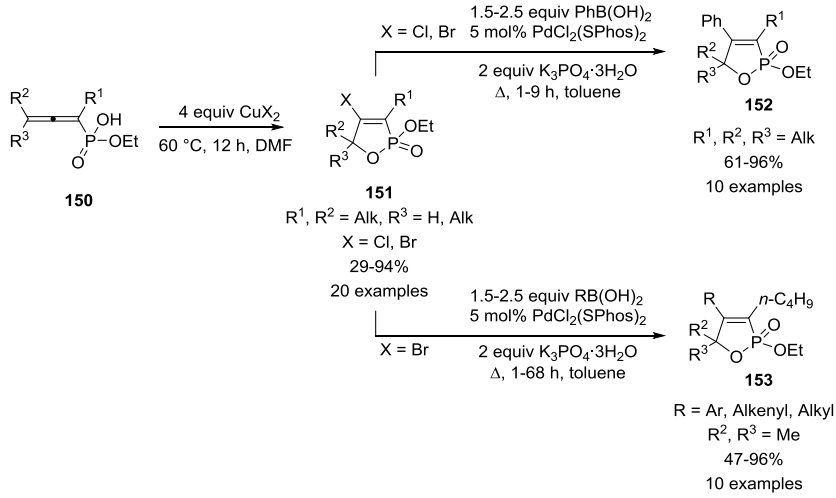
Scheme 30: Transformation of allenylphosphonates into oxaphospholenes carrying an aminomethyl substituent.

In the search for new antiviral compounds, the preparation of nucleoside analogues carrying an oxaphospholene moiety **148** was envisioned, as the authors reasoned that the heterocyclic moiety may mimic the ribose unit of natural nucleosides.[165, 166] Hence, 4-chloroallenylphosphonates **146** were prepared and reacted with adenine in the presence of a base, to yield the alkylated adenine derivatives **147**. These were subsequently cyclized with chlorine or bromine and eventually deprotected to give the oxaphospholenic acids **149** (Scheme 31).



Scheme 31: Preparation of an oxaphospholene with an adenine substituent.

In 2009, the group of Ma published their findings on the halolactonization of monoesters of allenyl phosphonic acids with copper halides (Scheme 32).[167] Reaction of the phosphonic acid monoesters **150**, which were prepared by partial hydrolysis of the corresponding dialkyl phosphonates, smoothly yielded the 4-halo oxaphospholenes **151** upon addition of copper (II) chloride or copper (II) bromide. Not only are the copper salts easier to handle than the corresponding halogens, they also leave allylic substituents on the allenyl phosphonic acid unchanged. Fully substituted allenes all reacted in good yields, but in the case of R^3 = H, the yield decreased considerably. When 1-monosubstituted and 3,3-disubstituted substrates were evaluated, no reaction occurred at all.

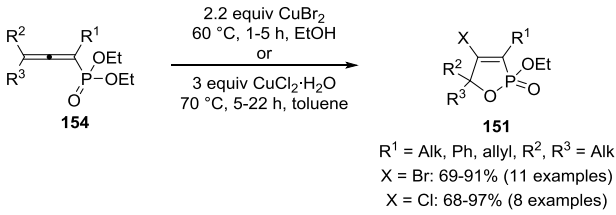


Scheme 32: Halolactonization of monoesters of allenylphosphonates.

The obtained 4-halo oxaphospholenes could further be derivatized by means of a Suzuki coupling with organo boronic acids (Scheme 32).[167] $PdCl_2(SPhos)_2$ proved to be the catalyst of choice, as other Pd catalysts produced the cross coupling products **152**-**153** only in low yields or not at all. Under optimized conditions, a set of 4-halo oxaphospholenes were coupled in moderate to near-quantitative yields. 4-Chloro oxaphospholenes reacted slower and required a larger excess of phenylboronic acid than their bromo counterparts to obtain the products in the same yields. Finally, both aryl boronic acids carrying EDGs and EWGs were successfully coupled, although a larger excess and longer reaction times were required and lower yields were obtained for electron poor aryl boronic acids. Alkenyl and alkyl boronic acids were also well tolerated.

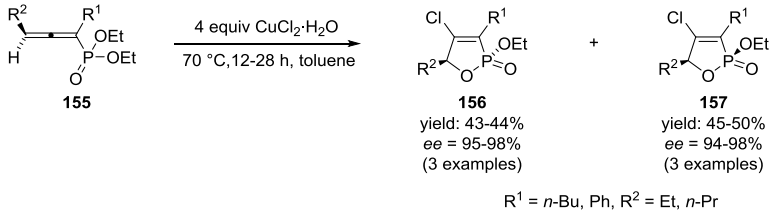
Two years later, Ma's group reported on the same halocyclization reaction using dialkyl phosphonate ester substrates **154** instead of mono alkyl phosphonate esters **150**, hence eliminating the need for an additional deprotection step in alkaline aqueous medium (Scheme 33).[168] Moreover, addition of 2.2 equivalents copperhalide - instead of 4 equivalents - was allowed and although the transformation worked well in a variety of solvents, the highest yields and fastest reaction were obtained in EtOH. Alkyl, allyl and phenyl substituents were all tolerated, producing the oxaphospholenes **151** in good to excellent yields. Next, reaction conditions were optimized as well for the $CuCl_2$-mediated transformation. Again, a variety of solvents does the job, but running the reaction in toluene produced the highest yields. The substrate scope and yields were more or less the same as for the $CuBr_2$-catalyzed reaction. One should note that for both catalytic systems, the less reactive 3,3-disubstituted,

1-monosubstituted or unsubstituted allenylphosphonates were not considered in the substrate scope. The $CuCl_2$-mediated synthesis on the other hand, offers a good alternative access to 4-chloro oxaphospholenes **151**, as the reagent is significantly more easy to handle than chlorine.



Scheme 33: $CuBr_2$-mediated cyclization of allenylphosphonates.

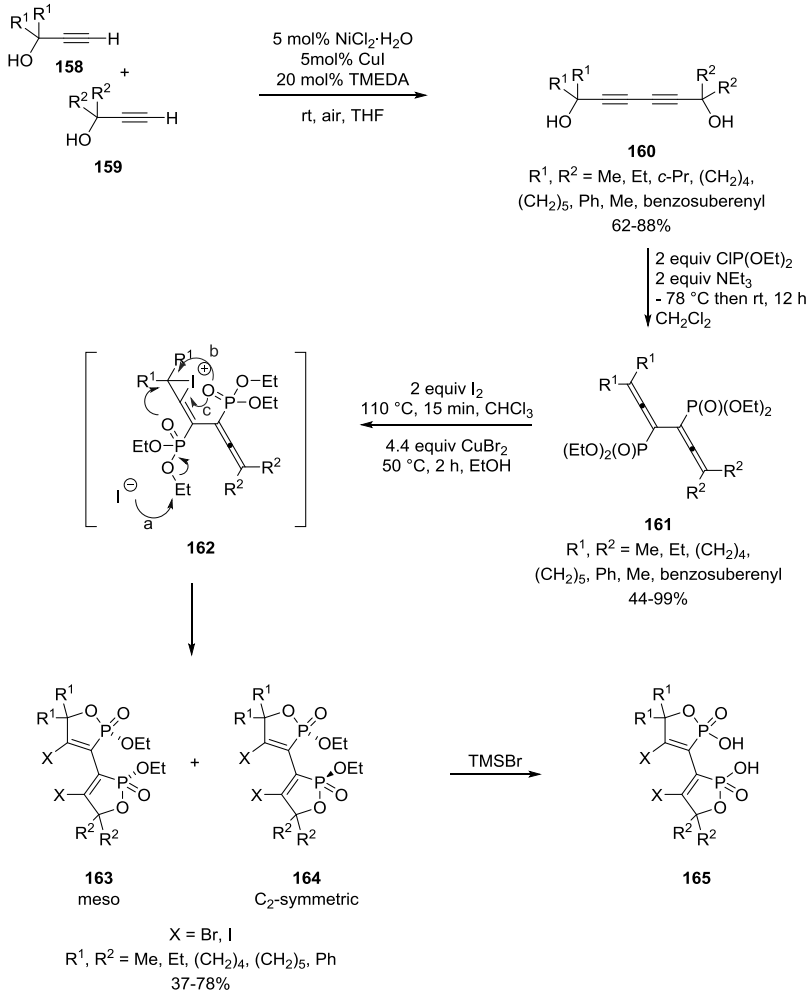
One example of a disubstituted allene **155** was synthesized and evaluated to check if chirality could be successfully transferred in the halolactonization reaction. With a larger excess of $CuCl_2$ and a slightly longer reaction time, two diastereomers were obtained in excellent yield with a 50/50 diastereomeric ratio, efficiently transferring the axial chirality of the allene to central chirality in the oxaphospholenes **156**-**157** (Scheme 34). The second stereogenic center is created at the phosphorus atom at the moment dealkylation occurs. The obtained oxaphospholenes **156**-**157** could again be further derivatized by means of Suzuki cross-coupling reactions.



Scheme 34: $CuCl_2$-mediated cyclization of allenylphosphonates.

Very recently, the group of Virieux reported on the double cyclization of bisallenylphosphonates **161** (Scheme 35).[169] These were prepared through a Glaser-Hay coupling reaction of the corresponding alkynes **158** and **159**, followed by a [2,3]-sigmatropic rearrangement of the resulting (un)symmetrical dialkynes **160** with diethyl chlorophosphite. All derivatives reacted in good to excellent yields in this two-step sequence, except for the cyclopropyl-substituted propargyl alcohol. Although it was successfully engaged in the Glaser-Hay coupling reaction, the cyclopropyl group probably ring-opened during the sigmatropic rearrangement step and a complex mixture was obtained. The conjugated

bisallenes **161** could be finally cyclized upon addition of I_2 to give two different products. Although more than one cyclization mode is possible, pathways b and c could be ruled out as deprotection of the ethyl phosphonic ester functions resulted in the detection of only one product. Before deprotection, the two singlets observed by ^{31}P NMR spectroscopy indeed resulted from meso and C_2-symmetric bisoxaphospholenes **163** and **164**. When the phosphonic acid **165** is obtained, the phosphorus atom is no longer a stereogenic center and thus one achiral product is detected by ^{31}P NMR spectroscopy. Moreover, the bisoxaphospholenic core was also confirmed by X-ray analysis.

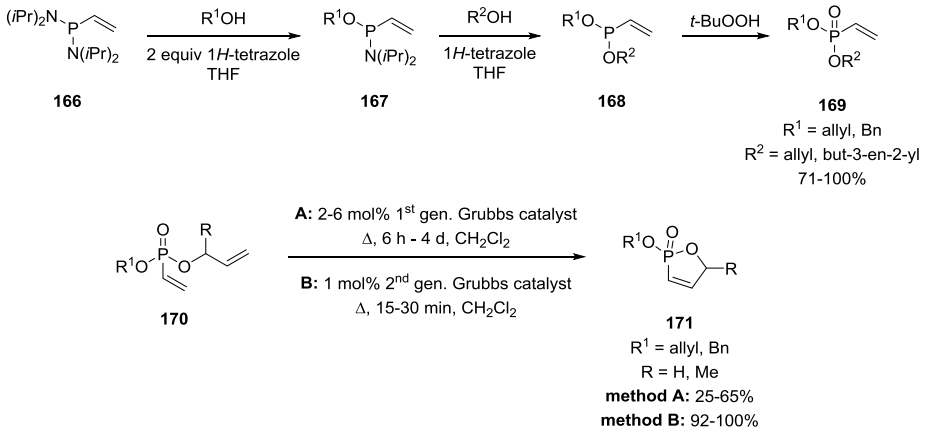


Scheme 35: Synthesis of bisoxaphospholenes from bisallenylphosphonates.

$CuBr_2$ also promoted cyclization and, depending on the substrate, some dibromo-bisoxaphospholenes **163**-**164** were obtained with high diastereoselectivities and in moderate to good yields. The dibenzosuberenyl-substituted derivative did not produce the corresponding bisoxaphospholene, as probably electrophilic addition preferentially took place at the double bond of the benzosuberenyl group.

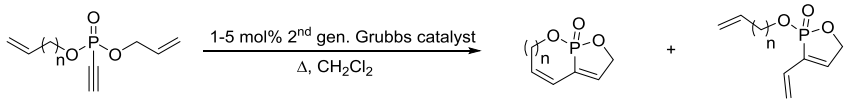
2.4. Through Ring-Closing Metathesis

With the breakthrough reports of Grubbs on RCM (ring-closing metathesis) in 1992, the potential of this method to synthesize all kinds of cycles was soon being explored.[170-172] A couple of years later, reports on the synthesis of oxaphospholenes through RCM were appearing.[173, 174] Symmetrical phosphonates were cyclized with the first generation Grubbs catalyst, although in low yields, with high catalyst loadings, reflux conditions and long reaction times (Scheme 36, method A).[173, 175] Moreover, the catalyst proved to be not very selective, resulting in the formation of mixtures of 5- and 7-membered cycles. In 2000, Timmer demonstrated the superiority of the second generation Grubbs catalyst, synthesizing oxaphospholenes **171** out of symmetrical or unsymmetrical vinyl phosphonates **170**.[175] These were easily, and often in excellent yields, accessible from bis(isopropyl)phosphine **166**, which was treated successively with two different alcohols or with an excess of one alcohol, to yield unsymmetrical or symmetrical phosphonites **168**. Oxidation with *t*-BuOOH afforded the desired vinyl phosphonates **169**, which were subjected to RCM. Yields were increased from 25-65% to 92-100%, while reaction times were decreased from several days to 30 minutes, with a catalyst loading as low as 1% (Scheme 36, method B). Moreover, no seven-membered cycles were produced.



Scheme 36: RCM of vinylphosphonates producing oxaphospholenes.

Timmer next expanded the scope of this method to construct bicylic oxaphospholene structures **173a**-**b** through ene-yne metathesis.[176] In the case of the symmetrical diallyl phosphonate **172a,** the monocycle **174a** was exclusively obtained (Scheme 37). Bicyclic oxaphospholenes **173b** were only obtained if the five-membered ring was fused to a seven-membered ring and if the catalyst loading was increased to 5 mol%. Monocyclic six-membered rings or bicyclic [4.4.0] ring products were not detected.



172a (n = 1)
172b (n = 2)

173a (4h): 0%
173b (3h): 66%

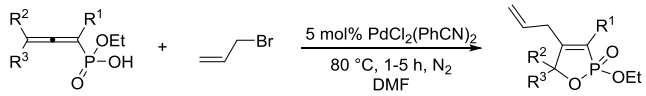
174a (4h): 98%
174b (3h): 23%

Scheme 37: RCM of alkynylphosphonates producing monocyclic and bicyclic oxaphospholenes.

2.5. Transition metal-catalyzed cyclization reactions

2.5.1. Palladium-catalyzed coupling-cyclizations

In 2007 Ma reported on the first Pd-catalyzed synthesis of oxaphospholenes.[177] Monoesters of allenyl phosphonic acids **150** were found to react with allylic halides in the presence of 5 mol% $PdCl_2(PhCN)_2$ and in the absence of a base to yield 4-allyl oxaphospholenes **176** in moderate to good yields (Scheme 38). Addition of a base seemed to be counterproductive, lowering the product yield or causing *O*-allylation to occur. Different alkyl substituents were tolerated as R^1 and even a bulky *t*-Bu group only lowered the yield to some extent. When there was no substituent in the alpha position (R^1 = H), the yield dropped more significantly. Substituents at the gamma position were well tolerated as well. Substituents at the allylic coupling partner were well tolerated as well since 3-chlorobut-1-ene and 2-methylallyl chloride were efficiently used in this coupling-cyclization reaction. The reaction time for the less reactive chloride coupling partners did increase however.



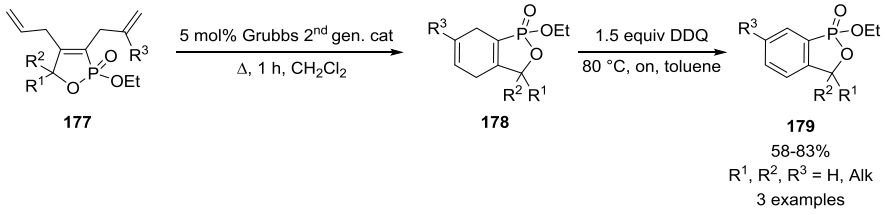
150

175

176
42-80%
R^1, R^2, R^3 = H, Alk
11 examples

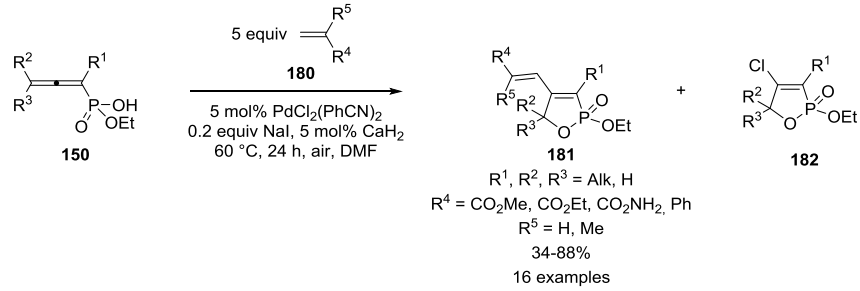
Scheme 38: Coupling-cyclization of allenylphosphonates with allyl bromide.

Treatment of three derivatives **177**, each carrying two allyl groups, with 5 mol% of Grubbs second generation catalyst swiftly yielded the corresponding tetrahydrobenzoxaphosphole oxides **178** through RCM (Scheme 39).[177] These could be efficiently transformed into dihydrobenzoxaphosphole oxides **179** through DDQ-mediated oxidation.



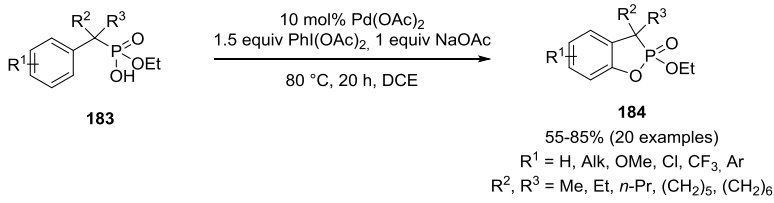
Scheme 39: Transformation of allyl-disubstituted oxaphospholenes into benzoxaphospholenes through RCM and oxidation.

The same authors next investigated whether it was possible to use alkenes instead of allyl halides in the cyclization/coupling reactions with the monoester of allenylphosphonic acids **150**.[178] Evaluation of the $PdCl_2(PhCN)_2$ catalytic system with acrylonitrile as the coupling partner, $CuCl_2$ as an oxidant and K_2CO_3 as the base, afforded one single isomer of the desired product **181**, albeit in low yield, alongside some 4-chloro oxaphospholene **182** (Scheme 40). During optimization experiments, $CuCl_2$ turned out not to be the best oxidant and reaction conditions were set as follows: a catalytic amount of NaI in air as the oxidant, no K_2CO_3 and 5 mol% CaH_2; yielding the desired alkenyl-substituted oxaphospholene **181** regio- and stereoselectively and in very good yields. A study of the scope of the reaction revealed that acrylates were excellent coupling partners. Less reactive alkenes, such as styrene, acrylamide and methyl methacrylate, proved to be more challenging substrates and the yields decreased significantly for those substrates. Using a stoichiometric amount of benzoquinone as the oxidant instead of NaI, yielded these derivatives in good yields nonetheless. On the other hand, different alkyl substituents on the allene were well tolerated, but yields dropped significantly when the allene was unsubstituted at one or multiple positions.



Scheme 40: Cyclization-coupling reaction of allenylphosphonate monoesters with alkenes.

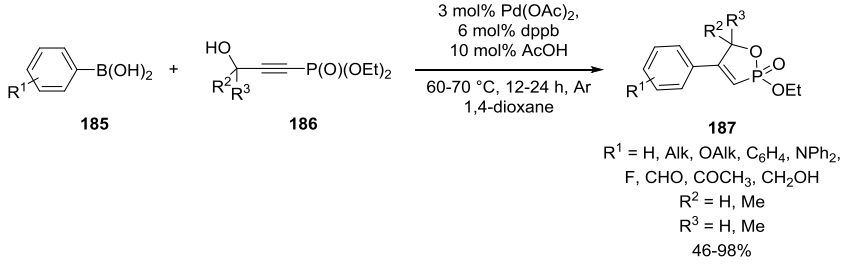
In 2013, Lee's group found that benzylphosphonic acid monoethyl esters **183** (R^2 = R^3 = Me) could undergo C-H activation (Scheme 41).[179-181] Optimization of reaction conditions showed that benzoxaphospholenes **184** were produced in the presence of $Pd(OAc)_2$, NaOAc and $PhI(OAc)_2$. A substrate scope study revealed that an *ortho* substituent was tolerated, which was not the case for the C-H activation of the related phenyl acetic acid.[182] In the case of a *meta* substituent, the cyclization unsurprisingly took place at the less hindered *ortho* position. Benzylphosphonates with different EDGs or EWGs all reacted well under the optimized conditions. The Thorpe-Ingold effect was illustrated as well, as unsubstituted or mono methyl substituted derivatives at the benzylic position did not react. Increasing the steric bulk to two propyl groups at the benzylic position, afforded the benzoxaphospholenes in almost quantitative yield on the other hand.



Scheme 41: C-H activation of benzylphosphonic acid monoethyl esters producing benzoxaphospholenes.

Very recently, Zhao's group found that phosphonylated propargyl alcohols **186** afforded 4-aryl oxaphospholenes **187** by means of a palladium-catalyzed domino addition, followed by a cyclization step (Scheme 42).[183] The alkyne **186** first undergoes hydropalladation, after which a transmetallation and reductive elimination step yields a γ-hydroxy alkenylphosphonate. This intermediate ultimately transesterifies to form the phosphonate. Under optimized conditions a multitude of arylboronic acids **185** was efficiently coupled in high to quantitative yields, tolerating various electron donating substituents on the aryl boronic acid **185**. Although aryl boronic acids containing reactive functionalities such as a carbonyl or hydroxyl group afforded

the desired products in lower yields, they did not require protecting groups. That steric hindrance had an impact on the cyclization step was demonstrated by varying the size of the alkoxy group of the phosphonate: diisopropyl esters of the phosphonate reacted in a lower 47% yield, while the dimethyl esters produced the reaction products in near-quantitative yields. Crowding the propargylic position with extra methyl groups, required an increase of the temperature and reaction time, but still afforded the products in excellent yields.



Scheme 42: Palladium-catalyzed domino addition of propargyl alcohols with boronic acid, followed by cyclization.

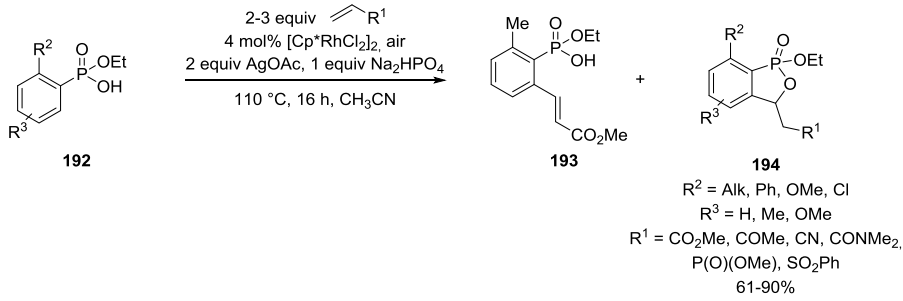
In 2015, Lee's group published another report on Pd-catalyzed C-H activation/C-O bond formation of phosphonate monoesters **188** (Scheme 43).[184] The important feature of this method is that unactivated alkenes could be engaged as substrates. Mixtures of phosphaisocoumarins **190** and benzoxaphospholenes **191** were initially obtained. By careful tuning of the reaction conditions, it was possible to shift the ratio of formed products in favor of the phosphaisocoumarins **190**. Although the reaction was selective for most substrates, some benzoxaphospholenes **191** were still isolated in low yields (7-17%).

Scheme 43: C-H activation of phosphonate monoesters with unactivated alkenes producing of phosphaisocoumarins and benzoxaphospholenes.

2.5.2. Rhodium-catalyzed cyclization

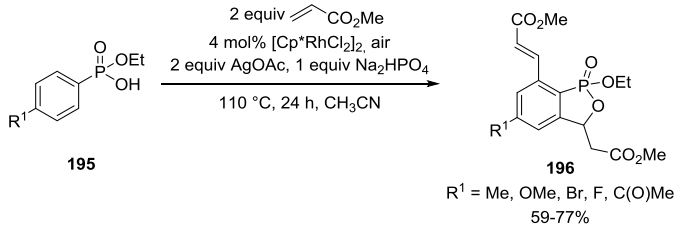
In 2013, the group of Lee reported on the C-H activation of *o*-tolylphosphonic acid monoethyl esters **192** (Scheme 44).[185] They found that when these compounds reacted with electron deficient alkenes in the presence of a Rh-catalyst, an oxidant (AgOAc) and a base, producing

two products in an almost equimolar ratio: alkenyl product **193** and benzoxaphosphole **194**. It is clear that benzoxaphosphole **194** results from intramolecular *oxa*-Michael addition of **193**. Base and solvent screening led to optimized conditions in which only the desired benzoxaphospholene **194** was produced in 85% isolated yield. Substrate scope determination revealed that a variety of electron-deficient alkenes readily reacted to give the benzoxaphospholenes **194** in high yields. Alkenes lacking an EWG however (styrene, 4-phenyl-1-butene, cyclohexene, vinyltriethoxysilane, vinyltrimethylsilane) did not engage in this reaction. Other substituents in *ortho* position of the phosphonate - such as halogens, alkoxy and phenyl groups - were well tolerated, as well as additional substituents on the aromatic ring. Adding a methyl substituent on the 5-position lowered the yield of the benzoxaphospholene considerably though, as it is probably generating too much steric hindrance for the C-H activation to occur efficiently.



Scheme 44: Rh-catalyzed C-H activation of *o*-tolylphosphonic acid monoethyl esters producing benzoxaphospholenes.

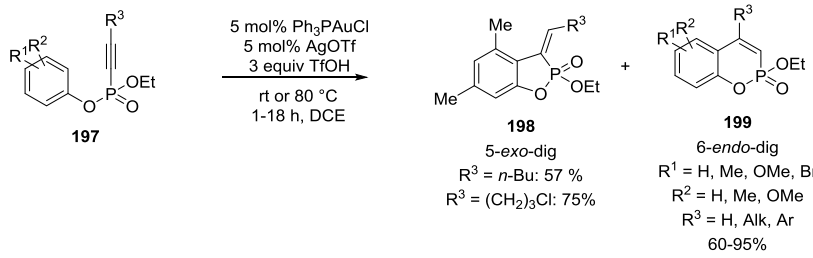
When phenylphosphonic acid monoethyl ester **195** was selected as a substrate for this reaction, dialkenylation of both *ortho*-positions occurred (Scheme 45). One of the two subsequently underwent an *oxa*-Michael addition, affording 3-alkenylated-7-alkylated benzoxaphospholenes **196**. Again, a variety of electron withdrawing or electron donating substituents in *para*-position was tolerated. *Meta*-substituted (R^1 = Me, Br) phenyl phosphonic acid monoethyl esters produced monoalkenylated benzoxaphospholenes, which did not undergo an *oxa*-Michael addition, seemingly illustrating that a subtle balance between the electronic and steric properties of the substituents on the aromatic ring is required for the tandem reaction.



Scheme 45: Rh-catalyzed dialkenylation of phenylphosphonic acid monoethyl ester.

2.5.3. Au-catalyzed hydroarylation

Just a couple of months later, Lee's group reported on the hydroarylation of aryl alkynylphosphonates **197** (Scheme 46).[186] Phosphacoumarins **199** were consistently produced in moderate to excellent yields via a 6-*endo*-dig cyclization. However, in the case of certain disubstituted aryl derivatives, a 5-*exo*-dig cyclization mode became the dominant or even exclusive pathway to yield benzoxaphospholenes **198** in decent yields.



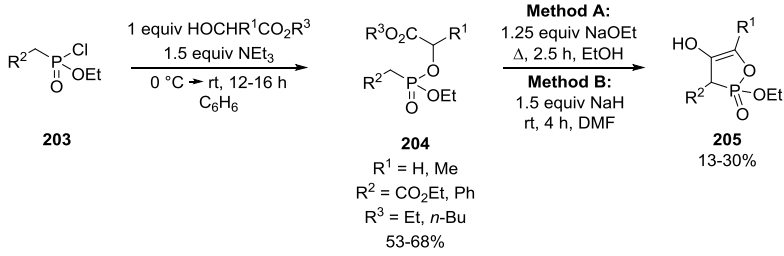
Scheme 46: Au-catalyzed hydroarylation of aryl alkynylphosphonates yielding benzoxaphospholenes and phosphacoumarins.

2.6. Horner-Wadsworth-Emmons-type reactions

In their quest for new pyridazine derivatives, Shaddy's group explored additions of stabilized phosphonate carbanions to a densely functionalized pyridazine **200**.[187] Treatment of pyridazine **200** with a small excess of methylthio methylphosphonate **201**, afforded the dihydro oxaphospholo pyridazine-2-oxide **202** under microwave irradiation in good yield (Scheme 47). In an antibacterial (versus *B. tumefaciens*, *S. aureus* and *K. pneumonia*) and antifungal (versus *A. niger*, *A. flavus*) screening, compound **202** was found to be 1.1 to 1.6 times as active as the standards Streptomycin and Mycostatin.

Scheme 47: Synthesis of dihydro oxaphospholo pyridazine-2-oxide 202 through addition of methylthio methylphosphonate to a pyridazinone.

When alkylphosphonochloridates **203** are reacted with α-hydroxyesters, phosphonates **204** are obtained in decent yields (Scheme 48).[188] After deprotonation, ring closure leads to 4-hydroxy oxaphospholenes **205** in poor yields.



Scheme 48: Reaction of alkylphosphonochloridates with α-hydroxyesters.

Quite recently, the Postel group synthesized a variety of saccharidic spirocyclic 4-amino oxaphospholenes **210** (Scheme 49).[189] These compounds were prepared as precursors for P-TSAO-T **207**, a family of spirocyclic, phosphorus-containing nucleoside analogues of TSAO-T **206** (Figure 9). TSAO-T and earlier described derivatives display significant activities against Reverse Transcriptase Human Immunodeficiency Virus type-1 (RT-HIV-1) and Hepatitis C Virus (HCV).[190-192] As they only differ in the heteroatom in the unsaturated ring, phosphorus instead of sulfur, these derivatives were of interest as new potential lead compounds. The difference in polarity of the P=O bond, because of the lower electronegativity of phosphorus, in comparison to the S=O bond, might induce important changes in the formation of hydrogen bonds in the binding pockets.

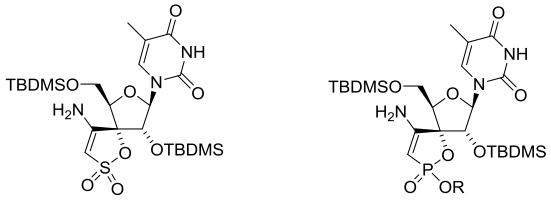
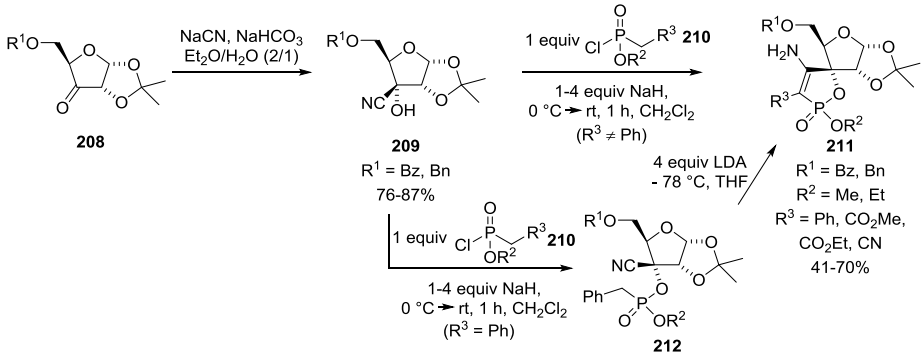


Figure 9: Structures of TSAO-T and P-TSAO-T (RT-HIV-1 and HCV inhibitors).

The key step in this synthesis consisted of the generation of a stabilized carbanion that would create the second ring upon attack of the nitrile function. A screening of reaction conditions revealed that an extra EWG, next to the phosphonate, was required to prevent degradation. Thus, *ribo*-cyanohydrin **209** was prepared from ketose **208**, an oxidized derivative of D-xylose, under Strecker conditions (Scheme 49). A one-pot two-step reaction with NaH and phosphonochloridates **210** afforded the desired spirocyclic oxaphospholenes **211** in moderate yields. The 3-phenyl substituted oxaphospholene could not be prepared in a one-pot sequence and required treatment of the phosphonate intermediate **212** with LDA to afford the corresponding spirocyclic oxaphospholene.

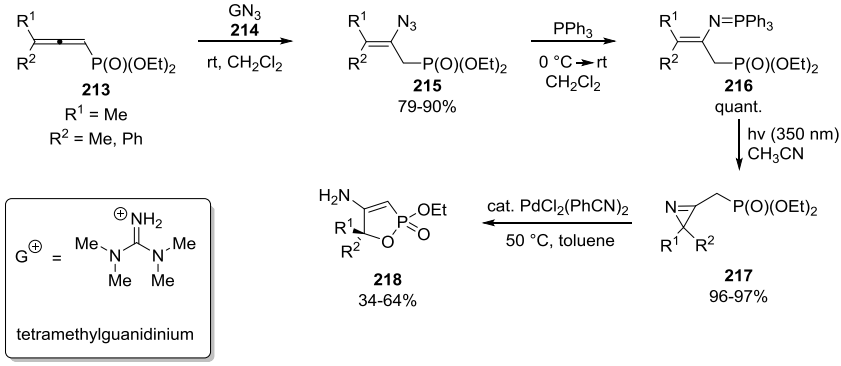


Scheme 49: Synthesis of P-TSAO-T precursors.

2.7. Other methods

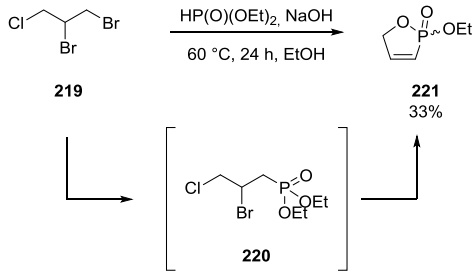
In 1990, Abramovitch reported on the thermolysis of azirinylmethylphosphonates **217** (Scheme 50).[193] These were prepared through addition of tetramethylguanidinium azide **214** to allenylphosphonates **213** and trapping of the resulting azido vinylphosphonates **215** with triphenylphosphine. The obtained phosphinimines **216** could be transformed into the corresponding azirinylmethylphosphonates **217** through photolysis in excellent yields.

Finally, the 4-amino oxaphospholenes **218** were obtained in moderate yields by heating in toluene with catalytic amounts of $PdCl_2(PhCN)_2$.



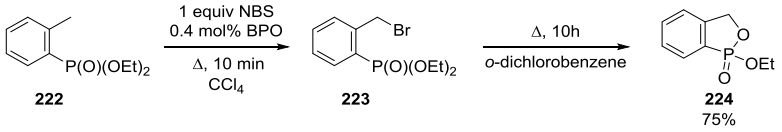
Scheme 50: Thermolysis of azirinylmethylphosphonates yielding oxaphospholenes.

A simple one-step synthesis of oxaphospholenes consists of a nucleophilic substitution reaction of 1,2-dibromo-3-chloropropane **219** with diethyl phosphite, first yielding a dihaloalkyl phosphonate intermediate **220**. Intramolecular displacement of the chloride by the phosphonate oxygen atom is then followed by dealkylation of the resulting phosphonium intermediate and elimination of HBr to yield the oxaphospholene **221** (Scheme 51).[194]



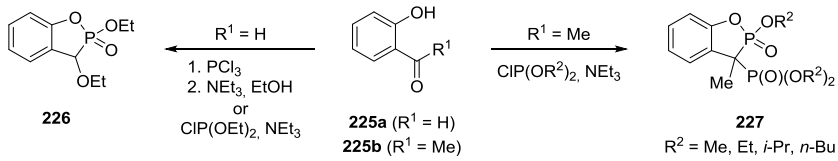
Scheme 51: Preparation of unsubstituted oxaphospholenes from 1,2-dibromo-3-chloropropane and diethyl phosphite.

In 1981, Miles published a synthesis starting from arylphosphonate **222** (Scheme 52).[195] After bromination with NBS and intramolecular displacement of the bromide in aryl phosphonate **223**, dealkylation of the resulting phosphonium intermediate yielded benzoxaphospholene **224** upon refluxing in *o*-dichlorobenzene.



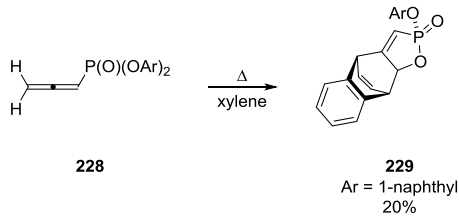
Scheme 52: Synthesis of benzoxaphospholenes through intramolecular reaction of *o*-phosphonylated benzyl bromides.

Benzoxaphosphole oxides could also be prepared from salicylaldehyde **225a** or from 1-(2-hydroxyphenyl)ethan-1-one **225b** in a reaction with $ClP(OEt)_2$ or with PCl_3 followed by ethanolysis.[196, 197] Depending on the substrate, benzoxaphospholene oxides **226** or **227** were obtained (Scheme 53).



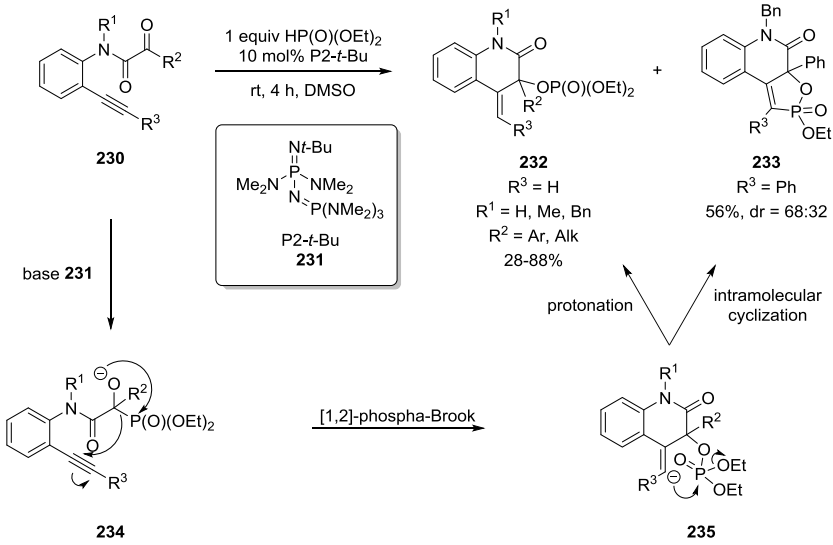
Scheme 53: Synthesis of benzoxaphospholenes through treatment of salicaldehydes with trivalent phosphorus compounds.

On prolonged heating in xylene, dinaphthyl propadienylphosphonate **228** afforded the tricylic structure **229** in poor yield through an intramolecular Diels-Alder reaction (Scheme 54).[198] Only one diastereomer is formed, presumably the one experiencing the least steric repulsion. Diphenyl propadienylphosphonate, nor dinaphthyl 3-methyl-1,2-propadienylphosphonate reacted in this intramolecular Diels-Alder reaction.



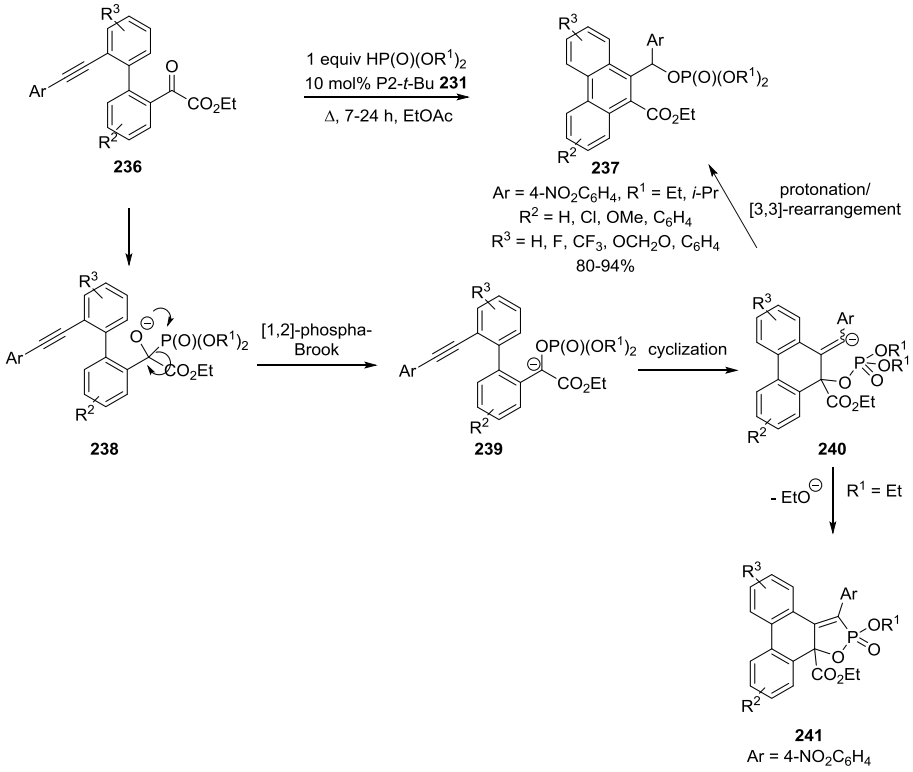
Scheme 54: Diels-Alder reaction of diaryl allenylphosphonates yielding tricylic benzoxapholenes.

Quite recently, Terada described a cyclization reaction of alkynyl α-ketoanilides **230**. Addition of dialkyl phosphites to the ketone moiety gives 3,4-dihydro-2-quinolones **232** after a 1,2-phospha-Brook rearrangement (Scheme 55).[199] In the case where the alkyne bears a phenyl substituent (R^3 = Ph), the vinylic anion attacks the phosphorus atom, eliminating one of the ethoxides and thus generating tricyclic structure **233**.



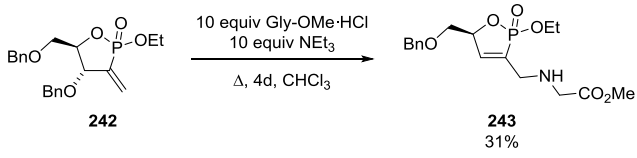
Scheme 55: Preparation of tricyclic oxaphospholenes from cyclization of alkynyl α-ketoanilides.

The group of Terada looked to extend this tandem [1,2]-phospha-Brook rearrangement/cyclization methodology to other derivatives. The addition of diethyl phosphites on 2-(2'-alkynylaryl)-benzoates **236** initially produced only limited amounts of the desired phenanthrene derivatives **237** until optimized conditions were found (Scheme 56).[200] An important by-product was tetracyclic oxaphospholene **241**, originating from an attack of the vinylic anion intermediate **240** on the phosphorus center, eliminating an ethoxide. Compound **241** was isolated, but the yield was not reported. This side reaction was suppressed by switching to diisopropyl phosphite as the nucleophile and the pathway to tetracyclic oxaphospholenes **241** was not further explored.



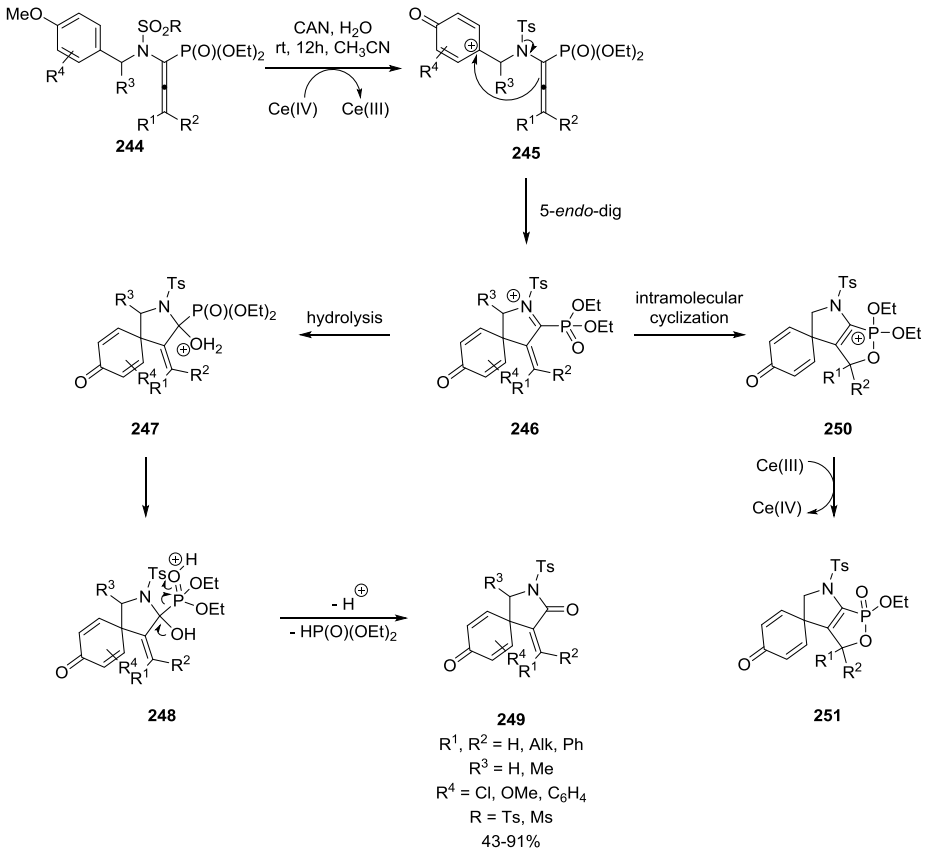
Scheme 56: [1,2]-Phospha-Brook rearrangement-cyclization yielding phenanthrenes and tetracyclic oxaphospholenes.

During their work on phosphonylated carbohydrate derivatives, the group of Suarez reported an S_N2' substitution reaction on phospha-1-oxo-pentofuranoses **242** by glycine methyl ester producing oxaphospholene **243** (one diastereomer shown) (Scheme 57).[201, 202]



Scheme 57: S_N2' substitution reaction on phospha-1-oxo-pentofuranoses by glycine methyl ester.

Attempting to deprotect the PMB protecting group of aminoallenylphosphonates **244** using CAN, the group of Rabasso discovered that a rearrangement took place, yielding spirodienone lactams **249** in moderate to high yields, with concomitant expulsion of diethyl phosphite (Scheme 58).[203]



Scheme 58: Proposed mechanism for the synthesis of spirodienone lactams upon treatment of PMB-protected 1-aminoallenylphosphonates with CAN.

In some cases the spirodienone lactams **249** were produced in reduced yields or not at all. In three of those cases, the authors were capable of isolating tricyclic structures **251** (Figure 10). In the case of the aminoallenylphosphonate derived from 4-chromanone, which did not produce the corresponding spirodiene lactam, spirocyclic oxaphospholene **254** was obtained in a high yield of 84%. A plausible mechanism was proposed in which intermediate **246** underwent intramolecular cyclization instead of the hydrolysis and subsequent diethyl phosphite expulsion steps. Oxidation of the resulting phosphonium ion **250** with CAN would lead to tricyclic oxaphospholenes **251**. The authors reasoned that without the addition of water, increased yields should be obtained as competitive formation of the spirodienone lactams would not be possible. However, this was true for only one example. Additionally, one substrate that did give a good conversion to the spirodienone lactam **249**, could also produce the tricyclic

oxaphospholene **255** in a fair 30% yield, when the reaction was run in the absence of water. Other substrates could not be engaged in this transformation.

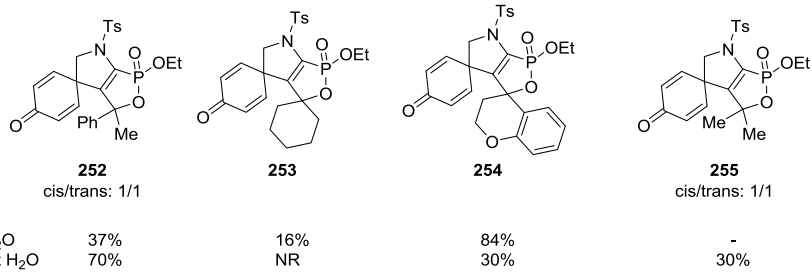


Figure 10: Prepared spirocyclic oxaphospholenes through treatment of PMB-protected 1-aminoallenylphosphonates with CAN.

3. Conclusions

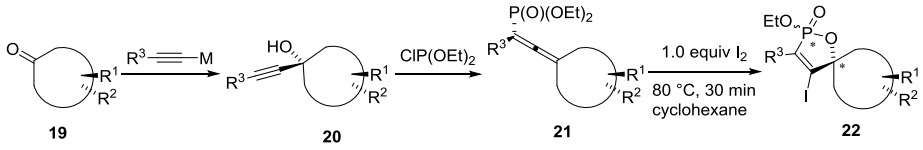
Benzoxaphospholenes and oxaphospholenes have been investigated for half a century now with new syntheses appearing frequently. The first synthetic routes were mainly focusing on benzoxaphospholenes and were conducted under harsh conditions. With allenylphosphonates becoming easily accessible precursors, the possible transformations towards oxaphospholenes really boomed. Initially, difficult to handle and toxic reagents such as halogens, alkylsulfenyl- and alkylselenylhalides were mainly employed. Later, safer alternatives such as copper halides made their entry. Transition-metal catalyzed reactions impressively opened up the structural variety of (benz)oxaphospholenes that could be prepared: cross coupling reactions afforded vinyl-substituted oxaphospholenes, C-H activitation yielded a multitude of substituted benzoxaphospholene derivatives while an alternative approach to (benz)oxaphospholenes was realized through RCM. The development of P-TSAO-T's as potentially new antiviral agents illustrates possible applications. With the emergence of more sophisticated precursors, such as bisallenylphosphonates or PMB-protected 1-aminoallenylphosphonates, the structural complexity of novel oxaphospholenes has drastically increased in recent years. New exciting studies on the design of novel methodologies for the preparation of oxaphospholenes with even more structural variety are definitely to be expected in the future.

Results and Discussion

1. Three-step synthesis of chiral spirocyclic oxaphospholenes

1.1. Introduction

The importance of chiral BINOL phosphate catalysts in asymmetric transformations may hardly be overestimated. Although many chiral catalysts have been prepared and assessed for their enantioselective properties, only few have been applied on a broad scope of substrates. Together with, amongst others, Salen complexes, bis(oxazoline) ligands and cinchona alkaloids, BINOL and the derived BINOL phosphates belong to the class of 'privileged chiral inducers'. Since the pioneering reports of the groups of Akiyama and Terada in 2004 on asymmetric Mannich-type reactions,[204, 205] BINOL phosphoric acid derivatives have been deployed in asymmetric versions of numerous and important organic transformations such as Friedel-Crafts,[206] Pictet-Spengler,[207] Strecker,[208] reductive amination[209] and hydrophosphonylation reactions,[210] as well as transfer hydrogenations.[211, 212] The outstanding characteristics of BINOL phosphates to control enantioselectivities originate from the phosphorus containing seven-membered ring and the chiral binaphthyl moiety, locking the conformation of the Brønsted acid function.[213] Inspired by our expertise in oxaphospholene chemistry,[174, 214] the synthesis of phosphorus containing allenes[53, 215] and heterocycles[40, 41, 216], we envisioned the synthesis of chiral spirocyclic oxaphospholenes **22**, which may be of interest for the design of new chiral phosphonic acid catalysts. Even though the halocyclization of (3-cyclohexyl)allenylphosphonates to spirocyclic oxaphospholenes has been known for a few decades,[121, 168] this is the first example of the design of such spirocyclic compounds that are chiral. The synthesis we envisioned is based on three successive transformations from readily available chiral starting materials. Addition of an organometallic acetylide to chiral pool ketoterpenes **19**[217] will be followed by treatment of the resulting propargylic alcohols **20** with diethyl chlorophosphite (Scheme 59).[107, 108] Subsequently, the obtained chiral allenylphosphonates **21** will finally be subjected to a halocyclization to give the desired chiral spirocyclic oxaphospholenes **22**.[168]



Scheme 59: Approach to chiral spirocyclic oxaphospholenes.

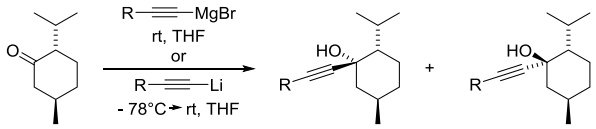
1.2. Synthesis of chiral spirocylic oxaphospholenes

1.2.1. With a varying alkyne substituent

a. Synthesis of propargylic alcohol precursors

The first objective was the synthesis of propargylic alcohols **257** from cheap and commercially available chiral pool ketoterpenes **256**. (-)-Menthone was selected as a model substrate and was reacted with ethynylmagnesium bromide to swiftly yield the corresponding propargylic alcohols **256a** and **257a**. A good diastereoselectivity was obtained and the diastereomers were easily separated and isolated in 87% yield (Table 1, entry 1).

Table 1: Optimized conditions for preparation of propargyl alcohol precursors.



256 **257a-e** **258a-e**

entry	R	equiv acetylide	t (h)	*dr*[a]	yield (%)[b]
1	H	1.3[c]	2	80/20	87
2	Ph	1.8[c]	16	75/25	79
3	4-MeC_6H_4	1.5[d]	24	73/27	91
4	2-MeC_6H_4	1.3[d]	16	76/24	89
5	*n*-Bu	1.5[d]	3	81/19	95

[a] determined by GC-MS [b] isolated yield of separated diastereomers combined
[c] commercially available Grignard reagent was used [d] lithium acetylide was prepared *in situ* with 1.6 equiv *n*-BuLi

A series of (-)-menthone derived propargylic alcohols was consecutively prepared, making use of different alkynes. In each reaction, conversions were complete and the diastereoselectivities of the acetylide addition were comparable (entries 2-5). The acetylides were prepared *in situ* by deprotonation of the corresponding alkynes with *n*-BuLi, unless a Grignard reagent was commercially available, as in the cases of acetylene and phenylacetylene.

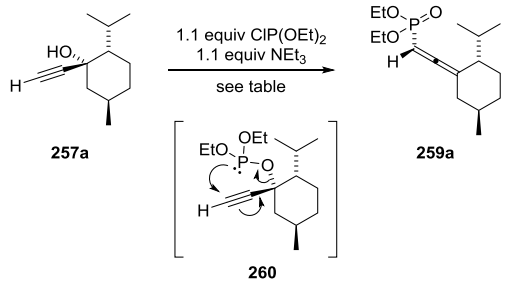
b. Synthesis of allenylphosphonates

Allenylphosphonates are traditionally prepared by phosphonylation of progargylic alcohols with dialkyl chlorophosphite in diethyl ether, after which the resulting dialkyl propargyl phosphite spontaneously rearranges to produce a thermodynamically more stable, pentavalent allenylphosphonate.[107, 108] Recently, catalytic transformations using non-toxic dialkyl phosphites, have been described by the groups of Stawinski, Han and Zhao. While the latter two methods either failed to produce or did not report on the transfer of central-to-axis

chirality,[218, 219] Stawinski conditions allowed a clear transfer of the chirality present in the propargylic starting materials.[220, 221] However, the catalytic system required the propargylic alcohol precursors to be modified to contain a good leaving group. We considered this extra derivatization step as a drawback and opted to use dialkyl chlorophosphites for the direct [2,3]-sigmatropic rearrangement using propargylic alcohols **257a**-**e**, as it displays simultaneous center-to-axial chirality transfer owing to a concerted mechanism.[168, 221, 222]

In a preliminary experiment, a mixture of diastereomers **257a** and **258a** (55/45) was treated with diethyl chlorophosphite and triethylamine (Table 2, one diastereomer shown). After one hour at room temperature, all of the **258a** starting material had been consumed (entry 1). Only after addition of a second portion of diethyl chlorophosphite and overnight stirring at room temperature, phosphonylation of the sterically more demanding propargylic alcohol **257a** started to take place. Refluxing **257a** in diethyl ether with an excess of diethyl chlorophosphite gave a complete conversion, but only after 6 days (entry 2). The product was not purified, because more optimized reaction conditions were first searched for. Preforming the alkoxide by treatment of alcohol **257a** with NaH prior to the addition of diethyl chlorophosphite, did not enhance the progress of the reaction at room temperature (entry 3).

Table 2: Optimized conditions for preparation of allenylphosphonate precursors.



entry	t (h)	T	solvent	**259a** (%)[a]	yield (%)[b]
1[c]	1	0 °C to rt	Et_2O	55	-
	16	rt		67	
2	6 days	Δ	Et_2O	100	-
3[d]	5	0 °C to rt	Et_2O	0	-
4[e]	17	Δ	THF	79	-
	2			98	43
5[f]	24	Δ	THF	95	75

[a] conversion determined by GC-MS [b] isolated yield [c] a 55/45 mixture of **257a**/**258a** was used
[d] NaH instead of NEt_3 [e] 0.5 equiv $ClP(OEt)_2$ was added after 17 h [f] 2 equiv $ClP(OEt)_2$

When refluxing propargyl alcohol **257a** in THF in the presence of diethyl chlorophosphite and triethylamine, 79% conversion to the corresponding allenylphosphonate **259a** was achieved

after 17 hours. Additionally adding half an equivalent of diethyl chlorophosphite, gave complete conversion with complete diastereoselectivity after heating for two more hours (entry 4).

Although Stawinski reported that racemization of allenylphosphonates may occur upon prolonged heating when even weakly nucleophilic chloride species are present in the reaction mixture,[221] no epimerization was observed in our case. With an excess of diethyl chlorophosphite (2 equivalents, added in one portion), the allenylphosphonate **259a** was isolated in 75% yield (entry 5). Under these optimised conditions, all of the (-)-menthone derived propargylic alcohols **257a**-**e** reacted smoothly to give the allenylphosphonates **259a**-**e** in yields up to 78% (Figure 11).

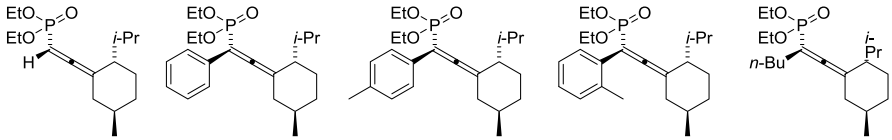
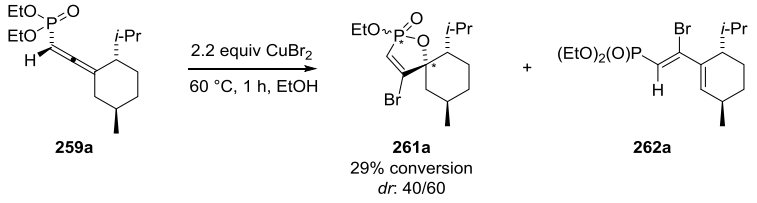


Figure 11: Allenylphosphonates based on the (-)-menthone backbone.

c. Cyclization to oxaphospholene spirocycles

Ma reported the copper-mediated cyclization of allenylphosphonates, using a twofold excess of CuX_2, to give halogenated oxaphospholenes.[168] Upon addition of 2.2 equivalents of $CuBr_2$, starting material **259a** was indeed entirely consumed and two epimers at the phosphorus atom were formed, along with three unidentified products and a monobrominated product **262a**, resulting from bromine addition followed by HBr elimination (Scheme 60). Unsurprisingly, purification on silicagel was unsuccessful, as oxaphospholenes are known to hydrolyse during chromatography.[85, 173]

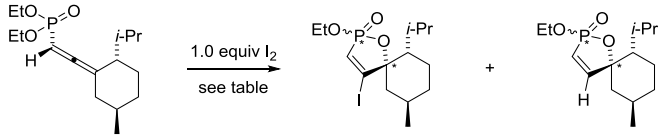


Scheme 60: $CuBr_2$-mediated synthesis of spirocyclic oxaphospholene 261a (conversion and *dr* determined *via* ^{31}P NMR).

Fortunately, when simply heating a solution of allenylphosphonate **259a** with one equivalent of I_2 in chloroform for half an hour, a mixture of only two oxaphospholene epimers **263a** was obtained (Table 3, entry 1).[115, 126, 169, 223, 224] In this transformation, two stereogenic centers were

simultaneously created and consequently four enantiopure diastereomers could be formed. Interestingly, only two diastereomers were obtained. Most probably, the control of chirality was highly efficient at the quaternary carbon, while dealkylation of the phosphonate was non-selective. The two stereoisomers are only epimers at the phosphorus atom. Unfortunately, the product was not crystalline and consequently, the absolute configuration could not be determined via X-ray diffraction. In previous research, however, it has been shown that the axial chirality was efficiently transferred to center chirality.[169] Thus, the stereochemistry depicted in Table 3 is mechanism-based. According to ^{31}P NMR, 8% of side-product **264a** was detected, probably resulting from Brønsted acid induced cyclization (HI). In order to minimize the moisture content in the mixture, different combinations of solvent, temperature, inert atmosphere and glassware were screened (entries 1-5). Heating the mixture in cyclohexane under nitrogen atmosphere in a dried Schlenk flask were found to be the optimal conditions. Attempts were made to influence the diastereomeric ratio by varying the temperature or the solvent (entries 1-3, 5, 6). A slightly better diastereomeric ratio was obtained, than those observed by Ma's copper-mediated synthesis of non-spirocyclic oxaphospholenes.[168]

Table 3: Optimization of spirocyclic oxaphospholene synthesis.



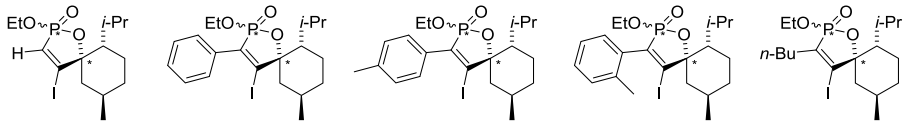
259a **263a** **264a**

entry	t (h)	T (°C)	solvent	**263a** (%)[a]	dr (%)[a]	yield (%)[b]
1	0.5	110	$CHCl_3$[c]	87	39/61	-
2	0.5	100	DCE[c]	93	39/61	-
3	0.5	80	DCE[c]	95	38/62	-
4	0.5	80	DCE[c]	92	39/61	-
5[d]	0.5	80	cyclohexane	100	40/60	91
6	3.5	35	*n*-pentane[d]	70	38/62	-

[a] conversion determined by ^{31}P NMR [b] combined isolated yield, no purification
[c] anhydrous [d] Ar instead of N_2 atmosphere

These optimized conditions were then applied to substrates **259a-e** to give a series of chiral spirocyclic oxaphospholenes while no purification step was needed (Figure 12). Cyclization was not hampered by the increased steric hindrance of a phenyl or *p*-tolyl substituent (87-94% yields). It was observed that an *o*-tolyl substituent was equally well tolerated and the oxaphospholene was isolated in excellent yield (91%). Thanks to rotation of the aromatic ring, the *o*-methyl group could be oriented away from the allene, allowing iodine also in this case to be attacked by the distal allenyl double bond. For such compounds, steric hindrance induces

slow rotation of the $C_{o\text{-tolyl}}$-$C_{oxaphospholene}$ bond and rotamers were observed in both ^{1}H NMR and ^{13}C NMR. An *n*-butyl substituent did not pose any problems either and the oxaphospholene **263e** was isolated in almost quantitative yield.



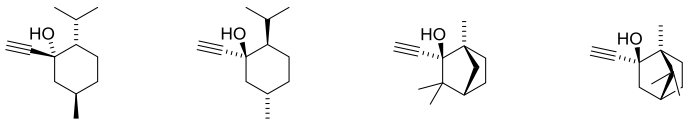
263a 91% 80 °C, 30 min | **263b** 94% 80 °C, 30 min | **263c** 87% 80 °C, 30 min | **263d** 91% 80 °C, 30 min | **263e** 95% 80 °C, 30 min

Figure 12: Spirocyclic oxaphospholenes based on the (-)-menthone backbone.

1.2.2. With a varying ketoterpenic backbone

a. Synthesis of propargylic alcohol precursors

In a second series of propargylic alcohols, the alkyne part remained unchanged while the ketoterpenic moiety was varied. Although commercially available, (+)-menthone was quantitatively prepared from the much cheaper (+)-menthol by Dess-Martin oxidation and subsequently transformed into the propargylic alcohol **257f** with ethynylmagnesium bromide (Figure 13, one diastereomer shown). (-)-Fenchone and (+)-camphor reacted sluggishly with the Grignard reagent and dimerization was observed when switching to less mild reaction conditions. Nevertheless, with the *in situ* generated lithium trimethylsilyl acetylide, the bicylic propargylic alcohols **257g** and **257h** were obtained in good yields after TMS-deprotection.[225] Moreover, thanks to the increased steric hindrance of the bicyclic backbone, one diastereomer was exclusively formed in both cases.



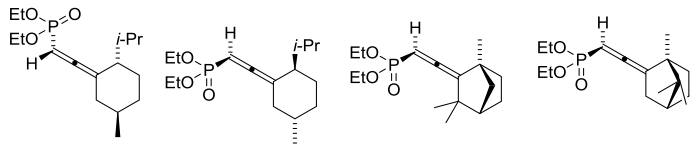
257a *dr*: 80/20[a] 87%, 2 h | **257f** *dr*: = 76/24[a] 73%, 2 h | **257g** *dr*: = 97/3[a] 72%[b], 2 h | **257h** *dr*: = 98/2[a] 58%[b], 2 h

[a] determined by GC-MS [b] yield over two steps

Figure 13: Propargyl alcohol precursors with varying terpenic backbone.

b. Synthesis of allenylphosphonates

Next, allenylphosphonates **259f-h** with a fenchone- or camphor-based structure were prepared, using the earlier optimized conditions (Figure 14). All allenylphosphonates were easily isolated in moderate to good yields (56-75%).



259a
75%, 24 h

259f
56%, 24 h

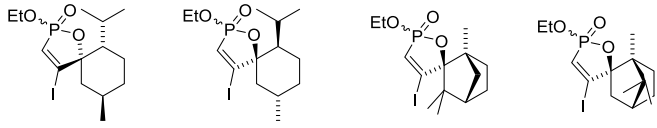
259g
67%, 24 h

259h
59%, 24 h

Figure 14: Allenylphosphonates with varying terpenic backbone.

c. Cyclization to oxaphospholene spirocycles

(+)-Menthone derived allenylphosphonate **259f** was easily cyclized to give spirocyclic oxaphospholene **263f** in excellent yield (Figure 15). Oxaphospholene **263g**, derived from (+)-fenchone, was not formed under standard conditions though. As the starting material was recovered unchanged, the reaction temperature was increased to 110 °C. Unfortunately, a mixture of starting material and unidentified rearrangement products was then obtained, while oxaphospholene **263g** was not detected. The decreased reactivity at 80 °C was probably a result of the increased steric hindrance around the distal double bond of allenylphosphonate **259g**, which prevented the electrophilic attack of iodine. When reacted at 80 °C for three hours, a mixture of at least ten phosphonylated compounds with an important amount of starting material was obtained. In the case of (+)-camphor derived allenylphosphonate **259h**, the starting material was rapidly consumed at 80 °C and a complex mixture of phosphonylated products was obtained, in which oxaphospholene **259h** was not present. Running the reaction at 60 °C instead, did not improve selectivity, while the starting material **259h** was not even entirely consumed. These results were not unsurprising though, as camphor is known to be prone to rearrangements in acidic media, of which fenchone is an intermediate.[226, 227] Although a stable tertiary carbocation is initially formed, isomeric intermediates must be formed just as easily.



263a
91%
80 °C, 30 min

263f
92%
80 °C, 30 min

263g
-
110 °C, 30 min

263h
-
60 °C, 30 min

Figure 15: Spirocylic oxaphospholenes with varying terpenic backbone.

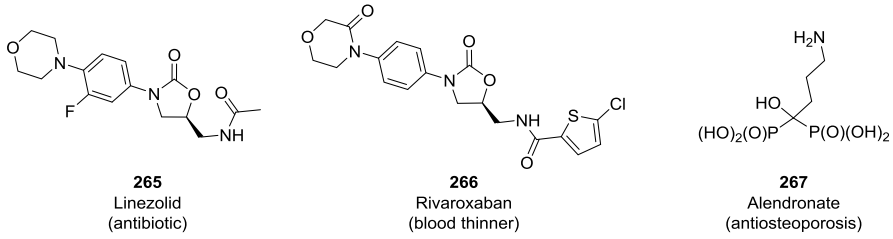
1.3. Conclusion

In conclusion, we have exemplified for the first time that chiral spirocyclic oxaphospholenes can be synthesized in a three-step sequence from chiral pool ketoterpenes. Addition of metal acetylides gives the corresponding propargylic alcohols in high yields with good to excellent diastereoselectivities, depending on the steric hindrance of the substrate. All of these propargyl alcohols were easily converted to the corresponding allenylphosphonates with diethyl chlorophosphite. Upon addition of a stoichiometric amount of iodine, bicyclic oxaphospholenes were swiftly obtained, without the need for purification. Bridged allenylphosphonates, derived from camphor and fenchone, either did not react due to steric hindrance or rearrangement, and did not yield the desired spirocyclic oxaphospholenes in both cases. The deprotection of the phosphonate moiety still needs to be addressed before the chirality inducing properties of the spirocyclic oxaphospholenic acids can be evaluated.

2. Synthesis of 5-bisphosphonomethyl oxazol-2-ones and 5-phosphonomethylidene oxazolidin-2-ones

2.1. Introduction

Oxazolidin-2-ones have attracted a lot of attention as chiral auxiliaries (e.g. Evans oxazolidinones),[228] as key structural components of natural products[229] and as the pharmacophore of antibiotics used in the treatment of multi-drug resistant infections[230-234] and blood thinners[235]. Linezolid **265**, for instance, was found to have the best pharmacokinetic properties in a series of oxazolidin-2-one antibiotics and got approved by the FDA in 2000 (Figure 16).[236] Rivaroxaban **266** was approved in 2008 by the European Commission to prevent thromboembolism.[235] Moreover, the oxazol-2-ones are interesting building blocks themselves,[237, 238] often used in the synthesis of natural products and their analogues.[239, 240] Bisphosphonomethyl oxazol-2-ones have never been reported before, although the bisphosphonomethyl moiety is a crucial motif of bisphosphonate drugs (f.i. Alendronate **267**), used in the treatment of osteoporosis. A facile entry into compounds containing both the oxazolone and bisphosphonomethyl motif would be of interest for the evaluation of their biological properties.



265
Linezolid
(antibiotic)

266
Rivaroxaban
(blood thinner)

267
Alendronate
(antiosteoporosis)

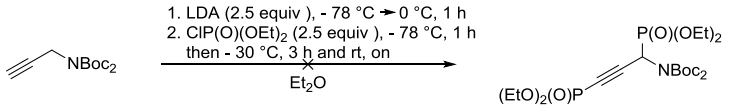
Figure 16: Examples of oxazolidin-2-one (left and center) and bisphosphonate (right) drugs.

2.2. One-pot synthesis of bisphosphonomethyl oxazol-2-ones

*2.2.1. Identification and plausible reaction mechanism of bisphosphonomethyl oxazol-2-one **24***

The synthesis of phosphonylated azaheterocycles on the one hand and gold-catalyzed cyclization reactions on the other hand, have attracted our group's interest for quite some time.[35, 40, 41, 50, 241-244] Looking to evaluate the gold-catalyzed cyclization reaction of phosphonylated propargylamines, we were interested in preparing the protected 3-amino, 3-phosphono prop-1-yn-1-yl phosphonate **268**.

N,*N*-di-*tert*-butylprop-2-yn-1-ylimidodicarbonate **23** was synthesized from propargylamine and di-*tert*-butyl dicarbonate in 83% yield.[245] Subsequently, it was treated with 2.5 equivalents of both LDA and diethyl chlorophosphate (Scheme 61).



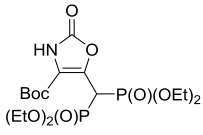
23 **268**

Scheme 61: Failed attempt to synthesize 3-phosphonopropargylamino phosphonate 268 in a one-pot procedure.

To our surprise, ^{31}P NMR indicated that the major product was no alkynylphosphonate (it lacked a characteristic shift around -7 ppm), but appeared in the region of phosphonates connected to an sp^2 or sp^3 carbon (around 15 ppm). LC-MS analysis, however, showed that the mass of the desired compound (minus isobutene) was present, so it was concluded that a rearrangement to an isomer had occurred. After purification, the major compound was isolated as a crystalline material. NMR data revealed that

- a bisphosphonate unit was clearly present (triplet in ^{13}C NMR at 37.5 ppm, $^1J_{CP}$ = 133.3 Hz, one single peak in ^{31}P NMR at 14.2 ppm)
- the alkyne carbons were changed to alkene carbons
- two carbamate-like carbons were present, although only one *t*-Bu group was present in ^{1}H NMR
- a proton on a heteroatom was present (broad singlet at 8.20 ppm in ^{1}H NMR)

This led to the conclusion that a cyclization reaction had taken place, with a *N* to *C* Boc-shift. X-ray diffraction confirmed the structure of the rearranged product to be the bisphosphonomethyl oxazol-2-one **24** (Figure 17).



24

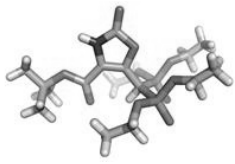
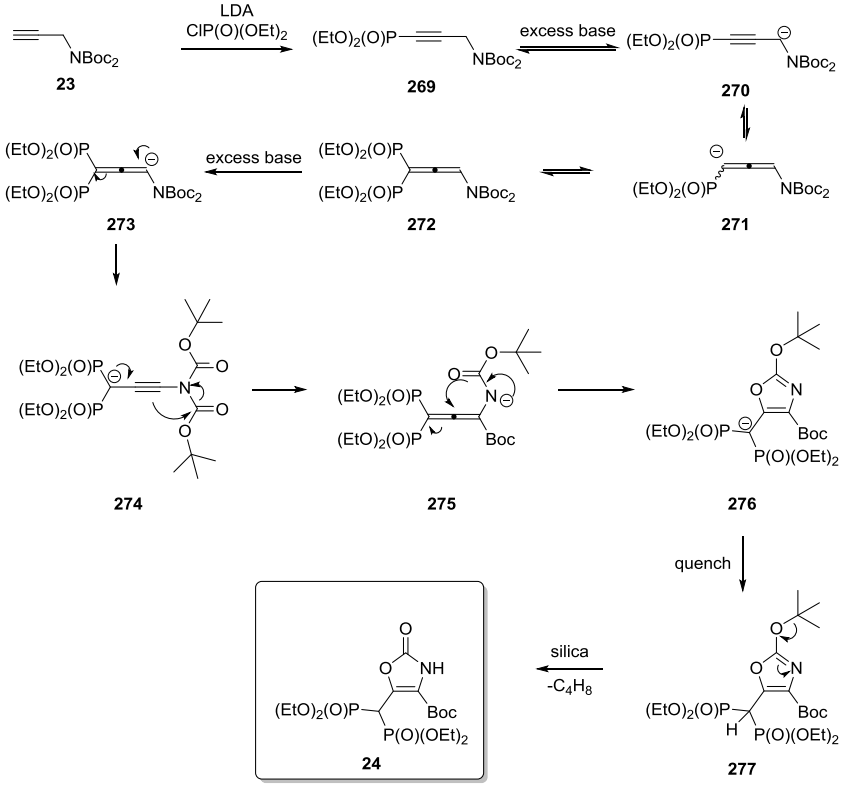


Figure 17: Structure of the bisphosphonomethyl oxazol-2-one 24 (left) formed in the attempted one-pot synthesis of 3-phosphonopropargylamino phosphonate and its X-ray structure (right).

The confirmation of the end product's structure allowed us to propose a plausible reaction mechanism. The alkyne **23** was probably first phosphonylated at the most acidic position (Scheme 62). The excess of base then creates a 3-aminoallenylphosphonate **271** which gets phosphonylated again at the carbon already carrying a phosphonate group. For a [1,2]-Boc-shift to occur, one of the two Boc-groups needs to be attacked. Thus, it is anticipated that after another deprotonation step and isomerization, the Boc-group gets installed on the carbon atom in α-position of the nitrogen atom. Next, the aminoallenylbisphosphonate **275** is ready to be attacked in a 5-exo-*dig* fashion by the carbamate, yielding oxazole **277**. Elimination of isobutene eventually yields the final product **24**. In a control experiment, ^{1}H NMR confirmed that the major product in the reaction mixture contained two *t*-Bu groups, while ^{31}P NMR showed that it had a slightly different shift (15.5 ppm) than the product that was isolated after chromatography. This indicated that the product formed in the reaction mixture most probably was oxazole **277**, which was converted to oxazol-2-one **24** when stirred with silica in ethyl acetate for 24 h.

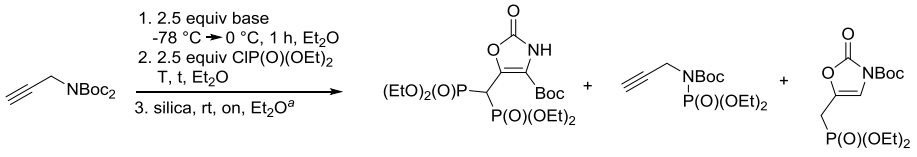


Scheme 62: Plausible mechanism for the formation of 5-bisphosphonomethyl oxazol-2-one 24.

2.2.2. Optimization of reaction conditions for the one-pot reaction

Although compound **24** was the major product in the initial experiment (Table 4, entry 1), conditions were screened to increase the selectivity towards the desired compound and to simplify the procedure. The reaction was run at 0 °C to speed up the conversion, but unfortunately, the desired product was not formed and a complex mixture was obtained (entry 2). When *n*-BuLi was used instead of LDA, it attacked the Boc-group after which the propargylamine was phosphonylated at the *N*-atom, yielding the phosphoramidate **278** as the major product (entry 3). When repeating the original procedure, it was observed that some of the phosphorus-containing side-products could be evaporated at 60 °C and 2 mbar, affording a mixture of 83% purity (entry 4). Besides the bisphosphonomethyl oxazol-2-one **24**, phosphoramidate **278** was detected along with phosphonomethyl oxazol-2-one **279**. This monophosphonylated heterocycle probably results from LDA-induced dealkylation of the Boc-group of alkyne **269**, followed by cyclization. Although the isolated yield could be improved to 17%, purification remained troublesome as the product partly eluted together with side-products such as the monophosphonylated oxazol-2-one **279**.

Table 4: Screened reaction conditions for the one-pot synthesis of 5-bisphosphonomethyl oxazol-2-one 24.



23 **24** **278** **279**

entry	base	T (°C)	t (h)	**24** (%)[b,c]	**278** (%)[b]	**279** (%)[b]
1	LDA	- 78	1	-	-	-
		- 42	3	-	-	-
		rt	on	67	0	0
2	LDA	0	1	-	-	-
		rt	3	0	5	0
3[d]	*n*-BuLi	- 78	1	-	-	-
		- 42	3	-	-	-
		rt	on	8	32	0
4	LDA	- 78	1	-	-	-
		- 42	3	-	-	-
		rt	on	83 (17)	1	2

[a] no anhydrous solvent [b] conversion based on ^{31}P NMR [c] isolated yield between brackets

[d] temperature was kept at - 78 °C for 1 h during deprotonation step

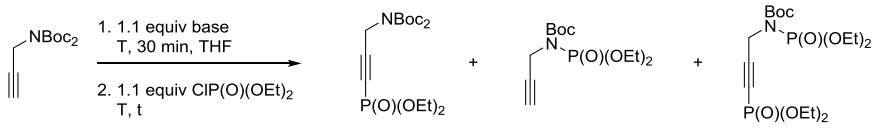
2.3. Stepwise synthesis of bisphosphonomethyl oxazol-2-ones

*2.3.1. Synthesis of 3-amino prop-1-yn-1-yl phosphonate **269***

a. *Via* organolithium bases

As the one-pot synthesis suffered from a low isolated yield, it was investigated whether a more selective reaction could be obtained through a stepwise approach.

Table 5: Phosphonylation of *N,N*-di-*tert*-butylprop-2-ynylimidodicarbonate 23 with diethyl chlorophosphate.



23 **269** **278** **280**

entry	base	T (°C)	t (min)	**269** (%)[b,c]	**278** (%)[b]	**280** (%)[b]
1	*n*-BuLi	- 78	30	54	9	10
2	*n*-BuLi	- 95	30	58	5	9
3[a]	*n*-BuLi	- 95	10	42	1	2
4	LDA	- 95	30	41(3)	0	0
5	LDA	- 95	60	43	6	4
6	LiHMDS	- 95	30	1	28	0

[a] 0.5 equiv *n*-BuLi, 0.5 equiv $ClP(O)(OEt)_2$

[b] conversion based on ^1H NMR [c] isolated yield between brackets

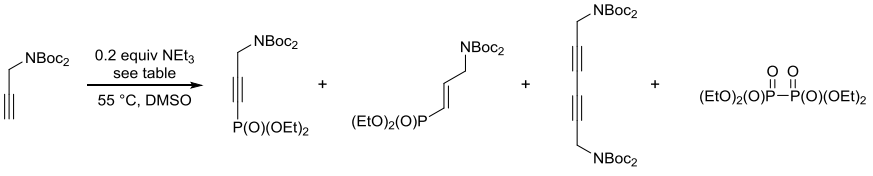
When *N,N*-di-*tert*-butylprop-2-ynylimidodicarbonate **23** was treated with a slight excess of both *n*-BuLi and diethyl chlorophosphate, about half of the starting material was converted to the phosphonylated propargylamine **269** (Table 5, entry 1). Products **278** and **280** result from *n*-BuLi-induced loss of a Boc-group, followed by *N*-phosphonylation. Lowering the temperature to - 95 °C did not result in a more selective reaction (entry 2). When only half an equivalent of reactants were used, selectivity did improve and a proportionally higher conversion was achieved (entry 3). The side-products **278** and **280** were still detected, indicating that these did not result from the excess *n*-BuLi initially used. Isolation of the desired alkyne **269** proved to be impossible as it eluted together with the phosphoramidate **280**. When LDA was employed, the desired product was formed as the major product, and the side-products **278** and **280** were not detected (entry 4). Other unseparable and unidentifiable side-products troubled the purification again, resulting in a low isolated yield of phosphonylated propargylamine **269** of 3%. An important part of the starting material (55%) had not been consumed in the reaction with LDA, so the reaction time was increased. The resulting

conversion did not increase significantly though, and the side-products **278** and **280** were detected again (entry 5). Although all of the starting material was consumed with LiHMDS as base, only trace amounts of phosphonylated alkyne **269** were detected, along with, amongst others, phosphoramidate **278** (entry 6).

b. *Via* a transition metal-catalyzed cross coupling reaction

As it proved to be difficult to obtain the phosphonylated alkyne **269**, an alternative approach was considered. A copper-catalyzed cross coupling reaction of alkynes with dialkyl phosphites under a dry air atmosphere had been reported in literature.[246] *N*-Tosyl propargylamine was oxidatively coupled to diethyl phosphite in the presence of 0.1 equivalent $Cu(OAc)_2$ and 0.2 equivalent NEt_3 in 83% yield on a scale of 0.5 mmol. A big advantage of this method is that diethyl phosphite is a cheap reactant and much more easy to handle than the toxic and moisture-sensitive diethyl chlorophosphate.

Table 6: Copper-catalyzed oxidative phosphonylation of *N,N*-di-*tert*-butylprop-2-ynylimidodicarbonate 23 with diethyl phosphite.



23 **269** **281** **282** **283**

entry	scale (mmol)	equiv DEP	equiv $Cu(OAc)_2$	atmosphere	t (h)	**269** (%)[c,d]	**281** (%)[c]	**282** (%)[c]
1[a]	1.8	0.83	0.083	air	16	21	9	21
2[a,b]	1.8	0.83	0.083	air	16	27	4	19
3[a,b]	1.8	1	0.1	air	16	47	2	3
4	1.8	1.2	0.1	air	16	52	2	6
5	1.8	2	0.1	air	16	74	1	1
6	1.8	4	0.1	air	16	83	12	5
7	10	2	0.1	air	16	3	3	0
8	1	2	0.3	O_2 (1 atm)	4	44	1	0
9	5	3	0.1 + 0.2	O_2 (1 atm)	5	87	1	0
10	5	2 + 1	0.1 + 0.2	O_2 (1 atm)	5	98 (72)	2	0
11	10	2 + 1	0.1 + 0.2	O_2 (1 atm)	5	98 (73)	2	0

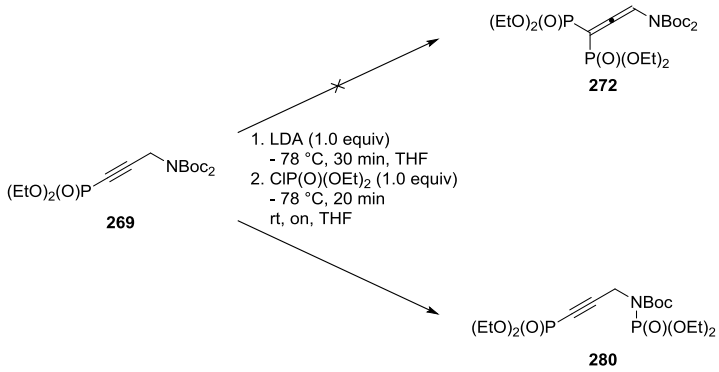
[a] 0.17 equiv NEt_3 was used [b] 80 °C [c] conversion according to ^{1}H NMR [d] isolated yield between brackets

When these conditions were applied on substrate **23** on a slightly bigger scale, a poor and non-selective conversion was obtained (Table 6, entry 1). Increasing the temperature from 55 °C to 80 °C hardly improved the conversion, nor the selectivity (entry 2). Vinylphosphonate **281** resulted from hydrophosphonylation of the alkyne, which occurs when the oxidation step is inhibited.[246] Dialkyne **282** results from a Glaser-Hay coupling because the

dialkyl phosphite was present in a lower than equimolar amount. A clear effect was observed however, when the amount of diethyl phosphite was increased. A conversion of up to 83% was then obtained (entries 1 vs 3-6). Part of the diethyl phosphite is inevitably converted to hypophosphate **283**, particularly when it is used in equimolar or excess amounts.[247] As the alkyne starting material was considered to be the more valuable substrate, it was decided to minimize the formation of Glaser-Hay coupling product **282**, and sacrifice the dialkyl phosphite by adding it in excess amounts. Unfortunately, when the reaction was scaled up, the conversion dropped significantly, indicative of a poor oxygen transfer into the medium (entry 7). To increase the oxygen concentration in solution, oxygen gas was bubbled through the mixture and after merely 4 hours, almost half of the starting material was selectively converted (entry 8). Only trace amounts of hydrophosphonylation product **281** were formed, while the Glaser-Hay coupling product was not detected at all. Further optimization showed that within 5 hours, all of the starting material was efficiently phosphonylated when three equivalents of diethyl phosphite and 0.3 equivalent of $Cu(OAc)_2$ were applied, irrespective of the scale of the reaction (up to 10 mmol, entries 9-11). It also proved to be advantageous to add the copper catalyst and the diethyl phosphite in two portions (entries 10, 11). In a control experiment, without alkyne substrate **23**, it was confirmed that under oxidative conditions in the presence of $Cu(OAc)_2$ and NEt_3, diethyl phosphite underwent homocoupling to yield the hypophosphate **283**. Adding the diethyl phosphite in portions avoided it from being consumed all at once in this side-reaction. After purification, the phosphonylated alkyne **269** was obtained in 73% isolated yield, using cheap and safe reagents.

*2.3.2. Attempted synthesis of the aminoallenyl bisphosphonate **272***

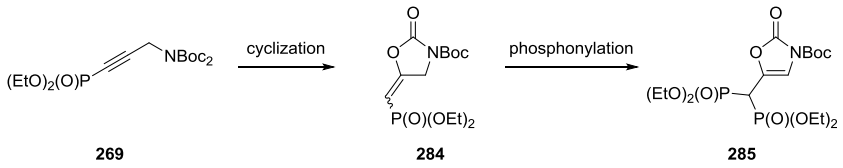
Next, it was attempted to generate a second intermediate, the aminoallenyl bisphosphonate **272**, which was thought to be involved in the formation of the bisphosphonomethyl oxazol-2-one **24** (Scheme 63). Thus, alkynylphosphonate **269** was consecutively treated with one equivalent of both LDA and diethyl chlorophosphate. After one hour, 48% of the starting material was converted to phosphoramidate **280**, after which conversion changed no more overnight. The aminoallenyl bisphosphonate **272** was not detected. As the Boc-group was attacked again, no further attempts were made to generate this intermediate.



Scheme 63: Attempted synthesis of aminoallenyl bisphosphonate 272.

*2.3.3. Transition metal-catalyzed 5-exo-dig cyclization of 3-amino prop-1-yn-1-yl phosphonate **269** yielding 5-phosphonomethylidene oxazolidin-2-one **284***

Transition metal-catalyzed cyclization of *N*-Boc protected propargylamines has been reported to efficiently yield the corresponding oxazolidin-2-ones in excellent yields, short reaction times and low catalyst loadings.[248-250] It was envisioned that a similar cyclization reaction of alkyne **269** would lead to 5-phosphonomethylidene oxazolidin-2-ones **284**. The 5-bisphosphonomethyl oxazolidin-2-ones **285**, which would obviously be bearing the Boc-group at the 3-position instead of at the 4-position as in **24**, would consequently be obtained after treatment of oxazolidin-2-one **284** with a base and diethyl chlorophosphate (Scheme 64). To that end, several catalysts were screened to provide 5-phosphonomethylidene oxazolidin-2-ones **284**.

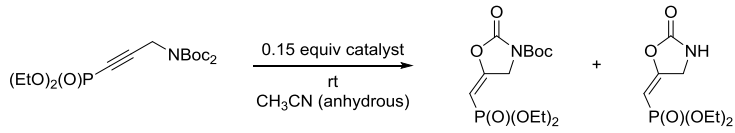


Scheme 64: Strategy towards 5-bisphosphonomethyl oxazol-2-one 284 *via* 5-phosphonomethylidene oxazolidin-2-one 283.

Copper catalysts were first screened but did not produce any 5-phosphonomethylidene oxazolidin-2-one **284** (Table 7, entries 1-3). Palladium catalysts did afford the desired product with a mediocre conversion in some cases (entries 4-6). $NiCl_2$, $ZnCl_2$, $RuCl_3$, $InCl_3$ and $RhCl_3$ all proved to be ineffective as only the starting material **269** was recovered (entries 7-11). Gold

catalysts, on the other hand, afforded the oxazolidin-2-one **284** smoothly, with AuCl giving a faster conversion than $AuCl_3$ (entries 12, 13). According to the Baldwin rules, both 5-exo-*dig* cyclization and 6-endo-*dig* cyclization modes are possible. The 6-endo-*dig* cyclization product was never observed.

Table 7: Transition metal-catalyzed synthesis of 5-phosphonomethylidene oxazolidin-2-one 284.



269 **284** **286**

entry	catalyst	t (h)	**284** (%)[a,b]	**286** (%)
1	CuCl	18	0	0
2	$Cu(OAc)_2$	24	0	0
3	$Cu(OTf)_2$	24	0	0
4	$Pd(dba)_2$	24	0	0
5	$PdCl_2$	18	38	2
6	$Pd(OAc)_2$	24	29	0
7	$NiCl_2$	18	0	0
8	$ZnCl_2$	24	0	0
9	$RuCl_3$	24	0	0
10	$InCl_3$	24	0	0
11	$RhCl_3$	24	0	0
12	AuCl	1	93 (56)	7
13	$AuCl_3$	3	87	13
14	AgOAc	24	0	0
15	AgOTf	24	0	0
16	$Au(PPh_3)Cl$	5d	2	0
17	AuOTf	20 min	76	0
18	$Au(PPh_3)OTf$	10 min	90	0
19	$Au(PPh_3)NTf_2$	10 min	89	0
20	$Au(OTf)_3$	20 min	14	0
21	HCl	24	0	0
22	*p*TsOH	24	0	0

[a] conversion based on ^{1}H NMR [b] isolated yield between brackets

Although silver salts and chloro(triphenylphosphine)gold(I) did not produce the desired product in more than trace amounts (entries 14-16), other cationic gold complexes consumed the starting material very quickly (entries 17-20). Several unidentifiable impurities were formed though. Control experiments with HCl and *p*TsOH on the other hand demonstrated that the cyclization reaction was not simply an acid-catalyzed process, as these Brønsted acids did not result in conversion to the oxazolidin-2-one **284** (entries 21, 22).

Partial Boc-deprotection of the alkyne starting material **269** occurred when HCl or $Cu(OTf)_2$ was used (entries 3, 21). In the AuCl and $AuCl_3$-catalyzed cyclizations, the oxazolidin-2-one **284** was partially deprotected as well. Oxazolidin-2-one **284** could be separated from the Boc-deprotected oxazolidin-2-one **286** in 56% yield. Literature data show that the coupling constant for the allylic carbon atom of *E*-vinylphosphonates is significantly bigger than for *Z*-vinylphosphonates ($^3J_{CP,\ E}$ = 18-30 Hz vs $^3J_{CP,\ Z}$ = 5-13 Hz).[251-256] The observed $^3J_{CP}$ coupling constant for the allylic carbon atom was 18 Hz and thus, the stereochemistry around the double bond was concluded to be *E*.

Next, a solvent screening was performed for the Au(I)Cl-catalyzed cyclization reaction. It was observed that Boc-deprotection did not occur when dichloromethane or THF was used (Table 8). As only one product was formed, the purification step could be eliminated and the oxazolidin-2-one **284** was isolated in 98% yield. Moreover, the catalyst loading was easily lowered down to 2 mol%, still achieving fast and complete conversion to the oxazolidin-2-one **284** (entries 2, 3). With a catalyst loading of 1 mol% however, the reaction rate dropped significantly (entry 4).

Table 8: Solvent screening for the synthesis of 5-phosphonomethylidene oxazolidin-2-one 284.

entry	catalyst (mol%)	t (h)	CH_2Cl_2 (%)[a]	THF (%)[a,b]	CH_3CN (%)[a,c]
1	15	1	ND	ND	100
2	5	1	100	100 (98)	27[d]
3	2	1	100	54	ND
		3	-	100	-
4	1	6	80	59	ND
		18	100	100	-

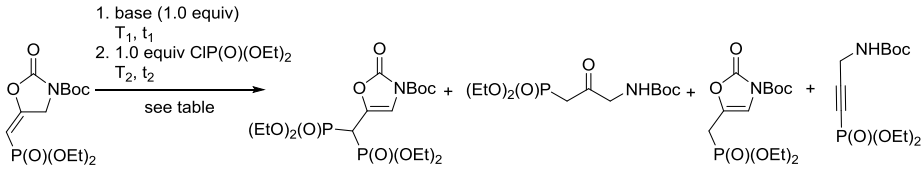
[a] conversion based on ^{1}H NMR [b] isolated yield between brackets [c] anhydrous [d] 5 days

*2.3.4. Attempted introduction of the second phosphonate group to 5-phosphonomethylidene oxazolidin-2-one **284***

Oxazolidin-2-one **284** was treated with one equivalent of LDA and diethyl chlorophosphate in order to obtain bisphosphonomethyl oxazol-2-one **285**. The starting material **284** was entirely consumed after one hour at - 78 °C, but unfortunately the bisphosphonomethyl oxazol-2-one **285** was not detected (Table 9, entry 1). Instead, a complex mixture was obtained. β-Ketophosphonate **287** was identified as one of the products and results from hydrolysis of the starting material with consecutive loss of CO_2 upon quenching with water. With NaH and KO*t*Bu, the starting material was entirely recovered, while the diethyl chlorophosphate was slowly converted to tetraethyl pyrophosphate (entries 2, 3). To evaluate how the oxazolidin-2-one **284** behaved when treated with strong bases, the reaction was run

without diethyl chlorophosphate. Phosphonomethylidene oxazolidin-2-one **284** effectively rearranged to oxazol-2-one **279**, as it was detected in low amounts upon treatment with an equimolar amount of *n*-BuLi (entry 4). Most of the product hydrolyzed to β-ketophosphonate **287** however. When oxazolidin-2-one **284** was treated with LDA and quenched with MeOH-d_4, it was entirely converted into oxazol-2-one **279** (entry 5). It was not possible however to isolate this product as it hydrolyzed upon filtration of the lithium salts over celite. The β-ketophosphonate **287** could be isolated and spectral data were consistent with literature values.[257, 258] No further attempts were undertaken to synthesize the bisphosphonomethyl oxazol-2-one **285**.

Table 9: Screened conditions for the phosphonylation of 5-phosphonomethylidene oxazolidin-2-one 284 with diethyl chlorophosphate.



284 **285** **287** **279** **288**

entry	base	solvent	T_1 (°C)	t_1 (min)	T_2 (°C)	t_2 (h)	**285** (%)[b]	**287** (%)[b]	**279** (%)[b]	**288** (%)[b]
1	LDA	THF	- 78 to 0	60	- 78	1	0	6	0	1
2	NaH	THF	rt	1	rt	48	0	0	0	0
3	KO*t*Bu	THF	rt	0	rt	24	0	0	0	0
4[a]	*n*-BuLi	Et_2O	- 78	5	-	-	0	95	3	2
5[a]	LDA	Et_2O	- 78	5	-	-	0	0	100	0

[a] no $ClP(O)(OEt)_2$ added [b] conversion based on ^{31}P NMR

2.4. Conclusion

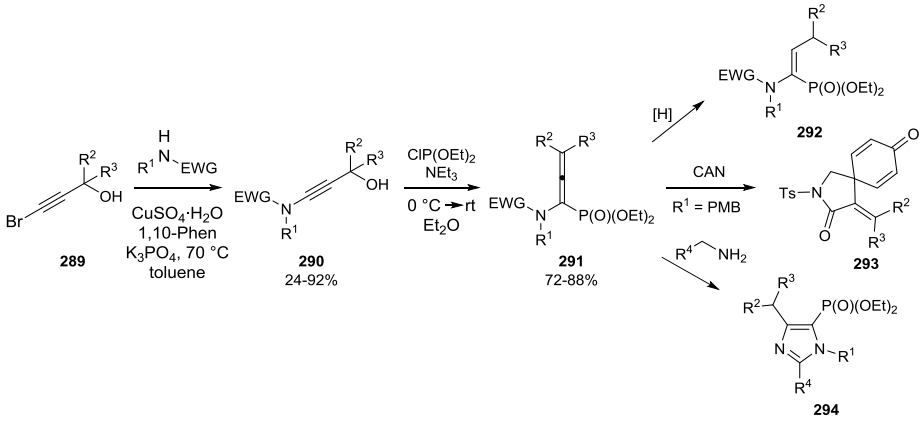
During the synthesis of 3-amino, 3-phosphono prop-1-yn-1-yl phosphonate **268** from *N*,*N*-di-*tert*-butylprop-2-yn-1-ylimidodicarbonate **23** and an excess diethyl chlorophosphate, a rearrangement reaction, yielding bisphosphonomethyl oxazol-2-one **24**, was observed. Unfortunately, in this one-pot procedure, several side-products were formed, which elute together with bisphosphonomethyl oxazol-2-one **24**, decreasing the isolated yield to 17%. In a stepwise approach, 3-amino prop-1-yn-1-yl phosphonate **269** was first prepared separately. A copper-catalyzed cross coupling procedure of terminal alkynes with dialkyl phosphites, which had been recently described in literature, was improved, affording alkynyl phosphonate **269** in short reaction times and good yields on a 10 mmol scale. Gold-catalyzed 5-exo-*dig* cyclization smoothly yielded 5-phosphonomethylidene oxazolidin-2-one **284** in quantitative yield. The second phosphonate moiety however, could not be introduced at the stage of alkynylphosphonate **269**, nor at the stage of 5-phosphonomethylidene oxazolidin-2-one **284**.

Remarkably, 5-phosphonomethylidene oxazolidin-2-one **284** and phosphonomethyl oxazol-2-one **279** are much more sensitive to hydrolysis than bisphosphonomethyl oxazol-2-one **24**.

3. Attempted syntheses of 1-*N*,*N*-dialkyl aminoallenylphosphonates and 3-*N*,*N*-dialkyl aminoallenylphosphonates

3.1. Introduction

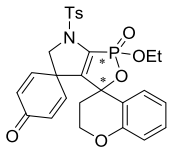
In the following four chapters, we explored the synthesis and unique reactivity pattern of allenylphosphonates bearing a nitrogen substituent. Although allenylphosphonates have been reported decades ago,[107, 108] the first synthesis of an aminoallenylphosphonate was published only recently. In 2012 Rabasso found that the same [2,3]-sigmatropic rearrangement that has been used for the synthesis of allenylphosphonates (*vide supra*), produces 1-aminoallenylphosphonates when ynamidols **290** are used instead of propargyl alcohols (Scheme 65).[259] A copper-catalyzed coupling reaction of amines with bromopropargyl alcohols **289** afforded the ynamides **290** in variable yields. 1-Aminoallenylphosphonates **291** were obtained after reaction with diethyl chlorophosphite in good yields.



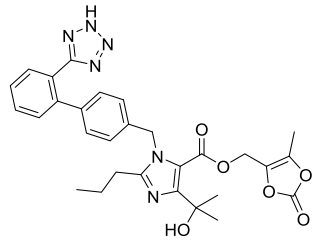
Scheme 65: The first synthesis of an aminoallenylphosphonate and its transformations.

Just like their allenylphosphonate counterparts, these 1-aminoallenylphosphonates could be selectively hydrogenated to produce α-aminovinylphosphonates **292**,[260] which could be further converted to 2-phosphono-2-pyrrolines through RCM, after the appropriate alkenyl group was introduced by a Mitsunobu reaction.[261] The group of Rabasso also discovered that PMB-protected 1-aminoallenylphosphonates **291** generated a spirodienone lactam **293** upon treatment with CAN. Consequently, they were able to generate a library of these spirocycles with an impressive structural complexity as pentacyclic structures with two spirocyclic

connections could be obtained (Figure 18, compound **254**).[203] Cao and coworkers found that acceptor-substituted aminoallenes, such as 1-aminoallenylphosphonates **291**, reacted well with a series of primary amines to yield persubstituted imidazoles **294**. Acceptor-substituted imidazoles are an important class of compounds as the imidazole motif is present in a lot of natural products and pharmaceutical compounds,[262-264] such as Olmesartan **295**, which is an angiotensin II receptor antagonist.[265]



254



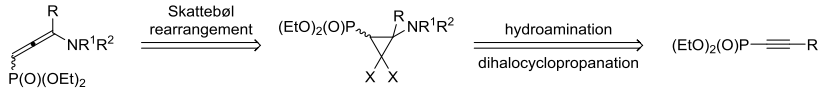
295

Figure 18: Example of a spirodienone lactam and structure of Olmesartan (angetionsin II receptor antagonist).

It is thus clear that aminoallenylphosphonates are useful building blocks for the synthesis of a variety of (heterocyclic) aminophosphonates. Since the first synthesis of aminoallenylphosphonates was reported only a couple of years ago, it is to be expected that the exploration of their potential is only starting. Moreover, only one isomer of aminoallenylphosphonates, the 1-aminoallenylphosphonates, was described. In our quest for alternative strategies to synthesize aminoallenylphosphonates, we mainly focused on preparing 3-aminoallenylphosphonates.

3.2. Preparation of 3-amino allenylphosphonates employing the Skattebøl rearrangement

A first strategy relied on the Skattebøl rearrangement, which transforms geminal dihalo cyclopropanes *via* a cyclopropylcarbene intermediate to the corresponding allene in the presence of an organolithium base.[266] In order to obtain 3-aminoallenylphosphonates, the dihalo cyclopropane had to be functionalized with a phosphorus and an amino substituent. It was envisioned that these dihalocyclopropyl aminophosphonates **26** were accessible through dihalocarbene addition to β-enaminophosphonates (Scheme 66). β-Enaminophosphonates would be obtained by copper-catalyzed hydroamination of alkynylphosphonates **27**,[59] which in turn could be prepared through the copper-catalyzed oxidative coupling of commercially available alkynes and dialkyl phosphites.[215]



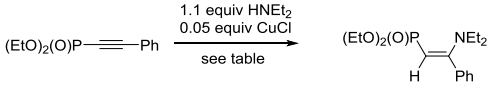
25 **26** **27**

Scheme 66: Retrosynthetic approach to 3-aminoallenylphosphonates using the Skattebøl rearrangement.

*3.2.1. Preparation of enaminophosphonate **297***

Phenylacetylene was readily phosphonylated with diethyl phosphite to afford the phenylethynyl phosphonate **296** in 82% yield. Phenylethynyl phosphonate **296** was next evaluated in the copper-catalyzed hydroamination reaction with diethylamine.[59] One day of reflux in dry THF only yielded trace amounts of the enaminophosphonate **297** (Table 10, entry 1). An almost complete conversion was reached however, when the mixture was heated during three days in dry methanol (entry 2). Under microwave heating to 70 °C during 16 hours, a slightly lower conversion was observed (entry 3). However, when the mixture was heated to 100 °C in the microwave, phenylethynyl phosphonate **296** was entirely converted to the enaminophosphonate **297** which was isolated in 75% yield (entry 4). Reaction time could be shortened to nine hours when the temperature was increased to 130 °C while conversion remained complete (entry 5).

Table 10: Optimization of conditions for the hydroamination of alkynylphosphonate 296.



296 **297**

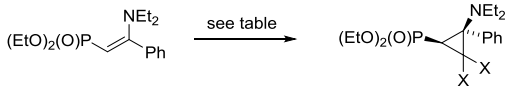
entry	solvent	T (°C)	t (h)	**297** (%)[b,c]
1	THF	Δ	24	traces
2	MeOH[a]	Δ	72	90
3[d]	MeOH[a]	70	16	70
4[d]	MeOH[a]	100	16	100 (75)
5[d]	MeOH[a]	130	9	100

[a] anhydrous [b] conversion based on ^{31}P NMR [c] isolated yield between brackets [d] microwave irradiation

*3.2.2. Attempted synthesis of dihalocyclopropyl aminophosphonate **298***

It has been shown that geminal dihalocyclopropanes can be prepared from alkenes through the addition of dihalocarbenes.[267-269] Thus, in a next step, enaminophosphonate **297** was reacted with a variety of species that can generate dihalocarbenes (Table 11).

Table 11: Screened conditions for the dihalocyclopropanation of enaminophosphonate 297.

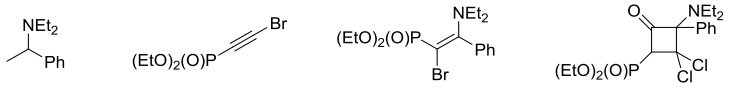


297 **298**

entry	dihalocarbene source	base	solvent	T (°C)	t (d)	reaction products
1[a]	25 equiv $CHCl_3$	40 equiv $NaOH_{(aq.)}$	heptane	rt	5	SM + **299**
2[a]	25 equiv $CHBr_3$	40 equiv $NaOH_{(aq.)}$	heptane	rt	7	SM + **299** + **300** + **301** + **298**
3	25 equiv $CHBr_3$	5 equiv KO*t*-Bu	-	rt	2	SM + **301**
4	1 equiv Cl_3CCO_2Na	-	DME	Δ	2	SM + **299**
5[b]	-	-	$CHBr_3$	Δ	1	SM
6	2 equiv $PhHgCCl_3$	-	toluene	80	1.25	SM + **302**

[a] 0.04 equiv PTC (TEBAC) [b] 8 equiv Mg turnings

Under phase-transfer conditions in chloroform, no conversion to the dihalocyclopropane took place, not even after five days (entry 1). Also Michael-type addition of the CCl_3 anion, which was reported to take place sometimes, was not observed.[267] A compound with the mass of diethyl (1-phenylethyl) amine **299** was found in minor amounts but was not isolated (Figure 19). With bromoform, the same compound **299** was present, together with trace amounts of the bromo alkyne **300**, the bromo enamino phosphonate **301** and the desired product **298** (entry 2). Again, Michael-type addition of the CBr_3 anion did not take place[270] and a longer reaction time (up to seven days) only resulted in a complex mixture in which the starting material was still the major compound. When KO*t*-Bu was added to a solution of the starting material in bromoform, an exothermic reaction took place, but disappointingly no conversion of the starting material was observed, not even after two days (entry 3). Only some trace amounts of bromo enaminophosphonate **301** were found. The base, used to generate the dihalocarbene, possibly competes with the olefin for reaction with the dihalocarbene.[271] Sodium trichloroacetate has been shown to be able to convert vinylphosphonates to the corresponding geminal dihalocyclopropyl phosphonates in the absence of a base.[267] When it was refluxed in DME with substrate **297**, a complex mixture was obtained in which only amine **299** could be identified (entry 4). In the case of poorly nucleophilic olefins, this method has been reported not to work well, as the generated dihalocarbenes rather react with the sodium trichloroacetate than with the alkene.[272]



299 **300** **301** **302**

Figure 19: Structure of detected products in the dihalocyclopropanation of enaminophosphonate 297.

However, recently it was shown that electrodeficient olefins were transformed in good yields to dibromocyclopropanes when treated with magnesium turnings in THF with a large excess

of bromoform.[270] When applied to substrate **297**, only starting material was recovered after 16 hours of reaction (entry 5). The use of the Seyferth reagent ($PhHgCCl_3$) has also been reported to be a source of dibromocarbenes which efficiently reacts with weakly nucleophilic olefins.[269, 271, 273, 274] When $PhHgCCl_3$ was heated with enamino phosphonate **297** to 80 °C in toluene, about half of the starting material was converted to three phosphorus-containing products (entry 6). One of them apparently underwent a CO insertion and is proposed to have structure **302**, the second one seems to result from the first one after dehydration. The third product could not be identified. Unfortunately, none of those products could be isolated, but NMR data – the characteristic CHP fragment was found in both ^{1}H and ^{13}C NMR spectra - supported the MS data found for structure **302**. Moreover, 2D NMR data showed a quaternary carbonyl signal that couples to the CHP fragment, suggesting that the carbonyl group has indeed been introduced next to phosphonate moiety. As the options to prepare dihalocyclopropanes seemed to be depleted, the Skattebøl strategy was not further investigated.

3.3. Attempted synthesis of phosphonylated (hetero)cycles through cycloaddition reactions with diazomethane

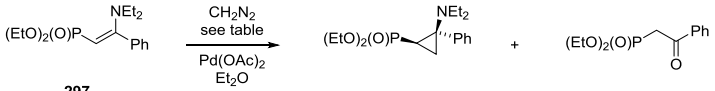
*3.3.1. Attempted cyclopropanation of enaminophosphonates **297** with diazomethane*

Since the search for new methods to synthesize aminophosphonates has been a research line of the research group for quite a while now,[29, 32, 36, 275] it was investigated whether the earlier prepared enaminophosphonates of type **297** could serve as precursors to aminocyclopropyl phosphonates **303**. Previous research in the group has focused on getting access to cyclopropylamines via a Simmons-Smith reaction of enamines.[276] Synthetic routes towards molecules carrying the aminocyclopropane phosphonate motif, however, are only scarcely reported in literature.[277-281] Although cyclopropanation of β-enaminophosphonates **297** has never been investigated, one example of a reaction of an α-enaminophosphonate with diazomethane has recently been reported.[282] Aminocyclopropanephosphonic acid has shown to be a potent inhibitor of aminocyclopropanecarboxylate (ACC) deaminase from *Pseudomonas sp.* and alanine racemase from *Bacillus stearothermophilus*.[283] The aminocyclopropanephosphonic moiety is also present in oligopeptides that are potent Hepatitis C virus (HCV) NS3 protease inhibitors.[284, 285]

When enaminophosphonate **297** was reacted with a five-fold excess of diazomethane, trace amounts of aminocyclopropyl phosphonate **303** were found after one hour at room temperature

(Table 12, entry 1). Reaction progress was monitored for two days, but unfortunately conversion did not increase. Pyrazoline intermediates were not observed either. It had been reported that when a catalyic amount of $Pd(OAc)_2$ was added to a solution of an alkene and diazomethane, cyclopropanes could be obtained.[286] In our case however, no cyclopropanation products were detected (entry 2). The only observed product, β-ketophosphonate **304**, results from hydrolysis of the starting material upon quenching of the reaction mixture with acetic acid.

Table 12: Screened conditions for the cyclopropanation of enaminophosphonate 297 with diazomethane.



297 **303** **304**

entry	equiv CH_2N_2	equiv $Pd(OAc)_2$	T (°C)	t (h)	conversion (%)
1	5	-	rt	48	traces
2	1	0.02	0	1	0
3[a]	20	0.01	rt	1	10
	10			2.5 + 1	
4[a]	20	0.10	Δ	2	0

[a] diazomethane is mixed with catalyst prior to addition of substrate

On the other hand, it is decribed in literature that $Pd(OAc)_2$ is reduced *in situ* by an excess of diazomethane, producing palladium nanoparticles which are more active than Pd(0) complexes, preformed nanoparticles or commercial palladium powder.[287] The authors stated that the reactant addition sequence is of utmost importance: Pd(0) formation and high conversions were only obtained when the diazomethane is added to a solution already containing the catalyst and the olefin. Although an immediate evolution of nitrogen gas, indicative of $Pd(OAc)_2$ reduction, was indeed observed when these conditions were applied, only 10% conversion of the starting material to unidentified reaction products was detected (entry 3). Increasing the amount of the catalyst did not alter the outcome (entry 4).

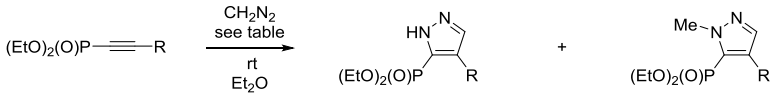
3.3.2. Synthesis of phosphonylated pyrazoles from alkynylphosphonates and diazomethane

Since the strategies to cyclopropanated products **303** were met with failure, this route was abandoned. However, with the easy acces to alkynylphosphonates **296** in mind, one last attempt was made to gain acces to phosphonylated heterocycles. One example of the reaction of diazomethane with an acceptor-substituted alkynylphosphonate was reported, yielding a mixture of phosphonylated pyrazoles regioisomers.[288] Pyrazoles are known as anticancer agents,[289] non-nucleoside HIV-1 reverse transcriptase inhibitors[290] and CNS depressants[291] and the motif occurs in many drugs such as Viagra, Celebrex and Acomplia. Most of the

reported syntheses rely on cyclocondensation strategies of hydrazines with 1,3-difunctional compounds.[292, 293] Only a small number of phosphonylated pyrazoles are prepared by cycloadditions of diazoalkanes.[282, 288, 294-298]

Two alkynylphosphonates were screened for their reactivity with an excess of diazomethane. Alkyne **296** gave the 1*H*-pyrazole **306a** and the *N*-methylated pyrazole **307a**, next to an important amount of starting material (Table 13, entry 1). *N*-phthaloyl-protected propargylamine **305** gave almost complete conversions, again yielding pyrazoles **306b** and **307b** which could both be isolated (entry 2). Values for the C-P coupling constants were consistent with literature values for 5-phosphonylated pyrazoles,[299] confirming that the C-terminus of diazomethane had attacked the carbon atom in β-position of the phosphonate.

Table 13: Tested conditions for the synthesis of phosphonylated pyrazoles 306 and 307.



296 (R = Ph)
305 (R = CH_2NPhth)

306a (R = Ph)
306b (R = CH_2NPhth)

307a (R = Ph)
307b (R = CH_2NPhth)

entry	R	equiv CH_2N_2	t (h)	**SM** (%)	**306** (%)[a]	**307** (%)[b]
1	Ph	5	4	66	26	5
2[c]	CH_2NPhth	5	3	0	37 (2)	44 (67)
3	Ph	1	3.5	85	11	0
4	CH_2NPhth	1	16	100	0	0
5	Ph	2	72	86	14	0
6	CH_2NPhth	2	72	100	0	0
7	CH_2NPhth	3	72	86	6	0
8	CH_2NPhth	5	72	15	28	11

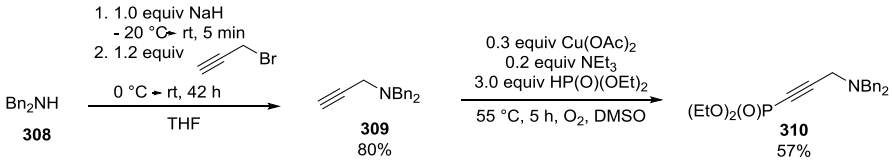
[a] isolated yield after 2 consecutive pTLC steps [b] isolated yield after pTLC [c] THF instead of Et_2O

Trying to get a more selective conversion to one of the products, several conditions were screened. To be able to dose exactly one equivalent of diazomethane, the diazomethane ethereal solution was titrated.[300] However, no or very poor conversions were obtained (entries 3, 4), even when the amount of diazomethane was doubled or if reaction times were increased (entries 5, 6). When larger excesses of diazomethane were used, conversions increased again (entries 7, 8), but as the reaction outcome was hard to reproduce and mixtures of at least three different products were obtained, this route was finally abandoned as well.

3.4. Preparation of 3-aminoallenylphosphonates through prototropic rearrangement

*3.4.1. Through isomerization of 3-(dibenzylamino)prop-1-yn-1-yl phosphonate **310***

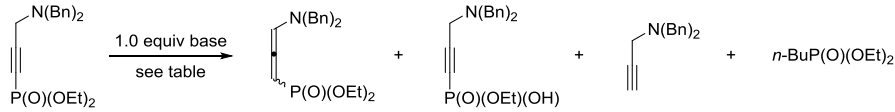
In an alternative strategy, it was attempted to get access to 3-amino allenylphosphonate **311** *via* isomerization of 3-(dibenzylamino)prop-1-yn-1-yl phosphonate **310** (Scheme 67). Dibenzylpropargylamine **309** was prepared by treating dibenzylamine with sodium hydride and propargyl bromide. Oxidative cross coupling with diethyl phosphite afforded 3-(dibenzylamino)prop-1-yn-1-yl phosphonate **310** in 57% yield.



Scheme 67: Preparation of 3-(dibenzylamino)prop-1-yn-1-yl phosphonate 310.

Next, isomerization of 3-(dibenzylamino)prop-1-yn-1-yl phosphonate **310** was evaluated with a variety of bases (Table 14). Isomerization of trifluoromethyl alkynes with an excess sodium hydroxide in a mixture of THF and water was reported in literature to yield the corresponding allenes.[301] When substrate **310** was subjected to these conditions, no conversion initially took place. Using longer reaction times, monodealkylation of the phosphonate ester, producing compound **312**, and dephosphonylation of the alkynylphosphonate, producing alkyne **309** and diethylphosphate, were observed (entry 1). Treatment with NaH resulted in complete recuperation of the starting material (entry 2). With one equivalent of LiHMDS, the starting material was entirely converted to a complex mixture of at least ten products within one hour at - 78 °C (entry 3). The only product that could be identified was dibenzylamine. *n*-BuLi also gave a complex mixture of at least twenty products after merely thirty seconds (entry 4). Both *N*,*N*-dibenzyl propargylamine **309** and *n*-butyl phosphonate **313** were detected, indicating that *n*-BuLi rather acted as a nucleophile. In a last attempt, the use of *t*-BuLi was evaluated as it was reasoned that the increased steric hindrance might lower the nucleophilic behaviour. Unfortunately, these conditions immediately resulted in a complex mixture as well (entry 5). Dibenzylamine was detected once more.

Table 14: Screened conditions for the isomerization of 3-(dibenzylamino)prop-1-yn-1-yl phosphonate 310.



310 **311** **312** **309** **313**

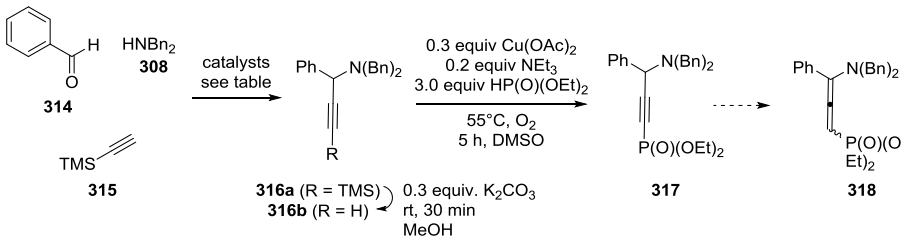
entry	base	solvent	T (°C)	t (h)	**SM** (%)[a]	**311** (%)[a]	**312** (%)[a]	**309** (%)[a]
1[b]	NaOH	2:1 THF[c]/H_2O	rt	19	100	0	0	0
				68	0	0	81	19
2	NaH	THF	0 to rt	3	100	0	0	0
3	LiHMDS	THF	- 78	1	0		CM	
4	*n*-BuLi	THF	- 78	30 sec	0		CM	
5	*t*-BuLi	THF	- 78	60 sec	0		CM	

[a] based on ^{1}H NMR [b] not anhydrous [c] 3.0 equiv base were used

*3.4.2. Through isomerization of 3-amino-3-phenylprop-1-yn-1-yl phosphonate **317***

Since the isomerization of 3-(dibenzylamino)prop-1-yn-1-yl phosphonate **310** with strong bases was not fruitful, it was investigated if the presence of a phenyl substituent in the propargylic position would be favourable. Alkynes are known to isomerize more easily to the corresponding allenes if a phenyl group is conjugated to the newly formed double bond.[52] Consequently the isomerization of 3-amino-3-phenylprop-1-yn-1-yl phosphonate **317** would be evaluated (Table 15).

Table 15: Conditions for the A^3 coupling of substituted propargylamine 316.



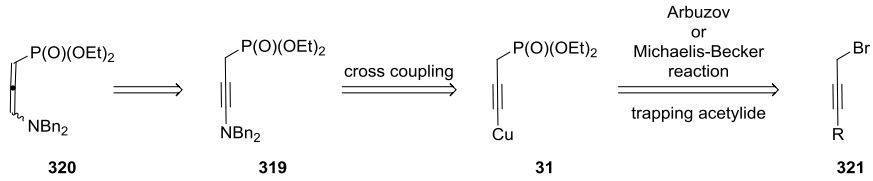
entry	equiv acetylene	equiv amine	equiv aldehyde	catalyst (mol%)	T (°C)	t (h)	solvent	**316** (%)[a,b]
1[c]	1	1	1.5	CuBr (0.05)	120	48	THF	92
2[d]	1	1.3	1.6	CuI (0.15)	100	0.5	neat	100 (5)

[a] conversion to **316a** based on ^{1}H NMR [b] isolated yield of **316b** between brackets [c] pressure vial [d] microwave heating

A³ coupling reactions are particularly suited to provide substituted propargylamines and consequently, benzaldehyde, dibenzylamine and trimethylsilyl acetylene were engaged in a copper-catalyzed A³ coupling reaction.[302-305] Almost full conversion was obtained after two days at 120 °C in a pressure vial (entry 1). Although the authors of the original procedure were able to isolate the substituted propargylamines in 15-30% yield, in our case, the product could unfortunately not be separated from the impurities. Under microwave conditions, the starting material was entirely converted after 30 minutes at 100 °C under neat conditions, and deprotected from the TMS-moiety with K_2CO_3 in MeOH (entry 2). Purification of this very apolar compound proved to be difficult once more and the substituted propargylamine was isolated in a poor 5% yield. It was next decided to repeat the reaction under those conditions and use the crude mixture as such in the cross coupling reaction with diethyl phosphite. The phosphonylated propargylamine **317** was obtained after five hours under the earlier developed conditions. Disappointingly, phosphonylated propargylamine **317** could not be isolated after meticulous purification and only a fraction of 90% purity was separated in 23% yield (yield over two steps). Given the difficulties encountered during the purification at both stages, further efforts were aborted and the isomerization reaction to the 3-phenyl-3-amino allenylphosphonate **318** was not evaluated.

*3.4.3. Through isomerization of 3-(dibenzylamino)prop-2-yn-1-yl phosphonate **319***

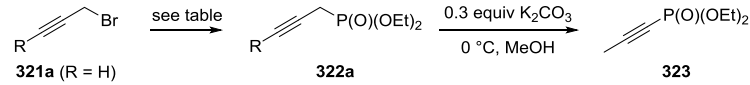
Since the syntheses of 3-amino allenylphosphonates **311** from phosphonylated propargylamines **310** or **317** were problematic, the preparation of 3-(dibenzylamino)prop-2-yn-1-yl phosphonate **319** as a precursor to 3-amino allenylphosphonate **320** was envisaged (Scheme 68). A literature protocol described the efficient synthesis of ynamides from copper acetylides and *N*-nucleophiles carrying an electron withdrawing group.[60] Thus, the coupling of copper acetylide **31** with dibenzylamine was envisioned. Since copper acetylides are reported to be conveniently generated from the corresponding alkynes and a copper source,[306, 307] the propargyl phosphonate would be prepared from a propargylbromide **321** with a phosphite.



Scheme 68: Retrosynthetic approach to 3-(dibenzylamino)propa-1,2-dienylphosphonate 320.

Thus, propargylbromide **321a** was engaged in an Arbuzov reaction with triethylphosphite (Table 16, entry 1). Propargyl phosphonate **322a** seemed to be present in a complex mixture with at least six other phosphorus-containing products, probably as a result of S_N' reactions. When lowering the temperature to 40 °C, propargyl phosphonate **322a** could no longer be detected (entry 2). Michaelis-Becker reaction on trimethylsilyl propargylbromide **321b** did however yield the desired TMS-protected propargylphosphonate **322b** in 41% yield after purification (entry 3).[308]

Table 16: Arbuzov and Michaelis-Becker reaction on substrate 321.



321a (R = H)
321b (R = TMS)

322a
322b

323

entry	R	nucleophile	equiv NaHMDS	solvent	T (°C)	t (h)	**322** (%)[a,b]
1	H	1.1 equiv $P(OEt)_3$	-	neat	110	20	ND
2	H	1.1 equiv $P(OEt)_3$	-	neat	40	2	0
3	TMS	1.0 equiv $HP(O)(OEt)_2$	1.1	THF	rt	1	90 (41)

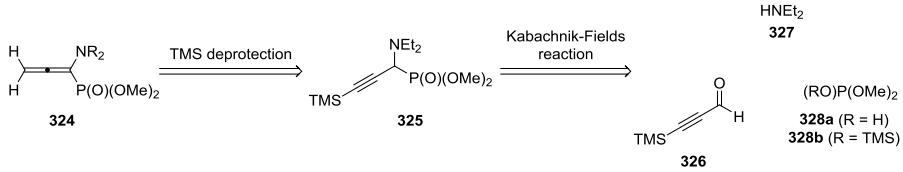
[a] conversion based on ^{1}H NMR [b] isolated yield between brackets

Upon deprotection of the TMS-group, instantaneous and complete rearrangement took place to internal alkynyl phosphonate **323** (Table 16). Trapping the acetylide anion at 0 °C with copper iodide in a mixture of ethanol and aqueous ammonia or in the presence of potassium carbonate in DMF, was unsuccessful. Once more, our efforts had to be prematurely discontinued.

3.5. Preparation of 1-aminoallenylphosphonates through spontaneous prototropic rearrangement

It was next anticipated, however, that due to the observed spontaneous rearrangement, a trimethylsilyl alkynylaminophosphonate **325** could provide a facile entry into 1-amino allenylphosphonate **324**. Upon deprotection of the TMS group, the rearrangement

would spontaneously yield 1-aminoallenylphosphonate **324**, provided that 1-amino-3-trimethylsilylprop-2-yn-1-yl phosphonate **325** could be prepared (Scheme 69).



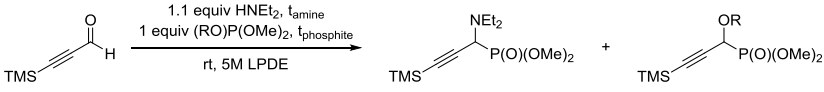
324 **325** **327** **326** **328a** (R = H) **328b** (R = TMS)

Scheme 69: Retrosynthetic approach to 1-aminoallenylphosphonates.

At first sight, an A^3 coupling reaction seemed an attractive approach to construct the alkynyl aminophosphonate **325**,[309] yet this route was not explored. The aldehyde part would in this case be the hydrate of formylphosphonate, which requires a three-step synthesis involving azides, diazo compounds and dimethyldioxirane.[310] A quicker, cheaper and slightly less explosive alternative consists of a $LiClO_4$-catalyzed three component Kabachnik-Fields reaction. In such a reaction, aminophosphonates are obtained from the corresponding aldehyde, an amine and a dialkyl phosphite, often in excellent yields and very short reaction times.[311] The precursors in this case are 3-(trimethylsilyl)propiolaldehyde **326**, diethylamine **327** and dimethyl phosphite **328a**.

However, upon addition of diethylamine to ynaldehyde **326** the amine reacts violently, while ^{31}P NMR indicated that no phosphorus-containing products other than the dimethyl phosphite starting material were present 8 minutes after the addition of the phosphorus nucleophile (Table 17, entry 1).

Table 17: Screened conditions for the Kabachnik-Fields reaction of propargylaminophosphonate 325.



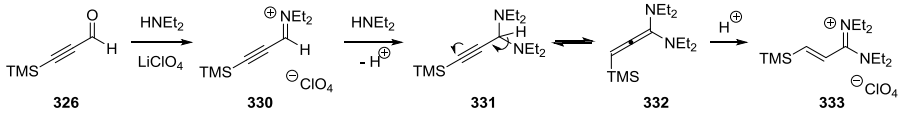
326 **325** **329a** (R = H) **329b** (R = TMS)

entry	order of addition		R	t_{amine} (min)	$t_{phosphite}$ (min)	result
	2	3				
1	amine **327**	phosphite **328a**	H	2	8	**333**
2	phosphite **328a**	amine **327**	H	5	1	mixture + **329a**[a]
3	phosphite **328b**	amine **327**	TMS	5	1	82% **329a** + 18% **329b**

[a] isolated in 33% yield

LC-MS analysis showed that the major compound had a mass corresponding to the corresponding amidinium compound **333** (Scheme 70). It is reported that in an ethereal solution of lithium perchlorate, iminium intermediates are easily generated and could even be

detected by ^{1}H NMR.[312] Presumably, a fast addition of a second molecule of diethylamine takes place, yielding aminal **331**, resulting in the amidinium **333** after prototropic rearrangement and protonation. Given the immediate violent reaction between the aldehyde and the amine, it is not surprising that the phosphorus nucleophile did not participate in the reaction. NMR data confirm the presence of the double bond (doublets at 5.48 and 7.79 ppm, J = 12.6 Hz) in amidinium **333**.



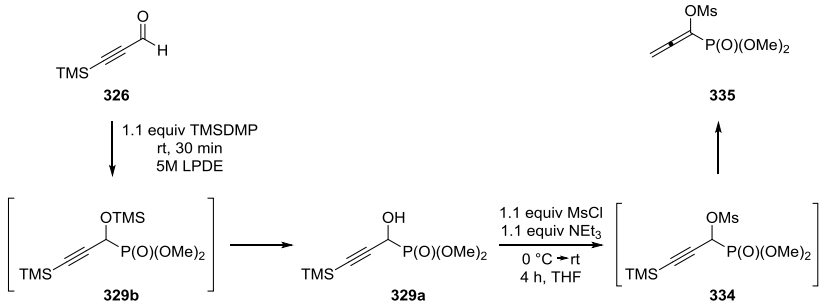
326 **330** **331** **332** **333**

Scheme 70: Plausible mechanism for the formation of amidinium 333.

To avoid that the phosphorus nucleophile is outcompeted and to make sure it can immediately attack the iminium intermediate, dimethyl phosphite was mixed with ynaldehyde **326** in LPDE. Adding the amine to this mixture, both the phosphorus nucleophile **328a** and the aldehyde **326** are effectively consumed within five minutes, giving rise to three phosphonylated products (20.7 ppm, 20.2 ppm, 19.3 ppm in a 2:1:2 ratio). The amidinium product **333** is not detected in ^{1}H NMR (entry 2). LC-MS analysis confirmed that two isomers of product **325** were present. Although alkynyl aminophosphonate **325** could not be recovered after purification, alkynyl hydroxyphosphonate **329a** was isolated in 33% yield. When diethylamine was added to a mixture of trimethylsilyl dimethyl phosphite **328b** and ynaldehyde **326** in LPDE, all of the DMTMSP, which is a stronger nucleophile than DMP, had reacted with the aldehyde **326** before the amine had the chance. A mixture of hydroxyphosphonate **329a** and *O*-trimethylsilyl hydroxyphosphonate **329b** was obtained (entry 3). It was thus concluded that this one-pot three-component reaction was not a feasible approach for the direct synthesis of precursor **325**.

Given the ease of formation of hydroxyphosphonate **329a**, it was investigated if the mesylate **334** could be prepared (Scheme 71). By means of a substitution reaction with an appropriate nitrogen nucleophile, alkynyl aminophosphonate **325** could then be obtained. When ynaldehyde **326** was phosphonylated with DMTMSP **328b** in LPDE, the starting material was entirely converted to an 80/20 mixture of hydroxyphosphonates **329a** and **329b** after merely one minute. Within half an hour, the TMS group had entirely hydrolyzed to give the hydroxyphosphonate **329a** along with a small amount of DMP **328a**. As the R_f value of DMP was almost equal to that of the product, it was evaluated whether hydroxyphosphonate could be purified after mesylation. One hour after the addition of mesylchloride, about 31% of the starting material **329a** was converted to *O*-mesylated alkynylphosphonate **334**. However, 16%

allene **335** was detected as well. The expelled chloride anion is able to entirely deprotect the TMS group within four hours. Eventually, it was decided to abandon this strategy.



Scheme 71: Attempted synthesis of mesylated propargyl hydroxyphosphonate 334.

3.6. Conclusion

In this chapter, various approaches were explored to access 3-aminoallenylphosphonates. First, it was tried to prepare dihalocyclopropyl aminophosphonates as substrates for the Skattebøl rearrangement. Oxidative cross coupling of terminal alkynes with dialkyl phosphites readily provided alkynylphosphonates which were hydroaminated in good yields. The resulting enaminophosphonates did not give dihalocyclopropyl aminophosphonates with *in situ* formed dihalocarbenes. The enaminophosphonates were successfully used to prepare phosphonylated pyrazoles with diazomethane, but the reaction proved to be hard to reproduce. Isomerization of phosphonylated propargylamines under alkaline conditions was unsuccessful. Preparation of copper acetylides from prop-2-yn-1-yl phosphonate, which was envisioned to react with amines to produce 3-amino-prop-2-yn-1-yl phosphonate precursors was not successful either. Finally, it was attempted to prepare 1-amino-3-trimethylsilylprop-2-yn-1-yl phosphonates through a Kabachnik-Fields reaction, as these substrates would probably rearrange to the corresponding 1-amino allenylphosphonates upon removal of the TMS group. Unfortunately, the 1-amino-3-trimethylsilylprop-2-yn-1-yl phosphonates were not obtained as the aldehyde immediately reacted with either the nitrogen or the phosphorus nucleophile to give amidinium or hydroxyphosphonate products.

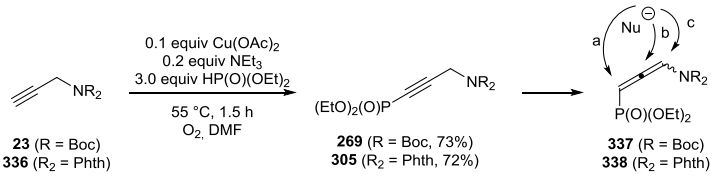
4. In situ formation and β-derivatization of 3-imidoallenylphosphonates

4.1. Introduction

In the previous chapter, the syntheses of dialkylamino allenylphosphonates were unsuccessful. When looking closer to the non-phosphonylated counterparts, amino-substituted allenes are sometimes reported to be difficult to handle. They tend to polymerize even at low temperatures, and are sensitive to moisture.[313] Amido-allenes, being less electron-rich, are more stable and display enamide reactivity. Dialkylamino allenylphosphonates are possibly too electron rich to be synthesized, so it was reasoned that the introduction of an electron withdrawing group on the nitrogen atom would be advantageous. Next, the isomerization reaction to the corresponding 3-amino allenylphosphonates would be evaluated again in order to study their reactivity towards nucleophiles.

4.2. Towards 3-imidoallenylphosphonates

To this end, di-Boc-protected propargylamine **23** and the commercially available *N*-propargyl phthalimide **336** were phosphonylated according to the earlier developed copper-catalyzed oxidative cross coupling with diethyl phosphite (Scheme 72). Although the phosphonylated alkynes were easily prepared on a 10 mmol scale, it was noticed that the DMSO solvent was oxidized under the oxidative conditions. Considerable amounts of dimethyl sulphone were produced and this complicated purification. Fortunately, running the reaction in DMF afforded the alkynylphosphonates **269** and **305** with comparable ease and in equally good yields.



23 (R = Boc)
336 (R_2 = Phth)

269 (R = Boc, 73%)
305 (R_2 = Phth, 72%)

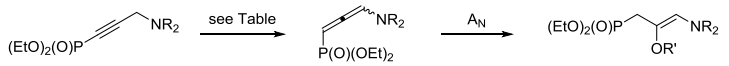
337 (R = Boc)
338 (R_2 = Phth)

Scheme 72: Approach towards 3-imidoallenylphosphonates 337 and 338.

In preliminary experiments, phosphonylated *N*,*N*-di-Boc-propargylamine **269** was used as starting material. At first, stoichiometric isomerization was evaluated with organolithium bases (*n*-BuLi, LDA) in aprotic media.[314, 315] However, the isomeric allenic products **337** could not be detected (Table 18, entries 1-2). With *n*-BuLi the alkyne **269** was dephosphonylated, while LDA attacked the *t*-Bu group producing the carbamic acid, which cyclized to produce the

corresponding oxazolidinone. Accordingly, phthaloyl protected alkyne **305** was then used exclusively, as the Boc-groups of alkyne **269** were not stable under the previously applied conditions. Next, the isomerization using a milder NaH or KO*t*Bu aprotic system was investigated. Using a stoichiometric amount of NaH, the 3-imidoallenylphosphonate **338** was detected for the first time as 32% conversion was observed within one hour,[316] after which degradation quickly occurred (entry 3). Using a catalytic amount of NaH led to a lower conversion, while secondary reactions still occurred (entry 4). When performing the reaction in DMSO with KO*t*Bu as the base,[317] 7% conversion to an addition product **339** was observed (entry 5). Although allene **338** was not detected, this addition product caught our interest given the position of the double bond. Switching the solvent to THF, and employing a stoichiometric amount of base[318] gave the allene intermediate **338** and the addition product **339** together for the first time (entry 6). Providing a proton source by adding one equivalent of *t*-BuOH markedly increased the conversion of the starting material, giving approximately 50% of the allene in only two minutes at 0 °C (entry 7). Longer reaction times gave complex mixtures.

Table 18: Optimization of isomerization and nucleophilic addition conditions.



269 (R = Boc)
305 (R_2 = Phth)

337 (R = Boc)
338 (R_2 = Phth)

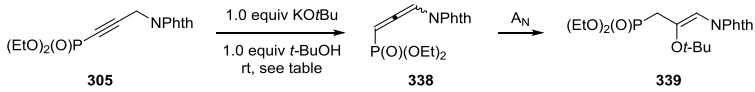
339 (R' = *t*Bu, R_2 = Phth)
340 (R' = Et, R_2 = Phth)

entry	SM	equiv base	base	solvent	T (°C)	t (min)	**337**/**338** (%)[a]	**339**/**340** (%)[a]
1	**269**	1	BuLi	Et_2O	- 78	60	0	0
2	**269**	1	LDA	Et_2O	0	180	0	0
3	**305**	1	NaH	THF	rt	60	32	0
4	**305**	0.2	NaH	THF	Δ	30	24	0
5	**305**	0.2	KO*t*Bu	DMSO	rt	5	0	7
6	**305**	1	KO*t*Bu	THF	rt	1	19	4
7[b]	**305**	0.2	KO*t*Bu	THF	0	2	47	0
8	**305**	1	KO*t*Bu	*t*-BuOH	40	5	34	25
9	**305**	2	KO*t*Bu	*t*-BuOH	40	1	0	100
10[c]	**305**	1	K_2CO_3	THF[d]	rt	8 days	0	100
11[c]	**305**	1	Cs_2CO_3	THF[d]	rt	40	0	100

[a] conversion based on ^{31}P NMR [b] 1 equivalent of *t*-BuOH added [c] 1 equivalent EtOH added [d] not anhydrous

Screening of different solvents in the KO*t*Bu/*t*-BuOH system revealed that conversion to allene **338** was rapid but a conversion higher than 50% could not be achieved (Table 19), as alkyne **305** and allene **338** were most likely in equilibrium. We then decided to scavenge the intermediate allene **338** in order to get full conversion to the addition product **339**.

Table 19: Solvent screening for the isomerization to imidoallenylphosphonate 338.



305 **338** **339**

entry	solvent[a]	t (min)[b]	**338** (%)[c]	**339** (%)[c]
1	THF	5	34	0
2	Et_2O	2	43	13
3	$CDCl_3$	5	10	0
4	CH_3CN	2	34	15
5	dioxane	2	34	10
6	toluene	2	14	15
7	CH_2Cl_2	2	24	26

[a] not anhydrous [b] reaction time indicates maximal conversion before degradation started to occur

[c] conversion based on ^{31}P NMR

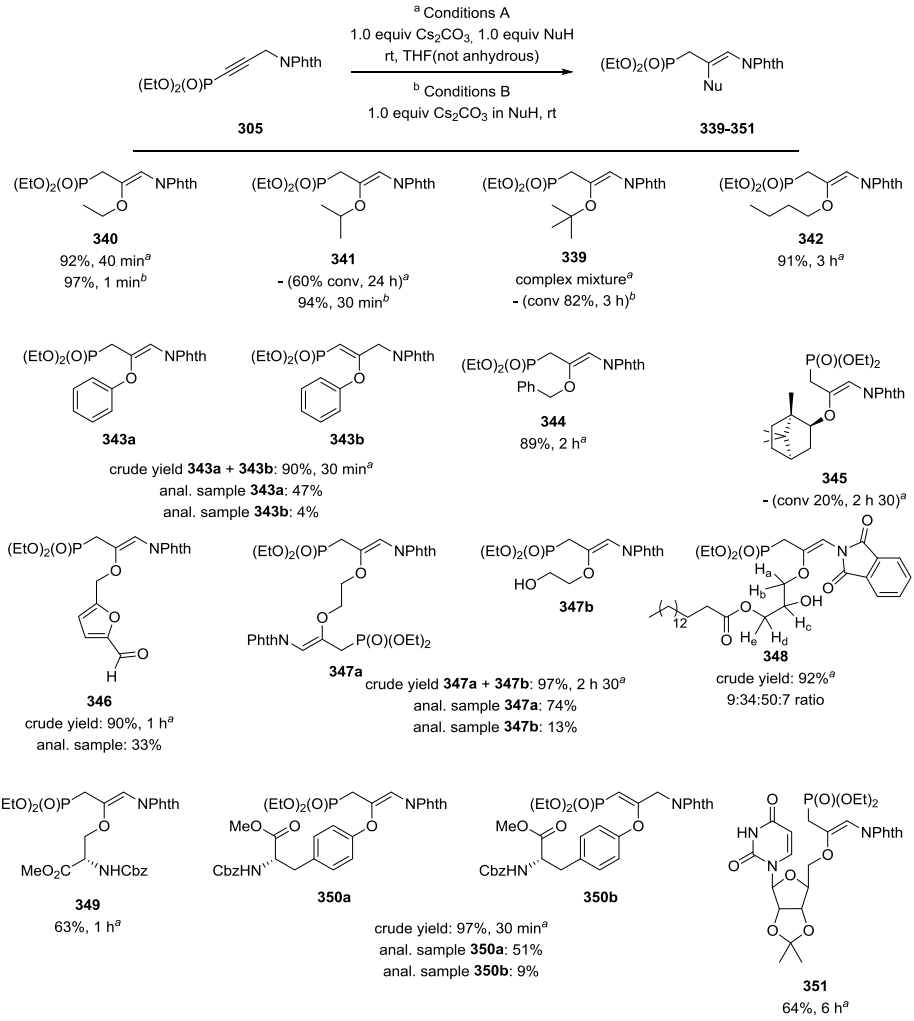
Performing the addition in *t*-BuOH instead of adding just one equivalent of *t*-BuOH as a proton source[319] clearly drives addition of the nucleophile to the allene intermediate **338** (entry 8). Increasing the amount of KO*t*Bu to two equivalents gave complete reaction in no more than 60 seconds (entry 9). We next investigated whether other - and eventually non-volatile - nucleophiles could be added. To that end, a non-nucleophilic base, an aprotic solvent, and the use of a stoichiometric amount of the nucleophile were required. Hence, K_2CO_3 and THF were selected, using one equivalent of EtOH as nucleophile. The addition product **340** was obtained as the single product, but full conversion required eight days (entry 10). We reasoned that the limited solubility of the base hampered reaction progress. Thus, replacing K_2CO_3 with Cs_2CO_3 gave a completed reaction in only 40 minutes (entry 11) and purification was superfluous. It was noted that when a catalytic amount of Cs_2CO_3 was used, full conversion could not be obtained. NMR disclosed a *Z*-configuration of the olefin based on a 2.5% NOE-enhancement of the vinylic proton when irradiating CH_2P. No NOE-effects were observed between OCH_2 and the vinylic proton.

4.3. β-alkoxylation of 3-imidoallenylphosphonates

4.3.1. Addition of O-nucleophiles

Next, we prepared a small library of derivatives. The addition of primary, secondary, and tertiary alcohols was first evaluated (Scheme 73, compounds **339**-**351**). As steric hindrance of the introduced nucleophile increased, the transformation proceeded more slowly, and in the case of *t*-BuOH, a complex mixture was obtained. With *i*-PrOH, the addition product was still the major product, along with some remaining alkyne and allene starting material and a

multitude of minor impurities. For volatile nucleophiles, the nucleophile could be applied as the solvent (conditions B). With EtOH, addition was rapid (60 seconds), and the addition product **340** was isolated in 97% yield.



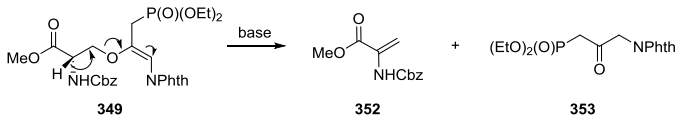
Scheme 73: Substrate scope of formation of β-functionalized aminophosphonates. Isolated yield and reaction time are indicated.

The *i*-PrOH derivative **341** could similarly be obtained in 94% yield. Upon conducting the reaction in *t*-BuOH as a solvent, 82% conversion to **339** was achieved after three hours at 40 °C. Longer reaction times gave secondary reactions that prevented isolation of **339**. Other primary alcohols such as *n*-BuOH and BnOH smoothly gave the desired compounds **342** and **344** in yields around 90% (conditions A), again without the need for purification. Phenol reacted

rapidly to give a mixture of two addition products **343a** and **343b** in a 6:1 ratio and 90% yield. With the sterically demanding (-)-borneol as a nucleophile, the intermediacy of the allene was illustrated once again, but a conversion higher than 20% to the addition product **345** could not be achieved, nor could **345** be isolated. The presence of an electrophilic group in the substrate, such as the aldehyde in 5-HMF (5-hydroxymethylfurfural), did not complicate matters giving full conversion to **346** in 90% crude yield in one hour. When preparing an analytical sample, the removal of some minor impurities required reversed phase flash chromatography causing partial degradation, which has been previously observed in the isolation of related HMF derivatives.[320] The coupling of two allene moieties with ethylene glycol also proved to be easily achievable as all of the starting material was converted into an easily separable 91:9 mixture of bis-adduct **347a** and mono-adduct **347b**. When water was evaluated as a nucleophile, the formation of the corresponding ketone was expected, but we instead observed formation of a complex reaction mixture, probably due to aldol-type reactions.

Finally, the addition of more complex and biologically relevant molecules was investigated. Addition of DL-α-palmitin gave rise to phospholipid-type product **348**. Full conversion was obtained in thirty minutes, resulting in four addition products (ratio 9:34:50:7 in 96% crude yield), which could not be separately isolated. Competition between the primary and secondary alcohol and *E*/*Z* isomerism accounts for the different products formed. Running the reaction at 0 °C resulted in a slower conversion, but not in a higher selectivity. One fraction could be enriched in the major isomer that was formed, giving rise to spectral data that allowed clear assignment of all relevant signals. Moreover, HMBC data indicated that the major isomer is the one resulting from addition of the primary alcohol. H_aH_b and H_dH_e have a different chemical shift and as H_dH_e couples with the ester carbon in HMBC, the shift of H_aH_b is known. As the phthalimidoyl carbonyl carbon for all other derivatives couples to H_aH_b (and <u>not</u> to H_c) in their HMBC spectrum, it is assumed that this is the case here as well. Thus, the major isomer is the addition of the primary alcohol.

Addition of protected amino acids resulted in side-chain O-derivatized amino acids **349** and **350**. Amino acid derivatives containing a phosphorus moiety often display important biological activities. Bialaphos for instance is an antibacterial metabolite, which also possesses strong herbicidal properties.[321] Adduct **349** was isolated in 63% yield as a 9/1 *Z*/*E* mixture. Partial elimination of the addition product **349**, giving **352** and **353** was unavoidable, even when running the reaction at 0 °C, and accounts for the slightly lowered yield in comparison to less complex nucleophiles (Scheme 74). Spectral data for elimination products **352** and **353** were in accordance with literature values.[322]



349 **352** **353**

Scheme 74: Elimination of the *N*-*Z*-L-serine methyl ester addition product.

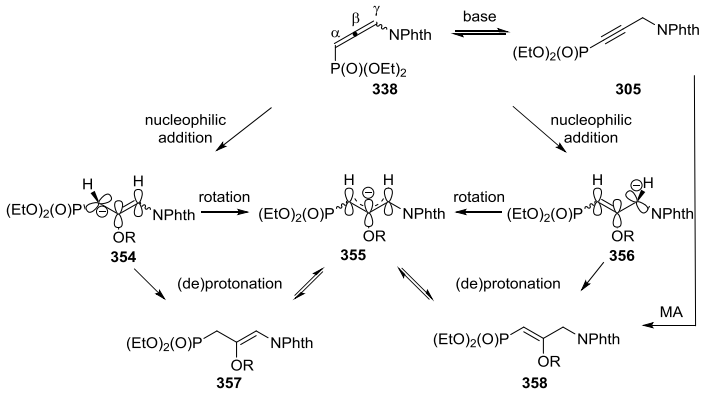
N-*Z*-L-tyrosine methyl ester was prepared following a literature procedure.[323] Addition of this protected amino acid did not suffer from this elimination reaction, since no appropriately positioned leaving group is present in the tyrosine methyl ester. As was the case with the addition of phenol, allylphosphonate **350a** and vinylphosphonate **350b** were swiftly formed in a 6:1 ratio in 97% crude yield, after which the regioisomers were separated from each other. The conformation of **350b** was confirmed to be *Z* since a 2% NOE-effect was found on the vinylic proton when irradiating NCH_2. Ultimately, the addition of protected uridine was evaluated, since phosphononucleosides like tenofovir and adefovir are used in the treatment of HIV. We were pleased to find that the uridine addition product **351** could be isolated in 64% yield. For all of the synthesized derivatives, addition selectively occurs at the central carbon atom. This illustrates that 3-imidoallenylphosphonates behave as acceptor substituted allenes.

4.3.2. Mechanistic considerations

Next, we investigated the mechanism of this alkoxylation reaction. Michael addition to alkyne **305**[324] would initially produce vinylphosphonate **358** which can isomerize to yield the allylphosphonate **357**. Although vinylphosphonate **358** was never detected in NMR experiments, only alkoxylation of isolated allene **338** can unambiguously rule out Michael addition. To this end, alkyne **305** was isomerized to the allene **338** with one equivalent of Cs_2CO_3 resulting in the first ever isolation of the 3-imidoallenylphosphonate **338** in 16% yield. First of all, it was found to be stable for at least several days, thus countering arguments that these allenes display low stability. Secondly, allene **338** was indeed in equilibrium with alkyne **305**, since 16% isomerization to **305** was found under the same conditions.

Most importantly, full conversion of allene **338** to allylphosphonate **357** in the presence of Cs_2CO_3 and EtOH is smoking gun evidence for the allene being the key intermediate in this one-pot, two-step reaction. However, it is clear that product **358** can also be produced from the addition to allene **338** (Scheme 75). Whether the nucleophile adds across the C_α-C_β or the C_β-C_γ double bond of the allene, it always results in the formation of a non-conjugated allyl anion - **354** or **356** - owing to the unique orbital structure of allenes. These non-conjugated anions can either be immediately protonated to give **357** or **358** respectively or they can rotate

around their single bond, and form the conjugated allyl anion **355**. After protonation this can either lead again to the formation of the allylphosphonate **357** or the vinylphosphonate **358**.



Scheme 75. Proposed mechanism.

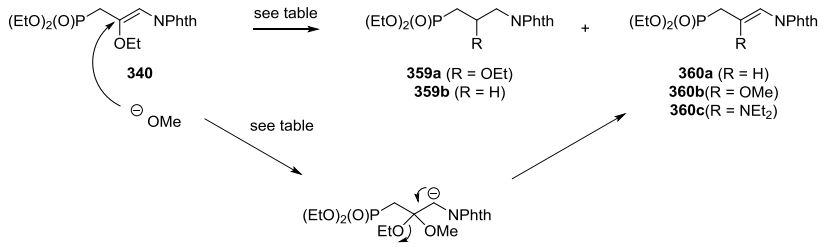
During our syntheses we exclusively observed the formation of allylphosphonates **357**, except for phenolic nucleophiles. In the case of phenol addition at room temperature, a 6:1 **357**:**358** ratio was found. When this addition was repeated at 0 °C we found a 12:1 **357**:**358** ratio. This indicates that the addition reaction is either under kinetic control or that Michael addition to alkyne **305** occurs (**305** to **358**) and is suppressed at this lower temperature. Under the applied conditions (room temperature, Cs_2CO_3) **358** did not isomerize to **357**. Furthermore, **357** was shown to be the thermodynamically more stable product, as **358** was entirely converted to **357** upon eighteen hours of reflux. Moreover, it was shown that the addition was irreversible under the applied conditions. No exchange of the alkoxide moiety was observed upon reacting **340** with BnOH and Cs_2CO_3.Thus, the formation of **358** is not a part of the major reaction pathway. This is in accordance with literature data as addition of NaN_3 to 3-phenylpropa-1,2-dienylphosphonate also gives the allylphosphonate, preserving the double bond conjugated to the aromatic group.[325]

*4.3.3. Attempted reduction and alkoxide exchange of addition product **340***

A peculiar reactivity was observed when reduction of the enimide **340** to γ-aminophosphonate **359a** was attempted. First, hydrogenation with palladium and platinum catalysts was evaluated and led only to recovery of the starting material **340** after prolonged reaction times (Table 20, entries 1, 2).[326] Also upon reduction with $NaBH(OAc)_3$ at reflux temperature in THF, the starting material **340** was exclusively recovered (entry 3). When $NaBH_4$ was used, 19% conversion to the γ-aminophosphonate **359b** was observed as the

enimido intermediate **360a** was probably overreduced (entry 4). Repeating the reaction in methanol at room temperature, did not result in any conversion initially (entry 5). When the mixture was refluxed overnight however, complete conversion to the β-methoxy-β-enimidophosphonate **360b** had taken place. Strikingly, full and clean conversion was also observed when β-ethoxy-β-enimidophosphonate **340** was refluxed for two hours with one equivalent of Cs_2CO_3 in methanol (entry 6). Unlike under the conditions of entry 4, the intermediacy of enamine **360a** was not possible in this case. Presumably, an addition-elimination reaction *via* intermediate **361** was responsible for this reactivity. Unfortunately, this strategy could not be further exploited for the synthesis of β-amino-β-enimidophosphonates **360c**. Prolonged heating in diethylamine did not result in any conversion of the starting material **340**, indicating that the amine is not sufficiently nucleophilic to react with enimide **340** (entry 7).

Table 20: Reduction and alkoxide exchange of addition product 340.



entry	reducing agent	catalyst	base	T	t (h)	solvent[a]	outcome
1	5 bar H_2	10 wt% Pd/C	-	rt	48	MeOH	SM
2	5 bar H_2	10 wt% PtO_2	-	rt	40	MeOH	SM
3[b]	1.0 equiv $NaBH(OAc)_3$	-	-	rt	2.5	THF	SM
				Δ	11		SM
4	1.0 equiv $NaBH_4$	-	-	rt[c]	on	THF	19% **359b**
5	1.0 equiv $NaBH_4$	-	-	rt[c]	0.75	MeOH	SM
	1.0 equiv $NaBH_4$			Δ	on		100% **360b**
6	-	-	1 equiv Cs_2CO_3	Δ	2	MeOH	100% **360b** (61%)[d]
7	-	-	1 equiv Cs_2CO_3	Δ	16	$HNEt_2$	SM

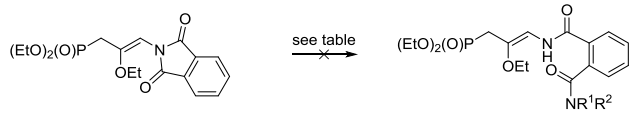
[a] not anhydrous [b] 1 equiv AcOH was added [c] $NaBH_4$ added at 0 °C [d] isolated yield

4.3.4. Attempted deprotection of the phthalimidoyl group

It was found that phosphonylated alkynes, bearing a phthalimidoyl group, were excellent substrates for the preparation and β-alkoxylation of 3-aminoallenylphosphonates. Next, it was

briefly investigated if this phthalimidoyl protective group could be easily removed. Given the enimide function present in allylphosphonate **340**, it was anticipated that, upon complete removal of the phthalimidoyl moiety with hydrazine, the generated enamine would immediately hydrolyze and complicate matters. On the other hand, substituted phthalimides were reported to undergo ring opening to afford phthalamides upon treatment with primary amines at room temperature.[327] However, no conversion took place when allylphosphonate **340** was mixed with *n*-$BuNH_2$ or $BnNH_2$ (Table 21, entries 1, 2). Treatment with isopropylamine did not alter the outcome, not even after heating at reflux temperature. When LDA is used instead, formation of small amounts of an unidentified compound is observed. The desired product **362** is not detected however. The base is possibly too sterically hindered to perform nucleophilic attack or is consumed when deprotonating the α-position of the phosphonate **340**. Further attempts were not undertaken to deprotect the phthalimidoyl moiety.

Table 21: Attempted deprotection of the phthalimidoyl group in allylphosphonate 340.



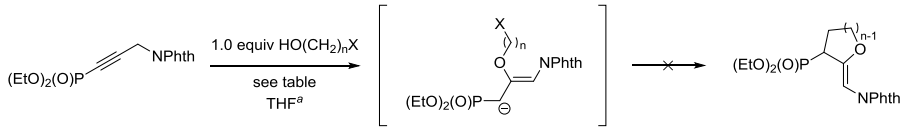
340 **362**

entry	nucleophile	R^1	R^2	T (°C)	t (h)	solvent	conversion (%)
1	*n*-$BuNH_2$	*n*-Bu	H	rt	27	neat	0
2	$BnNH_2$	Bn	H	rt	40	neat	0
3	*i*-$PrNH_2$	*i*-Pr	H	rt	17	neat	0
				Δ	7		0
4	LDA	*i*-Pr	*i*-Pr	- 40	1.5	THF	15
	(1.0 equiv)			rt	1		7

4.4. Towards 1-enimido-2-phosphonylated tetrahydrofurans

Next, it was investigated if cyclic structures of type **364** could be prepared by reaction of imidoallenylphosphonates with haloalcohols (Table 22). Half an hour after 2-chloro ethanol was added, 97% conversion to addition product **363a** was obtained. After another hour, conversion was complete and an extra equivalent of cesium carbonate was added to promote cyclization to tetrahydrofuran **364a**. After 16 hours, no conversion to tetrahydrofuran **364a** was observed and the addition product **363a** was isolated in 80% yield (entry 1). A similar result with 3-chloropropanol, bearing a longer linker, was obtained (entry 2).

Table 22: Screened conditions for the one-pot cyclization to substituted tetrahydrofurans and tetrahydropyrans.



305

363a (n = 2, X = Cl)
363b (n = 3, X = Cl)
363c (n = 3, X = Br)
363d (n = 3, X = I)

364a (n = 2, X = Cl)
364b (n = 3, X = Cl)
364c (n = 3, X = Br)
364d (n = 3, X = I)

entry	substrate	n	X	additive	T	t (h)	**363** (%)[b,c]	**364** (%)[b]
1	**305**	2	Cl	1 equiv Cs_2CO_3	rt	0.5	97	0
				1 equiv Cs_2CO_3		16	100 (80)	0
2	**305**	3	Cl	1 equiv Cs_2CO_3	rt	2	100 (84)	0
3	**305**	3	Br	1 equiv Cs_2CO_3	rt	5	100 (21)	0
			I	1 equiv NaI	rt	16	traces	0
			I	6 equiv NaI	rt	6	100	0
			I	-	Δ	16	100 (55)	0
4	**363b**	3	Cl	1 equiv Cs_2CO_3				
				1 equiv $AgNO_3$	rt	16	-	0
5	**363a**	2	Cl	1 equiv KO*t*Bu	rt	7	-[d]	0
6	**363a**	2	Cl	1 equiv KO*t*Bu	Δ	48	-	0
7	**363c**	3	Br	1 equiv KO*t*Bu	Δ	48	-	traces

[a] not anhydrous [b] conversion based on ^{31}P NMR [c] isolated yield between brackets [d] 72% deuteration upon quench with D_2O

The use of a nucleophile carrying a better leaving group, 3-bromopropanol, did not provide the tetrahydrofuran product **364c** either (entry 3). However, after five hours, a complete conversion to addition product **363c** was obtained. About one third of the mixture was isolated to yield compound **363c** in 21% yield. To the remainder of the mixture, one equivalent of NaI was added in order to install an even better leaving group. After reacting overnight, traces of the iodoalkoxylated product **363d** were detected. Complete conversion to iodoalkoxylated product **363d** was obtained after six hours of reaction with an excess of NaI. Refluxing this mixture overnight did not yield the cyclized product **364d** either.

Treatment of isolated haloalkoxylated product **363b** in the presence of $AgNO_3$ and Cs_2CO_3 did not change the outcome (entry 4). The use of a stronger base, KO*t*Bu, did not result in conversion of the starting material either (entry 5). Around 75% of the starting material **363a** was deuterated upon quench with D_2O, indicating that the substrate was effectively deprotonated in α-position of the phosphonate function. Refluxing the same substrate in THF with one equivalent of KO*t*Bu for two days did not yield any conversion either (entry 6).

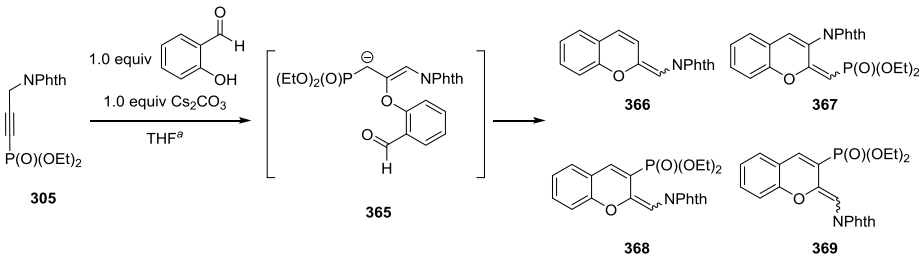
Although some traces of the tetrahydrofuran product **364c** were found after refluxing the bromo derivative **363c** for two days, it was concluded that cyclisation was not favourable (entry 7).

4.5. Towards phosphonylated chromenes

Given the ease with which alcohols reacted with the imidoallenylphosphonate **338**, the addition of salicylaldehyde was evaluated in order to obtain phosphonylated chromenes. Chromenes display interesting biological activities, e.g. they inhibit tubulin polymerization which is an important process in apoptosis.[328] At the same time they are important precursors in medicinal chemistry, for instance in the synthesis of the antihypertensive agent levcromakalim.[329] In THF at room temperature, starting material **305** was entirely consumed after half an hour, giving a mixture of cyclized products **366**-**369**, along with some unidentified minor compounds (Table 23, entry 1). Intermediate **365** was not detected. Phosphonylated chromenes **367**-**369** all originate from attack of an allylic anion to the aldehyde carbonyl group, followed by aromatization and concomittant elimination of water. It is not surprising that both 3-phosphonylated and 3-imidochromenes are formed, as it was illustrated earlier on that phenolic nucleophiles give a mixture of allyl and vinylphosphonate addition products (Scheme 73). Dephosphonylated chromene **366** is a result from a Horner-Wadsworth-Emmons reaction, in which a phosphate is eliminated instead of water during aromatization. This dephosphonylation had previously been observed as well when salicaldehyde was reacted with allenylphosphonates.[330, 331] Chromenes **366**, **368** and **369** were all isolated, albeit in low yields. Chromene **367** was characterized by a singlet at 19.57 ppm in ^{31}P NMR, a doublet of doublets at 5.60 ppm (J = 6.5 Hz and J = 3.5 Hz) in ^{1}H NMR and a doublet at 101.6 ppm in ^{13}C NMR ($^{1}J_{CP}$ = 192 Hz), but could not be isolated separately. It was observed earlier that allylphosphonate **357** is more selectively produced when lowering the temperature to 0 °C in the case of phenolic nucleophiles (*vide supra*). However, when keeping the temperature at 0 °C for 7 hours, it did not result in an increased selectivity, but only in a slower reaction progress (entry 2). It had also been observed that vinylphosphonate addition products **358** could be converted to allylphosphonate addition products **357** upon reflux in THF. When alkynylphosphonate **305** was refluxed in THF with salicylaldehyde, the starting material and the allene intermediate were consumed within half an hour (entry 3). The major product was indeed no longer the 3-imido chromene **367**, but the 3-phosphonochromene **368**. Moreover, 3-imidochromene **367** proved to be interconvertible to 3-phosphonochromene **368** and a high 61% conversion to the 3-phosphonochromene **368** was obtained after 2 hours of reflux. Further heating resulted in degradation and a complex mixture was obtained. Alternatively, the mixture was refluxed in toluene to further increase the selectivity. However, a complex mixture was

obtained quite fast and at no point a high conversion to one specific product was obtained (entry 4).

Table 23: Screened conditions for the one-pot synthesis of phosphonylated chromenes.



entry	solvent	T (°C)	t (h)	**366** (%)[b,c]	**367** (%)[b]	**368** (%)[b,c]	**369** (%)[b,c]	**other** (%)[d]
1	THF	rt	0.5	4	40	15	4	37
			1	6 (3)	39	26 (6)	8 (1)	22
2	THF	0	1.5	0	5	0	0	0
			7	5	26	14	2	19
		rt	16	5	42	21	7	26
3	THF	Δ	0.5	9	29	42	10	9
			2	11	14	61	11	3
			3	10	9	51	15	14
			19			CM		
4	toluene	Δ	0.5	9	26	21	5	40
			6	11	19	33	8	31
			20			CM		
5	CH_3CN	65	0.5	ND	27	12	28	10
			6	ND	22	28	37	13
6	dioxane	65	0.17	ND	49	7	30	13
			6	ND	26	14	60	0
			27	5	16	11	56	6
7	H_2O	65	3		0	0	0	100
			6		0	0	0	0
8	CH_2Cl_2	Δ	0.5		31	7	23	39
			6		4	18	62	17
			27		5	16	60	10

[a] not anhydrous [b] conversion calculated based on ^1H and ^{31}P NMR integrations [c] isolated yield after purification
[d] unidentified products, other than alkyn starting material **305** or allene intermediate **338**

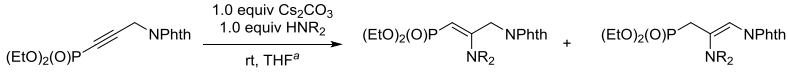
Since the most selective reaction occurred at 65 °C in THF, solvent screening was performed at this temperature. In all cases, the starting material was consumed within half an hour. When the reaction was run in CH_3CN, no pronounced selectivity was observed (entry 5), while a decent selectivity was obtained in dioxane (entry 6). Remarkably, the other isomer was predominantly formed as compared to the reaction in THF (entry 3). When water was used as

the solvent, the mass of the intermediate **365** was detected for the first time, while characteristic signals in ^{1}H NMR and ^{31}P NMR were found (entry 7). Unfortunately, the product degraded upon further heating. Refluxing in CH_2Cl_2 gave the same result as compared to dioxane (entry 8). It was concluded that the selectivity to one specific isomer was not sufficient and thus the synthesis of phosphonylated chromenes was not further investigated.

4.6. Addition of *N*-nucleophiles

In a later stage, it was investigated whether nucleophiles other than alcohols could be used in the one-pot synthesis and β-derivatization of 3-imidoallenylphosphonates. First, the addition of secondary amines was evaluated. Under the same conditions as for the β-alkoxylation, β-amino vinylphosphonate **370a** was obtained after one hour in 72% yield (Table 24, entry 1). Given the encountered difficulties with *iso*-propylalcohol (*vide supra*), conversion unsurprisingly proceeded sluggishly with the more sterically hindered diisopropylamine (entry 2). Although the addition product **370b** was detected, a complex mixture was obtained which consisted of several dimeric products of the starting material **305**. Addition of dibenzylamine resulted in complete consumption of the starting material **305** after 6 hours (entry 3). Along with two minor phosphorus-containing compounds, possibly the allylphosphonate **371c** and a dimer of the starting material **305**, vinylphosphonate **370c** was produced. Moreover, only 40% of the dibenzylamine seemed to be consumed, which is logical if a dimer of the starting material is effectively formed. After purification, the product was isolated together with β-ketophosphonate **353**, indicating that the desired product was not stable on silica gel. When the reaction was repeated and purified *via* reversed phase chromatography, the vinylphosphonate **370c** was obtained as a white crystalline material in 28% yield (entry 4). With pyrrolidine, the starting material was entirely consumed within one hour, giving rise to a 4/1 mixture of the vinylphosphonate **370d** and the allylphosphonate **371d**, which were not separated (entry 5). In the case of *N*-methyl phenylamine, addition of the nucleophile proved to be slow again, probably due to a high steric hindrance (entry 6). Although 24% of the starting material **305** was converted to the allene intermediate within 15 minutes, subsequent addition was hampered, after which secondary reactions started to occur. Eventually, a complex mixture was obtained after 6 hours, in which vinylphosphonate **370e** was one of the many products. It was clear that secondary amines did not react as easily as the corresponding alcohols. Remarkably, for the amines that did react, the stereoselectivity was opposite to the one observed during the alkoxylation of 3-imidoallenylphosphonates.

Table 24: Hydroamination of *in situ* prepared 3-imidoallenylphosphonates.



305 **370a-e** **371a-e**

entry	R^1	R^2	t (h)	**370** (%)[b]	**371** (%)[b]
1	Et	Et	1.5	100 (72)[c]	0
2	*i*Pr	*i*Pr	8	CM	
3	Bn	Bn	6	84	9
4	Bn	Bn	7	80 (28)[d]	7
5	$(CH_2)_4$		1	80	20
6	Ph	Me	6	CM	

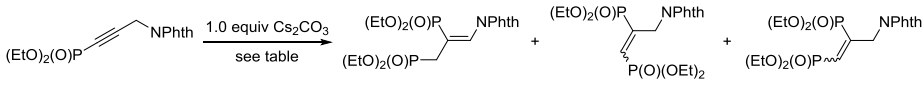
[a] not anhydrous [b] conversion based on 31P NMR [c] isolated yield after normal phase column chromatography
[d] isolated yield after reversed phase column chromatography

4.7. Addition of *P*-nucleophiles

Phosphorus nucleophiles could also be added to the allene intermediate. With one equivalent of diethyl phosphite in THF at room temperature, a mixture of four phosphonylated products was obtained (Table 25, entry 1). As in the case of addition of phenol and certain amines, the addition of diethyl phosphite is not stereoselective. Initially, the product **372**, with the double bond conjugated to the phthalimide moiety, is primarily formed. Overnight, compound **372** isomerizes to the *E*/*Z* stereoisomers **373** and **374** with the double bond between the two phosphonate groups. Ratios do not change significantly upon longer reaction times. A fourth product was detected, in which two equivalents of diethyl phosphite had been incorporated. The compound, now containing three phosphorus atoms, is characterized by two doublets in ^{31}P NMR (at 16.9 ppm and -1.3 ppm with a coupling constant of 35 Hz) and one singlet (at 21.6 ppm). Determination of its structure was not possible however, since the small amount of isolated product did not allow to record ^{13}C NMR spectra. In order to shift the reaction towards this triple phosphonylated product **375**, one equivalent of diethyl phosphite was added in excess (entry 2). Initially, more or less equal amounts of products **372**-**374** were obtained. Strikingly, after 7 hours, product **372** was no longer detected, while stereoisomers **373** and **374** now accounted for almost 90% of the reaction products. Continued stirring at room temperature did not alter the composition of the reaction mixture. Refluxing the mixture in THF with an equimolar amount of diethyl phosphite, also resulted in a more stereoselective reaction, as compound **372** was not detected (entry 3). Adding the phosphorus nucleophile at 0 °C, it was attempted to avoid the formation of the triple phosphonylated product (entry 4). Unfortunately, this was not successful. An intermediate temperature of 12 °C did not prove to be a fruitful compromise either, as the reaction was slowed down too drastically while selectivity was still not increased (entry 5). Changing the solvent to dioxane did not alter the outcome either (entry

6). Remarkably, when the reaction was run at 100 °C in acetonitrile with microwave heating, the triple phosphonylated product is predominantly produced (entry 7). While stereoisomers **373** and **374** seem to be convertible to compound **375**, full conversion could not be achieved and a fifth unidentified procuct was formed. An excess diethyl phosphite or heating to 130 °C did not enhance the formation of compound **375** (entry 8). Further attempts were not undertaken, as it was too difficult to obtain one of the products selectively.

Table 25: Hydrophosphonylation of *in situ* prepared 3-imidoallenylphosphonates.



305 **372** **373** **374**

entry	equiv HP(O)(OEt)$_2$	solvent[a]	T (°C)	t (h)	**372** (%)[b,c]	**373** (%)[b,c]	**374** (%)[b,c]	**375** (%)[b,c]
1	1	THF	rt	0.5	47	18	12	13
				on	22	45	19	13
				48	18[d]	49 (12)	20[d]	13 (1)
2	2	THF	rt	0.5	42	27	19	12
				1.5	12	49	25	14
				7	0	65	24	11
				72	0	63	24	13
3	1	THF	Δ	10 min	0	56	20	24
				9	0	67	11	22
4	1 (dropwise)	THF	0	1	11	3	6	2
5	1 (dropwise)	THF	12	2	6	2	2	1
6	1 (dropwise)	1,4-dioxane	12	2	5	1	1	0
7[e]	1	CH_3CN	100	0.5	0	38	8	42
				5.5	0	8	0	65
				on	0	7	0	59
8[e]	2	CH_3CN	100	0.5	0	35	16	42
				5.5	0	32	7	52
			130	1	0	28	5	47

[a] not anhydrous [b] conversion based on ^{31}P NMR [c] isolated yield between brackets

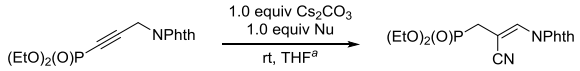
[d] compounds **372** and **374** could not be separated [e] microwave irradiation was applied

4.8. Addition of *C*-nucleophiles

To conclude, the addition of carbon nucleophiles was evaluated. With equimolar amounts of KCN and Cs_2CO_3, 13% of the starting material **305** was converted to addition product **376** (Table 26, entry 1). Upon longer reaction times, the remaining starting material was consumed, but a complex mixture was obtained. The experiment was repeated with a catalytic amount of base so that the starting material **305** can reprotonate the addition product **376**. This resulted

in a slow conversion of the starting material, but the desired product **376** was not detected (entry 2).

Table 26: Addition of cyanide to *in situ* prepared 3-imidoallenylphosphonates.



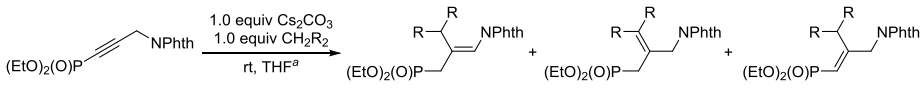
305 **376**

entry	Nu	t (h)	**376** (%)[b]
1	KCN	4	13
		22	CM
2[c]	KCN	72	0

[a] not anhydrous [b] conversion based on ^{31}P NMR [c] 0.1 equiv Cs_2CO_3 was used

Next, diethyl malonate, a protic carbon nucleophile with a low pK_a, was selected. The starting material **305** and the allene intermediate were consumed within 90 minutes, but afforded a mixture of regioisomers (Table 27, entry 1). The enimidophosphonate **377** seemed to be the initial addition product since it isomerizes to product **378** with the double bond conjugated to the malonate. After two hours, the vinylphosphonate **379** becomes the major product. On repetition of this reaction, vinylphosphonate **379** does not turn out to be the more stable product, as conversion in favour of compound **378** took place (entry 2). Enimidophosphonate **377** is detected in important amounts at the beginning of the reaction again. As stereoselectivity was increased upon heating in the case of phenol addition (*vide supra*), this parameter was varied in this case again. Within ten minutes, all of the starting material was consumed and the major compound was indeed altered. Vinylphosphonate **379** accounted for half of the phosphonylated compounds detected (entry 3). Addition of malononitrile resulted in 22% conversion to product **378** after one hour at room temperature (entry 4). Upon longer reaction times, at least ten other phosphonylated compounds were detected, while the starting material was still present. In all of the discussed cases with carbon nucleophiles, an important amount of unidentifiable products were detected as well and thus no further attempts were performed to optimise the selectivity of the addition of these nucleophiles.

Table 27: Addition of malonate-type nucleophiles to *in situ* prepared 3-imidoallenylphosphonates.



305 **377** **378** **379**

entry	R	t (h)	**377** (%)[b]	**378** (%)[b,c]	**379** (%)[b]
1	CO_2Et	10 min	17	4	1
		1.5	9	65	17
		2.25	4	23	50
2	CO_2Et	1	22	12	30
		3	6	16	45
		on	8	45 (10)	5
3[d]	CO_2Et	10 min	8	28	48
		0.5	5	13	53
		1.25	4	17	44
4	CN	1	0	22	0
		31		CM	

[a] not anhydrous [b] conversion based on ^{31}P NMR [c] isolated yield between brackets
[d] reflux instead of rt

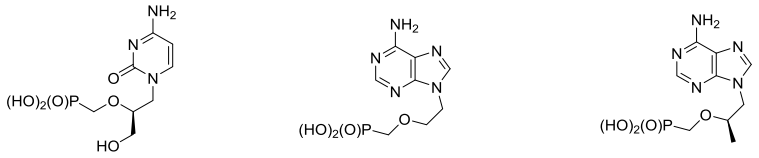
4.9. Conclusion

In conclusion, the first synthesis of 3-imidoallenylphosphonates was demonstrated. This transformation proceeds via a prototropic rearrangement under very mild conditions and the imidoallenylphosphonate was isolated and characterized. Moreover, it can be alkoxylated in a one-pot procedure in very short reaction times in excellent chemical yields. The method is applicable to an array of highly functionalized biologically relevant *O*-nucleophiles, furnishing these adducts in moderate to good yields. Purification on column was needed only in the case of the more complex nucleophiles. Treatment with haloalcohols did not afford substituted tetrahydrofurans, while an exchange of the alkoxide moiety was observed when the ethanol addition product was mixed with cesium carbonate in methanol. Addition of salicyl aldehyde afforded the envisioned phosphonylated chromenes, but a mixture of isomers was obtained. Diethylamine was easily added to the allene intermediate as well, but other *N*-nucleophiles were more challenging to add selectively. Phosphorus nucleophiles could also engage in this addition reaction, affording a mixture of four phosphonylated products. Carbon nucleophiles, such as the cyanide anion or diethylmalonate, could be introduced as well, but an incomplete reaction or a mixture of isomers was obtained.

5. Aminoallenylphosphonates as a key intermediate in the synthesis of new antiviral agents

5.1. Introduction

The interest in new antiviral compounds is huge. Yellow fever for instance is a viral disease for which an effective vaccin exists, but nonetheless resulted in 127 000 severe infections and 45 000 deaths in 2013.[332] As known antivirals were shown not to be successful, no cure is available once a person is infected. Influenza, on the other hand, is reported to result in about 250 000 to 500 000 deaths a year,[333] while in 2015 around 37 million people were living with HIV and 1.2 million people succumbed to AIDS-related illnesses.[334, 335] Between its discovery in 1981 and 2014, AIDS is estimated to have been responsible for no less than 39 million deaths worldwide.[336] In 1986, azidothymidine was approved by the FDA as the first drug for the treatment of HIV.[337] At the same time, acyclic nucleoside phosphonic acids turned out to be a class of very potent antiviral compounds. In 1986 and 1987, adefovir **12** and cidofovir **11** were discovered respectively (Figure 20).[338, 339] While the former has been approved for the treatment of HBV infections (Hepatitis B Virus), the latter is used to treat HCMV retinitis (human cytomegalovirus) in AIDS patients.[19] In 1993, the anti-HIV properties of tenofovir **13** were first described.[340] In 2001 tenofovir disoproxil fumarate (TDF) was licensed by the FDA for the treatment of HIV infections. Since 2008 it is also approved to treat HBV infections. Moreover, tenofovir might also be used prophylactically in order to prevent HIV infections.[19]



11 cidofovir HPMPC, Vistide®

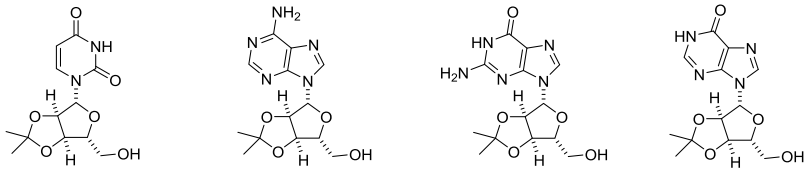
12 adefovir PMEA, Hepsera®

13 tenofovir PMPA, Viread®

Figure 20: Examples of antiviral acyclic nucleoside phosphonates.

As the straightforward addition of *O*-nucleophiles to 3-imidoallenylphosphonate **338** was demonstrated earlier, it was decided to create a set of nucleoside addition products which would then be tested in a broad spectrum antiviral test. Four protected nucleosides were selected, which were commercially available in their acetonide protected form: uridine acetonide **380**, adenosine acetonide **381**, guanosine acetonide **382** and inosine acetonide **383**, the latter being the nucleoside which is formed when hypoxanthine is attached to ribofuranose

(Figure 21). Cytidine and thymidine compounds were not selected, as derivatives with easily removable protecting groups, such as the acetonide, were not commercially available.



380 uridine acetonide | **381** adenosine acetonide | **382** guanosine acetonide | **383** inosine acetonide

Figure 21: Commercially available nucleosides acetonides.

The screening for antiviral activity would be assessed on two levels: virus-infected cell cultures – including herpes, HIV, influenza and yellow fever viruses – were to be used to test the nucleoside phosphonates. The deprotected phosphonic acid derivatives however are necessary to measure specific enzyme inhibition in enzyme assays. It was reasoned that a dibenzyl phosphonate precursor **384** would be a better choice than a diethyl phosphonate precursor **305**. Benzyl phosphonates are lipophilic, which means a better uptake in the cell, and are known to liberate the phosphonic acids upon cytochrome P450 oxidation, a process which ethyl phosphonates cannot undergo.[341] Also, benzylphosphonates can give the free phosphonic acids upon hydrogenation, which is interesting as the TMSBr deprotection method of dialkyl phosphonates is known to be troublesome in some cases.[342]

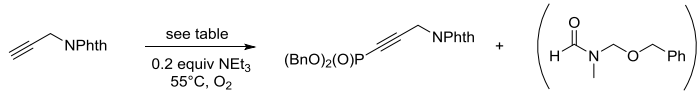
5.2. Synthesis of nucleoside phosphonates

*5.2.1. Preparation of dibenzyl alkynylphosphonate **384***

In view of the synthesis of nucleoside phosphonates, *N*-propargyl phthalimide **336** was phosphonylated with dibenzyl phosphite according to the earlier developed procedure. However, under standard conditions and after two consecutive purification steps, the isolated product **384** was still contaminated with *N*-((benzyloxy)methyl)-*N*-methylacetamide **385** (Table 28, entry 1). Probably an *N*-acetyl iminium intermediate was formed under the applied oxidative conditions, which was attacked by traces of free benzyl alcohol. An alternative solvent which is stable under the oxidative conditions was searched for. In sulfolane, a poor conversion of 37% was obtained after three hours (entry 2). In *N*-formyl morpholine, a better conversion was obtained after six hours (entry 3). A complete conversion was obtained when an equimolar amount of copper was used (entry 4). Adding three equivalents of the dibenzylphosphite at the beginning of the reaction, allowed the reaction to be completed within two hours (entry 5). Scaling up the reaction to a 10 mmol scale, required a slightly bigger excess of dibenzyl

phosphite to achieve complete conversion (entry 6). After extensive washing with brine and aqueous LiCl solution, followed by column chromatography, dibenzyl alkynylphosphonate **384** was isolated in 81% yield.

Table 28: Optimization of conditions for the preparation of dibenzyl alkynylphosphonate 384.



336 **384** **385** in DMF

entry	solvent	t (h)	equiv $Cu(OAc)_2$	equiv $HP(O)(OBn)_2$	**384** (%)[a,b]
1	DMF	0	0.1	1	-
		1	0.2	2	21
		2			77 (23)
2	sulfolane	0	0.1	2	-
		1			4
		2	0.2	1	6
		3			37
3	NFM	0	0.1	2	-
		1			15
		2			17
		2.5	0.2		-
		3.5			63
		4.5		1	-
		6			78
4	NFM	0	1	2	-
		1			70
		3		1	70
		4			100
5	NFM	0	1	3	-
		2			97
6[c]	NFM	0	1	3	-
		3			89
		3.75		0.5	
		4.5			100 (81)

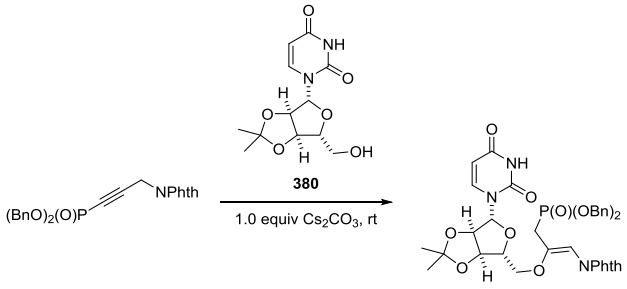
[a] conversion based on ^1H NMR [b] isolated yield between brackets [c] 10 mmol scale

*5.2.2. Addition of nucleobases to dibenzyl alkynylphosphonate **384***

Next, the addition of uridine acetonide **380** was evaluated. When an equimolar amount of nucleophile was used, the alkynylphosphonate **384** was entirely consumed after 6 hours, although the mixture contained 37% non-incorporated uridine acetonide starting material **380**

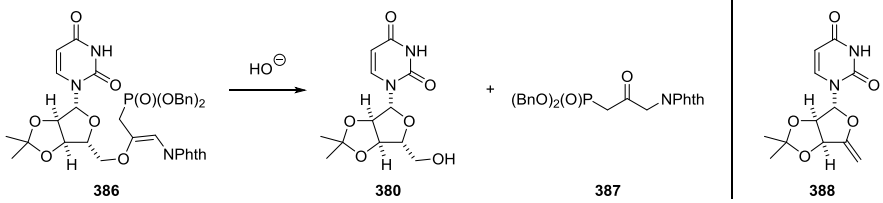
(Table 29, entry 1). Moreover, separation on column was not successful. Although the transformation previously never required the use of dried solvent, the reaction was now run in dry THF. According to ^{31}P NMR, the reaction was finished within 4 hours but ^{1}H NMR showed that even more uridine acetonide starting material **380** remained (entry 2). Even an excess of alkynylphosphate **384** was consumed within three hours, while the nucleoside starting material was still present (entry 3). A change of solvent resulted only in a small improvement (entry 4). Possibly, an addition-elimination step of hydroxide (as was observed when ethanol addition product **340** was mixed with Cs_2CO_3 in methanol, *vide supra*), yielded the starting material **380** and β-ketophosphonate **387** (Scheme 76). Elimination product **388** (the analogue of compound **352**, which was produced when serine was added to imidoallenylphosphonate **338**, *vide supra*) was not observed. The most successful conditions were repeated before the mixture was purified via reversed phase column chromatography (entry 4). Unfortunately, also in this way no analytically pure material could be obtained.

Table 29: Screened conditions for the synthesis of uridine acetonide addition product 386.



entry	equiv alkyne **384**	t (h)	solvent	**386** (%)[a]	remaining SM **380** (%)[b]
1	1	6	THF[c]	77	37
2	1	4	THF	62	45
3	1.5	3	THF	48	32
4	1	2	CH_3CN[d]	70	18
5	1	2	CH_3CN[d]	70	30

[a] conversion based on ^{31}P NMR [b] conversion based on ^{1}H NMR [c] not anhydrous [d] anhydrous

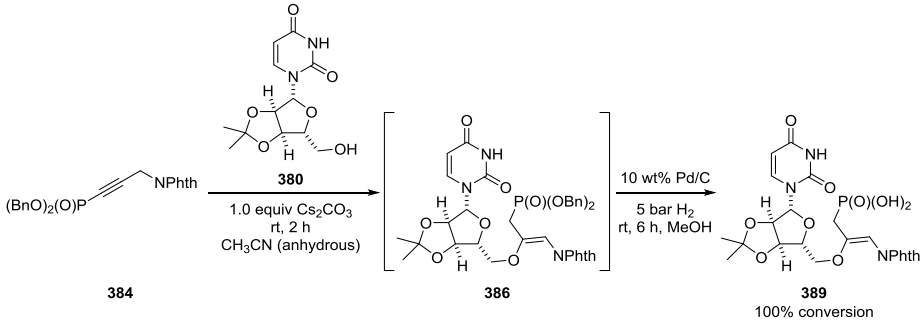


Scheme 76: Possible formation of β-ketophosphonate 387.

*5.2.3. Debenzylation of the dibenzyl phosphonate addition product **386***

It was then decided to deprotect the nucleoside phosphonate esters first and purify the mixture at the phosphonic acid stage. Treatment of nucleoside phosphonate **386** with 10 wt% Pd/C resulted in complete deprotection but three unidentified impurities were also formed (Table 30). Purification by means of preparative TLC (mobile phase: 8:2 *i*PrOH/water) did not result in a cleaner product. Moreover, most of the product could not be recovered. Also reversed phase chromatography proved to be unsuccessful as the product did not show any affinity for the stationary phase, eluting immediately with 100% water (entry 2).

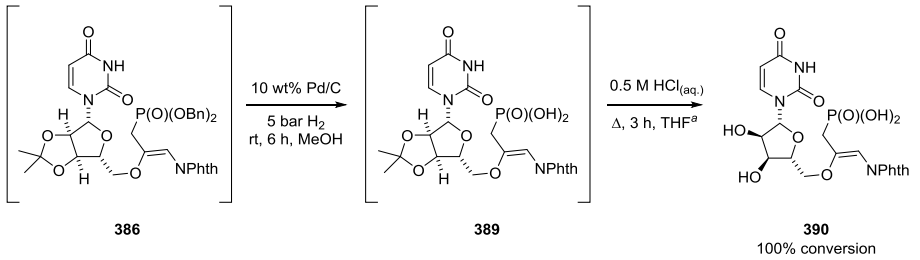
Table 30: Deprotection and conditions for the attempted purification of uridine acetonide phosphonic acid aduct 389.



entry	purification	result
1	pTLC (8/2 *i*PrOH/H_2O)	unsuccessful
2	RP chromatography (100% H_2O)	unsuccessful
3	Wash *n*-hexane	one apolar impurity removed
	Wash ethyl acetate	loss of material in organic phase
4	Recrystallization MeOH	unsuccessful

One of the three major impurities could be removed by dissolving the product in water and extracting the impurity with hexane (entry 3). Washing with ethyl acetate resulted in loss of the

product **389** in the organic phase, while the remaining product **389** in the aqueous phase was still contaminated with the other two impurities. Recrystallization from MeOH was also unsuccessful (entry 4). When the crude reaction mixture was refluxed in THF/$HCl_{(aq.)}$, the entirely deprotected target structure **390**, was easily obtained (Scheme 77). An analytically pure sample could once again not be obtained as recrystallization in water, adding acetone as an antisolvent, was unsuccessful.



386 **389** **390**
100% conversion

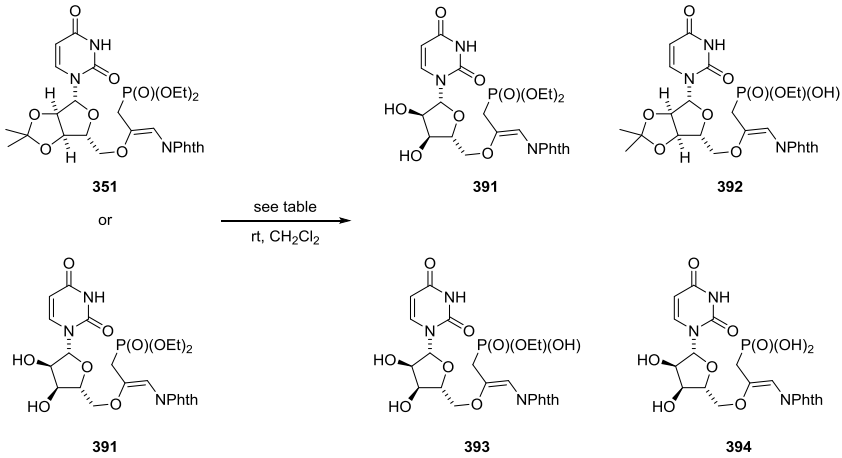
[a] not anhydrous

Scheme 77: Deprotection of the acetonide and phosphonate moieties.

*5.2.4. Deprotection of the diethyl phosphonate addition product **351** with TMSBr*

Although the uridine phosphonic acid **389** was predominantly obtained from the dibenzyl phosphonate **386**, purification was shown to be troublesome. Consequently, the deprotection of diethyl nucleoside phosphonate **351** (*vide supra*), with TMSBr was considered nonetheless (Table 31). Earlier on, diethyl nucleoside phosphonate **351** had been obtained from uridine acetonide addition to 3-imidoallenylphosphonate **338** and was easily purified *via* normal phase chromatography. Thus, diethyl nucleoside phosphonate **351** was selected as a model substrate for the deprotection of the diethyl phosphonate ester moiety. Treatment of nucleoside phosphonate **351** with two equivalents of TMSBr resulted both in phosphonate ester and acetonide deprotection (entry 1). After 4 hours, 80% of the starting material **351** was monodeprotected at the phosphorus center, producing compounds **392** and **393**. Unfortunately, after the addition of 1 extra equivalent TMSBr, no phosphonic acid product **394** could be detected. When analytically pure 2',3'-deprotected nucleoside phosphonate **391** (preparation, *vide infra*) was treated with four equivalents of TMSBr, small amounts of the phosphonic acid nucleoside **394** were detected (entry 2). The major product was still the mono ethyl phosphonic acid **393**. As the target phosphonic acids were hardly obtained, purification was not pursued.

Table 31: Deprotection of the phosphonate moiety in adducts 351 and 391 with TMSBr.



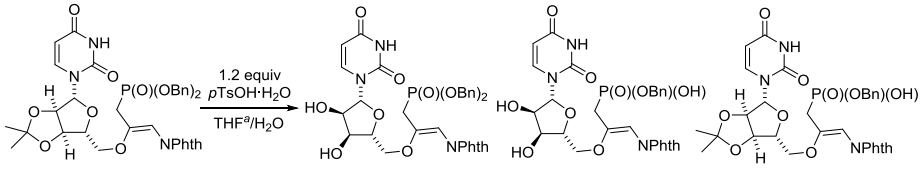
entry	equiv TMSBr	t (h)	starting material	SM[a]	**391** (%)[a]	**392** + **393** (%) [a,b]	**394** (%)[a]
1	2[c]	2	**351**	10	55	35	0
	1	4		10	10	80	0
		5		0	30	70	0
2	4[c]	20	**391**	25	-	70[d]	5

[a] determined through LC-MS [b] compounds **392** and **393** co-elute [c] added at start of reaction [d] only **393**

5.2.5. Acetonide deprotection of dibenzyl phosphonate prodrugs

Since no easy entry into nucleoside phosphonic acid **394** was found, it was decided to refocus on the preparation of dibenzyl phosphonate prodrugs **395** with a 2',3'-deprotected ribose moiety (Table 32). Treatment of dibenzyl nucleoside phosphonate **386** with *p*TsOH in THF resulted in almost complete consumption of the starting material, but next to dibenzylphosphonate **395**, monobenzyl phosphonate **396** was also detected (entry 1). The acetonide deprotection was as good as completed after 4.5 hours (entry 2). Deprotection of the phosphonate moiety only seemed to take place upon longer reaction times. Unfortunately, the product **395** could again not be separated from the impurities. Running the reaction at room temperature did not improve the selectivity and resulted in a poor conversion of the starting material **386** (entry 3).

Table 32: Deprotection of the acetonide moiety of dibenzyl phosphonate adduct 386.



386 **395** **396** **397**

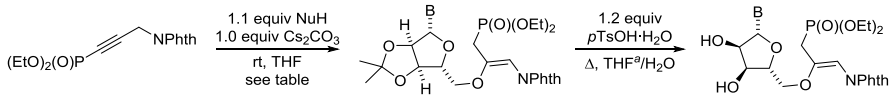
entry	T	t (h)	**386**[b]	**395**[b]	**396**[b]	**397**[b]
1	Δ	24	5	50	40	0
2	Δ	4.5	9	87	4	0
3	rt	6 days	72	25	3	0

[a] not anhydrous [b] determined through LC-MS

5.2.6. Acetonide deprotection of diethyl phosphonate prodrugs

Ultimately, it was attempted to prepare acetonide-deprotected diethyl nucleoside phosphonate prodrugs. Diethyl 2′,3′-*O*-isopropylideneuridine phosphonate **351**, which had been prepared earlier (*vide supra*), did undergo selective deprotection of the acetonide moiety upon treatment with *p*TsOH.[343] After one day of reflux in THF, uridine phosphonate **401** was isolated in 50% yield after extractive work-up (Table 33, entry 1). Deprotection of the phosphonate ester was not observed. Encouraged by this result, the addition of three other nucleosides and the subsequent deprotection step were evaluated. Reaction with 2′,3′-*O*-isopropylideneadenosine swiftly afforded the 2′,3′-*O*-isopropylideneadenosine phosphonate **398** after normal phase chromatography (entry 2). After deprotection of the 2′,3′-*O*-isopropylidene group, the adenosine phosphonate **402** was isolated, without the need for purification at this stage, in 80% yield. When 2′,3′-*O*-isopropylideneinosine **382** was used, a complex mixture was obtained, in which the aliphatic alkoxylated addition product **399** was observed along with the phenolic hydroxypurinyl double addition product **405** (entry 3 and Figure 22). Double alkylation was observed as well when 2′,3′-*O*-isopropylideneguanosine **383** was used as a substrate. In this case, only products **400** and **407** and no other impurities were formed and consequently, both addition products could be isolated in low yields *via* preparative reversed phase chromatography (entry 4). Ultimately, the acetonide protecting group of both alkoxylated products **400** and **407** was readily deprotected.

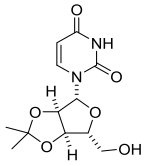
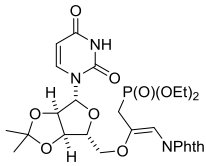
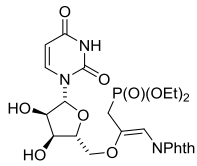
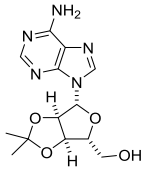
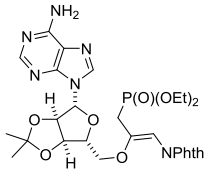
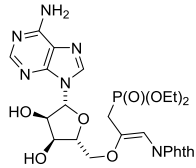
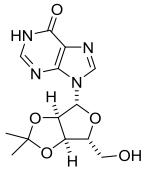
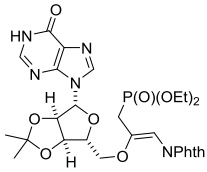
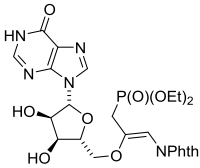
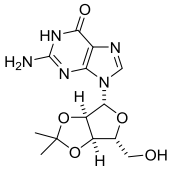
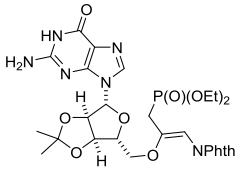
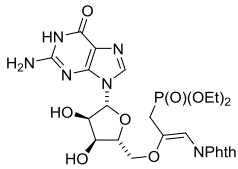
Table 33: Synthesis of acetonide-deprotected diethyl phosphonate prodrugs 401-404.



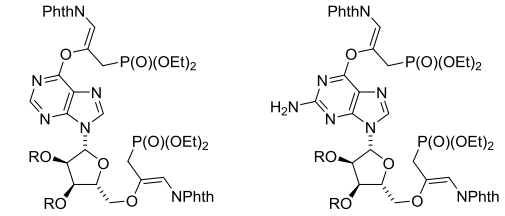
305

351 (B = uracil)
398 (B = adenine)
399 (B = hypoxanthine)
400 (B = guanidine)

401 (B = uracil)
402 (B = adenine)
403 (B = hypoxanthine)
404 (B = guanidine)

entry	NuH	Protected nucleoside phosphonates 351, 398-400	Deprotected nucleoside phosphonates 401-404
1	 **380**	 **351** (6 h, 64%[b])	 **401** (24 h, 50%[b])
2	 **381**	 **398** (3 h, 35%[b])	 **402** (27 h, 80%[b])
3	 **382**	 **399** (22 h, CM)	 **403** (-)
4	 **383**	 **400** (8 h, 5%[b])	 **404** (66 h, 87%[b])

[a] not anhydrous [b] isolated yield

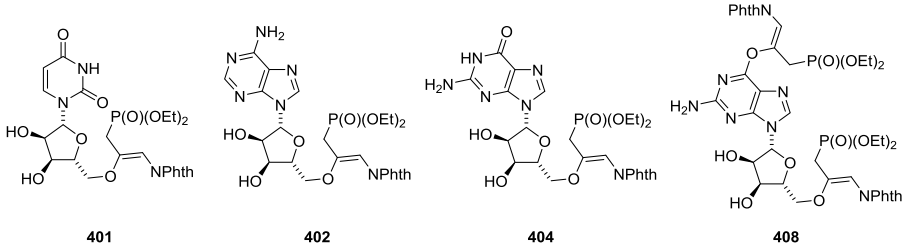


405 (R + R = $C_q(CH_3)_2$, 22 h, CM)
406 (R = H, -)
407 (R + R = $C_q(CH_3)_2$, 8 h, 2%[b])
408 (R = H, 66 h, 70%[b])

Figure 22: Double addition products 405 and 407 and the deprotected derivative 408.

5.3. Biological evaluation of nucleoside phosphonates

The antiviral properties of diethyl nucleoside phosphonates **401**, **402**, **404** and **408** were assessed at the Rega institute for Medical Research (KU Leuven) against several viruses in four different cell cultures (Figure 23).[344] HEL cell cultures (Human Embryonic Lung fibroblast cells) were used to test the activity against herpes simplex virus type 1 (HSV-1), an aciclovir resistant strain of thymidine kinase-deficient HSV-1, herpes simplex virus type 2 (HSV-2), vaccinia virus, human adeno virus type 2 (Ad2) and human coronavirus (Table 34). No activity was observed at the highest concentrations tested for any of the viruses.



401 **402** **404** **408**

Figure 23: Prepared diethylnucleoside phosphonates, used in the broad-spectrum antiviral screening.

Table 34: Cytotoxicity and antiviral activity in HEL cell cultures.

compound	Minimum cytotoxic concentration[a,b]	EC_{50}[a,c]					
		HSV-1	HSV-1 TK$^-$ ACV^r	HSV-2	Vaccinia virus	Ad2	Human coronavirus
401	>100	>100	>100	>100	>100	>100	>100
402	>100	>100	>100	>100	>100	>100	>100
404	>100	>100	>100	>100	>100	>100	>100
408	>100	>100	>100	>100	>100	>100	>100
Brivudin	>250	0.04	14	>250	22	-	-
Cidofovir	>250	2	5	5.8	19	10	-
Aciclovir	>250	0.9	100	3.4	>250	-	-
Ganciclovir	>100	0.07	0.8	0.4	>100	-	-
Zalcitabine	>250	-	-	-	-	29	-
Alovudine	>250	-	-	-	-	22	-
UDA[d]	>100	-	-	-	-	-	1.8
Ribavirin	>250	-	-	-	-	-	146

[a] concentrations expressed in µM, except for UDA: µg/mL [b] required to cause a microscopically detectable alteration of normal cell morphology [c] required to reduce virus-induced cytopathogenicity by 50% [d] Urtica dioica agglutinin

Next, the antiviral activity against vesicular stomatitis virus, coxsackie virus B4 and respiratory syncytial virus was tested in HeLa cell cultures. Unfortunately, no activity was observed at the highest concentrations tested (Table 35).

Table 35: Cytotoxicity and antiviral activity in HeLa cell cultures.

compound	Minimum cytotoxic concentration[a,b]	EC_{50}[a,c]		
		Vesicular stomatitis virus	Coxsackie virus B4	Respiratory syncytial virus
401	>100	>100	>100	>100
402	>100	>100	>100	>100
404	>100	>100	>100	>100
408	>100	>100	>100	>100
DS-10.000	>100	>100	34	0.4
Ribavirin	>250	8.9	45	1.5

[a] concentrations expressed in µM, except for DS-10.000: µg/mL [b] required to cause a microscopically detectable alteration of normal cell morphology [c] required to reduce virus-induced cytopathogenicity by 50%

Antiviral activity of compounds **401**, **402**, **404** and **408** was investigated against para-influenza-3-virus, reovirus-1, sindbis virus, Coxsackie virus B4, punta toro virus and yellow fever virus in Vero cell cultures. Again, at the highest concentrations tested, no activity was observed (Table 36).

Table 36: Cytotoxicity and antiviral activity in Vero cell cultures.

compound	Minimum cytotoxic concentration[a,b]	EC_{50}[a,c]					
		Para-influenza-3-virus	Reovirus-1	Sindbis virus	Coxsackie virus B4	Punta Toro virus	Yellow Fever virus
401	>100	>100	>100	>100	>100	>100	>100
402	>100	>100	>100	>100	>100	>100	>100
404	>100	>100	>100	>100	>100	>100	>100
408	>100	>100	>100	>100	>100	>100	>100
DS-10.000	>100	100	>100	45	20	>100	12
Ribavirin	>250	50	>250	>250	>250	45	>250
Mycophenolic acid	>100	0.5	6	45	>100	2.3	2

[a] concentrations expressed in µM, except for DS-10.000: µg/mL [b] required to cause a microscopically detectable alteration of normal cell morphology [c] required to reduce virus-induced cytopathogenicity by 50%

Next, the antiviral properties of nucleoside phosphonates **401**, **402**, **404** and **408** were tested against three types of influenza in MDCK (Madin Darby canine kidney cells) cell cultures. No activity was observed either (Table 37).

Table 37: Cytotoxicity and antiviral activity in MDCK cell cultures.

compound	Cytotoxicity		EC_{50}[b]					
			Influenza A/H1N1		Influenza A/H3N2		Influenza B	
	CC_{50}[a]	Minimum cytotoxic concentration[b,c]	visual CPE score	MTS	visual CPE score	MTS	visual CPE score	MTS
401	>100	>100	>100	>100	>100	>100	>100	>100
402	>100	>100	>100	>100	>100	>100	>100	>100
404	>100	>100	>100	>100	>100	>100	>100	>100
408	>100	>100	>100	>100	>100	>100	>100	>100
Zanamivir	>100	>100	0.1	0.3	0.4	0.01	0.4	0.4
Ribavirin	>100	>100	8.9	18.2	2.3	1.4	5.6	4.6
Amandatine	>100	>100	20	22.6	0.2	0.03	>100	>100
Rimandatine	>200	>200	>200	>200	0.01	0.01	>200	>200

[a] 50% Cytotoxic concentration, as determined by measuring the cell viability with the colorimetric formazan-based MTS assay [b] concentrations expressed in µM [c] Minimum compound concentration that causes a microscopically detectable alteration of normal cell morphology [c] 50% Effective concentration, or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by visual scoring of the CPE, or by measuring the cell viability with the colorimetric formazan-based MTS assay

Finally, the anti-HIV properties of nucleoside phosphonates **401**, **402**, **404** and **408** were evaluated against the HIV-1 NL4.3 and HIV-1 BaL strains in TZM-bl cells and against the HIV-1 NL4.3 and HIV-2 ROD strains in MT-4 cells. Disappointingly, no antiviral activity was observed against any of these strains in the TZM-bl or MT-4 cells (Table 38).

Table 38: Cytotoxicity and antiviral activity in TZM-bl cells and MT-4 cells.

compound	CC_{50}[a] and EC_{50}[b] in TZM-bl cells			CC_{50}[a] and EC_{50}[b] in MT-4 cells		
	CC_{50}[a]	EC_{50}[b,c] HIV-1 NL4.3	EC_{50}[b,c] HIV-1 BaL	CC_{50}[a]	EC_{50}[b,c] HIV-1 NL4.3	EC_{50}[b,c] HIV-2 ROD
401	>100	>100	>100	>100	>100	>100
402	>100	>100	>100	>100	>100	>100
404	>100	>100	>100	>100	>100	>100
408	>100	>100	>100	>100	>100	>100
AMD3100	>1000	1.3	-	>1000	17	16
AMD14031	>1000	-	3.0	>100[d]	8.5[d]	1.5[d]

[a] 50% cytotoxic concentration of the compound in this cell line [b] concentrations expressed in µM, except for AMD3100: ng/mL
[c] 50% effective concentration or compound concentration producing 50% inhibtion of HIV-induced cytopathic effect
[d] PMPA was used as a reference instead of AMD14031

In all of the cytotoxicity tests, none of the nucleoside phosphonates were found to be cytotoxic. The four nucleoside phosphonates were also tested in an enzymatic assay with influenza PA-Nter endonuclease.[345] Even at the highest concentrations tested, no inhibition of the influenza polymerase was observed (Table 39).

Table 39: Activity in enzymatic assay with influenza PA-Nter endonuclease.

compound	IC_{50}[a,b]
401	>500
402	>500
404	>500
408	>500
DPBA[c]	1.6

[a] compound concentration producing 50% inhibition of PA-Nter mediated cleavage of the DNA substrate
[b] concentrations expressed in µM [c] 2,4-dioxo-4-phenylbutanoic acid

5.4. Conclusion

In this chapter, it was investigated whether the earlier developed 3-imidoallenylphosphonate building block could be exploited for the synthesis of nucleoside phosphonate prodrugs and nucleoside phosphonic acids. Antiviral activity would be assessed in an enzymatic essay with influenza PA endonuclease, which required the preparation of the nucleoside phosphonic acids. Secondly, the nucleoside phosphonates would be tested as prodrugs in cell culture against a broad spectrum of viruses. To that end, a dibenzyl alkynylphosphonate precursor was prepared, as benzyl phosphonates can yield the corresponding phosphonic acids upon hydrogenation. Addition of the nucleoside occurred smoothly, but isolation of the pure compound proved to be cumbersome. Although the phosphonate ester and 2',3'-*O*-

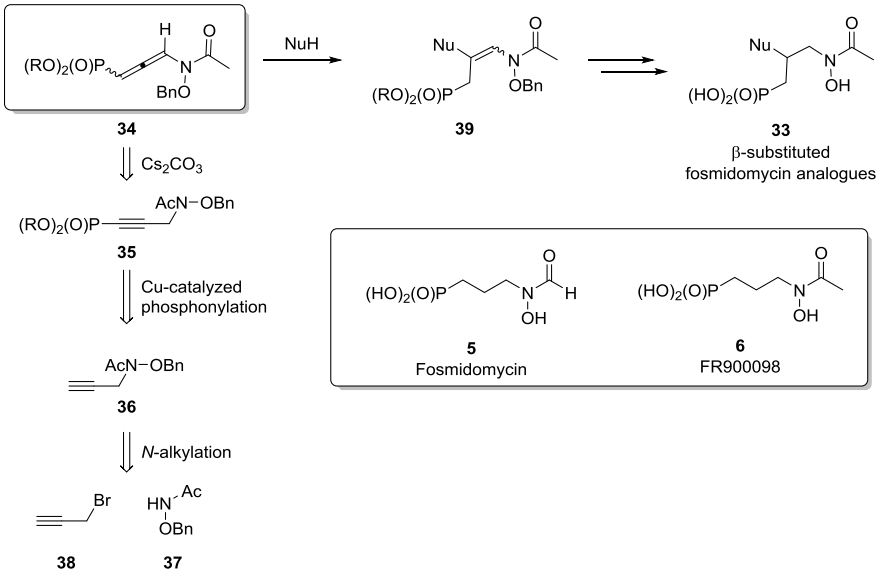
isopropylidene protecting groups were both readily removed, purification at either of these stages was not successful. Disappointingly, the diethyl nucleoside phosphonate could not yield the nucleoside phosphonic acid either. However, four diethyl nucleoside phosphonate prodrugs could be prepared, originating from the addition of either 2',3'-*O*-isopropylideneuridine, 2',3'-*O*-isopropylideneadenosine or 2',3'-*O*-isopropylideneguanosine to diethyl 3-imidoallenylphosphonate, followed by acetonide deprotection with *p*TsOH. The synthesized compounds showed no activity in a broad-spectrum antiviral screening in cell cultures or enzyme assays.

6. Applying the aminoallenylphosphonate strategy to the production of new fosmidomycin-based antimalarials

6.1. Introduction

Malaria is a tropical disease, spread most commonly by the female *Anopheles* mosquito. It was reported that in 2015, there were 296 million cases of malaria worldwide, probably causing around 731 000 deaths.[334, 335] With 90% of those deaths and infections occuring in Africa, the disease has a huge impact on these societies and their economic development.[346] Although several antimalarial medications exist, treatment becomes increasingly problematic because the parasite has developed resistance against all antimalarial drugs apart from artemisinins. Since treatment of malaria infections, caused by resistant strains, increasingly relied on the use of those last resort drugs, artemisinin resistance is developing as well.[347] It is universally acknowledged that new antimalarial drugs are urgently needed, but the resources for the development of a treatment of this poverty disease are sadly enough still limited. Fosmidomycin **5** is a natural product, first isolated from *Streptomyces lavendulae*, and was first investigated for its antibacterial activity.[348, 349] Later it was found that fosmidomycin **5** and its *N*-acetyl derivative FR900098 **6**, which is about twice as potent, display important activities against the parasite *Plasmodium falciparum*.[350, 351] Fosmidomycin inhibits DXP reductoisomerase, a key enzyme in the non-mevalonate pathway. Some organisms, such as the malaria parasite, rely on this pathway for their isoprenoid biosynthesis. Human beings use the mevalonate pathway for their isoprenoid biosynthesis, rendering this approach particularly attractive. Although quite some α- and γ-substituted fosmidomycin derivatives have been prepared,[352-354] only 14 examples of β-substituted fosmidomycin and FR 900098 derivatives have been reported in literature.[348, 355-364] In previous chapters, it has been demonstrated that 3-imidoallenylphosphonate **305** is an intermediate that can be easily prepared from phosphonylated *N*-propargyl phthalimide **336** and that it is easily derivatized at the central carbon atom. Oxygen nucleophiles react particularly well, in high yields, short reaction times and displaying good stereoselectivity. Although a decreased stereoselectivity was often observed, nitrogen, phosphorus and carbon nucleophiles could be introduced as well in some cases. Aptly substituted 3-aminoallenylphosphonate **34** could consequently serve as the precursor to make a small library of unsaturated β-substituted fosmidomycin derivatives **39** (Scheme 78). To effectively use the previously developed methodology, the phthalimidoyl group in precursor **338** had to be replaced by a masked hydroxamic acid functional group while

the free phosphonic acids instead of the phosphonate esters are desired in the target molecules. As the deprotection of diethyl phosphonates to the free phosphonic acids with TMSBr is often cumbersome, both ethyl and benzyl phosphonates would be prepared. The latter have the advantage that they can be be deprotected upon hydrogenation and ideally, the *O*-benzyl protected hydroxamic acid function would be deprotected at the same time. So, alkynylphosphonate precursors **35** would be prepared from successive alkylation of *O*-benzyl hydroxamic acid **37** and copper-catalyzed phosphonylation of the resulting alkyne **36** with dialkylphosphite.

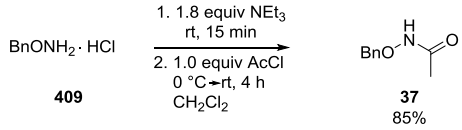


Scheme 78: Retrosynthetic approach to β-substituted analogues of FR900098 and structures of fosmidomycin and its *N*-acetyl analogue FR900098.

6.2. Synthesis of β-substituted FR900098 derivatives

*6.2.1. Preparation of N-alkylated hydroxamic acid **410***

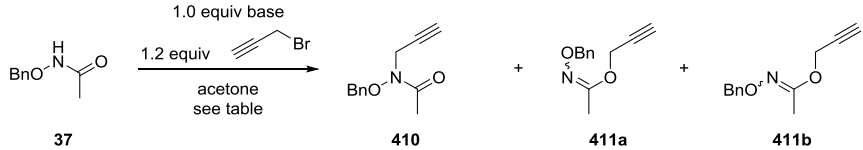
O-benzyl hydroxamic acid **37** is not commercially available but was conveniently prepared from *O*-benzyl hydroxylamine hydrochloride **409** with acetyl chloride (Scheme 79).[365] *O*-benzyl hydroxamic acid **37** was isolated as a mixture of rotamers with an isolated yield of 85%.



Scheme 79: Preparation of *O*-benzyl hydroxamic acid 37.

Alkylation with propargyl bromide predominantly gave the desired *N*-alkylated product **410**, next to two *O*-alkylated isomers **411a** and **411b** (Table 40).[366] Initially, *N*-alkylated hydroxamic acid **410** was isolated in 66% yield, although purification was not straightforward given the comparable R_f values of the products (entry 1).

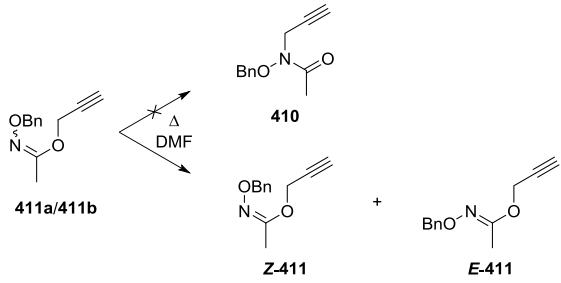
Table 40: Propargylation of *O*-benzyl hydroxamic acid 37.



entry	base	T	t (h)	**410** (%)[a,b]	**411a** (%)[a]	**411b** (%)[a,b]
1	K_2CO_3	Δ	15	86 (66)	3	11 (5)
2	Cs_2CO_3	Δ	0.5	89 (42)	2	8
3	Cs_2CO_3	rt	4	91 (66)	2	8
4	K_2CO_3	Δ	15	ND (88)[c]	ND	ND

[a] conversion based on ^{1}H NMR [b] isolated yield between brackets [c] work-up limited to solvent evaporation

To facilitate this purification step, conditions were screened in order to minimize the formation of the *O*-alkylated products **411a** and **411b**. Since *O*-allylated hydroxamic acids are known to undergo thermal [3,3]-rearrangement to their *N*-allylated counterparts,[367] one of the two *O*-propargyl, *O'*-benzyl hydroxamic acid isomers **411a** or **411b** was refluxed in DMF. *E*/*Z* isomerization was observed upon reflux in DMF for one day, but unfortunately no conversion to the *N*-propargyl hydroxamic acid **410** was observed (Scheme 80).



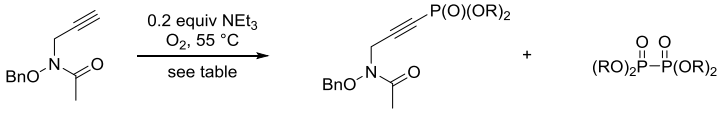
Scheme 80: Attempted *N* to *O* thermal rearrangement.

With Cs_2CO_3 instead of K_2CO_3 as the base in the alkylation step, the selectivity for the desired isomer **410** was only marginally improved (entry 2). Because of the higher solubility of Cs_2CO_3, the reaction sped up drastically. It was consequently investigated whether regioselectivity would be increased when running the reaction at a lower temperature. However, at room temperature, *O*-propargylation still occurred in small amounts (entry 3). Because of the higher price of Cs_2CO_3, it was decided to use K_2CO_3 from then on since comparable yields were obtained. It was also observed that a considerable amount of product was lost during aqueous work-up (entries 2 and 3). Hence, work-up was limited to evaporation of the solvent prior to purification of the crude mixture on column. This resulted in a high 88% isolated yield of *N*-propargyl hydroxamic acid **410** (entry 4).

*6.2.2. Synthesis of phosphonylated hydroxamic acid precursors **412a-b***

Next, *N*-alkylated hydroxamic acid **410** was successfully phosphonylated with dialkyl phosphites, using the earlier developed procedure (Table 41). The diethyl phosphonate precursor **412a** could be isolated in 66% yield (entry 1). Similarly, the dibenzyl phosphonate **412b** was prepared from reaction with dibenzyl phosphite in NFM, to avoid reaction with the solvent (*vide supra*). In the latter case, an equimolar amount of catalyst was used in order to obtain a complete conversion on a reasonable time scale (entry 2). Dibenzyl phosphonate **412b** was eventually isolated in 20% yield. Part of the product was probably lost during the extensive washing with aqueous LiCl solution, while another part eluted together with tetrabenzyl hypophosphate **413**.

Table 41: Preparation of dialkyl phosphonate precursors 412a-b.



410 — **412a** (R = Et), **412b** (R = Bn) — **282** (R = Et), **413** (R = Bn)

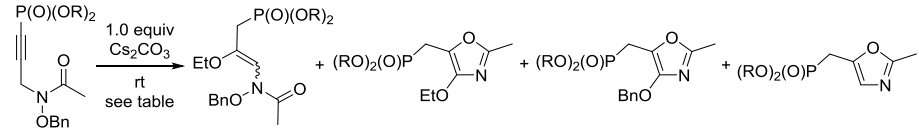
entry	R	equiv $Cu(OAc)_2$	equiv DAP	t (h)	solvent	**412** (%)[a,b]
1[c]	Et	0.4	2	1	DMF	97 (66)
2	Bn	1	3	3.5	NFM	96 (20)

[a] conversion based on ^{31}P NMR [b] isolated yield [c] 0.3 equiv NEt_3 was used

6.2.3. *Attempted addition of nucleophiles to phosphonylated hydroxamic acid precursors **414a-b***

With the alkynylphosphonate precursor **412a**-**b** in hand, the addition of *O*-nucleophiles was evaluated at room temperature (Table 42, entry 1). Twenty minutes after the addition of one equivalent ethanol, the starting material was entirely consumed, giving a complex mixture. After three hours, three major products were detected by ^{31}P NMR, while signals of the intermediates had disappeared.

Table 42: Attempted synthesis of β-alkoxylated FR900098 derivatives.



412a (R = Et)
412b (R = Bn)

414a-b **415a-b** **416a-b** **417a-b**

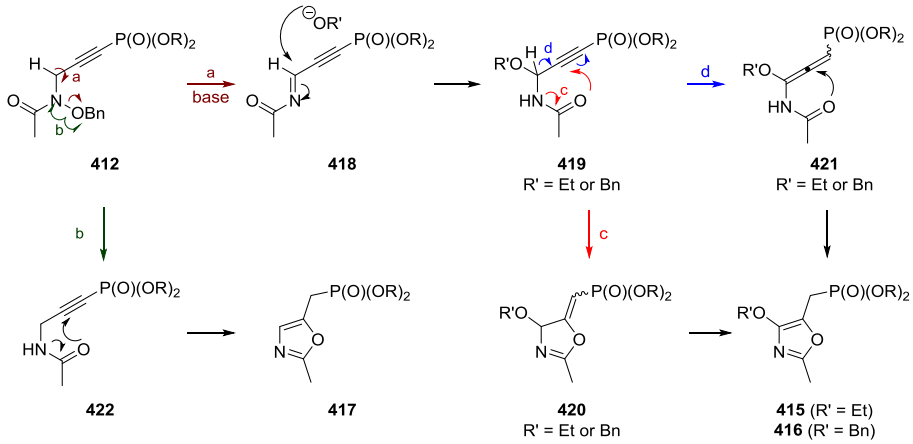
entry	SM	equiv EtOH	t (h)	solvent	**415** (%)[a]	**416** (%)[a,b]	**417** (%)[a]
1	**412a**	1	3	THF	20	54 (11)	26
2	**412b**	2	1 min	neat	47	37	16
3	**412b**	-	5 min	EtOH	75	15	10
4	**412b**	0	3	THF	0	60	40

[a] conversion based on ^{31}P NMR [b] isolated yield between brackets

Minor amounts of the addition product **414a** were detected, which could not be recovered after purification. However, oxazole **416a**, which was the major product, was isolated in 11% yield. Spectral data were in accordance with literature values for comparable compounds.[368] When substrate **412b** was allowed to react with two equivalents of EtOH, the starting material was entirely consumed within one minute yielding a mixture of oxazoles **415**-**417** (entry 2). When ethanol was added in excess, the benzyl alcohol addition product still accounts for 15% conversion (entry 3).

A plausible mechanism is suggested for the formation of oxazoles **415**-**417**, in which an apparent [1,2]-shift of the alkoxy group has occurred (Scheme 81). In alkaline medium, the highly conjugated *N*-acetyl ynimine **418** is presumably produced with concomittant expulsion of benzyloxide (path a). The *N*-acetyl ynimine **418** can then yield hemiaminal **419** after an attack of an alkoxide. A 5-exo-*dig* Michael-type cyclization followed by an isomerization step possibly yields the oxazoles **415** or **416** (path c). Alternatively, isomerization of the hemiaminal **419** occurs, giving the amino allenylphosphonate **421**, which yields the oxazoles **415** or **416** upon 5-exo-*dig* cyclization (path d). The intermediacy of the *N*-acetyl

ynimine **418** explains the presence of ethanol cross-over product **415**. Moreover, after 20 minutes the *N*-acetyl ynimine **418** is observed in ^{1}H NMR (doublet at 7.83 ppm (J_{HP} = 1.1 Hz)) and at -7.41 ppm in ^{31}P NMR. After three hours, these signals have disappeared, indicating that this intermediate is further converted. In addition to that, ^{31}P NMR data showed that P-C(sp^2) fragments were also present at the beginning of the reaction, possibly originating from the allene **421**. The presence of the reduced oxazole **417** can be explained by cyclization of secondary amide **422**, which could result from homolytic scission of the *N*-*O* bond (path b).



Scheme 81: Plausible mechanism for the formation of oxazoles 415-417.

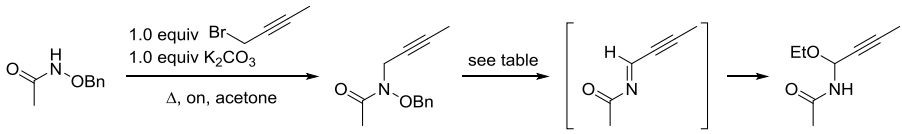
In an aprotic medium, the *N*-acetyl ynimine **418** was observed again and evidently no ethanol cross-over product was observed (entry 4). Further reaction to the benzyloxy substituted oxazole **416** and the reduced oxazole **417** could not be prevented.

6.2.4. Understanding the proposed mechanism through synthesizing intermediates and derivatives

In order to eventually prevent the formation of oxazoles **415**-**417**, proof for this pathway was sought for. The *N*-(benzyloxy)-*N*-(but-2-yn-1-yl)acetamide **423** was prepared to assess if the hemiaminal **419** is an intermediate indeed (Table 43). As the triple bond in the hemiaminal **425** is probably not sufficiently polarized to initiate 5-exo-*dig* cyclization, it was anticipated that hemiaminal **425** would be observed. When *N*-(benzyloxy)-*N*-(but-2-yn-1-yl)acetamide **423** was reacted with one equivalent of Cs_2CO_3, the starting material was recovered, even after a long reaction time (entry 1). The *N*-acetyl ynimine intermediate **424** was not observed in ^{1}H NMR. This is not surprising, as the propargylic protons in *N*-(benzyloxy)-*N*-(but-2-yn-1-yl)acetamide **423** are probably significantly less acidic as compared to those in that position in the phosphonate-containing hydroxamic acid **412**. When the reaction is repeated in

ethanol, 23% conversion to the *N*-(1-alkoxybut-2-yn-1-yl)acetamide **425** was detected after four days (entry 2). Moreover, the mass of the *N*-acetyl ynimine intermediate **424** was detected in trace amounts in LC-MS analysis. These two observations show that the hemiaminal **425** can indeed be formed under these mild conditions, even though the propargylic protons are not as acidic as in the phosphonylated substrate **412**. Cyclization of hemiaminal **425** did not occur indeed.

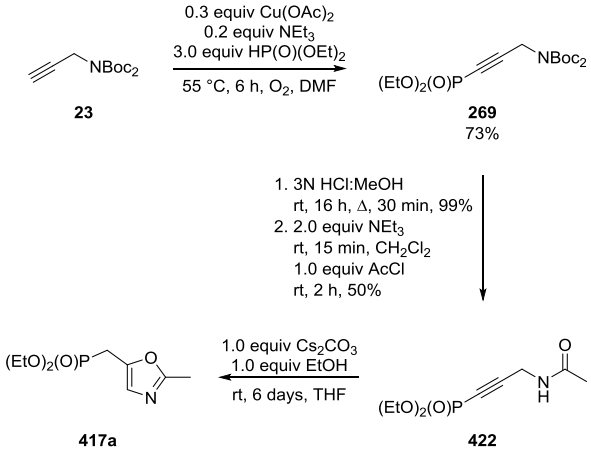
Table 43: Preparation of the non-phosphonylated analogue 425.



entry	equiv Cs_2CO_3	t (d)	solvent	**423** (%)[a]	**424** (%)[a]	**425** (%)[a]
1	1	14	THF	100	0	0
2	2	4	EtOH	77	0	23

[a] conversion based on ^{1}H NMR

Next, phosphonylated amide **422** was prepared to assess whether this proposed intermediate would cyclize in the presence of a mild base. Boc-protected propargylamine **23** was phosphonylated with diethyl phosphite, deprotected with HCl and then acetylated.[245] (Scheme 82).

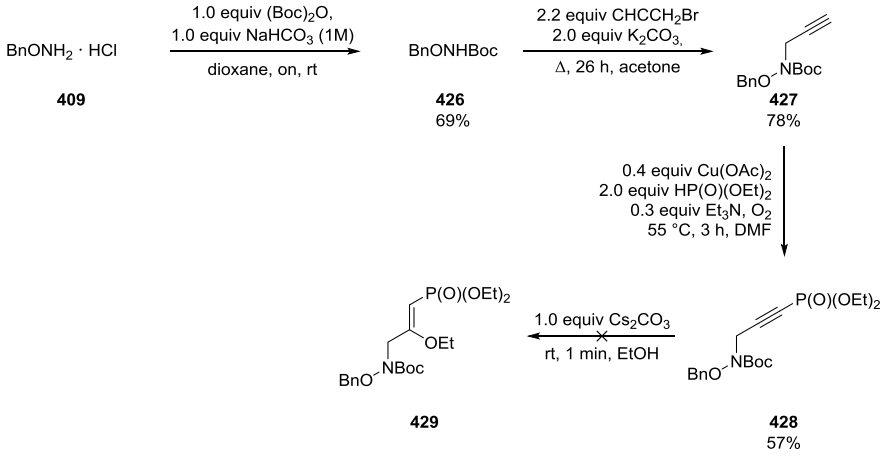


Scheme 82: Preparation and cyclization of the amide 422.

Upon treatment with one equivalent Cs_2CO_3 and one equivalent ethanol at room temperature, 95% of the amide **422** was converted to oxazole **417a** after 6 days. Spectral data are similar to literature values for comparable compounds.[368] Allenic intermediates were not observed and thus it is reasonable to assume that hemiaminal **419**, once formed, reacts in much the same way (pathway c). Given the difference in reaction rate however, the intermediacy of amino allenylphosphonate **421** cannot be excluded in the case of hemiaminal **419**.

*6.2.5. Nucleophilic addition to tert-butyl (benzyloxy)(3-(diethoxyphosphoryl)prop-2-yn-1-yl)carbamate **428***

Next, it was anticipated that the acidity of the propargylic protons in precursor **412** could be downregulated by replacing the acetyl group by a Boc group. *O*-benzyl hydroxylamine hydrochloride **409** was *N*-Boc protected and next propargylated in good yield (Scheme 83). Oxidative cross coupling with diethyl phosphite then yielded precursor **428**. Unfortunately, upon treatment of precursor **428** with one equivalent of Cs_2CO_3, loss of the OBn and Boc signals was observed in ^{1}H NMR. It was concluded that the present approach was too challenging and the β-alkoxylation strategy was abandoned.



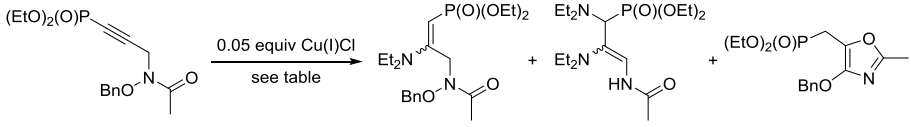
Scheme 83: Preparation and β-alkoxylation of *O*-benzyl-*N*-Boc protected hydroxylamine 428.

*6.2.6. Copper-catalyzed hydroamination of alkynylphosphonate **412***

As the introduction of an oxygen nucleophile in alkaline medium proved to be problematic, another approach for the introduction of nucleophiles was considered. In literature, the copper-catalyzed addition of secondary amines to alkynylphosphonates has been described.[59] This method was evaluated on substrate **412** in order to get access to β-enamino fosmidomycin

derivatives **430** (Table 44). Applying the conditions of the original procedure afforded a complex mixture, in which oxazole **416a** accounted for one third of the phosphorus-containing products (entry 1). When the reaction was run in $HNEt_2$ as a solvent, the starting material was consumed after one hour (entry 2). One isomer of the addition product **430** and one isomer of a double addition product **431** were detected.

Table 44: Screened conditions for the hydroamination of phosphonylated *O*-benzyl hydroxamic acid 412.

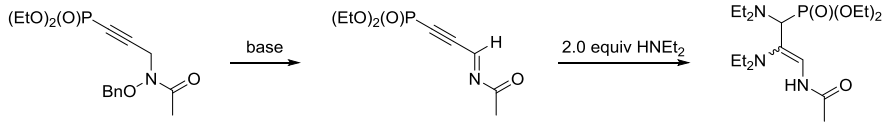


412 **430a-b** **431** **416a**

entry	equiv $HNEt_2$	T (°C)	t (h)	solvent	**430a** (%)[a]	**430b** (%)[a]	**431** (%)[a]	**416a** (%)[a]
1	1	100	16	MeOH	0	0	0	33
2	-	100	1	$HNEt_2$	0	6	39	0
3	-	rt	20	$HNEt_2$	7	13	39	0
4	1	rt	8 d	MeOH	0	0	32	0
5	-	- 41	4	$HNEt_2$	15	2	47	0

[a] conversion based on ^1H NMR

The latter can be explained by the intermediacy of ynamide **418**, which can then undergo two consecutive Michael addition steps, one in the direction of the phosphonate and another in the direction of the imine (Scheme 84). At room temperature, a slightly more encouraging result was obtained as both isomers **430a**-**b** were detected, along with the double addition product **431** (entry 3). At room temperature in methanol, the reaction slowed down dramatically, without detecting any addition product **430a**-**b** after eight days (entry 4). In diethylamine at even lower temperatures, selectivity towards addition products **430a**-**b** did not increase (entry 5). Eventually, this strategy was abandoned as well, as the abundancy of functional groups seemed to be too high for the introduction of an extra nucleophile.



412 **418** **431**

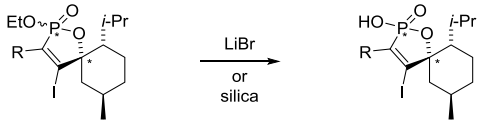
Scheme 84: Plausible mechanism for the formation of double addition product 431.

6.3. Conclusion

In our efforts to develop new fosmidomycin-inspired antimalarials, the hydroxamate-containing alkynylphosphonate precursors were successfully prepared through simple acylation and alkylation of *O*-benzyl hydroxylamine, followed by oxidative phosphonylation with dialkyl phosphites. When the one pot isomerization to the corresponding allene and subsequent introduction of an *O*-nucleophile was attempted, oxazoles were primarily obtained. Presumably, an elimination-addition reaction takes place yielding an amide that is prone to cyclization. Moreover, the *N*-*O* bond of the hydroxamic acid moiety seems to be a sensitive part of the molecule as well, as a reduced oxazole was observed. Copper-catalyzed hydroamination of the hydroxamate-containing alkynylphosphonate precursor was not successful either.

Perspectives

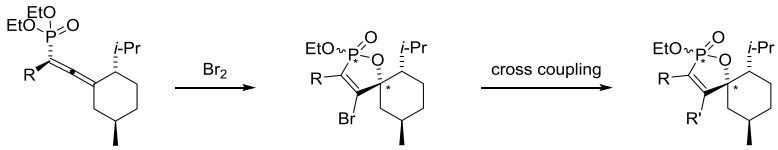
A very efficient strategy has been developed to prepare chiral, spirocyclic oxaphospholenes in a three-step synthesis from ketoterpenes. To evaluate the chiral inducing properties, the phosphonic acid **433** is required. Treatment of phosphonate esters with LiBr is a known method to prepare monodealkylated phosphonate esters.[369] Alternatively, treatment with silica could yield the phosphonic acid too, since the spontaneous hydrolysis of oxaphospholenes upon purification on silica has been described (Scheme 85).



432 **433**

Scheme 85: Proposed preparation of oxaphospholenic acids by deprotection of the corresponding phosphonate esters.

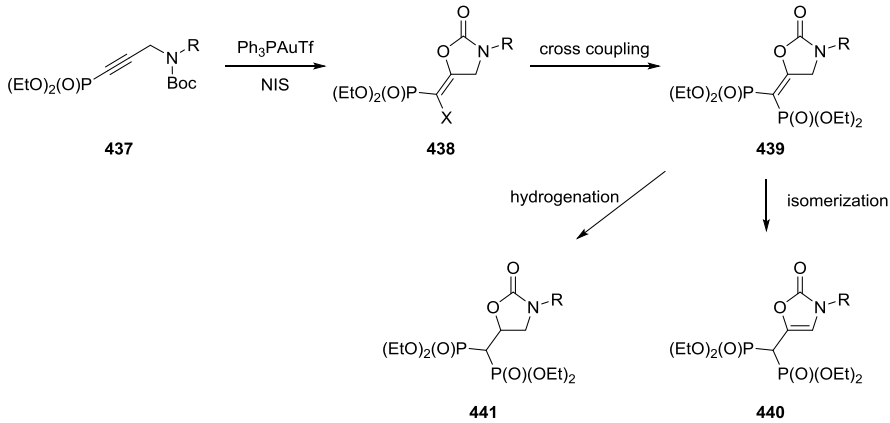
Although both the alkyne substituent and the ketoterpenic moiety were varied, more variation is still possible. Iodine was selected because it is an easy to add dihalogen. Other halogenated derivatives, particularly the brominated ones, would be interesting to prepare, as vinylbromides are widely used in cross coupling reactions (Scheme 86). *Via* a Suzuki coupling, additional structural variety can be introduced if, for instance, steric or electronic properties need to be altered.



434 **435** **436**

Scheme 86: Further exploration of the structural variety in the oxaphospholenic skeleton.

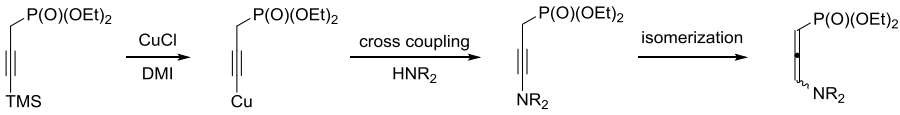
Since the stepwise synthesis of 5-bisphosphonomethyl oxazol-2-ones suffered from the use of strong bases, the second phosphonate group could not introduced. This attractive class of compounds could possibly be accessed even so through an alternative approach. The gold-catalyzed 5-exo-*dig* cyclization of Boc-protected propargylamines **437** has been described in literature.[249] Endowing substrate **438** with this vinyl halide handle, the second phosphonate moiety could then be installed *via* a cross coupling reaction with diethyl phosphite (Scheme 87).[370]



437 **438** **439** **441** **440**

Scheme 87: Alternative strategy to access 5-bisphosphonomethyl oxazol-2-ones 440 and 5-bisphosphonomethyl oxazolidin-2-ones 441.

In our approach to prepare 3-aminoallenylphosphonates through cross coupling of phosphorus-containing copper acetylides with amines, isomerization of the propargylphosphonate to the internal alkyne immediately occurred upon removal of the TMS-group. However, a direct alkynyl group transfer from silicon to copper is described in literature.[371] If the copper acetylide can be prepared in this way, the coupling reaction with *N*-nucleophiles and ultimately the isomerization to the allene can be evaluated (Scheme 88).



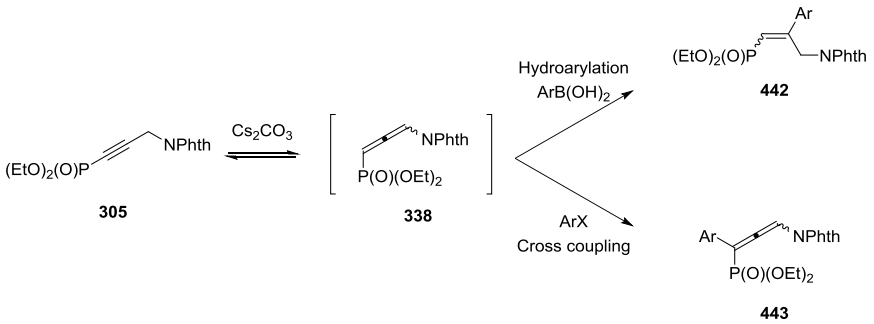
322b **31** **30** **28**

Scheme 88: Preparation of copper acetylide 31 through direct alkynyl group transfer from silicon to copper and its evaluation in the synthesis of 3-aminoallenylphosphonates.

3-Imidoallenylphosphonates have been shown to react very efficiently with a variety of *O*-nucleophiles. *N*, *P* and *C*-nucleophiles have also been employed, although less successfully because of selectivity issues. If suitable follow-up reactions can be found that convert two or more isomers to one product, these transformations could still prove to be useful. Hydrogenation, for instance, would respectively yield aminophosphonates, bisphosphonates and γ-phosphonomalonates.

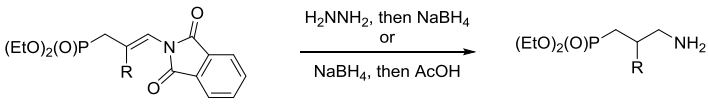
In the case of *C*-nucleophiles, substrates with a low pK_a were selected, given the mild conditions the transformation uses. Hydroarylation with aryl boronic acids and cross coupling with aryl halides could be interesting opportunities to further expand the scope of introducible *C*-substituents (Scheme 89). Examples of both hydroarylation[372, 373] and cross coupling[373] reactions have been reported in literature for allenylphosphonate substrates. A comparison of

the behaviour of aminoallenylphosphonates under these conditions would definitely be of interest.



Scheme 89: Proposed hydroarylation of 3-imidoallenylphosphonates with aryl boronic acids and cross coupling with aryl halides.

The influence of different substituents on the *N*-atom – with the possibility for their deprotection at a later stage in mind – on the preparation and reactivity of 3-aminoallenylphosphonates remains to be explored. So far, the phthalimidoyl group of the addition products could not be removed, although treatment with hydrazine and a reducing agent or with $NaBH_4$ in acidic medium should be evaluated (Scheme 90).[374] Aminoallenylphosphonates bearing alternative protective groups – like tosyl, Boc and benzyl groups – should definitely be looked into since the preparation of their alkynylphosphonate precursors has been realized already.

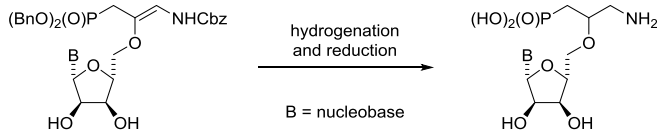


360 **440**

Scheme 90: Possible reduction methods for the deprotection of the phthalimidoyl moiety.

The antiviral evaluation of the first set of nucleoside phosphonates was not very promising. Some major issues need to be addressed. First of all, the conventional purification techniques were not successful for the isolation of the nucleoside phosphonic acids. Other chromatographic techniques, like the use of a cellulose stationary phase, need to be evaluated since the deprotection conditions for both the acetonide deprotection and debenzylation of the phosphonate, have been shown to be feasible. Secondly, the phthalimidoyl protecting group might prove to be too big and too apolar to fit in the active site of viral enzymes. If an easily removable protecting group can be found – for instance a Cbz group that can be simultaneously deprotected with the benzyl groups of the phosphonate – a primary enamine would be obtained that can be reduced to the amine and, if desired, further derivatized (Scheme 91). The antiviral potential of this new series of derivatives can then be assessed again. The synthetic potential of the aminoallenylphosphonate building block and its

applications has definitely not been maximally explored and will be of interest in future research.



445 **446**

Scheme 91: Suggested deprotection strategies for the synthesis of nucleoside phosphonic acids.

Experimental Procedures

1. General methods

Commercially available reagents were not purified and used as such, unless otherwise stated. Reactions were run in non-flame dried glassware and open to air, unless otherwise noted. Inert atmosphere refers to a N_2 atmosphere, if not indicated otherwise.

1.1. Solvents

Unless otherwise noted, anhydrous THF, Et_2O, CH_2Cl_2, *n*-pentane and toluene were used, either collected in a Schlenk tube (THF, Et_2O, CH_2Cl_2, *n*-pentane and toluene) from an MBRAUN Solvent Purification System or either freshly distilled from sodium benzophenone/ketyl (THF, Et_2O) or by distillation over calcium hydride (CH_2Cl_2).

Other solvents like CH_3CN, MeOH, EtOH, *t*-BuOH, dioxane, $CHCl_3$, $CHBr_3$, DMSO, DMF, DME, sulfolane, NFM and acetone were not dried before use, unless otherwise noted. Anhydrous methanol was obtained by heating methanol with dried magnesium turnings and iodine for two hours, before distillation. The distillate was stored on 4Å molecular sieves and under argon atmosphere. Anhydrous $CHCl_3$ was collected in a Schlenk tube from an MBRAUN Solvent Purification System. Anhydrous CH_3CN was distilled and stored over 4Å molecular sieves.

1.2. Pressure reactions

Hydrogenation reactions up to 5 bar H_2-pressure, were executed in a Parr-flask on a stirring plate, shielded by an iron cage in case of explosion.

1.3. Column chromatography

Purification on column was performed on silica gel (particle size 70-200 µm, pore diameter 60Å) in a glass column using appropriate mixtures of solvents, as determined by TLC. Spots were visualized by UV irradiation or by staining with $KMnO_4$ or phosphomolybdic acid solution. Reversed phase column chromatography was performed on a Reveleris® X2 Flash Chromatography System with a Reveleris® C18 RP cartridge.

1.4. Preparative TLC

Preparative TLC was run on 2000 µm 20 x 20 cm TLC plates in an elution chamber using an appropriate eluent. Visualization was done by means of UV irradiation or by staining a small part of the plate with a $KMnO_4$ solution.

1.5. Gas chromatography

GC analyses were performed on an Agilent 6890 Series Gas Chromatograph connected to a FID, using an Alltech EC-5 capillary column (30 m x 0.25 mm) having a film thickness of 0.25 µm and using He as the carrier gas. GC-MS analyses were run on a Shimadzu QP2010 SE gas chromatograph-mass spectrometer (Electron Impact), using an Phenomenex ZB 5ms capillary column (20 m x 0.18 mm) with a film thickness of 0.18 µm and He as the carrier gas.

1.6. Liquid chromatography

Routine follow-up analyses were run on an Agilent 1200 Series liquid chromatograph using a reversed phase column (Eclipse plus C18, 50 x 46 mm, particle size 3.5 µm) connected to a UV-VIS detector and an Agilent 1100 Series LC/MSD type SL mass spectrometer (ESI, 70 eV) using a mass selective single quadrupole detector. A mixture of water (5mM NH_4OAc) and CH_3CN was used as the mobile phase, employing a gradient starting from 30% CH_3CN to 100% CH_3CN.

1.7. Preparative HPLC

An Agilent 1100 Series liquid chromatograph with a reversed phase column (Zorbax Eclipse XDB-C18 column, 150 x 21.2 mm, particle size 5 µm), connected to a UV-VIS Variable Wavelength Detector, was used. A mixture of water and CH_3CN was used as the mobile phase.

1.8. Mass spectrometry

Low-resolution MS analyses were run on an Agilent 1100 Series LC/MSD type SL mass spectrometer (ESI, 70 eC) using a mass selective single quadrupole detector. High-resolution mass spectra were obtained with an Agilent Technologies 6210 Time-Of-Flight mass spectrometer (ESI or APCI).

1.9. NMR spectroscopy

High-resolution ^{1}H (400 MHz), ^{13}C (100 MHz), ^{19}F (376 MHz) and ^{31}P (162 MHz) NMR spectra were recorded on a Bruker Avance III Nanobay 400 MHz spectrometer at room temperature, unless otherwise noted. DEPT, APT, COSY, HSQC, HMBC, H2BC and NOESY techniques were used to assign peaks. Deuterated solvents with TMS as an internal standard were used to dissolve samples. Chemical shifts are expressed as parts per million (ppm).

1.10. Infrared spectroscopy

IR-spectra were recorded on a Perkin-Elmer Spectrum One BX FT-IR spectrophotometer with an ATR accessory. Samples were analyzed in neat form and selected peaks are listed.

1.11. Melting points

The melting point of crystalline compounds was determined on a Wagner & Munz WME Heizbank Kofler bench.

1.12. Microwave irradiation

Reactions were performed in a 10 mL thick-walled Pyrex reaction vessel in a CEM Discover Benchmate with a continuous power output (0 to 300 W). The vessel was closed with a snap-cap and equipped with a stirring bar, while stirring was performed using a rotating magnetic plate, located at the bottom of microwave cavity. The desired temperature was reached by increasing the temperature within a maximum ramp time of 5 minutes and was maintained during the course of the reaction. An external infrared sensor was used to measure the temperature at the bottom of the reaction vessel and was communicated to the on-board computer to adjust the power output (1 W increments). When the reaction was finished, the vessel was cooled down using a stream of air onto the vial to cool down the vial down to 40 °C in approximately 2 minutes.

1.13. Optical rotation

Optical rotation was determined by means of a Jasco P-2000 polarimeter.

1.14. X-ray analysis

X-ray diffraction was performed using an Agilent Supernova Dual Source (Cu at zero) diffractometer, equipped with an Atlas CCD detector using CuKα radiation (l = 1.54178 Å) and ω scans. The images were interpreted and integrated with the program CrysAlisPro (Agilent Technologies). Using Olex2, the structure was solved by direct methods using the ShelXL program package. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U (eq) of the parent atoms. The amide and amine hydrogen atoms were located from a difference electron density map and were unrestrainedly refined. All X-ray diffraction analyses were performed in collaboration with Prof. dr. Kristof Van Hecke, XStruct, Department of Inorganic and Physical Chemistry, Ghent University, Belgium.

2. Safety

2.1. General safety aspects

The practical work in this thesis was performed according to the SynBioC Research Group Internal Guidelines and with the aid of the internal safety document “Safety Instructions: How to work with chemicals”. Wherever possible, hazardous or toxic reagents were avoided and/or substituted by safer or greener alternatives.

2.2. Specific safety aspects

A list of the risks associated with each chemical is available in the corresponding safety data sheet (SDS), which can be found on the website of the supplier. Therein, a classification of the hazards was made according to the European Regulation (EC) No 1272/2008 [EU-GHS/CLP], which combines the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) and Classification, Labelling and Packaging regulations (CLP). A brief overview of the chemicals employed in this work classified as category 1, the most severe category, of the respective hazard class will be given below, along with the GHS hazards and precautions.

Alkyllithium reagents: pyrophoric liquids, substances and mixtures which in contact with water emit flammable gases, acute toxicity after inhalation, acute and chronic hazards to the aquatic environment. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid contact with air or water and work under an inert atmosphere. In case of fire use dry sand, dry chemical- or alcohol-resistant foam to extinguish.

Bromoform: specific target organ toxicity. Avoid inhalation. Acute oral toxicity.

Chloroform: specific target organ toxicity following repeated exposure. Avoid inhalation.

Diazomethane: extremely explosive gas. Preparation and manipulation should take place behind a blast shield. Use rounded glassware for distillation and check for sharp edges or scratches on any glassware that comes into contact with the substance. Explodes when heating above 100 °C, when exposed to intense light or in the presence of alkali metals. Toxic by inhalation and through skin contact. Deaths from diazomethane poisoning have been reported (fulminating pneumonia). Alkylating compound, so carcinogenic. Wear gloves and protective clothing.

Diethyl chlorophosphate: highly toxic through dermal absorption. Acts as a cholinesterase inhibitor. Wear gloves, protective clothes and respiratory protection. Wash hands immediately

after use. In case of contact with the skin, wash carefully with plenty of water and soap. In case of swallowing, immediately call a poison center.

Diethyl chlorophosphite: specific target organ toxicity. Wear protective gloves and clothing.

H_2-gas: flammable gas, especially when compressed. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

Inorganic acids (HCl, H_2SO_4): skin corrosion, corrosive to metals. Wear protective gloves and clothing.

Inorganic bases (NaOH, NaH): skin corrosion, corrosive to metals. Wear protective gloves and clothing. NaH releases flammable gases upon contact with water, which might ignite spontaneously.

Iodine (I_2): acute toxicity, skin corrosion. Avoid inhalation, wear protective gloves and clothing, avoid release in the environment.

Organic acids (acetic acid, para-toluenesulfonic acid): skin corrosion. Wear protective gloves and clothing.

Organic bases (NEt_3, KO*t*Bu, LDA, LiHMDS): skin corrosion. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing.

Phenyl trichloromethyl mercury ($PhHgCCl_3$): is a carcinogenic material and should be handled accordingly. Wear appropriate gloves, protective clothing and respiratory protection.

Palladium-based catalysts: highly flammable solids. Keep away from heat, sparks, open flames or hot surfaces.

Propargyl bromide: acute toxicity after inhalation. Avoid inhalation.

Solvents in general: acute toxicity after inhalation, specific target organ toxicity following single or repeated exposure. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing. A useful tool for solvent selection is the “GSK solvent selection guide” which lists a wide variety of hazards associated with specific solvent classes as well as more benign alternatives for commonly used solvents.

Transition metal salts: acute and chronic aquatic toxicity. Avoid release in the environment.

3. Biological evaluation

3.1. Broad spectrum antiviral evaluation in cell cultures

The antiviral activity of the compound in cell culture was assessed via cytopathic effect (CPE) reduction assays, using a diverse panel of viruses.[344] On human embryonic lung fibroblast cells, the following viruses were used: herpes simplex virus type 1 (HSV-1) strain KOS, a thymidine kinase-deficient (TK-) HSV-1 KOS strain resistant to acyclovir, herpes simplex virus type 2 (HSV-2) strain G, vaccinia virus (Lederle strain), a clinical isolate of human adenovirus type 2 (Ad2), and human coronavirus (strain 229E). To study the antiviral effect on vesicular stomatitis virus (VSV), Coxsackie B4 virus and respiratory syncytial virus (RSV), human cervix carcinoma HeLa cells were used. African Green Monkey Vero cells were used to investigate the antiviral activity on para-influenza-3 virus; reovirus-1, Sindbis virus, Coxsackie B4 virus and Punta Toro virus. The activity against human influenza A/H1N1, A/H3N2 and B viruses was assessed on Madin-Darby canine kidney (MDCK) cells. Finally, human immunodeficiency virus type 1 and type 2 were examined on human MT-4 lymphoblast cells. At a multiplicity of infection of 100 CCID50 (50% cell culture infective dose) or 20 PFU (plaque forming units) per well, semiconfluent cell cultures were inoculated with the virus in 96-well plates. Serial dilutions of the test or reference compounds were added simultaneously with the virus. The plates were next incubated at 37°C (or 35°C in the case of influenza virus) until clear CPE was reached, i.e. during 3 to 6 days. Ad2 required 10 days incubation. To determine the antiviral activity [expressed as 50% effective concentration (EC_{50})] and cytotoxicity [expressed as minimum cytotoxic concentration (MCC)], microscopic scoring was performed. The viral effects on cell viability were confirmed by the colorimetric formazan-based MTS cell viability assay for a selection of viruses.

3.2. Enzymatic assay with influenza PA-Nter endonuclease

The pET28a(+) plasmid was used to clone the coding sequence for PA-Nter (i.e. residues 1-217 from the PA protein of influenza virus strain A/X-31).[345] The protein was obtained after expression in *E. coli* BL21-CodonPlus cells and purification by 6xHis-Ni-NTA chromatography followed by buffer exchange. In the enzyme assay, 1 µg of recombinant PA-Nter was incubated with 1 µg (16.7 nM) of single-stranded circular DNA plasmid M13mp18 (Bayou Biolabs, Metairie, Louisiana) in the presence of the test compounds or the reference compound 2,4-dioxo-4-phenylbutanoic acid (DPBA), at a final volume of 25 µL. The buffer used in the assay, contained 50 mM Tris-HCl pH 8, 100 mM NaCl, 10 mM β-mercaptoethanol and 1 mM

$MnCl_2$. After incubation at 37 °C for 2 hours, the reaction was stopped by heat inactivation (80 °C, 20 min). Using gel electrophoresis on a 1% agarose gel with ethidium bromide staining, the endonucleolytic digestion of the plasmid was visualized. ImageQuant TL software (GE Healthcare) was used to quantify the amount of remaining intact plasmid. GraphPad Prism software (GraphPad Software, La Jolla, CA) was used to plot the percentage inhibition of PA endonuclease activity against the compound concentration on a semi-logarithmic plot. Nonlinear least-squares regression analysis afforded the 50% inhibitory concentrations (IC_{50}).

4. Synthetic procedures and spectral data

4.1. Synthesis of protected propargylamines

_N_,_N_-dibenzylprop-2-yn-1-amine 309

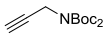
_N_,_N_-dibenzylprop-2-yn-1-amine **309** was prepared according to a literature procedure and spectral data were in accordance with literature values.[375]

309

1. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 2.28 (1H, t, *J* = 2.3 Hz, CH), 3.26 (2H, d, *J* = 2.3 Hz, NCH_2C_q) 3.69 (4H, s, $N(CH_2C_{q,ar})_2$) **Yield:** 80% (1214 mg), white crystals.

_N_,_N_-di-*tert*-butylprop-2-yn-1-ylimidodicarbonate 23

_N_,_N_-di-*tert*-butylprop-2-yn-1-ylimidodicarbonate **23** was prepared according to a literature procedure and spectral data were in accordance with literature values.[376]



23

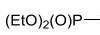
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (18H, s, $C_q(CH_3)_3$), 2.18 (1H, t, *J* = 2.4 Hz, CH), 4.36 (2H, d, *J* = 2.4 Hz, NCH_2) **Yield:** 83%, yellow oil.

4.2. Synthesis of phosphonylated alkynes through oxidative cross coupling with dialkylphosphites

4.2.1. Procedure for the preparation of diethyl alkynyl phosphonates

Representative example **305**: A round-bottom 100 mL flask was charged with 181 mg (1 mmol) $Cu(OAc)_2$, 40 mL DMF, 2.760 g (20 mmol) diethyl phosphite and 202 mg (2 mmol) triethylamine. An oxygen flow was allowed to bubble through the reaction mixture. Next, 1.850 g (10 mmol) of the alkyne was added and the mixture was magnetically stirred, while keeping a steady oxygen flow bubbling through the mixture. After one hour, a second portion of $Cu(OAc)_2$ (362 mg, 2 mmol) and diethyl phosphite (1.38 g, 10 mmol) were added. Reaction progress was followed by NMR. After another half an hour, the reaction was completed and the mixture was concentrated *in vacuo*, diluted in ethyl acetate and washed twice with a 1M aqueous solution of LiCl. The crude mixture was purified *via* column chromatography (1/1 PE/EtOAc) or crystallized from ethyl acetate to give white crystals. Spectral data were in accordance with literature data.

diethyl (phenylethynyl)phosphonate 296[246]

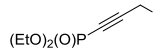


296

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 4.16-4.31 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 4.49 (2H, d, $^4J_{HP}$ = 3.7 Hz, $NC\underline{H}_2$), 7.33-7.42

(2H, m, CH_{ar}), 7.43-7.49 (1H, m, CH_{ar}), 7.54-7.61 (2H, m, CH_{ar}) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** -5.98 **MS (ESI, pos):** *m/z* 239.1/240.2 (M + H^+, 100/12). **R_f**: 0.20 (7/3 PE/EtOAc). **Yield:** 82% (1.961 mg), yellow oil.

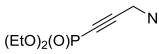
diethyl (3-(dibenzylamino)prop-1-yn-1-yl)phosphonate 310



310

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.421 (3H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)$), 1.422 (3H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)$), 3.39 (2H, d, $^4J_{HP}$ = 3.7 Hz, $NC\underline{H}_2C_q$), 3.71 (4H, s, $NCH_2C_{q,ar}$), 4.21 (2H, q, *J* = 7.1 Hz, $P(OC\underline{H}_2CH_3)$), 4.23 (2H, q, *J* = 7.2 Hz, $P(OC\underline{H}_2CH_3)$), 7.24-7.42 (10H, m, $C\underline{H}_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.2 (d, $^3J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)_2$), 41.5 (d, $^3J_{CP}$ = 4 Hz, $N\underline{C}H_2C_q$), 57.7 (s, $N(\underline{C}H_2C_{q,ar})_2$), 63.2 (d, $^2J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)_2$), 75.9 (d, $^1J_{CP}$ = 296 Hz, $P\underline{C}_q$), 96.8 (d, $^2J_{CP}$ = 50 Hz, $PC_q\underline{C}_q$), 127.4 ($\underline{C}_{ar}H$), 128.5 ($\underline{C}_{ar}H$), 128.9 ($\underline{C}_{ar}H$), 138.3 ($C_{q,ar}$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** -6.91. **MS (ESI, pos):** *m/z* 372.2/373.3 (M + H^+, 100/16). **R_f**: 0.18 (7/3 PE/EtOAc). **Yield:** 57% (4.229 g), white crystals. **mp:** 91-92 °C.

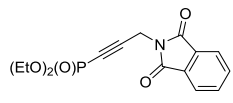
***N,N*-di-*tert*-butyl-3-(diethoxyphosphoryl)prop-2-yn-1-ylimidodicarbonate 269**



269

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 1.53 (18H, s, $C_q(CH_3)_3$), 4.11-4.19 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 4.49 (2H, d, $^4J_{HP}$ = 3.7 Hz, $NC\underline{H}_2$) **^{13}C NMR (100 MHz, C_6D_6) δ:** 16.0 (d, $^3J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)_2$), 28.0 ($C_q(\underline{C}H_3)_3$), 36.0 (d, $^3J_{CP}$ = 5 Hz, $N\underline{C}H_2$), 63.2 (d, $^2J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)_2$), 72.5 (d, $^1J_{CP}$ = 293 Hz, $P\underline{C}_q$), 83.7 ($\underline{C}_q(CH_3)_3$), 96.6 (d, $^2J_{CP}$ = 51 Hz, $PC_q\underline{C}_q$), 151.1 (NC(O)) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** -7.24. **MS (ESI, pos):** *m/z* 236.1/237.2 (M + H^+ - Boc - C_4H_9), 100/16). **IR (cm^{-1}) ν_{max}:** 1698 (C=O), 1226 (P=O), 1017 (P-O). **R_f**: 0.24 (65/35 PE/EtOAc). **Yield:** 73%, pale yellow oil.

diethyl (3-(1,3-dioxoisoindolin-2-yl)prop-1-yn-1-yl)phosphonate 305

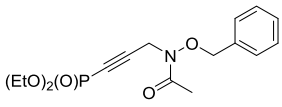


305

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 4.11-4.29 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 4.58 (2H, d, $^4J_{HP}$ = 3.9 Hz, $NC\underline{H}_2$), 7.78 (2H, dd, *J* = 5.5 Hz, *J* = 3.0 Hz, $C\underline{H}_{ar}$), 7.90 (2H, dd, *J* = 5.5 Hz, *J* = 3.0 Hz, $C\underline{H}_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.0 (d, $^3J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)_2$), 27.3 (d, $^3J_{CP}$ = 5 Hz, $N\underline{C}H_2$), 63.4 (d, $^2J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)_2$), 73.4 (d, $^1J_{CP}$ = 293 Hz, $P\underline{C}_q$), 93.5 (d, $^2J_{CP}$ = 51 Hz, $PC_q\underline{C}_q$), 123.7 (2 x $\underline{C}_{ar}H$), 131.7 (2 x $\underline{C}_{ar}H$), 134.5 (2 x $\underline{C}_{ar}H$), 166.5 (2 x $N\underline{C}(O)C_q$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** -7.87. **MS (ESI, pos):** *m/z* 322.1/323.2 (M + H^+, 100/16). **HRMS:** *m/z* calcd for $C_{15}H_{17}NO_5P$ (M + H)$^+$ 322.0839, found

322.0836. **IR (cm^{-1}) ν_{max}:** 2223 (C≡C), 1714 (C=O), 1260 (P=O), 1015 (P-O). **R_f**: 0.17 (1/1 PE/EtOAc). **Yield:** 72% (2311 mg), white crystals. **mp:** 86-87 °C.

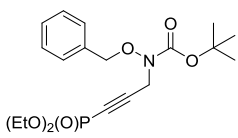
diethyl (3-(*N*-(benzyloxy)acetamido)prop-1-yn-1-yl)phosphonate 412a



412a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (6H, t, *J* = 7.1, ($C\underline{H}_3CH_2O)_2P$), 2.11 (3H, s, $CH_3C(O)$), 4.10-4.20 (4H, m, ($CH_3C\underline{H}_2O)_2P$), 4.47 (2H, m, J_{HP} = 3.9 Hz, NCH_2), 4.97 (2H, s, $C_{q,ar}CH_2$), 7.34-7.45 (5H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.1 (d, J_{CP} = 7 Hz, $\underline{C}H_3CH_2OP$), 20.5 ($C(O)\underline{C}H_3$), 37.1 (d, J_{CP} = 4 Hz, NCH_2), 63.3 (d, J_{CP} = 5 Hz, $CH_3\underline{C}H_2OP$), 74.1 (d, J_{CP} = 295 Hz, $C_q\underline{C}_qP$), 77.9 (CH_2ON), 94.8 (d, J_{CP} = 51 Hz, $\underline{C}_qC_qP$), 128.8 (C_{ar}), 129.2 (C_{ar}), 129.4 (C_{ar}), 134.1 ($C_{q,ar}$), 173.6 (C(O)) **^{31}P NMR (121 MHz, CDCl3) δ**: -7.66. **MS (ESI, pos)**: m/z 340.1/341.2 (M + H^+, 100/20). **IR (cm^{-1}) ν_{max}**: 1022 (P-O), 1263 (P=O), 1678 (C=O), 2212 (C≡C) **R_f**: 0.22 (2/8 PE/EtOAc) **Yield:** 66%, yellow oil.

***tert*-butyl (benzyloxy)(3-(diethoxyphosphoryl)prop-2-yn-1-yl)carbamate 428**



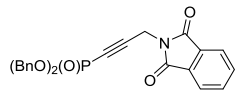
428

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (6H, t, *J* = 7.1 Hz, ($C\underline{H}_3CH_2O)_2P$), 1.51 (9H, s, $C_q(CH_3)_3$), 4.09-4.20 (4H, m, ($CH_3C\underline{H}_2O)_2P$), 4.24 (2H, d, J_{HP} = 3.8 Hz, NCH_2), 4.93 (2H, s, $CH_2C_{q,ar}$), 7.30-7.47 (5H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.0 (d, J_{CP} = 7 Hz, ($\underline{C}H_3CH_2O)_2P$), 28.1 ($C_q(\underline{C}H_3)_3$), 40.8 (d, J_{CP} = 4 Hz, NCH_2), 63.3 (d, J_{CP} = 6 Hz, ($CH_3\underline{C}H_2O)_2P$), 73.9 (d, J_{CP} = 296 Hz , $C_q\underline{C}_qP$), 78.0 ($\underline{C}H_2C_{q,ar}$), 82.9 ($\underline{C}_q(CH_3)_3$), 95.5 (d, J_{CP} = 51 Hz, $\underline{C}_qC_qP$), 128.5 (CH_{ar}), 128.7 (CH_{ar}), 129.5 (CH_{ar}), 135.2 ($C_{q,ar}$), 156.3 ($\underline{C}(O)OC_q(CH_3)_3$) **^{31}P NMR (121 MHz, $CDCl_3$) δ:** -7.47 **MS (ESI, neg):** *m/z* 294.1/295.1 (M + H^+, 100/15) **IR (cm^{-1}) ν_{max}:** 1171 (P=O), 1258 (br., P-O), 1711 (C=O) **R_f**: 0.35 (5/5 PE/EtOAc) **Rendement:** 57%, yellowish oil.

4.2.2. Procedure for the preparation of dibenzyl alkynyl phosphonates

Representative example **384**: A round-bottom 100 mL flask was charged with 1.81 g (10 mmol) $Cu(OAc)_2$, 40 mL NFM, 7860 g (30 mmol) dibenzyl phosphite and 202 mg (2 mmol) triethylamine. An oxygen flow was allowed to bubble through the reaction mixture. Next, 1.850 g (10 mmol) of the alkyne was added and the mixture was magnetically stirred, while keeping a steady oxygen flow bubbling through the mixture. Reaction progress was monitored by NMR spectroscopy and if necessary, a second partion of dibenzyl phosphite (1.31 g, 5 mmol) was added. After 4.5 hours, the reaction was completed and the mixture was diluted in 300 mL ethyl acetate and washed twenty times with a 1M aqueous solution of LiCl. The crude mixture was purified via column chromatography.

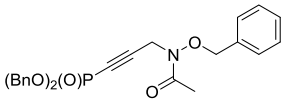
dibenzyl (3-(1,3-dioxoisoindolin-2-yl)prop-1-yn-1-yl)phosphonate 384



384

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.54 (2H, d, $^4J_{HP}$ = 4.0 Hz, NCH_2), 5.08 (d, $^2J_{CP}$ = 8.7 Hz, $P(OCH_2)_2$), 7.26-7.71 (10H, m, $P(OCH_2C_{q,ar}C\underline{H}_{ar})_2$), 7.74-7.82 (2H, m, $C\underline{H}_{ar}$), 7.85-7.94 (2H, m, $C\underline{H}_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 27.3 (d, $^3J_{CP}$ = 5 Hz, NCH_2), 68.7 (d, $^2J_{CP}$ = 5 Hz, $P(O\underline{C}H_2C_{q,ar})_2$), 73.2 (d, $^1J_{CP}$ = 299 Hz, $P\underline{C}_q$), 94.4 (d, $^2J_{CP}$ = 51 Hz, $PC_q\underline{C}_q$), 123.7 (2 x $C_{ar}H$), 128.1 (4 x $C_{ar}H$), 128.56 (2 x $\underline{C}_{ar}H$), 128.59 (4 x $\underline{C}_{ar}H$), 131.8 (2 x $\underline{C}_{q,ar}$), 134.5 (2 x $\underline{C}_{ar}H$), 135.2 (d, $^3J_{CP}$ = 7 Hz, 2 x $C_{q,ar}$), 166.4 (2 x $N\underline{C}(O)C_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** -7.43. **MS (ESI, pos):** *m/z* 446.1/44.72 ($M + H^+$, 100/27). **R_f**: 0.19 (65/35 PE/EtOAc). **Yield:** 81% (2311 mg), white solid.

dibenzyl (3-(N-(benzyloxy)acetamido)prop-1-yn-1-yl)phosphonate 412b



412b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.09 (3H, s, CH_3), 4.43 (2H, d, J_{HP} = 3.9 Hz, NCH_2), 4.91 (2H, s, CH_2ON), 5.06 (2H, s, $POCH_2$), 5.09 (2H, s, $POCH_2$), 7.28-7.34 (10H, m, $C\underline{H}_{ar}CH_2OP$), 7.34-7.43 (5H, m, $C\underline{H}_{ar}CH_2ON$).**^{13}C NMR (100 MHz, $CDCl_3$) δ:** 20.5 (CH_3), 37.1 (d, J_{CP} = 3 Hz, NCH_2), 68.6 (d, J_{CP} = 5 Hz, $POCH_2$), 73.7 (d, J_{CP} = 300 Hz, C_qP), 77.9 (CH_2ON), 95.9 (d, J_{CP} = 51 Hz, $\underline{C}_qC_qP$), 128.0 (CH_{ar}), 128.61 (CH_{ar}), 128.62 (CH_{ar}), 128.8 (CH_{ar}), 129.2 (CH_{ar}), 129.4 (CH_{ar}), 134.1 (CH_{ar}), 135.3 ($C_{q,ar}$), 135.4 ($C_{q,ar}$), 137.6 ($C_{q,ar}$), 173.6 (C(O)) **^{31}P NMR (121 MHz, $CDCl_3$) δ:** -7.18. **MS (ESI, pos):** *m/z* 464.2/465.3 ($M + H^+$, 100/30) **IR (cm^{-1}) ν_{max}:** 1263 (P=O), 1674 (C=O), 2210-2349 (C≡C) **R_f**: 0.20 (4/6 PE/EtOAc) **Yield:** 20%, yellow oil.

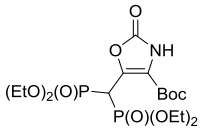
4.3. Synthesis of 5-bisphosphonomethyl oxazol-2-ones and 5-phosphonomethylidene oxazolidin-2-ones

*4.3.1. Procedure for the one-pot synthesis of 5-bisphosphonomethyl oxazol-2-ones **24***

A 100 mL round-bottom flask, equipped with a Claisen piece is flame dried under inert atmosphere. Next, the flask is charged with 1.87 mL distilled diisopropylamine (12.5 mmol) and 5 mL ether. After the mixture is cooled down to – 78 °C, 12.5 mmol *n*-butyllithium is added. The mixture is allowed to warm to 0 °C and is cooled down to – 78 °C again after one hour. Next, a solution of 1.278 g (5.0 mmol) *N,N*-di-*tert*-butylprop-2-ynylimidodicarbonate in 15 mL ether, is added and mixed for one hour at 0 °C. Subsequently, 1.82 mL (12.5 mmol) diethyl chlorophosphate is added at – 78 °C. After one hour at – 78 °C and three hours at – 42 °C, the mixture is left to stir at room temperature for another 24 hours. After addition of 30 mL of a

saturated $NaHCO_3$ solution, the organic phase is washed with 5 mL of water, dried over $MgSO_4$. After filtration and removal of the solvent *in vacuo*, volatile side-products can be removed by additional heating for one hour at 60 °C at 1 mbar. A dark viscous oil is obtained, which is redissolved in diethyl ether and stirred overnight with 300 mg silica. After column chromatography, orange crystals are obtained. Recrystallization in diethyl ether, the bisphosphonomethyl oxazol-2-one is finally obtained in 17% yield as white crystals (385 mg).

***tert*-butyl 5-(bis(diethoxyphosphoryl)methyl)oxazolon-4-carboxylate 24**



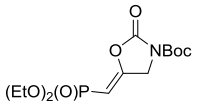
24

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (12H, t, *J* = 6.8 Hz, $P(OCH_2C\underline{H}_3)_2$), 1.55 (9H, s, $C_q(C\underline{H}_3)_3$), 4.20-4.30 (8H, m, $P(OC\underline{H}_2CH_3)_2$), 4.80 (1H, t, PCHP, $^2J_{HP}$ = 24.8 Hz), 8.77 (1H, br. s, NH). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 28.1 ($C_q(\underline{C}H_3)_3$), 37.5 (t, $^1J_{CP}$ = 133 Hz, PCHP), 63.7 (d, $^2J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)$), 63.8 (d, $^2J_{CP}$ = 7 Hz, $P(O\underline{C}H_2CH_3)$), 84.3 ($O\underline{C}_q(CH_3)_3$), 117.5 (t, $^3J_{CP}$ = 10 Hz, C_qNH), 138.4 (t, $^2J_{CP}$ = 14 Hz, $O\underline{C}_qCH$), 152.8 (OC(O)N), 157.3 (t, $^4J_{CP}$ = 3 Hz, $(O)\underline{C}OC_q(CH_3)_3$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 14.15. **MS (ESI, pos):** *m/z* 416.1 ($M + H^+ - C_4H_9$), 472.2 ($M + H^+$). **IR (cm^{-1}) ν_{max}:** 1780 (C=O), 1716 (C=O), 1257 (P=O), 1022 (P-O). **R_f**: 0.12 (40/60 PE/EtOAc). **Yield:** 17%, white crystals.

*4.3.2. Procedure for the gold-catalyzed cyclization towards 5-phosphonomethylidene oxazolidin-2-ones **283***

A 25 mL round-bottom flask, equipped with a Claisen piece is flame dried under inert atmosphere. Next, 30 mg (0.125 mmol) Au(I)Cl, 10 mL THF and 978 mg (2.5 mmol) *N*,*N*-di-*tert*-butyl-3-(diethoxyphosphoryl)prop-2-ynylimidodicarbonate **269** were added. After stirring the mixture for one hour at room temperature, it is filtered twice over a pasteur pipette, filled with silica. After concentration of the filtrate *in vacuo*, a yellow viscous oil is obtained with an isolated yield of 98% (802 mg).

***tert*-butyl (*Z*)-5-((diethoxyphosphoryl)methylene)-2-oxooxazolidine-3-carboxylate 283**



283

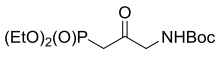
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.353 (3H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)$), 1.354 (3H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)$), 1.55 (9H, s, $C_q(C\underline{H}_3)_3$), 4.14 (2H, q, *J* = 7.0 Hz, $P(OC\underline{H}_2CH_3)$), 4.16 (2H, q, *J* = 7.0 Hz, $P(OC\underline{H}_2CH_3)$), 4.58 (2H, dd, $^4J_{HP}$ = 4.8 Hz, $^4J_{HH}$ = 2.1 Hz, NCH_2), 4.97 (1H, dt, $^2J_{HP}$ = 5.8 Hz, $^4J_{HH}$ = 2.1 Hz, $C\underline{H}P$). **^{13}C NMR (100 MHz, C_6D_6) δ:** 16.7 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 28.0 ($C_q(\underline{C}H_3)_3$), 47.9 (d, $^3J_{CP}$ = 18 Hz, $N\underline{C}H_2$), 62.1 (d, $^2J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)_2$), 84.0 ($\underline{C}_q(CH_3)_3$), 90.9 (d, $^1J_{CP}$ = 197 Hz, $\underline{C}HP$), 147.8 ($CHPC_qO\underline{C}(O)N$ or $(CH_3)_3C_qO\underline{C}(O)N$), 148.5

($CHPC_qO\underline{C}(O)N$ or $(CH_3)_3C_qO\underline{C}(O)N$), 154.4 (d, $^2J_{CP}$ = 4 Hz, ($O\underline{C}_qCH_2$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 12.07. **IR (cm^{-1}) ν_{max}:** 1022 (P-O), 1272 (P=O), 1678 (C=O), 1834 (C=O). **MS m/z (%)**: (ESI, pos) 336 (M + H^+). **Yield:** 98%.

*4.3.3. Procedure for the synthesis of β-ketophosphonate **287***

A 10 mL round-bottom flask, equipped with a Claisen piece, is flame dried under inert atmosphere. After addition of 0.073 ml (0.50 mmol) distilled diisopropylamine, dissolved in 5 mL ether, 0.50 mmol *n*-butyllithium is added at – 78 °C. After stirring for one hour at 0 °C, 168 mg (0.50 mmol) *tert*-butyl (*Z*)-5-((diethoxyphosphoryl)methylene)-2-oxooxazolidine-3-carboxylate **283** was added at – 78 °C. After 10 minutes at – 78 °C, the mixture is quenched with two drops of water, filtered over silica and concentrated *in vacuo*. A slightly yellow oil is obtained with an isolated yield of 38% (120 mg).

***tert*-butyl (3-(diethoxyphosphoryl)-2-oxopropyl)carbamate 287**



287

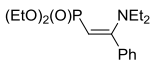
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 1.45 (9H, s, $C_q(C\underline{H}_3)_3$), 3.12 (2H, d, $^2J_{HP}$ = 22.9 Hz, $PC\underline{H}_2$), 4.05-4.28 (6H, m, $NC\underline{H}_2$, $P(OC\underline{H}_2CH_3)_2$), 5.30 (1H, br. s, N$\underline{H}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 28.3 ($C_q(\underline{C}H_3)_3$), 39.8 (d, $^1J_{CP}$ = 128 Hz, $\underline{C}$HP), 51.3 ppm ($\underline{C}H_2N$), 62.9 (d, $^2J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)_2$), 80.0 ($\underline{C}_q(CH_3)_3$), 155.6 ($(O)\underline{C}_qOC_q(CH_3)_3$), 198.1 (d, $^2J_{CP}$ = 6 Hz, $\underline{C}(O)CH_2$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 18.75. **IR (cm^{-1}) ν_{max}:** 3304 (NH), 1711 (C=O), 1246 (P=O), 1022 (P-O). **MS m/z (%)**: (ESI, pos) 254 (M + H^+ - C_4H_9). **Yield:** 38%.

4.4. Synthetic entry into *N,N*-dialkylamino allenylphosphonates

*4.4.1. Procedure for the synthesis of β-enaminophosphonate **297***

β-Enaminophosphonate **297** was prepared according to a literature procedure and spectral data were in accordance with those literature values that were available.[59] The compound had not entirely been characterized however, and is hence described.

diethyl (Z)-(2-(diethylamino)-2-phenylvinyl)phosphonate 297



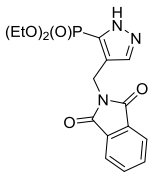
297

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08 (6H, t, *J* = 7.0 Hz, $N(CH_2\underline{C}H_3)_2$), 1.10 (6H, t, *J* = 7.1 Hz, $P(OCH_2\underline{C}H_3)_2$), 3.00-3.21 (4H, m, $N(\underline{C}H_2CH_3)_2$), 3.62-3.88 (4H, m, $P(O\underline{C}H_2CH_3)_2$), 4.21 (2H, d, $^{4}J_{HP}$ = 5.2 Hz, CHP), 7.28-7.42 (5H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 12.7 ($N(CH_2\underline{C}H_3)_2$), 16.1 (d, $^{3}J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)_2$), 43.6 ($N(\underline{C}H_2CH_3)_2$), 41.5 (d, $^{3}J_{CP}$ = 4 Hz, $N\underline{C}H_2C_q$), 60.4 (d, $^{2}J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)_2$), 77.1 (d, $^{1}J_{CP}$ = 218 Hz, $P\underline{C}H$), 127.6 ($\underline{C}_{ar}H$), 128.5 ($\underline{C}_{ar}H$), 129.0 ($\underline{C}_{ar}H$), 136.0 (d, $^{3}J_{CP}$ = 5 Hz, $C_{q,ar}$), 162.2 (d, $^{2}J_{CP}$ = 19 Hz, $PCH\underline{C}_q$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 25.08 **MS (ESI, pos):** *m/z* 312.2/313.3 ($M + H^+$, 100/16). **Yield:** 75% (971 mg), yellowish oil.

4.4.2. Synthesis of phosphonylated pyrazoles

An excess of a freshly distilled ethereal solution of diazomethane (+/-2.5 mmol) is added to a solution of diethyl (3-(13-dioxoisoindolin-2-yl)prop-1-yn-1-yl)phosphonate **305** (0.5 mmol) in 5 mL THF and allowed to stir at room temperature. Reaction progress was monitored by NMR spectroscopy and LC-MS analysis and the mixture was quenched with acetic acid after 4 hours until the yellow color of diazomethane had disappeared. Next, 20 mL ethyl acetate was added and the organic phase was washed with 5 mL of a saturated $NaHCO_3$ solution. The aqueous phase was extracted once with 5 mL ethyl acetate and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purified via pTLC (98/2 EtOAc/MeOH). After a first purification via pTLC (3/7 PE/EtOAc) pyrazole **307b** could be obtained. Pyrazole **306b** was isolated together with some impurities, but could be obtained as a pure compound after a second purification via pTLC (98/2 EtOAc/MeOH).

diethyl (4-((1,3-dioxoisoindolin-2-yl)methyl)-1H-pyrazol-5-yl)phosphonate 306b

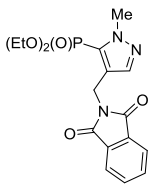


306b

^{1}H NMR (400 MHz,$CDCl_3$): δ: 1.33 (6H, t, *J* = 7.0 Hz, $P(OCH_2\underline{C}H_3)_2$), 4.01-4.26 (4H, m, $P(O\underline{C}H_2CH_3)_2$), 5.08 (2H, s, NCH_2), 7.37 (1H, d, *J* = 2.0 Hz, NCH_{ar}), 7.70-7.77 (2H, m, CH_{ar}), 7.82-7.99 (2H, m, CH_{ar}), 7.91 (1H, d, $^{3}J_{CP}$ = 1.9 Hz, NCH_{ar}), 11.14 (1H, br. s, NH) **^{13}C NMR (100 MHz,$CDCl_3$): δ:** 16.3 (d, $^{3}J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)_2$), 34.1 ($NCH_2$), 62.2 (d, $^{2}J_{CP}$ = 5 Hz, $P(O\underline{C}H_2CH_3)_2$), 105.1 (d, $^{1}J_{CP}$ = 219 Hz, $P\underline{C}_q$), 123.5 ($C_{ar}H$), 132.1 ($\underline{C}_qC(O)$), 134.1 ($C_{ar}H$), 138.6 (d, $^{3}J_{CP}$ = 22 Hz, $NC_{ar}H$), 147.7 (d, $^{2}J_{CP}$ = 16 Hz, $PC_q\underline{C}_q$), 168.0 ($N(C(O))_2$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 13.55 **MS (ESI, pos):** *m/z* 364.1/365.2 ($M + H^+$, 100/15). **Yield:** 2% (4 mg), yellowish oil.

Both 3-phosphonopyrazoles and 5-phosphonopyrazoles can arise from cycloaddition. However, the observed coupling constants in ^{13}C NMR are a perfect match with literature values for 5-phosphonopyrazoles.[299]

diethyl (4-((1,3-dioxoisoindolin-2-yl)methyl)-1-methyl-1H-pyrazol-5-yl)phosphonate 307b



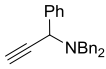
307b

^{1}H NMR (400 MHz,$CDCl_3$): δ: 1.38 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 4.05 (3H, s, NCH_3), 4.11-4.35 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 5.06 (2H, s, NCH_2), 7.37 (1H, d, *J* = 2.0 Hz, NCH_{ar}), 7.68-7.77 (2H, m, CH_{ar}), 7.82-7.90 (2H, m, CH_{ar}) **^{13}C NMR (100 MHz,$CDCl_3$): δ:** 16.2 (d, $^3J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)_2$), 32.4 ($NCH_2$), 39.5 ($NCH_3$), 62.8 (d, $^2J_{CP}$ = 5 Hz, $P(O\underline{C}H_2CH_3)_2$), 123.3 ($C_{ar}H$), 126.1 (d, $^2J_{CP}$ = 20 Hz, $PC_q\underline{C}_q$), 127.7 (d, $^1J_{CP}$ = 212 Hz, $P\underline{C}_q$), 132.1 ($\underline{C}_qC(O)$), 134.0 ($C_{ar}H$), 138.0 (d, $^3J_{CP}$ = 17 Hz, $NC_{ar}H$), 167.9 ($N(C(O))_2$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 5.64 **MS (ESI, pos):** *m/z* 378.1/379.2 ($M + H^+$, 100/16). **Yield:** 67% (126 mg), yellowish oil.

*4.4.3. Procedure of the A³ coupling affording N,N-dibenzyl-1-phenylprop-2-yn-1-amine **316b***

N,N-dibenzyl-1-phenylprop-2-yn-1-amine **316b** was prepared according to a literature procedure.[377] Full conversion was obtained and the crude mixture was purified via flash chromatography (100/0 PE/EtOAc to 98/2 PE/EtOAc).

***N,N*-dibenzyl-1-phenylprop-2-yn-1-amine 316b**



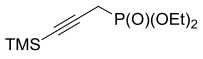
316b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.65 (1H, d, *J* = 2.3 Hz, CHC_q), 3.44 (2H, d, J_{AB} = 13.5 Hz, $N(C\underline{H}_aH_b)_2$), 3.73 (2H, d, J_{AB} = 13.5 Hz, $N(CH_a\underline{H}_b)_2$), 4.72 (1H, d, *J* = 2.0 Hz), 7.18-7.46 (13H, m, CH_{ar}), 7.60-7.73 (2H, m, CH_{ar}) **MS m/z (%)**: (ESI, pos) 312.2/313.3 ($M + H^+$ 100/24). **Yield:** 5%.

*4.4.4. Procedure for the synthesis of diethyl (3-(trimethylsilyl)prop-2-yn-1-yl)phosphonate **322b***

Diethyl (3-(trimethylsilyl)prop-2-yn-1-yl)phosphonate **322b** was prepared according to a literature procedure.[308] Spectral data were in accordance with literature values.

diethyl (3-(trimethylsilyl)prop-2-yn-1-yl)phosphonate 322b



322b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.15 (9H, s, $Si(CH_3)_3$), 1.36 (6H, t, *J* = 7.1 Hz, $P(OCH_2\underline{C}H_3)_2$), 2.81 (2H, d, $^2J_{HP}$ = 22.2 Hz, $PC\underline{H}_2$), 4.12-4.32 (4H, m, $P(OC\underline{H}_2CH_3)_2$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 20.97 **MS (ESI, pos):** *m/z* 249.1/250.2 ($M + H^+$, 100/11). **R_f**: 0.19 (6/4 PE/EtOAc). **Yield:** 41% (673 mg), transparent oil.

4.5. Synthesis of β-functionalized γ-aminophosphonates

4.5.1. Synthesis of β-alkoxylated derivatives

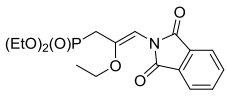
Method A

In a typical experiment, 250 mg (0.78 mmol) alkyne **305** was dissolved in 3 mL THF in a 10 mL flask. 254 mg (0.78 mmol) Cs_2CO_3 and one equivalent (0.78 mmol) of the alcohol were added. The reaction progress was monitored via TLC or NMR. After completion of the reaction, the mixture was quenched with water, concentrated *in vacuo*, three times extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to give the desired product. Adducts **339**-**351** were purified *via* chromatography.

Method B

In a typical experiment, 250 mg (0.78 mmol) alkyne **305** was dissolved in 3 mL of the alcohol in a 10 mL flask. 254 mg (0.78 mmol) Cs_2CO_3 was added and the reaction progress was monitored via TLC. After completion of the reaction, the mixture was quenched with water, concentrated *in vacuo*, three times extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to give the desired product.

diethyl (Z)-(3-(1,3-dioxoisoindolin-2-yl)-2-ethoxyallyl)phosphonate 340

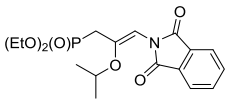


340

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, *J* = 7.2 Hz, $C_qOCH_2C\underline{H}_3$), 1.32 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 3.29 (2H, d, $^2J_{HP}$ = 20.9 Hz, $PC\underline{H}_2$), 4.09-4.20 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 4.33 (2H, q, *J* = 7.1 Hz, $C_qOC\underline{H}_2CH_3$), 7.10 (1H, d, $^4J_{HP}$ = 3.7 Hz, $NC\underline{H}$), 7.51 (1H, td, *J* = 7.5 Hz, *J* = 1.3 Hz, $C\underline{H}_{ar}$), 7.56 (1H, td, *J* = 7.6 Hz, *J* = 1.6 Hz, $C\underline{H}_{ar}$), 7.72 (1H, dd, *J* = 7.5 Hz, *J* = 1.4 Hz, $C\underline{H}_{ar}$), 7.85 (1H, dd, *J* = 7.4 Hz, *J* = 1.3 Hz, $C\underline{H}_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 14.0 ($C_qOCH_2\underline{C}H_3$), 16.4 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 24.4 (d, $^1J_{CP}$ = 145 Hz, $P\underline{C}H_2$), 61.6 ($C_qO\underline{C}H_2CH_3$), 62.6 (d, $^2J_{CP}$ = 7 Hz, $P(O\underline{C}H_2CH_3)_2$), 126.4 (d, $^3J_{CP}$ = 7 Hz, $N\underline{C}H$, $\underline{C}_{q,ar}$), 129.1 ($\underline{C}_{ar}H$), 129.2 ($\underline{C}_{ar}H$), 130.0 ($\underline{C}_{ar}H$), 130.8 ($\underline{C}_{ar}H$), 132.2 ($\underline{C}_{q,ar}$), 143.8 (d, $^2J_{CP}$ = 8 Hz, $O\underline{C}_q$), 160.2 (d, $^5J_{CP}$ = 2 Hz, $N\underline{C}(O)C_q$), 168.1 ($N\underline{C}(O)C_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.54. **MS (ESI,**

pos): *m/z* 367.9/368.9 (M + H$^+$, 100/19). **HRMS:** *m/z* calcd for $C_{17}H_{23}NO_6P$ (M + H)$^+$ 368.1258, found 368.1269. **IR (cm^{-1}) ν_{max}:** 1721 (C=O), 1256 (P=O), 1019 (P-O). **Yield:** 92%, orange oil.

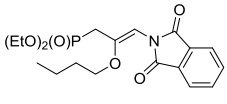
diethyl (Z)-(3-(1,3-dioxoisoindolin-2-yl)-2-isopropoxyallyl)phosphonate 341



341

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (6H, d, *J* = 6.3 Hz, OCH(C$\underline{H}_3$)$_2$), 1.32 (6H, t, *J* = 7.1 Hz, P(OCH$_2$C$\underline{H}_3$)$_2$), 3.29 (2H, d, $^2J_{HP}$ = 21.0 Hz, PC$\underline{H}_2$), 4.09-4.19 (4H, m, P(OC$\underline{H}_2$CH$_3$)$_2$), 5.21 (1H, sept, *J* = 6.2 Hz, OC$\underline{H}$(CH$_3$)$_2$), 7.10 (1H, d, $^4J_{HP}$ = 3.6 Hz, NC$\underline{H}$), 7.48-7.58 (2H, m, C$\underline{H}_{ar}$), 7.69-7.74 (1H, m, C$\underline{H}_{ar}$), 7.80-7.85 (1H, m, C$\underline{H}_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.4 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$C$\underline{H}_3$)$_2$), 21.7 (OCH(C$\underline{H}_3$)$_2$), 24.5 (d, $^1J_{CP}$ = 145 Hz, PC$\underline{H}_2$), 62.6 (d, $^2J_{CP}$ = 7 Hz, P(OC$\underline{H}_2$CH$_3$)$_2$), 69.1 (OC$\underline{H}$(CH$_3$)$_2$), 126.4 (d, $^3J_{CP}$ = 7 Hz, NC$\underline{H}$, C$\underline{_{q,ar}}$), 129.1 (C$\underline{_{ar}}$H), 129.2 (C$\underline{_{ar}}$H), 130.0 (C$\underline{_{ar}}$H), 130.7 (C$\underline{_{ar}}$H), 132.6 (C$\underline{_{q,ar}}$), 143.8 (d, $^2J_{CP}$ = 8 Hz, OC$\underline{_q}$), 160.3 (d, $^5J_{CP}$ = 2 Hz, NC$\underline{(O)}$C$_q$), 167.6 (NC$\underline{(O)}$C$_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.56 **MS (ESI, pos):** *m/z* 381.9/382.9 (M + H$^+$, 100/19). **HRMS:** *m/z* calcd for $C_{18}H_{25}NO_6P$ (M + H)$^+$ 382.1414, found 382.1412. **IR (cm^{-1}) ν_{max}:** 1720 (C=O), 1257 (P=O), 1019 (P-O). **Yield:** 94%, orange oil.

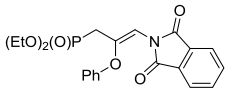
diethyl (Z)-(2-butoxy-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 342



342

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (3H, t, *J* = 7.4 Hz, CH$_2$CH$_2$C$\underline{H}_3$), 1.32 (6H, t, *J* = 7.1 Hz, P(OCH$_2$C$\underline{H}_3$)$_2$), 1.37 (2H, sext., *J* = 7.6 Hz, CH$_2$C$\underline{H}_2$CH$_3$), 1.58-1.68 (2H, m, C$\underline{H}_2$CH$_2$CH$_3$), 3.29 (2H, d, $^2J_{HP}$ = 20.9 Hz, PC$\underline{H}_2$), 4.09-4.19 (4H, m, P(OC$\underline{H}_2$CH$_3$)$_2$), 4.28 (2H, t, *J* = 6.7 Hz, OC$\underline{H}_2$CH$_2$), 7.09 (1H, d, $^4J_{HP}$ = 3.6 Hz, NC$\underline{H}$), 7.48-7.59 (2H, m, C$\underline{H}_{ar}$), 7.68-7.74 (1H, m, C$\underline{H}_{ar}$), 7.83-7.88 (1H, m, C$\underline{H}_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 13.6 (CH$_2$CH$_2$C$\underline{H}_3$), 16.3 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$C$\underline{H}_3$)$_2$), 19.0 (CH$_2$C$\underline{H}_2$CH$_3$), 24.4 (d, $^1J_{CP}$ = 145 Hz, PC$\underline{H}_2$), 30.4 (C$\underline{H}_2$CH$_2$CH$_3$), 62.5 (d, $^2J_{CP}$ = 7 Hz, P(OC$\underline{H}_2$CH$_3$)$_2$), 65.4 (OC$\underline{H}_2$CH$_2$), 126.3 (C$\underline{_{q,ar}}$), 126.4 (d, $^3J_{CP}$ = 7 Hz, NC$\underline{H}$) 128.9 (C$\underline{_{ar}}$H), 129.1 (C$\underline{_{ar}}$H), 130.0 (C$\underline{_{ar}}$H), 130.7 (C$\underline{_{ar}}$H), 132.1 (C$\underline{_{q,ar}}$), 143.8 (d, $^2J_{CP}$ = 8 Hz, OC$\underline{_q}$), 160.1 (d, $^5J_{CP}$ = 2 Hz, NC$\underline{(O)}$C$_q$), 168.2 (NC$\underline{(O)}$C$_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.53. **MS (ESI, pos):** *m/z* 395.9/396.9 (M + H$^+$, 100/22). **HRMS:** *m/z* calcd for $C_{19}H_{27}NO_6P$ (M + H)$^+$ 396.1571, found 396.1553. **IR (cm^{-1}) ν_{max}:** 1723 (C=O), 1256 (P=O), 1020 (P-O). **Yield:** 83%, orange oil.

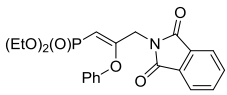
diethyl (Z)-(3-(1,3-dioxoisoindolin-2-yl)-2-phenoxyallyl)phosphonate 343a



343a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (6H, t, *J* = 7.1 Hz, P(OCH$_2$C<u>H</u>$_3$)$_2$), 3.28 (2H, d, $^2J_{HP}$ = 20.9 Hz, PC<u>H</u>$_2$), 4.05-4.15 (4H, m, P(OC<u>H</u>$_2$CH$_3$)$_2$), 7.13 (1H, d, $^4J_{HP}$ = 3.6 Hz, NC<u>H</u>), 7.21-7.30 (3H, m, C<u>H</u>$_{ar}$), 7.41 (2H, t, *J* = 7.9 Hz, C<u>H</u>$_{ar}$), 7.58 (1H, ~t, C<u>H</u>$_{ar}$), 7.64 (1H, ~t, C<u>H</u>$_{ar}$), 7.87 (1H, d, *J* = 7.4 Hz, C<u>H</u>$_{ar}$), 7.94 (1H, d, *J* = 7.3 Hz, C<u>H</u>$_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.4 (d, $^1J_{CP}$ = 145 Hz, P<u>C</u>H$_2$), 62.6 (d, $^2J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 121.3 (2 x <u>C</u>$_{ar}$H), 125.9 (<u>C</u>$_{ar}$H), 126.5 (<u>C</u>$_{ar,q}$), 126.6 (d, $^3J_{CP}$ = 7 Hz, N<u>C</u>H), 129.1 (<u>C</u>$_{ar}$H), 129.4 (3 x <u>C</u>$_{ar}$H), 130.1 (<u>C</u>$_{ar}$H), 131.2 (<u>C</u>$_{q,ar}$), 131.4 (<u>C</u>$_{ar}$H), 144.2 (d, $^2J_{CP}$ = 8 Hz, O<u>C</u>$_q$), 150.9 (O<u>C</u>$_{q,ar}$), 159.8 (d, $^5J_{CP}$ = 2 Hz, N<u>C</u>(O)C$_q$), 166.6 (N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.47. **MS (ESI, pos):** *m/z* 415.8/416.8 (M + H$^+$, 100/23). **HRMS:** *m/z* calcd for $C_{21}H_{23}NO_6P$ (M + H)$^+$ 416.1258, found 416.1253. **IR (cm^{-1}) ν_{max}:** 1743 (C=O), 1244 (P=O), 1020 (P-O). **R_f**: 0.17 (1/9 PE/EtOAc). **Yield:** 47%, orange oil.

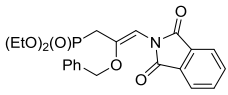
diethyl (Z)-(3-(1,3-dioxoisoindolin-2-yl)-2-phenoxyprop-1-en-1-yl)phosphonate 343b



343b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (6H, t, *J* = 7.1 Hz, P(OCH$_2$C<u>H</u>$_3$)$_2$), 4.09-4.19 (4H, m, P(OC<u>H</u>$_2$CH$_3$)$_2$), 4.49 (1H, d, $^2J_{HP}$ = 4.3 Hz, PC<u>H</u>), 5.17 (2H, d, $^4J_{HP}$ = 1.5 Hz, NC<u>H</u>$_2$), 6.95 (2H, d, *J* = 7.7 Hz, C<u>H</u>$_{ar}$), 7.19 (1H, t, *J* = 7.4 Hz, C<u>H</u>$_{ar}$), 7.34 (2H, t, *J* = 7.4 Hz, C<u>H</u>$_{ar}$), 7.70-7.76 (2H, m, C<u>H</u>$_{ar}$), 7.85-7.91 (2H, m, C<u>H</u>$_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 7 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 37.9 (d, $^3J_{CP}$ = 2 Hz, N<u>C</u>H$_2$), 61.7 (d, $^2J_{CP}$ = 5 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 89.9 (d, $^2J_{CP}$ = 201 Hz, P<u>C</u>H), 121.7 (2 x <u>C</u>$_{ar}$H), 123.4 (2 x <u>C</u>$_{ar}$H), 126.0 (<u>C</u>$_{ar}$H), 130.0 (2 x <u>C</u>$_{ar}$H), 132.1 (<u>C</u>$_{ar,q}$), 134.1 (2 x <u>C</u>$_{ar}$H), 152.9 (<u>C</u>$_{ar,q}$), 167.7 (d, $^2J_{CP}$ = 24 Hz, O<u>C</u>$_q$), 167.9 (2 x N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 19.35. **MS (ESI, pos):** *m/z* 415.9/416.8 (M + H$^+$, 100/23). **IR (cm^{-1}) ν_{max}:** 1716 (C=O), 1209 (P=O), 1021 (P-O). **R_f**: 0.26 (1/9 PE/EtOAc). **Yield:** 4%, orange oil.

diethyl (Z)-(2-(benzyloxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 344

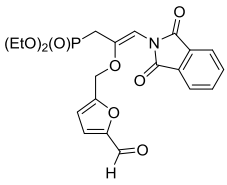


344

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (6H, t, *J* = 7.1 Hz, P(OCH$_2$C<u>H</u>$_3$)$_2$), 1.37 (2H, sext., *J* = 7.6 Hz, CH$_2$C<u>H</u>$_2$CH$_3$), 3.15 (2H, d, $^2J_{HP}$ = 20.8 Hz, PC<u>H</u>$_2$), 4.06-4.16 (4H, m, P(OC<u>H</u>$_2$CH$_3$)$_2$), 5.32 (2H, s, OC<u>H</u>$_2$Cq), 7.04 (1H, d, $^4J_{HP}$ = 3.7 Hz, NC<u>H</u>), 7.34 (5H, br. s, C<u>H</u>$_{ar}$), 7.51(1H, t, *J* = 7.4 Hz, C<u>H</u>$_{ar}$), 7.56 (1H, t, *J* =7.3 Hz, C<u>H</u>$_{ar}$), 7.73 (1H, d, *J* = 7.4 Hz, C<u>H</u>$_{ar}$), 7.86 (1H, d, *J* = 7.6 Hz, C<u>H</u>$_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.2 (d, $^1J_{CP}$ = 145

Hz, P<u>C</u>H$_2$), 62.5 (d, $^2J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 67.3 (O<u>C</u>H$_2$C$_q$), 126.4 (d, $^3J_{CP}$ = 8 Hz, N<u>C</u>H) 128.2 (<u>C</u>$_{ar}$H), 128.3 (2 x <u>C</u>$_{ar}$H), 128.5 (2 x <u>C</u>$_{ar}$H), 129.1 (<u>C</u>$_{ar}$H), 129.1 (<u>C</u>$_{ar}$H), 130.0 (<u>C</u>$_{ar}$H), 131.0 (<u>C</u>$_{ar}$H), 131.7 (2 x <u>C</u>$_{q,ar}$), 135.5 (C$_{q,ar}$), 144.0 (d, $^2J_{CP}$ = 8 Hz, O<u>C</u>$_q$), 160.0 (d, $^5J_{CP}$ = 2 Hz, N<u>C</u>(O)C$_q$), 167.9 (N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, CDCl$_3$) δ:** 21.58. **MS (ESI, pos):** *m/z* 429.8/430.8 (M + H$^+$, 100/23). **HRMS:** *m/z* calcd for $C_{22}H_{25}NO_6P$ (M + H)$^+$ 430.1414, found 430.1413. **IR (cm^{-1}) ν_{max}:** 1725 (C=O), 1255 (P=O), 1020 (P-O). **Yield:** 89%, orange oil.

diethyl (Z)-(3-(1,3-dioxoisoindolin-2-yl)-2-((5-formylfuran-2-yl)methoxy)allyl) phosphonate 346

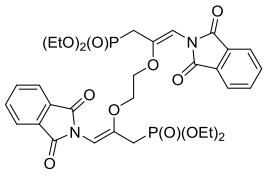


346

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.32 (6H, t, *J* = 7.1 Hz, P(OCH$_2$C<u>H</u>$_3$)$_2$), 3.30 (2H, d, $^2J_{HP}$ = 20.9 Hz, PC<u>H</u>$_2$), 4.08-4.21 (4H, m, P(OC<u>H</u>$_2$CH$_3$)$_2$), 5.35 (2H, s, C$_q$C<u>H</u>$_2$O), 6.63 (1H, d, *J* = 3.5 Hz, C<u>H</u>$_{ar}$C$_{q,ar}$CH$_2$), 7.05 (1H, d, *J* = 3.8 Hz, C<u>H</u>$_{ar}$C$_{q,ar}$CHO), 7.21 (1H, d, *J* = 3.6 Hz, NC<u>H</u>), 7.51 (1H, td, *J* = 7.6 Hz, *J* = 1.2 Hz, C<u>H</u>$_{ar}$), 7.58 (1H, td, *J* = 7.6 Hz, *J* = 1.2 Hz, C<u>H</u>$_{ar}$), 7.71 (1H, dd, *J* = 7.7 Hz, 0.9 Hz, C<u>H</u>$_{ar}$), 7.87 (1H, d, *J* = 7.5 Hz, C<u>H</u>$_{ar}$), 9.63 (1H, s, CHO) **^{13}C NMR (100 MHz, CDCl$_3$) δ:** 16.3 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.4 (d, $^1J_{CP}$ = 145 Hz, P<u>C</u>H$_2$), 58.9 (O<u>C</u>H$_2$C$_{q,ar}$), 62.6 (d, $^2J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 112.9 (<u>C</u>HC$_q$CH$_2$O), 121.8 (br. s, <u>C</u>$_{ar}$HC$_{q,ar}$CHO), 126.3 (<u>C</u>$_{q,ar}$C(O)N), 126.5 (d, $^3J_{CP}$ = 8 Hz, N<u>C</u>H), 129.0 (<u>C</u>$_{ar}$H), 129.1 (<u>C</u>$_{ar}$H), 130.0 (<u>C</u>$_{ar}$H), 130.8 (<u>C</u>$_{ar,q}$C(O)N), 131.2 (<u>C</u>$_{ar}$H), 144.1 (d, $^2J_{CP}$ = 9 Hz, O<u>C</u>$_q$CH$_2$P), 152.8 (<u>C</u>$_q$CHO), 155 (<u>C</u>$_q$CH$_2$), 160 (d, $^5J_{CP}$ = 1 Hz, N<u>C</u>(O)C$_q$), 167.5 (N<u>C</u>(O)C$_q$), 177.7 (CHO). **^{31}P NMR (161 MHz, CDCl$_3$) δ:** 21.55. **MS (ESI, pos):** *m/z* 448.2/449.3 (M + H$^+$, 100/22). **HRMS:** *m/z* calcd for $C_{21}H_{23}NO_8P$ (M + H)$^+$ 448.1156, found 448.1156. **Yield:** 33%, yellow oil.

The product was obtained after purification by reversed phase chromatography (5 CVs 5/95 CH$_3$CN/H$_2$O, over 9 CVs to 12% CH$_3$CN, over 6 CVs to 30% CH$_3$CN, 4 CVs 30% CH$_3$CN, over 3 CVs to 50% CH$_3$CN, 6 CVs 50% CH$_3$CN).

diethyl ((Z)-2-(2-(((Z)-3-(diethoxyphosphoryl)-1-(1,3-dioxoisoindolin-2-yl)prop-1-en-2-yl)oxy)ethoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 347a

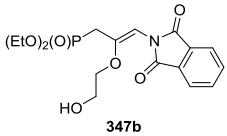


347a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (12H, t, *J* = 7.1 Hz, 2 x $P(OCH_2C\underline{H}_3)_2$), 3.22 (4H, dd, $^{1}J_{HP}$ = 20.9 Hz, $^{3}J_{HH}$ = 0.8 Hz, 2 x PCH_2), 4.10 (4H, q, $^{3}J_{HP}$ = 7.1 Hz, 2 x $P(OC\underline{H}_aH_bCH_3)_2$), 4.12 (4H, q, $^{3}J_{HP}$ = 7.1 Hz, 2 x $P(OCH_a\underline{H}_bCH_3)_2$), 4.53 (4H, s, $OC\underline{H}_2C\underline{H}_2O$), 6.99 (2H, d, $^{4}J_{HP}$ = 3.8 Hz, 2 x $NC\underline{H}$), 7.50 (2H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.3 Hz, $C\underline{H}_{ar}$), 7.56 (2H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.4 Hz, $C\underline{H}_{ar}$), 7.65 (2H, dd, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.2 Hz, $C\underline{H}_{ar}$), 7.86 (2H, d, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.0 Hz, $C\underline{H}_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^{3}J_{CP}$ = 6 Hz, 2 x $P(OCH_2\underline{C}H_3)_2$), 24.2 (d, $^{1}J_{CP}$ = 144 Hz, 2 x $P\underline{C}H_2$), 62.5 (d, $^{2}J_{CP}$ = 7 Hz, 2 x $P(O\underline{C}H_2CH_3)_2$), 63.0 (2 x $O\underline{C}H_2$), 126.1 (2 x $\underline{C}_{ar,q}$), 126.4 (d, $^{3}J_{CP}$ = 8 Hz, 2 x $N\underline{C}H$), 128.8 (2 x $\underline{C}_{ar}H$), 128.9 (2 x $\underline{C}_{ar}H$), 129.9 (2 x $\underline{C}_{ar}H$), 130.9 (2 x $\underline{C}H$), 131.4 (2 x $\underline{C}_{ar,q}$), 143.9 (d, $^{2}J_{CP}$ = 9 Hz, $O\underline{C}_q$), 159.7 (2 x $N\underline{C}(O)C_q$), 167.8 (2 x $N\underline{C}(O)C_q$ **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.50. **MS (ESI, pos):** *m/z* 705.3/706.3/707.3 ($M + H^+$, 100/33/9). **HRMS:** *m/z* calcd for $C_{32}H_{39}N_2O_{12}P_2$ $(M + H)^+$ 705.1973, found 705.1990. **Yield:** 74%, yellow oil.

The product was obtained after purification by reversed phase chromatography (2 CVs 30/70 CH_3CN/H_2O, over 20 CVs to 100% CH_3CN, 2 CVs 100% CH_3CN).

diethyl (Z)-(3-(1,3-dioxoisoindolin-2-yl)-2-(2-hydroxyethoxy)allyl)phosphonate 347b

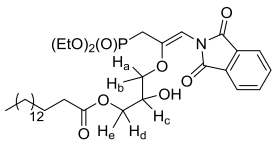


347b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 3.33 (2H, dd, $^{2}J_{HP}$ = 21.0 Hz, $^{4}J_{HP}$ = 0.8 Hz, $PC\underline{H}_2$), 3.82-3.91 (2H, m, $C\underline{H}_2OH$), 4.10-4.21 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 4.46-4.53 (2H, m, $C\underline{H}_2O$), 7.08 (1H, d, *J* = 3.8 Hz, $NC\underline{H}$), 7.50-7.60 (2H, m, $C\underline{H}_{ar}$), 7.64-7.69 (1H, m, $C\underline{H}_{ar}$), 7.90-7.95 (1H, m, $C\underline{H}_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.4 (d, $^{3}J_{CP}$ = 6 Hz, 2 x $P(OCH_2\underline{C}H_3)_2$), 24.5 (d, $^{1}J_{CP}$ = 145 Hz, 2 x $P\underline{C}H_2$), 60.7 ($\underline{C}H_2O$), 62.8 (d, $^{2}J_{CP}$ = 7 Hz, 2 x $P(O\underline{C}H_2CH_3)_2$), 67.3 ($C\underline{H}_2OH$), 125.1 ($\underline{C}_{ar,q}$), 126.3 (d, $^{3}J_{CP}$ = 8 Hz, $N\underline{C}H$), 128.7 ($\underline{C}_{ar}H$), 128.8 ($\underline{C}_{ar}H$), 130.3 ($\underline{C}_{ar}H$), 130.7 ($\underline{C}_{ar}H$), 132.1 ($\underline{C}_{ar,q}$), 144.1 (d, $^{2}J_{CP}$ = 2 Hz, $O\underline{C}_q$), 159.9 (d, $^{5}J_{CP}$ = 2 Hz, $N\underline{C}(O)C_q$), 168.8 ($N\underline{C}(O)C_q$ **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.44. **MS (ESI, pos):** *m/z* 384.2/385.2 ($M + H^+$, 100/19). **HRMS:** *m/z* calcd for $C_{17}H_{23}NO_7P$ $(M + H)^+$ 384.1207, found 384.1217. **Yield:** 13%, yellow oil.

The product was obtained after purification by reversed phase chromatography (2 CVs 30/70 CH_3CN/H_2O, over 20 CVs to 100% CH_3CN, 2 CVs 100% CH_3CN).

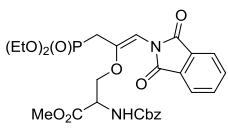
(Z)-3-((3-(diethoxyphosphoryl)-1-(1,3-dioxoisoindolin-2-yl)prop-1-en-2-yl)oxy)-2-hydroxypropyl palmitate 348 (major isomer)



348

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83-0.92 (3H, m, CH_3), 1.18-1.38 (30H, m, $(CH_2)_{12}$, $P(OCH_2\underline{C}H_3)_2$), 1.52-1.70 (2H, m, CH_2), 2.23-2.41 (2H, m, CH_2), 3.30 (2H, d, $^2J_{HP}$ = 20.9 Hz, $^3J_{HH}$ = 2.7 Hz, PCH_2), 4.04-4.29 (7H, m, $P(OCH_2CH_3)_2$, H_c, H_d, H_e), 4.30-4.44 (1H, m, H_a), 4.45-4.52 (1H, m, H_b), 4.57 (1H, br. s, OH), 7.03-7.12 (1H, m, NCH), 7.46-7.71 (3H, m, CH_{ar}), 7.83-7.98 (1H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 14.1 (CH_3), 16.4 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 22.7 ($CH_2$), 24.4 (d, $^1J_{CP}$ = 145 Hz, $P\underline{C}H_2$), 24.9 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6-26.7 (m, 5 x CH_2), 31.9 (CH_2), 34.1 (CH_2), 62.8 (d, $^2J_{CP}$ = 7 Hz, $P(O\underline{C}H_2CH_3)$), 62.8 (d, $^2J_{CP}$ = 7 Hz, $P(O\underline{C}H_2CH_3)$), 64.8 ($O\underline{C}H_dH_e$), 66.8 ($O\underline{C}H_aH_b$), 67.7 ($O\underline{C}H_c$), 125.0 ($C_{q,ar}$), 126.4 (d, $^3J_{CP}$ = 8 Hz, N$\underline{C}$H), 128.7 ($\underline{C}_{ar}H$), 128.7 ($\underline{C}_{ar}H$), 130.3 ($\underline{C}_{ar}H$), 130.7 ($\underline{C}_{ar}H$), 130.8 ($\underline{C}_{ar,q}C(O)N$), 131.8 ($C_{q,ar}$), 144.1 (d, $^2J_{CP}$ = 10 Hz, $O\underline{C}_qCH_2P$), 152.8 ($\underline{C}_qCHO$), 159.8 (d, $^5J_{CP}$ = 3 Hz, N$\underline{C}$(O)C_q), 168.6 (N$\underline{C}$(O)C_q), 173.7 (C(O)O). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.34. **MS (ESI, pos):** *m/z* 652.5/653.5/654.5 ($M + H^+$, 100/42/9). **HRMS:** *m/z* calcd for $C_{34}H_{55}NO_9P$ $(M + H)^+$ 652.3609, found 652.3608. **Crude yield:** 92%, orange oil.

methyl (Z)-N-((benzyloxy)carbonyl)-O-(3-(diethoxyphosphoryl)-1-(1,3-dioxoisoindolin-2-yl)prop-1-en-2-yl)serinate 349

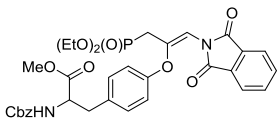


349

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (3H, t, *J* = 7.0 Hz, $P(OCH_2\underline{C}H_3)$), 1.29 (3H, t, *J* = 7.0 Hz, $P(OCH_2\underline{C}H_3)$), 1.37 (2H, sext., *J* = 7.6 Hz, $CH_2\underline{C}H_2CH_3$), 3.17 (2H, d, $^2J_{HP}$ = 20.9 Hz, PCH_2), 3.72 (3H, s, OCH_3), 4.04-4.18 (4H, m, $P(OCH_2CH_3)_2$), 4.61 (1H, dd, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 3.9 Hz, OCH_2), 4.69 (1H, td, $^3J_{NH}$ =8.4 Hz, $^3J_{HH}$ = 3.9 Hz, OCH), 4.90 (1H, dd, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 3.9 Hz, OCH_2), 5.14 (2H, s, OCH_2C_q), 6.71 (1H, d, *J* = 8.6 Hz, NH), 6.97 (1H, d, $^4J_{HP}$ = 3.8 Hz, NCH), 7.29-7.40 (5H, m, CH_{ar}), 7.45-7.59(3H, m, CH_{ar}), 7.86-7.96 (1H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.4 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 24.3 (d, $^1J_{CP}$ = 145 Hz, $P\underline{C}H_2$), 52.7 (OCH_3), 53.7 (OCH), 62.6 (d, $^2J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)$), 62.6 (d, $^2J_{CP}$ = 7 Hz, $P(O\underline{C}H_2CH_3)$), 64.8 (OCH_2), 67.1 ($O\underline{C}H_2C_q$), 125.1 (C_q), 126.7 (d, $^3J_{CP}$ = 8 Hz, N$\underline{C}$H) 128.2 ($\underline{C}_{ar}H$), 128.3 (2 x $\underline{C}_{ar}H$), 128.5 (3 x $\underline{C}_{ar}H$), 128.6 ($\underline{C}_{ar}H$), 130.1 ($\underline{C}_{ar}H$), 130.8 ($\underline{C}_{ar}H$), 131.4 ($\underline{C}_{q,ar}$), 136.2 ($C_{q,ar}$), 143.9 (d, $^2J_{CP}$ = 10 Hz, $O\underline{C}_q$), 156.2 (N$\underline{C}$(O)O), 159.4 (d, $^5J_{CP}$ = 2 Hz, N$\underline{C}$(O)C_q), 168.2 (N$\underline{C}$(O)C_q), 170.0 ($\underline{C}$(O)O). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.30. **MS (ESI, pos):** *m/z* 575.3/576.3/577.3 ($M + H^+$, 100/30/6). **HRMS:** *m/z* calcd for $C_{27}H_{32}N_2O_{10}P$ $(M + H)^+$

575.1789, found 575.1773. **R_f**: 0.19 (2/8 PE/EtOAc). **Yield:** 63%, yellow oil. **$[\alpha]_D$** = -5.4° (c 0.4, acetone)

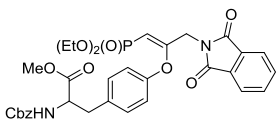
methyl (Z)-2-(((benzyloxy)carbonyl)amino)-3-(4-((3-(diethoxyphosphoryl)-1-(1,3-dioxoisoindolin-2-yl)prop-1-en-2-yl)oxy)phenyl)propanoate 350a



350a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (6H, t, *J* = 7.1 Hz, P(OCH$_2$CH$_3$)$_2$), 3.05 (2H, m, CHCH$_2$C$_q$), 3.26 (2H, d, $^2J_{HP}$ = 20.9 Hz, PCH$_2$), 3.73 (3H, s, OCH$_3$), 4.04-4.20 (4H, m, P(OCH$_2$CH$_3$)$_2$), 4.66 (1H, m, CHNH), 5.11 (2H, s, OCH$_2$C$_q$), 5.29 (1H, d, *J* = 8.0 Hz, NH), 7.08-7.22 (5H, m, NCH, CH$_{ar}$), 7.28-7.41 (5H, m, CH$_{ar}$), 7.58 (1H, td, *J* = 7.5 Hz, *J* = 1.4 Hz, CH$_{ar}$), 7.58 (1H, td, *J* = 7.6 Hz, *J* = 1.5 Hz, CH$_{ar}$), 7.84 (1H, dd, *J* = 7.6 Hz, *J* = 1.3 Hz, CH$_{ar}$), 7.93 (1H, dd, *J* = 7.5 Hz, *J* = 1.1 Hz, CH$_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$CH$_3$)$_2$), 24.4 (d, $^1J_{CP}$ = 144 Hz, PCH$_2$), 37.4 (CHCH$_2$C$_q$), 52.5 (OCH$_3$), 54.9 (CHNH), 62.6 (d, $^2J_{CP}$ = 7 Hz, P(OCH$_2$CH$_3$)$_2$), 66.8 (OCH$_2$C$_q$), 121.4 (C$_{ar}$H), 126.4 (C$_{q,ar}$), 126.6 (d, $^3J_{CP}$ = 7 Hz, NCH), 128.0 (C$_{ar}$H), 128.1 (C$_{ar}$H), 128.5 (2 x C$_{ar}$H), 129.1 (C$_{ar}$H), 129.4 (C$_{ar}$H), 130.1 (C$_{ar}$H), 130.2 (2 x C$_{ar}$H), 131.2 (C$_{q,ar}$), 131.4 (C$_{ar}$H), 133.8 (C$_{q,ar}$), 136.3 (C$_{q,ar}$), 144.2 (br. s, OC$_q$), 150.0 (OC$_{q,ar}$), 155.1 (NC(O)O), 159.8 (br. s, NC(O)C$_q$), 166.5 (NC(O)C$_q$), 171.9 (C(O)O). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.43. **MS (ESI, pos):** *m/z* 651.3/652.3/653.3 (M + H$^+$, 100/37/9). **HRMS:** *m/z* calcd for $C_{19}H_{27}NO_6P$ (M + H)$^+$ 396.1571, found 396.1553. **R_f**: 0.19 (4/6 PE/EtOAc). **Yield:** 52%, dark yellow oil. **$[\alpha]_D$** = 0.0° (c 0.3, acetone)

methyl (Z)-2-(((benzyloxy)carbonyl)amino)-3-(4-((1-(diethoxyphosphoryl)-3-(1,3-dioxoisoindolin-2-yl)prop-1-en-2-yl)oxy)phenyl)propanoate 350b

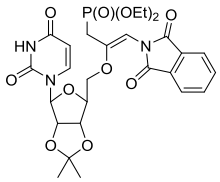


350b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (6H, t, *J* = 7.1 Hz, P(OCH$_2$CH$_3$)$_2$), 3.02 (1H, dd, *J* = 13.7 Hz, *J* = 6.1 Hz, CH$_a$H$_b$CHN), 3.11 (1H, dd, *J* = 14.0 Hz, *J* = 5.7 Hz, CH$_a$H$_b$CHN), 3.69 (3H, s, OCH$_3$), 4.08-4.19 (4H, m, P(OCH$_2$CH$_3$)$_2$), 4.46 (1H, d, $^2J_{HP}$ = 5 Hz, PCH), 4.56-4.67 (1H, m, CHNH), 5.06 (2H, s, OCH$_2$C$_q$), 5.15 (2H, d, *J* = 1.5 Hz, CHNH), 5.21 (1H, d, *J* = 8.2 Hz, NH), 6.85 (2H, d, *J* = 8.5 Hz, CH$_{ar}$), 7.06 (2H, d, *J* = 8.4 Hz, CH$_{ar}$), 7.27-7.38 (5H, m, CH$_{ar}$), 7.72 (2H, dd, *J* = 5.5 Hz, *J* = 3.1 Hz, CH$_{ar}$), 7.87 (2H, dd, *J* = 5.5 Hz, *J* = 3.0 Hz, CH$_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 7 Hz, P(OCH$_2$CH$_3$)$_2$), 37.6 (CHCH$_2$C$_q$), 37.8 (d, $^3J_{CP}$ = 2 Hz, NCH$_2$), 52.4 (OCH$_3$), 54.8 (CHNH), 61.7 (d, $^2J_{CP}$ = 5 Hz, P(OCH$_2$CH$_3$)$_2$), 67.0 (OCH$_2$C$_q$), 90.0 (d, $^3J_{CP}$ = 201 Hz,

CHP), 121.8 (2 x C_{ar}H), 123.4 (2 x C_{ar}H), 128.1 (2 x C_{ar}H), 128.2 (C_{ar}H), 128.5 (2 x C_{ar}H), 130.1 (2 x C_{ar}H), 132.1 (2 x $C_{q,ar}$), 133.7 ($C_{q,ar}$), 134.1 (2 x C_{ar}H), 136.1 ($C_{q,ar}$), 151.9 (O$C_{q,ar}$), 155.5 (NC(O)O), 167.6 (d, $^2J_{CP}$ = 24 Hz, OC_q), 167.9 (2 x NC(O)C_q), 171.7 (C(O)O). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 19.24. **MS (ESI, pos):** *m/z* 651.3/652.3/653.3 (M + H^+, 100/37/9). **R_f**: 0.19 (4/6 PE/EtOAc). **Yield:** 9%, dark yellow oil. **$[\alpha]_D$** = 0.0° (c 0.2, acetone)

diethyl ((Z)-2-(((3aS,4S,6S,6aS)-6-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 351



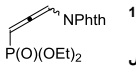
351

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (6H, t, *J* = 7.1 Hz, P(OCH_2CH_3)$_2$), 1.33 (3H, s, C_qCH_3), 1.55 (3H, s, C_qCH_3), 3.29 (1H, dd, $^2J_{HP}$ = 20.7, Hz, $^3J_{ab}$ = 16.5 Hz, PCH_aH$_b$), 3.36 (1H, dd, $^2J_{HP}$ = 21.1 Hz, $^3J_{ab}$ = 16.5 Hz, PCH_aH$_b$), 4.10-4.22 (4H, m, P(OCH_2CH$_3$)$_2$), 4.40-4.49 (1H, m, OCHCH_2), 4.49-4.63 (2H, m, OCH_2CH), 4.76 (1H, dd, *J* = 6.4 Hz, *J* = 3.4 Hz, NCHCHO or OCH$_2$CHCHO), 4.79 (1H, dd, *J* = 6.4 Hz, *J* = 2.1 Hz, NCHCHO or OCH$_2$CHCHO), 5.44 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{NH}$ = 1.1 Hz, CHC(O)), 5.71 (1H, d, *J* = 2.1 Hz, NCHO), 7.07 (1H, d, $^4J_{HP}$ = 3.6 Hz, NCH), 7.20 (1H, d, $^3J_{HH}$ = 8.1 Hz, CHCHC(O)), 7.48-7.67 (3H, m, CH_{ar}), 7.91 (1H, td, *J* =7.8 Hz, *J* = 0.9 Hz, CH_{ar}), 8.89 (1H, br. s, NH). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 6 Hz, P(OCH_2CH_3)$_2$), 24.3 (d, $^1J_{CP}$ = 145 Hz, PCH$_2$), 25.2 (C_qCH_3), 27.1 (C_qCH_3), 62.7 (d, $^2J_{CP}$ = 6 Hz, P(OCH$_2$CH$_3$)$_2$), 65.2 (OCH$_2$CH), 81.0 (OCH$_2$CHCHO), 84.5 (NCHCHO), 84.8 (OCHCH$_2$), 93.8 (NCHO), 102.3 (CHC(O)), 114.2 (C_q(CH$_3$)$_2$), 123.4 ($C_{q,ar}$), 126.4 (d, $^3J_{CP}$ = 7 Hz, NCH), 128.7 (C_{ar}H), 128.9 (C_{ar}H), 130.2 (C_{ar}H), 131.1 (C_{ar}H), 131.3 ($C_{q,ar}$), 141.6 (CHCHC(O)), 144.3 (d, $^2J_{CP}$ = 8 Hz, OC_q), 150.2 (NCONH), 160.0 (d, $^5J_{CP}$ = 2 Hz, NC(O)C_q), 163.6 (CHC(O)), 167.8 (NC(O)C_q). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.60. **MS (ESI, pos):** *m/z* 606.3/607.3/608.3 (M + H^+, 100/30/7). **R_f**: 0.16 (99/1 EtOAc/MeOH). **Yield:** 64%, white foam.

*4.5.2. Synthesis of 3-imidoallenylphosphonate **338***

64 mg (0.20 mmol) phosphonylated alkyne was dissolved in 3 mL of the THF in a 10 mL flask. 65 mg (0.20 mmol) Cs_2CO_3 was added and the reaction progress was monitored via NMR. After 3 hours the mixture was quenched with water, concentrated *in vacuo*, three times extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. The 3-aminoallenylphosphonate was isolated in 16% yield after preparative TLC.

diethyl (3-(1,3-dioxoisoindolin-2-yl)propa-1,2-dien-1-yl)phosphonate 338

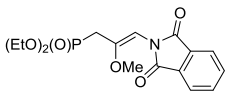


^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, t, *J* = 6.8 Hz, $P(OCH_2C\underline{H}_3)$), 1.38 (3H, t, *J* = 6.8 Hz, $P(OCH_2C\underline{H}_3)$), 4.15-4.28 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 6.08 (1H, dd, $^3J_{HH}$ = 6.4 Hz, $^2J_{HP}$ = 1.7 Hz, PC<u>H</u>), 7.21 (1H, dd, $^4J_{HP}$ = 12.8 Hz, $^3J_{HH}$ = 6.4 Hz, NC<u>H</u>), 7.76 (2H, dd, *J* = 5.5 Hz, *J* = 3.0 Hz, $C\underline{H}_{ar}$), 7.89 (2H, dd, *J* = 5.5 Hz, *J* = 3.1 Hz, $C\underline{H}_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)$), 16.4 (d, $^3J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)$), 62.7 (d, $^2J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)$), 62.9 (d, $^2J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)$), 89.9 (d, $^3J_{CP}$ = 17 Hz, N<u>C</u>H), 90.8 (d, $^1J_{CP}$ = 194 Hz, P<u>C</u>H), 123.8 ($\underline{C}_{ar}H$), 131.9 ($\underline{C}_{ar}H$), 134.6 ($\underline{C}_{ar}H$), 164.9 ($N\underline{C}(O)C_q$), 209.6 ($CH\underline{C}_qCH$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 11.47. **MS (ESI, pos):** *m/z* 322.1/323.2 ($M + H^+$, 100/14). **R_f**: 0.33 (2/8 PE/EtOAc). **Yield:** 16%, orange oil.

4.5.3 Procedure for the alkoxide exchange reaction

Phosphonate **340** (101 mg, 0.28 mmol) was dissolved in 4 mL MeOH. After addition of 90 mg (0.28 mmol) Cs_2CO_3, the mixture was refluxed and reaction progress was monitored via ^{1}H NMR. After 2 hours, the mixture was quenched with 1 mL water. The solvent was evaporated under reduced pressure and 1 mL water and 10 mL EtOAc were added. The organic layer was separated and dried over $MgSO_4$. After evaporation of the solvent *in vacuo*, the desired product was obtained in 61% yield.

diethyl (Z)-(3-(1,3-dioxoisoindolin-2-yl)-2-methoxyallyl)phosphonate 360b



360b

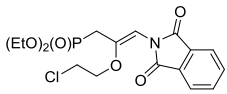
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (6H, t, *J* = 7.0 Hz, $P(OCH_2C\underline{H}_3)_2$), 3.30 (2H, dd, $^2J_{HP}$ = 21.1 Hz, $^4J_{HH}$ = 0.9 Hz, $PC\underline{H}_2$), 3.69 (3H, s, $C_qOC\underline{H}_3$), 4.08-4.20 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 7.09 (1H, d, $^4J_{HP}$ = 3.6 Hz, $^4J_{HH}$ = 1.0 Hz, NC<u>H</u>), 7.51 (1H, td, *J* = 7.4 Hz, *J* = 1.3 Hz, $C\underline{H}_{ar}$), 7.56 (1H, td, *J* = 7.5 Hz, *J* = 1.4 Hz, $C\underline{H}_{ar}$), 7.68-7.72 (1H, m, $C\underline{H}_{ar}$), 7.85-7.90 (1H, m, $C\underline{H}_{ar}$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.54. **MS (ESI, pos):** *m/z* 354.1/355.2 ($M + H^+$, 100/17). **Yield:** 61%, orange oil.

4.5.4. Procedure for the addition of haloalcohols

In a typical experiment, 160 mg (0.50 mmol) alkyne **305** was dissolved in 1.5 mL THF in a 10 mL flask. 163 mg (0.50 mmol) Cs_2CO_3 and 33 µL (0.50 mmol) of the haloalcohol were added at room temperature. Reaction progress was monitored via NMR spectroscopy. After completion of the reaction, the mixture was quenched with water, concentrated *in vacuo*, three

times extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to give the desired product.

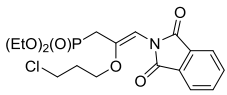
diethyl (Z)-(2-(2-chloroethoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 363a



363a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 3.30 (2H, d, $^2J_{HP}$ = 20.9 Hz, $PC\underline{H}_2$), 3.73 (3H, t, *J* = 5.8 Hz, $OCH_2C\underline{H}_2Cl$), 4.06-4.22 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 4.54 (2H, t, *J* = 5.8 Hz, $OC\underline{H}_2CH_2Cl$), 7.09 (1H, d, $^4J_{HP}$ = 3.7 Hz, $NC\underline{H}$), 7.52 (1H, td, *J* = 7.5 Hz, *J* = 1.3 Hz, $C\underline{H}_{ar}$), 7.58 (1H, td, *J* = 7.4 Hz, *J* = 1.4 Hz, $C\underline{H}_{ar}$), 7.73 (1H, dd, *J* = 7.56Hz, *J* = 1.2 Hz, $C\underline{H}_{ar}$), 7.87 (1H, dd, *J* = 7.5 Hz, *J* = 1.1 Hz, $C\underline{H}_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.4 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 24.5 (d, $^1J_{CP}$ = 145 Hz, $P\underline{C}H_2$), 41.2 ($OCH_2\underline{C}H_2Cl$), 62.6 (d, $^2J_{CP}$ = 7 Hz, $P(O\underline{C}H_2CH_3)_2$), 65.1 ($OCH_2\underline{C}H_2Cl$), 126.4 ($\underline{C}_{q,ar}$), 126.5 (d, $^3J_{CP}$ = 8 Hz, $N\underline{C}H$), 129.07 ($\underline{C}_{ar}H$), 129.13 ($\underline{C}_{ar}H$), 130.1 ($\underline{C}_{ar}H$), 131.1 ($\underline{C}_{ar}H$), 131.3 ($\underline{C}_{q,ar}$), 144.0 (d, $^2J_{CP}$ = 8 Hz, $O\underline{C}_q$), 159.9 (d, $^5J_{CP}$ = 2 Hz, $N\underline{C}(O)C_q$), 167.8 ($N\underline{C}(O)C_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.49. **MS (ESI, pos):** *m/z* 402.1/404.1 ($M + H^+$, 100/32). **Yield:** 80%, yellow oil.

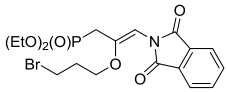
diethyl (Z)-(2-(3-chloropropoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 363b



363b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 2.12 (2H, quint, *J* = 6.1 Hz, $C\underline{H}_2CH_2Cl$), 3.31 (2H, d, $^2J_{HP}$ = 21.0 Hz, $PC\underline{H}_2$), 3.55 (t, J = 6.5 Hz, CH_2Cl), 4.06-4.21 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 4.43 (2H, t, *J* = 6.0 Hz, $C_qOC\underline{H}_2$), 7.10 (1H, d, $^4J_{HP}$ = 3.7 Hz, $NC\underline{H}$), 7.52 (1H, td, *J* = 7.7 Hz, *J* = 1.4 Hz, $C\underline{H}_{ar}$), 7.57 (1H, td, *J* = 7.8 Hz, *J* = 1.4 Hz, $C\underline{H}_{ar}$), 7.69 (1H, dd, *J* = 7.4 Hz, *J* = 1.3 Hz, $C\underline{H}_{ar}$), 7.86 (1H, dd, *J* = 7.6 Hz, *J* = 1.1 Hz, $C\underline{H}_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 24.3 (d, $^1J_{CP}$ = 145 Hz, $P\underline{C}H_2$), 31.4 ($C\underline{H}_2CH_2Cl$), 41.2 ($C\underline{H}_2Cl$), 62.2 ($C_qO\underline{C}H_2$), 62.5 (d, $^2J_{CP}$ = 7 Hz, $P(O\underline{C}H_2CH_3)_2$), 126.0 ($\underline{C}_{q,ar}$), 126.4 (d, $^3J_{CP}$ = 7 Hz, $N\underline{C}H$) 128.87 ($\underline{C}_{ar}H$), 128.89 ($\underline{C}_{ar}H$), 130.0 ($\underline{C}_{ar}H$), 130.8 ($\underline{C}_{ar}H$), 132.2 ($\underline{C}_{q,ar}$), 144.0 (d, $^2J_{CP}$ = 9 Hz, $O\underline{C}_q$), 159.9 (d, $^5J_{CP}$ = 2 Hz, $N\underline{C}(O)C_q$), 168.0 ($N\underline{C}(O)C_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.41. **MS (ESI, pos):** *m/z* 416.1/418.1 ($M + H^+$, 100/33). **Yield:** 84%, yellow oil.

diethyl (Z)-(2-(3-bromopropoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 363c



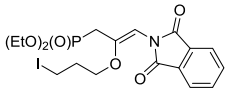
363c

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (6H, t, *J* = 7.1 Hz, P(OCH$_2$C<u>H</u>$_3$)$_2$), 2.12 (2H, quint, *J* = 6.3 Hz, C<u>H</u>$_2$CH$_2$Br), 3.31 (2H, dd, $^{2}J_{HP}$ = 21.0 Hz, $^{3}J_{HH}$ = 0.8 Hz, PC<u>H</u>$_2$), 3.41 (t, J = 6.6 Hz, CH$_2$Br), 4.14 (2H, q, *J* = 7.2 Hz, P(OC<u>H</u>$_2$CH$_3$)), 4.16 (2H, q, *J* = 7.2 Hz, P(OC<u>H</u>$_2$CH$_3$)), 4.35 (2H, t, *J* = 5.9 Hz, C$_q$OC<u>H</u>$_2$), 7.11 (1H, d, $^{4}J_{HP}$ = 3.8 Hz, NC<u>H</u>), 7.52 (1H, td, *J* = 7.4 Hz, *J* = 1.3 Hz, C<u>H</u>$_{ar}$), 7.57 (1H, td, *J* = 7.4 Hz, *J* = 1.3 Hz, C<u>H</u>$_{ar}$), 7.69 (1H, dd, *J* = 7.4 Hz, *J* = 1.5 Hz, C<u>H</u>$_{ar}$), 7.86 (1H, dd, *J* = 7.3 Hz, *J* = 1.5 Hz, C<u>H</u>$_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.4 (d, $^{3}J_{CP}$ = 6 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.5 (d, $^{1}J_{CP}$ = 145 Hz, P<u>C</u>H$_2$), 29.6 (C<u>H</u>$_2$CH$_2$Br), 31.7 (C<u>H</u>$_2$Br), 62.6 (d, $^{2}J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 63.3 (C$_q$O<u>C</u>H$_2$), 126.2 (<u>C</u>$_{q,ar}$), 126.6 (d, $^{3}J_{CP}$ = 8 Hz, N<u>C</u>H) 128.98 (<u>C</u>$_{ar}$H), 129.01 (<u>C</u>$_{ar}$H), 130.1 (<u>C</u>$_{ar}$H), 130.9 (<u>C</u>$_{ar}$H), 131.8 (<u>C</u>$_{q,ar}$), 144.0 (d, $^{2}J_{CP}$ = 8 Hz, O<u>C</u>$_q$), 160.0 (d, $^{5}J_{CP}$ = 2 Hz, N<u>C</u>(O)C$_q$), 168.2 (N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.47. **MS (ESI, pos):** *m/z* 460.1/462.1 (M + H$^+$, 100/97). **Yield:** 22%, yellow oil.

*4.5.5. Procedure for the synthesis of iodopropoxy derivative **363d***

302 mg (1.98 mmol) NaI was added to a mixture of diethyl (Z)-(2-(3-bromopropoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate **363c** in THF at room temperature. Reaction progress was monitored via NMR spectroscopy. After completion of the reaction, the mixture was quenched with water, concentrated *in vacuo*, three times extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to give the desired product.

diethyl (Z)-(2-(3-iodopropoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 363d



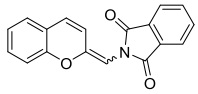
363d

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (6H, t, *J* = 7.1 Hz, P(OCH$_2$C<u>H</u>$_3$)$_2$), 2.18 (2H, quint, *J* = 6.4 Hz, C<u>H</u>$_2$CH$_2$I), 3.18 (t, J = 6.9 Hz, CH$_2$I), 3.32 (2H, dd, $^{2}J_{HP}$ = 21.0 Hz, $^{3}J_{HH}$ = 0.6 Hz, PC<u>H</u>$_2$), 4.13 (2H, q, *J* = 7.1 Hz, P(OC<u>H</u>$_2$CH$_3$)), 4.15 (2H, q, *J* = 7.1 Hz, P(OC<u>H</u>$_2$CH$_3$)), 4.42 (2H, t, *J* = 6.0 Hz, C$_q$OC<u>H</u>$_2$), 7.10 (1H, d, $^{4}J_{HP}$ = 3.8 Hz, NC<u>H</u>), 7.52 (1H, td, *J* = 7.5 Hz, *J* = 1.3 Hz, C<u>H</u>$_{ar}$), 7.57 (1H, td, *J* = 7.5 Hz, *J* = 1.3 Hz, C<u>H</u>$_{ar}$), 7.69 (1H, dd, *J* = 7.5 Hz, *J* = 1.4 Hz, C<u>H</u>$_{ar}$), 7.86 (1H, dd, *J* = 7.5 Hz, *J* = 1.4 Hz, C<u>H</u>$_{ar}$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 1.33 (C<u>H</u>$_2$I), 16.4 (d, $^{3}J_{CP}$ = 7 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.6 (d, $^{1}J_{CP}$ = 145 Hz, P<u>C</u>H$_2$), 32.4 (C<u>H</u>$_2$CH$_2$I), 62.6 (d, $^{2}J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 65.2 (C$_q$O<u>C</u>H$_2$), 126.2 (<u>C</u>$_{q,ar}$), 126.6 (d, $^{3}J_{CP}$ = 7 Hz, N<u>C</u>H) 128.97 (<u>C</u>$_{ar}$H), 128.99 (<u>C</u>$_{ar}$H), 130.0 (<u>C</u>$_{ar}$H), 130.9 (<u>C</u>$_{ar}$H), 131.8 (<u>C</u>$_{q,ar}$), 144.0 (d, $^{2}J_{CP}$ = 9 Hz, O<u>C</u>$_q$), 160.0 (d, $^{5}J_{CP}$ = 3 Hz, N<u>C</u>(O)C$_q$), 168.1 (N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 21.46. **MS (ESI, pos):** *m/z* 508.0/509.0 (M + H$^+$, 100/20). **Yield:** 55%, yellow oil.

4.5.6. Procedure for the preparation of phosphonylated chromenes

In a typical experiment, 160 mg (0.50 mmol) alkyne **305** was dissolved in 1.5 mL THF in a 10 mL flask. 163 mg (0.50 mmol) Cs_2CO_3 and 61 mg (0.50 mmol) salicylaldehyde were added at room temperature. Reaction progress was monitored via NMR spectroscopy. After completion of the reaction, the mixture was quenched with water, concentrated *in vacuo*, three times extracted with ethyl acetate and dried over $MgSO_4$. Chromenes **366** and **368**-**369** were purified via pTLC (3/7 PE/EtOAc).

2-((2*H*-chromen-2-ylidene)methyl)isoindoline-1,3-dione 366

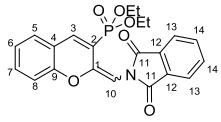


366

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.47 (1H, s, mi), 5.81 (1H, d, *J* = 1.3 Hz, Ma), 6.14 (1H, d, *J* = 10.0 Hz, Ma), 6.33 (1H, d, *J* = 9.8 Hz, mi), 6.61 (1H, d, *J* = 9.8 Hz, Ma), 6.83 (1H, d, *J* = 8.1 Hz, mi), 6.90-7.01 (2H, m, Ma), 7.04-7.10 (2H, m, mi), 7.14 (1H, td, *J* = 7.8 Hz, *J* = 1.3 Hz, mi), 7.23 (1H, td, *J* = 7.8 Hz, *J* = 1.3 Hz, Ma), 7.71-7.80 (3H, m), 7.85-7.94 (3H, m) **MS (ESI, pos):** *m/z* 290.1/291.2 (M + H^+, 100/21). **Yield:** 3%, transparent liquid.

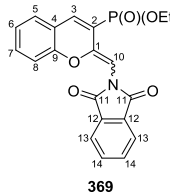
A mixture of *E*/*Z* isomers was obtained. The predominant stereoisomer is described as Ma (Major), the other one as mi (minor). The stereoisomers were isolated in a 78/22 ratio. Assignment of the stereoisomerism was not possible. Given the low amount of isolated product, no complete characterization could be done.

diethyl (2-((1,3-dioxoisoindolin-2-yl)methylene)-2H-chromen-3-yl)phosphonate 368 and **369**



368

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (6H, t, *J* = 7.2 Hz, $P(OCH_2C\underline{H}_3)_2$), 3.83-4.01 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 5.93 (1H, t, $^4J_{HP}$ = 1.5 Hz, $C^{10}H$), 6.97 (1H, d, *J* = 8.2 Hz, C^8H), 7.03 (1H, td, *J* = 7.5 Hz, *J* = 1.0 Hz, C^6H), 7.22 (1H, dd, *J* = 7.6 Hz, *J* = 1.4 Hz, C^5H), 7.36 (1H, td, *J* = 7.9 Hz, *J* = 1.4 Hz, C^7H), 7.71 (1H, d, *J* = 19.5 Hz, C^3H), 7.70-7.80 (2H, m, $C^{13}H$), 7.83-7.94 (2H,m, $C^{14}H$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 15.9 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 63.0 (d, $^2J_{CP}$ = 5 Hz, $P(O\underline{C}H_2CH_3)_2$), 98.9 ($C^{10}$), 115.2 ($C^8$), 118.9 (d, $^1J_{CP}$ = 189 Hz, C^2), 119.0 (d, $^3J_{CP}$ = 15 Hz, C^4), 123.0 (C^6), 123.2 (2 x C^{13}), 128.7 (C^5), 132.9 (2 x C^{12}), 133.3 (C^7), 133.9 (C^{14}), 140.3 (d, $^2J_{CP}$= 7 Hz, C^3), 144.1 (d, $^2J_{CP}$ = 6 Hz, C^1), 153.9 (d, $^4J_{CP}$ = 2 Hz, C^9), 168.3 (2 x C^{11}). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 13.99. **MS (ESI, pos):** *m/z* 426.1/427.2 (M + H^+, 100/24). **Yield:** 1%, transparent liquid.



369

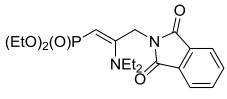
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 4.17-4.32 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 6.05 (1H, s, $C^{10}H$), 6.82 (1H, d, *J* = 8.2 Hz, $C^{8}H$), 7.00 (1H, t, *J* = 7.4 Hz, $C^{6}H$), 7.19 (1H, dd, *J* = 7.7 Hz, *J* = 1.3 Hz, $C^{5}H$), 7.27 (1H, td, *J* = 11.7 Hz, *J* = 1.4 Hz, $C^{7}H$), 7.56 (1H, d, *J* = 18.9 Hz, $C^{3}H$), 7.70-7.81 (2H, m, $C^{13}H$), 7.84-7.98 (2H,m, $C^{14}H$). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^{3}J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)_2$), 62.8 (d, $^{2}J_{CP}$ = 4 Hz, $P(O\underline{C}H_2CH_3)_2$), 96.6 ($C^{10}$), 115.5 ($C^{8}$), 118.9 (d, $^{1}J_{CP}$ = 187 Hz, C^{2}), 119.1 (d, $^{3}J_{CP}$ = 15 Hz, C^{4}), 123.3 (C^{6}), 123.4 (2 x C^{13}), 128.5 (C^{5}), 132.5 (2 x C^{12}), 132.6 (C^{7}), 134.1 (C^{14}), 140.3 (d, $^{2}J_{CP}$= 6 Hz, C^{3}), 145.6 (d, $^{2}J_{CP}$ = 19 Hz, C^{1}), 153.4 (d, $^{4}J_{CP}$ = 1 Hz, C^{9}), 166.4 (2 x C^{11}). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 13.46. **MS (ESI, pos):** *m/z* 426.1/427.2 ($M + H^+$, 100/24). **Yield:** 6%, transparent liquid.

Both stereoisomers are described, but the stereochemistry of the double bond was not determined.

4.5.7. Procedure for the synthesis of β-hydroaminated products

In a typical experiment, 250 mg (0.78 mmol) alkyne **305** was dissolved in 3 mL THF in a 10 mL flask. 254 mg (0.78 mmol) Cs_2CO_3 and 57 mg (0.78 mmol) diethylamine were added at room temperature. Reaction progress was monitored via NMR spectroscopy. After completion of the reaction, the mixture was quenched with water, concentrated *in vacuo*, three times extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to give 283 mg (0.56 mmol) of the desired product. Dibenzylamine addition product **370c** required purification. As hydrolysis occurred during normal phase column chromatography, the mixture was purified via reversed phase column chromatography (5 CV 90/10 H_2O/CH_3CN, 20 CV 90/10 to 70/30 H_2O/CH_3CN, 10 CV 70/30 H_2O/CH_3CN). Only small amounts of product were obtained, which did not allow a full characterization.

diethyl (Z)-(2-(diethylamino)-3-(1,3-dioxoisoindolin-2-yl)prop-1-en-1-yl)phosphonate 370a

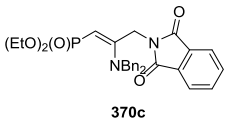


370a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99 (3H, t, J = 7.0 Hz, $N(CH_2C\underline{H}_3)_2$), 1.33 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 3.14 (4H, q, *J* = 7.0 Hz, $N(C\underline{H}_2CH_3)_2$), 4.03-4.21 (5H, m, $P(OC\underline{H}_2CH_3)_2$, PCH), 5.10 (2H, s, NCH_2), 7.68-7.73 (2H, m, CH_{ar}), 7.79-7.87 (2H, m, CH_{ar}). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 12.0 ($N(CH_2C\underline{H}_3)_2$), 16.3 (d, $^{3}J_{CP}$ = 7 Hz, $P(OCH_2\underline{C}H_3)_2$), 36.9 (d, $^{2}J_{CP}$ = 4 Hz, NCH_2), 43.2 ($N(C\underline{H}_2CH_3)_2$), 60.8 (d, $^{2}J_{CP}$ = 4 Hz, $P(O\underline{C}H_2CH_3)_2$), 80.2 (d, $^{1}J_{CP}$ = 211 Hz), 123.1 (2 x $C_{ar}H$), 134.0 (2 x $C_{ar}H$), 131.7 (2 x $C_{q,ar}$), 156.7 (d, $^{2}J_{CP}$ = 19 Hz, NC_q), 167.4 (2 x

N<u>C</u>(O)C_q). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 24.96. **MS (ESI, pos):** *m/z* 395.2/396.3 ($M + H^+$, 100/18). **Yield:** 72%, transparent liquid.

diethyl (Z)-(2-(dibenzylamino)-3-(1,3-dioxoisoindolin-2-yl)prop-1-en-1-yl)phosphonate 370c.



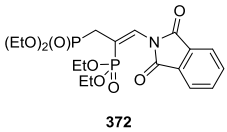
370c

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (6H, t, *J* = 7.1 Hz, P(OCH_2C<u>H</u>$_3$)$_2$), 4.48 (4H, s, *J* = 7.0 Hz, N(C<u>H</u>$_2$C$_{q,ar}$)$_2$), 3.96-4.12 (4H, m, P(OC<u>H</u>$_2$CH$_3$)$_2$), 4.25 (1H, d, *J* = 5 Hz, PCH), 5.33 (2H, d, *J* = 1.0 Hz, NCH_2), 6.96-7.07 (6H, CH_{ar}), 7.07-7.17 (4H, CH_{ar}), 7.53-7.63 (4H, m, CH_{ar}). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 23.68. **MS (ESI, pos):** *m/z* 519.2/520.3 ($M + H^+$, 100/31). **Yield:** 28%, white crystals.

4.5.8. Procedure for the synthesis of hydrophosphonylated products

In a typical experiment, 80 mg (0.25 mmol) alkyne **305** was dissolved in 1.0 mL THF in a 10 mL flask. 81 mg (0.25 mmol) Cs_2CO_3 and 35 mg (0.25 mmol) diethyl phosphite were added at room temperature. Reaction progress was monitored via NMR spectroscopy. After completion of the reaction, the mixture was quenched with water, concentrated *in vacuo*, three times extracted with ethyl acetate and dried over $MgSO_4$. The mixture was purified via pTLC (4/6 PE/EtOAc). Compounds **372** and **374** were obtained as a 38/62 mixture in a combined 18% yield and spectral data were easily extracted from the NMR spectra of the mixture of the two regioisomers.

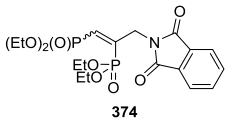
diethyl (Z)-(3-diethylphosphoryl-1-(1,3-dioxoisoindolin-2-yl) prop-1-en-2-yl)phosphonate 372



372

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08-1.34 (12H, m, 2 x P(OCH_2C<u>H</u>$_3$)$_2$), 2.75 (2H, ddd, $^2J_{HP}$ = 21.1 Hz, $^3J_{HP}$ = 3.7, Hz, $^4J_{HH}$ = 1.2 Hz, PCH_2), 3.87-4.25 (8H, m, 2 x P(OC<u>H</u>$_2$CH$_3$)$_2$), 6.38 (1H, ddd, $^3J_{HP}$ = 2.6 Hz, $^4J_{HP}$ = 1.4 Hz, $^4J_{HH}$ = 1.4 Hz, NCH), 7.53-7.68 (2H, m, CH_{ar}), 7.75-7.90 (2H, m CH_{ar}). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.1-16.8 (m, 2 x P(OCH_2C<u>H</u>$_3$)$_2$), 25.0 (d, $^1J_{CP}$ = 145 Hz, PCH_2), 62.5 (d, $^2J_{CP}$ = 4 Hz, P(O<u>C</u>H_2CH$_3$)), 62.6 (d, $^2J_{CP}$ = 4 Hz, P(O<u>C</u>H_2CH$_3$)), 64.7 (d, $^2J_{CP}$ = 7 Hz, P(O<u>C</u>H_2CH$_3$)), 64.9 (d, $^2J_{CP}$ = 4 Hz, P(O<u>C</u>H_2CH$_3$)), 99.8 (d, $^1J_{CP}$ = 208 Hz, PC_q), 107.8 (d, J_{CP} = 9 Hz, NCH), 125.3 (2 x <u>C</u>$_{ar}$H), 132.7 (d, J_{CP} = 3 Hz, 2 x <u>C</u>$_{q,ar}$), 133.8 (C_{ar}H),165.0 (d, J_{CP} = 6 Hz, N<u>C</u>(O)C_q), 166.6 (d, J_{CP} = 2 Hz, N<u>C</u>(O)C_q). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 11.06, 21.32. **MS (ESI, pos):** *m/z* 460.1/461.1 ($M + H^+$, 100/20).

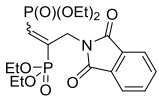
tetraethyl (3-(1,3-dioxoisoindolin-2-yl)prop-1-ene-1,2-diyl)bis(phosphonate) 374



374

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08-1.34 (12H, m, 2 x $P(OCH_2C\underline{H}_3)_2$), 3.87-4.25 (8H, m, 2 x $P(OC\underline{H}_2CH_3)_2$), 4.28 (1H, ddd, $^{2}J_{HH}$ = 15.9 Hz, $^{3}J_{HP}$ = 4.2, Hz, *J* = 1.4 Hz, $NC\underline{H}_aH_b$), 4.58 (1H, ddd, $^{2}J_{HP}$ = 7.5 Hz, *J* = 1.4 Hz, CHP), 4.65 (1H, ddd, $^{2}J_{HH}$ = 15.7 Hz, $^{3}J_{HP}$ = 3.0 Hz, $^{4}J_{HH}$ = 1.0 Hz, $NCH_a\underline{H}_b$), 7.53-7.68 (2H, m, CH_{ar}), 7.75-7.90 (2H, m CH_{ar}). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.1-16.8 (m, 2 x $P(OCH_2\underline{C}H_3)_2$), 48.1 (d, $^{2}J_{CP}$ = 17 Hz, NCH_aH_b), 61.6 (d, $^{2}J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)$), 61.7 (d, $^{2}J_{CP}$ = 6 Hz, $P(O\underline{C}H_2CH_3)$), 64.4 (d, $^{2}J_{CP}$ = 2 Hz, $P(O\underline{C}H_2CH_3)$), 64.5 (d, $^{2}J_{CP}$ = 2 Hz, $P(O\underline{C}H_2CH_3)$), 84.4 (d, $^{1}J_{CP}$ = 196 Hz, CHP), 125.0 ($C_{ar}H$), 125.4 ($C_{ar}H$), 131.8 ($C_{ar}H$), 131.7 (d, $^{4}J_{CP}$ = 4 Hz, $C_{q,ar}$), 133.6 ($C_{ar}H$), 140.7 (d, $^{4}J_{CP}$ = 9 Hz, $C_{q,ar}$), 144.0 (dd, $^{1}J_{CP}$ = 254 Hz, $^{2}J_{CP}$ = 9 Hz, PC_q), 166.4 (d, J_{CP} = 2 Hz, $N\underline{C}(O)C_q$). 172.9 (d, J_{CP} = 10 Hz, $N\underline{C}(O)C_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 11.66, 14.97. **MS (ESI, pos):** *m/z* 460.1/461.1 (M + H^+, 100/20).

diethyl (Z)-(2-(diethylamino)-3-(1,3-dioxoisoindolin-2-yl)prop-1-en-1-yl)phosphonate 373.



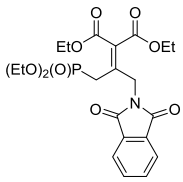
373

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (3H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)$), 1.28 (3H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)$), 1.30 (3H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)$), 1.33 (3H, t, *J* = 7.0 Hz, $P(OCH_2C\underline{H}_3)$), 3.93-4.30 (8H, m, 2 x $P(OC\underline{H}_2CH_3)_2$), 4.44 (1H, dt, $^{2}J_{HH}$ = 16.9 Hz, *J* = 2.6 Hz, $NC\underline{H}_aH_b$), 5.00 (1H, dt, *J* = 7.5 Hz, *J* = 1.8 Hz, CHP), 5.18 (1H, ddd, $^{2}J_{HH}$ = 17.0 Hz, *J* = 2.8 Hz, *J* = 1.6 Hz, $NCH_a\underline{H}_b$), 7.62-7.74 (2H, m, CH_{ar}), 7.84-7.90 (1H, m, CH_{ar}), 7.92-7.99 (1H, m, CH_{ar}). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.2-16.5 (m, 2x $P(OCH_2\underline{C}H_3)_2$), 47.5 ($NCH_2$), 43.2 ($N(C\underline{H}_2CH_3)_2$), 61.6 (d, J_{CP} = 5 Hz, $P(O\underline{C}H_2CH_3)$), 61.7 (d, J_{CP} = 5 Hz, $P(O\underline{C}H_2CH_3)$), 64.5 (d, $^{2}J_{CP}$ = 3 Hz, $P(O\underline{C}H_2CH_3)$), 64.6 (d, $^{2}J_{CP}$ = 3 Hz, $P(O\underline{C}H_2CH_3)$), 84.7 (d, $^{1}J_{CP}$ = 204 Hz), 98.0 (d, $^{1}J_{CP}$ = 208 Hz), 125.0 ($C_{ar}H$), 125.4 ($C_{ar}H$), 131.9 ($C_{ar}H$), 132.0 (d, $^{4}J_{CP}$ = 3 Hz, $C_{q,ar}$), 133.7 ($C_{ar}H$), 140.5 (d, $^{4}J_{CP}$ = 10 Hz, $C_{q,ar}$), 170.3 (d, $^{2}J_{CP}$ = 25 Hz, $N\underline{C}(O)C_q$), 172.8 ($N\underline{C}(O)C_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 12.25, 18.51. **MS (ESI, pos):** *m/z* 460.1/461.1 (M + H^+, 100/20). **Yield:** 12%, transparent liquid.

4.5.9 Procedure for the synthesis of malonate addition products

In a typical experiment, 160 mg (0.50 mmol) alkyne **305** was dissolved in 1.5 mL THF in a 10 mL flask. 163 mg (0.50 mmol) Cs_2CO_3 and 80 mg (0.50 mmol) diethyl malonate were added at room temperature. Reaction progress was monitored via NMR spectroscopy. After completion of the reaction, the mixture was quenched with water, concentrated *in vacuo*, three times extracted with ethyl acetate and dried over $MgSO_4$. The mixture was purified via pTLC (3/7 PE/EtOAc).

diethyl 2-(1-diethoxyphosphoryl)-3-(1,3-dioxoisoindolin-2-yl) propan-2-ylidene)malonate 378



378

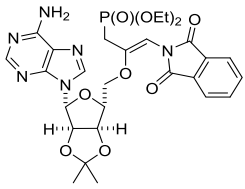
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23-1.40 (12H, m, 2 x C(O)$OCH_2C\underline{H}_3$, $P(OCH_2C\underline{H}_3)_2$), 3.39 (2H, d, $^2J_{HP}$ = 24.6 Hz, PCH_2), 4.01-4.19 (4H, m, $P(O\underline{C}H_2CH_3)_2$), 4.25 (2H, q, *J* = 7.1 Hz, C(O)$O\underline{C}H_2CH_3$), 4.31 (2H, q, *J* = 7.1 Hz, C(O)$O\underline{C}H_2CH_3$), 4.77 (2H, d, $^4J_{HP}$ = 2.5 Hz, NCH_2), 7.68-7.79 (2H, m, CH_{ar}), 7.81-7.92 (2H, m, CH_{ar}). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 13.94 (C(O)$OCH_2\underline{C}H_3$), 13.97 (C(O)$OCH_2\underline{C}H_3$), 16.3 (d, $^3J_{CP}$ = 6 Hz, $P(OCH_2\underline{C}H_3)_2$), 29.5 (d, $^2J_{CP}$ = 133 Hz, PCH_2), 39.9 (d, $^3J_{CP}$ = 1 Hz, NCH_2), 61.4 (C(O)$O\underline{C}H_2CH_3$), 61.7 (C(O)$O\underline{C}H_2CH_3$), 62.4 (d, $^2J_{CP}$ = 7 Hz, $P(O\underline{C}H_2CH_3)_2$), 123.6 (2 x $C_{ar}H$), 130.3 (d, $^3J_{CP}$ = 12 Hz, $\underline{C}_q$(C(O))$_2$), 132.0 ($C_{q,ar}$), 134.3 ($C_{ar}H$), 143.2 (d, $^2J_{CP}$ = 12 Hz, $PCH_2\underline{C}_q$), 164.2 (d, $^4J_{CP}$ = 4 Hz, $\underline{C}$(O)), 164.9 (d, $^4J_{CP}$ = 4 Hz, $\underline{C}$(O)), 167.9 (2 x N$\underline{C}$(O)C_q). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 23.36. **MS (ESI, pos):** *m/z* 482.3/4.83.3 ($M + H^+$, 100/23). **Yield:** 10%, transparent liquid.

4.6. Synthesis of diethyl nucleosides phosphonate prodrugs

4.6.1. Preparation of acetonide-protected nucleoside phosphonates

In a typical experiment, 321 mg (1.00 mmol) alkyne **305** was dissolved in 8 mL THF in a 25 mL flask. 326 mg (1.00 mmol) Cs_2CO_3 and 323 mg (1.00 mmol) acetonide-protected nucleoside were added. The reaction progress was monitored via NMR spectroscopy. After completion of the reaction, the mixture was quenched with water, concentrated *in vacuo*, three times extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. Adenosine derivative **398** was purified via normal phase column chromatography. Guanosine derivatives **400** and **407** were purified via preparative LC.

diethyl ((*Z*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 398



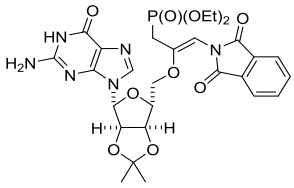
398

^{1}H NMR (400 MHz, CD_3OD) δ: 1.32 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 1.40 (3H, s, $C_qC\underline{H}_3$), 1.60 (3H, s, $C_qC\underline{H}_3$), 3.46 (2H, d, $^2J_{HP}$ = 20.9 Hz, PCH_2), 4.08-4.23 (4H, m, $P(O\underline{C}H_2CH_3)_2$), 4.40-4.62 (3H, m, $OC\underline{H}CH_2$, $OC\underline{H}_2CH$), 4.99 (1H, dd, *J* = 6.2 Hz, *J* = 2.6 Hz, NCHC$\underline{H}$O or $OCH_2CHC\underline{H}$O), 5.45 (1H, dd, *J* = 6.2 Hz, *J* = 2.1 Hz, NCHC$\underline{H}$O or $OCH_2CHC\underline{H}$O), 6.15 (1H, d, *J* = 2.1 Hz, NC$\underline{H}$O),

7.08 (1H, d, $^4J_{HP}$ = 4.0 Hz, NC<u>H</u>), 7.54-7.69 (3H, m, C<u>H</u>$_{ar}$), 7.77-7.82 (1H, m, CH$_{ar}$), 8.12 (1H, s, C<u>H</u>$_{ar}$), 8.13 (1H, s, C<u>H</u>$_{ar}$). **^{13}C NMR (100 MHz, CD$_3$OD) δ:** 16.7 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.3 (d, $^1J_{CP}$ = 144 Hz, P<u>C</u>H$_2$), 25.6 (C$_q$<u>C</u>H$_3$), 27.4 (C$_q$<u>C</u>H$_3$), 64.2 (d, $^2J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 66.4 (O<u>C</u>H$_2$CH), 83.0 (NCH<u>C</u>HO or OCH$_2$CH<u>C</u>HO), 85.4 (NCH<u>C</u>HO or OCH$_2$CH<u>C</u>HO), 86.0 (OC<u>H</u>CH$_2$), 92.5 (N<u>C</u>HO),115.3 (<u>C</u>$_q$(CH$_3$)$_2$), 120.5 (<u>C</u>$_{q,ar}$), 127.20 (<u>C</u>$_{q,ar}$), 127.22 (d, $^3J_{CP}$ = 9 Hz, N<u>C</u>H), 130.25 (<u>C</u>$_{ar}$H), 130.34 (<u>C</u>$_{ar}$H), 131.6 (<u>C</u>$_{ar}$H), 132.4 (C$_{q,ar}$), 132.6 (<u>C</u>$_{ar}$H), 141.2 ((N)<u>C</u>HNCHO), 146.2 (d, $^2J_{CP}$ = 10 Hz, O<u>C</u>$_q$), 150.1 (C$_{q,ar}$), 153.9 (N<u>C</u>HNC$_{q,ar}$N), 157.2 (C$_{q,ar}$), 161.8 (d, $^5J_{CP}$ = 3 Hz, N<u>C</u>(O)C$_q$), 168.7 (N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, CD$_3$OD) δ:** 26.67. **MS (ESI, pos):** *m/z* 629.2/630.3 (M + H$^+$, 100/30). **R$_f$**: 0.18 (9/1 EtOAc/MeOH). **Yield:** 35%, white foam.

diethyl ((*Z*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(2-amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 400

Due to low amounts of product, not all signals could be observed and assigned.

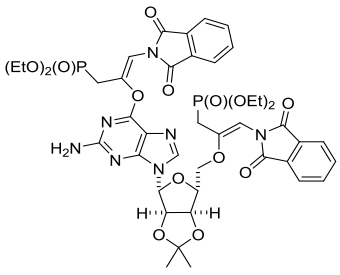


400

^{1}H NMR (400 MHz, CD$_3$OD) δ: 1.30 (3H, t, *J* = 7.0 Hz, P(OCH$_2$C<u>H</u>$_3$)), 1.31 (3H, t, *J* = 7.0 Hz, P(OCH$_2$C<u>H</u>$_3$)), 1.37 (3H, s, C$_q$C<u>H</u>$_3$), 1.56 (3H, s, C$_q$C<u>H</u>$_3$), 3.44 (2H, d, $^2J_{HP}$ = 20.9 Hz, PCH$_2$), 4.07-4.20 (4H, m, P(OC<u>H</u>$_2$CH$_3$)$_2$), 4.35-4.48 (2H, m), 4.55-4.64 (1H, m), 5.00 (1H, dd, *J* = 6.1 Hz, *J* = 3.0 Hz), 5.33 (1H, dd, *J* = 6.1 Hz, *J* = 1.4 Hz), 5.98 (1H, d, *J* = 1.4 Hz, NC<u>H</u>O), 7.08 (1H, d, $^4J_{HP}$ = 4.0 Hz, NCH), 7.53-7.69 (3H, m, CH$_{ar}$), 7.74 (1H, s, C<u>H</u>$_{ar}$), 7.77-7.84 (1H, m, CH$_{ar}$). **^{13}C NMR (100 MHz, CD$_3$OD) δ:** 16.7 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.3 (d, $^1J_{CP}$ = 144 Hz, P<u>C</u>H$_2$), 25.7 (C$_q$<u>C</u>H$_3$), 27.5 (C$_q$<u>C</u>H$_3$), 64.2 (d, $^2J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 66.6 (O<u>C</u>H$_2$CH), 83.1 (NCH<u>C</u>HO or OCH$_2$CH<u>C</u>HO), 85.5 (NCH<u>C</u>HO or OCH$_2$CH<u>C</u>HO), 86.2 (OC<u>H</u>CH$_2$), 92.1 (N<u>C</u>HO), 115.1 (<u>C</u>$_q$(CH$_3$)$_2$), 118.2 (<u>C</u>$_{q,ar}$), 127.15 (N<u>C</u>H), 127.23 (<u>C</u>$_{q,ar}$), 130.3 (<u>C</u>$_{ar}$H), 130.5 (<u>C</u>$_{ar}$H), 131.7 (<u>C</u>$_{ar}$H), 132.4 (<u>C</u>$_{q,ar}$), 132.6 (<u>C</u>$_{ar}$H), 146.2 (d, $^2J_{CP}$ = 10 Hz, O<u>C</u>$_q$), 152.2 (C$_{q,ar}$), 155.3 (C$_{q,ar}$), 159.5 (C$_q$), 161.2 (d, $^5J_{CP}$ = 3 Hz, N<u>C</u>(O)C$_q$), 168.8 (N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, CD$_3$OD) δ:** 22.80. **MS (ESI, pos):** *m/z* 645.2/646.3 (M + H$^+$, 100/29). **Yield:** 5%, white foam.

diethyl ((*Z*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(2-amino-6-(((*Z*)-3-(diethoxyphosphoryl)-1-(1,3-dioxoisoindolin-2-yl)prop-1-en-2-yl)oxy)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 407

Due to low amounts of product, no ^{13}C NMR data could be collected.



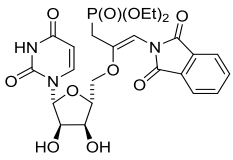
407

^{1}H NMR (400 MHz, CD_3OD) δ: 1.24-1.34 (12H, m, 2 x $P(OCH_2C\underline{H}_3)_2$), 1.36 (3H, s, $C_qC\underline{H}_3$), 1.56 (3H, s, $C_qC\underline{H}_3$), 3.46 (2H, d, $^{2}J_{HP}$ = 20.9 Hz, PCH_2), 3.47 (2H, d, $^{2}J_{HP}$ = 20.9 Hz, PCH_2), 4.01-4.24 (8H, m, $P(OC\underline{H}_2CH_3)_2$), 4.30-4.41 (1H, m), 4.46.-4.62 (2H, m), 4.91-4.99 (1H, m), 5.37 (1H, d, *J* = 6.1 Hz), 5.98 (1H, br. s, NC$\underline{H}$O), 7.09 (1H, d, $^{4}J_{HP}$ = 3.9 Hz, NCH), 7.13 (1H, d, $^{4}J_{HP}$ = 4.0 Hz, NCH), 7.54-7.81 (7H, m, CH_{ar}), 8.00 (1H, s, C$\underline{H}_{ar}$), 8.03-8.11 (1H, m, CH_{ar}). **^{31}P NMR (161 MHz, CD_3OD) δ:** 22.64. **MS (ESI, pos):** *m/z* 966.3/967.4 (M + H^+, 100/45). **Yield:** 2%, white foam.

4.6.2. Preparation of acetonide-deprotected nucleoside phosphonates

In a typical experiment, 36 mg (0.06 mmol) addition product **351** was dissolved in 3 mL of a 1/1 THF/H_2O mixture in a 10 mL flask. 14 mg (0.07 mmol) *p*TsOH·H_2O was added before the mixture was refluxed. The reaction progress was monitored via NMR spectroscopy. After completion of the reaction, the mixture was washed with 2 mL of a saturated $NaHCO_3$ solution. The aqueous phase was extracted three times with 5 mL CH_2Cl_2, dried over $MgSO_4$ and concentrated under reduced pressure to afford 17 mg (0.03 mmol) of the deprotected nucleoside phosphonate.

diethyl ((*Z*)-2-(((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 401

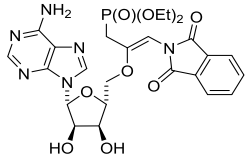


401

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (3H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 1.22 (3H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 3.41 (2H, d, $^{2}J_{HP}$ = 20.9 Hz, PCH_2), 3.88-3.98 (2H, m, $OCH_2CHC\underline{H}O$, $NCHC\underline{H}O$), 3.98-4.11 (5H, m, $P(OC\underline{H}_2CH_3)_2$, $OC\underline{H}CH_2$), 4.41-4.52 (2H, m, $OC\underline{H}_2CH$), 5.18 (1H, dd, $^{3}J_{HH}$ = 8.1 Hz, C$\underline{H}$C(O)), 5.70 (1H, d, *J* = 3.6 Hz, NC$\underline{H}$O), 7.03 (1H, d, $^{4}J_{HP}$ = 4.0 Hz, NC$\underline{H}$), 7.39 (1H, d, $^{3}J_{HH}$ = 8.1 Hz, C$\underline{H}$CHC(O)), 7.52-7.65 (2H, m, C$\underline{H}_{ar}$), 7.66-7.77 (1H, m, CH_{ar}), 7.91 (1H, m, C$\underline{H}_{ar}$). **^{13}C NMR (100 MHz,**

$CDCl_3$) δ: 16.7 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.3 (d, $^1J_{CP}$ = 145 Hz, P<u>C</u>H$_2$), 64.3 (d, $^2J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 65.7 (O<u>C</u>H$_2$CH), 71.2 (OCH$_2$<u>C</u>HCHO), 75.3 (NCH<u>C</u>HO), 82.8 (O<u>C</u>HCH$_2$), 91.6 (N<u>C</u>HO), 102.5 (<u>C</u>HC(O)) 127.3 (<u>C</u>$_{q,ar}$), 127.4 (d, $^3J_{CP}$ = 8 Hz, N<u>C</u>H), 130.32 (<u>C</u>$_{ar}$H), 130.34 (<u>C</u>$_{ar}$H), 131.9 (<u>C</u>$_{ar}$H), 132.7 (<u>C</u>$_{ar}$H), 132.9 (C$_{q,ar}$), 141.9 (<u>C</u>HCHC(O)), 146.4 (d, $^2J_{CP}$ = 10 Hz, O<u>C</u>$_q$), 150.1 (N<u>C</u>ONH), 161.6 (d, $^5J_{CP}$ = 3 Hz, N<u>C</u>(O)C$_q$), 165.9 (CH<u>C</u>(O)), 169.0 (N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 22.83. **MS (ESI, pos):** *m/z* 566.1/567.2 (M + H$^+$, 100/25). **Yield:** 50%, white foam.

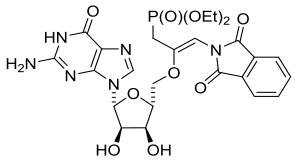
diethyl ((*Z*)-2-(((2*R*,3*S*,4*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 402



402

^{1}H NMR (400 MHz, CD_3OD) δ: 1.20-1.36 (6H, m, P(OCH$_2$C<u>H</u>$_3$)$_2$), 3.43 (2H, d, $^2J_{HP}$ = 20.9 Hz, PCH$_2$), 4.04-4.19 (4H, m, P(OC<u>H</u>$_2$CH$_3$)$_2$), 4.25-4.32 (1H, m, OC<u>H</u>CH$_2$ or NCHC<u>H</u>O or OCH$_2$CHC<u>H</u>O), 4.39 (1H, t, *J* = 5.2 Hz, OC<u>H</u>CH$_2$ or NCHC<u>H</u>O or OCH$_2$CHC<u>H</u>O), 4.45 (1H, dd, J_{AB} = 12.2 Hz, *J* = 3.8 Hz, OC<u>H</u>$_A$H$_B$CH), 4.63 (1H, dd, J_{AB} = 12.2 Hz, *J* = 3.8 Hz, OCH$_A$<u>H</u>$_B$CH), 4.67 (1H, t, *J* = 4.8 Hz, OC<u>H</u>CH$_2$ or NCHC<u>H</u>O or OCH$_2$CHC<u>H</u>O), 6.00 (1H, d, *J* = 4.2 Hz, NC<u>H</u>O), 7.07 (1H, d, $^4J_{HP}$ = 3.9 Hz, NC<u>H</u>), 7.54-7.75 (3H, m, C<u>H</u>$_{ar}$), 7.80-7.89 (1H, m, CH$_{ar}$), 8.08 (1H, s, C<u>H</u>$_{ar}$), 8.12 (1H, s, C<u>H</u>$_{ar}$). **^{13}C NMR (100 MHz, CD_3OD) δ:** 16.6 (d, $^3J_{CP}$ = 6 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.3 (d, $^1J_{CP}$ = 144 Hz, P<u>C</u>H$_2$), 64.2 (d, $^2J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 66.0 (O<u>C</u>H$_A$H$_B$CH), 71.8 (O<u>C</u>HCH$_2$ or NCH<u>C</u>HO or OCH$_2$CH<u>C</u>HO), 75.2 (O<u>C</u>HCH$_2$ or NCH<u>C</u>HO or OCH$_2$CH<u>C</u>HO), 83.3 (O<u>C</u>HCH$_2$ or NCH<u>C</u>HO or OCH$_2$CH<u>C</u>HO), 90.4 (N<u>C</u>HO), 120.4 (<u>C</u>$_{q,ar}$), 127.2 (d, $^3J_{CP}$ = 8 Hz, N<u>C</u>H), 127.4 (<u>C</u>$_{q,ar}$), 130.38 (<u>C</u>$_{ar}$H), 130.40 (<u>C</u>$_{ar}$H), 131.7 (<u>C</u>$_{ar}$H), 132.7 (<u>C</u>$_{ar}$H), 132.7 (C$_{q,ar}$), 140.3 ((N)<u>C</u>HNCHO), 146.1 (d, $^2J_{CP}$ = 10 Hz, O<u>C</u>$_q$), 150.5 (C$_{q,ar}$), 153.9 (N<u>C</u>HNC$_{q,ar}$N), 157.2 (C$_{q,ar}$), 161.7 (d, $^5J_{CP}$ = 2 Hz, N<u>C</u>(O)C$_q$), 169.0 (N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, CD_3OD) δ:** 22.83. **MS (ESI, pos):** *m/z* 589.2/590.3 (M + H$^+$, 100/26). **Yield:** 80%, white foam.

diethyl ((Z)-2-(((2R,3S,4R,5R)-5-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 404

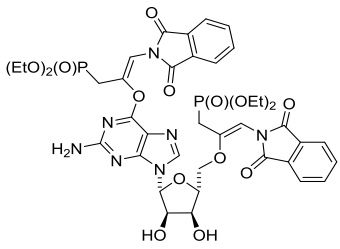


404

^{1}H NMR (400 MHz, CD_3OD) δ: 1.30 (3H, t, *J* = 7.1 Hz, P(OCH$_2$C<u>H</u>$_3$)), 1.31 (3H, t, *J* = 7.2 Hz, P(OCH$_2$C<u>H</u>$_3$)), 3.44 (2H, d, $^{2}J_{HP}$ = 20.9 Hz, PCH$_2$), 4.07-4.18 (4H, m, P(OC<u>H</u>$_2$CH$_3$)$_2$), 4.18-4.25 (1H, m, OC<u>H</u>CH$_2$), 4.37 (1H, t, *J* = 5.4 Hz, OCH$_2$CHC<u>H</u>O or NCHC<u>H</u>O), 4.47-4.69 (3H, m, OC<u>H</u>$_2$CH + OCH$_2$CHC<u>H</u>O or NCHC<u>H</u>O), 5.82 (1H, d, *J* = 4.4 Hz, NCHO), 7.08 (1H, d, $^{4}J_{HP}$ = 4.0 Hz, NCH), 7.56-7.76 (4H, m, CH$_{ar}$), 7.81-7.87 (1H, m, CH$_{ar}$). **^{13}C NMR (100 MHz, CD_3OD) δ:** 16.7 (d, $^{3}J_{CP}$ = 6 Hz, P(OCH$_2$<u>C</u>H$_3$)$_2$), 24.3 (d, $^{1}J_{CP}$ = 144 Hz, P<u>C</u>H$_2$), 64.3 (d, $^{2}J_{CP}$ = 7 Hz, P(O<u>C</u>H$_2$CH$_3$)$_2$), 66.3 (O<u>C</u>H$_2$CH), 72.0 (NCH<u>C</u>HO or OCH$_2$CH<u>C</u>HO), 75.1 (NCH<u>C</u>HO or OCH$_2$CH<u>C</u>HO), 83.2 (OC<u>H</u>CH$_2$), 90.2 (N<u>C</u>HO), 118.1 (<u>C</u>$_{q,ar}$), 127.2 (N<u>C</u>H), 127.3 (<u>C</u>$_{q,ar}$), 130.46 (<u>C</u>$_{ar}$H), 130.48 (<u>C</u>$_{ar}$H), 131.8 (<u>C</u>$_{ar}$H), 132.72 (<u>C</u>$_{ar}$H), 132.74 (<u>C</u>$_{q,ar}$), 138.0 (C$_{ar}$H), 146.2 (d, $^{2}J_{CP}$ = 10 Hz, O<u>C</u>$_q$), 152.9 (C$_{q,ar}$), 155.2 (C$_{q,ar}$), 159.3 (NC$_q$(O)), 161.8 (d, $^{5}J_{CP}$ = 3 Hz, N<u>C</u>(O)C$_q$), 169.1 (N<u>C</u>(O)C$_q$). **^{31}P NMR (161 MHz, CD_3OD) δ:** 22.88. **MS (ESI, pos):** *m/z* 605.2/606.3 (M + H$^+$, 100/27). **Yield:** 87%, white foam.

diethyl ((Z)-2-(((2R,3S,4R,5R)-5-(2-amino-6-(((Z)-3-(diethoxyphosphoryl)-1-(1,3-dioxoisoindolin-2-yl)prop-1-en-2-yl)oxy)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)-3-(1,3-dioxoisoindolin-2-yl)allyl)phosphonate 408

Due to low amounts of product, no ^{13}C NMR data could be collected.



408

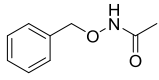
^{1}H NMR (400 MHz, CD_3OD) δ: 1.22-1.35 (12H, m, 2 x P(OCH$_2$C<u>H</u>$_3$)$_2$), 3.43 (2H, d, $^{2}J_{HP}$ = 20.9 Hz, PCH$_2$), 3.45 (2H, d, $^{2}J_{HP}$ = 21.1, Hz, PCH$_2$), 4.02-4.16 (8H, m, P(OC<u>H</u>$_2$CH$_3$)$_2$), 4.17-4.23 (1H, m), 4.30-4.35 (1H, m), 4.44-4.61 (3H, m), 5.89 (1H, d, *J* = 4.4 Hz, NC<u>H</u>O), 7.04 (1H, d, $^{4}J_{HP}$ = 4.2 Hz, NCH), 7.10 (1H, d, $^{4}J_{HP}$ = 4.2 Hz, NCH), 7.56-7.74 (6H, m, CH$_{ar}$), 7.78-7.88 (2H, m, CH$_{ar}$), 7.96 (1H, s, C<u>H</u>$_{ar}$), 8.02-8.09 (1H, m, CH$_{ar}$). **^{31}P NMR (161 MHz, CD_3OD) δ:** 22.69, 22.82. **MS (ESI, pos):** *m/z* 926.3/927.4 (M + H$^+$, 100/42). **Yield:** 70%, white foam.

4.7. Synthetic entry into fosmidomycin-inspired antimalarial analogues

*4.7.1. Procedure for the synthesis of N-(benzyloxy)acetamide **37***

N-(benzyloxy)acetamide was prepared according to a literature procedure.[365] The desired compound was obtained as a mixture of rotamers (major rotamer depicted as M, minor rotamer depicted as m). Spectral data were in accordance with literature values.

***N*-(benzyloxy)acetamide 37**



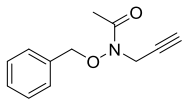
37

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.72-1.97 (3H, br. s, CH_3, M), 1.97-2.22 (3H, br. s, CH_3, m), 4.63-4.87 (2H, br. s, CH_2, m), 4.87-5.02 (2H, s, CH_2, M), 7.30-7.48 (5H, br. s, CH_{ar}), 7.65-7.91 (1H, br. s, NH, m), 7.91-8.14 (1H, br. s, NH, M) **MS (ESI, pos):** *m/z* 166.1/167.2 ($M + H^+$, 100/9). **R_f**: 0.25 (1/1 PE/EtOAc) **Yield:** 82%, yellow oil.

*4.7.2. Procedure for the alkylation of N-(benzyloxy)acetamide N-(benzyloxy)-N-(prop-2-yn-1-yl)acetamide **37***

In a typical experiment, 2.607 g *N*-benzyloxyacetamide **37** (15.8 mmol) is dissolved in 25 ml acetone in a 50 ml round-bottom flask. To this solution, 2.184 g K_2CO_3 (15.8 mmol, 1.0 equiv) and 2.1 mL (18.9 mmol) of a 80% propargyl bromide solution in toluene was added. The mixture is refluxed until the starting material disappears according to TLC analysis. The solvent is removed *in vacuo* and the crude mixture is purified on column. *N*-(benzyloxy)-*N*-(prop-2-yn-1-yl)acetamide is isolated in 75% yield.

***N*-(benzyloxy)acetamide *N*-(benzyloxy)-*N*-(prop-2-yn-1-yl)acetamide 410**

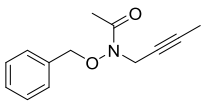


410

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (3H, s, CH_3), 2.27 (1H, t, *J* = 2.5 Hz, C_qCH), 4.38 (2H, d, *J* = 2.4 Hz, NCH_2), 5.00 (2H, s, CH_2O), 7.35-7.51 (5H, m, CH_{ar}). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 20.6 (CH_3), 36.7 (NCH_2), 72.1 (C_qCH), 77.6 ($C_{q,ar}CH_2O$), 78.2 (C_qCH), 128.7 (CH_{ar}), 129.1 (CH_{ar}), 129.4 (CH_{ar}), 134.4 ($C_{q,ar}$), 173.4 (C(O)) **MS (ESI, pos):** *m/z* 204.1/205.2 ($M + H^+$, 100/15) **HRMS:** *m/z* calcd for $C_{12}H_{13}NO_2$ $(M + H)^+$ 204.0946, found 204.1026. **IR (cm^{-1}) ν_{max}:** 1666 (C=O) **R_f**: 0.18 (9/1 PE/EtOAc) **Yield:** 75%, yellow oil.

***N*-(benzyloxy)-*N*-(but-2-yn-1-yl)acetamide 423.**

The desired compound was obtained as a mixture of rotamers (major rotamer depicted as M, minor rotamer depicted as m).



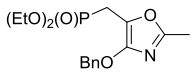
423

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.83 (3H, t, *J* = 2.4 Hz, C_qCH_3, M), 1.86 (3H, t, *J* = 2.4 Hz, C_qCH_3, m), 1.97 (3H, s, $C(O)CH_3$, m), 2.08 (3H, s, $C(O)CH_3$, M), 4.34 (2H, m, NCH_2, M), 4.56 (2H, q, *J* = 2.4 Hz, NCH_2, m), 4.94 (2H, s, $C_{q,ar}CH_2$, m), 4.98 (2H, s, $C_{q,ar}CH_2$, M), 7.29-7.48 (5H, m, CH_{ar}). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 0.02 ($C_qC_q\underline{C}H_3$, m), 3.7 ($C_qC_q\underline{C}H_3$, M), 13.6 ($C(O)\underline{C}H_3$, m), 20.6 ($C(O)\underline{C}H_3$, M), 37.0 (NCH_2, M), 55.0 (NCH_2, m), 73.3 ($\underline{C}_qC_qCH_3$ of $C_q\underline{C}_qCH_3$), 75.8 ($C_{q,ar}\underline{C}H_2O$, m), 77.5 ($C_{q,ar}\underline{C}H_2O$, M), 79.7 ($\underline{C}_qC_qCH_3$ of $C_q\underline{C}_qCH_3$), 127.7 (CH_{ar}, m), 128.26 (CH_{ar}, m), 128.35 (CH_{ar}, m), 128.7 (CH_{ar}, M), 129.0 (CH_{ar}, M), 129.4 (CH_{ar}, M), 134.5 ($C_{q,ar}$), 173.2 (C(O)) **MS (ESI, pos):** *m/z* 218.1/219.2 (M + H^+, 100/15) **IR (cm^{-1}) ν_{max}:** 1672 (C=O) 2000-2300 (C≡C) **R_f**: 0.16 (9/1 PE/EtOAc) **Yield**: 27%, white solid.

*4.7.2. Procedure for the preparation of oxazole **416a***

A 10 mL round-bottom flask was flame dried under inert atmosphere and shielded from moisture, using a $CaCl_2$-tube. After dissolving 339 mg (1.0 mmol) dibenzyl (3-(*N*-(benzyloxy)acetamido)prop-1-yn-1-yl)phosphonate **412a** in 5 mL THF, 326 mg Cs_2CO_3 (1.0 mmol) was added and stirred at room temperature. Reaction progress was followed by NMR spectroscopy and after complete consumption of the starting material, the mixture was quenched with 2 mL H_2O. The mixture is diluted in 30 mL EtOAc en washed three times with 5 mL H_2O. After drying over $MgSO_4$ and filtration, the filtrate is concentrated under reduced pressure. Purification on column finally yields the desired product.

diethyl ((4-(benzyloxy)-2-methyloxazol-5-yl)methyl)phosphonate 416a



416a

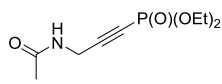
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (6H, t, *J* = 7.1 Hz, $(\underline{C}H_3CH_2O)_2P$), 2.38 (3H, d, *J* = 2.1 Hz, $C_qC\underline{H}_3$), 3.10 (2H, d, J_{HP} = 19.6 Hz, $C\underline{H}_2P$), 4.08 (4H, m, *J* = 7.3 Hz, $(CH_3C\underline{H}_2O)_2P$), 5.17 (2H, s, $C\underline{H}_2C_{q,ar}$), 7.26-7.43 (5H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 14.5 (d, J_{CP} = 1 Hz, $C_q\underline{C}H_3$), 16.3 (d, J_{CP} = 6 Hz, $\underline{C}H_3CH_2O$), 22.4 (d, J_{CP} = 146 Hz, CH_2P), 62.3 (d, J_{CP}=7 Hz, $\underline{C}H_2OP$), 72.2 ($\underline{C}H_2C_{ar}$), 122.9 (d, J_{CP} = 14 Hz, $PCH_2\underline{C}_q$), 127.9 (CH_{ar}), 128.1 (CH_{ar}), 128.4 (CH_{ar}), 136.9 ($C_{q,ar}$), 150.4 (d, J_{CP} = 10 Hz, $OC_{q,ar}\underline{C}_{q,ar}N$), 157.4 (d, J_{CP} = 3.6 Hz , $O\underline{C}_{ar,q}(CH_3)N$) **^{31}P NMR (121 MHz, $CDCl_3$) δ:** 22.48. **MS (ESI, pos):** *m/z* 340.1/341.2 (M + H^+, 100/18) **HRMS:** *m/z* calcd for $C_{16}H_{22}NO_5P$ (M + H)$^+$

340.1236, found 340.1298. **IR (cm^{-1}) ν_{max}:** 966 (P-O), 1022 (P=O) **R_f**: 0.10 (2/8 PE/EtOAc) **Yield:** 22%, brownish oil.

*4.7.3. Preparation of amide intermediate **422***

Diethyl (3-aminoprop-1-yn-1-yl)phosphonate hydrochloride was prepared according to a literature procedure. Spectral data were in accordance with literature values.[376] A 10 mL round-bottom flask, equipped with a Claisen piece, is flame dried under inert atmosphere. Next, 455 mg (2.0 mmol) of the diethyl (3-aminoprop-1-yn-1-yl)phosphonate hydrochloride and 0.56 mL (4.0 mmol) NEt_3 are dissolved in 10 mL CH_2Cl_2 at room temperature. After 15 minutes, the mixture is cooled to 0 °C and 0.14 mL (2.0 mmol) AcCl is added dropwise. The mixture is allowed to warm to room temperature and reaction progress is followed by TLC analysis. After complete consumption of the starting material, 1 mL H_2O is added and the mixture is diluted in 25 mL EtOAc. The organic layer is washed five times with 3 mL of a saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated under reduced pressure. Purification on column finally yielded the desired product.

diethyl (3-acetamidoprop-1-yn-1-yl)phosphonate 422



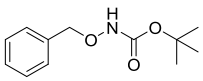
422

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 (6H, t, *J* = 7.1 Hz, ($C\underline{H}_3CH_2O)_2P$), 2.02 (3H, s, CH_3), 4.09-4.29 (6H, m, $NC\underline{H}_2$ and ($CH_3C\underline{H}_2O)_2P$), 7.02-7.26 (1H, br. s, NH) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.0 (d, J_{CP}=7 Hz, $\underline{C}H_3CH_2OP$), 22.8 (CH_3), 29.2 (d, J_{CP} = 4 Hz, NCH_2), 63.5 (d, J_{CP} = 6 Hz, $CH_3\underline{C}H_2OP$), 72.1 (d, J_{CP} = 297 Hz, $C_q\underline{C}_qP$), 97.7 (d, J_{CP}=51 Hz, $\underline{C}_qC_qP$), 170.2 (C(O)) **^{31}P NMR (121 MHz, $CDCl_3$) δ:** -7.41. **MS (ESI, pos):** *m/z* 234.1/235.2 ($M + H^+$, 100/11) **IR (cm^{-1}) ν_{max}:** 1258 (P-O), 1660 (C=O), 2210 (C≡C), 3275 (NH) **R_f**: 0.27 (9/1 EtOAc/MeOH) **Yield:** 50%, yellowish oil.

4.7.4. Preparation of Boc-protected hydroxamic acids

***tert*-butyl (benzyloxy)carbamate 426**

Tert-butyl (benzyloxy)carbamate **426** was prepared according to a literature procedure. Spectral data are in accordance with literature values.[378]

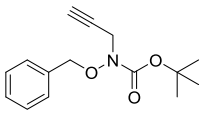


426

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (9H, s, $C_q(CH_3)_3$), 4.86 (2H, s, CH_2), 7.01-7.13 (1H, br. s, NH), 7.28-7.47 (5H, m, CH_{ar}) **Yield:** 69%, yellow oil.

***tert*-butyl (benzyloxy)(prop-2-yn-1-yl)carbamate 427**

Tert-butyl (benzyloxy)(prop-2-yn-1-yl)carbamate was prepared according to a literature procedure. Spectral data were in accordance with literature values.[379]



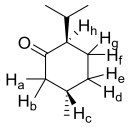
427

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (9H, s, $C_q(CH_3)_3$), 2.24 (1H, t, *J* = 2.4 Hz, C_qCH), 4.13 (2H, d, *J* = 2.4 Hz, NCH_2), 4.90-4.98 (2H, br. s, $CH_2C_{q,ar}$), 7.28-7.48 (5H, m, CH_{ar}) **R_f**: 0.26 (95/5 PE/EtOAc) **Yield:** 78%, yellow oil.

4.8. Synthetic entry into chiral spirocyclic oxaphospholenes

4.8.1. Procedure for the synthesis of (+)-menthone

A three-necked flask, equipped with a dropping funnel was charged with 2.970 g (7.0 mmol) Dess-Martin periodinane, dissolved in 30 mL dry dichloromethane.[380] Next, a solution of (+)-menthol (0.780 g, 5.0 mmol) in 20 mL dry dichloromethane was added dropwise over fifteen minutes at room temperature. After one hour the reaction was completed as indicated by GC-MS analysis and was poured into 80 mL of a 1M $NaOH_{(aq.)}$ solution. 100 mL diethylether was added and the organic phase separated. The aqueous phase was extracted with 100 mL diethylether. After combination of both organic phases, they were washed twice with 50 mL water, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 770 mg (5.0 mmol) (+)-menthone as a yellowish oil. No purification was needed and the (+)-menthone could be used as such in the next step. Spectral properties were in accordance with literature values.[381]



^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85 (3H, d, *J* = 6.6 Hz, $CH(C\underline{H}_3)(CH_3)$), 0.91 (3H, d, *J* = 6.8 Hz, $CH(CH_3)(C\underline{H}_3)$), 1.00 (3H, d, *J* = 6.3 Hz, $CHC\underline{H}_3$), 1.30-1.46 (2H, m, $C\underline{H}_dH_e$, $C\underline{H}_fH_g$), 1.77-2.21 (6H, m, $C\underline{H}_aH_b$, $C\underline{H}_c$, $CH_d\underline{H}_e$, $CH_f\underline{H}_g$, $C\underline{H}_h$, $C\underline{H}(CH_3)_2$), 2.35 (1H, ddd, *J* = 12.9 Hz, *J* = 4.0 Hz, *J* = 2.3 Hz, $CH_a\underline{H}_b$) Yield: 100% (770 mg), yellowish oil.

4.8.2. Procedure for the preparation of propargylic alcohols

*Method A: representative example **257a***

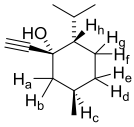
30 mL commercially available ethynylmagnesium bromide solution (0.26 M in THF, 7.8 mmol) was added to 1 mL THF in a 50 mL round-bottom flask, before the addition of 1.04 mL *L*-menthone (6.0 mmol). The reaction was allowed to proceed at room temperature. After

complete consumption of the starting material, as indicated by GC-MS analysis, the reaction was quenched with water after which the reaction mixture was extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and eventually the solvent was removed under reduced pressure. The two diastereoisomers could be chromatographically separated.

Method B: representative example ***257e***

A round-bottom flask was charged with 20 mL THF and cooled to -84 °C, before 1.72 mL 1-hexyne (15.0 mmol) was introduced. Next, 11.2 ml of *n*-BuLi (16 mmol, 1.43 M in hexanes) was added dropwise. The mixture was allowed to warm to room temperature while stirring for 15 minutes. After the addition of *L*-menthone at - 84 °C, the mixture was allowed warm to room temperature again and reaction progress was monitored by GC-MS analysis. After completion of the reaction, the reaction was quenched with water after which the mixture was extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and eventually the solvent was removed under reduced pressure. The two diastereoisomers could be chromatographically separated.

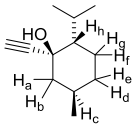
(1S,2S,5R)-1-ethynyl-2-isopropyl-5-methylcyclohexan-1-ol 257a



257a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84-0.97 (1H, m, C$\underline{H}_d$H$_e$), 0.88 (3H, d, *J* = 6.3 Hz, CHC$\underline{H}_3$), 0.94 (3H, d, *J* = 7.1 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 0.97 (3H, d, *J* = 7.1 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 1.26-1.55 (4H, m, C$\underline{H}_a$H$_b$, C$\underline{H}_f$H$_g$, C$\underline{H}_h$), 1.59 (1H, br. s, OH), 1.66-1.83 (2H, m, C$\underline{H}_c$, CH$_d$$\underline{H}_e$), 1.93-2.02 (1H, m, CH$_a$$\underline{H}_b$), 2.34-2.49 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 2.46 (1H, s, CH) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 18.6 (CH(C$\underline{H}_3$)$_2$), 20.3 (C$\underline{H}_f$H$_g$), 21.9 (CHC$\underline{H}_3$), 23.9 (CH(C$\underline{H}_3$)$_2$), 27.2 (C$\underline{H}_c$), 28.3 (C$\underline{H}$(CH$_3$)$_2$), 34.7 (C$\underline{H}_d$H$_e$), 50.1 (C$\underline{H}_a$H$_b$), 50.3 (C$\underline{H}_h$), 71.5 (CH), 71.8 (OC$_q$), 88.7 (OC$_q$C$_q$) **HRMS:** m/z calcd for $C_{12}H_{19}$ (M - H_2O + H) 163.1487, found 163.1486. **$[\alpha]^{23}_D$ =** +8.85 (*c* 2.26, CH_2Cl_2) **Rf:** 0.17 (95/5 cyclohexane/EtOAc). **Yield:** 66% (717 mg), yellow liquid.

(1R,2S,5R)-1-ethynyl-2-isopropyl-5-methylcyclohexan-1-ol 258a



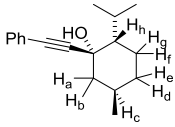
258a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.74-0.86 (1H, m, C$\underline{H}_d$H$_e$), 0.92 (3H, d, *J* = 6.2 Hz, CHC$\underline{H}_3$), 0.98 (3H, d, *J* = 6.7 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 1.00 (3H, d, *J* = 6.6 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 1.17-1.39 (3H, m, C$\underline{H}_a$H$_b$, C$\underline{H}_f$H$_g$, C$\underline{H}_h$), 1.58 (1H, br. s, OH), 1.66-1.83 (3H, m, C$\underline{H}_c$, CH$_d$$\underline{H}_e$, CH$_f$$\underline{H}_g$), 1.94-2.01 (1H, m, CH$_a$$\underline{H}_b$), 2.12-2.24 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 2.49 (1H, s, CH) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 18.3 (CH(C$\underline{H}_3$)$_2$), 21.8 (CHC$\underline{H}_3$), 24.0 (CH(C$\underline{H}_3$)$_2$), 24.3 (C$\underline{H}_f$H$_g$), 26.5 (C$\underline{H}$(CH$_3$)$_2$), 30.6 (C$\underline{H}_c$), 34.7

($\underline{C}H_dH_e$), 51.3 ($\underline{C}H_aH_b$), 52.7 ($\underline{C}H_h$), 71.8 (OC_q), 74.5 (CH), 86.5 ($OC_q\underline{C}_q$) **HRMS:** m/z calcd for $C_{12}H_{21}O$ (M + H) 181.1592, found 181.1593. **$[\alpha]^{23}_D$ =** -26.67 (*c* 0.30, CH_2Cl_2) **Rf:** 0.10 (95/5 cyclohexane/EtOAc). **Yield:** 21% (223 mg), yellow liquid.

One proton not correctly assigned in literature data.[217] CH_d was reported to resonate at 1.41-1.58 ppm, but HSQC shows it resonates at 0.83-0.96 ppm.

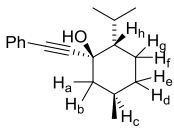
(1S,2S,5R)-2-isopropyl-5-methyl-1-(phenylethynyl)cyclohexan-1-ol 257b



257b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83-0.96 (1H, m, $C\underline{H}_dH_e$), 0.90 (3H, d, *J* = 6.3 Hz, $CHC\underline{H}_3$), 0.97 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)(CH_3)$), 1.01 (3H, d, *J* = 6.6 Hz, $CH(CH_3)(C\underline{H}_3)$), 1.35-1.59 (4H, m, $C\underline{H}_aH_b$, $C\underline{H}_fH_g$, $C\underline{H}_h$), 1.61 (1H, br. s, OH), 1.72-1.88 (2H, m, $C\underline{H}_c$, $CH_d\underline{H}_e$), 2.00-2.14 (1H, m, $CH_a\underline{H}_b$), 2.40-2.56 (1H, m, $\underline{C}H(CH_3)_2$), 7.28-7.33 (3H, m, CH_{ar}), 7.38-7.45 (2H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 18.9 ($CH(\underline{C}H_3)_2$), 20.8 ($\underline{C}H_fH_g$), 22.0 ($CHC\underline{H}_3$), 24.0 ($CH(\underline{C}H_3)_2$), 27.4 ($\underline{C}H_c$), 28.6 ($\underline{C}H(CH_3)_2$), 34.9 ($\underline{C}H_dH_e$), 50.1 ($\underline{C}H_aH_b$), 50.7 ($\underline{C}H_h$), 72.3 (OC_q), 83.5 ($\underline{C}_qC_{q,ar}$), 94.0 ($OC_q\underline{C}_q$), 123.0 ($C_q\underline{C}_{q,ar}$), 128.1 (CH_{ar}), 128.3 (2 x CH_{ar}), 131.7 (2 x CH_{ar}) **HRMS:** m/z calcd for $C_{18}H_{23}$ (M - H_2O + H) 239.1800, found 239.1802. **$[\alpha]^{23}_D$ =** +4.88 (*c* 0.82, CH_2Cl_2) **Rf:** 0.11 (95/5 cyclohexane/EtOAc). **Yield:** 54% (821 mg), transparent liquid.

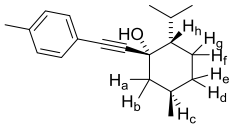
(1R,2S,5R)-2-isopropyl-5-methyl-1-(phenylethynyl)cyclohexan-1-ol 258b



258b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.74-0.85 (1H, m, $C\underline{H}_dH_e$), 0.94 (3H, d, *J* = 6.5 Hz, $CHC\underline{H}_3$), 1.02 (3H, d, *J* = 7.1 Hz, $CH(C\underline{H}_3)(CH_3)$), 1.04 (3H, d, *J* = 7.1 Hz, $CH(CH_3)(C\underline{H}_3)$), 1.22-1.46 (3H, m, $C\underline{H}_aH_b$, $C\underline{H}_fH_g$, $C\underline{H}_h$), 1.55 (1H, br. s, OH), 1.66-1.91 (3H, m, $C\underline{H}_c$, $CH_d\underline{H}_e$, $CH_f\underline{H}_g$), 2.02-2.12 (1H, m, $CH_a\underline{H}_b$), 2.21-2.33 (1H, m, $\underline{C}H(CH_3)_2$), 7.28-7.34 (3H, m, CH_{ar}), 7.38-7.46 (2H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 18.3 ($CH(\underline{C}H_3)_2$), 22.0 ($CHC\underline{H}_3$), 24.0 ($CH(\underline{C}H_3)_2$), 24.2 ($\underline{C}H_fH_g$), 26.4 ($\underline{C}H(CH_3)_2$), 30.8 ($\underline{C}H_c$), 34.8 ($\underline{C}H_dH_e$), 51.4 ($\underline{C}H_aH_b$), 53.8 ($\underline{C}H_h$), 72.2 (OC_q), 86.4 ($\underline{C}_qC_{q,ar}$), 92.0 ($OC_q\underline{C}_q$), 123.1 ($C_q\underline{C}_{q,ar}$), 128.2 (CH_{ar}), 128.3 (2 x CH_{ar}), 131.2 (2 x CH_{ar}) **HRMS:** m/z calcd for $C_{18}H_{23}$ (M - H_2O + H) 239.1800, found 239.1803. **$[\alpha]^{23}_D$ =** -14.29 (*c* 0.84, CH_2Cl_2) **Rf:** 0.05 (95/5 cyclohexane/EtOAc). **Yield:** 25% (387 mg), yellow needles.

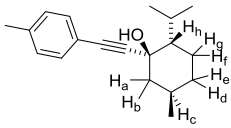
(1S,2S,5R)-2-isopropyl-5-methyl-1-(*p*-tolylethynyl)cyclohexan-1-ol 257c



257c

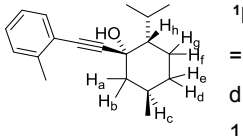
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, d, *J* = 6.3 Hz, $CHC\underline{H}_3$), 0.93-1.00 (1H, m, $C\underline{H}_dH_e$), 0.97 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)(CH_3)$), 1.00 (3H, d, *J* = 7.1 Hz, $CH(CH_3)(C\underline{H}_3)$), 1.36-1.57 (5H, m, $C\underline{H}_aH_b$, $C\underline{H}_fH_g$, $C\underline{H}_h$, OH), 1.73-1.85 (2H, m, $C\underline{H}_c$, $CH_d\underline{H}_e$), 2.00-2.10 (1H, m, $CH_a\underline{H}_b$), 2.34 (1H, s, $\underline{C}H_3C_{q,ar}$), 2.47 (1H, quintd, *J* = 6.9 Hz, *J* = 2.0 Hz, $C\underline{H}(CH_3)_2$), 7.10 (2H, d, *J* = 7.8 Hz, $CH_3C_qC\underline{H}_{ar}$), 7.31 (2H, d, *J* = 8.1 Hz, $C_qC_{q,ar}CH_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 18.9 ($CH(\underline{C}H_3)_2$), 20.8 ($\underline{C}H_fH_g$), 21.5 ($\underline{C}H_3C_{q,ar}$), 22.1 ($CHC\underline{H}_3$), 24.0 ($CH(\underline{C}H_3)_2$), 27.4 ($\underline{C}H_c$), 28.5 ($\underline{C}H(CH_3)_2$), 34.9 ($\underline{C}H_dH_e$), 50.2 ($\underline{C}H_aH_b$), 50.7 ($\underline{C}H_h$), 72.3 (OC_q), 83.6 ($\underline{C}_qC_{q,ar}$), 93.4 ($OC_q\underline{C}_q$), 120.0 ($C_q\underline{C}_{q,ar}$), 129.0 ($CH_3C_{q,ar}\underline{C}H_{ar}$), 131.6 ($C_qC_{q,ar}\underline{C}H_{ar}$), 138.2 ($CH_3\underline{C}_{q,ar}$) **HRMS:** m/z calcd for $C_{19}H_{25}$ (M - H_2O + H) 253.1956, found 253.1958. **$[\alpha]^{23}_D$ =** +3.28 (*c* 1.22, CH_2Cl_2) **Rf:** 0.17 (95/5 cyclohexane/EtOAc). **Yield:** 58% (473 mg), yellow liquid.

(1R,2S,5R)-2-isopropyl-5-methyl-1-(*p*-tolylethynyl)cyclohexan-1-ol 258c



^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85-0.97 (1H, m, $C\underline{H}_dH_e$), 0.93 (3H, d, *J* = 6.6 Hz, $CHC\underline{H}_3$), 1.01 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)(CH_3)$), 1.03 (3H, d, *J* = 6.8 Hz, $CH(CH_3)(C\underline{H}_3)$), 1.22-1.46 (3H, m, $C\underline{H}_aH_b$, $C\underline{H}_fH_g$, $C\underline{H}_h$), 1.64-1.89 (3H, m, $C\underline{H}_c$, $CH_d\underline{H}_e$, $CH_f\underline{H}_g$), 2.02-2.09 (1H, m, $CH_a\underline{H}_b$), 2.18 (1H, br. s, OH), 2.21-2.26 (1H, quintd, *J* = 7.0 Hz, *J* = 2.5 Hz, $C\underline{H}(CH_3)_2$), 2.34 ((1H, s, $\underline{C}H_3C_{q,ar}$), 7.08-7.14 (2H, m, $CH_3C_{q,ar}\underline{C}H_{ar}$), 7.28-7.34 (2H, m, $C_qC_{q,ar}CH_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 18.2 ($CH(\underline{C}H_3)_2$), 21.5 ($\underline{C}H_3C_{q,ar}$), 22.0 ($CHC\underline{H}_3$), 24.0 ($CH(\underline{C}H_3)_2$), 24.2 ($\underline{C}H_fH_g$), 26.4 ($\underline{C}H(CH_3)_2$), 30.8 ($\underline{C}H_c$), 34.8 ($\underline{C}H_dH_e$), 51.4 ($\underline{C}H_aH_b$), 53.8 ($\underline{C}H_h$), 72.2 (OC_q), 86.6 ($\underline{C}_qC_{q,ar}$), 91.1 ($OC_q\underline{C}_q$), 120.0 ($C_q\underline{C}_{q,ar}$), 129.1 ($CH_3C_{q,ar}\underline{C}H_{ar}$), 131.4 ($C_qC_{q,ar}\underline{C}H_{ar}$), 138.3 ($CH_3\underline{C}_{q,ar}$) **HRMS:** m/z calcd for $C_{19}H_{25}$ (M - H_2O + H) 253.1956, found 253.1956. **$[\alpha]^{23}_D$ =** -12.50 (*c* 0.32, CH_2Cl_2) **Rf:** 0.07 (95/5 cyclohexane/EtOAc). **Yield:** 33% (271 mg), yellow liquid.

(1S,2S,5R)-2-isopropyl-5-methyl-1-(*o*-tolylethynyl)cyclohexan-1-ol 257d

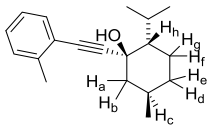


257d

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87-1.05 (1H, m, $C\underline{H}_dH_e$), 0.91 (3H, d, *J* = 6.3 Hz, $CHC\underline{H}_3$), 0.98 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)(CH_3)$), 1.00 (3H, d, *J* = 7.1 Hz, $CH(CH_3)(C\underline{H}_3)$), 1.36-1.56 (4H, m, $C\underline{H}_aH_b$, $C\underline{H}_fH_g$, $C\underline{H}_h$), 1.67 (1H, br. s, OH), 1.75-1.87 (2H, m, $C\underline{H}_c$, $CH_d\underline{H}_e$), 2.03-2.13 (1H, m, $CH_a\underline{H}_b$), 2.42 (1H, s, $\underline{C}H_3C_{q,ar}$), 2.54 (1H, quintd, *J* = 6.9 Hz, *J* = 1.8 Hz, $C\underline{H}(CH_3)_2$), 7.08-7.22 (3H, m, CH_{ar}), 7.36-7.41 (1H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:**

18.8 (CH($\underline{C}H_3$)$_2$), 20.7 ($\underline{C}H_fH_g$), 20.8 ($\underline{C}H_3C_{q,ar}$), 22.0 (CHC$\underline{H}_3$), 24.0 (CH($\underline{C}H_3$)$_2$), 27.4 ($\underline{C}H_c$), 28.6 ($\underline{C}H(CH_3)_2$), 34.9 ($\underline{C}H_dH_e$), 50.3 ($\underline{C}H_aH_b$), 50.8 ($\underline{C}H_h$), 72.6 (OC_q), 82.4 ($\underline{C}_qC_{q,ar}$), 98.2 ($OC_q\underline{C}_q$), 122.8 ($C_q\underline{C}_{q,ar}$), 125.6 (CH_{ar}), 128.2 (CH_{ar}), 129.4 (CH_{ar}), 132.0 (CH_{ar}), 140.1 ($CH_3\underline{C}_{q,ar}$) **HRMS:** m/z calcd $C_{19}H_{25}$ (M - H_2O + H) 253.1956, found 253.1957. **[α]$^{23}_D$ =** -3.08 (*c* 1.30, CH_2Cl_2) **Rf:** 0.20 (95/5 cyclohexane/EtOAc). **Yield:** 75% (405 mg), transparent liquid.

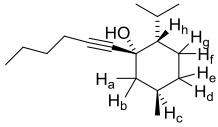
(1R,2S,5R)-2-isopropyl-5-methyl-1-(*o*-tolylethynyl)cyclohexan-1-ol 258d



258d

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84-0.99 (1H, m, C$\underline{H}_dH_e$), 0.95 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$), 1.04 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 1.04 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 1.23-1.49 (3H, m, C$\underline{H}_aH_b$, C$\underline{H}_fH_g$, C$\underline{H}_h$), 2.33 (1H, br. s, OH), 1.67-1.91 (3H, m, C$\underline{H}_c$, CH$_d\underline{H}_e$, CH$_f\underline{H}_g$), 2.04-2.12 (1H, m, CH$_a\underline{H}_b$), 2.25 (1H, quintd, *J* = 6.9 Hz, *J* = 2.8 Hz, C$\underline{H}(CH_3)_2$), 2.43 (1H, s, $\underline{C}H_3C_{q,ar}$), 7.09-7.22 (3H, m, CH_{ar}), 7.36-7.41 (1H, m, CH_{ar}) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 18.5 (CH($\underline{C}H_3$)$_2$), 20.9 ($\underline{C}H_3C_{q,ar}$), 22.0 (CHC$\underline{H}_3$), 24.0 (CH($\underline{C}H_3$)$_2$), 24.5 ($\underline{C}H_fH_g$), 26.8 ($\underline{C}H(CH_3)_2$), 30.9 ($\underline{C}H_c$), 34.8 ($\underline{C}H_dH_e$), 51.6 ($\underline{C}H_aH_b$), 53.1 ($\underline{C}H_h$), 72.6 (OC_q), 85.4 ($\underline{C}_qC_{q,ar}$), 95.9 ($OC_q\underline{C}_q$), 122.8 ($C_q\underline{C}_{q,ar}$), 125.6 (CH_{ar}), 128.2 (CH_{ar}), 129.4 (CH_{ar}), 132.0 (CH_{ar}), 140.0 ($CH_3\underline{C}_{q,ar}$) **HRMS:** m/z calcd for $C_{19}H_{25}$ (M - H_2O + H) 253.1956, found 253.1960. **[α]$^{23}_D$ =** -20.00 (*c* 0.20, CH_2Cl_2) **Rf:** 0.10 (95/5 cyclohexane/EtOAc). **Yield:** 14% (74 mg), transparent liquid.

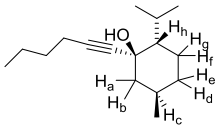
(1S,2S,5R)-1-(hex-1-yn-1-yl)-2-isopropyl-5-methylcyclohexan-1-ol 257e



257e

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84-1.01 (1H, m, C$\underline{H}_dH_e$), 0.86 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$), 0.91 (3H, t, *J* = 7.2 Hz, C$\underline{H}_3$CH$_2$), 0.92 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 0.95 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 1.22-1.58 (9H, m, C$\underline{H}_aH_b$, C$\underline{H}_fH_g$, C$\underline{H}_h$, CH$_3$C$\underline{H}_2$, CH$_3$CH$_2$C$\underline{H}_2$, OH), 1.65-1.79 (2H, m, C$\underline{H}_c$, CH$_d\underline{H}_e$), 1.87-1.97 (1H, m, CH$_a\underline{H}_b$), 2.20 (2H, t, *J* = 6.9 Hz, C$\underline{H}_2C_qC_q$), 2.32-2.47 (1H, m, C$\underline{H}(CH_3)_2$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 13.6 ($\underline{C}H_3CH_2$), 18.4 ($\underline{C}H_2C_qC_q$), 18.7 (CH($\underline{C}H_3$)$_2$), 20.6 ($\underline{C}H_fH_g$), 21.9 ($CH_3\underline{C}H_2$), 22.0 (CHC$\underline{H}_3$), 23.9 (CH($\underline{C}H_3$)$_2$), 27.3 ($\underline{C}H_c$), 28.2 ($\underline{C}H(CH_3)_2$), 30.9 ($CH_3CH_2\underline{C}H_2$), 34.9 ($\underline{C}H_dH_e$), 50.5 ($\underline{C}H_aH_b$), 50.7 ($\underline{C}H_h$), 71.9 (OC_q), 83.8 ($OC_q\underline{C}_qC_q$ or $OC_qC_q\underline{C}_q$), 85.0 ($OC_qC_q\underline{C}_q$ or $OC_q\underline{C}_qC_q$) **HRMS:** m/z calcd for $C_{16}H_{27}$ (M - H_2O + H) 219.2113, found 219.2111. **[α]$^{23}_D$ =** +6.12 (*c* 1.96, CH_2Cl_2) **Rf:** 0.12 (99/1 pentane/EtOAc). **Yield:** 76% (537 mg), transparent liquid.

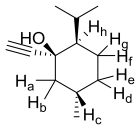
(1R,2S,5R)-1-(hex-1-yn-1-yl)-2-isopropyl-5-methylcyclohexan-1-ol 258e



258e

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.75-0.89 (1H, m, C$\underline{H}_d$H$_e$), 0.87 (3H, d, *J* = 6.0 Hz, CHC$\underline{H}_3$), 0.88 (3H, t, *J* = 7.1 Hz, C$\underline{H}_3$CH$_2$), 0.93 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 0.94 (3H, d, *J* = 6.9 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 1.07-1.53 (7H, m, C$\underline{H}_a$H$_b$, C$\underline{H}_f$H$_g$, C$\underline{H}_h$, CH$_3$C$\underline{H}_2$, CH$_3$CH$_2$C$\underline{H}_2$), 1.53-1.77 (3H, m, CH$_f$$\underline{H}_g$, C$\underline{H}_c$, CH$_d$$\underline{H}_e$), 1.84-1.92 (1H, m, CH$_a$$\underline{H}_b$), 2.17 (2H, t, *J* = 6.9 Hz, C$\underline{H}_2$C$_q$C$_q$), 2.07-2.23 (2H, m, C$\underline{H}$(CH$_3$)$_2$, OH) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 13.6 (C$\underline{H}_3$CH$_2$), 18.2 (CH(C$\underline{H}_3$)$_2$), 18.5 (C$\underline{H}_2$C$_q$C$_q$), 21.9 (CHC$\underline{H}_3$), 22.0 (CH$_3$C$\underline{H}_2$), 24.0 (CH(C$\underline{H}_3$)$_2$), 24.3 (C$\underline{H}_f$H$_g$), 26.4 (C$\underline{H}$(CH$_3$)$_2$), 30.7 (C$\underline{H}_c$), 30.8 (CH$_3$CH$_2$C$\underline{H}_2$), 34.8 (C$\underline{H}_d$H$_e$), 51.6 (C$\underline{H}_a$H$_b$), 52.9 (C$\underline{H}_h$), 71.9 (OC$_q$), 82.5 (OC$_q$C$_q$C$_q$ or OC$_q$C$_q$C$_q$), 86.7 (OC$_q$C$_q$C$_q$ or OC$_q$C$_q$C$_q$) **HRMS:** m/z calcd for $C_{16}H_{27}$ (M - H_2O + H) 2119.2113, found 219.2112. **[α]$^{23}_D$ =** -13.33 (*c* 0.30, CH_2Cl_2) **Rf:** 0.03 (99/1 pentane/EtOAc). **Yield:** 19% (133 mg), transparent liquid.

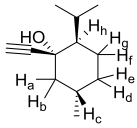
(1R,2R,5S)-1-ethynyl-2-isopropyl-5-methylcyclohexan-1-ol 257f



257f

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85-0.94 (1H, m, C$\underline{H}_d$H$_e$), 0.87 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$), 0.93 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 0.96 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 1.27-1.55 (4H, m, C$\underline{H}_a$H$_b$, C$\underline{H}_f$H$_g$, C$\underline{H}_h$), 1.62 (1H, br. s, OH), 1.65-1.81 (2H, m, C$\underline{H}_c$, CH$_d$$\underline{H}_e$), 1.92-2.02 (1H, m, CH$_a$$\underline{H}_b$), 2.33-2.48 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 2.46 (1H, s, CH) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 18.6 (CH(C$\underline{H}_3$)$_2$), 20.3 (C$\underline{H}_f$H$_g$), 21.9 (CHC$\underline{H}_3$), 23.9 (CH(C$\underline{H}_3$)$_2$), 27.3 (C$\underline{H}_c$), 28.3 (C$\underline{H}$(CH$_3$)$_2$), 34.8 (C$\underline{H}_d$H$_e$), 50.1 (C$\underline{H}_a$H$_b$), 50.3 (C$\underline{H}_h$), 71.5 (CH), 71.9 (OC$_q$), 88.7 (OC$_q$C$_q$) **HRMS:** m/z calcd for $C_{12}H_{19}$ (M - H_2O + H)$^+$ 163.1487, found 163.1485. **[α]$^{23}_D$ =** -10.53 (*c* 0.38, CH_2Cl_2) **Rf:** 0.18 (95/5 hexane/EtOAc). **Yield:** 55% (443 mg), transparent liquid.

(1S,2R,5S)-1-ethynyl-2-isopropyl-5-methylcyclohexan-1-ol 258f



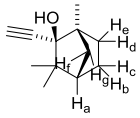
258f

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.76-0.88 (1H, m, C$\underline{H}_d$H$_e$), 0.89 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$), 0.95 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 0.96 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 1.14-1.37 (3H, m, C$\underline{H}_a$H$_b$, C$\underline{H}_f$H$_g$, C$\underline{H}_h$), 1.59-1.81 (3H, m, C$\underline{H}_c$, CH$_d$$\underline{H}_e$, CH$_f$$\underline{H}_g$), 1.92-2.00 (1H, m, CH$_a$$\underline{H}_b$), 2.17 (1H, septd, *J* = 6.9 Hz, *J* = 2.8 Hz, C$\underline{H}$(CH$_3$)$_2$), 2.32 (1H, br. s, OH), 2.47 (1H, s, CH) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 18.3 (CH(C$\underline{H}_3$)$_2$), 21.8 (CHC$\underline{H}_3$), 24.0 (CH(C$\underline{H}_3$)$_2$), 24.2 (C$\underline{H}_f$H$_g$), 26.5 (C$\underline{H}_c$), 30.5 (C$\underline{H}$(CH$_3$)$_2$), 34.7 (C$\underline{H}_d$H$_e$), 51.3 (C$\underline{H}_a$H$_b$), 52.7 (C$\underline{H}_h$), 71.8 (OC$_q$), 74.5 (CH), 86.5 (OC$_q$C$_q$)

HRMS: m/z calcd for $C_{12}H_{19}$ $(M - H_2O + H)^+$ 163.1487, found 163.1486. **$[\alpha]^{23}_D$ =** +18.18 (*c* 0.22, CH_2Cl_2) **Rf:** 0.19 (95/5 hexane/EtOAc). **Yield:** 17% (138 mg), transparent liquid.

(1R,2R,4S)-2-ethynyl-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol 257g

A literature protocol was followed. The two diastereomers were present in a 98/2 ratio and the mixture was used as such in the next step. Spectral properties were in accordance with literature data.[382]

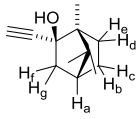


257g

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (3H, s, $C(CH_3)(C\underline{H}_3)$), 1.08-1.17 (2H, m, $C\underline{H}_dH_e$, $C\underline{H}_fH_g$), 1.15 (3H, s, $C(C\underline{H}_3)(CH_3)$), 1.20 (3H, s, $CH_2CC\underline{H}_3$), 1.35-1.47 (1H, m, $C\underline{H}_bH_c$), 1.65-1.78 (3H, m, CH_a, $CH_f\underline{H}_g$, $CH_b\underline{H}_c$), 1.85-1.95 (1H, m, $CH_d\underline{H}_e$), 2.56 (1H, s, CH) Yield: 72% (168 mg), transparent liquid.

(1R,2S,4R)-2-ethynyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 257h

Standard protocol B afforded a mixture of two diastereomers, which were present in a 98/2 ratio. These were recovered in the same ratio after column chromatography (R_f: 0.30 (97.5/2.5 hexane/EA)) in 55% yield. Next, the alkyne (546 mg, 2.18 mmol) was dissolved in 15 mL MeOH and refluxed with K_2CO_3 (177 mg, 0.33 m%). After 90 minutes, the reaction was quenched with water and the solvent was evaporated under reduced pressure before 20 mL of diethylether and 5 mL of brine were added. The aqueous phase was extracted twice with 10 mL of diethylether. The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The two diastereomers were present in a 98/2 ratio and the mixture was used as such in the next step. Spectral properties were in accordance with literature data.[383]



257h

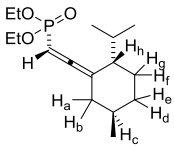
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, s, $C(CH_3)(C\underline{H}_3)$), 0.96 (3H, s, $C(C\underline{H}_3)(CH_2)$), 1.06 (3H, s, $C(C\underline{H}_3)(CH_3)$), 1.10-1.18 (1H, m, $C\underline{H}_bH_c$), 1.42-1.52 (1H, m, $C\underline{H}_fH_g$), 1.53-1.64 (1H, br. s, OH), 1.65-1.75 (1H, m, $CH_b\underline{H}_c$), 1.77 (1H, t, *J* = 4.4 Hz, CH_a), 1.84-1.95 (1H, m, $CH_f\underline{H}_g$), 1.88 (1H, d, *J* = 13.6 Hz, $C\underline{H}_dH_e$), 2.23 (1H, dt, *J* = 13.4 Hz, *J* = 3.8 Hz, $CH_d\underline{H}_e$), 2.46 (1H, s, CH) Yield: 58% (278 mg, two steps), white needles.

4.8.3. Synthesis of chiral allenylphosphonates

Diethylchlorophosphite (0.58 mL, 4.0 mmol) was added to a solution of propargylic alcohol **257b** (512 mg, 2.0 mmol) in 20 mL THF at room temperature. After the addition of triethylamine (0.32 mL, 2.2 mmol), the mixture was refluxed for 24 hours. The reaction was quenched with 20 mL of water and brine. Next, the mixture was extracted three times with 20 mL diethylether,

the organic layers were combined and dried over $MgSO_4$. After concentration of the mixture *in vacuo* and purification *via* flash chromatography, enantiomerically pure allenylphosphonate **259b** (481 mg, 1.28 mmol) was obtained.

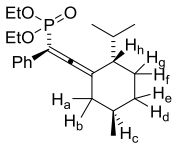
(S)-diethyl (2-((2S,5R)-2-isopropyl-5-methylcyclohexylidene)-vinyl)phosphonate 259a



259a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, d, *J* = 6.8 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 0.93 (3H, d, *J* = 6.3 Hz, CHC$\underline{H}_3$), 0.94 (3H, d, *J* = 6.6 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 0.94-1.06 (1H, m, C$\underline{H}_d$H$_e$), 1.17-1.30 (1H, m, C$\underline{H}_f$H$_g$), 1.33 (6H, t, *J* = 7.2 Hz, P(OCH$_2$C$\underline{H}_3$)$_2$), 1.53-1.94 (6H, m, C$\underline{H}_c$, CH$_a$$\underline{H}_b$, C$\underline{H}$(CH$_3$)$_2$, C$\underline{H}_h$, CH$_d$$\underline{H}_e$, CH$_f$$\underline{H}_g$), 2.30-2.36 (1H, m, C$\underline{H}_aH_b$), 4.02-4.18 (4H, m, P(OC$\underline{H}_2$CH$_3$)$_2$), 5.25 (1H, td, $^2J_{PH}$ = 7.5 Hz, $^5J_{HH}$ = 3.8 Hz, PCH) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.4 (d, $^3J_{PC}$ = 2 Hz, P(OCH$_2$C$\underline{H}_3$)), 16.4 (d, $^3J_{PC}$ = 2 Hz, P(OCH$_2$C$\underline{H}_3$)), 18.9 (CH(C$\underline{H}_3$)$_2$), 22.0 (CH(C$\underline{H}_3$)$_2$), 22.0 (CHC$\underline{H}_3$), 28.1 (d, $^5J_{PC}$ = 5 Hz, C$\underline{H}_f$H$_g$), 29.4 (C$\underline{H}$(CH$_3$)$_2$), 33.6 (d, $^5J_{PC}$ = 4 Hz, C$\underline{H}_c$), 34.5 (C$\underline{H}_d$H$_e$), 39.6 (d, $^4J_{PC}$ = 7 Hz, C$\underline{H}_a$H$_b$), 46.3 (d, $^4J_{PC}$ = 5 Hz, C$\underline{H}_h$), 61.9 (d, $^2J_{PC}$ = 6 Hz, P(OC$\underline{H}_2$CH$_3$)), 62.1 (d, $^2J_{PC}$ = 6 Hz, P(OC$\underline{H}_2$CH$_3$)), 79.5 (d, $^1J_{PC}$ = 201 Hz, PC$\underline{H}$), 107.3 (d, $^3J_{PC}$ = 18 Hz, PCHC$_q$C$\underline{C}_q$), 207.7 (PCH$\underline{C}_q$C$_q$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 16.62. **HRMS:** m/z calcd for $C_{16}H_{30}O_3P$ (M + H) 301.1933, found 301.1935. **$[\alpha]^{23}_D$ =** -2.90 (*c* 1.38, CH_2Cl_2) **Rf:** 0.19 (3/7 cyclohexane/EtOAc). **Yield:** 75% (441 mg), yellow liquid.

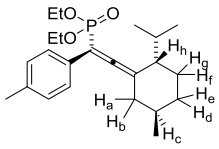
(S)-diethyl (2-((2S,5R)-2-isopropyl-5-methylcyclohexylidene)-1-phenyl-vinyl)phosphonate 259b



259b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, d, *J* = 6.7 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 0.92 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 0.96 (3H, d, *J* = 6.3 Hz, CHC$\underline{H}_3$), 0.99-1.13 (1H, m, C$\underline{H}_d$H$_e$), 1.24-1.38 (1H, m, C$\underline{H}_f$H$_g$), 1.29 (6H, t, *J* = 7.0 Hz, P(OCH$_2$C$\underline{H}_3$)$_2$), 1.52-1.94 (6H, m, C$\underline{H}_c$, CH$_a$$\underline{H}_b$, C$\underline{H}$(CH$_3$)$_2$, C$\underline{H}_h$, CH$_d$$\underline{H}_e$, CH$_f$$\underline{H}_g$), 2.40-2.50 (1H, m, C$\underline{H}_aH_b$), 4.01-4.21 (4H, m, P(OC$\underline{H}_2$CH$_3$)$_2$), 7.19-7.24 (1H, m, C$\underline{H}_{ar}$), 7.28-7.36 (2H, m, C$\underline{H}_{ar}$), 7.52-759 (2H, m, C$\underline{H}_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{PC}$ = 2 Hz, P(OCH$_2$C$\underline{H}_3$)), 16.4 (d, $^3J_{PC}$ = 2 Hz, P(OCH$_2$C$\underline{H}_3$)), 19.0 (CH(C$\underline{H}_3$)$_2$), 22.0 (CH(C$\underline{H}_3$)$_2$), 22.1 (CHC$\underline{H}_3$), 28.0 (d, $^5J_{PC}$ = 4 Hz, C$\underline{H}_f$H$_g$), 29.9 (C$\underline{H}$(CH$_3$)$_2$), 33.5 (d, $^5J_{PC}$ = 4 Hz, C$\underline{H}_c$), 34.5 (C$\underline{H}_d$H$_e$), 39.9 (d, $^4J_{PC}$ = 6 Hz, C$\underline{H}_a$H$_b$), 47.1 (d, $^4J_{PC}$ = 5 Hz, C$\underline{H}_h$), 62.1 (d, $^2J_{PC}$ = 6 Hz, P(OC$\underline{H}_2$CH$_3$)), 62.3 (d, $^2J_{PC}$ = 6 Hz, P(OC$\underline{H}_2$CH$_3$)), 96.6 (d, $^1J_{PC}$ = 193 Hz, P$\underline{C}_q$C$_q$C$_q$), 109.7 (d, $^3J_{PC}$ = 15 Hz, PC$_q$C$_q$C$\underline{C}_q$), 127.0 (C$\underline{H}_{ar}$), 127.4 (C$\underline{H}_{ar}$), 127.5 (C$\underline{H}_{ar}$), 128.4 (2 x C$\underline{H}_{ar}$), 133.3 (d, $^2J_{PC}$ = 6 Hz, C$\underline{C}_{q,ar}$), 207.2 (d, $^2J_{PC}$ = 5 Hz, PC$_q$C$\underline{C}_q$C$_q$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 16.58. **HRMS:** m/z calcd for $C_{22}H_{34}O_3P$ (M + H) 377.2246, found 377.2244. **$[\alpha]^{23}_D$ =** -23.81 (*c* 0.84, CH_2Cl_2) **Rf:** 0.19 (7/3 cyclohexane/EtOAc). **Yield:** 64% (481 mg), transparent liquid.

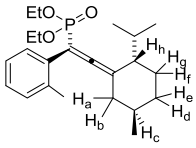
(S)-diethyl (2-((2S,5R)-2-isopropyl-5-methylcyclohexylidene)-1-(*p*-tolyl)-vinyl)phosphonate 259c



259c

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (3H, d, *J* = 6.5 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 0.90 (3H, d, *J* = 6.5 Hz, CHC$\underline{H}_3$), 0.94 (3H, d, *J* = 6.5 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 0.99-1.08 (1H, m, C$\underline{H}_d$H$_e$), 1.24-1.29 (7H, m, P(OCH$_2$C$\underline{H}_3$)$_2$, C$\underline{H}_f$H$_g$), 1.62-1.90 (6H, m, C$\underline{H}_c$, CH$_a$C$\underline{H}_b$, C$\underline{H}$(CH$_3$)$_2$, CH$_h$, CH$_d$C$\underline{H}_e$, CH$_f$C$\underline{H}_g$), 2.30 (3H, s, C$\underline{H}_3$C$_{q,ar}$), 2.41-2.46 (1H, m, C$\underline{H}_a$CH$_b$), 4.00-4.18 (4H, m, P(OC$\underline{H}_2$CH$_3$)$_2$), 7.10 (2H, d, *J* = 8.3 Hz, C$\underline{H}_{ar}$), 7.43 (2H, d, *J* = 8.3 Hz, C$\underline{H}_{ar}$) **^{13}C NMR (100MHz, $CDCl_3$) δ:** 16.3 (P(OCH$_2$C$\underline{H}_3$)) 16.4 (P(OCH$_2$C$\underline{H}_3$)), 19.0 (CH(C$\underline{H}_3$)$_2$), 21.1 (C$\underline{H}_3$C$_{q,ar}$), 21.9 (CH(C$\underline{H}_3$)), 22.0 (CHC$\underline{H}_3$), 28.0 (d, $^5J_{PC}$ = 4 Hz, C$\underline{H}_f$H$_g$), 29.8 (C$\underline{H}$(CH$_3$)$_2$), 33.5 (d, $^5J_{PC}$ = 5 Hz ,C$\underline{H}_c$), 34.5 (C$\underline{H}_d$H$_e$), 39.9 (d, $^4J_{PC}$ = 6 Hz, CH$_a$H$_b$), 47.1 (d, $^4J_{PC}$ = 6 Hz ,C$\underline{H}_h$), 61.9 (d, $^2J_{PC}$ = 6 Hz, P(OC$\underline{H}_2$CH$_3$)), 62.1 (d, $^2J_{PC}$ = 6 Hz, P(OC$\underline{H}_2$CH$_3$)), 96.3 (d, $^1J_{PC}$ = 193 Hz, PC$\underline{q}$C$_q$C$_q$), 109.5 (d, $^3J_{PC}$ = 15 Hz, PC$_q$C$_q$C$\underline{q}$), 127.3 (d, $^3J_{PC}$ = 6 Hz, C$\underline{ar}$H), 129.1 (C$\underline{ar}$H), 130.2 (d, $^2J_{PC}$ = 10 Hz, C$\underline{q,ar}$), 136.4 (C$\underline{q,ar}$), 206.2 (d, $^2J_{PC}$ = 4 Hz, PC$_q$C$\underline{q}$C$_q$). **^{31}P NMR δ:** 16.70. **HRMS:** m/z calcd for $C_{23}H_{36}O_3P$ (M+H)$^+$ 391.2402, found 391.2396. **$[\alpha]_D^{20}$** = -18.39 (c 2.04, CH_2Cl_2) **R_f:** 0.20 (4/6 EtOAc/*n*-hexane). **Yield:** 72% (280 mg), yellow oil.

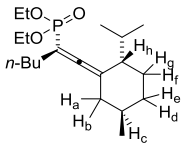
(S)-diethyl (2-((2S,5R)-2-isopropyl-5-methylcyclohexylidene)-1-(*o*-tolyl)-vinyl)phosphonate 259d



259d

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (3H, d, *J* = 6.6 Hz, CH(C$\underline{H}_3$)(CH$_3$)), 0.94 (3H, d, *J* = 6.7 Hz, CH(CH$_3$)(C$\underline{H}_3$)), 0.92-1.04 (1H, m, C$\underline{H}_d$H$_e$), 0.96 (3H, d, *J* = 5.6 Hz, CHC$\underline{H}_3$), 1.19-1.32 (7H, m, C$\underline{H}_f$H$_g$, P(OCH$_2$C$\underline{H}_3$)$_2$), 1.57-1.91 (6H, m, C$\underline{H}_c$, C$\underline{H}_a$H$_b$, C$\underline{H}$(CH$_3$)$_2$, C$\underline{H}_h$, CH$_d$C$\underline{H}_e$, CH$_f$C$\underline{H}_g$), 2.37 (3H, br. s, C$\underline{H}_3$C$_{q,ar}$), 2.43-2.51 (1H, m, C$\underline{H}_a$H$_b$), 3.94-4.15 (4H, m, P(OC$\underline{H}_2$CH$_3$)$_2$), 7.11-7.22 (3H, m, C$\underline{H}_{ar}$), 7.30-7.37 (1H, m, C$\underline{H}_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.37 (d, $^3J_{PC}$ = 4 Hz, P(OCH$_2$C$\underline{H}_3$)), 16.44 (d, $^3J_{PC}$ = 4 Hz, P(OCH$_2$C$\underline{H}_3$)), 18.9 (CH(C$\underline{H}_3$)$_2$), 20.5 (C$\underline{H}_3$C$_{q,ar}$), 22.1 (CH(C$\underline{H}_3$)$_2$), 22.2 (CHC$\underline{H}_3$), 28.1 (d, $^5J_{PC}$ = 4 Hz, C$\underline{H}_f$H$_g$), 29.7 (C$\underline{H}$(CH$_3$)$_2$), 33.8 (d, $^5J_{PC}$ = 4 Hz, C$\underline{H}_c$), 34.7 (C$\underline{H}_d$H$_e$), 39.6 (d, $^4J_{PC}$ = 7 Hz, C$\underline{H}_a$H$_b$), 46.8 (d, $^4J_{PC}$ = 5 Hz, C$\underline{H}_h$), 62.2 (d, $^2J_{PC}$ = 7 Hz, P(OC$\underline{H}_2$CH$_3$)), 62.3 (d, $^2J_{PC}$ = 7 Hz, P(OC$\underline{H}_2$CH$_3$)), 95.3 (d, $^1J_{PC}$ = 196 Hz, PC$\underline{q}$C$_q$C$_q$), 107.3 (d, $^3J_{PC}$ = 16 Hz, PC$_q$C$_q$C$\underline{q}$), 125.6 (d, J_{PC} = 2 Hz, C$\underline{ar}$H), 127.6 (d, J_{PC} = 2 Hz, C$\underline{ar}$H), 130.0 (d, J_{PC} = 4 Hz, C$\underline{ar}$H), 130.3 (C$\underline{ar}$H), 132.9 (d, J_{PC} = 8 Hz, C$\underline{q,ar}$), 133.3 (d, J_{PC} = 6 Hz, C$\underline{q,ar}$), 205.0 (d, $^2J_{PC}$ = 6 Hz, PC$_q$C$\underline{q}$C$_q$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 15.91 **HRMS:** m/z calcd for $C_{23}H_{36}O_3P$ (M + H) 391.2402, found 391.2401. **$[\alpha]^{23}_D$ =** +17.05 (*c* 2.33, CH_2Cl_2) **Rf:** 0.20 (7/3 pentane/EtOAc). **Yield:** 66% (514 mg), yellow liquid.

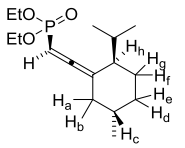
(S)-diethyl (1-((2S,5R)-2-isopropyl-5-methylcyclohexylidene)-hex-1-en-2-yl)phosphonate 259e



259e

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86-1.07 (13H, m, $CH(C\underline{H}_3)_2$, $CHC\underline{H}_3$, $C\underline{H}_dH_e$, $C\underline{H}_3CH_2$), 1.17-1.29 (1H, m, $C\underline{H}_fH_g$), 1.31 (6H, t, *J* = 7.1 Hz, $P(OCH_2C\underline{H}_3)_2$), 1.31-1.39 (2H, m, $CH_3C\underline{H}_2CH_2$), 1.41-1.50 (2H, m, $CH_3CH_2C\underline{H}_2$), 1.60-1.65 (CH_c), 1.67-1.73 (2H, m, $C\underline{H}_aH_b$, $C\underline{H}_h$) 1.73-1.78 ($C\underline{H}(CH_3)_2$), 1.78-1.88 (2H, $CH_d\underline{H}_e$, $CH_f\underline{H}_g$), 2.08-2.18 (2H, m, $C\underline{H}_2C_qC_qC_q$), 2.23-2.37 (1H, m, $C\underline{H}_aH_b$), 3.98-4.19 (4H, m, $P(OC\underline{H}_2CH_3)_2$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 14.0 ($\underline{C}H_3CH_2$), 16.4 (d, $^3J_{PC}$ = 2 Hz, $P(OCH_2\underline{C}H_3)$), 16.5 (d, $^3J_{PC}$ = 2 Hz, $P(OCH_2\underline{C}H_3)$), 19.0 ($CH(CH_3)(\underline{C}H_3)$), 21.96 ($CH(\underline{C}H_3)(CH_3)$ + $CHC\underline{H}_3$), 22.3 ($CH_3\underline{C}H_2CH_2$), 27.9 (d, $^5J_{PC}$ = 5 Hz, $\underline{C}H_fH_g$), 28.6 (d, $^2J_{PC}$ = 9 Hz, $\underline{C}H_2C_qC_qC_q$), 29.5 ($\underline{C}H(CH_3)_2$), 30.7 (d, $^3J_{PC}$ = 7 Hz, $CH_3CH_2\underline{C}H_2$), 33.5 (d, $^5J_{PC}$ = 4 Hz, $\underline{C}H_c$), 34.5 ($\underline{C}H_dH_e$), 40.2 (d, $^4J_{PC}$ = 7 Hz, $\underline{C}H_aH_b$), 46.6 (d, $^4J_{PC}$ = 5 Hz, $\underline{C}H_h$), 61.6 (d, $^2J_{PC}$ = 6 Hz, $P(O\underline{C}H_2CH_3)$), 61.9 (d, $^2J_{PC}$ = 7 Hz, $P(O\underline{C}H_2CH_3)$), 93.1 (d, $^1J_{PC}$ = 197 Hz, $P\underline{C}_q$), 108.1 (d, $^3J_{PC}$ = 17 Hz, $PC_qC_q\underline{C}_q$), 204.1 (d, $^2J_{PC}$ = 6 Hz, $PC_q\underline{C}_qC_q$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 19.61. **HRMS:** m/z calcd for $C_{20}H_{38}O_3P$ (M + H) 357.2559, found 357.2561. **$[\alpha]^{23}_D$ =** -15.44 (*c* 2.05, CH_2Cl_2) **Rf:** 0.18 (7/3 pentane/EtOAc). **Yield:** 78% (555 mg), transparent liquid.

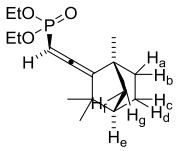
(R)-diethyl (2-((2R,5S)-2-isopropyl-5-methylcyclohexylidene)-vinyl)phosphonate 259f



259f

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)(CH_3)$), 0.91 (3H, d, *J* = 6.0 Hz, $CHC\underline{H}_3$), 0.92 (3H, d, *J* = 6.7 Hz, $CH(CH_3)(C\underline{H}_3)$), 0.96-1.01 (1H, m, $C\underline{H}_dH_e$), 1.17-1.30 (1H, m, $C\underline{H}_fH_g$), 1.30 (6H, t, *J* = 7.2 Hz, $P(OCH_2C\underline{H}_3)_2$), 1.52-1.85 (6H, m, $C\underline{H}_c$, $CH_a\underline{H}_b$, $C\underline{H}(CH_3)_2$, $C\underline{H}_h$, $CH_d\underline{H}_e$, $CH_f\underline{H}_g$), 2.29-2.32 (1H, m, $C\underline{H}_aH_b$), 4.01-4.14 (4H, m, $P(OC\underline{H}_2CH_3)_2$), 5.22 (1H, dt, $^2J_{PH}$ = 7.4 Hz , $^5J_{HH}$ = 3.7 Hz, PCH). **^{13}C NMR (100MHz, $CDCl_3$) δ:** 16.3 (d, $^3J_{PC}$ = 1 Hz, $P(OCH_2\underline{C}H_3)$), 16.3 (d, $^3J_{PC}$ = 1 Hz, $P(OCH_2\underline{C}H_3)$), 18.9 ($CH(\underline{C}H_3)_2$), 21.8 ($CH(\underline{C}H_3)_2$), 21.8 ($CH\underline{C}H_3$), 28.1 (d, $^5J_{PC}$ = 5 Hz, $\underline{C}H_fH_g$), 29.3 ($\underline{C}H(CH_3)_2$), 33.6 (d, $^5J_{PC}$ = 4 Hz, $\underline{C}H_c$), 34.4 ($\underline{C}H_dH_e$), 39.5 (d, $^5J_{PC}$ = 7 Hz, $\underline{C}H_aH_b$), 46.3 (d, $^4J_{PC}$ = 6 Hz, $\underline{C}H_h$), 61.8 (d, $^2J_{PC}$ = 6 Hz, $P(O\underline{C}H_2CH_3)$), 61.9 (d, $^2J_{PC}$ = 6 Hz, $P(O\underline{C}H_2CH_3)$), 79.5 (d, $^1J_{PC}$ = 201 Hz, $P\underline{C}H$), 107.2 (d, $^3J_{PC}$ = 17 Hz, $PCHC_q\underline{C}_q$), 207 ($PCH\underline{C}_qC_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 16.54 **HRMS:** m/z calcd for $C_{16}H_{30}O_3P$ $(M+H)^+$ 301.1933, found 301.1913. **$[\alpha]_D^{20}$ =** +2.27 (*c* 2.07, CH_2Cl_2), **Rf:** 0.17 (4:6 EtOAc/*n*-hexane). **Yield:** 56% (336 mg), yellow oil.

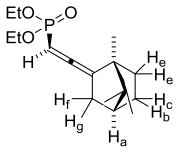
(S)-diethyl (2-((1R,4S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ylidene)-vinyl)phosphonate 259g



259g

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (3H, s, C(CH_3)($C\underline{H}_3$)), 1.16 (3H, s, C($C\underline{H}_3$)(CH_3)), 1.20 (3H, s, $C\underline{H}_3C_qCH_aH_b$), 1.30-1.35 (1H, m, $C\underline{H}_aH_b$), 1.33 (6H, t, J = 7.1 Hz, P($OCH_2C\underline{H}_3$)$_2$), 1.46-1.58 (3H, m, $C\underline{H}_cH_d$, $C\underline{H}_fH_g$), 1.69-1.75 (1H, m, $CH_a\underline{H}_b$), 1.77-1.84 (1H, m, $CH_c\underline{H}_d$), 1.87-1.92 (1H, m, $C\underline{H}_e$), 3.99-4.20 (4H, m, P($OC\underline{H}_2CH_3$)$_2$), 5.42 (1H, d, J = 8.6 Hz, C$\underline{H}$P) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 15.3 (P($OCH_2\underline{C}H_3$)), 15.4 (P($OCH_2\underline{C}H_3$)), 17.9 ($\underline{C}H_3C_qCH_aH_b$), 24.31 (($\underline{C}H_3$)($CH_3$)$C_q$), 24.34 ($\underline{C}H_cH_d$), 27.7 (d, $^5J_{PC}$ = 6 Hz, (CH_3)($\underline{C}H_3$)C_q), 34.1 (d, $^5J_{PC}$ = 7 Hz, $\underline{C}H_fH_g$), 43.3 (d, $^4J_{PC}$ = 6 Hz, $\underline{C}_qCH_e$), 44.0 (d, $^5J_{PC}$ = 1 Hz, $\underline{C}H_aH_b$), 46.8 ($\underline{C}H_e$), 49.1 (d, $^4J_{PC}$ = 5 Hz, $\underline{C}_qCH_aH_b$), 60.8 (d, $^2J_{PC}$ = 3 Hz, P($O\underline{C}H_2CH_3$)), 60.9 (d, $^2J_{PC}$ = 3 Hz, P($O\underline{C}H_2CH_3$)), 83.0 (d, $^1J_{PC}$ = 200 Hz, P$\underline{C}$H), 121.7 (d, $^3J_{PC}$ = 18 Hz, $PCHC_q\underline{C}_q$), 203.6 ($PCH\underline{C}_qC_q$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 16.70 **HRMS:** m/z calcd for $C_{16}H_{28}O_3P$ (M + H) 299.1776, found 299.1779. **$[\alpha]^{23}_D$ =** -65.77 (*c* 2.12, CH_2Cl_2) **Rf:** 0.17 (5/5 EtOAc/*n*-hexane). **Yield:** 67% (598 mg), transparent liquid.

(R)-diethyl (2-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)-vinyl)phosphonate 259h



259h

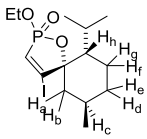
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, s, C($C\underline{H}_3$)(CH_3)), 0.91 (3H, s, C(CH_3)($C\underline{H}_3$)), 0.94 (3H, s, $C\underline{H}_3C_qCH_dH_e$), 1.19-1.26 (1H, m, $C\underline{H}_bH_c$), 1.31 (3H, t, $^3J_{HH}$ = 7.0 Hz, P($OCH_2C\underline{H}_3$)), 1.32 (3H, t, $^3J_{HH}$ = 7.1 Hz, P($OCH_2C\underline{H}_3$)), 1.44-1.50 (1H, m, $C\underline{H}_gH_f$), 1.62-1.71 (1H, m, $C\underline{H}_eH_d$), 1.75-1.85 (2H, m, $CH_b\underline{H}_c$, $C\underline{H}_a$), 2.05-2.12 (1H, m, $C\underline{H}_fH_g$), 2.56-2.66 (1H, m, $CH_e\underline{H}_d$), 3.99-4.12 (4H, m, P($OC\underline{H}_2CH_3$)$_2$), 5.26-5.30 (1H, m, P$\underline{C}$H). **^{13}C NMR (100MHz, $CDCl_3$) δ:** 13.0 ($\underline{C}H_3C_qCH_dH_e$), 16.3 (P($OCH_2\underline{C}H_3$)), 16.4 (P($OCH_2\underline{C}H_3$)), 18.6 (C($\underline{C}H_3$)($CH_3$)), 19.7 (C($CH_3$)($\underline{C}H_3$)), 27.7 ($\underline{C}H_bH_c$), 34.5 (d, $^4J_{PC}$ = 6 Hz, $\underline{C}H_fH_g$), 34.9 (d, $^5J_{PC}$ = 6 Hz, $\underline{C}H_dH_e$), 44.9 ($\underline{C}H_a$), 48.6 (d, $^5J_{PC}$ = 2 Hz, $\underline{C}$(CH_3)(CH_3)), 52.5 (d, $^4J_{PC}$ = 5 Hz, $CH_2\underline{C}CH_3$), 61.8 (d, $^2J_{PC}$ = 6 Hz, P($O\underline{C}H_2CH_3$)), 61.9 (d, $^2J_{PC}$ = 6 Hz, P($O\underline{C}H_2CH_3$)), 81.9 (d, $^1J_{PC}$ = 198 Hz, P$\underline{C}$H), 112.8 (d, $^3J_{PC}$ = 17 Hz, $PCHC_q\underline{C}_q$), 205.9 ($PCH\underline{C}_qC_q$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 16.50. **HRMS:** m/z calcd for $C_{16}H_{28}O_3P$ $(M+H)^+$, 299.1776, found 299.1771. **$[\alpha]^{23}_D$ =** -99.80 (*c* 9.98, CH_2Cl_2) **Rf:** 0.19 (5:5 EtOAc/*n*-hexane). **Yield:** 59% (351 mg), yellow oil.

4.8.4. Synthesis of chiral spirocyclic oxaphospholenes

Iodine (84 mg, 0.3 mmol) was added to a Schlenk tube, charged with a solution of allenylphosphonate **259b** (100 mg, 0.3 mmol) in cyclohexane. The reaction was stirred for 30 minutes at 80 °C, after which 10 mL dichloromethane, $Na_2S_2O_5$ and few drops of water were added and stirred until completely decolorization. The organic layer was eventually dried over $MgSO_4$ and the solvent evaporated under reduced pressure to immediately give the desired spirocyclic oxaphospholenes **263b** (121 mg, 0.31 mmol) as a mixture of diastereomers at the phosphorus atom.

(5S,6S,9R)-2-ethoxy-4-iodo-6-isopropyl-9-methyl-1-oxa-2-phosphaspiro[4.5]dec-3-ene 2-oxide 263a

dr: 61/39

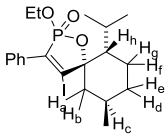


263a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.75-1.02 (10 H, m, CH($C\underline{H}_3$)$_2$, CHC$\underline{H}_3$, C$\underline{H}_d$H$_e$), 1.32 (3H, t, *J* = 7.1 Hz, POCH$_2$C$\underline{H}_3$), 1.43-1.94 (8H, m, C$\underline{H}_c$, C$\underline{H}_a\underline{H}_b$, C$\underline{H}$(CH$_3$)$_2$, C$\underline{H}_h$, CH$_d\underline{H}_e$, C$\underline{H}_f\underline{H}_g$), 3.95-4.37 (2H, m, POC$\underline{H}_2CH_3$), 6.56 (1H, d, $^2J_{PH}$ = 26.3 Hz, PC$\underline{H}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.7 (d, $^3J_{PC}$ = 5 Hz, POCH$_2$C$\underline{H}_3$), 17.5 (CH($\underline{C}H_3$)$_2$), 21.1 ($\underline{C}H_fH_g$), 22.0 (CHC$\underline{H}_3$), 23.8 (d, $^5J_{PC}$ = 4 Hz, CH($\underline{C}H_3$)$_2$), 26.5 ($\underline{C}H_c$), 28.5 (d, $^4J_{PC}$ = 4 Hz, $\underline{C}$H(CH$_3$)$_2$), 34.3 ($\underline{C}H_dH_e$), 45.3 ($\underline{C}H_aH_b$), 46.9 (d, $^3J_{PC}$ = 4 Hz, $\underline{C}H_h$), 63.1 (d, $^2J_{PC}$ = 7 Hz, PO$\underline{C}$H$_2$CH$_3$), 94.6 (d, $^2J_{PC}$ = 4 Hz, O$\underline{C}_q$), 127.5 (d, $^1J_{PC}$ = 156 Hz, P$\underline{C}$H), 127.7 (d, $^2J_{PC}$ = 27 Hz, I$\underline{C}_q$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 33.47 **HRMS:** m/z calcd for $C_{14}H_{25}IO_3P$ (M + H) 399.0586, found 399.0587. **Yield:** 91% (108 mg), yellow liquid.

(5S,6S,9R)-2-ethoxy-4-iodo-6-isopropyl-9-methyl-3-phenyl-1-oxa-2-phosphaspiro[4.5]dec-3-ene 2-oxide 263b

dr: 61/39



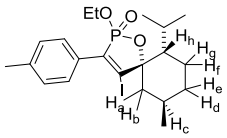
263b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.81-1.05 (10 H, m, CH($C\underline{H}_3$)$_2$, CHC$\underline{H}_3$, C$\underline{H}_d$H$_e$), 1.16 (3H, t, *J* = 6.6 Hz, POCH$_2$C$\underline{H}_3$), 1.51-1.97 (8H, m, C$\underline{H}_c$, C$\underline{H}_a\underline{H}_b$, C$\underline{H}$(CH$_3$)$_2$, C$\underline{H}_h$, CH$_d\underline{H}_e$, C$\underline{H}_f\underline{H}_g$), 3.95-4.30 (2H, m, POC$\underline{H}_2CH_3$), 7.33-7.45 (3H, m, CH$_{ar}$), 7.50-7.60 (2H, m, CH$_{ar}$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 16.6 (d, $^3J_{PC}$ = 5 Hz, POCH$_2$C$\underline{H}_3$), 17.7 (CH($\underline{C}H_3$)$_2$), 21.2 ($\underline{C}H_fH_g$), 22.1 (CHC$\underline{H}_3$), 23.9 (d, $^5J_{PC}$ = 4 Hz, CH($\underline{C}H_3$)$_2$), 26.6 ($\underline{C}H_c$), 28.5 ($\underline{C}$H(CH$_3$)$_2$), 34.3 ($\underline{C}H_dH_e$), 46.0 (s, $\underline{C}H_aH_b$), 46.7 (d, $^3J_{PC}$ = 4 Hz, $\underline{C}H_h$), 63.4 (d, $^2J_{PC}$ = 7 Hz, PO$\underline{C}$H$_2$CH$_3$), 92.6 (d, $^2J_{PC}$ = 4 Hz, O$\underline{C}_q$), 125.2 (d, $^2J_{CP}$ = 39 Hz, I$\underline{C}_q$), 128.3 (d, $^4J_{CP}$ = 6 Hz, $\underline{C}H_{ar,o}$), 128.6 (2x $CH_{ar,m}$), 129.0 (d, $^6J_{CP}$ = 1 Hz, $CH_{ar,p}$), 132.6 (d, $^2J_{CP}$ = 11 Hz, $C_{q,\,ar}$), 136.6 (d, $^1J_{PC}$ = 151 Hz, P$\underline{C}_q$) **^{31}P NMR (161 MHz, $CDCl_3$)**

δ: 33.47 **HRMS:** m/z calcd for $C_{20}H_{29}IO_3P$ (M + H) 475.0899, found 475.0898. **Yield:** 94 % (133 mg), yellow liquid.

(5S,6S,9R)-2-ethoxy-4-iodo-6-isopropyl-9-methyl-3-(*p*-tolyl)-1-oxa-2-phosphaspiro[4.5]dec-3-ene 2-oxide 263c

dr: 62/48

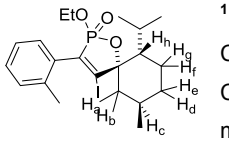


263c

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85-0.98 (10H, m, CH($C\underline{H}_3$)$_2$, CHC$\underline{H}_3$, C$\underline{H}_d\underline{H}_e$), 1.18 (3H, t, *J* = 7.1 Hz, POCH$_2$C$\underline{H}_3$), 1.53-2.06 (8H, m, C$\underline{H}_c$, C$\underline{H}_a\underline{H}_b$, C$\underline{H}$(CH$_3$)$_2$, C$\underline{H}_h$, C$\underline{H}_f\underline{H}_g$, CH$_d\underline{H}_e$), 2.37 (3H, s, $C\underline{H}_3C_{q,ar}$), 3.98-4.22 (2H, m, P(OC$\underline{H}_2$CH$_3$)), 7.22 (2H, *J* = 7.9 Hz, C$\underline{H}_{ar}$), 7.45-7.51 (2H, m, C$\underline{H}_{ar}$). **^{13}C NMR (100MHz, $CDCl_3$) δ:** 16.5 (d, $^3J_{PC}$ = 5 Hz, P(OCH$_2\underline{C}$H$_3$)), 17.7 (CH($\underline{C}$H$_3$)(CH$_3$)), 21.1 ($\underline{C}H_fH_g$), 21.4 ($\underline{C}H_3C_{q,ar}$), 22.0 (CH(CH$_3$)($\underline{C}$H$_3$)), 23.8 (CH$\underline{C}$H$_3$), 26.5($\underline{C}H_c$), 28.5 ($\underline{C}H_h$), 34.4 ($\underline{C}H_dH_e$), 46.0($\underline{C}H_aH_b$), 46.6($\underline{C}$H(CH$_3$)$_2$), 63.3 (d, $^2J_{PC}$ = 7 Hz, P(O$\underline{C}$H$_2$CH$_3$)), 92.4 (d, $^2J_{PC}$ = 4 Hz, O$\underline{C}_q$), 124.2 (d, $^2J_{PC}$ = 40 Hz, PC$_q\underline{C}_q$I), 127.9 (d, $^3J_{PC}$ = 6 Hz, C_{ar}H), 129.2 (C_{ar}H), 129.5 (d, $^2J_{PC}$ = 10 Hz, PC$_q\underline{C}_{q,ar}$), 136.0 (d, $^1J_{PC}$ = 150 Hz, P$\underline{C}_q$), 139.0 (d, $^5J_{PC}$ = 1 Hz, $\underline{C}_{q,ar}$CH$_3$). **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 28.87 **HRMS:** m/z calcd for $C_{21}H_{31}IO_3P$ $(M+H)^+$ 489.1056, found 489.1043. **Yield:** 87% (127 mg), yellow oil.

(5S,6S,9R)-2-ethoxy-4-iodo-6-isopropyl-9-methyl-3-(*o*-tolyl)-1-oxa-2-phosphaspiro[4.5]dec-3-ene 2-oxide 263d

For each epimer, a pair of rotamers is observed at room temperature, due to hindered rotation around the $C_{oxaphospholene}$ - $C_{o\text{-}tolyl}$ bond. When recording the ^{1}H NMR spectrum at 60 °C, the signals for the benzylic protons of each epimer merge together, appearing as one, almost entirely superimposed broad singlet. At 75 °C, carbon signals sufficiently sharpened to reduce hindered rotation and one epimer could be described as was the case for the previous derivatives. In ^{31}P NMR, a hump of broadened signals was observed. An accurate measurement of the diastereomeric ratio could not be obtained.



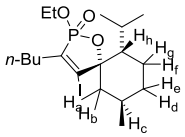
263d

^{1}H NMR (400 MHz, DMSO-d_6, 60 °C) δ: 0.88-0.99 (10H, m, CH($C\underline{H}_3$)$_2$, CHC$\underline{H}_3$, C$\underline{H}_d\underline{H}_e$), 1.00-1.14 (3H, m, P(OCH$_2$C$\underline{H}_3$)), 1.46-1.91 (8H, m, C$\underline{H}_c$, C$\underline{H}_a\underline{H}_b$, C$\underline{H}$(CH$_3$)$_2$, C$\underline{H}_h$, C$\underline{H}_f\underline{H}_g$, CH$_d\underline{H}_e$), 2.26 (3H, s, $C\underline{H}_3C_{q,ar}$, major), 2.27 (3H, s, $C\underline{H}_3C_{q,ar}$, minor), 3.92-4.08 (2H, m, P(OC$\underline{H}_2$CH$_3$)), 6.90-7.10 (1H, m, C$\underline{H}_{ar}$), 7.22-7.35 (3H, m, C$\underline{H}_{ar}$). **^{13}C NMR (100MHz, DMSO-d_6, 75 °C) δ:** 16.7 (d, $^3J_{CP}$ = 4 Hz, P(OCH$_2\underline{C}$H$_3$)), 17.8 (CH($\underline{C}$H$_3$)(CH$_3$)), 19. (d, $^3J_{CP}$ = 1

Hz, $\underline{C}H_3C_{q,ar}$), 21.4 ($\underline{C}H_fH_g$), 22.1 ($CH(CH_3)(\underline{C}H_3)$), 24.1 ($CH\underline{C}H_3$), 26.7 ($\underline{C}H_c$), 28.5 ($\underline{C}H_h$), 34.4 ($\underline{C}H_dH_e$), 46.0 ($\underline{C}H_aH_b$), 47.2 ($\underline{C}H(CH_3)_2$), 63.2 (d, $^2J_{PC}$ = 7 Hz, $P(O\underline{C}H_2CH_3)$), 92.8 (d, $^2J_{PC}$ = 4 Hz, $O\underline{C}_q$), 126 ($C_{ar}H$), 128.6 ($C_{ar}H$), 129.1 ($C_{ar}H$), 129.7 (d, $^2J_{PC}$ = 37 Hz, $PC_q\underline{C}_qI$), 130.0 (d, $^1J_{PC}$ = 170 Hz, $P\underline{C}_q$), 130.8 ($C_{ar}H$), 138.0 ($PC_q\underline{C}_{q,ar}$), 139.5 ($PC_qC_q\underline{C}_{q,ar}$). **^{31}P NMR (161 MHz, DMSO-d_6, 60 °C) δ:** 28.0-30.7 (broadened peaks). **HRMS:** m/z calcd for $C_{21}H_{31}IO_3P$ $(M+H)^+$ 489.1056, found 489.1035. **Yield:** 91% (133 mg), yellow oil.

(5S,6S,9R)-3-butyl-2-ethoxy-4-iodo-6-isopropyl-9-methyl-1-oxa-2-phosphaspiro[4.5]dec-3-ene 2-oxide 263e

dr = 57/43

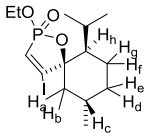


263e

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)(CH_3)$ or $C\underline{H}_3CH_c$), 0.89-1.02 (1H, m, $C\underline{H}_dH_e$), 0.898 (3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)(CH_3)$ or $C\underline{H}_3CH_c$), 0.904 (3H, d, *J* = 7.1 Hz, $CH(C\underline{H}_3)(CH_3)$ or $C\underline{H}_3CH_c$), 0.94 (3H, t, *J* = 7.3 Hz, $C\underline{H}_3CH_2$), 1.32 (3H, t, *J* = 7.1 Hz, $POCH_2C\underline{H}_3$), 1.21-1.99 (12H, m, $CH_3C\underline{H}_2$, $CH_3CH_2C\underline{H}_2$, $C\underline{H}_c$, $\underline{C}H(CH_3)_2$, $C\underline{H}_gCH_f$, $CH_d\underline{H}_e$, $C\underline{H}_aH_b$, $C\underline{H}_h$), 2.21-2.48 (2H, m, $C\underline{H}_2C_qP$), 4.08-4.33 (2H, m, $POC\underline{H}_2CH_3$) **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 12.8 ($\underline{C}H_3CH_2$), 15.7 (d, $^3J_{PC}$ = 5 Hz, $POCH_2\underline{C}H_3$), 16.6 (($\underline{C}H_3)_2CH$) or $\underline{C}H_3CH_c$), 20.0 ($CH_3\underline{C}H_2$ or $CH_3CH_2\underline{C}H_2$ or $CH_g\underline{C}H_f$), 21.0 (($\underline{C}H_3)_2CH$) or $\underline{C}H_3CH_c$), 21.50 ($CH_3\underline{C}H_2$ or $CH_3CH_2\underline{C}H_2$ or $CH_g\underline{C}H_f$), 22.8 (($\underline{C}H_3)_2CH$) or $\underline{C}H_3CH_c$), 25.4 ($\underline{C}H_c$ or $\underline{C}H(CH_3)_2$), 27.5 ($\underline{C}H_c$ or $\underline{C}H(CH_3)_2$), 28.6 ($CH_3\underline{C}H_2$ or $CH_3CH_2\underline{C}H_2$ or $CH_g\underline{C}H_f$), 30.5 (d, $^2J_{PC}$ = 12 Hz, $\underline{C}H_2C_qP$), 33.4 ($\underline{C}H_dH_e$), 44.7 ($\underline{C}H_aH_b$), 45.9 (d, $^3J_{PC}$ = 4 Hz, $\underline{C}H_h$), 61.7 (d, $^2J_{PC}$ = 7 Hz, $PO\underline{C}H_2CH_3$), 91.1 (d, $^2J_{PC}$ = 4 Hz, $O\underline{C}_q$), 124.8 (d, $^2J_{CP}$ = 40 Hz, $I\underline{C}_q$), 135.4 (d, $^1J_{PC}$ = 148 Hz, $P\underline{C}_q$) **^{31}P NMR (161 MHz, $CDCl_3$) δ:** 30.98 **HRMS:** m/z calcd for $C_{18}H_{33}IO_3P$ (M + H) 455.1212, found 455.1211. **Yield:** 95 % (129 mg), transparent liquid.

(5R,6R,9S)-2-ethoxy-4-iodo-6-isopropyl-9-methyl-1-oxa-2-phosphaspiro[4.5]dec-3-ene 2-oxide 263f

dr: 64/36



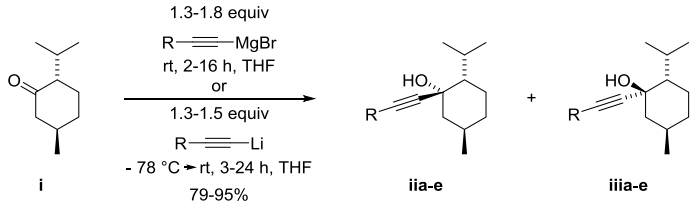
263f

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.81-0.97 (10H, m, $CH(C\underline{H}_3)_2$, $CHC\underline{H}_3$, $C\underline{H}_dH_e$), 1.33 (3H, t, ^3J = 7.1 Hz, $P(OCH_2C\underline{H}_3)$), 1.49-1.68 (6H, m, $C\underline{H}_c$, $CH_a\underline{H}_b$, $C\underline{H}(CH_3)_2$, $C\underline{H}_h$, $C\underline{H}_fH_g$), 1.81-1.85 (2H, m, $CH_d\underline{H}_e$, $C\underline{H}_aH_b$), 4.14-4.23 (2H, m, $P(OC\underline{H}_2CH_3)$), 6.57 (1H, $^2J_{PH}$ = 26.5 Hz, CHP). **^{13}C NMR (100MHz, $CDCl_3$) δ:** 16.5 (d $^3J_{PC}$ = 5 Hz, $POCH_2\underline{C}H_3$), 17.5 ($CH(\underline{C}H_3)(CH_3)$), 21.0 ($CHC\underline{H}_3$), 21.9

($\underline{C}H_fH_g$), 23.7 ($CH(CH_3)(\underline{C}H_3)$), 26.3 ($\underline{C}H_c$), 28.3 ($\underline{C}H(CH_3)_2$), 34.3 ($\underline{C}H_dH_e$), 45.4 ($CH_aH_b$), 46.8 (d, $^3J_{PC}$ = 4 Hz, $\underline{C}H_h$), 63.0 ($P(O\underline{C}H_2CH_3)$), 94.5 ($PO\underline{C}$), 127.4 (d, $^2J_{PC}$ = 30 Hz, C_qI), 127.5 (d, $^1J_{PC}$ = 155 Hz, $P\underline{C}H$). **^{31}P NMR δ:** 33.4 **HRMS:** m/z calcd for $C_{14}H_{25}IO_3P$ $(M+H)^+$ 399.0586, found 399.0596. **Yield:** 92% (109 mg), yellow oil.

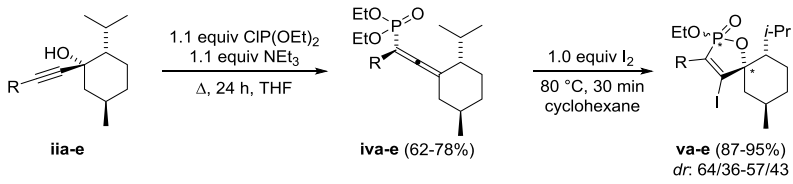
Summary

In order to explore the potential of novel reactive intermediates bearing a phosphonate moiety, a synthetic transformation of allenylphosphonates **iv** towards chiral, spirocyclic oxaphospholenes **v** was designed. Upon deprotection, these chiral spirocyclic oxaphospholenes could make up for interesting chiral inducers. Like BINOL phosphate catalysts, which are configurationally restricted because of hindered rotation around the binaphthyl bond, the spirocyclic connection locks the configuration in the case of the spirocyclic oxaphospholenes. The chirality in the products was introduced from chiral pool ketoterpenes. So first, a series of acetylides was added to (+)-menthone in excellent yields and good diastereoselectivities (Scheme 92)



Scheme 92: Addition of acetylides to ketoterpenes, yielding the corresponding propargyl alcohols.

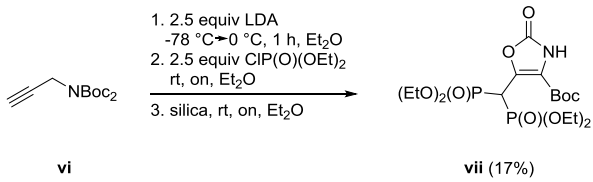
Propargylic alcohols are known to spontaneously rearrange to the corresponding allenylphosphonates upon treatment with diethyl chlorophosphite. Thus, using this [2,3]-sigmatropic rearrangement, an array of menthone-based allenylphosphonates **iva**-**e** were easily obtained (Scheme 93). Next, cyclization of the allenylphosphonates with a Lewis acid was found to be very effective. While a copper-catalysed procedure gave a mixture of the desired oxaphospholenes together with some other compounds, simple addition of an equimolar amount of iodine smoothly afforded the target compounds **va**-**e** as a mixture of epimers at the phosphorus atom in a 40/60 ratio in almost quantitative yields. Solvent screening revealed that Brønsted acid-catalysed cyclization could be avoided when the reaction was run in cyclohexane. No purification was needed at this stage. Different substituents on the allene were well tolerated, as even an *ortho*-methyl group did not prevent the iodine from being attacked by the distal double bond of the allene.



Scheme 93: Treatment of propargyl alcohols with diethyl chlorophosphite followed by cyclization of the resulting allenylphosphonates to yield chiral spirocyclic oxaphospholenes.

In a second series of derivatives, an ethynyl moiety was introduced to different ketoterpenic substrates. The (-)-menthone derived propargylic alcohol was isolated in excellent yield once again, while addition of the acetylide to (+)-fenchone and (-)-camphor occurred with almost perfect diastereoselectivity because of the increased steric hindrance. Under the optimized conditions the corresponding allenes were all obtained in decent yields. Although the (-)-menthone derivative reacted with similar ease as the first series of allenylphosphonates, (+)-fenchone and (-)-camphor based allenylphosphonates only reacted reluctantly. Increased steric hindrance around the double bond in the case of (+)-fenchone was thought to hamper the electrophilic addition, while rearrangements immediately occurred in the case of (-)-camphor. The created carbocation was found to be very prone to rearrangement, before the internal phosphonate nucleophile could intercept the carbocation.

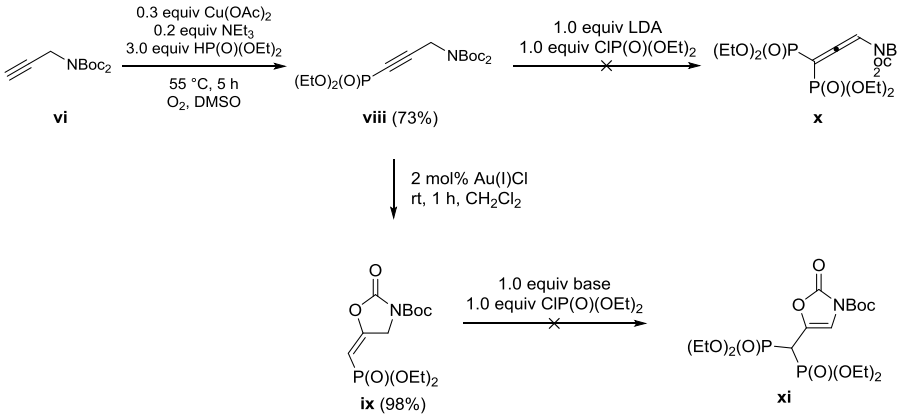
In a second part of this work, a one-pot procedure for the synthesis of 5-bisphosphonomethyl oxazol-2-ones was discovered (Scheme 94). The bisphosphonomethyl motif is present in important antiosteoporotic drugs, while the saturated counterparts of oxazol-2-ones, oxazolidin-2-ones, are pharmacophores in numerous other marketed drugs. Treatment of *N*,*N*-di-*tert*-butylprop-2-yn-1-ylimidodicarbonate **vi** with an excess of LDA and diethyl chlorophosphate afforded the 5-bisphosphonomethyl oxazol-2-one **vii** as the major product. Difficult purification resulted in a low 17% isolated yield and hence a stepwise approach was evaluated.



Scheme 94: One-pot synthesis of 5-bisphosphonomethyl oxazol-2-ones.

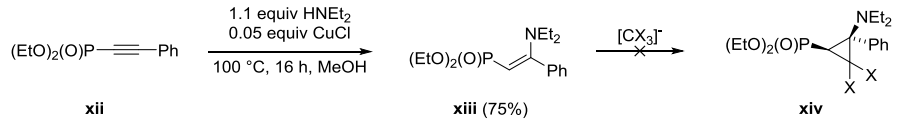
Treatment of *N*,*N*-di-*tert*-butylprop-2-yn-1-ylimidodicarbonate **vi** with a slight excess of organolithium base and diethyl chlorophosphate did afford the desired phosphonylated alkyne **viii**, but not very selectively (Scheme 95). Moreover, the phosphonylated alkyne could not be entirely separated from the other reaction products during purification. However, a

copper-catalyzed oxidative cross coupling of *N*,*N*-di-*tert*-butylprop-2-yn-1-ylimidodicarbonate with diethyl phosphite did yield the phosphonylated alkyne **viii**. With an excess of diethyl phosphite and a sufficient supply of oxygen, this literature procedure could be improved to produce phosphonylated alkynes on a 10 mmol scale in good yields. With 2 mol% Au(I)Cl, this intermediate was very efficiently cyclized to 5-phosphonomethylidene oxazol-2-ones **ix** in quantitative yield. Unfortunately, a second phosphonate group could not be introduced on the 5-phosphonomethylidene oxazol-2-one **ix**, nor on the alkynylphosphonate **viii**.



Scheme 95: Attempted stepwise preparation of 5-bisphosphonomethyl oxazol-2-ones.

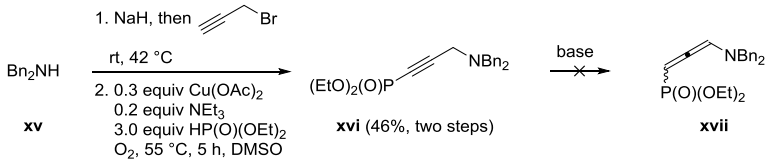
While an aminoallenylbisphosphonate **x** was thought to be an intermediate in the one-pot synthesis of 5-bisphosphonomethyl oxazol-2-one **vii**, this could not be confirmed experimentally. It was next investigated in the third chapter if aminoallenylphosphonates, which had never been reported at the start of this research, could be prepared and isolated. A Skattebøl rearrangement, converting dihalocyclopropanes to the corresponding allenes, was the key step in the first approach. Phosphonylated alkyne **xii** was easily accessible from the earlier improved literature procedure and was readily hydroaminated in good yield (Scheme 96). Unfortunately, the obtained enaminophosphonate **xiii** did not afford the dihalocyclopropyl aminophosphonate **xiv** upon treatment with various dihalocarbene sources.



Scheme 96: Attempted preparation of dihalocyclopropyl aminophosphonates.

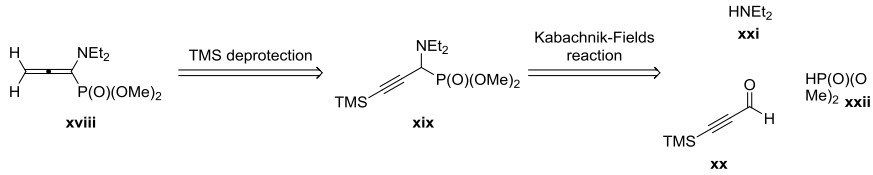
In a second approach, the isomerization of phosphonylated propargylamine **xvi** was evaluated (Scheme 97). None of the investigated bases was able to produce the 3-aminoallenylphosphonate **xvii**. Introduction of a phenyl group could favour the alkyne-allene isomerization step, but the preparation of the corresponding precursor *via* an A³ coupling was

not straightforward and efforts were cancelled even before the isomerization could be investigated.



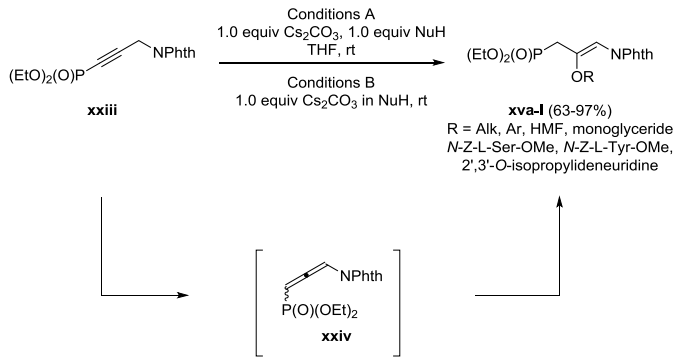
Scheme 97: Attempted synthesis of 3-aminoallenylphosphonates *via* 3-aminoprop-1-yn-1-ylphosphonates.

Alternatively, it was observed that the acetylide of prop-2-yn-1-yl phosphonate rearranged to the internal alkyne upon removal of the TMS group at the terminal alkyne. This spontaneous rearrangement would, however, be interesting to produce 1-aminoallenylphosphonates **xviii** if the TMS-protected alkyne **xix** could be aptly substituted (Scheme 98). To that end, a Kabachnik-Fields reaction between an ynaldehyde, a secondary amine and a dialkyl phosphite was evaluated. Irrespective of the order of the addition of the reagents, the three component reaction failed to produce the aminophosphonate **xix**.



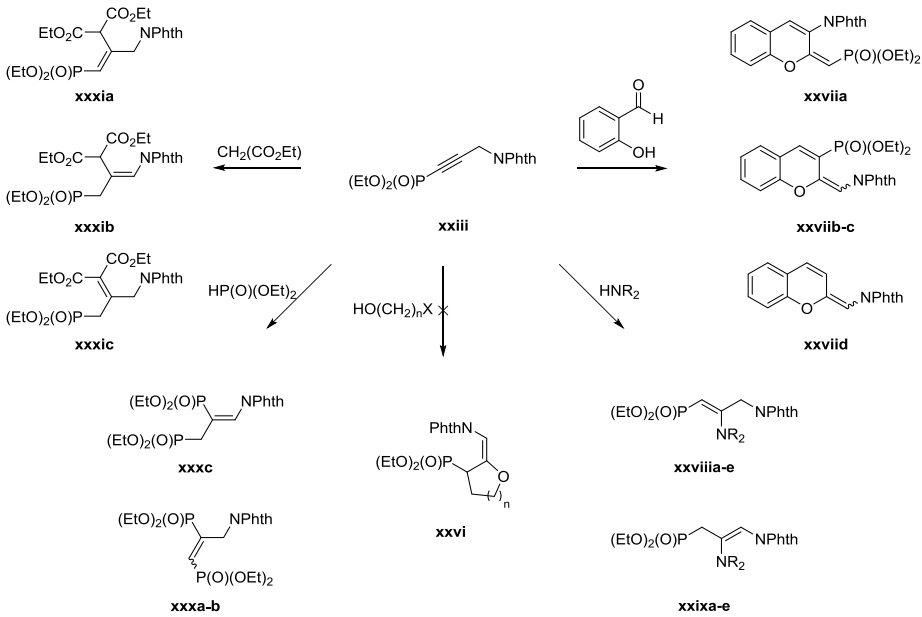
Scheme 98: Retrosynthetic approach towards 1-aminoallenylphosphonates.

As it was reasoned that *N*,*N*-dialkylaminoallenylphosphonates might be too electron rich to be formed, it was decided to study the isomerization of phthaloyl protected alkyne **xxiii**. A series of bases was evaluated and the 3-imidoallenylphosphonate **xxiv** was almost immediately detected in important amounts. With KO*t*-Bu, addition of *tert*-butoxide to the imidoallenylphosphonate **xxiv** was noticed. When focussing on this one-pot isomerization and β-alkoxylation, it was found that *O*-nucleophiles could add extremely easily under very mild conditions, in short reaction times and high yields (Scheme 99). More complex nucleophiles such as amino acids, monoglycerides and nucleobases could be coupled in similar fashion.



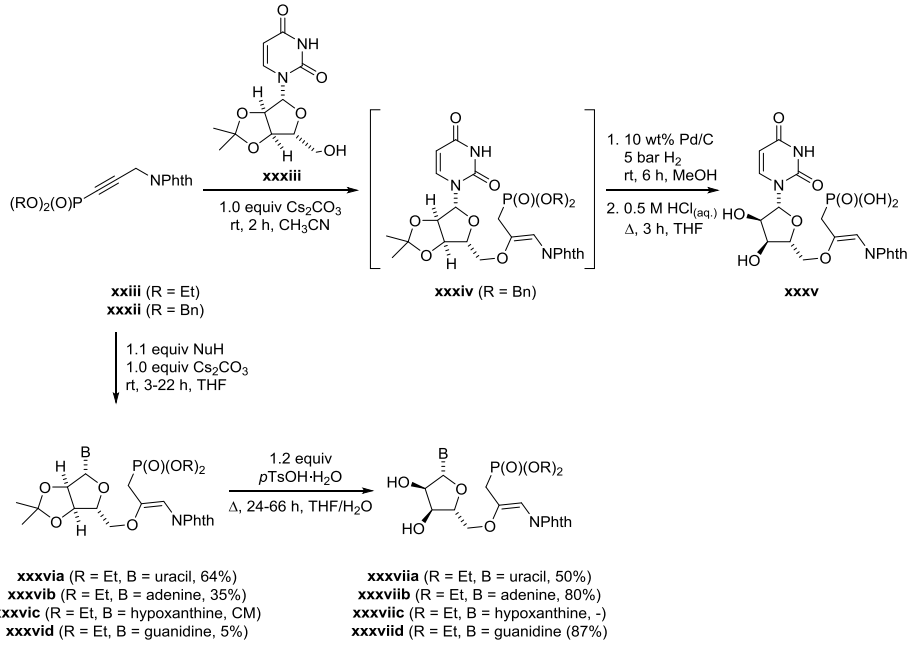
Scheme 99: Preparation of 3-imidoallenylphosphonates and *in situ* β-alkoxylation.

Next, it was investigated if substituted tetrahydrofurans **xxvi** could be obtained when treating the same precursor with haloalcohols (Scheme 100). Haloalcohols efficiently participated in the one-pot alkoxylation, although ring-closure did not occur. Ring-closure could be realized, on the other hand, when salicylaldehyde was used as a nucleophile. Three phosphonylated chromene isomers **xxviia**-**c** were produced, along a dephosphonylated chromene **xxviid**, originating from a Horner-Wadsworth-Emmons reaction. However, no conditions could be found that brought about a sufficient selectivity towards one of the reaction products. *N*-nucleophiles could be introduced as well, although not in each case with the same ease as *O*-nucleophiles. Diethylamine selectively yielded one regioisomer, while pyrrolidine and dibenzylamine gave a mixture of regioisomers. Diisopropylamine and *N*-methylphenylamine gave complex mixtures. Addition of diethylphosphite afforded novel imido-substituted vicinal bisphosphonates **xxvxa**-**c** and one product in which two equivalents of diethyl phosphite had been incorporated. Unfortunately, no conditions could be found that allowed the selective synthesis of one of these compounds. Carbon nucleophiles reacted as well, but only limited conversion was observed for the introduction of the cyanide anion. Diethyl malonate did efficiently add to the 3-imidoallenylphosphonate **xxiii**, but no selective conversion to one of the three regioisomers **xxxia**-**c** could be obtained.



Scheme 100: Overview of the nucleophiles reacted with 3-imidoallenylphosphonates.

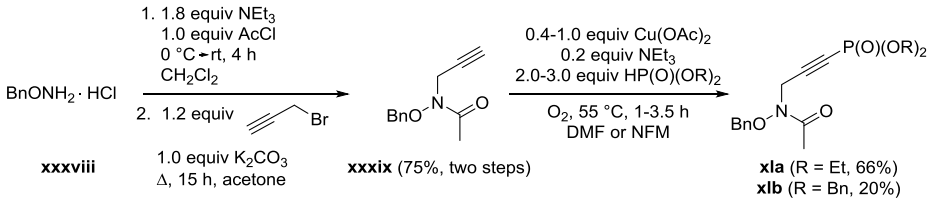
In a fifth chapter, it was investigated whether 3-imidoallenylphosphonates could be applied for the synthesis of new nucleoside phosphonates (Scheme 101). These nucleosides would be tested in a broad-spectrum antiviral test and should preferably have a deprotected ribose and phosphonic acid unit. Because dibenzyl phosphonates can give the corresponding phosphonic acid upon hydrogenation, addition of uridine acetonide to dibenzyl alkynylphosphonate **xxxii** was first evaluated. This was successful but the addition product could not be separated from the impurities. Purification at the stage of the deprotected ribose phosphonate or at the stage of the fully deprotected nucleoside phosphonic acid **xxxv**, both failed as well.



Scheme 101: Preparation of diethyl nucleoside phosphonate prodrugs.

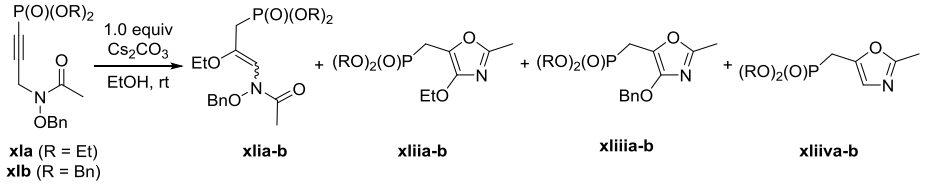
Except in the case of inosine addition, the diethyl nucleoside phosphonates **xxxvia**-**b** and **xxxvid** were successfully prepared, purified and accordingly treated with *p*TsOH. Eventually, four new diethyl nucleoside phosphonate prodrugs were obtained and screened for their biological properties. No antiviral activity of the nucleoside phosphonates was detected in cell cultures against any of the selected viruses – including HSV-1, HSV-2, para-influenza-3-virus, HIV-1, HIV-2 and yellow fever virus – at the highest concentrations tested. Influenza PA-Nter endonuclease was not inhibited by any of the four compounds either. On the other hand, the compounds were not found to be cytotoxic.

In the last chapter, a strategy towards new β-substituted fosmidomycin derivatives was explored, in which an aminoallenylphosphonate would be the key intermediate. Hydroxamic acid **xxxix** was obtained from *O*-benzyl hydroxylamine hydrochloride after acylation with acetyl chloride and alkylation with propargyl bromide (Scheme 102). The earlier developed cross coupling procedure with dialkyl phosphites could be applied once more, yielding the phosphonylated alkynes **xla**-**b**.



Scheme 102: Preparation of aminoallenylphosphonate precursors through acylation and alkylation of *O*-benzylhydroxylamine hydrochloride, followed by oxidative cross coupling with dialkyl phosphites.

When the introduction of ethanol was attempted, the addition product **xli** could be detected but not isolated (Scheme 103). Moreover, a cyclization reaction occurred, producing oxazoles **xlii**-**xliv**. A mechanism was proposed which explains the formation of these products and presumably starts with the elimination of the benzyloxy moiety. A few intermediates of this pathway could be obtained.



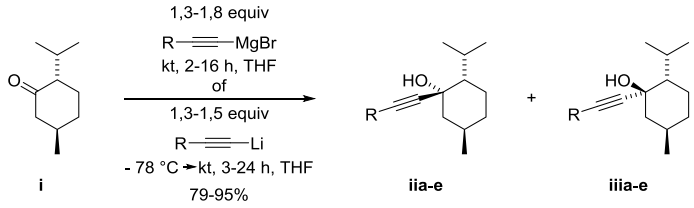
Scheme 103: Attempted preparation of β-substituted fosmidomycin derivatives.

Downregulating the acidity of the propargylic protons by replacing the *N*-acetyl group with a *N*-Boc group was not successful either, as loss of the benzyloxy group was observed again. In a final attempt to obtain β-substituted fosmidomycin derivatives, substrate **xla** was evaluated in the copper-catalyzed hydroamination reaction with diethylamine. Minor amounts of the desired product were detected in a complex mixture, but a double Michael addition seemed to have taken place. This route was finally abandoned as well.

In retrospect, it was illustrated that chiral allenylphosphonates with a ketoterpenic skeleton bring about an elegant entry into chiral spirocyclic oxaphospholenes. Further efforts should be made to produce the corresponding phosphonic acids in order to gauge their chiral inducing properties in asymmetric transformations. A second pinnacle was the first ever synthesis of 3-imidoallenylphosphonates. These hynod functionalized small molecules were prepared under extremely mild conditions from simple precursors and were swiftly functionalized at the central carbon atom with a variety of nucleophiles. Several transformations were characterized by a mediocre selectivity and their potential has to be elaborated in further research. In the search for novel antiviral lead compounds, these 3-imidoallenylphosphonates have engendered novel nucleoside phosphonates, while they were also evaluated in the design of novel fosmidomycin analogues.

Samenvatting

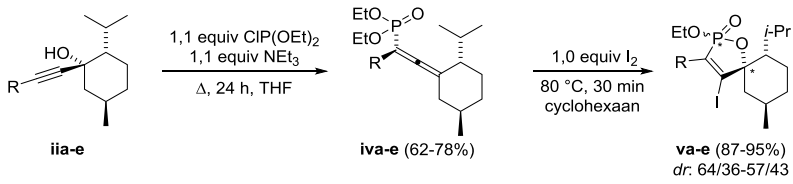
Om het potentieel van nieuwe reactieve intermediairen met een fosfonaatgroep te onderzoeken, werd een synthetische transformatie van allenylfosfonaten **iv** naar chirale, spirocyclische oxafosfolenen **v** ontworpen. Na ontscherming kunnen deze verbindingen dienen als interessante chirale *inducers*. Zoals BINOL-fosfaatkatalysatoren, die configurationeel beperkt zijn vanwege de gehinderde rotatie rond de binaftylbinding, legt ook de spirocyclische connectie in deze chirale molecule de configuratie vast. De chiraliteit in deze verbindingen werd geïntroduceerd gebruikmakende van ketoterpenen uit de *chiral pool*. Zodoende werd in eerste instantie een reeks acetyliden geaddeerd aan (+)-menthon met uitstekende rendementen en een goede diastereoselectiviteit (Schema 104).



dr **iia-e**/**iiia-e**: 73/27-81/19

Schema 104: Addtie van acetyliden aan ketoterpenen om de overeenkomstige propargylalcoholen te bekomen.

Propargylische alcoholen ondergaan spontaan een omlegging tot de overeenkomstige allenylfosfonaten wanneer ze behandeld worden met diëthylchloorfosfiet. Gebruikmakende van deze [2,3]-sigmatrope omlegging, werd op eenvoudige wijze een verzameling menthon-gebaseerde allenylfosfonaten **iva**-**e** bekomen (Schema 105). Een Lewiszuurgemedieerde ringsluiting bleek zeer doeltreffend te zijn. Hoewel een $CuBr_2$-gemedieerde procedure een mengsel van de gewenste oxafosfolenen gaf samen met enkele onzuiverheden, leverde het toevoegen van een equimolaire hoeveelheid dijood de doelstructuren **va**-**e** bijna kwantitatief als een mengsel van epimeren aan het fosforatoom. Brønstedzuurgekatalyseerde ringsluiting kon worden vermeden als de reactie uitgevoerd werd in cyclohexaan. Opzuivering was overbodig na deze reactiestap. Een verscheidenheid aan substituenten op het alleen werd goed getolereerd, aangezien zelfs een *ortho*-methylgroep de elektrofiele additie van jood aan de dubbele binding niet verhinderde.

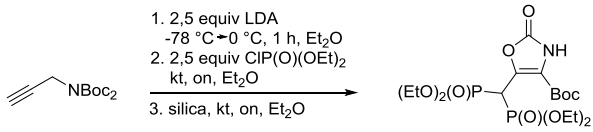


iia-e **iva-e** (62-78%) **va-e** (87-95%)
dr: 64/36-57/43

Schema 105: Behandeling van propargylalcoholen met diëthylchloorfosfiet, gevolgd door cyclisatie van de bekomen allenylfosfonaten om chirale spirocyclische oxafosfolenen te bekomen.

In een tweede reeks derivaten werd een ethynylgroep geïntroduceerd op een aantal verschillende ketoterpeensubstraten. Het propargylisch alcohol, afgeleid van (-)-menthon, kon opnieuw geïsoleerd worden met een uitstekend rendement, terwijl de additie van het acetylide aan (+)-fenchon en (-)-kamfer dankzij de grote sterische hinder met een bijna perfecte diastereoselectiviteit verliep. Onder de eerder geoptimaliseerde omstandigheden konden de overeenkomstige allenylfosfonaten opnieuw geïsoleerd worden met degelijke rendementen. Het (-)-menthonderivaat leverde, volledig analoog aan de vorige gevallen, het oxafosfoleen, maar de op (+)-fenchon- en (-)-kamfergebaseerde allenylfosfonaten reageerden slechts moeizaam in de cyclisatiestap. In het geval van (+)-fenchon verhinderde de grote sterische hinder rond de distale dubbele binding vermoedelijk de elektrofiele additie, terwijl er meteen allerhande omleggingen optraden in het geval van (-)-kamfer. Deze omleggingen vonden plaats voordat het gecreëerde carbokation door het interne nucleofiel onderschept kon worden.

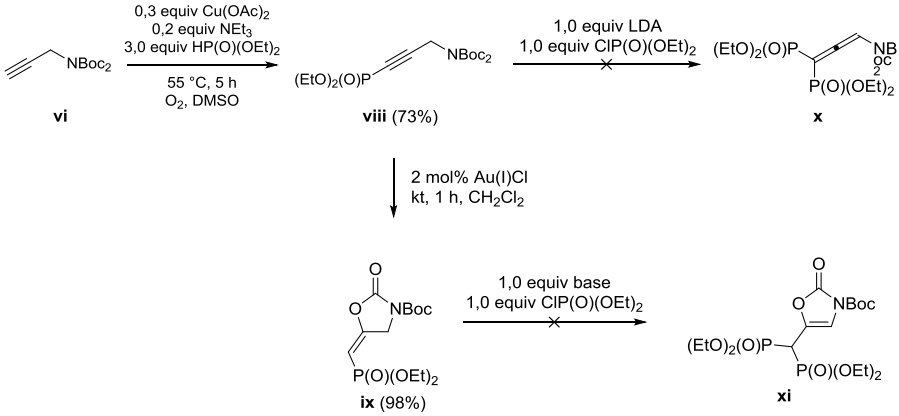
In een tweede hoofdstuk werd de *one-pot*-procedure voor de synthese van 5-bisfosfonomethyl oxazol-2-onen **vii** onderzocht (Schema 106). Het bisfosfonomethylmotief vindt men terug in geneesmiddelen, gebruikt voor de behandeling van osteoporose, terwijl de verzadigde tegenhangers van de oxazol-2-onen, oxazolidin-2-onen, de farmacofore eenheid vormen van verschillende andere geneesmiddelen. Behandeling van *N*,*N*-di-*tert*-butylprop-2-yn-1-ylimidodicarbonaat **vi** met een overmaat aan LDA en diëthylchloorfosfaat leverde het 5-bisfosfonomethyloxazol-2-on **vii** als het voornaamste reactieproduct. Een moeilijke opzuivering resulteerde echter in een laag rendement van 17% en bijgevolg werd een stapsgewijze benadering overwogen.



vi **vii** (17%)

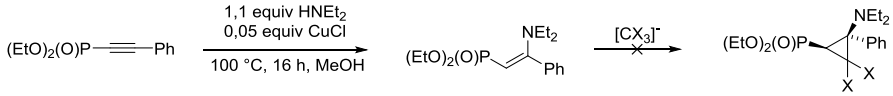
Schema 106: *One-pot* synthese van 5-bisfosfonomethyl oxazol-2-onen.

Via behandeling van *N*,*N*-di-*tert*-butylprop-2-yn-1-ylimidodicarbonaat **vi** met een lichte overmaat aan organolithiumbase en diëthylchloorfosfaat werd het gefosfonyleerd alkyn **viii** bekomen, maar niet op een selectieve manier (Schema 107). Bovendien kon het gewenste product tijdens opzuivering niet volledig gescheiden worden van andere onzuiverheden. Een koper-gekatalyseerde oxidatieve *cross*-koppelingsreactie van *N*,*N*-di-*tert*-butylprop-2-yn-1-ylimidodicarbonaat **vi** met diëthylfosfiet leverde echter wel het gefosfonyleerde alkyn **viii**. Met behulp van een overmaat diëthylfosfiet en voldoende zuurstofgas kon deze literatuurprocedure geoptimaliseerd worden zodat gefosfonyleerde alkynen eenvoudig op een 10 mmol-schaal bereid konden worden. Dit intermediair kon vervolgens eenvoudig en kwantitatief ringsluiting ondergaan tot het 5-fosfonomethinoxazol-2-on **ix** door middel van 2 mol% Au(I)Cl. Helaas kon een tweede fosfonaatgroep niet ingevoerd worden, niet op het niveau van het 5-fosfonomethinoxazol-2-on **ix**, noch in de reactie met alkynylfosfonaat **viii**.



Schema 107: Poging tot stapsgewijze bereiding van 5-bisfosfonomethyl oxazol-2-onen.

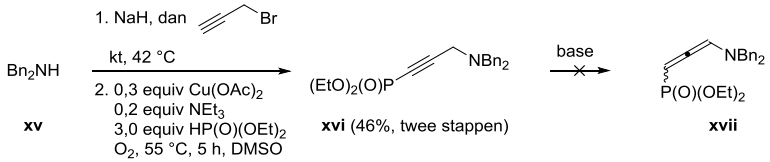
Hoewel vermoed werd dat aminoallenylbisfosfonaat **x** een intermediair was in de *one-pot*-synthese van 5-bisfosfonomethyloxazol-2-on **vii**, kon dit niet experimenteel bewezen worden. In het derde luik van dit werk werd onderzocht of aminoallenylfosfonaten, waarvan bij het begin van dit onderzoek nog nooit een synthese gerapporteerd was, bereid en geïsoleerd konden worden. Een Skattebøl omlegging, een reactie die dihalocyclopropanen omzet in de overeenkomstige allenen, was de cruciale stap in deze eerste benadering. Gefosfonyleerde alkynen konden nu eenvoudig bereid worden dankzij de eerder ontwikkelde koppelingsreactie met dialkylfosfieten (Schema 108). Alkyn **xii** kon vlot gehydroamineerd worden. Helaas gaven de bekomen enaminofosfonaten **xiii** geen aanleiding tot de vorming van dihalocyclopropylaminofosfonaten **xiv**, wanneer deze eerste behandeld werden met verschillende dihalocarbeenprecursoren.



xii **xiii** (75%) **xiv**

Schema 108: Poging tot bereiding van dihalocyclopropyl aminofosfonaten.

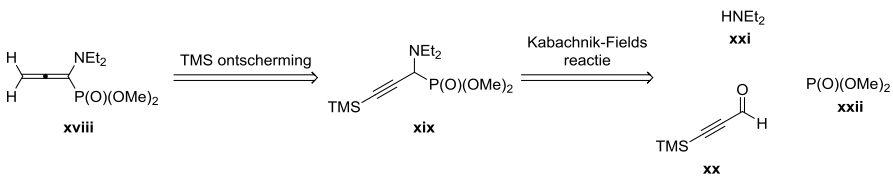
In een tweede strategie werd de isomerisatie van gefosfonyleerde propargylamines **xvi** geëvalueerd (Schema 109). Geen enkele van de onderzochte basen was in staat om het 3-aminoallenylfosfonaat **xvii** te genereren. Het invoeren van een extra fenylgroep zou de daaropvolgende isomerisatie gunstig kunnen beïnvloeden, maar de bereiding van precursor *via* een A³ koppelingsreactie bleek niet voordehandliggend te zijn. Uiteindelijk werd deze strategie verlaten voordat de isomerisatiereactie onderzocht kon worden.



xv **xvi** (46%, twee stappen) **xvii**

Schema 109: Poging tot synthese van 3-aminoallenylfosfonaten via 3-aminoprop-1-yn-1-ylfosfonaten.

Anderzijds werd vastgesteld dat het acetylide van prop-2-yn-1-ylfosfonaat zich spontaan omlegde tot het intern alkyn wanneer de TMS-groep op het eindstandig alkyn ontschermd werd. Deze spontane omlegging zou echter op een elegante manier aanleiding kunnen geven tot 1-aminoallenylfosfonaten als het TMS-beschermd alkyn **xix** met de gepaste substituenten uitgerust zou kunnen worden (Schema 110). Daarom werd de Kabachnik-Fieldsreactie tussen een ynaldehyde, een secundair amine en een dialkylfosfiet onderzocht. Onafhankelijk van de volgorde waarin de reagentia toegevoegd worden, kon het aminofosfonaat **xix** niet bereid worden.

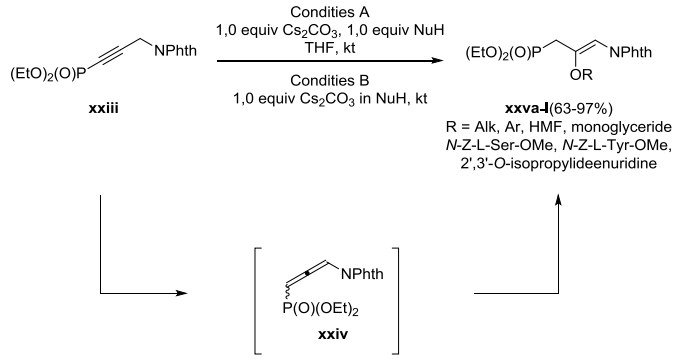


xviii **xix** **xx** **xxi** **xxii**

Schema 110: Retrosynthetische benadering tot 1-aminoallenylfosfonaten.

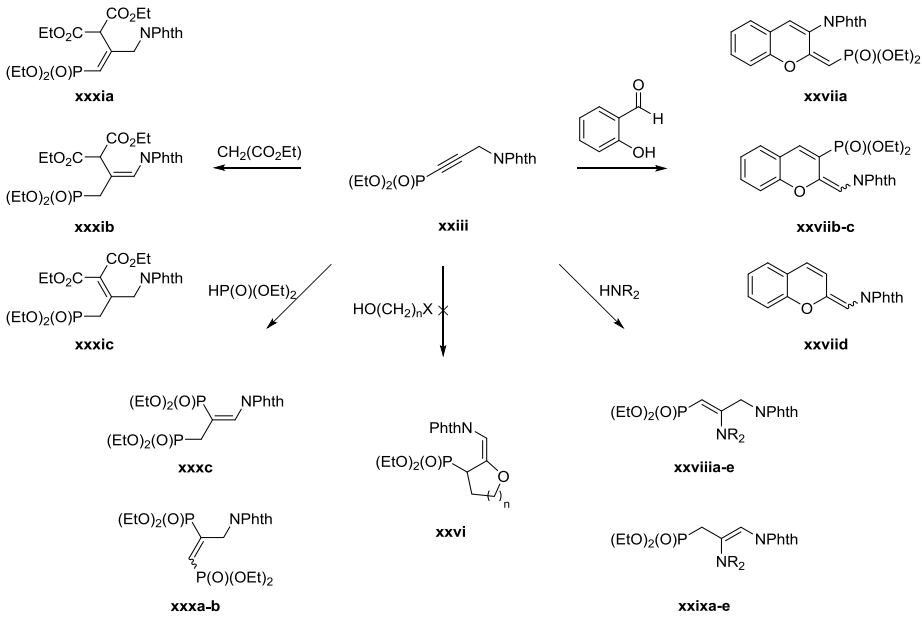
Vermoedelijk zijn de *N*,*N*-dialkylaminoallenylfosfonaten te elektronenrijk om gevormd te worden. Daarom werd beslist om de isomerisatiereactie van het ftaloylbeschermd alkyn **xxiii** te bestuderen. Het gebruik van een aantal verschillende basen werd geëvalueerd en bijna onmiddellijk kon het 3-imidoallenylfosfonaat **xxiv** gedetecteerd worden in belangrijke hoeveelheden. Wanneer KO*t*-Bu gebruikt werd, trad additie van *tert*-butoxide op aan het imidoallenylfosfonaat **xxiv**. Wanneer de focus op deze *one-pot* isomerisatie en β-alkoxylering

gelegd werd, bleken *O*-nucleofielen zeer snel, onder zeer milde omstandigheden, en met uitstekende rendementen te adderen (Schema 111). Complexere nucleofielen zoals aminozuren, monoglyceriden en nucleosiden konden op dezelfde manier gekoppeld worden.



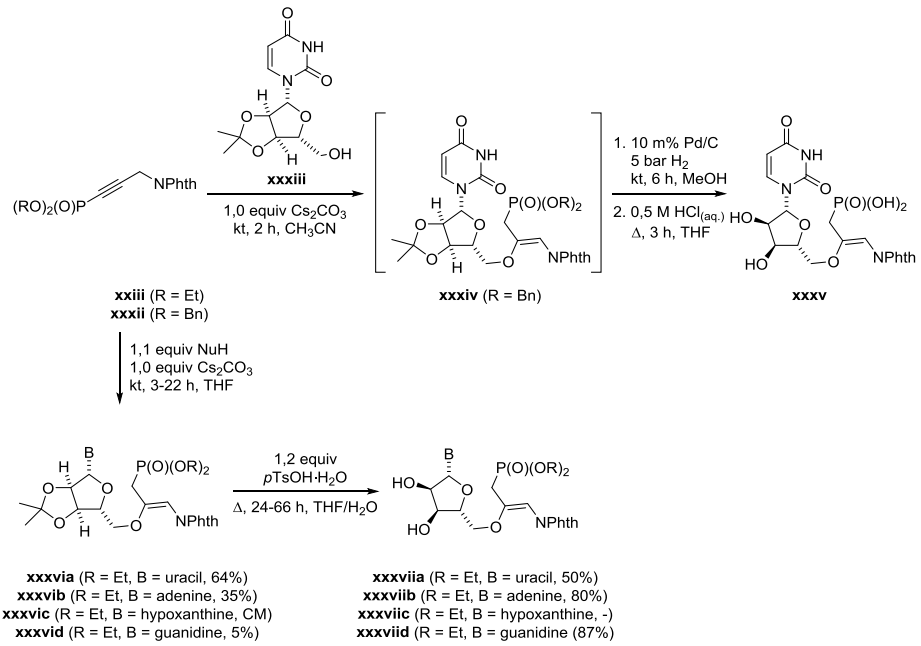
Schema 111: Bereiding van 3-imidoallenylfosfonaten en *in situ* β-alkoxylering.

Vervolgens werd onderzocht of gesubstitueerde tetrahydrofuranen **xxvi** bereid konden worden bij behandeling van dezelfde precursoren met haloalcoholen (Schema 112). Deze haloalcoholen reageren weldegelijk in deze *one-pot*-alkoxylering, hoewel er geen ringsluiting optrad. Ringsluiting was wel mogelijk wanneer salicylaldehyde gebruikt werd als nucleofiel. Drie gefosfonyleerde chromeenisomeren **xxviia**-**c** werden gevormd, in combinatie met een gedefosfonyleerd chromeen **xxviid** als resultaat van een Horner-Wadsworth-Emmonsreactie. Er konden geen reactieomstandigheden gevonden worden die leidden tot de selectieve vorming van één van deze producten. *N*-nucleofielen konden ook geïntroduceerd worden, hoewel deze niet allemaal even vlot reageerden als *O*-nucleofielen. Diëthylamine gaf selectief één regioisomeer, terwijl pyrrolidine en dibenzylamine een mengsel van regioisomeren leverden. Di-isopropylamine en *N*-methylfenylamine leidden tot complexe mengsels. Additie van diëthylfosfiet leverde nieuwe imido-gesubstitueerde vicinale bisfosfonaten **xxxa**-**c** en een product waarbij twee equivalenten diëthylfosfiet ingebouwd werden. Helaas werden geen reactieomstandigheden gevonden die de selectieve synthese van één van deze producten mogelijk maakte. Koolstofnucleofielen konden ook ingezet worden, hoewel er slechts een beperkte conversie waargenomen werd in het geval van het cyanide-anion. Diëthylmalonaat reageerde vlot met 3-imidoallenylfosfonaat **xxiii**, maar de reactie kon niet selectief naar één van de drie bekomen regioisomeren **xxxia**-**c** gestuurd worden.



Schema 112: Overzicht van de nucleofielen die reageren met 3-imidoallenylfosfonaten.

In een vijfde hoofdstuk werd onderzocht of 3-imidoallenylfosfonaten ingezet konden worden voor de synthese van nieuwe nucleosidefosfonaten. Omdat deze nucleosidefosfonaten later getest zouden worden op hun activiteit in een breed-spectrum antivirale test, dienen deze bij voorkeur te beschikken over ontschermde ribose- en fosfonaateenheden. Aangezien dibenzylfosfonaten de vrije fosfonzuren kunnen geven via hydrogenatie, werd eerst de additie van uridineacetonide geëvalueerd aan dibenzylalkynylfosfonaat **xxxii** (Schema 113). Dit trad op met goed gevolg, maar het additieproduct kon niet gescheiden worden van enkele onzuiverheden, gevormd in deze reactie. Opzuivering na ontschermen van enkel de ribose-eenheid of na ontschermen van zowel de ribose-eenheid als het fosfonaat, slaagde evenmin.



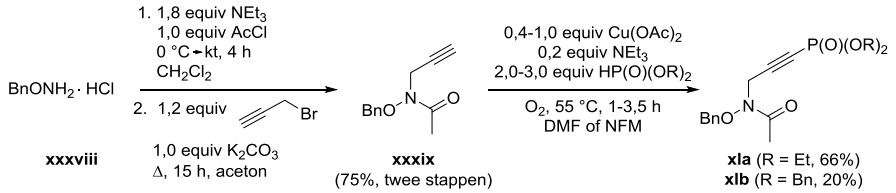
xxxvia (R = Et, B = uracil, 64%)
xxxvib (R = Et, B = adenine, 35%)
xxxvic (R = Et, B = hypoxanthine, CM)
xxxvid (R = Et, B = guanidine, 5%)

xxxviia (R = Et, B = uracil, 50%)
xxxviib (R = Et, B = adenine, 80%)
xxxviic (R = Et, B = hypoxanthine, -)
xxxviid (R = Et, B = guanidine (87%)

Schema 113: Bereiding van diethyl nucleosidefosfonaat *prodrugs*.

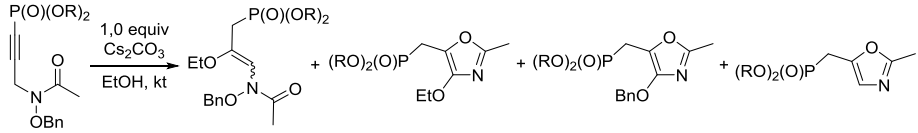
Diëthylnucleosidefosfonaten **xxxvia**-**b** en **xxxvia**-**d** konden wel met succes opgezuiverd worden en werden nadien behandeld met *p*TsOH. Uiteindelijk werden vier nieuwe diëthylnucleosidefosfonaat *prodrugs* bekomen en vervolgens gescreend op hun biologische activiteit. Helaas werd in celcultuur voor geen enkele van deze verbindingen antivirale activiteit tegen de geselecteerde virussen gedetecteerd. HSV-1, HSV-2, para-influenza-3-virus, HIV-1, HIV-2 en gelekoortsvirus behoorden onder andere tot het panel van de breed-spectrum antivirale test. In een enzymassay werd ook influenza PA-Nter endonuclease niet geïnhibeerd door één van de vier nucleosidefosfonaten. De verbindingen bleken wel niet cytotoxisch te zijn.

In het laatste hoofdstuk werd een strategie voor de toetreding tot β-gesubstitueerde fosmidomycinederivaten onderzocht, waarin het aminoallenylfosfonaatintermediair centraal stond. Hydroxamaat **xxxix** werd bekomen na acylering van *O*-benzylhydroxylamine hydrochloride met acetylchloride en alkylering met propargylbromide (Schema 114). De eerder ontwikkelde *cross*-koppelingsreactie met dialkylfosfieten kon opnieuw toegepast worden, zodat de gefosfonyleerde alkynen **xla**-**b** met succes bekomen werden.



Schema 114: Bereiding van aminoallenylfosfonaatprecursoren door acylering en alkylering van *O*-benzyl hydroxylamine hydrochloride, gevolgd door oxidatieve *cross* koppeling met dialkylfosfieten.

Wanneer gepoogd werd ethanol te introduceren, kon het additieproduct **xli** wel gedetecteerd maar niet geïsoleerd worden (Schema 115). Bovendien trad een ringsluitingsreactie op tot oxazolen **xlii**-**xliv**. Een reactiemechanisme werd voorgesteld dat de vorming van deze producten kan verklaren en vermoedelijk startte met de eliminatie van een benzyloxygroep. Enkele intermediairen konden gesynthetiseerd worden die deze hypothese ondersteunen.



Schema 115: Poging tot bereiding van β-gesubstitueerde fosmidomycine derivaten.

Het verlagen van de zuurtegraad van de protonen in de propargylische positie, door vervanging van de *N*-acetylgroep door een *N*-Boc-groep, was niet succesvol en verlies van de benzyloxygroep werd opnieuw geobserveerd. In een ultieme poging om β-gesubstitueerde fosmidomycinederivaten te bekomen, werd substraat **xl** bestudeerd in de koper-gekatalyseerde hydroamineringsreactie met diëthylamine. In het bekomen complex mengsel werden kleine hoeveelheden van product **xli** gedecteerd, naast een product dat een dubbele Michael-additie ondergaan leek te hebben. Uiteindelijk werd ook deze strategie verlaten.

Samenvattend werd aangetoond dat chirale allenylfosfonaten met een ketoterpeenskelet op elegante wijze toetreding verlenen tot chirale spirocyclische oxafosfolenen. Verdere inspanningen moeten gevoerd worden om de corresponderende fosfonzuren vrij te stellen zodat hun chiraliteitsinducerende eigenschappen in asymmetrische transformaties beoordeeld kunnen worden. Centraal stond ook de bereiding van de nooit eerder gerapporteerde 3-imidoallenylfosfonaten. Deze sterk gefunctionaliseerde kleine moleculen konden bereid worden onder zeer milde omstandigheden uit eenvoudige precursoren en reageerden zeer vlot met een verscheidenheid aan nucleofielen. Een aantal transformaties vertoonden slechts een matige selectiviteit en hun potentieel moet in verder onderzoek bestudeerd worden. Zoekende naar nieuwe antivirale *lead compounds*, hebben deze sleutelbouwsteen een aantal

nieuwe nucleosidefosfonaten voortgebracht terwijl ze ook onderzocht werden voor het ontwerpen van nieuwe fosmidomycine analoga.

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SCIENTIFIC PUBLICATIONS IN INTERNATIONAL PEER-REVIEWED JOURNALS (A1)

1. Protasova, L., Bulut, M., Ormerod, D., Buekenhoudt, A., **Berton**, **J**., Stevens, C., 'Latest Highlights in Liquid-Phase Reactions for Organic Synthesis in Microreactors', *Org. Process Res. Dev.*, **2013**, *17*, 760-791.

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4. Valotteau, C., Calers, C., Casale, S., **Berton**, **J.**, Stevens, C., Babonneau, F., Pradier, C., Humblot, V., Baccile, N., 'Biocidal Properties of a Glycosylated Surface: Sophorolipids on Au(111)', *Appl. Mater. Interfaces*, **2015**, *7*, 18086.

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6. Cuvier, A., Babonneau, F., **Berton**, **J.**, Stevens, C., Fadda, G., Péhau-Arnaudet, G., Le Griel, P., Prévost, S., Perez, J., Baccile, N., 'Nanoscale platelet formation by monounsaturated and saturated sophorolipids under basic pH conditions', *Chem. Eur. J.*, **2015**, *21*, 19265.

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8. **Berton**, **J.**, Andersen, S. J., Naert, P., Gildemyn, S., Rabaey, K., Stevens, C., Chemistry, 'Extraction and esterification of low-titre short chain volatile fatty acids from anaerobic fermentation with ionic liquids', *ChemSusChem*, **2016**, *9*, 2059.

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10. Baccile, N., Cuvier, A., Prevost, S., Stevens, C., Delbeke, E., **Berton**, **J.**, Soetaert, W., Van Bogaert, I., Roelants, S., 'Self-assembly mechanism of pH-responsive glycolipids: micelles, fibers, vesicles, and bilayers', *Langmuir*, **2016**, *32*, 10881.

11. Jebli, N., Debrouwer, W., **Berton**, **J.**, Van Hecke, K., Stevens, C., Touil, S., 'Direct Regio- and Diastereoselective Diphosphonylation of Cyclic Enamines: One-Pot Synthesis of α,α'-Bis(diphenylphosphoryl)- and α,α'-Bis(diphenylphosphorothioyl)cycloalkanones', *Synlett*, **2017**, *28*, 1160.

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13. **Berton**, **J.**, Salemi, H., Virieux, D., Stevens, C., 'Three-step Synthesis of Chiral Spirocyclic Oxaphospholenes', *submitted*, **2017**.

ACTIVE PARTICIPATIONS AT CONFERENCES

1. 21st International Conference on Phosphorus Chemistry (ICPC 2016), June 5-10, 2016, Kazan, Russia.
   Oral presentation: **Berton**, **J.**, Heugebaert, T., Debrouwer, W., Stevens, C. 3-Imidoallenylphosphonates: formation, isolation and reactivity of a highly functionalized, reactive intermediate.

2. 21st International Conference on Phosphorus Chemistry (ICPC 2016), June 5-10, 2016, Kazan, Russia.
   Poster presentation: **Berton**, **J.**, Heugebaert, T., Debrouwer, W., Stevens, C. 3-Imidoallenylphosphonates trapped at last.

3. International Conference on Phosphorus Boron and Silicon (PBSi 2017), July 3-5, 2017, Paris, France.
   Berton, **J.**, Salemi, H., Virieux, D., Stevens, C.
   Oral presentation: Synthesis of chiral spiro oxaphospholenes.

TUTORING OF BACHELOR AND MASTER THESIS STUDENTS

1. M. Movsisyan, 'Benzenesulfonyl chloride: synthesis through mesoreactor technology and environmental sustainability assessment' (2012-2013).

2. N. Sevrain, 'Synthesis of phosphonylated azaheterocycles by gold-induced cyclization' (2013).

3. B. Wuyts, 'Esterification of fermentation products' (2013).

4. S. Gilles, 'Studie van fosfono-allenen als toetreding tot azaheterocyclische fosfonaten' (2013-2014).

5. J. Mariën, 'Synthese van gefosfonyleerde oxazolidinonen en oxazolonen via goud-gemedieerde ringsluiting' (2013-2014).

6. H. Mahjoub, 'Synthesis of 3,5-diphosphonylpyridines' (2014 and 2015).

7. P. Naert, 'Ionic liquid driven esterification of aqueous fermentation product' (2014-2015).

8. B. Withoeck, 'Synthese van gefosfonyleerde γ-lactamen via Kharasch reactie' (2016).

9. G. Saborit i Canals, 'Synthesis of phosphonylated γ-lactams' (2016).

10. D. Vanavermaete, 'Fosmidomycine-geïnspireerde zoektocht naar anti-malariamiddelen' (2016-2017).